Isolated Severe Immune Thrombocytopenia due to Acute Brucellosis

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Abstract Mild anemia and leukopenia are the most common hematologic findings in the course of acute brucellosis. However severe form of thrombocytopenia is less frequently reported. The patient was admitted to the hospital with fever, gingival bleeding, and petechial skin lesions related to severe thrombocytopenia. He was investigated for the causes of thrombocytopenia. Test results showed that Wright agglutination test was positive at 1/5120 titer, and blood culture was positive for *Brucella melitensis*. Finally, he was diagnosed as acute brucellosis. Rifampicin and doxycycline treatment was started on the third day of admission. A bone marrow aspiration was performed on the seventh day of admission because of severe thrombocytopenia did not response to brucellosis treatment. The result of bone marrow aspiration was consistent with idiopathic thrombocytopenic purpura. With the addition of corticosteroid treatment, his complaints resolved immediately, and thrombocyte count rose to normal range. He was discharged on the 12th day of rifampicin and doxycycline therapy, and he was successfully completed 6-week therapy. In cases of brucella induced immune thrombocytopenia, corticosteroid treatment might be useful for the prevention of bleeding complications.

Keywords Brucellosis · Immune thrombocytopenia · Corticosteroid treatment

Introduction

Brucellosis is an infectious disease of animals caused by gram-negative coccobacilli of the genus *Brucella*. Brucellosis is a major health problem especially in Mediterranean Region and Middle Eastern countries as well as in Turkey [1]. Human brucellosis is a multisystem disease with a broad spectrum of clinical and laboratory manifestations which might lead to diagnostic difficulties. A variety of hematologic abnormalities have been reported in the course of brucellosis as most commonly in the mild forms of anemia and leukopenia [1–4]. Severe thrombocytopenia is rarely reported in brucellosis, and its mechanism is not fully understood [5–9].

In this report we present a case of brucellosis with severe isolated thrombocytopenia. We aimed to discuss and review the hematological complications of brucellosis in this article.

Case

A 75 year-old male was admitted to the Gazi University Hospital, Ankara with the complaints of fever, sweating, and arthralgia for 15 days. Three days before admission, he had petechia on lower extremities. In physical examination, he had fever (38.2 °C), but the other findings of vital signs were normal. He had also gingival bleeding, and petechial-purpuric skin lesions on the legs. Initially, a viral infection including Crimean-Congo hemorrhagic fever, which is endemic in Turkey, was suspected in the case and no antibiotic started. The results of laboratory tests were as follows: white blood cell count (WBC) 4,220/mm³ with 67.8 % neutrophils, 22 % lymphocytes, 9.2 % monocytes; hematocrit 37 %; haemoglobin 13.5 g/dL; platelets 8,940/mm³;

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erythrocyte sedimentation rate (ESR) 28 mm/h (normal range 0–15 mm/h); C-reactive protein (CRP) 96 mg/L (normal range 0–6 mg/L); prothrombin time (PT) 12.4 s; activated partial thromboplastin time (aPTT) 23.3 s; fibrinogen and D-dimer level was normal, Liver function tests showed the following values: alanine aminotransferase (ALT), 44 U/L (normal range 0–40 U/L); aspartate aminotransferase (AST), 49 U/L (normal range 0–40 U/L); lactate dehydrogenase (LDH) 406 U/L (normal range 125–243 U/L), and total bilirubin 1.8 mg/dL, direct bilirubin 0.97 mg/dL. Viral markers for cytomegalovirus, epstein barr virus, parvovirus, human immunodeficiency virus, Crimean-Congo hemorrhagic fever (CCHF) virus were found to be negative. A disseminated intravascular coagulation (DIC) was excluded because there was no schistocytes at peripheric blood smear, and PT, aPTT levels were normal.

Brucella agglutinin titer was found to be positive at 1:5,120 on the 3rd day of hospital admission. A treatment of doxycycline 100 mg bid, and rifampicin 600 mg/day was started with the diagnosis of acute brucellosis. The blood cultures taken on admission yielded *Brucella* spp. on the seventh day of hospital admission. On the fifth day of brucellosis treatment, a bone marrow aspiration and biopsy was performed for the differential diagnosis of isolated thrombocytopenia because of severe thrombocytopenia did not response to brucellosis treatment and the patient's gingival bleeding continued intermittently. A non-necrotic granuloma formation was detected in bone marrow biopsy. Other findings were normal except than an increased number of megakaryocyte. The patient was diagnosed as having an acute brucellosis associated thrombocytopenia because of thrombocytopenia was unresponsive to the treatment and there were increased numbers of megakaryocytes in bone marrow examination. A corticosteroid therapy (metilprednisolone 1 mg/kg/day) was added to on the sixth day of doxycycline and rifampicin. The patient's symptoms and laboratory findings improved significantly with this treatment. His fever was discontinued and a rapid rise in his platelet number ($194,000/\text{mm}^3$) was observed at fourth day of corticosteroid treatment. He was discharged on the 12th day with rifampicin and doxycycline for maintenance therapy. Corticosteroid treatment was rapidly tapered and discontinued within one month.

Discussion

Brucella is still an endemic disease in Turkey [1]. Hematologic complications, especially anemia and leukopenia, is frequently defined in mild forms in the course of brucellosis [1, 2]. In the Madkour's [4] series of 500 patients with active brucellosis, abnormal hematologic findings were seen mildly in 27.2 % of the patients. However severe

forms of isolated thrombocytopenia or pancytopenia are rarely defined in brucellosis. The presence of pancytopenia with severe thrombocytopenia in acute brucellosis can mimic several primary hematological diseases [6, 9, 10]. Thrombocytopenia was reported in 1–26 % of cases, even though severe thrombocytopenia was very rare [2, 11–13].

Thrombocytopenia related to systemic infections may be due to a variety of causes: hypersplenism, disseminated intravascular coagulation, hemophagocytosis, bone marrow suppression, immune destruction of platelets and adherence of thrombocyte to damaged vascular surfaces [4, 6, 9]. Severe thrombocytopenia may occur secondary to hematological abnormalities or infections. Especially, viral infections such as cytomegalovirus, epstein barr virus, parvovirus, human immunodeficiency virus, and hemorrhagic fever viruses including CCHF virus may cause to thrombocytopenia. CCHF is endemic in northern and middle regions of Turkey. It should be considered in patients with thrombocytopenia who comes from rural areas. Therefore, brucellosis may not to have been noticed in the differential diagnosis at initial. Clinicians should be awakened about its rare hematological complications.

Thrombocytopenia develops usually in moderate form in the course of brucellosis and occurs secondary to bone marrow suppression or hypersplenism. Immune destruction of platelets in the course of brucellosis is also reported by hemaphagocytosis and granulomatous infiltration in the bone marrow [4, 6, 9].

Granulomatous infiltration of bone marrow is an important hematological finding which it was seen in our patient. Non-caseating granulomas in the bone marrow are frequent findings in brucellosis and seen in approximately 30 % of patients [9]. Sari et al. [2] reported that granulomas were detected in 33.3 % of 30 cases. Even though several possible mechanisms have been suggested for thrombocytopenia caused by brucellosis, such as hemophagocytosis, hypersplenism, bone marrow hypoplasia [2, 4], we think that granulomatous infiltration of the bone marrow could be an explanation for the mechanism of brucellosis-associated thrombocytopenia in this case.

Splenomegaly occurs in 15–20 % of uncomplicated brucellosis, however, its incidence may be as higher as 46 % in complicated cases [13, 14]. Splenic enlargement has been said to correlate with the severity of illness in brucellosis. Hypersplenism is rarely defined in the course of thrombocytopenia that responded only to splenectomy [6]. However, there was no splenomegaly in our patient, therefore, we cannot refer the thrombocytopenia to splenomegaly.

Most of the hematological abnormalities related to infections are reversible and they resolve promptly with the initiation of specific antimicrobial therapy [6]. Platelet recovery usually occurs with the initiation of appropriate brucella treatment within first 2–3 weeks [15]. In some

cases, immune destruction of platelets due to antiplatelet antibodies might be the reason of thrombocytopenia [7]. Evidence for an immune mechanism includes the apparent response to corticosteroids by the majority of patients and positive Coombs tests for approximately one-third of the patients. Due to the high mortality rate, a short-term trial of intravenous immunoglobulin treatment may be recommended in emergent cases to increase platelet count and to control for bleeding complications in these patients [7, 11]. It is also recommended to use corticosteroids in patients of which platelet count is $<10,000 \mu\text{L}$ [8]. An immune mechanism could be suspected in our patient because he responded to the combination of corticosteroid and anti-brucellosis treatment. Platelet recovery was detected on the 10th day in our patient, and he was discharged on the 12th day of the corticosteroid treatment. He had no complication during the 6-week anti-brucellosis treatment course.

In conclusion, the differential diagnosis of severe immune thrombocytopenia should include brucellosis especially in endemic countries. In the treatment of brucellosis-induced severe thrombocytopenia, a short-term corticosteroid therapy might be useful for the prevention of bleeding complications.

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