

Thrombocytopenia in Brucellosis: Case Report and Literature Review

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Background: Brucellosis, constituting a major health problem in many parts of the world—particularly in the Mediterranean and the Middle East—is a multisystem disease with a broad spectrum of clinical manifestations. Hematological abnormalities ranging from a fulminant state of disseminated intravascular coagulopathy to subtle hemostatic alterations have been reported in brucella infection. Immune-mediated thrombocytopenia is also a clinically important mechanism that can be encountered during brucellosis.

Case: A young lady with fever was referred to a university hospital because of thrombocytopenia. The provisional diagnosis was idiopathic thrombocytopenic purpura, as the bone marrow examination showed an increased number of megakaryocytes and the absence of fever after hospitalization. The patient responded well to corticosteroid treatment. However, she was finally diagnosed with brucellosis with positive bone marrow and blood cultures for *B. abortus* and agglutination test of 1:320. The patient was discharged from the hospital 10 days later in good health on rifampicin and doxycycline therapy. The follow-up of the patient revealed normal hematological findings together with a progressive reduction in the titer of the agglutination test for brucella.

Conclusion: Brucella infection may cause severe thrombocytopenia, mimicking a primary hematological disease that is reversible after appropriate antimicrobial therapy. In cases of brucellosis-induced immune thrombocytopenic purpura, a short-term standard dose of corticosteroid treatment might be an alternative and additional treatment as an urgent approach for thrombocytopenia while initiating antibrucellosis treatment.

Key words: brucellosis ■ fever ■ thrombocytopenia ■ corticosteroid

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INTRODUCTION

Patients hospitalized with provisional diagnosis of hematological-oncological diseases are still found to have underlying infectious etiologies in the hematology-oncology departments. We previously reported interesting cases of brucellosis,^{1,2} salmonellosis³ and tuberculosis^{4,5} in patients presenting with either initial hematological manifestations or unexplained fever that were referred to a university hospital's hematology-oncology clinics.

Brucellosis, a zoonotic disease of worldwide distribution, is an infectious disease primarily of domestic and wild animals. It constitutes a major health problem in many parts of the world, particularly in the Mediterranean and the Middle East. The true incidence of human brucellosis is unknown. The World Health Organization points out that 500,000 cases are reported each year around the world.

Human brucellosis has a wide clinical spectrum and presents various diagnostic difficulties as it mimics many other diseases. The disease is caused by coccobacilli of the genus *Brucella* and transmissible to man through direct contact with infected animals and consumption of infected animal products. At present, there are six known species of brucellae, including *B. melitensis*, *B. abortus*, *B. suis*, *B. canis*, *B. ovis* and *B. neotomae*. Human brucellosis can occur in any age group, but young men make up the majority of cases that are generally related to occupational hazard.

Hematological abnormalities, ranging from a fulminant state of disseminated intravascular coagulopathy to subtle hemostatic alterations have been reported in Brucella infection.^{6,7} The commonly seen hematologic abnormalities are anemia and leukopenia. Isolated thrombocytopenia (platelets <150 x 10⁹/L) was seen in 8% of cases in a study reported from Turkey.⁸ Immune-mediated thrombocytopenia may also occur during the course of brucellosis.⁹ In this case report, we presented a patient with a history of fever and thrombocytopenia. The patient was initially diagnosed as idiopathic thrombocytopenic

purpura (ITP) and received corticosteroid treatment. However, blood and bone marrow cultures taken on the day of hospitalization because of the history of fever revealed *B. abortus*. The patient received the antibrucellosis treatment, and thrombocytopenia was improved and reverted to normal.

CASE REPORT

A 29-year-old female patient with a history of fever of up to 40°C for the last week was hospitalized because of severe thrombocytopenia. The patient first applied to a state hospital with complaint of fever. She was then referred to a university hospital, where the routine blood investigation revealed thrombocytopenia. Her physical examination revealed a fever of 36.6°C and a systolic/diastolic blood pressure of 90/60 mmHg. A complete blood count showed Hb 11.7 g/dL, Hct 0.35, MCV 85.5 fl, WBC $5.5 \times 10^9/L$, platelet $9 \times 10^9/L$, and mean platelet volume (MPV) 10.3. A peripheral blood smear examination showed inadequate platelets. The bone marrow appearance was normal except for a slightly increased number of megakaryocytes. While performing bone marrow aspiration, we also obtained bone marrow cultures for possible infectious etiologies. Moreover, synchronous blood cultures were taken, as the patient had history of fever (Bactec 9120 and Sceptor Identification System, Becton-Dickson Diagnostic Instrument System, Sparks, USA). She was hospitalized with a suspected diagnosis of ITP. The markers for hepatitis B and C were both negative. Her erythrocyte sedimentation rate, serum LDH, fibrinogen and D-dimer levels, prothrombin time, and activated partial thromboplastin time were normal.

The absence of fever for the last three days after hospitalization and the slightly increased megakaryocytes in the bone marrow examination made us to think ITP. The patient also responded well to corticosteroid treatment supporting our view (platelet $238 \times 10^9/L$ on the fourth day). However, on day five, *B. abortus* was isolated both from the blood and bone marrow cultures performed on the day of admission. The Wright tube agglutination test was 1:320. Rifampicin 600 mg/d and doxycycline 200 mg/d were commenced. In the first week of treatment, thrombocyte count was $392 \times 10^9/L$ with groups of thrombocytes in the peripheral blood smear (Hb 12.5 g/dL, Hct 0.38, MCV 85.1 fl, WBC $8.5 \times 10^9/L$). She was discharged from the hospital 10 days after admission in good health on rifampicin and doxycycline therapy. Thrombocyte count was $281 \times 10^9/L$ and $259 \times 10^9/L$ one and three months later, respectively. The duration of the antibrucellosis treatment was three months. Follow-up of the patient six months later showed a progressive reduc-

tion in the titer of the agglutination test for *Brucella* with normal thrombocyte count.

DISCUSSION

Brucellosis is a systemic disease in which any organ or body system can be involved. The symptoms are nonspecific; however, the majority complain of fever, sweats, malaise, anorexia, headache, arthralgia and backache. Although brucellosis has been controlled or eradicated in many developed countries, it still remains a health problem in developing countries. As no characteristic constellation of symptoms and signs exists, the diagnosis may be readily missed.¹⁰ The nonspecific antibiotic usage also lowered the rate of positive blood cultures and led to difficulties in the diagnostic work-up.¹¹

Hematological abnormalities of brucellosis have been reported in the literature.^{6,7} The incidence of thrombocytopenia was reported in the range of 2.4–33%.^{6,12–15} Akdeniz et al.⁸ reported 8% of isolated thrombocytopenia (platelets $<150 \times 10^9/L$) in 233 patients with brucellosis, but clinically detectable bleeding (epistaxis, gross hematuria, cutaneous petechiae) was seen in only three (1% of) cases, which were all mild. On the other hand, Galanakis et al.¹³ reported 6% of thrombocytopenia, with no isolated case, in 52 patients with childhood brucellosis who did not have extremely low platelet counts on admission (range: $95–150 \times 10^9/L$). Moreover, isolated thrombocytopenia was also not encountered in al-Eissa's study, which reported 5% of thrombocytopenia (range: $4–126 \times 10^9/L$) in a total of 110 children with brucellosis.⁶ Gur et al.¹⁵ described 2.4% of thrombocytopenia, with no isolated case, in a retrospective analysis of 283 adult patients from southeastern Turkey.

The etiology of thrombocytopenia in brucellosis remains obscure. Multiple possible mechanisms to clarify the pathogenesis of thrombocytopenia include hypersplenism, bone marrow suppression, disseminated intravascular coagulation, direct damage to platelets by viruses and bacteria, hemophagocytosis, granulomas^{6,12,16–18} and immune-mediated.⁹ Patients with septic thrombocytopenia were found to have elevated platelet-associated IgG levels in the range of 52–82%. The platelet damage is caused by the splenic destruction of immune complex-coated platelets.^{19,20} The mechanism of thrombocytopenia for our patient is possibly related to brucellosis-induced immune peripheral destruction of platelets by antiplatelet antibodies, since the patient initially responded to steroid treatment.

The presented patient was initially misdiagnosed as ITP. Moreover, thrombocytopenia was improved after four days of standard dose of methylprednisolone treatment supporting our initial diagnosis. However, the treatment changed to antibrucellosis

therapy after culturing *B. abortus* both in the blood and bone marrow. In our previous report,¹ however, thrombocytopenia was resistant to eight days of high-dose steroid treatment. Both patients' findings seem to be contradictory to each other; however, the presented patient would have possibly relapsed in the first two weeks after the steroid treatment unless the antibrucellosis treatment has been initiated. Benecos et al.²¹ reported an eight-year-old boy with complaints of epistaxis and buccal bleeding who initially responded to steroid and gammaglobulin treatment for the first two weeks but relapsed immediately afterwards. The presented patient was diagnosed as brucellosis on the fifth day, and antibrucellosis treatment was commenced before relapsing of thrombocytopenia. Gurkan et al.⁹ reported a brucellosis case that was initially diagnosed as ITP and received high-dose corticosteroid treatment accordingly. The platelet count was only increased to $13.3 \times 10^9/L$ from $3.6 \times 10^9/L$ on day five. In our patient, a prompt rise of platelet count was observed after the steroid treatment supporting our view of ITP. Young et al.²² reported an apparent response to corticosteroids by the majority of patients with brucella-induced immune-mediated thrombocytopenia. Gurkan et al. also recommended a short-term trial of high-dose corticosteroid treatment to patients with brucellosis-induced thrombocytopenia. However, unless there is a response to steroid treatment in 3–5 days, it is of no use to extend the treatment period.⁹ The similarity between the pathogenesis of ITP and infection-induced, immune-mediated thrombocytopenia makes the rationale for using corticosteroid treatment. However, at the same time, the therapy should also be directed to the underlying infection. In patients at high risk of bleeding due to brucella-induced, immune-mediated thrombocytopenia, synchronous commencement of steroid and antibrucellosis treatment should be applied.

The presence of fever challenges the diagnosis of ITP.^{1,3} An infectious etiology should be sought immediately in those cases with ITP and fever. Not only the presence of fever during hospitalization but also a fever history prior to hospitalization were also found to be important in patients with provisional diagnosis of ITP. The fever indirectly tells us the underlying possible immune mechanism rather than ITP.

In the diagnosis of brucellosis, bone marrow cultures were found to be significantly more sensitive than cultures of the blood (92% vs. 70%, respectively), and the time to detection was shorter for bone marrow cultures.²³ In the presented patient, blood and bone marrow cultures were taken as the patient was hospitalized with a history of fever. Both the bone marrow and blood cultures were found to have positivity for brucellosis on the fifth day.

In their excellent review regarding the thrombocytopenic purpura in brucellosis, Young et al.²² reviewed 41 cases of brucellosis complicated by thrombocytopenia severe enough to cause purpura and mucosal bleeding. The principal sites of mucosal hemorrhage included epistaxis (69%), gingivorrhoea (44%) and hematuria (64%). However, in our patient, no mucosal bleeding was detected. In addition, 31 out of 41 reported patients (72%) were found to receive steroid for periods of up to eight weeks. Thirty-nine patients (90.7%) were found to be survived, and antimicrobial therapy with or without steroids led to rapid resolution of thrombocytopenia. In addition to the literature review by Young et al.,²² there are several brucellosis-induced thrombocytopenic patients receiving intravenous gammaglobulin, steroids and/or antibrucellosis treatment.²⁴⁻³³ While thrombocytopenia is a component of pancytopenia in first four cases,²⁴⁻²⁷ the others had isolated thrombocytopenia.²⁸⁻³³ However, the interesting point in the presented patient is the acute response of isolated thrombocytopenia to corticosteroid treatment similar to cases of ITP. The diagnosis of infection-induced immune thrombocytopenia was put forward only after the positive cultures of bone marrow and blood cultures revealed brucellosis.

The patient was discharged from the hospital 10 days later in good health on rifampicin and doxycycline therapy. The follow-up of the patient revealed normal hematological findings together with a progressive reduction in the titer of the agglutination test for brucella. In conclusion, brucella infection may cause severe thrombocytopenia, mimicking a primary hematological disease, that is reversible after appropriate antimicrobial therapy. In rare cases, thrombocytopenia can be severe; therefore, prompt recognition of this complication and aggressive therapy are essential. In cases of brucellosis-induced, immune thrombocytopenic purpura, a short-term standard dose of corticosteroid treatment might be an alternative and additional treatment as an urgent approach for thrombocytopenia while initiating antibrucellosis treatment. Further studies should also be carried out to demonstrate the benefits of corticosteroid treatment for brucellosis as an additional treatment to antibrucellosis therapy.

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