Clinical Research Report

Brucella-induced thrombocytopenia: a retrospective study of 16 patients

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Abstract
Objective: We aimed to describe the clinical characteristics and treatment outcomes of 16 patients with Brucella-induced thrombocytopenia.
Methods: We assessed 16 patients with Brucella-induced thrombocytopenia between 2012 and 2016 in The First Affiliated Hospital of Xinjiang Medical University. The diagnosis of Brucella-induced thrombocytopenia was <100,000 platelets/mm³.
Results: All patients were men. The most common symptoms of patients were fever (100%), sweating (81.2%), fatigue (75%), and joint pain (25%). The most common signs of physical examinations were an enlarged liver (75%) and enlarged spleen (50%). The lowest thrombocyte count was 2000/mm³ and the highest count was 72,000/mm³. An agglutination test antibody was positive (≥1:160) in 12 (75%) patients with the highest antibody titer of 1:800. Brucella melitensis was isolated from blood cultures in nine (56.3%) patients. All patients were administered antimicrobial agents. The patients’ platelet counts were normal at a follow-up of 12 months.
Conclusion: Classical brucellosis therapy is adequate for patients with a platelet count >20,000/mm³. The five-drug regimen of doxycycline + rifampin + platelet transfusions + corticosteroids + intravenous immunoglobulin is recommended for patients when the platelet count is <10,000/mm³. These findings have important implications for improving treatment outcome in patients with Brucella-induced thrombocytopenia.

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Introduction

Brucellosis, which is caused by intracellular Gram-negative cocccobacilli of the Brucella species, is considered one of the most relevant bacterial zoonoses worldwide. More than half a million new cases of Brucella are found annually and the prevalence rate in some countries exceeds 10 cases per 100,000 population.\(^1,2\) Clinical manifestations of brucellosis are varied and range from minimal symptoms to extreme morbidity and occasional fatalities. Among the various clinical manifestations, thrombocytopenia is less common, and has been reported in 3\% to 26\% of cases.\(^2,4\) There have been few reports of Brucella-induced thrombocytopenia, most of which were case reports.\(^3,5\) This study aimed to describe 16 cases of thrombocytopenia due to Brucella and to present a relevant literature review.

Materials and methods

Study population

From 2012 to 2016, 170 brucellosis cases were recorded, of which 9.4\% (16 cases) with thrombocytopenia (\(\leq 100,000\) platelets/mm\(^3\)) due to Brucella were diagnosed. These patients were followed up at The First Affiliated Hospital of Xinjiang Medical University, located in Urumqi, China. In China, brucellosis cases have been reported in almost every province and year since 2010.\(^8\)

The diagnosis of brucellosis was made by isolating Brucella species from blood culture or by standard tube agglutination testing \(\geq 1:160\) and clinical findings (e.g., fever or fatigue, sweating, splenomegaly, hepatomegaly).\(^2\) The diagnosis of thrombocytopenia was \(\leq 150,000\) platelets/mm\(^3\).\(^2,9\) However, the diagnosis of Brucella-induced thrombocytopenia was \(\leq 100,000\) platelets/mm\(^3\) based on the literature.\(^3\) Additionally, when platelet counts are \(> 100,000/mm^3\), people have slight symptoms. Therefore, in this study, platelet counts of all of the patients were \(< 100,000/mm^3\). Platelet counts of \(< 20,000/mm^3\) were diagnosed as severe thrombocytopenia.\(^10\)

Clinical assessment and definitions

All 16 patients with thrombocytopenia due to Brucella were assessed prospectively, including demographic, clinical, and laboratory data. Ultrasonography was performed in all of the patients. The patients were assessed initially, at 6 and 42 days, and at 6 and 12 months. The study protocol was approved by the Ethics Committee of The First Affiliated Hospital of Xinjiang Medical University. Written informed consent was obtained from every patient.

All 16 cases were divided into three groups according to the platelet count as follows: (1) \(\leq 100,000\) platelets/mm\(^3\) and \(\geq 50,000\) platelets/mm\(^3\); (2) \(< 50,000\) platelets/mm\(^3\) and \(\geq 20,000\) platelets/mm\(^3\); and (3) \(< 20,000\) platelets/mm\(^3\).

Results

Patients’ characteristics

All of the 16 patients were men. The average age of the patients was 47 years (range: 20–72 years). Of them, 11 (68.7\%) were...
Han, three (18.5%) were Uighur, and two (12.5%) were Kazak. Most (n = 8, 50.0%) of the patients were farmers who had cows and sheep. Four (25.0%) patients presented with occupational exposure and four (25.0%) patients had unknown causes. None of the patients had a history of thrombocytopenia or bleeding.

**Presentation of symptoms and signs**

Table 1 shows the clinical characteristics of the 16 patients, including common symptoms and complications. The most common symptoms of the patients were fever, sweating, and fatigue. Some of the patients had joint pain or back pain. The most common physical finding was an enlarged liver, followed by an enlarged spleen. There were two (12.5%) cases of skin purpura and one (6.3%) case of epistaxis.

**Laboratory tests**

Table 2 shows the results of laboratory examinations. All 16 (100%) patients presented with thrombocytopenia. The lowest thrombocyte count was 2000/mm$^3$ and the highest count was 72,000/mm$^3$. Most of the patients had anemia and one quarter had leukopenia. Twelve (75%) patients had an elevated erythrocyte sedimentation rate and 11 (68.8%) had high C-reactive protein levels. None of the patients had leukocytosis. Standard tube agglutination testing was positive ($\geq 1:160$) in three quarters of the cases, of which the highest antibody titer was 1:800. Most of the patients had elevated transaminase levels. Approximately half of the patients had a positive blood culture for *Brucella melitensis*.

**Treatment and prognosis**

All of the patients received antibiotic treatment. The average treatment time was
84 days (range, 42–126 days) and 50% of patients with a platelet count ≤50,000/mm³ received therapy for ≥84 days. Eleven (68.8%) patients received combination therapy of rifampicin and doxycycline. Three (18.8%) patients received doxycycline and moxifloxacin. Two (12.5%) patients received rifampicin and moxifloxacin. Additionally, two patients with a platelet count ≤10,000/mm³ used a combination of doxycycline + rifampicin + platelet transfusions + corticosteroids + intravenous immunoglobulin. The other two patients (platelets ≥10,000/mm³ and ≤20,000/mm³) used a combination of doxycycline and rifampicin and platelet suspensions. Twelve patients (platelets ≥20,000/mm³) only used a combination of two antibiotics. At 7 days after antibiotic treatment, the platelet counts of all patients started to rise. The platelet counts of six patients became normal at 42 days after antibiotic treatment. All of the patients’ platelet counts were normal at a follow-up of 12 months.

**Discussion**

Brucellosis remains a serious concern in low- and middle-income countries. Brucellosis can be severely debilitating and disabling, although it is rarely fatal. For the past few years, the incidence rate of human brucellosis has significantly increased in the population. In China, brucellosis cases have been reported in almost every province and year since 2010. However, human brucellosis is easy to be misdiagnosed because of its non-specific clinical features, slow growth rate in blood cultures, and the complexity of its serodiagnosis.

In this study, abnormal blood results were usually non-specific. Four (25%) patients had leukopenia. None of the patients had leukocytosis. Anemia was found in 13 (81%) patients. Elevated serum transaminase levels were observed in 13 (81%) patients. Our data clearly demonstrated that laboratory manifestations in the 16 patients with Brucella-induced thrombocytopenia were not different from those in patients infected by Brucella without thrombocytopenia. In this study, splenomegaly was found in 50% of the 16 cases, which is higher than the rate of 16% to 26% reported for uncomplicated brucellosis. Some authors considered that splenic enlargement was associated with the severity of brucellosis. Nevertheless, hypersplenism due to an enlarged spleen may be a reason for thrombocytopenia. The liver is the largest organ of the reticuloendothelial system and it is probably always related to brucellosis. In our study, 12 (75%) patients presented with an enlarged liver. However, only 13 patients had increased transaminase levels and liver enzyme levels were only mildly elevated. Interestingly, two patients had severe thrombocytopenia (≤10,000/mm³) without hepatosplenomegaly. The reasons for these manifestations are not clear.

Thrombocytopenia can be found in 3% to 26% of patients with brucellosis. In the present study, 16 (9.4%) patients had thrombocytopenia with ≤100,000 platelets/mm³. There have been few reports of Brucella-induced thrombocytopenia, most of which were case reports. The precise pathological characteristics of this process are unclear. However, there are some possible mechanisms, including bone marrow suppression, hypersplenism, hemophagocytosis, disseminated intravascular coagulation, and immune destruction of platelets. Interestingly, although the mechanism of thrombocytopenia in brucellosis is unclear, thrombocytopenia, similar to other hematological complications of brucellosis, is generally mild, and may cause a dramatic increase in treatment of rifampin and doxycycline. According to the World Health Organization recommendations, the choices of antimicrobials for
treatment of brucellosis are doxycycline and rifampicin. Our results are consistent with the above-mentioned studies.\textsuperscript{6,10} The combination of doxycycline and rifampicin remain appropriate to treat \textit{Brucella}-induced thrombocytopenia.

Different causes of thrombocytopenia require different treatment strategies. First-line treatments for immune thrombocytopenic purpura are corticosteroids and intravenous immunoglobulin. However, as emergency treatment, platelet transfusions rapidly increase the platelet count.\textsuperscript{12} Corticosteroids and intravenous immunoglobulin therapy in \textit{Brucella}-induced thrombocytopenia is controversial. Karsen et al.\textsuperscript{10} reported that without corticosteroids and intravenous immunoglobulin, combination therapy including doxycycline and rifampicin and platelet suspensions led to a better treatment outcome for 10 patients with severe thrombocytopenia (platelets < 20,000/mm\textsuperscript{3}). Additionally, some authors have reported successful results with administration of intravenous immunoglobulin and/or steroids in conjunction with brucellosis treatment.\textsuperscript{3–5} If an immunological mechanism is the main reason for thrombocytopenia, patients have a better prognosis following intravenous gamma globulin and steroids in conjunction with brucellosis treatment.\textsuperscript{4,6,7} \textit{Brucella}-induced thrombocytopenia that results from other different mechanisms should have corresponding treatment. Some reports have shown that antibiotics alone can cure thrombocytopenia due to \textit{Brucella}. Whether intravenous gamma globulin and steroids need to be administered for thrombocytopenia due to \textit{Brucella} requires further confirmation. In the present study, two patients with a platelet count ≤10,000/mm\textsuperscript{3} used a combination of doxycycline + rifampicin + platelet transfusions + corticosteroids + immunoglobulin. The other two patients (platelets ≥10,000/mm\textsuperscript{3} and ≤20,000/mm\textsuperscript{3}) used a combination of doxycycline, rifampicin, and platelet suspensions. All four patients with severe thrombocytopenia (platelet counts of <20,000/mm\textsuperscript{3}) had a good treatment outcome. Twelve patients (platelets ≥20,000/mm\textsuperscript{3}) only used a combination of two antibiotics. All of the patients were treated successfully with no evidence of recurrence at follow-up visits. These findings have important implications for improving the treatment outcome in patients with \textit{Brucella}-induced thrombocytopenia.

Rad et al.\textsuperscript{6} reported a woman with a history of co-trimoxazole and gentamycin treatment for brucellosis for 1 week. She was then admitted to hospital with severe thrombocytopenia. The reason for this condition was drug-induced thrombocytopenia. An alternative regimen of anti-brucellosis antibiotic therapy with doxycycline and rifampicin led to a dramatic increase in platelet counts. Co-trimoxazole may cause isolated thrombocytopenia. However, the precise etiology of platelet destruction resulting from drugs remains unclear. While co-trimoxazole can be administrated to patients for brucellosis, platelet counts should be evaluated.

**Conclusion**

Because of protean clinical manifestations of idiopathic hematological system diseases, early and accurate diagnosis requires a thorough history and physical examination, as well as laboratory tests. We also suggest that the five-drug regimen of doxycycline + rifampin + corticosteroids + intravenous immunoglobulin + platelet transfusions be administered to patients with \textit{Brucella}-induced thrombocytopenia when the platelet count is ≤10,000/mm\textsuperscript{3}. The three-drug regimen of doxycycline + rifampin + platelet transfusions is recommended for patients with \textit{Brucella}-induced thrombocytopenia when the platelet count is ≥10,000/mm\textsuperscript{3} and ≤20,000/mm\textsuperscript{3}.
Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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