

## Original Article

# Severe Thrombocytopenia and Hemorrhagic Diathesis due to Brucellosis

Hasan Karsen MD<sup>1</sup>, Fazilet Duygu MD<sup>2</sup>, Kubilay Yapıcı MD<sup>3</sup>, Ali İrfan Baran MD<sup>3</sup>, Huseyin Taskiran MD<sup>4</sup>, İrfan Binici MD<sup>3</sup>

## Abstract

**Background:** We aimed to examine cases of brucellosis that presented with severe thrombocytopenia and hemorrhagic diathesis.

**Methods:** A total of 10 brucellosis cases with severe thrombocytopenia were included in this case-series study. Patients' files were reviewed for their clinical and laboratory findings, as well as clinical outcomes and complications. Platelet counts of  $< 20000/\text{mm}^3$  were diagnosed as severe thrombocytopenia.

**Results:** The lowest thrombocyte count was  $3000/\text{mm}^3$  while the highest was  $19000/\text{mm}^3$  (mean:  $12000/\text{mm}^3$ ). Patients had the following symptoms: epistaxis (7 cases), petechia with epistaxis (4 cases), bleeding gums (3 cases), ecchymosis with epistaxis (2 cases), melena and renal failure (2 cases), and hematuria (1 case). Patients were given rifampicin and doxycycline along with supportive hematological therapy. All were treated successfully with no evidence of recurrence at follow-up visits.

**Conclusion:** Since brucellosis is endemic in developing countries, it must be considered in the differential diagnosis of cases that present with severe thrombocytopenia and hemorrhagic diathesis.

**Keywords:** Brucellosis, hemorrhagic diathesis, severe thrombocytopenia

**Cite this article as:** Karsen H, Duygu F, Yapıcı K, Baran AI, Taskiran H, Binici I. Severe Thrombocytopenia and Hemorrhagic Diathesis due to Brucellosis. *Arch Iran Med.* 2012; **15**(5): 303 – 305.

## Introduction

Brucellosis is a multisystem disease with a wide variety of symptoms that include hematological abnormalities such as anemia, thrombocytopenia, pancytopenia and leucopenia. Disseminated intravascular coagulation (DIC) and hemorrhagic diathesis are rarely seen.<sup>1,2</sup> In some studies, hematological findings ranging from mild anemia to pancytopenia are reported to be more than 50%.<sup>3,4</sup> Various rates of thrombocytopenia due to brucellosis have been reported; however, to the best of our knowledge, all published studies except for case-reports regarding severe thrombocytopenia due to brucellosis were pediatric case-series, until now. In this paper, 10 adults cases with severe thrombocytopenia and hemorrhagic diathesis due to brucellosis have been presented.

## Materials and Methods

This was a case-series study. Patients' files were reviewed for their clinical and laboratory findings, symptoms, prognosis, age and gender as well as complications and clinical outcomes. The study protocol was approved by the local research committee for ethics. The Brucella Wright test; blood culture; complete blood count; erythrocyte sedimentation rate (ESR); C-reactive prote-

in (CRP); liver and renal function profiles; urinalysis; IgM anti-CCHF (Crimean-Congo hemorrhagic fever); as well as coagulation parameters such as prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen levels were measured. Complete blood cell count was repeated when the results were abnormal or when indicated. We also tested patients for enteric fever, malaria, acute viral hepatitis, and toxoplasmosis.

Brucellosis was diagnosed by the presence of antibodies against brucella with a titer of  $\geq 1:160$  by the standard tube agglutination test (Brucella abortus antisera, Cromatest, Linear Chemicals, Barcelona, Spain) and/or by isolation of brucella from blood (BACTEC, Becton Dickinson, USA) in addition to clinical symptoms consistent with brucellosis. Anemia, thrombocytopenia, and leucopenia were defined as hemoglobin (Hb) levels of  $< 12 \text{ g/dL}$ , a platelet count of  $< 150000/\text{mm}^3$ , and leukocyte count of  $< 4000/\text{mm}^3$ , respectively. Platelet counts  $< 20000/\text{mm}^3$  were considered as severe thrombocytopenia.<sup>5</sup>

## Results

There were 4 male and 6 female patients with severe thrombocytopenia. Patients' mean age was  $35.24 \pm 6.12$  years (range: 18 to 64 years). Standard agglutination test was positive in all patients, however *B. melitensis* was present in the blood cultures of only 3 patients.

Pancytopenia was present in 5 cases, bicytopenia (thrombocytopenia and anemia or thrombocytopenia and leucopenia) was seen in 4 cases, and there was only one case of isolated thrombocytopenia. The lowest thrombocyte count was  $3000/\text{mm}^3$  while the highest was  $19000/\text{mm}^3$  (mean:  $12000/\text{mm}^3$ ). The mean Hb level was  $9.17 \text{ g/dL}$  and white blood cell level was  $5720/\text{mm}^3$ . Totally, the mean decrease in thrombocytes was 92% while it was 23.6% in Hb levels. There was no decrease in white blood cell count.

**Authors' Affiliations:** <sup>1</sup>Harran University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Sanliurfa, Turkey, <sup>2</sup>Tokat State Hospital, Clinical Infectious Diseases, Tokat, Turkey, <sup>3</sup>Yuzuncu Yil University, Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Van, Turkey, <sup>4</sup>Private Zirve Medical Center, Internal Medicine Clinic, Nizip, Turkey.

**Corresponding author and reprints:** Hasan Karsen MD, Harran University, Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Sanliurfa, Turkey. Tel: +904143183000, E-mail: hasankarsen@hotmail.com. Accepted for publication: 7 September 2011

**Table 1.** The cases of thrombocyte, hemoglobin, and leukocyte values and clinical symptoms

Case Number	Platelet/(mm <sup>3</sup> )	Hb(g/dL)	WBC/(mm <sup>3</sup> )	Complications seen in cases
1	3000	12.4	9000	Epistaxis, petechia, neuropsychiatric symptoms
2	7000	8.5	2700	Melena, gum bleeding
3	9000	10.6	73000	Epistaxis, ecchymose
4	10000	9.5	4900	Epistaxis, ecchymose, gum bleeding
5	10000	5.5	3900	Melena, hematuria, renal failure, psychiatric symptoms
6	13000	7	3700	This case had no bleeding symptoms
7	15000	7.8	7600	Neuropsychiatric symptoms
8	16000	4.7	10900	Epistaxis, petechia, renal failure, psychiatric symptoms
9	18000	12.7	3700	Epistaxis, petechia,
10	19000	13	3500	Epistaxis
<b>Mean±SD</b>	<b>12000±51</b>	<b>9.17±2.96</b>	<b>6800±2150.21</b>	-----
Hb: Hemoglobin, WBC: White blood cell				

As seen in Table 1, clinical symptoms were as follows: epistaxis (7 cases), petechia with epistaxis (4 cases), bleeding gums (3 cases), ecchymosis with epistaxis (2 cases), melena and renal failure (2 cases), and hematuria (one case). The following elevated laboratory abnormalities were present: ESR (6 cases), CRP (10 cases), PT (7 cases), PTT (2 cases), and PT together with aPTT and INR (one case). The one case which had elevated PT, aPTT and INR levels also had a low fibrinogen result. All patients were treated with rifampicin and doxycycline and platelet suspensions. Hb levels were < 8 gr/dL in 4 patients and each of them received whole blood transfusions. All cases were negative for CCHF, enteric fever, malaria, acute viral hepatitis, and toxoplasmosis.

## Discussion

Mild hematological abnormalities such as anemia and leucopenia are common in the course of human brucellosis. Severe thrombocytopenia, acute hemolysis, DIC, hemorrhagic diathesis, immune thrombocytopenia, capillary leak syndrome (CLS), thrombotic thrombocytopenic purpura (TTP), and Evan's syndrome are rarely seen.<sup>6-10</sup> In our study, the mainly affected blood elements were thrombocytes. The pathogenesis of thrombocytopenia in brucellosis remains obscure but several possible mechanisms, including hypersplenism, hemophagocytosis, granulomas, increased clearance of damaged thrombocytes with endotoxins, thrombocyte adherence to vascular surfaces, and bone marrow suppression due to septicemia may account for it.<sup>11</sup> In various studies, thrombocytopenia prevalence has been reported to be 3.4%-26%.<sup>3,4,12-15</sup> Severe thrombocytopenia and bleeding disorder due to brucellosis have generally been studied in children. The papers regarding adults are only case reports.<sup>16-18</sup> Although severe thrombocytopenia, bleeding disorder, DIC, and thrombotic thrombocytopenic purpura (TTP) are rarely seen in brucellosis,<sup>4,6,15</sup> in our study all cases had severe thrombocytopenia and bleeding disorders, 2 cases had TTP, and one case had DIC.

According to a study by Kiki et al., a 19-year-old woman presented with complaints of headache, fever, sweating, malaise, and jaundice. Her clinical signs and laboratory findings were consistent with TTP. She received plasma exchange and antibiotic therapy.<sup>17</sup> In a case presented by Erdem et al., a 51-year-old man had complaints of moderate confusion, depressed mood and dysarthria, fever (38.5°C), jaundice, and petechial-purpuric skin lesions. Laboratory tests showed white blood cell count of 9600/mm<sup>3</sup>, Hb 7.1 g/dL, and platelets 18000/mm<sup>3</sup>. He received a plasma infusion and antimicrobial treatment.<sup>19</sup>

The clinical picture of our fifth case was as follows: confusion and speech disturbance, fever of 38.8°C, thrombocyte count of

10000/mm<sup>3</sup>, Hb of 5.5 mg/dL, creatinine level of 9.1 mg/dL (normal 0.8 – 1.2), total bilirubin of 4.1 mg/dL (normal 0.2 – 1.2), and indirect bilirubin of 3.4 mg/dL (normal 0 – 0.75). He received thrombocyte infusion and antimicrobial treatment

Our eighth case had the following clinical symptoms: convulsion and hallucinations, loss of consciousness, fever of 39.8°C, thrombocyte count of 16000/mm<sup>3</sup>, Hb of 4.7 mg/dL, creatinine level of 2.52 mg/dL, total bilirubin level of 4.8 mg/dL, and indirect bilirubin level of 4 mg/dL. He received antimicrobial treatment, platelet suspensions and whole blood transfusions.

Our third patient presented with DIC, whose laboratory findings were: PT 26 sec (normal 10 – 15), active partial thromboplastin time (aPTT) 59 sec (normal 26 – 41) and INR 1.8 (normal: 0.8-1.22), fibrinogen 67 mg/dL (normal: 150 – 400), and D-dimer 4.05 ug/mL (normal: 0 – 0.4). He received antibiotics, platelet suspensions and fresh-frozen plasma.

Bleeding disorders such as epistaxis and hematuria have rarely been reported.<sup>19</sup> We have not seen any case report of brucellosis-induced melena, gum bleeding, and ecchymosis in the literature. As mentioned in Table 1, in addition to severe thrombocytopenia, our cases had complaints of epistaxis, ecchymosis, melena, hematuria, gum bleeding, neuropsychiatric symptoms, and renal failure. The symptoms of our brucellosis cases were similar to those of hematologic malignancies and hemorrhagic viral diseases.<sup>20,21</sup> Therefore, hematologists, ENT specialists, psychiatrists, dermatologists, dentists, urologists, and gastroenterologists should bear in mind the possibility of brucellosis in patients who present with bleeding.

We agree with some authors who have suggested that thrombocytopenia is a result of immunological reactions.<sup>16</sup> In some of our cases thrombocytopenia had developed as a result of an immunological mechanism, which was the main reason for severe thrombocytopenia. Hemorrhage results from either a decrease in platelet counts or platelet dysfunction. Thrombocytopenia is rare; only in very rare cases of brucellosis is it severe enough to cause bleeding.<sup>22</sup> The high rates of bleeding in our cases (100%) warrant attention. After 4 days of treatment with antibiotics (rifampicin and doxycycline) and platelet suspensions, the hemorrhage stopped in all our cases with bleeding. Fortunately, the severe thrombocytopenia which occurs in brucellosis is responsive to antibiotics and hematological supportive therapy.

Within 2 weeks, thrombocytopenia improved in the majority of cases. At the end of the third week, platelet counts were > 150000/mm<sup>3</sup> in all patients. At the end of the fourth week of treatment with anti-brucellosis drugs, hematological abnormalities as well as renal insufficiency, neuropsychiatric symptoms, and other symptoms had completely disappeared. Akdeniz et al. have reported that platelet counts returned to normal within 2 – 3 weeks of initiating

antibiotics.<sup>2</sup> Dilek et al. have reported restoration of thrombocytopenia to normal ranges within one week after initiation of antimicrobial therapy.<sup>6</sup> We have completed the antimicrobial treatment to 6 weeks in all patients.

All our patients were treated successfully then discharged. Patients were followed monthly for 12 months with clinical and laboratory findings. No recurrence of brucellosis was noted at follow-ups.

Some authors have reported successful results with the administration of plasma, plasma exchange, intravenous gamma globulin, and steroids in conjunction with brucellosis treatment.<sup>21,22</sup> However, in our cases, those treatment modalities were not necessary.

In conclusion, since brucellosis is endemic in developing countries, it must be considered in the differential diagnosis of viral hemorrhagic diseases and cases presenting with severe thrombocytopenia and bleeding disorders. Even with the development of severe thrombocytopenia and bleeding in patients with brucellosis, successful results can be obtained with antibiotics and hematologic supportive therapy.

## References

1. Franco MP, Mulder M, Gilman RH, Smits HL. Human brucellosis. *Lancet Infect Dis*. 2007; **7**: 775 – 786.
2. Akdeniz H, Irmak H, Seçkinli T, Buzgan T, Demiröz AP. Hematological manifestations in brucellosis cases in Turkey. *Acta Med Okayama*. 1998; **52**: 63 – 65.
3. Aygen B, Doganay M, Sumerkan B, Yildiz O, Kayabas U. Clinical manifestations, complications and treatment of brucellosis: A retrospective evaluation of 480 patients. *Med Mal Infect*. 2002; **32**: 485 – 493.
4. Buzgan T, Karahocagil MK, Irmak H, Baran AI, Karsen H, Evirgen O. Clinical manifestations and complications in 1028 cases of brucellosis: A retrospective evaluation and review of the literature. *Int J Infect Dis*. 2010; **6**: 469 – 478.
5. Yodonawa S, Goto Y, Ogawa I, Yoshida S, Itoh H, Nozaki R, et al. Laparoscopic splenectomy for idiopathic thrombocytopenic purpura in a woman with situs inversus: Report of a case. *Surg Today*. 2010; **12**: 1176 – 1178.
6. Dilek I, Durmuş A, Karahocagil MK, Akdeniz H, Karsen H, Baran AI, Evirgen Ö. Hematological complications in 787 cases of acute brucellosis in Eastern Turkey. *Turk J Med Sci*. 2008; **38**: 421 – 424.
7. Sari I, Kocayigit I, Altuntas F, Kaynar L, Eser B. An unusual case of acute brucellosis presenting with Coombs-positive autoimmune hemolytic anemia. *Intern Med*. 2008; **47**: 1043 – 1045.
8. Turunc T, Demiroglu YZ, Kizilkilic E, Aliskan H, Boga C, Arslan H. A case of disseminated intravascular coagulation caused by *Brucella melitensis*. *J Thromb Thrombolysis*. 2008; **1**: 71 – 73.
9. Pappas G, Kitsanou M, Christou L, Tsianos E. Immune thrombocytopenia attributed to brucellosis and other mechanisms of *Brucella*-induced thrombocytopenia. *Am J Hematol*. 2004; **75**: 139 – 141.
10. Erkurt MA, Sari I, Gül HC, Coskun O, Eyigün CP, Beyan C. The first documented case of brucellosis manifested with pancytopenia and capillary leak syndrome. *Intern Med*. 2008; **47**: 863 – 865.
11. Al-Eissa Y, Al-Nasser M. Hematological manifestation of childhood brucellosis. *Infection*. 1993; **21**: 29 – 32.
12. Demiroglu YZ, Turunc T, Calis Kan H, Colakoglu S, Arslan H. Brucellosis: Retrospective evaluation of the clinical, laboratory and epidemiological features in 151 cases. *Mikrobiyol Bul*. 2007; **41**: 517 – 527.
13. Hasanjan Roushan MR, Mohrez M, Smailnejad Gangi SM, Solemani Amiri MJ, Hajiahmadi M. Epidemiological features and clinical manifestations in 469 adult patients with brucellosis in Babol, Northern Iran. *Epidemiol Infect*. 2004; **132**: 1109 – 1114.
14. Lulu AR, Araj GF, Khateeb MI, Mustafa MY, Yusuf AR, Fenech FF. Human brucellosis in Kuwait: A prospective study of 400 cases. *Q J Med*. 1988; **66**: 39 – 54.
15. Colmenero JD, Reguera JM, Martos F, Sanchez De Mora D, Delgado M, Causse M, et al. Complications associated with *Brucella melitensis* infection: A study of 530 cases. *Medicine*. (Baltimore) 1996; **75**: 195 – 211.
16. Yilmaz M, Tiryaki O, Namiduru M, Okan V, Oguz A, Buyukhatipoglu H, et al. Brucellosis-induced immune thrombocytopenia mimicking ITP: A report of seven cases. *Int J Lab Hematol*. 2007; **29**: 442 – 445.
17. Kiki I, Gundogdu M, Albayrak B, Bilgiç Y. Thrombotic thrombocytopenic purpura associated with *Brucella* infection. *Am J Med Sc*. 2008; **335**: 230 – 232.
18. Erdem F, Kiki I, Gundogdu M, Kaya H. Thrombotic thrombocytopenic purpura in a patient with *Brucella* infection is highly responsive to combined plasma infusion and antimicrobial therapy. *Med Princ Pract*. 2007; **16**: 324 – 326.
19. Sevinc A, Buyukberber N, Camci C, Buyukberber S, Karsligil T. Thrombocytopenia in brucellosis: Case report and literature review. *J Natl Med Assoc*. 2005; **97**: 290 – 293.
20. Vorou R, Pierrotsakos IN, Maltezou HC. Crimean-Congo hemorrhagic fever. *Curr Opin Infect Dis*. 2007; **20**: 495 – 500.
21. Giordano S, Failla MC, Di Gangi M, Miceli S, Abbagnato L, Dones P. Thrombocytopenia associated with brucellosis: A case report. [Article in Italian]. *Infez Med*. 2008; **16**: 158 – 161.
22. Tsirka A, Markesinis I, Getsi V, Chaloulou S. Severe thrombocytopenic purpura due to brucellosis. *Scand J Infect Dis*. 2002; **34**: 535 – 536.