Mild hematologic abnormalities are common in the course of human brucellosis; however, they generally resolve promptly with treatment of the disease. Occasionally, thrombocytopenia is severe and can be associated with bleeding into the skin (purpura) and from mucosal sites. We describe 2 patients infected with *Brucella melitensis* who presented with thrombocytopenic purpura, and we review 41 additional cases from the literature. Patients ranged in age from 2 to 77 years, and both sexes were affected equally. In the majority of cases, examination of the bone marrow revealed abundant megakaryocytes. Possible mechanisms involved in thrombocytopenia include hypersplenism, reactive hemophagocytosis, and immune destruction of platelets. Recognition of this complication is essential, since hemorrhage into the central nervous system is associated with a high mortality rate.

Mild hematologic abnormalities, such as anemia and leukopenia, are common in the course of human brucellosis [1]. Thrombocytopenia is less common, having been reported in only 1%–8% of cases, and it is rarely severe enough to cause bleeding. We describe 2 patients infected with *Brucella melitensis* who had bleeding consistent with immune thrombocytopenic purpura, 1 of whom died of intracerebral hemorrhage. We also review 41 cases of brucellosis complicated by thrombocytopenic purpura that have been reported in the world literature.

Case Reports

**Case 1.** A 54-year-old woman sought medical attention at the Dahiliye Klinigi (Istanbul, Turkey) for back pain and unsteady gait of 1 month’s duration. Vertebral disk disease was suspected; however, conservative therapy with bed rest failed to resolve the symptoms. She then developed fever, headache, arthralgia, nausea, and vomiting, and 3 days before admission she voided dark urine.

On examination she appeared acutely ill and was unable to walk without assistance. Vital signs were normal except for a temperature of 38°C. Her sclera were icteric, and conjunctival hemorrhages were present in both eyes. Petechial-purpuric skin lesions covered her arms and legs. The abdomen was tender to palpation and the liver and spleen were enlarged. A neurological examination revealed asymmetric pupils, weakness in the lower extremities, ataxic gait, and a positive Romberg test.

Laboratory tests showed the following values: hematocrit, 22%; hemoglobin, 7.5 mg/dL; WBCs, 5200 cells/mm³; platelets, 5000 cells/dL; erythrocyte sedimentation rate, 77 mm/h; prothrombin time, 1.8 s; partial thromboplastin time, 49.2 s; and international normalized ratio, 1.15. The peripheral blood smear revealed fragmented RBCs and a complete absence of platelets. The urine was dark brown (specific gravity value, 1.020), was positive for bilirubin, urobilinogen, and protein, and the sediment contained 3–5 WBCs per high-power field, with RBCs too numerous to count. Liver function tests showed the following values: alanine aminotransferase, 50 U/L; aspartate aminotransferase, 67 U/L; lactate dehydrogenase, 2675 U/L; and total bilirubin, 10.4 mg/dL (4.9 mg/dL direct). The fibrinogen level was 2.1 mg/L, but tests for antinuclear antibodies and antiplatelet antibodies were negative. Brucella agglutinin titer was positive at 1:1280, and the Coombs test was positive at 1:1280.

A diagnosis of brucellosis with microangiopathic hemolytic anemia was considered, and treatment was begun with platelet transfusion, fresh-frozen plasma, prednisolone (1 mg/kg/day), tetracycline HCl (500 mg every 6 hours) and streptomycin (1 g/day). Twenty-four hours later the patient became somnolent and responded only to painful stimuli. Deep-tendon reflexes were normal in the upper extremities but markedly reduced in the legs. On day 5, blood cultures performed on specimens obtained at the time of admission yielded *B. melitensis*. MRI
of the brain revealed enlargement of the fourth ventricle with cerebellar atrophy.

Neurobrucellosis was suspected, and antibiotic therapy was changed to administration of doxycycline (200 mg/day), ceftriaxone (2 g every 12 h), and ciprofloxacin (500 mg every 12 h). After 7 days the patient’s condition improved dramatically. The hemolytic abnormalities resolved completely, and after 1 month she was discharged to complete another month of therapy with doxycycline and ciprofloxacin. Two months later MRI was performed again and revealed complete resolution of hydrocephalus and disappearance of cerebellar lesions.

Case 2. A 17-year-old Hispanic man was admitted to a Houston hospital because of fever, headache, hip pain, purpura, and petechiae. Six months before, he had emigrated from a farm in Mexico. Two weeks before admission, he had consulted a local practitioner for fever, sweats, fatigue, and hip pain. The symptoms had begun suddenly, but he admitted to weight loss of 30 pounds over the previous 5 months. A history of ingesting unpasteurized goat’s milk was reported, and a serological test for brucellosis was positive at a titer of 1:320. Therapy with doxycycline (200 mg/day for 10 days) was prescribed, and ibuprofen was given for pain. When the symptoms persisted, the patient returned to his practitioner, who renewed the prescription for doxycycline.

Three days before admission he developed unrelenting occipital pain, and 2 days later he noted bleeding gums and petechiae on his legs. At admission the patient appeared acutely ill, malnourished, and anxious. Vital signs were normal except for a temperature of 38°C. There were conjunctival hemorrhages in both eyes, shallow ulcers in the mouth, tongue, and lips, and a hemorrhagic bulla on the left cheek (figure 1). His neck was supple, with no meningeal signs. A grade 2/6 systolic murmur was present at the left sternal border. The liver span was normal and the spleen was not felt. Petechiae and purpura were present on the arms, groin, and legs.

Laboratory tests showed a hematocrit of 35%, reticulocyte count of $2.7 \times 10^4$ and WBC count of 7200 cells/mm$^3$ with 76% neutrophils, 19% lymphocytes, and 5% monocytes (platelets, 3000 cells/dL). Liver function tests showed the following values: alanine aminotransferase, 94 U/L; aspartate aminotransferase, 85 U/L; alkaline phosphatase, 112 U/L; and lactate dehydrogenase, 141 U/L. The urine sediment contained 10 RBCs per high-power field. A brucella agglutinin test was positive (to 1:5120), unchanged after treatment with 2-mercaptoethanol. A bone marrow biopsy showed hypercellularity but no granulomas or evidence of hemophagocytosis. Blood cultures were sterile, but B. melitensis was recovered from the bone marrow.

Treatment was initiated with doxycycline (200 mg/day), gentamicin (5 mg/kg/day), and trimethoprim-sulfamethoxazole (2 double-strength tablets, each containing 160 mg of trimethoprim and 800 mg of sulfamethoxazole, 4 times per day). In addition, he received platelet transfusion, fresh-frozen plasma, transexamic acid, and dexamethasone (200 mg/day). Despite treatment, the platelet count never rose above 8000/dL. On the second day he complained of increased headache, and CT of the brain showed 2 areas of hemorrhage in the cerebellum, with compression of the brain stem. Shortly thereafter, he lapsed into a coma with decerebrate posture and was placed on a respirator. His condition failed to improve, and on day 5, at the request of his family, he was removed from life support and died.

An Autopsy was performed. Hemorrhage was the principal finding in the integument, skeletal muscles, lymph nodes, spleen, stomach, small and large intestines, kidneys, thyroid, and adrenal and pituitary glands. Sections of gallbladder, pancreas, urinary bladder, prostate, and testes were normal.

There was diffuse consolidation of both lungs with extensive intra-alveolar hemorrhage, pulmonary edema, and atelectasis. Foci of fibrin were deposited within alveolar walls and there was evidence of hyaline membrane formation. Within the right middle lobe were areas of bronchopneumonia, but no granulomas were seen.

Sections of heart revealed subendocardial hemorrhage near the tricuspid valve, but there were no vegetations. A section from the right ventricle showed a single focus of inflammation consisting of lymphocytes and neutrophils compatible with focal myocarditis (figure 2).

Sections of liver showed centrilobular congestion and intraparenchymal hemorrhage. On closer examination, there were scattered aggregates of inflammation consisting of neutrophils and lymphocytes within the liver lobules (figure 3), but no granulomas were observed.

The meninges showed chronic inflammation (figure 4) with subarachnoid hemorrhage in the posterior fossa and covering the brain stem. The surfaces of the cerebrum were edematous, with softening of the medial temporal and occipital lobes. There was herniation of the tonsils of the cerebellum. No thromboses or aneurysms were detected in the cerebral arteries or the circle
of Willis. The ventricles were enlarged secondary to massive intraventricular hemorrhage. There were multiple areas of hemorrhage within the gray and white matter associated with surrounding areas of necrosis. Perivascular cuffing with lymphocytes was noted near areas of necrosis, and rare perivascular microglial nodules were found (figure 5). Tissue Gram staining did not allow the organisms to be identified. Attempts to demonstrate \textit{Brucella} antigen in samples of lung, heart, liver, spleen and testes with use of a fluorescent-tagged rabbit polyclonal antibody to \textit{Brucella abortus} and \textit{B. melitensis} did not reveal unequivocal specific staining.

\textbf{Literature Review}

We searched the literature and found reports of 41 cases of brucellosis complicated by thrombocytopenia severe enough to cause purpura and mucosal bleeding (in addition to the 2 cases reported here) [2–15]. The first such case, reported by MacLeod in 1897, involved a British naval officer who contracted brucellosis in Malta. After an illness of 7 weeks, he was invalided to England, where he died from purpura hemorrhagica characterized by skin lesions and bleeding from all orifices [2]. Between 1939 and 1946, Castañeda encountered 8 cases of thrombocytopenic purpura (leading to 4 deaths) among 880 cases of brucellosis in Mexico; subsequently, he reported only 2 cases during the era in which effective antibiotic therapy became available (referenced in [3]). A series of 27 cases of this complication among 1051 patients with brucellosis in Peru was reported by Ulloa and associates [15].

Characteristics of the 43 patients with brucellosis complicated by thrombocytopenic purpura are summarized in table 1. The patients ranged in age from 2 to 77 years; men and women were affected in equal numbers, except in the series in Peru, where women outnumbered men 3.5 to 1 [15]. Gotuzzo et al. [16] and Alarcon et al. [17] have reported a similar preponderance of females among patients with brucellosis complicated by arthritis. The reasons for this preponderance are not clear. Bleeding into the skin (purpura) was the defining feature of these cases. In addition, the principal sites of mucosal hemorrhage included epistaxis (69%), gingivorrhea (44%), and hematuria (64%). Splenomegaly was documented in 46% of cases, which is higher than the 15%–20% incidence reported for uncomplicated brucellosis [18]. Splenic enlargement has been said to correlate with the severity of illness in brucellosis; however, as illustrated by case 2, physical examination is not always a reliable method to detect the size of the spleen.

Selected laboratory studies were performed for these 43 patients. Six (54.5%) of 11 patients were anemic (hemoglobin, <10 g/dL) (in the 27 patients described by Ulloa et al. [15], anemia was termed “mild” in 34.7%, “moderate” in 47.8%, and “severe” in 17.3%). The WBC count was within the normal range (5–10 \times 10^9 cells/L) in 7 (50%) of 14 and <5 \times 10^9 cells/L in 6 (43%) of 14. In the Peruvian series [15], “leukopenia” was reported to have occurred in 37%. Thrombocytopenia was a defining characteristic in all cases; platelet counts ranged from 3000 cells/dL to 67,000 cells/dL (mean, 18,500 cells/dL). In the Peruvian study [16], platelets were “decreased” in 88% and <10,000 cells/dL in 40%. Coombs tests were reportedly performed in 16 cases; results were positive in 6 (37.5%). Bone marrow results were reported in 33 cases, showing megakaryocyte hyperplasia in 64%, granulomas in 21%, and evidence of histiocytic hemophagocytosis in 8 (31%) of 26 in which it was specifically sought. Antibodies to \textit{Brucella} were found in 42 cases, at titers ranging from \(\geq 1:160\) to 1:5120. A \textit{Brucella} species was recovered from blood or bone marrow in only 10 cases;
however, it is uncertain in how many cases attempts to isolate the organism were negative. The three major Brucella species were involved: B. melitensis (5 cases), B. abortus (4 cases), and Brucella suis (1 case). The 27 patients described by Ulloa et al. [15] were all believed to be infected with B. melitensis, since it is the predominant enzootic species of Brucella in Peru.

With the exception of 2 cases in the preantibiotic era, all patients described in the literature received \( \geq 1 \) antimicrobial agent, usually a tetracycline analogue plus rifampin or an aminoglycoside. In addition, 31 patients (72%) received a steroid preparation for periods of up to 8 weeks. Thirty-nine patients (90.7%) survived, and antimicrobial therapy with or without steroids led to rapid resolution of the thrombocytopenia. Three patients required splenectomy in order to achieve complete and sustained resolution of thrombocytopenia. One patient in the preantibiotic era died and 3 others died as a result of intracerebral hemorrhage, despite treatment.

Discussion

Most hematologic abnormalities that occur in patients with brucellosis are mild and resolve promptly with antimicrobial therapy [1]. Thrombocytopenia has been reported to occur in \( \sim 1\% \)–\( 8\% \) of patients with brucellosis [19, 20] and invariably occurs in patients who suffer from hemorrhage into the skin and from mucosal sites [1]. Thrombocytopenic purpura was reported in only 13 patients among 880 with cases of brucellosis in Mexico from 1939 through 1946, as cited in the report by Tovar [21]. Ariza et al. [22] reported purpura in 2 of 27 patients with cutaneous manifestations of brucellosis in Spain. Although mild reductions in platelets can occur without hemorrhage [23, 24], severe thrombocytopenia can presage serious consequences, as evidenced by a mortality of 9.3% among the patients described here.

The mechanism responsible for thrombocytopenia in brucellosis is not understood with certainty. Among the proposed mechanisms are hypersplenism, disseminated intravascular coagulation (DIC), bone marrow suppression, hemophagocytosis, and immune destruction of platelets. Splenomegaly is reported to occur in \( \sim 20\%–40\% \) of patients with brucellosis [18] and was present in approximately one-half of the patients in this series. In 2 cases reported by Tovar [21] and 4 reported by Ulloa et al. [15], thrombocytopenia failed to resolve until splenectomy was performed. In addition to platelet sequestration, the hypertrophied spleen can be a site for the production of cytotoxic antibodies [25], and occasionally it is a site of hemophagocytic histiocytes [26].

DIC is common in patients with bacterial septicemia; however, it is rare in patients with brucellosis. Bacterial products such as endotoxin can cause endothelial damage or bind to platelets, causing them to aggregate and be removed from the circulation [27]. Moreover, the presence of platelet-associated antibodies has been documented in patients with septicemia and thrombocytopenia in the absence of overt DIC [28]. Coagulopathy and purpura are especially common in meningococemia, perhaps because of the greater propensity for meningococcal endotoxin to elicit the dermal Shwartzman reaction [29, 30]. However, Brucella endotoxin appears to be less toxic than are lipopolysaccharides from other gram-negative bacteria, and it does not induce the Shwartzman reaction [31]. Furthermore, evidence of DIC was found in only 2 of 43 patients with brucellosis complicated by thrombocytopenic purpura.

Bone marrow failure also seems an unlikely explanation for thrombocytopenia in brucellosis, since the majority of cases (63.3%) showed hypercellular marrows with abundant megakaryocytes. Although granulomas were seen in the marrows of...
Regardless, there is often little correlation between their agglutinin titer, range 43 160–5120 and the degree of thrombocytopenia. Regardless, a negative assay for antiplatelet antibodies does not exclude the diagnosis of immune thrombocytopenia.

Patient 2 died of intracerebral hemorrhage secondary to severe thrombocytopenia and meningitis. In view of the history of significant weight loss over a period of 5 months, it is likely that the infection had been present for some time before the diagnosis of brucellosis was made. Before hospitalization, his treatment was with doxycycline alone, initially prescribed for only 10 days. It is well known that prolonged antibiotic therapy (usually for 6 weeks) is necessary in order to prevent relapse [39], and most authorities recommend multiple-drug therapy for neurobrucellosis, although the optimal duration of treatment remains unknown [40].

With the availability of effective therapy, the mortality rate associated with brucellosis has declined to ~1%–2%; consequently, there is a paucity of autopsy studies. Nevertheless, the findings in case 2 are consistent with previous reports showing principally hyperplasia of elements of the reticuloendothelial system and small-vessel vasculitis [41, 42]. Vasculitis and severe thrombocytopenia were responsible for the fatal hemorrhage, since no aneurysms or thromboses of the cerebral blood vessels were found. As the largest organ of the reticuloendothelial system, the liver is probably always involved in brucellosis. However, in patient 2, liver enzyme levels were only mildly elevated, and the hepatic lesions were subtle and might have been missed had the diagnosis not been known. Typical of infection with B. melitensis, the hepatic lesions consisted of small aggregates of neutrophils and lymphocytes within the liver lobules and around necrotic hepatocytes without granuloma formation [43, 44].

Thrombocytopenia, like other hematologic complications of brucellosis, is generally mild and resolves promptly with treatment of the disease. In rare cases, thrombocytopenia can be severe and may result in bleeding into the skin and from mucosal sites. The mechanism responsible for thrombocytopenia in brucellosis is not understood with certainty but is probably multifactorial, including hypersplenism, hemophagocytosis, and immune destruction of platelets. Prompt recognition of this complication and aggressive therapy are essential, since the mortality associated with bleeding into the CNS is high.

Acknowledgments

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References


Table 1. Characteristics of 43 patients with brucellosis and thrombocytopenic purpura.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients for whom characteristic was reported</th>
<th>No. (%) of patients or other value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age range, y</td>
<td>41</td>
<td>2–77</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Clinical findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site of mucosal bleeding</td>
<td>43</td>
<td>33 (77)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>41</td>
<td>19 (46)</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia (hemoglobin ≤10 mg/dL)</td>
<td>11</td>
<td>6 (54.5)</td>
</tr>
<tr>
<td>WBC count</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>5–10 Cells × 10^9/L</td>
<td>14</td>
<td>7 (50)</td>
</tr>
<tr>
<td>&lt;5–10 Cells × 10^9/L</td>
<td>6</td>
<td>4 (43)</td>
</tr>
<tr>
<td>Platelet count</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Mean, cells/dL</td>
<td>18,500</td>
<td>3000–67,000</td>
</tr>
<tr>
<td>Range, cells/dL</td>
<td></td>
<td></td>
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<tr>
<td>Coombs test</td>
<td>16</td>
<td></td>
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<tr>
<td>Positive</td>
<td>6 (37.5)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>10 (62.5)</td>
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</tr>
<tr>
<td>Bone marrow analysis</td>
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</tr>
<tr>
<td>Elevated no. of megakaryocytes</td>
<td>33</td>
<td>21 (64)</td>
</tr>
<tr>
<td>Granulomas</td>
<td>23</td>
<td>7 (30)</td>
</tr>
<tr>
<td>Hemophagocytosis</td>
<td></td>
<td>8 (31)</td>
</tr>
<tr>
<td>Brucella species isolated</td>
<td>26</td>
<td>160–5120</td>
</tr>
<tr>
<td>B. abortus</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>B. melitensis</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>B. suis</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>With antimicrobials</td>
<td></td>
<td>31 (90.7)</td>
</tr>
<tr>
<td>With corticosteroids</td>
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<td>12 (9.3)</td>
</tr>
<tr>
<td>Outcome</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Survived</td>
<td>39 (90.7)</td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>4 (9.3)</td>
<td></td>
</tr>
</tbody>
</table>

7 of 23 patients (30%), they were not present in sufficient numbers to have a myelophthisic effect.

Another possible mechanism that has received attention recently is reactive hemophagocytosis [32]. Brucellosis associated with pancytopenia and evidence of reactive hemophagocytosis was first reported by Zuazu et al. in 1979 [33]. The finding of hemophagocytic histiocytes in the marrow of patients with brucellosis has been reported with varying frequency [20, 34–38], and their significance remains conjectural. Evidence of hemophagocytosis was found in only 8 (30.8%) of 26 patients in whom it was sought in this series.

Immune destruction of platelets has been considered to be responsible for pancytopenia in brucellosis [9], and the presence of antiplatelet antibodies has been demonstrated in some patients with thrombocytopenic purpura [6, 24]. 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 reviewed here. Antiplatelet antibodies can be difficult to detect by the usual tests, and when present, there is often little correlation between their titer and the degree of thrombocytopenia. Regardless, a negative
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15. Ulloa V, Rojas J, Gotuzzo E. Purpura trombocitopénica asociada a brucel-
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