Thrombocytopenic Purpura Associated with Brucellosis: Report of 2 Cases and Literature Review

Edward J. Young,1,3 Ann Tarry,5,a Robert M. Genta,2,4 Neslihan Ayden,6 and Eduardo Gotuzzo7

1Medical and 3Laboratory Services, Veterans Affairs Medical Center, Departments of 1Medicine and 3Pathology, Baylor College of Medicine, and 1Department of Medicine, University of Texas Medical School at Houston, Houston, Texas, USA; 6Dahiliye Klinigi, Haydarpasa Numune Hastanesi, Istanbul, Turkey; and 7Departamento de Medicina, Hospital Nacional Cayetano Heredia, Lima, Peru

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), cef-
triaxone (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 ther-
apy with doxycycline and ciprofloxacin. Two months later MRI
was performed again and revealed complete resolution of hy-
drocephalus 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 serologi-
cal 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 pre-
scription for doxycycline.

Three days before admission he developed unremitting oc-
cipital pain, and 2 days later he noted bleeding gums and pe-
techiae 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 hemor-
rhages 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 dehydro-
genase, 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 granulo-
mas or evidence of hemophagocytosis. Blood cultures were ster-
ile, but $B. melitensis$ was recovered from the bone marrow.

Treatment was initiated with doxycycline (200 mg/day), gen-
tamicin (5 mg/kg/day), and trimethoprim-sulfamethoxazole (2
double-strength tablets, each containing 160 mg of trimetho-
prim 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, pan-
creas, 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 granu-
ломas 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 fo-
cal myocarditis (figure 2).

Sections of liver showed centrilobular congestion and intra-
parenchymal hemorrhage. On closer examination, there were
scattered aggregates of inflammation consisting of neutrophils
and lymphocytes within the liver lobules (figure 3), but no granu-
ломas 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

Figure 1. Patient 2 had shallow bleeding ulcers of the tongue and
lips and a hemorrhagic bulla on the cheek.
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 Brucella antigen in samples of lung, heart, liver, spleen and testes with use of a fluorescent-tagged rabbit polyclonal antibody to Brucella abortus and B. melitensis did not reveal unequivocal specific staining.

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 invalidated 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 × 10^9 cells/L) in 7 (50%) of 14 and <5 × 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 Brucella were found in 42 cases, at titers ranging from ≥1:160 to 1:5120. A Brucella species was recovered from blood or bone marrow in only 10 cases;
Figure 4. Section from the cerebral cortex of patient 2, including the meninges, showing a moderate chronic inflammatory infiltrate within the leptomeninges, which focally spills into the brain parenchyma. Original magnification, ×200.

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 >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 ~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 ~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 meningococcemia, 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

Figure 5. Medium-power microphotograph showing one of a few perivascular microglial nodules that were noted near areas of gliosis in the cerebral cortex of patient 2. Original magnification, ×200.
Immune destruction of platelets has been considered to be 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.

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

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