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# Severe Thrombotic Microangiopathy Associated with Brucellosis: Successful Treatment with Plasmapheresis

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**Summary:** Brucellosis is a disease that may lead to changes in hematologic parameters such as anemia, neutropenia, and thrombocytopenia; however, thrombotic microangiopathy (TMA) is a rare finding. Severe TMA may be associated with life-threatening hematologic, renal, and neurologic disorders. To prevent this mortality caused by brucellosis, prompt recognition of this complication and prompt therapy are essential. A patient with TMA associated with *Brucella melitensis* is presented who initially presented with fever, skin purpura, epistaxis, confusion, microangiopathic hemolytic anemia, and thrombocytopenia. TMA was treated with plasmapheresis with cryosupernatant plasma replacement, energetically. A rapid improvement in platelet count, lactate dehydrogenase level, hemolytic anemia, and neurologic symptoms was observed with this treatment. For cases with infection-induced thrombotic microangiopathy, short-term plasmapheresis may be applied as an urgent therapy in addition to antimicrobial therapy.
**Key Words:** Brucellosis—Thrombotic microangiopathy—Plasmapheresis.

Brucellosis has occasionally been associated with mild hematologic abnormalities such as anemia, leukopenia, and thrombocytopenia (1). Thrombotic microangiopathy (TMA) associated with brucellosis is a rare complication. TMA is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and thrombi composed of platelets and von Willebrand's factor in different organs (2). Platelet thrombi may cause life-threatening brain and kidney damage due to circulation defects. TMA results from multiple possible mechanisms. Among the proposed mechanisms are release of circulating endotoxins, exotoxins, immune complexes in the circulation, direct platelet toxicity, and damage in the endothelium of small blood vessels (3–8).

Microangiopathic hemolytic anemia is characterized by fragmentation of the red blood cells within the circulatory system, leading to intravascular hemolysis. Sepsis, gram-negative bacteria, and gastrointestinal infections, such as *Shigella dystenteria*, *Escherichia coli*, or HIV, can induce microangiopathic hemolysis (7–10). However, it has been extremely rare in patients with brucellosis. We describe a patient who had TMA associated with brucellosis that was treated with plasmapheresis plus antimicrobial therapy.

## CASE REPORT

A 71-year-old man presented with fever, epistaxis, skin purpura, and headache. His physical and neurologic examination revealed pallor, ecchymotic lesions on the legs, and confusion. Laboratory tests showed the following values:

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hematocrit, 27%; hemoglobin, 9.8 g/dL; white blood cells, 4600 cells/dL; platelets, 7000 cells/dL; and erythrocyte sedimentation rate, 53 mm/h. The peripheral blood smear revealed fragmented erythrocytes and inadequate platelets (Fig. 1). The urine was dark brown and tested negative for bilirubin. Renal function test results were within normal ranges. Liver function tests showed the following values: alanine aminotransferase, 31 U/L; aspartate aminotransferase, 94 U/L; lactate dehydrogenase (LDH), 1986 U/L; and total bilirubin, 3.1 mg/dL (0.6 mg/dL direct). The direct antiglobulin test result was negative. Corrected reticulocyte count was 3.8%. Test results for antinuclear antibodies, Anti-ds-DNA, ANCA, RF, and antiplatelet antibodies were negative. Initial tests revealed that prothrombin time, international normalized ratio, activated partial thromboplastin time, and fibrinogen level were 16.8 seconds (normal, 12–16), 1.22 (normal, 0.95–1.5), 33.5 seconds (normal, 26–46), and 320 mg/dL (normal, 146–380), respectively. The bone marrow specimen was hypercellular with increased megakaryopoiesis and erythropoiesis. Cranial tomography was normal. There were no abnormal results in cerebrospinal fluid studies. Serologic tests for hepatitis A, B, and C virus; Epstein-Barr virus, cytomegalovirus, rubella, toxoplasma, and blood culture were negative. Initially, a diagnosis of microangiopathic hemolytic disease was considered with fever, confusion, thrombocytopenia, hemolytic anemia, fragmented erythrocytes, reticulocytosis, increased LDH level, and indirect hyperbilirubinemia. Urgent plasmapheresis treatment was performed with cryosupernatant plasma replacement (2000 mL/day, Fresenius AS 204). *Brucella* agglutinin titer was positive at 1:1280 on the second day of admission. *Brucella melitensis* was isolated from the blood cultures on the 22nd day. After diagnosis of brucellosis, rifampicin (600 mg/day) and doxycycline (200 mg/day) treatment was added for 6 weeks. Plasma exchange therapy was continued until the LDH level and platelet count returned to normal value (Fig. 2). He was discharged on the 24th day. Follow-up of the patient 1 year later showed no relapse associated with *Brucella* and/or microangiopathic hemolytic disease.

## DISCUSSION

Brucellosis is a disorder characterized by fever, malaise, chills, sweats, fatigue, weakness, myalgias, arthralgias, anorexia, and weight loss. Splenomegaly, lymphadenopathy, and hepatomegaly are present in approximately 10% to 15% of the cases. Neurobrucellosis is characterized by neurologic abnormalities, such as headache and confusion, somnolence, seizures, coma, and psychosis (11). Brucellosis produces a variety of nonspecific hematologic abnormalities (12,13). Acute onset of brucellosis can mimic TMA with fever, anemia, thrombocytopenia, and neurologic symptoms, especially in regions where brucellosis is endemic. Therefore, the differential diagnosis of neurobrucellosis should include TMA. The accurate diagnosis of brucellosis is based on positive results of blood or bone marrow culture, but serologic tests (Wright agglutination test above 1/160 titers) are helpful for diagnosis. In our patient, the agglutination test was positive at a titer of 1:1280, and blood and/or bone mar-

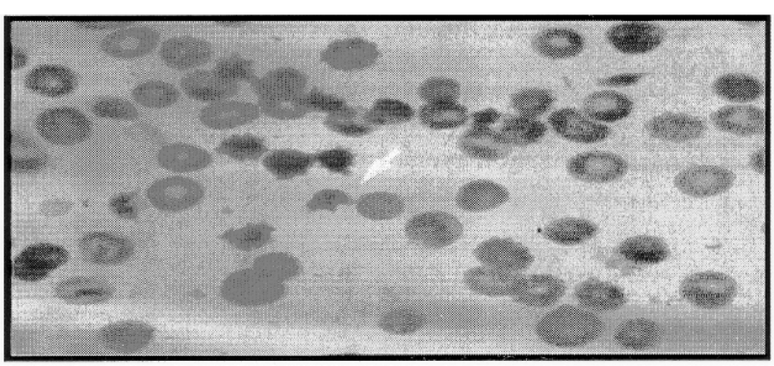


**FIG. 1.** Peripheral blood smear shows fragmented erythrocytes and inadequate platelets.

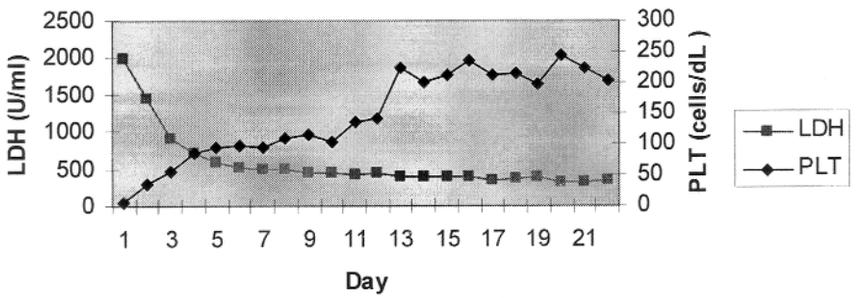



**FIG. 2.** The change of lactate dehydrogenase (LDH) and platelet (PLT) levels with plasmapheresis and/or antibiotic therapy.

row culture specimens for *B. melitensis* infection were positive.

The hematologic manifestations of brucellosis are extremely varied (1,12,16). Pancytopenia has been described in patients with brucellosis and its incidence varies from 3% to 21% (12–16). Anemia and leukopenia are the most frequently observed hematologic abnormality in brucellosis. Thrombocytopenia is reported in 1% to 8% of cases and can also cause bleeding in only very rare cases (14). Systemic infection can be associated with thrombocytopenia that is caused by mechanisms such as hypersplenism; bone marrow suppression; disseminated intravascular coagulation; increased clearance of damaged platelets with endotoxins, exotoxins, platelet-activating factor, or direct platelet toxicity caused by the microorganism; immune-mediated destruction of the platelets; hemophagocytosis; and platelet adherence to damaged vascular surfaces (3–8,17).

The term TMA refers to a group of clinical disorders characterized by microangiopathic hemolytic anemia, thrombocytopenia, fever, and renal and neurologic disorders (9). Red blood cells are fragmented as they pass through the platelet-fibrin mesh present in microthrombi that are deposited in capillaries and arterioles. The term hemolytic uremic syndrome has entered clinical use to describe childhood cases of TMA dominated by renal impairment, while the term thrombotic thrombocytopenic purpura (TTP) refers to adult cases of TMA with predominantly neurologic abnormalities (18). The cases of microangiopathic hemolytic anemia and thrombocytopenia in relation to infectious diseases have been reported. It is rare hematologic complication of bacterial infection (7,8,10). Microangiopathic hemolytic anemia caused by these agents may occur due to release of circulating endotoxins and/or immune complexes in the circulation, which may result in alterations in the function of several organs (hematopoietic system, brain, kidney) and damage in the endothelium of small blood vessels (7,8). Identification of the microangiopathic process and its specific etiology can help clinicians institute prompt and energetic treatment that frequently improves the hemolytic process and reverses end-organ failure.

Di Mario and colleagues (19) and Yaramıs and colleagues (20) reported that cases of severe microangiopathic hemolytic anemia, thrombocytopenia, and bleeding are associated with Brucella infection. Our case presented with epistaxis and skin purpura, and showed the features of this illness, such as hemolytic anemia, severe thrombocytopenia, fragmentation of erythrocytes and inadequate platelets in the peripheral blood smear, reticulocytosis, increased erythropoiesis, and megakaryopoiesis in the bone marrow. He had headache and confusion. Cranial tomography was normal and cytologic examination and biochemistry parameters of the cerebrospinal fluid were normal. Also, there was no renal impairment.

It is well known that the most important therapy for infection-related TMA is that directed at the underlying infection and co-morbid hemolytic process. Our case, which presented with epistaxis, skin purpura, headache, and fever, initially was diagnosed as TTP. Therefore, plasmapheresis with cryosupernatant plasma replacement was started urgently. Subsequently, we obtained a good hemotologic and clinical response with this treatment.

In conclusion, because TMA is a fatal disease, we propose institution of plasmapheresis as an urgent treatment, which may result in an improved clinical and hemotologic status of the patient until the microbial therapy takes effect.

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