Two Cases of Autoimmune Hemolytic Anemia Secondary to Brucellosis: A Review of Hemolytic Disorders in Patients with Brucellosis

Ahmet Emre Eskazan¹, Mehmet Sinan Dal², Safak Kaya³, Tuba Dal⁴, Orhan Ayyildiz² and Teoman Soysal¹

Abstract

Brucellosis is a worldwide zoonotic disease associated with hemolytic complications, including thrombotic microangiopathy (TMA) and hemolytic anemia. Autoimmune hemolytic anemia (AIHA) is a rare clinical presentation of this disease. In this report, we describe the cases of two patients with brucellosis who presented with Coombs-positive AIHA. We also include a review of the literature on the hemolytic complications of brucellosis. Both patients were successfully treated with a combination of doxycycline and rifampicin in addition to steroids. In the medical literature, there are several cases of TMA associated with brucellosis, although only a few cases of Coombs test-positive AIHA have been reported. Antibiotic therapy is the mainstay of treatment, and the selection of antibiotics and duration of treatment do not differ between brucellosis patients with and without hemolysis. Although rare, the potential for brucellosis should always be kept in mind in patients who present with hemolysis, especially those living in areas where brucellosis is endemic.

Key words: brucellosis, hemolysis, anemia, thrombotic thrombocytopenic purpura, Coombs, rituximab

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Introduction

Brucellosis is a worldwide zoonotic disease that is particularly endemic in the mediterranean region, including Turkey (1). Humans are infected by close animal contact or the consumption of meat and dairy products infected by bacteria of the genus Brucellae (2). Brucellosis is a systemic infection; the musculoskeletal system, spleen, liver and bone marrow are the most frequently involved sites. There are various hematologic manifestations of the disease, including anemia, leukopenia, thrombocytopenia, pancytopenia and bone marrow hypoplasia, as well as hemolytic complications, including disseminated intravascular coagulation (DIC) and thrombotic thrombocytopenic purpura (TTP) (3-12).

Anemia is common in patients with brucellosis, although the etiology of the anemia varies (13). The development of hemolytic anemia during the course of brucellosis has often been described in the context of microangiopathy (6-12); however, autoimmune hemolytic anemia (AIHA) is a rare clinical presentation of this disease (14-16). We herein describe the cases of two patients with acute brucellosis who presented with Coombs-positive AIHA. We also review the current published literature regarding hemolytic complications of brucellosis.

Case Reports

Case 1

A 72-year-old man was admitted to the hospital with fever, dyspnea, fatigue and generalized arthralgia lasting for two weeks in November 2012. His medical history revealed...
chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD) and a habit of eating unpasteurized cheese. On a physical examination, the patient was pale, icteric and febrile, and splenomegaly was detected 3 cm below the left costal margin. His body temperature was 38.3 °C, while his heart rate and blood pressure (BP) were 112 beats per minute (bpm) and 110/60 mmHg, respectively.

A complete blood count (CBC) revealed anemia (hemoglobin: 7.1 g/dL, mean corpuscular volume (MCV): 96 fL) and mild thrombocytopenia (4.2×10^9/L) with a normal leukocyte count (4.2×10^9/L). A peripheral blood smear showed polychromasia with nucleated red blood cells in the absence of fragmented erythrocytes (schistocytes). Indirect hyperbilirubinemia with a high lactate dehydrogenase (LDH) level and low haptoglobin level was detected. The corrected reticulocyte percentage was 6.9%. A direct Coombs test was 3+ positive for IgG, although the results for C3 were negative. Tests for antinuclear antibodies, anti-double-stranded DNA, C3, C4 and anticardiolipin antibodies were normal. The patient was negative for hepatitis B and C and human immunodeficiency virus (HIV). The prothrombin time, activated partial thromboplastin time and fibrinogen level were within the normal ranges. Thoracic and abdominal computed tomography (CT) revealed findings consistent with COPD in both lungs, and splenomegaly measuring 170 mm.

A diagnosis of Coombs-positive AIHA was made, and corticosteroid therapy (1 mg/kg/day) was initiated. The patient had a history of CAD and was symptomatic; therefore, one unit of packed red blood cells (RBCs) was transfused. Since the patient was febrile and had a history of unpasteurized milk and cheese consumption, a diagnosis of brucellosis was suspected. A Brucella standard tube agglutination (STA) test performed on the second day was positive at a dilution of 1:320, and Brucella melitensis was isolated from two blood cultures on the 10th day of hospital admission. The patient was treated with oral doxycycline at a dose of 100 mg twice daily plus oral rifampicin at a dose of 600 mg once daily, and his fever rapidly regressed two days after the initiation of treatment.

After two weeks of corticosteroid therapy, the patient’s hemoglobin level was 14.6 g/dL, and his leukocyte and platelet counts were 8.1×10^9/L and 156×10^9/L, respectively. The levels of LDH and bilirubin and the percentage of reticulocytes were within the normal limits. The dose of corticosteroids was gradually tapered, and the treatment was discontinued after four weeks. The patient received doxycycline+rifampicin combination therapy for six weeks. He is currently well and in remission for both AIHA and brucellosis after three months of follow-up, as of February 2013.

**Case 2**

A 50-year-old woman was admitted with fatigue, fever, dyspnea and left knee pain persisting for three weeks in May 2012. She had no medical history and was living in the village and practicing animal husbandry. On a physical examination, she was pale, icteric and febrile, with splenomegaly measuring 4 cm. Her body temperature was 38.5 °C, her resting heart rate was 96 bpm and her BP was 100/70 mmHg.

The patient had macrocytic anemia (hemoglobin: 6 g/dL, MCV: 105 fL) and thrombocytopenia (112×10^9/L), with a normal leukocyte count (4.8×10^9/L). A peripheral blood smear revealed spherocytes, polychromasia and erythroblasts, although no schistocytes were detected. She also exhibited indirect hyperbilirubinemia, a high LDH level, a low haptoglobin level and a corrected reticulocyte percentage of 8%, with a direct Coombs test of 4+ positive both for IgG and C3. Serological tests were negative, with normal rheumatological markers. Abdominal CT revealed splenomegaly measuring 180 mm, although thoracic CT was normal. The diagnosis was Coombs-positive AIHA, and treatment with 1 mg/kg/day of corticosteroids was initiated.

Brucellosis is endemic in our area, and the patient was febrile with a history of practicing animal husbandry. A Brucella STA test was positive at a dilution of 1:640; thus, treatment with a combination of doxycycline (200 mg daily)
and rifampicin (600 mg/day) was started on the third day after hospital admission. *Brucella melitensis* was isolated from blood cultures on the seventh day of follow-up. The patient’s hemoglobin level was 13.6 g/dL, while her leukocyte and platelet counts were 5.1×10^9/L and 189×10^9/L, respectively, two weeks after the initiation of corticosteroids. The corticosteroid therapy was slowly tapered, then discontinued after one month.

The patient received combination therapy with antibiotics for brucellosis for six weeks and was found to be in remission for both Coombs-positive AIHA and brucellosis after three months of follow-up. The state of remission was maintained as of November 2012, when the patient was last admitted to the hospital. Her laboratory results and clinical course are shown in Figure B.

**Discussion**

**Diagnosis of brucellosis**

Brucellosis, an endemic disease in many countries, is a systemic infectious disease. The diagnosis is based on the demographic and epidemiologic characteristics of the disease, as well as the presence of symptoms, results of serological tests and isolation of the microorganism from the blood and/or bone marrow.

In the present two patients, we diagnosed brucellosis using both STA examinations and blood cultures. Among the brucellosis cases of hemolysis published in the literature, 13 involved positive STA results, and *Brucella* spp. were also detected in blood/bone marrow cultures in 11 patients. In one case (16), the diagnosis was made using an enzyme-linked immunoassay for antibodies to brucellosis.

**Anemia in brucellosis**

Anemia is common in patients with brucellosis; however, the etiology of the anemia varies, including that involving hemolytic anemia (13), and various hemolytic complications can occur during the course of the disease. Autoimmune hemolysis is a rare entity in patients with brucellosis, with only three cases published in the literature thus far (14-16). In the present report, we described two patients with *Brucella melitensis* who presented with direct antiglobulin test (DAT)-positive AIHA.

The most common hemolytic disorders associated with brucellosis are discussed below, and previous brucellosis cases of hemolysis published in the literature are displayed in Table.

**Microangiopathic hemolytic anemia**

Microangiopathic hemolytic anemia (MAHA) refers to a group of disorders including DIC and TTP/hemolytic uremic syndrome (HUS). Infectious agents, such as verotoxin-producing *E. coli*, HIV and *Shigella*, have been reported to play a role in the pathogenesis of TTP (17), and DIC and/or TTP/HUS can be components of the clinical presentation of brucellosis, with MAHA being the most common hemolytic manifestation of brucellosis described in the literature (6-12, 18-21).

**Clinical and laboratory features:** Among the published cases of brucellosis and TTP/DIC, the most common presenting sign/symptom was fever (10/10, 100%). On physical examinations, the most common finding was petechial-purpuric skin lesions (100%), followed by jaundice (50%), neurological disturbances (50%) and organomegaly (hepatomegaly and/or splenomegaly) (50%) (Table). Four of the 10 patients had a history of unpasteurized dairy product consumption and direct contact with animals. Only one patient (11%) had renal impairment (19) among the nine patients with TTP and brucellosis (7-12, 18-20). Neurological disturbances are observed in nearly 70% of patients with TTP, with multiple presentations, such as headaches, an altered personality, reduced cognition, transient ischemic attacks and fluctuating levels of consciousness including coma (21). Six of the previously reported patients (67%) had various nonspecific neurological clinical features at presentation (9-12, 18, 19) (Table).

**Treatment of MAHA and brucellosis:** Combined antibiotic therapy is usually applied in the treatment of brucellosis. Eight patients (80%) received a combination of two antibiotics, while a three-drug combination was administered in only one patient (Table). Three patients received six-week antibiotic treatment, while two patients received antibiotic therapy for 12 and eight weeks, respectively (12, 18). In five patients, the duration of antibiotic therapy was not reported (6, 7, 10, 11, 20). Nine of the 10 patients (90%) were successfully treated, while one patient (10) died, with a median follow-up duration of 7.5 months (range, 1-18 months).

Regarding the treatment of *Brucella*-associated TTP/DIC cases, with respect to blood component therapy, six patients (60%) received fresh frozen plasma (FFP) transfusion, four patients (40%) received therapeutic plasma exchange (TPE) and platelet (PLT) transfusion and three (30%) patients received RBC transfusion. Corticosteroids were administered in four patients (40%), and intravenous immunoglobulin (IVIG) was administered in one patient (10%).

In addition, it has clearly been shown that TTP may be the initial presenting feature of HIV disease (21). One previously reported patient with brucellosis and TTP was also HIV-positive (12). Perhaps the underlying HIV infection was the causative factor responsible for thrombotic microangiopathy in this patient.

**Antimicrobial treatment:** Regarding antimicrobial therapy, combined antibiotic treatment against brucellosis was administered in all previously reported patients. TTP should be treated as a medical emergency, and, in view of the high risk of preventable, early death, TPE should be initiated as soon as possible. However, the transfusion of TPE and/or FFP is not a benign therapy. These treatment modalities are associated with potential morbidities, including plasma-related adverse events, such as allergic reactions, anaphylaxis, transfusion-related acute lung injury and central ve-
<table>
<thead>
<tr>
<th>Reference</th>
<th>Age yrs/sex</th>
<th>Country</th>
<th>Fever, sweating, malaise, headache, jaundice, dark urine</th>
<th>Physical examination</th>
<th>Medical history</th>
<th>Hematologic disorder</th>
<th>HR (L/D), g/dL</th>
<th>WBC white blood cell count, 10^9/L</th>
<th>FBC red blood cell count, 10^12/L</th>
<th>Coagulation test</th>
<th>Disease stage (Groupe-Classé)</th>
<th>Treatment of hematologic disorder</th>
<th>Scrum regimens</th>
<th>Blood NM cytokines</th>
<th>Antithrombin (antithrombin III, heparinase, streptase)</th>
<th>Timing of the antitrombic treatment (fraction, dose, weeks)</th>
<th>Follow up time months</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>17 M</td>
<td>Turkey</td>
<td>Fever, sweating, malaise, headache, jaundice, dark urine</td>
<td>LAD, HSM, palpation, jaundice, splenic, reticular</td>
<td>Uncontrolled daily product consumption, direct control to retinoids</td>
<td>G6PD deficiency</td>
<td>8.2</td>
<td>4.2</td>
<td>108</td>
<td>NA</td>
<td>Negative</td>
<td>Policy and replacement, RBC transfusion</td>
<td>1:20,000</td>
<td>Pleuraparin, danaparoid (6)</td>
<td>12</td>
<td>Corticosteroids (6)</td>
<td>On the 4th day after admission</td>
<td>30</td>
</tr>
<tr>
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<td>35 M</td>
<td>Turkey</td>
<td>Fever, sweating, abdominal pain, jaundice, dark urine</td>
<td>HSM, palpation, jaundice, splenic, reticular</td>
<td>Uncontrolled daily product consumption, direct control to retinoids</td>
<td>DIC</td>
<td>7</td>
<td>2</td>
<td>20</td>
<td>NA</td>
<td>Negative</td>
<td>PLT and FFP transfusions</td>
<td>12,080</td>
<td>Bruxella app.</td>
<td>B. melitensis, danaparoid (6)</td>
<td>On the 5th day after admission</td>
<td>NA</td>
<td>Cure</td>
</tr>
<tr>
<td>7</td>
<td>50 M</td>
<td>Italy</td>
<td>Fever, sweating, chills, malaise</td>
<td>LAD, HSM, palpation, jaundice, splenic, reticular</td>
<td>Uncontrolled daily product consumption, direct control to retinoids</td>
<td>MASHA + TCP</td>
<td>6.7</td>
<td>4</td>
<td>5</td>
<td>NA</td>
<td>Negative</td>
<td>Normal PT, aPTT, B. melitensis, and FFP levels</td>
<td>11,200</td>
<td>B. melitensis, danaparoid (6)</td>
<td>12</td>
<td>Corticosteroids (6)</td>
<td>On the 3rd day after admission</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>11 F</td>
<td>Turkey</td>
<td>Fever, sweating, chills, malaise</td>
<td>LAD, HSM, palpation, jaundice, splenic, reticular</td>
<td>Uncontrolled daily product consumption, direct control to retinoids</td>
<td>MASHA + TCP</td>
<td>5.6</td>
<td>1.6</td>
<td>12</td>
<td>NA</td>
<td>Negative</td>
<td>RBC transfusions</td>
<td>12,080</td>
<td>B. melitensis, danaparoid (6)</td>
<td>12</td>
<td>On the 2nd day after admission</td>
<td>12</td>
<td>Cure</td>
</tr>
<tr>
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<td>Turkey</td>
<td>Fever, epigastric pain, headache, malaise, jaundice, dark urine</td>
<td>Erythematous lesions, confusen</td>
<td>None</td>
<td>TTP</td>
<td>9.8</td>
<td>4.6</td>
<td>7</td>
<td>NA</td>
<td>Negative</td>
<td>Normal PT, INR, aPTT, B. melitensis</td>
<td>12,080</td>
<td>B. melitensis, danaparoid (6)</td>
<td>NA</td>
<td>Primary hemoglobinemia</td>
<td>Dead</td>
<td>11</td>
</tr>
<tr>
<td>10</td>
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<td>Turkey</td>
<td>Fever, sweating, malaise, headache, abdominal pain, vomiting</td>
<td>SPM, palpation, jaundice, splenic, reticular</td>
<td>Uncontrolled daily product consumption, direct control to retinoids</td>
<td>TTP</td>
<td>4.8</td>
<td>20</td>
<td>9</td>
<td>NA</td>
<td>Negative</td>
<td>MP and FFP transfusions</td>
<td>12,080</td>
<td>B. melitensis, danaparoid (6)</td>
<td>NA</td>
<td>NA</td>
<td>Cure</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>21 F</td>
<td>Israel</td>
<td>Fever, abdominal pain, headache, malaise</td>
<td>SPM, palpation, jaundice, splenic, reticular</td>
<td>None</td>
<td>TTP</td>
<td>9.9</td>
<td>5.4</td>
<td>7</td>
<td>NA</td>
<td>Negative</td>
<td>Normal PLT, INR, aPTT, B. melitensis</td>
<td>12,080</td>
<td>B. melitensis, danaparoid (6)</td>
<td>12</td>
<td>On the 4th day after admission</td>
<td>12</td>
<td>Cure</td>
</tr>
<tr>
<td>12</td>
<td>66 F</td>
<td>Turkey</td>
<td>Fever, palpation, jaundice, splenic, reticular</td>
<td>LAD, HSM, palpation, jaundice, splenic, reticular</td>
<td>Uncontrolled daily product consumption, direct control to retinoids</td>
<td>G6PD deficiency</td>
<td>8.5</td>
<td>2.3</td>
<td>14</td>
<td>NA</td>
<td>Negative</td>
<td>Normal PT, INR, aPTT, B. melitensis</td>
<td>11,000</td>
<td>HAART, danaparoid (12)</td>
<td>NA</td>
<td>NA</td>
<td>Cure</td>
<td>3</td>
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<tr>
<td>14</td>
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<td>USA</td>
<td>Fever, sweating, malaise, jaundice, dark urine, vomiting</td>
<td>LAD, HSM, palpation, jaundice, splenic, reticular</td>
<td>Uncontrolled daily product consumption, direct control to retinoids</td>
<td>G6PD deficiency</td>
<td>8.7</td>
<td>2.6</td>
<td>12</td>
<td>NA</td>
<td>Positive</td>
<td>Normal PT, INR, aPTT, B. melitensis</td>
<td>11,000</td>
<td>NA</td>
<td>NA</td>
<td>Cure</td>
<td>2</td>
<td>12</td>
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<td>15</td>
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<td>Turkey</td>
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<td>LAD, HSM, palpation, jaundice, splenic, reticular</td>
<td>Uncontrolled daily product consumption, direct control to retinoids</td>
<td>MSH</td>
<td>7.4</td>
<td>5.2</td>
<td>22</td>
<td>NA</td>
<td>Positive</td>
<td>MP and FFP transfusions</td>
<td>11,000</td>
<td>B. melitensis, danaparoid (6)</td>
<td>NA</td>
<td>NA</td>
<td>Cure</td>
<td>3</td>
</tr>
<tr>
<td>16</td>
<td>70 F</td>
<td>Greece</td>
<td>Fever, low back pain</td>
<td>SPM, palpation, jaundice, splenic, reticular</td>
<td>Direct control to retinoids</td>
<td>BMH</td>
<td>6</td>
<td>16.9</td>
<td>NA</td>
<td>NA</td>
<td>Positive</td>
<td>Problems (5g), H. YU, R. X., HAART</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Cure</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
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<td>Turkey</td>
<td>Fever, sweating, malaise, hay fever, vomiting, dark urine</td>
<td>LAD, HSM, palpation, jaundice, splenic, reticular</td>
<td>Uncontrolled daily product consumption, direct control to retinoids</td>
<td>G6PD deficiency</td>
<td>7.5</td>
<td>5.2</td>
<td>5</td>
<td>NA</td>
<td>Negative</td>
<td>PLT and FFP transfusions, prednisone</td>
<td>1:1200</td>
<td>B. melitensis, danaparoid (6)</td>
<td>NA</td>
<td>Cure</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>18</td>
<td>55 M</td>
<td>Turkey</td>
<td>Fever, headache, asthenia, anemia, sweating, dark urine</td>
<td>LAD, HSM, palpation, jaundice, splenic, reticular</td>
<td>Uncontrolled daily product consumption, direct control to retinoids</td>
<td>MASHA + TCP</td>
<td>7.1</td>
<td>9.8</td>
<td>16</td>
<td>NA</td>
<td>Negative</td>
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<td>1:160</td>
<td>B. melitensis, danaparoid (6)</td>
<td>12,080</td>
<td>B. melitensis, danaparoid (6)</td>
<td>12</td>
<td>On the 6th day after admission</td>
</tr>
<tr>
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<td>19 F</td>
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<td>Fever, headache, malaise, malaise, swollen lymph nodes, generalized body pain</td>
<td>HPML, palpation, jaundice, splenic, reticular</td>
<td>None</td>
<td>TTP</td>
<td>4.9</td>
<td>NA</td>
<td>19</td>
<td>NA</td>
<td>Negative</td>
<td>Normal PT, INR, aPTT, B. melitensis</td>
<td>12,080</td>
<td>B. melitensis, danaparoid (6)</td>
<td>12</td>
<td>On the 6th day after admission</td>
<td>12</td>
<td>Cure</td>
</tr>
<tr>
<td>20</td>
<td>52 M</td>
<td>Argentina</td>
<td>Fever, asthenia, malaise</td>
<td>SPM, palpation, jaundice, splenic, reticular</td>
<td>None</td>
<td>HA</td>
<td>11.2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Negative</td>
<td>HAART, danaparoid (6)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Cure</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>21</td>
<td>72 M</td>
<td>Turkey</td>
<td>Fever, dyspnea, fatigue, anemia</td>
<td>SPM, palpation, jaundice, splenic, reticular</td>
<td>Uncontrolled daily product consumption, direct control to retinoids</td>
<td>MASHA + TCP</td>
<td>7.1</td>
<td>4.2</td>
<td>12</td>
<td>NA</td>
<td>Positive</td>
<td>MP and FFP transfusions</td>
<td>12,080</td>
<td>B. melitensis, danaparoid (6)</td>
<td>12</td>
<td>On the 3rd day after admission</td>
<td>3</td>
<td>Cure</td>
</tr>
<tr>
<td>22</td>
<td>50 F</td>
<td>Turkey</td>
<td>Fever, headache, malaise, left knee pain</td>
<td>SPM, palpation, jaundice, splenic, reticular</td>
<td>None</td>
<td>HA</td>
<td>11.2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Negative</td>
<td>HAART, danaparoid (6)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Cure</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

* The diagnosis was made using an enzyme-linked immunosorbent assay for antibodies to Brucella. ** The antibiotic treatment was reported in the paper. ** The patient was treated with no antibiotic treatment; however, he relapsed 10 months later, and was treated again for 10 weeks. *** The patient was treated with no antibiotic treatment; however, he relapsed 10 months later, and was treated again for 10 weeks. " Internal medicine" 53: 1153-1158, 2014 DOI: 10.2169/internalmedicine.53.0936
nous catheter thrombosis and/or infection. Therefore, physicians should focus on treating the underlying infection and never forget that the underlying disease should be treated vigorously and appropriately in order to overwhelm the clinical course of brucellosis. Physicians must also apply steroids, FFP and TPE as adjunct treatment to antimicrobial therapy, for example in more severe cases.

**Direct antiglobulin test-positive autoimmune hemolytic anemia**

In the current medical literature, there are only three case reports of brucella-associated DAT-positive AIHA (14-16).

**Clinical and laboratory features:** The most common initial symptoms in the affected patients included fever and jaundice in all cases (100%). Meanwhile, organomegaly and lymphadenopathy were detected in two cases (2/3, 67%). All of the patients had a history of unpasteurized dairy product consumption and/or direct contact with animals (Table). Among the two cases of brucellosis-induced DAT-positive AIHA reported in this paper, both patients had fever and jaundice at admission, with splenomegaly being detected during hospitalization. Both patients also had a medical history of unpasteurized dairy product consumption and direct contact with animals.

**Treatment of AIHA and brucellosis:** Among the published cases of AIHA and brucellosis, none of the patients received RBC transfusions (14-16). With respect to the treatment of Brucella-associated hematological disorders, one patient received high-dose methylprednisolone (HDMP), one patient received corticosteroids, IVIG and rituximab (RTX) and one patient received doxycycline alone. As in patients with Brucella-associated thrombotic microangiopathy (TMA), antimicrobial therapy is the mainstay of treatment in cases of AIHA and brucellosis. RBC transfusions should be administered in symptomatic patients, especially those with comorbidities. Since steroids and RTX have possible adverse effects, these medications should be administered with caution.

Concerning both the TMA and AIHA cases of brucellosis published in the literature in addition to the two new cases presented herein, treatment for the hematological disorder was started before antimicrobial therapy in all but one case (7) (Table). Perhaps, in some patients, it is reasonable to wait without starting immunosuppressive and/or blood component therapy until the search for possible secondary causes (i.e., brucellosis) is complete. Secondary AIHA may be a distinct entity; consequently, the main treatment strategy should be focused on curing brucellosis, which would most likely shorten the duration of immunosuppressive therapy, if such treatment is needed. This was the case in the present two patients, in whom we treated the AIHA with a combination of antibiotics and a four-week course of corticosteroids. Furthermore, no recurrence of AIHA was observed in either case, although the corticosteroid treatment was gradually tapered.

In conclusion, there are several hematologic manifesta-

tions of brucellosis, including hemolytic anemia. MAHA and AIHA often occur during the course of the disease, and antibiotic therapy directed against brucellosis is the mainstay of treatment. In addition, the choice of antibiotics and duration of treatment do not differ between brucellosis patients with and without hemolysis. Blood components, TPE and immunosuppressives can also be administered; however, these are not benign therapies, and one should never forget that these treatment modalities are associated with potential morbidities. For this reason, physicians should focus on treating the underlying infection (i.e., brucellosis), saving these treatment options for the right patients, administering them at the right time.

Although rare, the potential for brucellosis should always be kept in mind in patients who present with MAHA or Coombs-positive AIHA, especially in areas where brucellosis is endemic.

**The authors state that they have no Conflict of Interest (COI).**

**References**

14. Wehbe E, Moore TA. Cold agglutinin-associated hemolytic anemia