Pancytopenia secondary to a *Brucella abortus* infection

A rare presentation

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Abstract

Brucellosis is an anthropozoonotic disease that is very important in healthcare, with varying clinical and paraclinical characteristics that make it difficult to diagnose. We present the case of a 30-year-old patient from a rural area with nonspecific symptoms and physical exam findings of ascites, hepatosplenomegaly and skin disorders. Laboratory tests showed pancytopenia, abnormal liver function, and elevated acute phase reactants, and imaging studies revealed hepatosplenomegaly. With the suspicion of an associated infection, immunology and serology tests were run, showing a positive Rose Bengal Test and *Brucella abortus*-positive febrile antigens at a 1:640 dilution. Pancytopenia secondary to a *Brucella* infection is a rare laboratory characteristic which makes the diagnosis even more difficult, worsening the epidemiological notification of this disease. **(Acta Med Colomb 2024; 49. DOI: https://doi.org/10.36104/amc.2024.2925).**

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Introduction

Brucellosis is one of the most important zoonotic diseases in Latin America (1), caused by a Gram-negative, aerobic intracellular coccobacillus of the genus Brucella. Various pathogenic species have been identified in humans, with the most common globally being the *Brucella melitensis species*, followed by *Brucella abortus, Brucella suis and Brucella canis* (2–4). *In Colombia, most infections in humans are caused by Brucella abortus, with Brucella melitensis infections being rare* (5). This pathogen leads to more than 500,000 infections per year around the world (2); likewise, an estimated 2.4 billion people are at risk of acquiring it (6, 7), mainly due to eating contaminated food or working with animal reservoirs (8), and ages between 25 and 54 years (66.1%).

Its clinical characteristics vary, with a fluctuating course secondary to the pathogen's infectious mechanism. Patients may have nonspecific symptoms like headache, cyclical fever, migratory arthralgia, myalgia, asthenia, anorexia, fatigue, weakness, sweating, vomiting, diarrhea and abdominal pain (2). The physical exam findings depend on the host's immune response, with the most common being joint problems and gall bladder, liver and spleen abnormalities (9). In Colombia, due to its nonspecific findings and similarity to other prevalent diseases, brucellosis has become an underdiagnosed disease (1).

The diagnosis is made by isolating the infectious agent in a sample of biological material; other methods include immunoserology like the "Rose Bengal" test and competitive ELISA testing for specific antigens (9). Other possible paraclinical findings include cytopenia due to bone marrow and spleen involvement, mainly manifesting as leukopenia and anemia, while platelet abnormalities like thrombocytopenia, and pancytopenia are uncommon findings (3, 10).

Treatment seeks to reduce symptoms, as well as the rate of recurrence, and is based on dual antibiotic therapy regimens (9). The objective of the following article is to present a case of pancytopenia associated with brucellosis, with a positive agglutination test for *Brucella abortus*, an uncommon clinical presentation that requires more attention.

Case report

We present the case of a 30-year-old man from the rural area of the department of Casanare in Colombia, with a history of severe head trauma due to a motor vehicle accident in 2015, requiring invasive mechanical ventilation. He consulted due to a one-month history of asthenia, weakness, skin color changes, gingival bleeding, left-sided abdominal pain, and occasional dyspnea. His vital signs on admission showed a heart rate of 68 beats per minute, respiratory rate of 18 breaths per minute, blood pressure 116/78 mmHg, temperature 36.4 degrees, weight 64 kg, and height 160 cm. His physical exam showed mild gingival bleeding, abdominal ascites and splenomegaly, jaundiced skin, upper and lower extremity ecchymoses, and generalized petechiae.

The laboratory tests reported a complete blood count with leukopenia (total leukocytes: 2,110 cel/mm^3), moderate normocytic anemia (Hgb: 9.5 g/dL), moderate thrombocytopenia (manual platelet count: 69,300 cel/mm^3) which progressed during hospitalization to severe thrombocytopenia (manual platelet count: 44,100 cel/mm^3), and a reticulocyte count of 1%, with a reticulocyte production index (RPI) of 0.3. Liver function tests showed hyperbilirubinemia (1.66 mg/dL) with direct bilirubin predominance (0.98 mg/dL), mildly elevated INR (1.48), significantly elevated alkaline phosphatase (899 U/L), and elevated gamma-glutamyl transferase (GGT) (76.52 U/L). Acute phase reactants showed elevated ESR (110 mm/h), a positive CRP (12 mg/L), and elevated LDH (440 U/L). Immunological and infectious studies revealed a positive rheumatoid factor (128 U/L), negative direct Coombs, and negative HIV, hepatitis C antibody and hepatitis B surface antigen tests. A peripheral blood smear showed a few macroplatelets, leukopenia with atypical lymphocytes, mild anisocytosis with the presence of microcytes, mild hypochromia, and a bleeding time of 3 min and 45 sec.

Imaging studies included a total abdominal ultrasound showing hepatomegaly, indirect signs of portal hypertension, homogeneous splenomegaly, and free fluid in Morrison's pouch and the pelvic cavity. A portal Doppler reported portal hypertension, hepatosplenomegaly, an enlarged liver measuring 160 mm, and a 1.1 cm splenic vein. A total abdominal computed tomography with contrast showed hepatosplenomegaly (Figure 1), fluid striations in both paracolic gutters, and obliteration of the mesenteric fat planes toward the right iliac fossa, with small, reactive-looking lymph node structures and left basal atelectasis.

Serum tests yielded positive febrile antigens for *Brucella abortus* at 1:640 dilutions and a positive Rose Bengal agglutination test. With these findings and a diagnosis of brucellosis, treatment was started with dual antibiotic therapy using doxycycline 100 mg/12 hours and rifampicin 600 mg/day/six weeks. Currently, the patient is being treated as an outpatient, with improved symptoms.

Discussion

The patient had a nonspecific clinical picture with significant laboratory abnormalities which caused diagnostic uncertainty. The initial suspicion was myelodysplastic syndrome; however, his work and demographic risk factors led to the discovery of a zoonotic *Brucella abortus* infection.

This disease is directly transmitted by inhalation or contact with the skin and conjunctiva, and indirectly through the ingestion of unpasteurized milk products and improperly cooked meat (2, 3). Some occupations are at higher risk for this infection, with workers who have direct contact with infected animals being the most affected; people who handle animal meat and organs, as well as laboratory workers, are also considered to be at high risk (6, 9, 11). The patient we presented worked in a rural area, in constant contact with cattle, which is an important exposure factor.

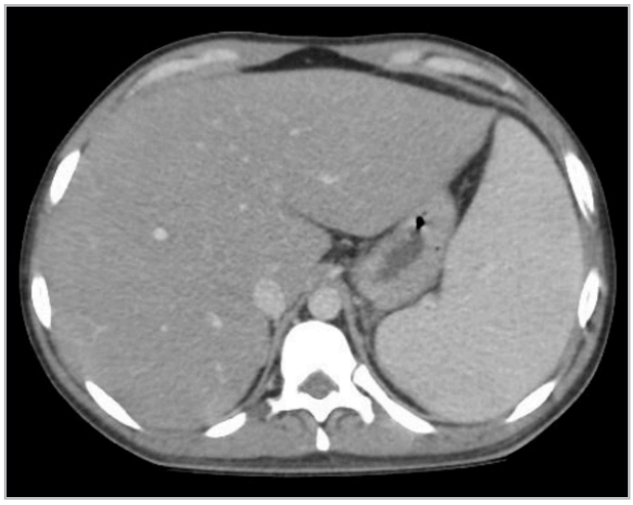

Figure 1. *A simple axial abdominal CT of a patient at Hospital Regional de la Orinoquía with a clinical picture of brucellosis, showing hepatosplenomegaly.*

The pathogen's incubation is anywhere from three days to weeks. When the microorganism is ingested, it is phagocytized by the neutrophils and monocytes and then transported by the blood to the liver, spleen, bone marrow and lymph node sinusoids (2, 9). The symptoms are characteristically varied, with acute or chronic symptoms. Physical exam findings may be normal or nonspecific, such as lymphadenopathy, splenomegaly and hepatomegaly, with the last two found in our patient's case (2, 7, 9). Endocarditis rarely occurs but is the main cause of death (2). Skin manifestations include maculopapular rashes, erythema nodosum, ulcerations, petechiae, abscesses and panniculitis (2, 7).

The diagnostic methods used to detect these microorganisms vary, with pathogen isolation on culture being the most effective method with the greatest sensitivity if it is done on the bone marrow; however, these studies require a longer time to produce results. In serum, the Rose Bengal screening test may provide rapid results with a sensitivity and specificity of 95 and 100%, respectively. Other methods include enzyme-linked immunosorbent assays (ELISA) and agglutination tests; the latter are positive with titers greater than 1:160 in nonendemic areas and greater than 1:320 in endemic areas; higher titers are more specific (2, 7, 12). This patient had a positive Rose Bengal test and positive febrile antigens for *Brucella abortus* in 1:640 dilutions.

The most common laboratory abnormalities are in the cell lines, with neutropenia and anemia, while thrombocytopenia and pancytopenia are less common, with a possible frequency of 2 to 14% of affected individuals (10). The pathogenesis of pancytopenia has not been clearly determined; one possible mechanism is hemophagocytic histiocytosis, a condition characterized by phagocytosis of all types of blood cells by activated histiocytes. Other conditions include hypersplenism, bone marrow granulomas or hypoplasia and immune destruction (13-15). Brucellosis has also been related to abnormal liver enzymes and elevated

inflammatory markers (2). This patient had several laboratory abnormalities, including reductions in three cell lines, possibly associated with hypersplenism.

This patient's treatment was based on the guidelines provided by the World Health Organization, with dual antibiotic therapy using synergistic medications (2, 6, 10). These regimens include doxycycline and rifampicin for six weeks; other treatment options may include streptomycin, tetracycline, trimethoprim-sulfamethoxazole, and quinolones (10). There may be other treatments; however, additional treatment beyond antibiotic therapy depends on the disease complications and must be personalized for each case (2). The goal of treatment is to reduce the risk of recurrence, which occurs in 5 to 15% of patients even up to 12 months later. It also seeks to reduce the risk of chronicity, which develops in 10 to 30% (5, 16).

Conclusions

Brucellosis is an anthropozoonotic disease of great public importance. Despite this, proper epidemiological surveillance is lacking in Colombia, affected by the lack of knowledge regarding its symptomatology and its underdiagnosis by healthcare facilities. The country's socioeconomic differences are important in proper monitoring of this disease, and therefore awareness raising policies regarding the causal agent and its mode of transmission must be implemented, especially in rural areas.

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