

# A Case Report: A Case of Brucellosis Presenting with Pancytopenia

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## Abstract

Brucellosis is one of the most prevalent zoonotic infections in the world. The disease begins with nonspecific symptoms and may affect hematopoietic, musculoskeletal, nervous and gastrointestinal system with a wide variety of symptoms and signs. In this study, we present a six-year-old girl who was admitted with fever and arthralgia diagnosed as brucellosis after excluding malignancy in the differential diagnosis. The patient recovered completely with gentamicin and trimethoprim-sulfamethoxazole (TMP-SMZ).

Keywords: Brucellosis; child; pancytopenia.

Brucellosis, which is transmitted by bacteria of the genus *Brucella*, is an important health problem all over the world, mainly in Mediterranean Countries, Central and South America and Turkey. Brucellosis can be transmitted from animals to humans by digestion (unpasteurized milk and contaminated food), direct contact with infected tissue, and rarely by inhalation. Brucellosis may start with nonspecific symptoms, such as fever, weakness, weight loss, arthralgia, myalgia, abdominal pain and headache, and may show acute, subacute or chronic course. The disease may occur with the cardiovascular, hematopoietic, skeletal and nervous system, skin and gastrointestinal system involvement. Diagnosis is made by isolating the agent from blood, bone marrow, lymph node, or granulomatous lesions or serological tests [1]. In this study, we present a 6-year-old girl who presented with complaints

of fever and arthralgia whose tests revealed the presence of pancytopenia, so the differential diagnosis was made in consideration of any malignancy. Finally, the diagnosis of brucellosis was made.

## Case Report

A 6-year-old female patient was admitted to our hospital with a fever of 39 °C for 12 days, especially in the morning and evening, and pain in her right leg during the last two days, and she was using paracetamol syrup prescribed by a family medicine specialist. This first child born from nonconsanguineous healthy parents had received all her due vaccines, and there was no history of any disease or chronic drug use. Her brothers were healthy. Her growth and development were normal for her age. The patient had fever (39 °C), oropharyngeal hyperemia, and microlym-

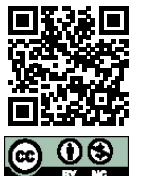
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phadenopathies were detected on her neck. She was conscious and had no signs of meningeal irritation.

She had splenomegaly that extended below the costal margin for 3 cm at the midclavicular line. Any signs of joint inflammation were observed during examinations of the joints. Complete blood count results were as follows: leukocyte count: 3100/mm<sup>3</sup>, Hgb: 7.7 g/dl, Htc: 22%, platelet: 71.000/mm<sup>3</sup>, MCV: 72.3 fl, RDW: 14.2, ANS: 1200/mm<sup>3</sup>, reticulocytes: 1.75%. Peripheral smear results were as follows: lymphocytes, 46%, PNL 38%, 12% band and monocytes, 4%, FBG: 104 mg/dl, BUN: 13 mg/dl, creatinine: 0.5 mg/dl, AST: 322 U/ml, ALT: 290 U/ml, LDH: 1116 U/l, and serum electrolytes were within normal levels.

Results of coagulation tests, complete urinalysis and urine culture were not remarkable. PA chest and sinus radiograms were not abnormal. The PPD test was negative. No pathology was found in the lumbar puncture. Bone marrow aspiration was performed, and findings supporting bone marrow infection were detected. Treatment with ceftriaxone was started for the patient with pancytopenia and CRP elevation. Serologic tests for HBsAg negative, anti-HBs: 665 IU/ml, HIV, HCV, EBV, Toxoplasma, CMV, Rubella, Parvovirus B-19, Herpes simplex virus type 1 did not demonstrate any abnormality. Haemophilus parainfluenza susceptible to all antibiotics was detected in blood culture.

Gruber-Widal and Monospot tests were negative. The standard tube agglutination test for Brucella was positive at 1/10240 titer. When the nutritional history of the family was taken in detail, it was learned that the family consumed cheese produced from raw milk provided from the village. Arthritis was not considered, especially in the patient's right leg pain. The abdominal US did not reveal any abnormal findings except splenomegaly (130 mm long splenic axis). Treatment with oral TMP (10 mg/kg/day) -SMZ (50 mg/kg/day) and IM gentamicin (5 mg/kg/day) was started. After the third day of treatment, the patient's body temperature dropped to normal levels and her complaints improved. Predischage hematologic and biochemical values were within normal levels, including leukocytes: 4000/mm<sup>3</sup>, Hct: 23%, Hgb: 7.5 g/dl, platelets: 110.000/mm<sup>3</sup>, AST: 193 U/l, ALT: 186 U/l, LDH: 600 U/L. The other remaining biochemical parameters were also within normal levels.

The patient was discharged on the seventh day of hospitalization at the request of the family. Gentamicin treatment was continued for a total of 14 days and TMP-SMZ treatment was completed in six weeks. At the end of this period, the patient recovered completely, and she remained healthy during her 1-year-long follow-up period.

## Discussion

Brucellosis, which is also frequently observed in our country, may show a very different course. In some patients, subclinical brucella infection, which is only shown by serological methods, is observed, while in some patients, recurrent signs and symptoms may be observed for years. In brucellosis, symptoms begin 2-3 weeks after the ingestion of the bacteria. Despite many personal complaints, such as fever, sweating, loss of appetite and fatigue, physical examination findings are markedly scarce. The most common findings are fever and lymphadenopathy [1].

In a study conducted in our country, Turkey, the most common presenting complaints of the patients with brucellosis were fever (15/21) and joint pain (12/21) [2]. In another case series, high fever (88.7%) and joint pain (64.5%) were the most common presenting complaints. In this series, 51.6% of the patients were consuming raw milk and dairy products [3].

Arthritis is the most common regional complication of brucellosis. Generally, a large single joint (hip, knee and sacroiliac joint) is involved [4]. Spondylitis and osteomyelitis are less common in children than in adults [5]. The patient's admission complaints were fever and arthralgia. She had pain in his right leg that started three days before the admission. Physical examination and orthopedic consultations did not reveal any sign of arthritis. Most patients with brucellosis are also affected by the liver. Liver function test (LFT) results of the cases are usually found to be normal or slightly increased. Liver involvement may be shown, although LFT results are within normal levels [6]. We found elevated serum AST and ALT levels in our patient. After six weeks of treatment, AST and ALT levels returned to normal.

Many organ systems can be affected during the course of Brucella infection. Observable hematological changes may be in the wide range of intravascular coagulation with fulminant course from mild hemostatic disorder. The most common hematologic findings are anemia, leukopenia, thrombocytopenia and pancytopenia [7]. Yılmaz et al. [2] found anemia in nine, leukopenia in four, thrombocytopenia in three, and pancytopenia in one of 21 children diagnosed with brucellosis. The prevalence of pancytopenia varies between 3-20% [2, 8]. Possible mechanisms leading to pancytopenia include hypersplenism, reactive hemophagocytosis, sepsis-induced bone marrow suppression, and the presence of granuloma in the bone marrow [7]. Pancytopenia, usually seen in the course of brucellosis, is transient and treatment improves the blood picture [9]. We found pancytopenia in our patient's hematologic ex-

aminations. Pancytopenia of our patient improved in the second week of our treatment for Brucella infection.

Tularemia, cat scratch disease, typhoid infection, fungal infections, tuberculosis, atypical mycobacteria and Yersinia infections should be considered in the differential diagnosis of brucellosis [10]. Since pancytopenia may be observed in brucellosis, other conditions that may cause pancytopenia (e.g. malignancies, infections, drugs, hypersplenism, storage diseases and aplastic anemia) should be excluded. Our patient had fever and arthralgia, pancytopenia and CRP positivity. Conditions that may cause pancytopenia (e.g. malignancy, aplastic anemia) were excluded by peripheral smear and bone marrow aspiration.

In serological examinations for infectious agents that could cause pancytopenia, we found Brucella tube agglutination titer positivity at 1/10240 titer and supported our diagnosis by nutritional history.

In a case series where 202 adult patients with brucellosis were evaluated retrospectively and 30 patients had pancytopenia, bone marrow aspiration and biopsies of these patients showed predominantly hypercellularity, hemophagocytosis, histiocytic hyperplasia, and granulomatous lesions. Hematologic malignancy (2 ALL, 1 AML, 2 multiple myeloma) was detected in five of thirty cases with brucellosis aged 39-76 years examined for pancytopenia. Blast marrow examinations of the blast, myeloma cell infiltrates and erythroid hyperplasia have been observed in patients with hematologic malignancies [8]. Solid tumor and hematologic malignancies may be observed in adult brucellosis patients, albeit rarely [11]. We have not encountered with hematological malignancy due to brucella infection in children.

Serum tests, such as the standard tube agglutination test and Brucella specific IgG and IgM antibody detection by ELISA, are used in the diagnosis of brucellosis. In a study comparing these two methods, positive and negative predictive values for the standard tube agglutination test were 100%, and 90.9%, 96.3%, 76% for IgG antibodies detected by ELISA and 90.9% and 89.5% for IgM antibodies by ELISA, respectively. In conclusion, it is recommended that the standard tube agglutination test is preferred in acute brucellosis because it is cheaper and usable [12]. False negativity may be detected in the presence of IgG and IgA type blocking antibodies in the standard tube agglutination test during brucellosis infection. In this case, even if there is antigen-antibody interaction, positive agglutination is not observed, and sera should be studied with the Coombs method [13].

Haemophilus parainfluenza susceptible to all antibiotics was isolated from the blood culture taken at the time of hospitalization. If automated diagnostic systems are used in blood cultures, isolates may be mistakenly identified as gram-negative microorganisms (Haemophilus influenza spp.vs). Therefore, clinical evaluation and laboratory results should be interpreted together [10]. We thought that the patient's condition supported the diagnosis of brucellosis based on the clinical picture, nutritional history, clinical and laboratory response during treatment and follow-up process, and the blood culture obtained may be related to this condition.

Antimicrobial treatment options for brucellosis vary according to age. Doxycycline-rifampicin or doxycycline-streptomycin/gentamicin may be used in children older than eight years, and rifampicin with TMP-SMZ for children younger than eight years. Duration of the treatment is 1-2 weeks for gentamicin or streptomycin (IV/IM) and 4-6 weeks for other drugs used orally [10]. Physicians who follow patients with brucellosis requiring long-term treatment (6-8 weeks) inform their patients and their families about their medications and their use and follow-up. Although the drug is being used appropriately, relapses may be observed within the year following treatment. In various studies, relapses have been found with a frequency of 0-32% in brucellosis treatment regimens lasting at least four weeks [3, 14].

We applied gentamicin for two weeks, and TMP-SMZ treatment for six weeks. At the end of the treatment, our patient recovered completely and did not have any health problems during one year of follow-up. In conclusion, brucellosis is common in our country, and patients may present with different clinical signs and symptoms. In case of clinical suspicion, anamnesis of nutrition should be questioned, and laboratory tests should be used in diagnosis. Brucellosis should be treated with appropriate combined and long-term antibiotic therapy, and the prevention of relapses should be aimed.

**Informed Consent:** Written informed consent was obtained from the parents of the patient for the publication of the case report and the accompanying images.

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