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Case Report

False-Positive *Brucella* Agglutination in a Pediatric Case with Non-Hodgkin Lymphoma

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ABSTRACT

Brucellosis, also known as Mediterranean fever or Malta fever, is a zoonotic infection which is prevalent in developing countries and remains an important public health concern. The most common symptoms in children include fever, malaise, myalgia, night sweats, arthritis, and arthralgia. The differential diagnosis of brucellosis encompasses a wide range of infectious, rheumatological, and malignant disorders. Although several reports describing false-positive serological results have been published, this is one of the rare pediatric cases of Burkitt lymphoma presenting with positive *Brucella* agglutination test results to be reported in the literature. The gold standard for the diagnosis of brucellosis is the isolation of the organism from tissue specimens or specific body fluid cultures. Although *Brucella* agglutination and other serological tests are useful diagnostic tools, false-positive results may occur, particularly in those patients with rheumatological diseases and infections caused by other microorganisms.

Keywords: Brucellosis, false positivity, lymphoma, lymphadenopathy

Introduction

Brucellosis, also known as Mediterranean fever or Malta fever, is a zoonotic infection which is prevalent in developing countries and remains a significant public health concern. It is transmitted from infected animals such as cattle, sheep, goats, camels, pigs, etc. (1). Approximately 500,000 new cases of brucellosis are reported worldwide each year (2). Children account for approximately 10-30% of all reported cases (3). According to the Public Health data of Türkiye in 2017, the incidence rate of brucellosis is 7.99 per 100,000, although this rate has tended to decrease over the years (4). Although it varies according to geographical regions in different studies, between 1% and 26.7% of cases are pediatric cases (5). The most common modes of transmission are the consumption of infected, unpasteurized products, the contact of skin or mucous membranes with infected animal tissue or body fluids such as blood, urine, milk, or the inhalation of infected aerosols (1,6).

The most common symptoms in children are malaise, myalgia, night sweats, arthritis and arthralgia with fever (6). The differential diagnosis of brucellosis includes

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many diseases such as malaria, tuberculosis, visceral leishmaniosis, endocarditis, acquired immune deficiency syndrome (AIDS), enteric fever, tularemia, cat scratch disease, atypical mycobacterial infections, rickettsia, yersinia, malignancy, spondyloarthritis, reactive arthritis, septic arthritis, sarcoidosis, and fungal infections (3). In the definitive diagnosis of brucellosis, the gold standard method is isolating the organism in tissue or specific body fluid cultures (1,6). The *Brucella* agglutination test and other serological tests are also helpful in its diagnosis but false positivity can be encountered since positivity of these tests is possible, especially in rheumatological diseases and infectious diseases caused by other microorganisms. Herein, a case with false positivity of *Brucella* agglutination due to Burkitt lymphoma diagnosis is presented.

Case Report

A previously healthy four-year-old boy presented with fever, night sweats, weight loss (33% of body weight), and abdominal pain which persisted for two months. Fever typically occurred in the evenings reaching temperatures of up to 38.2 °C. Febrile episodes were accompanied by sweating and were relieved by non-steroidal anti-inflammatory drugs.

Based on the history provided by the family, the patient lived in a rural area but had no known exposure to livestock or other farm animals. There was no history of consumption of unpasteurized milk or dairy products, and no similar illness was reported in the family.

On physical examination, body temperature was 37.7 °C, and other vital signs were normal. A palpable abdominal mass was detected in the periumbilical region. Except for the palpable abdominal mass, no additional abnormalities were detected on physical examination. Complete blood count, and biochemistry were normal. C-reactive protein was 46 mg/L and the erythrocyte sedimentation rate was 52 mm/hr. On his abdominal ultrasonography, splenomegaly and a 5x6 cm lymphadenopathy were present in the paraaortic region. Serological investigations for *Salmonella* infections, *Toxoplasma gondii*, cytomegalovirus, Epstein-Barr virus, Hepatitis B virus, Hepatitis C virus, and human immunodeficiency virus were negative and were performed in order to exclude infectious causes of lymphadenopathy and prolonged fever. Tru-cut biopsy from the abdominal lymphadenopathy and bone marrow aspiration were performed. Histopathological examination of the abdominal lymph node biopsy and bone marrow aspirate demonstrated reactive inflammatory changes. There was no growth in the blood culture, bone marrow culture, or tissue culture. *Brucella* antibodies detected by serum tube agglutination (SAT) were positive, with a titer of 1:640. The Rose Bengal test, Coombs test, and *Brucella* ELISA IgM/IgG were also positive. Therefore, anti-brucellosis therapy consisting of trimethoprim-sulfamethoxazole [TMP (10 mg/kg/day) and SMX (50 mg/kg/day) in two divided doses] plus rifampicin (15-20 mg/kg/day orally once daily) was initiated. At the outpatient clinic follow-up after 2 weeks, the patient was still complaining of abdominal pain, fever and loss of appetite. *Brucella* serological assays were repeated, and positive results were consistently observed on serial evaluations. As the lymph nodes were enlarged (7 cm x 7 cm) in the abdominal tomography (Figure 1) despite *Brucella* treatment, an excisional lymph node biopsy was planned.

Histopathological examination revealed a diagnosis of Burkitt lymphoma. Brucellosis treatment was discontinued, and the patient subsequently completed the planned oncological treatment. He achieved complete remission and remained disease-free during long-term follow-up. No clinical signs, symptoms, or laboratory findings suggestive of brucellosis were observed throughout the follow-up period.

Written informed consent was obtained from the patient's parents for the publication of this case report.

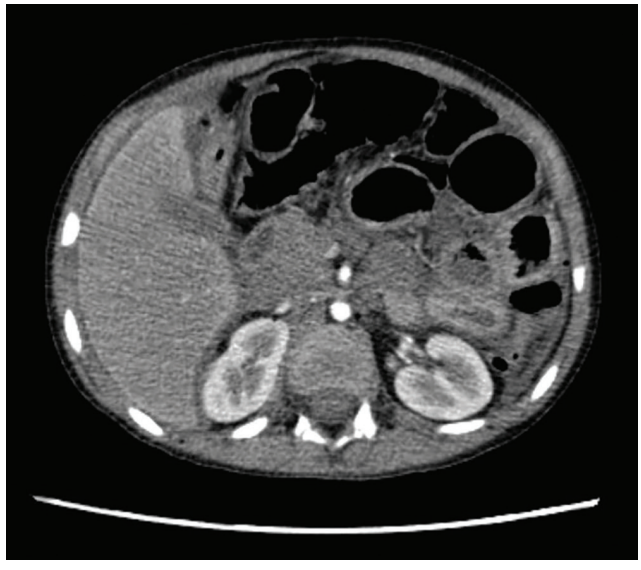


Figure 1. Contrast-enhanced abdominal computed tomography demonstrating a large heterogeneous mesenteric mass occupying the periumbilical region, associated with multiple enlarged intra-abdominal lymph nodes. The findings were highly suggestive of a lymphoproliferative malignancy

Discussion

To the best of our knowledge, Burkitt lymphoma associated with positive *Brucella* agglutination test results is a rare finding in the pediatric literature. Some of the expected clinical findings in *Brucella* infection in childhood are fever, night sweats, weakness, weight loss, abdominal pain, and osteoarticular findings (6). Lymphadenopathy is seen in only 10-20% of these cases (7). These clinical findings are also common in children with lymphoma.

Among the laboratory findings of brucellosis**,** transaminase elevation, anemia, leukopenia, leukocytosis with relative lymphocytosis, and thrombocytopenia may be seen or they may be completely normal as in our case (6). The sensitivity of blood culture in the diagnosis of brucellosis is between 15-70%. As *Brucella* spp. are facultative intracellular bacteria, bone marrow cultures are more sensitive than blood cultures and are considered to be the gold standard diagnostic method (6,8). Blood and bone marrow cultures did not reveal brucellosis in our patient. In suspected cases of brucellosis in which the organism cannot be isolated by culture, polymerase chain reaction assays for *Brucella* and SAT tests may aid diagnosis (2). The combined use of two serological tests allows the diagnosis to be optimized. Generally, serum agglutination titer >1:160 in the non-endemic area and >1:320 in the endemic region are accepted as positive (6).

The differential diagnosis of *Brucella* includes tuberculosis, visceral leishmaniosis, endocarditis, AIDS, enteric fever, tularemia, atypical mycobacteria, malignancy, sarcoidosis, and fungal infections. These diseases other than brucellosis were excluded in our patient by history, physical examination and also laboratory tests when need. Brucellosis was considered as the initial pathological examination did not lead to a specific diagnosis and due to the positive serological test results for brucellosis. Additionally, the patient was living in an endemic region for brucellosis in Türkiye.

The greatest disadvantage of serological tests is false positivity due to cross reactions with other bacteria and different diseases (9). Organisms which cause cross-reactivity include *Francisella tularensis*, *Yersinia enterocolitica*, *Serratia marcescens*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *Escherichia coli*, *Vibrio cholera*, *Mycobacterium tuberculosis* and malaria. Other diseases which cause false positivity are systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis and lymphoma (6,10-13).

Similar to the case presented in this report, hematological malignancies, particularly lymphomas, may lead to false-positive serological reactions because of polyclonal B-cell activation, hypergammaglobulinemia, and non-specific antibody production. Memish et al. (14) evaluated 280 patients with diseases clinically mimicking brucellosis, including 63 patients with active lymphoma, and reported false-positive Rose Bengal and Wright agglutination test results in a subset of these patients.

Although the exact mechanism remains unclear, lymphoma-associated immune dysregulation may have contributed to the persistent false-positive *Brucella* serology in our patient. The absence of microbiological evidence of brucellosis, the lack of response to anti-brucellosis therapy, and the complete resolution of symptoms following lymphoma-directed chemotherapy strongly support this interpretation.

In conclusion, clinicians practicing in endemic regions should be aware that positive *Brucella* serology alone is insufficient for diagnosis and should always be interpreted in conjunction with clinical, microbiological, radiological, and histopathological findings. Different diagnostic serological tests other than gold standards such as cultures may mislead clinicians in cases implying brucellosis due to clinical findings. Those patients who do not respond to disease-specific treatment should be carefully re-evaluated for alternative diagnoses, including malignancies and other diseases in order to avoid diagnostic delays and inappropriate treatment.

Ethics

Informed Consent: Informed consent was obtained from the parents before including the patient details and clinical photographs in this manuscript.

Footnotes

Authorship Contributions

Concept: N.A.Ü., T.B.D., A.O., A.T., F.G.P., Design: N.A.Ü., T.B.D., A.T., F.G.P., Analysis or Interpretation: T.B.D., B.C.C.Y., C.G., A.O., M.P., H.T., A.T., F.G.P., Literature Search: N.A.Ü., T.B.D., B.C.C.Y., C.G., A.T., F.G.P., Writing: N.A.Ü., T.B.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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