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Lymphoma or Brucellosis: A Case Series Study

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ABSTRACT

Human Brucellosis is a zoonotic disease with various clinical manifestations, ranging from asymptomatic infection to multisystem involvement. Cases with hematological abnormalities and lymphadenopathy, which were referred to the hematology department of the hospital, were described from September 2021 to August 2022. These Iranian patients included a 38-year-old man and two 64- and 24-year-old women. Due to the region's endemicity and strong clinical suspicion of brucellosis, therapeutic management and invasive procedures such as splenectomy were avoided in one case.

Based on the available literature, it is evident that the infrequent symptoms that accompany the typical symptoms of brucellosis may give rise to uncertainty and hinder prompt diagnosis. The reason is that patients presenting with indications of pancytopenia, coupled with splenomegaly or lymphadenopathy, are typically referred to hematologists. Hence, the purpose of these case reports is to highlight the symptoms of brucellosis that mimic a primary hematologic disorder, facilitating faster and more accurate diagnosis.

Introduction

Brucellosis, known as a zoonotic disease, is one of the most widespread infections caused by species of Brucella, gram-negative bacilli [1]. This disease can occur in humans due to four species: Brucella abortus, Brucella canis, Brucella suis, and Brucella melitensis [2]. Brucellosis is a major public health issue worldwide. Many parts of the world are still endemic for brucellosis, where humans live close to livestock or consume its derived unpasteurized food products, especially in developing countries [1, 2]. It has high morbidity for humans and animals, leading to economic loss in many developing countries [3].

Although thousands of new human cases of brucellosis are reported worldwide, it is believed that the incidence of the disease is underestimated, and some cases are not detected [1, 2]. There is considerable variation in the frequency of brucellosis in different parts of Iran. The incidence reported in 2017 varied between 98 and 130 per 100,000 population.

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According to data from the Iranian Ministry of Health published in 2022, the average incidence of brucellosis in Iran was 22 cases per 100,000 population, with a decreasing trend in surveillance [2, 4].

Brucellosis may cause fever, malaise, night sweats, and arthralgia, which, although nonspecific, are the most frequent symptoms. Identifying brucellosis can be difficult as its symptoms can resemble those of other diseases. In the laboratory, bacterial culture testing is the most reliable method for its diagnosis; serological techniques and molecular assays are also commonly employed [5, 6].

In our literature review, retroperitoneal and mesenteric lymphadenopathies are extremely rare in brucellosis. Here, we present patients whose workup for hematologic malignancy led to the diagnosis of brucellosis.

Case presentation

Case 1

A 38-year-old Iranian man, previously in good health, presented to the emergency department in September 2021. He reported experiencing fever, significant weight loss, sweating, and loss of appetite continuously for the past two months. He denied a history of specific diseases and reported no contact with livestock. However, he was unsure if he had consumed local dairy products.

Several potential diseases were suspected, including malignancy, HIV, zoonotic infections, infectious mononucleosis, and tuberculosis. Consequently, a series of laboratory tests were conducted to establish a diagnosis. Hematological and biochemical tests were assessed, as indicated in Table 1. Interestingly, investigation of the clinical abdomen by computerized tomography (CT) scan revealed mesenteric lymphadenopathy. The Brucella agglutination test returned positive (Table 1). In addition to serological tests, including agglutination tests and ELISA, a blood culture for brucellosis was also performed and returned positive. Therefore, he was treated with doxycycline and rifampin for six weeks.

The patient's signs and symptoms, along with laboratory findings—including serological, hematological, and imaging data—showed significant improvement.

Case 2

A 24-year-old previously healthy Iranian pregnant woman presented to the emergency department in February 2022 with a 4-week history of fever, submandibular lymphadenopathy, and anemia. She denied contact with livestock and had no history of consuming dairy products.

Various factors such as mumps, sialadenitis, Sjögren's syndrome, cysts, some infections, some hematologic malignancy can cause this condition. Additionally, submandibular lymphadenopathy can result from infections of the teeth, upper respiratory tract, sinuses, and tonsils. Therefore, hematologic and biochemical tests were evaluated (Table 1).

Submandibular ultrasonography showed lymphadenopathy. Following consultation with an infectious disease specialist, Brucella agglutination tests were performed, given the potential exposure to non-sterile dairy products in regions where Brucella is prevalent. These tests yielded positive results, including titration levels. A blood culture for brucellosis also returned positive.

Table 1. Hematological and biochemical tests in patients

Tests	Patient 1	Patient 2	Patient 3	Reference Value
Hemoglobin Test (Hb)	9.5	11.5	9.8	12.5-16.5 g/dL
White Blood Count (WBC)	4550	10990	2000	4.0-10 × 1000 mm^3
Platelet Count (PLT)	165	177	100	(: 150-450 × 1000 mm^3
Erythrocyte Sedimentation Rate (ESR)	45	45	35	0-15 mm/hr
Aspartate Aminotransferase (AST)	45	35	131	up to 40 IU/L
Alkaline Phosphatase (ALP)	213	172	283	70-330 IU/L
Alanine Transaminase (ALT)	40	38	89	up to 37 IU/L
Lactate Dehydrogenase (LDH)	650	320	1220	Adult < 480 IU/L
Wright	1/320	1/160	1/640	Titration
2ME- Wright	1/160	1/80	1/320	Titration
Coombs Wright	1/320	1/160	1/640	Titration

After the diagnosis of brucellosis, treatment was started. As described earlier in a review report, associations between hematologic malignancy and brucellosis have been observed [7]. Therefore, a biopsy of lymphadenopathy to investigate hematologic malignancy was performed, which was reactive.

The patient's signs and symptoms, along with laboratory findings—including serological, hematological, and imaging results—showed significant improvement.

Case 3

A 64-year-old Iranian woman, previously healthy, presented to the emergency department in May 2022 with fever, fatigue, sweating, and anorexia. She denied any history of specific diseases and had no contact with livestock, although she used to consume local dairy products.

Hematologic and biochemical tests were performed (Table 1). Abdominal ultrasonography and CT indicated splenomegaly (165 mm) with a negative result for the Brucella agglutination test (Figure 1). Further evaluation for hematologic malignancy through Bone Marrow Aspirate (BMA) and biopsy revealed hypercellular marrow with trilineage hematopoiesis and progressive maturation (Figure 2). No fibrosis, lymphoid nodules, or increased megakaryocytes were observed. The PET scan reported nonspecific splenomegaly. Liver disease, hematologic malignancies, neoplastic cells, cytopenia, splenic sequestration, connective tissue diseases, infiltrative disorders, acute or chronic infection, and immune-mediated destruction can cause splenomegaly. Therefore, based on laboratory testing and PET scan results, a splenic biopsy was recommended, but it was not performed due to thrombocytopenia.

During a repeat consultation with an infectious disease specialist, the Brucella agglutination test was repeated three weeks after the first test, and positive results were reported, including Wright: 1/640, 2ME: 1/320, and Coombs Wright: 1/640. A positive result in the blood culture for brucellosis was also observed. For treatment, a combination of doxycycline and rifampin was used for eight weeks.

The patient's signs and symptoms, as well as

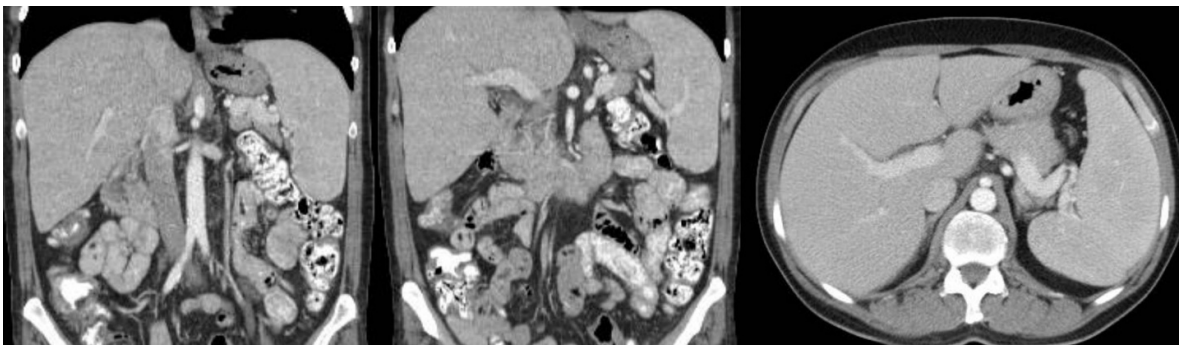

Fig. 1. Abdominal ultrasonography and computed tomography (CT) scans indicated splenomegaly, measuring 165 mm.

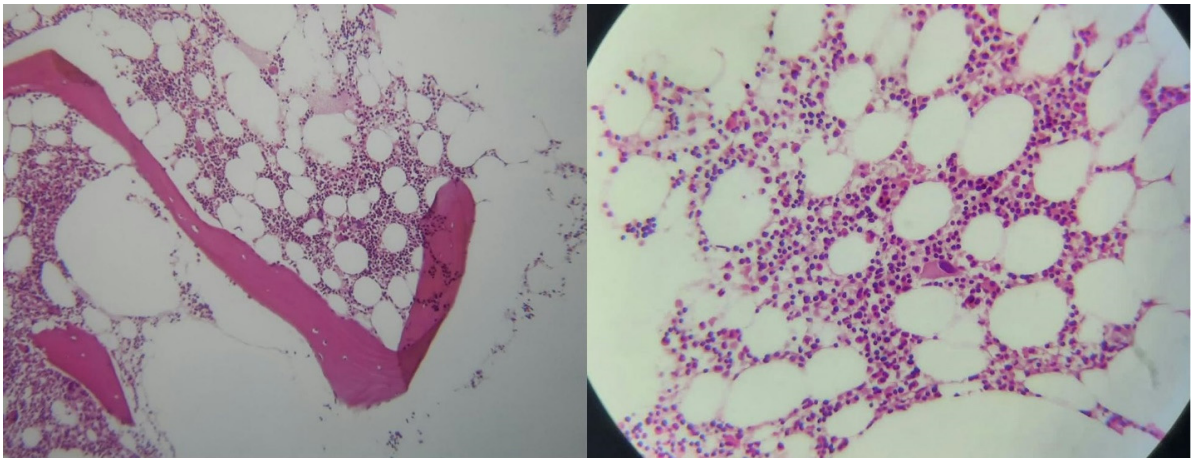

Fig. 2. Bone marrow aspiration and biopsy were performed for hematologic malignancy assessment, revealing hypercellular marrow with trilineage hematopoiesis.

laboratory and imaging data, showed significant improvement.

Discussion

Brucellosis is a systemic disease that can involve any organ. Misdiagnosis occurs due to common manifestations and symptoms of brucellosis with other diseases [8]. The clinical manifestations of brucellosis are variable. Fever is the most common symptom, along with rigors, anorexia, malaise, weight loss, backache, bony pains, arthritis, arthralgias, and hepatosplenomegaly [9, 10]. A wide range of hematological abnormalities may be observed in patients with brucellosis, including anemia, leukopenia, thrombocytopenia, pancytopenia, bleeding diathesis, and disseminated intravascular coagulation (DIC) [10-12]. Although rare, symptoms such as lymphadenopathy are possible presentations [13]. The presence of hematological abnormalities associated with other symptoms in the cases of our series was challenging in terms of diagnosis because brucellosis is usually considered after excluding other diseases [8].

In general, lymphadenopathies found in cases of brucellosis are uncommon. The Centers for Disease Control and Prevention (CDC) brucellosis reference guide reported lymphadenopathy in 10-20% of patients with brucellosis. While several studies in brucellosis research observed lymphadenopathy in less than 3% of patients with brucellosis [10, 12, 14]. In patient 1, there are rare retroperitoneal and mesenteric lymphadenopathies, which are uncommon even in livestock [15]. To the best of our knowledge, only one case of a brucellosis patient was reported with retroperitoneal and mesenteric lymphadenopathies [12]. In patient 2, submandibular lymphadenopathies were detected and observed. Awareness of brucellosis-specific lymphadenopathy may prevent misdiagnosis of conditions such as lymphoma and leukemia [16].

The companionship of pancytopenia with splenomegaly and a negative Brucella agglutination test for patient 3 confused our diagnosis because the standard tube agglutination test (SAT) is the most widely used serologic test for the confirmation of human brucellosis [17]. After the BMA and PET scan, along with clinical symptoms and consultation with an infectious disease specialist, the Brucella agglutination test was requested again, and an ELISA test was also performed. In suspected cases of Brucella infection, it's crucial to have a comprehensive diagnostic strategy for effective management. This should include detailed clinical evaluations, serological testing, and repeat assessments to monitor for persistent infection. Culturing a bone marrow sample can significantly increase the likelihood of isolating Brucella spp., especially in chronic cases where bacteremia may be less pronounced. The positive results of Brucella agglutination after two weeks and the positive ELISA test helped correct diagnosis and treatment.

Provided an appropriate therapy is rapidly instituted in patients with brucellosis, almost all the changes in the hematological parameters are reversible [18]. All our patients were treated with anti-brucellosis drugs only and followed for six months. All the patients underwent serological tests for Brucella, including the Wright, 2ME, and Coombs tests, conducted every three months, along with assessments of hematological parameters. Ultimately, all patients demonstrated significant improvement in their signs and symptoms.

Conclusion

Despite simplifying the treatment of brucellosis and improving efficacy, different clinical manifestations of the disease challenge the treatment of human brucellosis because of diverse and complex problems in diagnosis. Therefore, it is necessary to pay attention to the rare symptoms of brucellosis for diagnosis and treatment. Our case reports can highlight brucellosis symptoms similar to primary hematologic disorders for better and faster diagnosis. In areas where brucellosis is endemic, patients with lymphadenopathy should be referred to a hematologist-oncologist after ruling out infectious causes.

List of abbreviations

Hemoglobin Test: Hb

White Blood Count: WBC

Platelet Count: PLT

Erythrocyte Sedimentation Rate: ESR

Aspartate Aminotransferase: AST

Alkaline Phosphatase: ALP

Alanine Transaminase: ALT

Lactate Dehydrogenase: LDH

Computerized tomography: C.T.

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Not applicable.

Ethical Considerations

Author Contributions

Shiva Shabani: Conceptualization; Writing – original draft and treating patients.

Parsa Rostami: Conceptualization; Investigation and treating patients.

Azin Ahmari: Investigation and Writing – review & editing.

All authors read and approved the final manuscript.

Ethics Approval Statement

The Arak University of Medical Sciences Research Ethics Committee approved the study protocol with the ethics code I.R.ARAKMU.REC.1401.088. All procedures performed in this study were in accordance with the 1964 Helsinki Declaration and its later amendments. Additionally, informed consent was obtained from all participants included in the study at the time of sample collection, following the above-mentioned ethical standards.

Compliance with ethical guidelines

Consent was obtained from the patients.

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Conflict of Interests

All authors declare that they have no conflict of interest.

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