Case report

Brucellosis presenting with sepsis and cholestasis: A rare presentation of an endemic disease with review of the literature

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\textbf{ABSTRACT}

Brucellosis is a zoonotic disease endemic to the Middle East and Mediterranean basin. It has gained diagnostic challenge recently due to its increasingly non-specific and vague manifestations at presentation. Here, we report a 53-year-old man presenting with undulating fever and shaking chills and frequency, dysuria, hesitancy and malodorous urine. He had prior complicated urinary tract infection treated with intravenous antibiotics. Further evaluation revealed negative urine culture, intra-hepatic cholestasis due to underlying infection, elevated acute phase reactants and pancytopenia. The diagnosis of brucella was established as blood cultures grew Brucella melitensis and serum serology for Brucellosis returned positive. Following initiation of anti-brucella drugs, fever and laboratory abnormalities gradually returned to normal. Brucellosis should be always considered in the differential diagnosis of patients presenting with sepsis in endemic regions or when empiric antibiotic therapy fails to improve clinical and laboratory abnormalities. Diagnosis requires high level of suspicious based on the clinical history and constellation of symptoms.

\textbf{Introduction}

Brucellosis is one of the most common zoonotic illnesses globally, with about 500,000 new cases identified each year \cite{3}. Brucellosis is caused by a Brucella genus non-motile, gram-negative, non-spore producing intracellular bacteria. Brucellosis is most commonly spread to humans by the inhalational route or through close human contact with infected animals. It can also be transferred among laboratory workers through direct mucosal contact with infected fetal products \cite{3}. Brucellosis is endemic to many developing countries, particularly Asia, Africa, the Mediterranean rim, the Middle East, central and south America \cite{8}. The most common clinical presentations of brucellosis include constitutional symptoms such as recurrent fever, profuse sweating, weakness, enlargement of the reticuloendothelial organs as lymphadenopathy, hepatosplenomegaly and osteoarticular involvement including arthralgia, back pain and occasionally spondyloarthropathies and peripheral arthritids \cite{9}.

Although brucella-associated bacteremia is not uncommon, few cases of brucellosis presenting with bacteremia and acute sepsis remains in the literature \cite{12}. Brucellosis may frequently present with cytopenia, particularly during febrile bacteremia.However, pancytopenia is not a common presenting symptom \cite{6}. Herein we report a case of brucellosis presenting with acute bacterial sepsis and cytopenia and present a review on the reported cases in the literature.

\textbf{Case presentation}

A 53-year-old Iranian man with a history of Charcot-Marie-Tooth disease, hypertension, hyperlipidemia, benign prostatic hyperplasia and diabetes mellitus presented to our hospital with a complaint of fever and shaking chills of 3 days duration. The patient did not use any tobacco products, illicit drugs or alcohol. He denied previous history of consumption of unpasteurized dairy products. His past surgical history was significant for amputation of the left lower foot due to recurrent osteomyelitis 2 years prior to presentation.

His physical examination was normal except for the presence of systolic murmur of 3/6 severity best heard on the left sternal border and lower limb deformities. Blood tests showed anemia (hemoglobin

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2214-2509/© 2022 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Brucellosis is one of the most common zoonotic diseases worldwide, particularly in developing countries and is endemic in the Mediterranean region, Africa, Asia, central and south America, Mexico and the Arabian peninsula, with Iran being the second most frequent disease region, Africa, Asia, central and south America, Mexico and the Arabian peninsula, with Iran being the second most frequent disease region. Human acquire infection primarily via ingestion of contaminated unpasteurized milk products or contact with infected animal products. *Brucella melitensis* and *Brucella abortus* comprise the major disease-causing agents in Iran [1].

Brucellosis may present with a wide range of non-specific clinical manifestations, including constitutional symptoms such as recurrent fever, malaise, fatigue, weight loss, lymphadenopathy and hepatosplenomegaly. Other symptoms due to multi-organ involvement may also be present including arthralgia, sacroileitis, epididymo-orchitis, cardiitis and neurobrucellosis [9]. Common hematologic abnormalities include anemia, thrombocytopenia, leukopenia and less commonly pancytopenia [7]. Currently there are no unique disease characteristics that help differentiate brucellosis-induced pancytopenia from other non-infectious causes, which may lead to misdiagnosis of malignancy or other hematologic diseases instead of brucellosis infection [9]. Patients with significant involvement of the hepato biliary system were studied in a study by Ozturk-Engin et al. Clinical hepatitis was the most frequently detected hepatobiliary involvement with 87.3% of patients, followed by cholestasis in 66.1%. Half of the affected patients have elevated alkaline phosphatase and bilirubin and one-fourth have also elevated GGT [11].

Guo et al. reported a child with thalassemia presenting with a 3-week history of fever and patellar discomfort and night sweats was diagnosed with anemia, leukopenia and elevated inflammatory markers; ESR. The patient underwent blood and bone marrow sampling and blood culture became positive for Brucella. This child was treated with antibiotics with the diagnosis of sepsis [4]. Haran et al. reported a 76-year-old male patient presented with hypotension, tachycardia and fever and a 3-week history of low back pain. His prior medical history was notable for fever, sweating, bruising on abdomen and gingival bleeding. Further abnormalities involved elevated serum D-Dimer level, prolonged PT (partial thromboplastin time) and low fibrinogen level. The patient was treated with doxycycline and rifampin [14].

**Table 1**

A summary of previously reported cases of sepsis due to brucellosis.

| Author       | Age | Gender | Symptoms and signs                          | Laboratory abnormalities                                      | Treatment                                                                 | Reference |
|--------------|-----|--------|--------------------------------------------|-------------------------------------------------------------|--------------------------------------------------------------------------|-----------|
| Guo et al.   | 62  | M      | Fever, sweating, right patellar pain       | Leukopenia, anemia, elevated erythrocyte sedimentation rate (ESR), slightly elevated AST, ALT and procalcitonin | doxycycline, rifampin                                                   | [4]       |
| Bhatnagar et al. | 6   | F      | Failure to thrive, lethargy, fever, poor feeding | Elevated AST, ALT and LDH, increased D-Dimer, increased PT (partial thromboplastin time), low fibrinogen level | doxycycline, rifampin                                                   | [2]       |
| McCormick et al. | 26  | M      | Fever during rehabilitation of spinal cord injury, tachycardia | Elevated AST, ALT and LDH, increased D-Dimer, increased PT (partial thromboplastin time), low fibrinogen level | doxycycline, rifampin                                                   | [10]      |
| Haran et al. | 76  | M      | Fever, low back pain                       | Anemia, thrombocytopenia, elevated erythrocyte sedimentation rate, slightly elevated AST, ALT and procalcitonin | doxycycline, rifampin                                                   | [5]       |
| Solmaz et al. | 56  | M      | Fever, petechial/purpura                   | Anemia, leukocytosis, thrombocytopenia, elevated erythrocyte sedimentation rate, slightly elevated AST, ALT and procalcitonin | doxycycline, rifampin                                                   | [13]      |
| Turunc et al. | 55  | F      | Fever, gingival bleeding, echymoses and sweating | Mild hepatosplenomegaly, elevated erythrocyte sedimentation rate, slightly elevated AST, ALT and procalcitonin | doxycycline, rifampin                                                   | [14]      |
Conclusion

Brucellosis should be kept in the differential diagnosis of patients presenting from endemic regions with fever and other symptoms suggestive of sepsis. Treatment with anti-brucella medications result in complete resolution of clinical and laboratory symptoms in these patients.

Conflict of interest

All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version. This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue. The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

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Ethics approval and consent to participate

Informed written consent was obtained from the patient for publication of this report and any accompanying images.

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