



Case report

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

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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 suspicion based on the clinical history and constellation of symptoms.

Introduction

Brucellosis is one of the most common zoonotic illnesses globally, with about 500,000 new cases identified each year [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 [3]. Brucellosis is endemic to many developing countries, particularly Asia, Africa, the Mediterranean rim, the Middle East, central and south America [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 spondyloarthritis and peripheral arthritis [9].

Although brucella-associated bacteremia is not uncommon, few cases of brucellosis presenting with bacteremia and acute sepsis remains

in the literature [12]. Brucellosis may frequently present with cytopenia, particularly during febrile bacteremia. However, pancytopenia is not a common presenting symptom [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.

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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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.	6 Y	male	Fever,sweating,right patellar pain Diffuse mesenteric lymph node enlargement	Leukopenia,anemia,elevated ESR, slightly elevated AST,ALT and procalcitonin Positive blood culture	–	Guo et al., [4]
Bhatnagar et al.	6 W	female	Failure to thrive,lethargy,fever, poor feeding	urea/creatinine= 157/0.71 mg/dl Positive Blood culture, 1:320 agglutination titre	Intravenous fluids, amikacin and oral rifampin	Bhatnagar et al., [2]
McCormick et al.	26 Y	male	Fever during rehabilitation of spinal cord injury, tachycardia	Positive urine culture for pseudomonas and enterococci, positive blood culture and polymerase chain reaction	Intravenous doxycycline and oral rifampin	McCormick et al., [10]
Haran et al.	76Y	male	Fever, low back pain	anemia,thrombocytopenia Positive blood culture	Gentamycine, doxycyclin and rifampin	Haran et al., [5]
Solmaz et al.	56Y	male	Fever,petechial/purpura	anemia,leukocytosis,thrombocytopenia(AML-M1) positive blood culture, 1/320 agglutination titer	Doxycycline,rifampin	Solmaz et al., [13]
Turunc et al.	55Y	female	Fever,gingival bleeding, ecchymoses and sweating Mild hepatosplenomegaly	Anemia,thrombocytopenia,leukopenia, fragmented red blood cells, prolonged PT(prothrombine time) and PTT (partial thromboplastin time), increased D-Dimer Elevated AST,ALT and LDH agglutinin titer of 1:640 and positive blood culture	Doxycycline and rifampin	Turunc et al., [14]

level:11.8 g/dl), thrombocytopenia (platelet count: 60 K/uL) and leukopenia (white blood cell count:2.2 K/l). Liver function tests revealed significantly elevated alkaline phosphatase (ALK) of 3179 IU/L and less significantly elevated aminotransferases. Erythrocyte sedimentation rate (ESR) was 13 mm/h and C-reactive protein was 52 mg/L. There was direct (conjugated) hyperbilirubinemia at the second day of hospitalization. Ultrasonography of the abdomen and pelvis showed hepatosplenomegaly and increased thickness of the gallbladder wall, with the calculated liver and spleen index of 160 mm and 150 mm respectively. Transthoracic echocardiography was obtained and mild mitral regurgitation with no vegetative lesions was reported. Urine analysis revealed red blood cells with no pyuria or bacteriuria and urine culture was negative. The patient had collapsed gallbladder with normal intra- and extra hepatic bile ducts, suggesting intra-hepatic cholestasis primarily due to an underlying infection. The peripheral blood smear showed leukopenia with no circulating blasts, thrombocytopenia and mild anisocytosis and hypochromia. In order to exclude possible infectious endocarditis, Transthoracic echocardiography was obtained and no vegetative lesions were reported. The patient's condition improved gradually during the hospitalization, suggesting an underlying reactive inflammatory process. The patient experienced undulating fever during the course of hospitalization. Blood cultures obtained at the first day of hospitalization, became positive for *Brucella melitensis* on eighth day of hospitalization. *Brucella* serology(IgG/IgM) became positive as part of ordered laboratory values for sepsis workup. Further detailed history was obtained and it became apparent that the patient had occasionally used raw traditional cheese in previous years. Based on the patient clinical history, laboratory findings, *Brucella melitensis* on the blood culture and a positive blood serology, a diagnosis of brucellosis was confirmed. The patient was treated with oral doxycycline and rifampin for 3 months and the follow-up tests showed no abnormality 2 weeks after initiation of therapy.

Discussion

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 rates worldwide [8]. 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-causative 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, carditis 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 [7]. 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 brucellosis many years prior to recent presentation which was treated with streptomycin and tetracycline. He was hospitalized and central venous line was inserted, through which he received doxycycline and rifampin for six weeks and gentamycin for four weeks. The patient remained relapse free during the follow-up [5]. Brucellosis may rarely present with sepsis and disseminated intravascular coagulation (DIC). In a study of Turunc et al., a 55-year-old female patient presented with fever, sweating, bruising on abdomen and gingival bleeding. Further abnormalities involved elevated serum D-Dimer level, prolonged PTT (partial thromboplastin time) and low fibrinogen level. The patient was treated with doxycycline and rifampicin in conjunction with fresh frozen plasma and platelet transfusion [14]. The remainder of the reported cases are depicted in Table 1.

Brucellosis should be considered in the expanded differential diagnosis of patients presenting with sepsis, particularly in endemic regions or in the presence of recent travel to these areas, even in the absence of precise consumption of raw dairy products. Brucellosis did not become apparent as the diagnosis until blood cultures became positive for *Brucella melitensis*. Broad spectrum empiric antibiotics were initiated, which did not lead to significant clinical and laboratory improvement.

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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