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Case Report

Unexplained Fever and Arthritis in a Teenager with Type 1 Diabetes

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Abstract

Brucellosis is a relatively prevalent zoonotic infection in the Mediterranean region and the Arabian Peninsula. Due to the multi-system involvement and nonspecific nature of the complaints, making a diagnosis can sometimes be particularly challenging. We present the case of a Libyan-American adolescent with type 1 diabetes mellitus (T1DM) residing in the United Arab Emirates who presented with fever, flu-like symptoms, and arthritis. When his initial septic workup did not reveal a focus of infection, and he continued to be febrile with the development of multiple painful and swollen joints, a diagnosis of autoimmune arthritis was entertained given his background history of autoimmune T1DM. However, on further probing, we ascertained a history of raw camel cheese ingestion. This redirected us to look for and subsequently confirm the diagnosis of brucellosis. Appropriate antibiotic treatment led to rapid recovery of the patient.

Keywords: Autoimmune, brucellosis, fever, polyarthritis

Introduction

Brucellosis is one of the differential diagnoses of fever of unknown origin and is one of the most widespread zoonosis worldwide. Exact data regarding the practice of drinking raw milk in our population is unknown; although, several cases of brucellosis have been reported from the United Arab Emirates.[1]

Osteoarticular involvement is common in brucellosis. However, it is not the first thing that usually comes to mind in a patient from an urban background presenting with fever and arthritis.

Case Report

A 14-year-old boy presented with a 6 day history of fever, sore throat, coryza, and productive cough. This was associated with generalized joint pains, muscle aches, redness, and swelling of some large and small joints. He also described an erythematous rash in the initial course of his illness which had settled spontaneously. There was nausea with loss of appetite but no documented weight loss. Fever was intermittent, high grade, and temporarily relieved by paracetamol. There was no history of recent travel or sick contacts. He had no exposure to tobacco, ethanol, or history of sexual contact. No contact with animals was reported. His current medications consisted of a combination of short- and intermediate-acting insulin 3 times per day.

On examination, he was a pleasant boy who appeared lethargic. He was febrile with a temperature of 38.4°C and tachycardia with a blood pressure of 129/75 mmHg. He had a mild fading erythematous macular rash on his face and abdomen, and the throat was congested. Examination of the cardiovascular and respiratory system was unremarkable. On abdominal examination, he had mild generalized abdominal tenderness but no organomegaly. There were mild swelling and redness of the metacarpophalangeal and proximal interphalangeal joints of the right middle finger, left big toe, and left knee. The right shoulder also was tender, but no swelling or erythema was noted.

Given the history and initial laboratory workup [Table 1], he was managed as a case of upper respiratory tract infection possibly atypical pneumonia with reactive arthritis. He was

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empirically commenced on intravenous (IV) ceftriaxone and azithromycin. The persistence of fever and rising white blood cells count prompted a change in antibiotic to IV tazobactam/piperacillin. However, he showed no response and continued to have high-grade fever with new sites of peripheral joint involvement over the following few days. Thus, additional investigations were requested.

Outcome and follow-up

Due to the significant inflammatory polyarthritis and history of autoimmune type 1 diabetes mellitus, we consulted the rheumatology services. While awaiting investigations [Table 2], the rheumatologist recommended initiation of steroids entertaining a diagnosis of Still's disease or juvenile rheumatoid arthritis. We reviewed the history with the patient, and this time when asked about contact with animals or ingestion of raw milk, he remembered consuming camel milk cheese at a friend's farm a few weeks before his presentation. Serological tests for Brucella were requested which was reported as significantly positive [Table 3]; although, Brucella could not be isolated from the blood culture. Steroids were discontinued, and he was commenced on a combination of IV gentamicin with oral doxycyline and Rifampicin. After 1 week of treatment, there was a significant improvement in his symptoms as well as inflammatory markers. The antibiotics were continued for 8 weeks, and he remained asymptomatic after that. Repeat serological testing was negative [Table 3].

Discussion

Brucellosis, commonly known as, "undulent fever" is caused by Gram-negative, intracellular bacterium belonging to the genus *Brucella* which has many subtypes.[2] The species known to cause disease in humans are *Brucella melitensis, Brucella suis, Brucella Abortus*, and *Brucella canis*. Both *B. melitensis* and *B. abortus* can be found in camels.[3] Human brucellosis is usually associated with occupational or domestic exposure to infected animals or their products. Brucellosis may be acquired by ingestion, inhalation, or percutaneous exposure. Human-to-human transmission is extremely rare. The fact that our patient was diabetic did not make him at increased risk of this disease as there is no evidence that its prevalence is higher in diabetic patients.[2] A detailed history clearly helps in suspecting the diagnosis; although in a small percentage of cases, no risk factors can be identified.[4]

Osteoarticular involvement is quite common in brucellosis and is the most common symptom along with fever.[4,5] Peripheral arthritis is probably the most common form of skeletal involvement in children.[6] Sacroiliitis and spondylitis are the other common forms of arthritis observed.[7]

In a study of 195 cases from Turkey, musculoskeletal involvement was found in 69% of cases[7] and in a more recent Turkish analysis of 1028 cases osteoarticular involvement occurred in 25.3% of cases.[4] In another systematic review from Iran, the prevalence of peripheral joint involvement with brucellosis ranged from 13.6% to 50%.[6] Joints can be directly involved in infection causing septic arthritis, but reactive arthritis is also known to occur. Involvement of the small joints of hands and feet is rare.

Although the definitive diagnosis of brucellosis requires isolation of the bacterium from blood or tissue sample, this is not invariably possible. The percentage of cases with positive cultures ranges from 15% to 70%.[5] Serological tests involving serum agglutination are commonly used for diagnosing cases. Real-time polymerase chain reaction is most likely the

Table 1: Initial investigations

Investigations	Results
FBC	WBC count - 25.2×10^3/µl (87% neutrophils, 8% lymphocytes) Hb - 13.7 g/dl Platelet - 213×10^3/µl
Procalcitonin	1.25 ng/ml
C-reactive protein	>120 mg/L
Chest X-ray	Normal
Urine culture	No growth
Blood culture × 2	No growth
Legionella Ab	<1:16
Mycoplasma pneumonia Ab	Positive titer 1:160
HbA1c	10.3%
Ferritin	901.6 ng/ml
EBV IgM, CMV IgM, Rubeola IgM and rubella IgM	Negative
H1N1 RNA PCR	Negative
MERS corona RNA PCR - Swab	Negative
EBV DNA PCR - blood and CMV DNA PCR - blood	Negative
Hepatitis B surface antigen, hepatitis C virus Ab, HIV antigen and Ab	Negative
X-ray of affected joints	Normal
Ultrasound of knee	Minimal effusion in the right suprapatellar bursa
Transthoracic echocardiogram	Normal
Ultrasound abdomen	Moderate hepatomegaly with mild ascites
Other labs including liver function tests, Urea and electrolytes, Creatinine, lipids, amylase and lipase were all within normal	

FBC: Full blood count, Hb: Hemoglobin, EBV: Epstein barr virus, CMV: Cytomegalovirus, PCR: Polymerase chain reaction, MERS: Middle east respiratory syndrome, Ab: Antibodies

Table 2: Autoimmune workup

Investigations	Results	Reference range
Rheumatoid factor	IgG - 7.7 U/ml IgM - 5.6 U/ml IgA - 16.5 U/ml	<20 U/ml negative
Antinuclear factor	Negative	
Cyclic citrullinated peptide Ab	2 U/ml	<5 U/ml negative
Anti-ds DNA Ab	30.7 IU/ml	<100 IU/ml negative
Complement C3	1.79 g/L	0.93-2.03 g/L
Complement C4	0.42 g/L	0.13-0.52 g/L

Table 3: Brucella serology and follow up investigations

Investigations	At diagnosis	After 2 weeks of treatment
Brucella serology (ELISA) Reference value: <9 NTU units negative 9-11 NTU units grey zone >11 NTU units positive	IgG - 1.56 NTU units IgM - 32.69 NTU units	IgG - 2.98 NTU units IgM - 6.53 NTU units
FBC	WBC - 20.6×10^3/µl Hb - 11.4 g/dl Platelet - 351×10^3/µl	WBC - 6.9×10^3/µl Hb - 14.4 g/dl Platelet - 250×10^3/µl
C-reactive protein	>120 mg/L	<10 mg/L

FBC: Full blood count, WBC: White blood cells, Hb: Hemoglobin, NTU: NovaTec Units, Ab: Antibodies.

diagnostic tool of the future, offering the possibility of results in 30 min; although, it is not currently widely available.[5]

Treatment of brucellosis requires a prolonged course of combination antibiotics.[8,9] The latest recommendation from the Centers for Disease Control in 2012 is a combination of rifampicin and doxycycline for a minimum of 6–8 weeks.[10] The course of antibiotics can be extended to up to 3 months for focal and more complex cases. Brucellosis has a high incidence of relapse and patients ideally require long-term follow-up.

We chose to report this case due to the initial diagnostic uncertainty with a strong suspicion of a rheumatological process. Brucellosis was not suspected until the history was reviewed, clearly indicating the importance of good history taking. Brucellosis should always be considered in the differential diagnosis of fever and polyarthritis, especially in endemic areas.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Authors' contributions

All authors contributed to the care of the patient, drafting of the case report, revision, and approval of its final version.

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Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

No prior ethical approval is usually required for single case reports. However, the patient provided consent for publication as stated above.

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