Undulant Fever in ED: A Case Report

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Abstract

Brucellosis is the most common zoonosis worldwide. It is an uncommon entity in humans in the United States, with Texas reporting a third of cases. It is difficult to diagnose and hence can be easily missed. If not recognized and treated in a timely manner, brucellosis can lead to serious complications including death. The majority of cases in the United States are linked to consumption of unpasteurized dairy products imported from Mexico or travel to endemic areas. All health care providers should keep this infection in mind while dealing with patients presenting with fever. Clinicians should be vigilant and investigate for recent travel, consumption of unpasteurized dairy products, and animal exposure in these patients. More importantly, this pathogen can be used as a biological weapon as well. The article depicts a case of acute brucellosis in a patient who presented to an emergency room with a low-grade fever and nonspecific symptoms. Additionally, it reviews the crucial information regarding brucellosis and emphasizes important points on how to avoid misdiagnosis.

Introduction

Patients often seek medical attention in an urgent manner when experiencing fever. An elevated body temperature is usually associated with an acute, common infectious illness. All clinicians are aware and familiar with how to diagnose and manage these cases. However, a rare infectious entity will occasionally be linked to those cases, particularly when the fever is of unknown origin (no clear source can be easily identified based on history and physical examination). Brucellosis is the most common zoonosis found in humans worldwide, particularly in endemic areas and in high-risk groups including animal handlers, slaughterhouse workers, veterinarians, laboratory workers, and people consuming unusual foods. It is also called undulant fever because of its characteristic of recurrent febrile episodes. It is paramount that all health care providers in both endemic and non-endemic areas are aware of this febrile illness, as brucellosis is often misdiagnosed or overlooked. Untreated brucellosis leads to severe debilitation as well as high morbidity in patients of all ages. This article will present a patient case and review the crucial information regarding brucellosis.

Case Scenario

RR, a 34-year-old male who is a welder, presents to the emergency department (ED) in a large city in Texas. He only speaks Spanish and has no significant past medical, surgical, social, or family history. Patient complains of headache, low back pain, fever occurring at random, and anorexia for three days. His review of systems is negative. He takes no medications.

Physical examination

Vital Signs: Temperature 38.7°C, Pulse 96, Blood Pressure 122/71, Respiration Rate 20

General: Alert and oriented times three, no distress, well-developed, and nourished male.

Head, Eyes, Ears, Nose, Throat: Normocephalic, pupils equally round and reactive to light and accommodation, extraocular muscles intact, normal tympanic membranes and pharynx.

Neck: Supple, no adenopathy, masses, or jugular venous distension.

Chest: Non-tender, lungs clear to auscultation, good air movement.

CV: Heart with regular rate and rhythm, no murmur or gallop, pulses equal and strong.

Abdomen: Non-tender, soft, not distended, no organomegaly, bowel sounds normal.

Extremities: No cyanosis, clubbing, or edema; capillary refill less than 2 seconds.

Back: Normal inspection, no costovertebral angle tenderness or rebound.

Neurological: Cranial nerves II-XII grossly intact, no focal deficits, normal gait, negative Romberg, Kerning's, and Brudzinski's signs.

The initial workup included complete blood count, comprehensive metabolic panel, sedimentation rate, blood cultures, chest x-ray, computed tomography (CT) of the head, urine analysis, influenza screen, and cerebrospinal fluid (CSF) analysis. The results were remarkable for monocytosis on complete blood count, hyponatremia of 128, and sedimentation rate of 17 (mild elevation). Patient was treated with acetaminophen, intravenous fluids, and intravenous antibiotics in ED. His condition improved and he was discharged home with a prescription for levofloxacin and a recommendation to return if his symptoms deteriorate. Three days later, blood cultures revealed a growth for gram-negative rods, and further laboratory testing was positive for *Brucella melitensis*. The patient was called and prescribed doxycycline plus rifampin for six weeks.

Background

Human brucellosis is a major bacterial zoonosis of global importance.[1] In the United States, anywhere from 200 to 900 cases are reported annually,[2] mostly due to *Brucella melitensis*.[3] The disease is transmitted by inhalation, animal contact (cattle, sheep, goats, pigs, dogs), and consumption of unpasteurized dairy products and undercooked meat products.[4,5] The vast majority of cases in the United States are linked to consumption of unpasteurized dairy products imported from Mexico.[6] Of note, this pathogen can potentially be used as a biological weapon as well.[7]

Historically, the bacterium was first isolated in 1887 by David Bruce from the spleen tissue of a patient that had died as a result of undulant fever.[1] However, organisms resembling brucellae have been detected in carbonized cheese from the Roman era.[8] The bacterium is a small, non-motile, facultative, intracellular, and aerobic coccobacillus.[7] Gram staining demonstrates tiny gram-negative rods lacking capsules, spores, and flagella.[7] Bacterial growth is slow and requires special handling by a laboratory (need for 10% carbon dioxide). There are several isolated species of the bacterium. *Brucella melitensis* is the most common causative agent of human infection.[6]

The incubation period is usually between one and four weeks which is followed by flu-like symptoms characterized by an undulating fever pattern, weakness, malaise, headache, low back pain, rash, and fatigue.[9] Physical examination is often non-specific but may reveal hepatomegaly, splenomegaly, and/or lymphadenopathy.[7] Besides acute illness, brucellosis can be manifested as a focal process affecting practically any organ with osteomyelitis as most the common complication.[10] In addition, some cases will progress into a chronic illness characterized by intermittent back pains, arthralgia, sweats, and psychosis with personality changes.[11] Apart from high clinical suspicion, a clinician has several diagnostic tools to make a diagnosis of brucellosis. Diagnosis is predominantly based on serological assays and includes cultures, antigen detection by enzyme-linked immunosorbent assay (ELISA), genome detection using polymerase chain reaction (PCR), antibody detection, agglutination tests, and Coombs test.[12] Unfortunately, the recognition of this zoonosis may be missed at presentation. As a result, there is often a delay in starting proper antibiotics and follow-up care. This is likely due to the fact that the symptoms are non-specific with few clues in the patient's history.

Currently, there is no vaccine available to prevent brucellosis in humans. Vaccines are available for cattle, sheep, and goats, but not pigs. The vaccines are live attenuated ones and they require careful handling as accidental exposure can lead to infection.[13] Pasteurization of milk is also extremely important in the prevention of acquiring the disease by humans.

Discussion

Our patient presented with non-specific symptoms suggesting an infectious process. Differential diagnosis includes upper respiratory infection (bacterial or viral), pneumonia, meningitis, or fever of unknown origin. He had a few symptoms and clinical clues that should have prompted us to consider brucellosis as part of the differential diagnosis list. One of them was low back pain that likely represented sacroiliac joint inflammation, a frequent finding in acute brucellosis.[15,16,17]

Non-specific symptoms and signs, a language barrier, a busy ED setting, and a well appearing patient did not prompt providers to look for other clues in the patient's history that might reveal possible exposure to zoonotic infection. In fact, this patient was previously misdiagnosed and discharged with a diagnosis of a viral syndrome. The only reason he was properly diagnosed was by obtaining blood cultures. On the third day of incubation, the blood cultures revealed a growth of gram-negative small rods in aerobic bottles. They were fastidious organisms requiring a longer incubation time for growth. The identification was performed by PCR from the Centers for Disease Control and Prevention (CDC) confirming *Brucella melitensis*.

Our case shows a classic scenario of a patient presenting with acute febrile illness to ED that was eventually diagnosed with the most common human zoonosis, namely brucellosis. However, it is an entity that is rarely seen in most clinical settings and therefore can be easily missed and mismanaged.[11] Missing brucellosis or delay in diagnosis may be associated with several clinically significant consequences. Acute untreated brucellosis may lead to a chronic illness that can linger for years.[11,18] These patients will develop a cyclic course characterized by sweats,

arthralgias, back pain, and psychosis.[19] Further, untreated brucellosis can lead to potentially life-threatening complications and subsequently death.[10,13,18,20] These complications may be associated with the following system involvement:

- osteoarticular such as inflammation of any joint; most commonly sacroiliac and sternoclavicular.[15,16,17]
- genitourinary such as orchitis, epididymitis, prostatitis, cystitis, nephritis, and glomerulonephritis.[4,21]
- pulmonary.[10, 22]
- gastrointestinal such as hepatitis, acalculous cholecystitis, pancreatitis, colitis, peritonitis, and abscesses.[18]
- hematological such as anemia, leukopenia, thrombocytopenia, pancytopenia, and disseminated intravascular coagulation (DIC).[5,20]
- neurological/psychiatric such as meningitis, encephalitis, myelitis, radiculitis, neuritis, behavior changes, and psychosis.[4,13,18,20]
- cardiac such as endocarditis, myocarditis, pericarditis, and aneurysm of the aorta or ventricles.[10,13,18,20,23,24,25]
- ocular such as uveitis, keratoconjunctivitis, corneal ulcers, optic neuritis, papilledema, and endophthalmitis[15,26]
- dermatological such as skin ulcerations, petechiae, vasculitis, abscesses, and variety eruptions.[10,20,27]

Interestingly, patients with untreated acute brucellosis represent a potential occupational and environmental hazard to health care workers including laboratory workers who handle specimens without brucellosis precautions.[28,29,30]

Conclusion

Brucellosis is diagnostically challenging and an uncommon disease in the United States, with Texas reporting approximately a third of cases.[14] In the last decade, a new surge in brucellosis cases in animals has been detected in several states including Alaska, Montana, Wyoming, and Idaho.[31,32] In Alaska, the surge might be explained by the impact of climate change which allows more animals to survive cold weather and subsequently increases the opportunity for transmission to humans. In addition, travel and exposure of military personnel during deployment to military conflicts in the Middle East and other endemic regions could potentially contribute to the increased number of brucellosis cases on US soil.[33]

Clinicians are encouraged to remember that brucellosis is an important zoonosis posing substantial health threats and morbidity in untreated cases. It is imperative to recognize the clinical symptomatology of brucellosis: fever of unknown origin, low back pain, myalgias, rash, arthralgia, or lymphadenopathy. Another key point is to obtain an exposure history (ask about potential exposures to animals, including pets, ingestion of unpasteurized milk or cheese, and a travel history). The understanding of local and endemic epidemiology is also crucial.

In addition, *Brucella* species are of interest as a biological weapon by various enemy groups and the military.[7,34,35] In 1954, *Brucella suis* was first used as a biological weapon in the US.[36] No other cases have been reported since then. The Armed Forces Health Surveillance Center (AFHSC), which is a part of the US Department of Defense, lists brucellosis as a potential biological agent.[37] This organism offers several features that make it suitable for use as a bioarm: it is the most common zoonosis worldwide; airborne transmission is possible; it is highly contagious; it can enter the human body through conjunctivae, oropharynx, respiratory tract, and skin abrasions; only 10-100 organisms in aerosol are required to establish infection; and it is extremely difficult to diagnose.[7,37,38,39] Hence, ED providers should have the ability to effectively triage those patients that might have been exposed to the infection as a result of a biological weapon.

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