CASES

Brucellosis in a returned traveller

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A 68-year-old woman sought care at our emergency department because of a three-month history of lower back pain, which had started during a recent trip abroad. She complained of difficulty walking and had been experiencing low-grade fevers. Just before presentation, she had noted mild redness of her right leg. She had a history of osteoarthritis and non–insulin dependent diabetes mellitus. When she was 18 years of age, she had fallen from a tree and sustained a lumbar injury, requiring surgery with bone grafting from the right femur. The surgery had taken place in Italy. The procedure had been uncomplicated and she had recovered quickly.

On physical examination, the patient was obese and in no distress. Her vital signs were as follows: pulse 100 beats/min, blood pressure 130/72 mm Hg, oxygen saturation 97% on room air and maximum temperature 38.5°C. Head and neck examination showed no abnormalities, normal cranial nerves and no nuchal rigidity. Chest auscultation was clear, and examination of the cardiovascular system and abdomen was unremarkable. Examination of the cervical, thoracic and lumbar spine showed a well-healed lumbar scar from the previous surgery and mild pain in the lumbar region on palpation. There were no rashes, no tender or swollen joints, and no regional adenopathy or edema. Examination of the right leg showed mild erythema and a well-healed scar from the remote bone harvest site.

Computed tomography showed erosive changes at the end plates adjacent to the L2/3 disk. Magnetic resonance imaging demonstrated fluid signal intensity within the L2/3 disk and bone marrow replacement adjacent to it (Figure 1). The imaging findings were reported as consistent with diskitis. Blood cultures recovered gram-negative aerobic bacteria in five of five sets that were not immediately speciated.

The patient had been in Italy for the previous five months. On further questioning, we found that she had spent most of her time in the province of Calabria and had consumed raw and unpasteurized goat milk and cheeses from local farmers.

A provisional diagnosis of brucellosis was made, and the patient was given gentamicin, 3.5 mg/kg total daily dose, plus doxycycline, 100 mg orally twice a day. The National Reference Laboratory in Winnipeg, Manitoba, confirmed *Brucella melitensis* from agar subcultures recovered in the original blood cultures. The antibiogram showed a strain susceptible to doxycycline, ceftriaxone, ciprofloxacin and rifampin. Gentamicin was replaced with rifampin, 900 mg orally once daily, on day 9 because of aminoglycoside nephrotoxicity. The patient developed intractable vomiting with the combination of doxycycline and rifampin. Because of the multiple drug intolerances, advice was sought from a clinical authority on brucellosis. On day 25, the patient was given tigecycline, 50 mg intravenously twice a day, and ciprofloxacin, 500 mg orally twice a day, for a six-week period. She tolerated this regimen well and her back pain resolved. After six weeks, her medication was changed to doxycycline 100 mg and ciprofloxacin 500 mg, both orally twice a day, for an additional six weeks.

KEY POINTS

- Brucellosis is primarily a zoonotic infection that is rare in Canada and most commonly acquired after consumption of unpasteurized milk and foodstuffs.
- Although the presentation of brucellosis can vary, it usually presents with high fever; the development of focal disease (e.g., osteoarticular) is common.
- Standard treatment is a prolonged course of doxycycline plus rifampin.

Discussion

Human brucellosis is a zoonotic infection, also known as undulant fever and Malta fever. It is rare in Canada, with about eight instances reported annually.[1,2] There have been few endemic cases reported, historically mostly in northern First Nations populations from consumption of caribou. Canada reported eradication of bovine

brucellosis in 1989.[3] In contrast, in the Middle East, the Mediterranean region, western Asia, Africa and Latin America, brucellosis remains an endemic zoonotic infection of humans. The proliferation of international travel and globalization has made brucellosis, not uncommonly, an imported disease in the developed world.

Brucellosis is characterized by high fever in almost all patients (91%) and is irregularly accompanied by weight loss, night sweats, arthralgia and fatigue.[4] It should be considered in the differential diagnosis of fever of unknown origin. In the acute phase, the fever often exceeds 39°C and occurs during periods of bacteremia.

The infection commonly localizes hematogenously and then manifests focal symptoms consistent with the site of localization. These sites are commonly osteoarticular (28% of instances; vertebral sites comprise over 40% of these), but can also be found in the genitourinary system, central nervous system and the endocardium.[4] There are three main types of osteoarticular infection: peripheral arthritis, sacroiliitis and suppurative spondylitis.[4]

Focal disease is associated with a less favourable prognosis. Overall mortality is low, ranging from less than 2% to 5%, and is usually a result of endocarditis or neurologic complications of abscess or meningoencephalitis.[4] The risk of localization increases with the duration of infection; prompt intervention is therefore important.

Microbiology

Brucella is a genus of gram-negative aerobic coccobacilli composed of seven species, four of which have moderate to substantial human pathogenicity. *Brucella suis* (from pigs) and *B. melitensis* (from sheep) have the highest human pathogenicity. *Brucella abortus* (from cattle) and *Brucella canis* (from dogs) have moderate pathogenicity. Other domesticated placental mammals such as goats may be infected.

Infection with *Brucella* is most commonly due to ingestion of raw meat or unpasteurized dairy products.[5] Other modes of infection include aerosol inhalation, passage through the conjunctiva and via open wounds.

Brucellosis is one of the most common laboratory-acquired infections.[6] A number of factors contribute to the risk of an accidental exposure to *Brucella*. Laboratories may lack experience working with the organism. In addition, the organism is often "unknown" when the sample arrives for analysis. Work may be performed on an open bench before the sample is recognized as a gram-negative rod. Certain characteristics of the bacterium, such as its low infectious dose and the fact that it is easily aerosolized, also contribute to the risk of infection with the organisms in a laboratory setting. The pathogen has the capacity to reside intracellularly within macrophages and possesses a variety of mechanisms to evade host immunity that are beyond the scope of this report but well described elsewhere.[4]

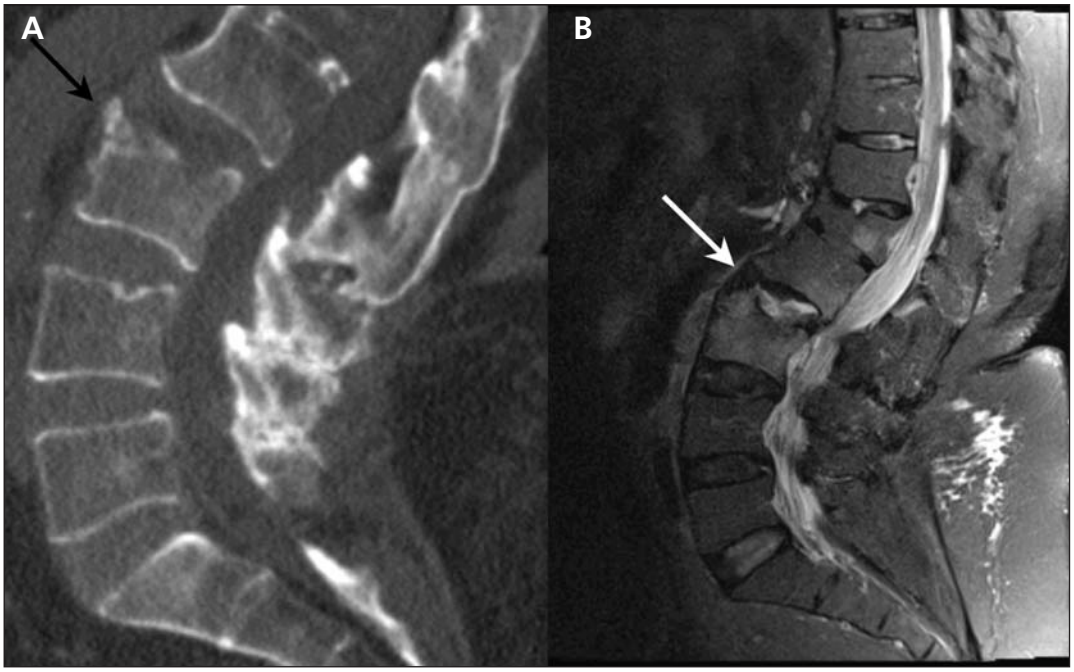

Figure 1: (A) Sagittal computed tomographic reconstruction of the spine of a 68-year-old woman with lower back pain showing erosive changes at the superior end plate of L3 (black arrow). (B) Sagittal T_2 fat-saturated magnetic resonance image showing fluid signal intensity within the L2/3 (white arrow) disk with high signal intensity in the adjacent vertebral bodies.

Diagnosis

Definitive diagnosis of brucellosis is usually made by blood culture, although the organism may be recovered from other sterile sites such as bone marrow. Cultures from aspirations or biopsies of localized disease may also provide positive identification. The rate of isolation ranges from 15% to greater than 90% depending on the methods used.[4] *Brucella* is a fastidious organism, and often weeks are required for positive cultures to be obtained. Identification of focal disease is aided by the use of radiologic imaging. Rapid serological tests may be useful but do not replace the need for cultures.[7] Definitive speciation is usually performed at a reference laboratory. Practitioners should inform laboratory staff of suspected brucellosis. Prolonged incubation is necessary to facilitate diagnosis, and vigilance in handling the specimens is required. The pathogen is considered to require level 3 biosafety precautions in laboratory protocols.

Treatment

There is no widely accepted regimen for treating brucellosis, and a variety of antimicrobial agents have been reviewed.[8] Doxycycline plus rifampin or streptomycin is recommended by the World Health Organization.[9] Fluoroquinolones plus rifampin have been shown to be of equal efficacy.[4] Doxycycline–rifampin may be less effective in patients with spondylitis. An equally efficacious combination is oral doxycycline in combination with either intramuscular streptomycin or intravenous gentamicin.[10] Ceftriaxone is a poor option in the treatment of brucellosis.[11] The duration of doxycycline–rifampin therapy is 6 weeks.[4] Brucellosis is associated with high rates of relapse if monotherapy is used or if the diagnosis is delayed. Focal disease may require surgical treatment to improve the prognosis.

The clinical course presented here is interesting in that the patient's adverse reactions to the traditional drugs used for the treatment of brucellosis (i.e., doxycycline, rifampin and gentamicin) led to the use of the novel combination of tigecycline and ciprofloxacin as induction therapy for brucellosis. In vivo data on the clinical efficacy of tigecycline in treatment of brucellosis are lacking; however, tigecycline has shown greater antimicrobial action against *Brucella* species than doxycycline in vitro.[12]

This case report also highlights the importance of thoroughly exploring the patient's exposure history. When infectious disease is suspected, a detailed interview should be conducted, focusing not only on place and duration of travel, movements within rural and urban areas, and exposure to arthropod vectors, but also questions related to exposure to water sources, contact with sick animals, persons or communities, and ingestion of types of food predicated on local customs and patterns specific to the ethno-geographic setting. The possibility of infectious disease should be considered in returning travellers who present with fever, not only in those returning from the tropics, but also in travellers returning from areas of emerging infections or where zoonotic diseases are endemic.

References

1. *Brucellosis*. Ottawa (ON): Public Health Agency of Canada; 2006. Available: http://dsol-smed.phac-aspc.gc.ca/dsol-smed/ndis/disease2/bruc_e.html (accessed 2009 Sept. 29).
2. Chan J, Baxter C, Wenman W. Brucellosis in an Inuit child, probably related to caribou meat consumption. *Scand J Infect Dis* 1989;21:337-8.
3. Corbel MJ. Brucellosis: an overview. *Emerg Infect Dis* 1997; 3: 213-21.
4. Pappas G, Akritidis N, Bosilkovski M, et al. Brucellosis. *N Engl J Med* 2005;352:2325-36.
5. Acha PN, Szyfres B. *Zoonoses and communicable diseases common to man and animals*. 3rd ed. Washington (DC): Pan American Health Organization; 2001.
6. Pike RM. Laboratory-associated infections: summary and analysis of 3921 cases. *Health Lab Sci* 1976;13:105.
7. Young EJ. Serologic diagnosis of human brucellosis: analysis of 214 cases by agglutination tests and review of the literature. *Rev Infect Dis* 1991;13:359-72.
8. Skalsky K, Yahav D, Bishara J, et al. Treatment of human brucellosis: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2008;336:701-4.
9. Corbel MJ. *Brucellosis in humans and animals*. Geneva: World Health Organization; 2006.
10. Hasanjani Roushan MR, Mohraz M, Hajiahmadi M, et al. Efficacy of gentamicin plus doxycycline versus streptomycin plus doxycycline in the treatment of brucellosis in humans. *Clin Infect Dis* 2006;42:1075.
11. Lang R, Dagan R, Potasman I, et al. Failure of ceftriaxone in the treatment of acute brucellosis. *Clin Infect Dis* 1992;14:506.
12. Turan H, Hande A, Ozlem K, et al. In vitro antibacterial activity of tigecycline in comparison with doxycycline, ciprofloxacin, and rifampin against *Brucella* spp. *Int J Antimicrob Agents* 2007;30:186-7.

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