Brucellosis in a Singaporean with prolonged fever

Seow C J, Barkham T, Wong P M, Lin L, Pada S K, Tan S H

ABSTRACT

Brucellosis, a zoonotic disease of worldwide distribution, is common in many developing countries as well as in countries of the Mediterranean basin. We report brucellosis in a 52-year-old man, who had a recent travel history to Saudi Arabia, and who presented with prolonged fever and deranged liver enzymes. In view of the rarity of brucellosis and its potential life-threatening complications, patients returning from an endemic country need to be questioned for possible *Brucella* exposure, to ensure that diagnostic tests and treatment are carried out in a timely fashion. In addition to notifying the authorities, the clinician should also warn the laboratory early as cultures of brucellosis are highly transmissible and are one of the most common laboratory-acquired infections.

Keywords: *Brucella melitensis*, *Brucella abortus*, Brucellosis, laboratory-acquired infection

INTRODUCTION

Brucella spp., the causative agent of brucellosis, is a Gram-negative intracellular coccobacillus discovered by David Bruce in 1887. Historically, it has also been called undulant fever, Bang's disease, Gibraltar fever, Mediterranean fever and Malta fever. An increasingly complex pattern of strains has emerged with the identification of *Brucella (B.) abortus*, *B. melitensis*, *B. suis*, *B. neotomae*, *B. ovis* and *B. canis*, and more recently, other types infecting marine mammals.[1] Four species, *B. melitensis*, *B. abortus*, *B. suis* and *B. canis*, are known to cause disease in humans. The true incidence of human brucellosis is unknown, largely due to under-reporting. The incidence in endemic areas varies widely, from < 0.01 to > 200 per 100,000 population.[2] The incidence of brucellosis varies, depending on the social and cultural characteristics of the local population, and the intensity of the local brucellosis eradication programmes. Consumption of contaminated foods, occupational contact and inhalation of infectious particles remain the major routes of infection. The incubation period is typically

3–60 days, with air-borne brucellosis having a shorter incubation period than food-borne brucellosis. Like many developed countries, Singapore has successfully eradicated brucellosis by means of intensive livestock control measures. Over the past decade, there have been only a handful of cases in Singapore, with the last known reported case of brucellosis in Singapore occurring in 1998.[3] However, we recently encountered a patient who was diagnosed with brucellosis three months after returning from Saudi Arabia.

CASE REPORT

A 52-year-old Malay man presented with a three-week history of fever and cough. He had been previously well, with a background history of hypertension and hyperlipidaemia. In the preceding month, he had experienced intermittent fevers which had become more persistent, but which responded to antipyretics. He denied headache, photophobia or neck stiffness. There was no shortness of breath or skin lesion. Of note, he had gone on a pilgrimage to Mecca in Saudi Arabia three months earlier and had ingested unpasteurised camel's milk during the trip. He was a chronic smoker of more than 40 years, did not consume alcohol and denied extramarital sexual activities. On physical examination, he looked well, had a temperature of 38°C and had normal cardiorespiratory, gastrointestinal, neurological and musculoskeletal examinations. He had no evidence of conjunctivitis or palpable peripheral lymphadenopathy.

The common infective causes of a patient with such features include bacteraemia, typhus, tuberculosis, infective mononucleosis and leptospirosis. Pneumonia and intra-abdominal sepsis were also considered. Investigations revealed a white cell count of 5.4 (reference range [RF] 4.0–10.0) × 10^9/L (neutrophils 67.7%, lymphocytes 26%); haemoglobin 13.2 (RF 13.0–17.0) g/dL; platelets 258 (RF 160–390) × 10^9/L; creatinine 92 (RF 55–100) μmol/L; albumin 43 (RF 35–48) g/L; total bilirubin 12 (RF 3–24) μmol/L; alanine aminotransferase 132 (RF 7–36) U/L; aspartate aminotransferase 91 (RF 15–33) U/L; alkaline phosphatase 351 (RF 38–126) U/L; C-reactive protein 49.5 (RF 0–5) mg/L; procalcitonin < 0.5 ng/mL. Urine microscopy and culture were normal. Sputum smear for acid-fast bacilli was negative. Blood

Department of General Medicine, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433

Seow CJ, MBBS, DFD Medical Officer

Wong PM, MBBS, MRCP Medical Officer

Tan SH, MBBS, FRCP, FAMS Senior Consultant

Department of Laboratory Medicine

Barkham T, MBBS, MSc, FRCPath Senior Consultant

Department of Infectious Disease

Lin L, BSc, MSc, MD Consultant

Pada SK, BSc, MBBS Registrar

Correspondence to Dr Seow Cherng Jye Tel: (65) 9125 8032 Fax: (65) 6357 7588 Email: cherngjye. seow@mohh.com.sg

films for malarial parasites and hepatitis A, hepatitis B and hepatitis C serology were negative.

The chest radiograph was normal. The ultrasonography of the hepatobiliary system showed multiple gallstones with no dilatation of the common bile duct and no ultrasonographical features of acute cholecystitis. Computed tomography (CT) of the chest, abdomen and pelvis did not show focal lesions except for a few tiny hypodensities scattered throughout the spleen that were too small to characterise. Magnetic resonance cholangiopancreatography (MRCP) demonstrated cholelithiasis with no evidence of common bile duct stones or biliary ductal dilatation. Transthoracic two-dimensional echocardiogram showed no evidence of endocarditis.

Initially, the patient was treated empirically with amoxicillin-clavulanic acid. The antibiotics were changed to intravenous ceftriaxone and oral metronidazole on the second day of admission as the patient was still experiencing high fever, chills and rigors, with a maximum temperature of 39.4°C. Oral doxycycline was added to cover for rickettsial infection. The temperature settled 48 hours later. Leptospiral and rickettsial serology were both negative. On the fifth day of admission, a blood culture taken on the day of admission grew Gram-negative rods, which were identified as a *Brucella* spp. The antibiotics were changed to intravenous gentamicin (5 mg/kg/day) and oral doxycycline was continued. The brucella agglutination test was ≥ 1/320 for both *B. melitensis* and *B. abortus*. At the same time, an advisory was sent out to the healthcare professionals in the hospital to highlight the possibility of brucellosis in returning pilgrims and alert laboratory staff of body fluids or tissue specimens of patients suspected to have brucellosis, so that appropriate safety measures could be taken to prevent laboratory-acquired brucellosis. The patient completed seven days of intravenous gentamicin, and continued to be treated with oral doxycycline for a total of six weeks.

DISCUSSION

Brucellosis, the commonest zoonotic infection worldwide, is transmitted to humans mainly through direct animal contact, ingestion of infected, unpasteurised dairy products or inhalation of infectious particles. The geographical distribution of the disease is in constant flux due to socioeconomic and political reasons, coupled with the evolution of international travel. Ironically, areas traditionally considered to be endemic, such as France, Israel, and most of Latin America, have achieved control of the disease. However, new foci of human brucellosis have emerged, particularly in central Asia, while the situation in certain countries of the Near East, like Syria, is rapidly worsening. Furthermore, the disease is still present, in varying trends, both in European countries and in the United States.[4] Its potential use as a bioterrorism agent has been recognised recently as it is easily produced in a steady aerosolised form.[5]

Brucellosis is a well-documented cause of fever of unknown origin, with varied and nonspecific symptoms. However, the diagnosis is infrequently considered in non-endemic regions, especially when a travel history is not elicited. The onset of fever may be abrupt or insidious, developing over several days to weeks. Patients tend to have a multitude of nonspecific complaints. Physical findings in the early course of the disease, when present, are usually limited to minimal lymphadenopathy and occasional hepatosplenomegaly. If left untreated, virtually any organ system can be involved. In one report of 530 cases studied prospectively, 32% developed a focal complication,[6] the most common of which were sacroiliitis (20%–30%), epididymo-orchitis (2%–40% of males) and meningitis (1%–2%). Although rare, left-sided endocarditis (1%) remains the major cause of mortality in patients with brucellosis.

The initial evaluation of a febrile patient should take into account both local and travel-related pathogens. The importance of a travel history is clearly emphasised in our case. Brucellosis should be considered in an individual with an unexplained chronic fever and nonspecific complaints, and who has had contact with animal tissues or ingested unpasteurised dairy products. Ideally, the diagnosis is made by isolation of the organism from cultures of blood or other sites, especially bone marrow or liver biopsy specimens. However, in a large series, blood cultures were positive in only 80% of the initial infections.[7] In this setting, *Brucella* serology is useful, where an agglutination titre of ≥ 1:160 is considered positive. A convalescent serology for confirmation is usually required. Early treatment is believed to shorten the duration of the symptoms, prevent relapse, and avert complications such as arthritis, sacroiliitis, spondylitis, encephalitis, endocarditis, epididymo-orchitis and abortion.[8] Undiagnosed and untreated brucellosis can be symptomatic for months, and it is well known that some previously-treated patients may relapse.[7] Routine laboratory studies are nonspecific. The commonest haemotological abnormalities are relative lymphomonocytosis (71.6%) and anaemia (36.6%). Pancytopenia can occur with a long-standing illness. Minor disturbances in hepatic enzymes are relatively common.[9] While studies such as radiographs, bone scans, CT, magnetic resonance imaging and echocardiography

may be helpful in locating focal disease, they do not provide a definitive diagnosis. Biopsy of a lesion may be required to differentiate it from other infectious processes such as tuberculosis.

Although human brucellosis has been recognised for 121 years, it remains difficult to treat.[9] The first-line treatment regimen is doxycycline 100 mg twice daily for six weeks, with additional intravenous gentamicin 5 mg/kg/day for the first seven days. The World Health Organization recommends the use of a combination of oral doxycycline 100 mg twice daily and rifampicin 600–900 mg daily for the entire six weeks. However, this is associated with a relapse rate of 4.6%–24%.[10,11] A recent study by Skalsky et al concluded that a triple regimen of doxycycline, aminoglycoside and rifampicin is the optimal combination, (relative risk of failure compared with doxycycline–aminoglycoside 0.40, 95% confidence interval 0.20–0.79) with aminoglycoside administered in the first 7–14 days and doxycycline–rifampicin continued for 6–8 weeks.[10] However, the main difference was seen only in therapeutic failure; notably, the confidence intervals were wide and the number-needed-to-treat was 10 (range 6–33), with triple therapy to prevent one therapeutic failure compared with dual therapy. Given that only 2.2% experienced therapeutic failure when using doxycyclin and gentamicin alone, triple therapy results in a small overall benefit.[10] These results, hence, have to be interpreted in the light of the potential risk of added toxicity when using triple regimens for treatment. About 5%–10% of the patients relapse after the therapy, with most relapses occurring within three months of stopping the therapy.[12,13] If a relapse of brucellosis does occur, the patient should be carefully evaluated for the presence of focal disease that may need surgical intervention. If surgical therapy is not warranted, one may want to use an alternative treatment regimen. However, the development of *in vitro* resistance to antimicrobial agents by *Brucella* spp. is extremely rare, and a second course of treatment with the initial regimen may be effective.

In our patient, it took more than five days before a diagnosis of brucellosis was made and the appropriate antibiotic therapy instituted. Cholestatic liver dysfunction deterred us from using rifampicin. The doxycycline–gentamicin combination treatment was instituted for our patient and is regarded, in general, as the optimal therapy for brucellosis. Failure to consider brucellosis in this patient had inadvertently led to the exposure of our laboratory staff to this highly infectious agent. As it is almost unheard of in Singapore in recent times, most laboratory staff would not initially consider *Brucella* spp. without some clinical epidemiological clues, so extra protective measures might not be implemented until after

significant exposure. Brucellosis has been considered the most common laboratory-acquired bacterial infection.[14] Despite high standards of biosafety, exposures and laboratory-acquired infections continue, especially in non-endemic countries. Aerosol transmission generated while manipulating the organism is the proposed route of transmission. *Brucella* spp. are highly infectious because the infection dose by an aerosol is only 10–100 organisms. Laboratory staff needs to be alerted to the possibility of the disease at the earliest instance. The laboratory staff that had been in the same room were seen in a special clinic and offered post-exposure prophylaxis with doxycycline and rifampicin. They were also subjected to serosurveillance for six months at two-weekly and subsequently monthly intervals. Fortunately, no one seroconverted.

In conclusion, brucellosis is an uncommon cause of infectious disease in Singapore. Vigilance and a high index of suspicion are required when treating individuals with unexplained fever, and who have been exposed to unpasteurised milk products and/or with a recent travel history to an endemic area.

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