CASE REPORT

BRUCELLOSIS: A RE-EMERGING DISEASE IN THAILAND

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Abstract. Brucellosis is a zoonotic disease prevalent in many countries, but it has been reported only once in Thailand, 36 years ago. We describe here two consecutive cases of brucellosis in Bangkok, Thailand. Both cases presented with prolonged fever and weight loss. Blood cultures taken from 2 patients yielded *Brucella melitensis*. The slide agglutination test of blood samples were also positive, with a titer of 1:64 for antibodies to *Brucella*. The first patient responded to a combination of doxycycline, gentamicin, and ciprofloxacin; the other responded to doxycycline and rifampicin. Brucellosis is a potential public health threat, therefore, preventive measures should be actively implemented. This clinical syndrome should be included in the differential diagnosis of patients presenting with prolonged fever, particularly those with contact to animals which could serve as reservoirs.

Brucellosis, a zoonotic disease of worldwide distribution, is a systemic infection caused by facultative intracellular bacteria of the genus *Brucella* involving many organs and tissues (Young, 1995). Brucellae are gram-negative coccobacilli that are nonmotile and do not form spores (Edward, 2000). *Brucella mellitensis* was first discovered in the spleens of victims of Malta fever by Bruce in 1887 (Bruce, 1887). Various Brucella species affect sheep, goats, cattle, deer, pigs, dogs, and several other animals. The pathogenic organisms are *Brucella melitensis, Brucella suis, Brucella abortus,* and *Brucella canis* (Edward, 2000). In animals, brucellosis is a chronic infection that persists for life. Localization of brucellae within the reproductive organs accounts for the major manifestations: abortion and sterility (Enright, 1990). Humans are generally infected in one of three ways: ingestion of contaminated animal products, inhalation, or direct contact via skin abrasion. The most common way to be infected is by consuming contaminated milk products, such as unpasteurized milk or cheeses. Inhalation of brucella organisms is not a common route of infection, but it can be a significant hazard for people in certain occupations, such as those who work in laboratories where the organism is cultured (Young, 1975). In Thailand, Visudhiphan and Na-Nakhon reported the first case of brucellosis in 1970; that patient presented with prolonged fever and hepatosplenomegaly, *Brucella melitensis* was identified from blood and bone marrow cultures (Visudhipan and Na-Nakorn, 1970). No additional cases have been reported since then. Here, we report two cases of brucellosis that presented with prolonged fever.

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Case report 1

A 52-year-old Thai man living in Tha-Muang district, Kanchanaburi Province was hospitalized on July 21, 2003 with fever, chills, malaise, and sweating for 2 months. He also had symptoms of anorexia and weight loss of 7 kg during the illness. He had experienced no headaches, abdominal pain, or joint pain. Three weeks before admission, he developed severe low back pain aggravated by movement, without a prior history

of trauma. He had not been taking any traditional or herbal medications. He had no habits of drinking alcohol or smoking. He was admitted to Ratchaburi General Hospital from June 29, 2003 to July 12, 2003, and then referred to Ramathibodi Hospital for further investigation and management. Additional history was obtained upon admission to Ramathibodi Hospital. He had a history of drinking goats' milk twice a week for a month before the illness. These milk products were neither pasteurized nor sterilized, but only warmed for five minutes.

Physical examination revealed a body temperature of 38.5ºC, blood pressure of 130/80 mm/Hg, pulse rate of 90 per minute, and respiratory rate of 18 per minute. He was mildly pale, but no jaundice was observed. There was bilateral cervical lymph node enlargement, approximately 0.3-0.5 cm in diameter, without any signs of inflammation. The cardiovascular and respiratory systems were unremarkable. Abdominal examination revealed mild tenderness in the right upper quadrant, but neither liver nor spleen were palpable. Initial investigation revealed a hemoglobin concentration level of 9.76 g/dl, 4,590 white blood cells/mm^3, 60% neutrophils, 35% lymphocytes, 4% monocytes, 1% basophils, and 197,000 platelets/mm^3. Red blood cell morphology showed anisocytosis 1+, microcyte 1+, hypochromia 1+, ovalocyte 1+, and few cells with polychromasia. The erythrocyte sedimentation rate was 19 mm/hour. The liver function test revealed an increased serum alkaline phosphatase level of 453 U/l, GGT 318 U/l, AST 151 U/l, total protein 76.1 g/l, albumin 34.7 g/l, and total bilirubin 1.0 mg/dl. He had a normal chest roentgenogram. Computerized tomography scan of the abdomen revealed mild hepatosplenomegaly without focal masses or abscesses. There was no para-aortic lymphadenopathy or ascites. Magnetic resonance imaging of the thoraco-lumbrosacral spine revealed diffuse osteoporosis with mild spondylotic changes and mild bulging of the L4-5 disc. There was no sign of an epidural abscess or osteomyelitis. Three consecutive blood cultures by the automated incubation method (BacT/Alert) yielded pale stained gram-negative coccobacilli at 72 hours after blood collection. The organism was identified by standard laboratory procedures (Daniel, 1999). The patient was then treated with a combination therapy of 200 mg/day of doxycycline orally, 240 mg/day of gentamicin intravenously, and 1,000 mg/day of ciprofloxacin orally. The organism was identified as *Brucella meilitensis* based on biochemical testing. It was susceptible to ampicillin, cephalosporin, ofloxacin, gentamicin, and cotrimoxazole. The slide agglutination testing of the blood sample had a positive titer of 1:64, for antibodies to brucella. The patient underwent liver biopsy on the seventh day of admission; the liver tissue smear for Gram stain found numerous small gram-negative coccobacilli. The histopathology of the liver revealed nonspecific hepatitis and scattered microgranuloma as show in Fig 1. The result of the bone marrow aspiration revealed a reactive bone marrow. The result of both liver tissue and bone marrow cultures yielded negative results. His fever subsided on the fifth day of therapy and the

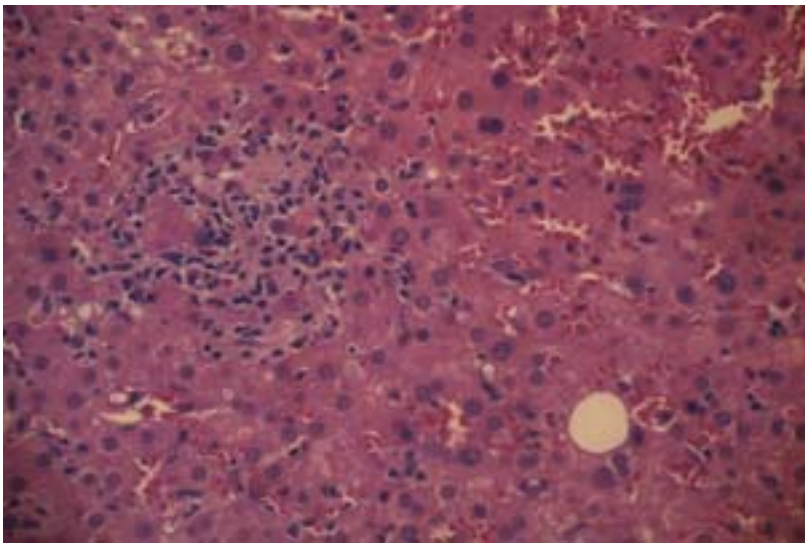

Fig 1–Microgranuloma. Liver histopathological finding. H&E. x400.

low back pain gradually improved.

Case report 2

A 37-year-old-man, an architect in Bangkok, was hospitalized on May 10, 2003 because of prolonged fever for two months. He had been somewhat healthy until two months before this admission, when he experienced low grade fever, malaise, anorexia, and loose stools 1-2 times daily. Physical examination on the fifth day of illness was unremarkable. Initial investigation showed a hemoglobin level of 13 g/dl, 44% hematocrit, 5,720 white blood cells/mm^3, 54% neutrophils, 40% lymphocytes, 6% monocytes, and 240,000 platelets/mm^3. He was prescribed 400 mg oral ofloxacin daily. His symptoms gradually improved after 5 days of therapy and ofloxacin was continued for a total of 14 days. Previously, on April 18, 2003, the patient was admitted to a private hospital with repeated episodes of high grade fever and anorexia. Physical examination revealed a body temperature of 39ºC, blood pressure of 110/90 mm/Hg, pulse rate of 80 per minute and respiratory rate of 20 per minute. He had neither paleness nor jaundice. There was no lymphadenopathy. The liver and the spleen were unremarkable. Initial investigation revealed a hemoglobin concentration of 11.5 g/dl, 40% hematocrit, 6,940 white blood cells/mm^3, 58% neutrophils, 35% lymphocytes, 7% monocytes and a normal platelet count. The liver function test indicated a serum alkaline phosphatase level of 75 U/l, AST 38 U/l, ALT 40 U/l, total protein 68 g/l, albumin 38 g/l, and total bilirubin 0.4 mg/dl. Urinalysis and chest roentgenography were within normal limits. The patient was started on ceftriaxone 2 grams daily. On the fourth day of admission, all three blood cultures grew gram-negative coccobacilli, but the species of the pathogen could not be identified. Gentamicin 1 mg/kg every 8 hours was given along with ceftriaxone. Ultrasound of the whole abdomen showed a moderately distended gall bladder with multiple stones. On the tenth day of admission, the bacteria grown from the blood cultures was identified as *Neisseria* species, and this was sent to the Microbiology Laboratory of Ramathibodi Hospital for further identification. The three blood cultures were repeatedly performed, but yielded negative results. The fever still persisted, but he was able to return to work. Upon discharge on April 29, 2003, he was given ceftriaxone 2 grams daily as an out-patient case for 14 days, but his symptoms did not abate. Five days before the second admission (May 10, 2003), he developed painful, enlarged left submandibular and right occipital lymph nodes of 0.5 to 1 cm in diameter. A complete blood count revealed a hemoglobin level of 10.4 g/dl, 34% hematocrit, 6,490 white blood cells/mm^3, 56% neutrophils, 40% lymphocytes, 4% monocytes, and 325,000 platelets/mm^3. An erythrocyte sedimentation rate was 36 mm/hour. On the second day of this admission, the Microbiology Laboratory of Ramathibodi Hospital reported the bacterium was indeed *Brucella melitensis*. The susceptibility test indicated sensitivity to ampicillin, cephalosporin, ofloxacin, and gentamicin. Additional history was obtained. He had a history of drinking goat's milk one month before this illness. The patient was started on a combination of doxycycline 200 mg and rifampicin 600 mg daily for a duration of six weeks. His symptoms gradually subsided on the fifth day after starting therapy.

In Thailand, brucellosis is considered a rare etiology of chronic fever of unknown origin. To the best of our knowledge, only one patient was reported from Siriraj Hospital in 1970 that was documented in MEDLINE database (Visudhipan and Na-Nakorn, 1970); this is the second report in our country. Our first patient presented with chronic fever and low back pain. Osteoarticular complications are common in brucellosis, having been reported in 20% to 60% of cases (Rose-Querol, 1957). The spectrum of bone and joint lesions includes arthritis, spondylitis, osteoarthritis, tenosynovitis, and bursitis (Mausa *et al*, 1987). Sarcroilitis is the most commonly reported complication (Gutuzzo *et al*, 1982; Khateeb *et al*, 1990). We suspected he might have osteoarticular complications but neither vertebral osteomyelitis nor paravertebral abscess could be definitely detected by MRI spine. This symptom subsided after starting antibiotic therapy. In 1986, the World Health Organization recommended the use of doxycycline (200 mg/day) in combination with rifampicin (600 to 900 mg/day), both administered for 6 weeks, as a combination of choice (Joint FAO/WHO Expert Committee on Brucel-

losis, 1986). Subsequent studies comparing doxycycline and rifampicin to doxycycline and streptomycin concluded that the latter treatment is more effective, especially for patients with complications such as spondylitis (Ariza *et al*, 1992; Luzzi *et al*, 1993). Although most studies had employed streptomycin as the preferred aminoglycoside, there was a compelling reason to use gentamicin instead.

The second case experienced chronic fever without localizing signs, which was partially improved with short courses of a third generation cephalosporin and quinolone. According to a published report, activity of cephalosporin against brucella is variable, and *in vivo* sensitivity should be ensured (Lang and Dagan, 1992). Furthermore, *Brucella melitensis* is an intracellular organism, so cephalosporin is not recommended. The use of quinolone antibiotics has been disappointing despite *in vitro* activity and good penetration into cells (Lang and Rubinstein, 1992). The partial response of our patient to quinolone emphasized the discordances between *in vitro* and clinical efficacy of this agent for brucellosis. Subsequently, this patient gradually improved with a combination of doxycycline plus rifampicin.

After reporting the cases to the Ministry of Public Heath, a field epidemiological investigation team conducted a serological survey in Ratchaburi Province. In July 2003, the Weekly Epidemiological Surveillance Report from the Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health reported the outcome of the investigation that 247 of 365 goats' blood samples (67.7%) showed a positive serology for brucella in the Suan Phung district, Ratchaburi Province (Bureau of Epidemiology, 2003). Urgent measures to control disease in animals were implemented.

Brucellosis is potentially a public health threat, since goat's milk is gaining more popularity among certain groups of people, therefore preventive measures *ie*, control and elimination of the infected domestic goat, and better sanitation, should be implemented early, and physicians should keep this in mind when evaluating patients presenting with prolonged fever in this area.

REFERENCES

Ariza J, Gudiol F, Pallares R, *et al*. Treatment of human brucellosis with doxycycline plus rifampicin or doxycycline plus streptomycin. *Ann Intern Med* 1992; 117: 25-30.

Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health Thailand. *Weekly Epidemiol Surv Rep* 2003; 34: 495-8.

Bruce D. Notes on the recovery of a microorganism in Malta fever. *Practitioner* 1887; 39: 161.

Daniel SS, Jane DW. Brucella. In: Patrick RM, Ellen J, Michael AP, eds. Manual of clinical microbiology. Washington, DC: American Society for Microbiology. 1999: 625-31.

Edward JY. Brucellosis. In: Gerald LM, John EB, Rapheal D, eds. Principle and practice of infectious disease. Churchill Livingstone, 2000: 2386-93.

Enright FM. The pathogenesis and pathobiology of Brucella infection in domestic animals. In: Nielson K, Duncan JR, eds. Animal brucellosis. Boca Raton, Fla: CRC Press, 1990: 301-20.

Gutuzzo E, Alarcon GS, Bocanagra TS, *et al.* Articular involvement in human brucellosis: a retrospective analysis of 304 cases. *Semin Arthritis Rheum* 1982; 12: 245-55.

Joint FAO/WHO Expert Committee on Brucellosis (Sixth Report). Geneva: World Health Organization, 1986.

Khateeb MI, Araj GF, Majeed SA, *et al.* Brucella arthritis: a study of 96 cases in Kuwait. *Ann Rheum Dis* 1990; 49: 994-8.

Lang R, Dagan R, Potasman I, *et al.* Failure of ceftriaxone in the treatment of acute brucellosis. *Clin Infect Dis* 1992; 37: 1831-4.

Lang R, Rubinstein E. Quinolone for the treatment of brucellosis. *J Antimicrob Chemother* 1992; 29: 357-63.

Luzzi GA, Brindle R, Sockett PN, *et al*. Brucellosis: imported and laboratory acquired case, and an overview of treatment trials. *Trans R Soc Trop Med Hyg* 1993; 87: 138-41.

Mausa AR, Muhtaseb SA, Almudalla DS, *et al*. Osteoarticular complications of brucellosis: a study of 169 cases. *Rev Infect Dis* 1987; 9: 531-43.

Rosed-Querol J. Osteoarticular sites of brucellosis. *Ann Rheum Dis* 1957; 16: 63-8.

Visudhiphan S, Na-Nakorn S. Brucellosis first case report in Thailand. *J Med Assoc Thai* 1970; 53: 289-93.

Young EJ. An overview of human brucellosis. *Clin Infect Dis* 1995; 21: 283-9.

Young EJ, Suvannoparrat U. Brucellosis outbreak attributed to ingestion of unpasteurized goat cheese. *Arch Intern Med* 1975; 135: 240-3.