

Emergency response to occupational brucellosis in a pharmaceutical manufacturing enterprise

Dear Editor

The authors reported two outbreaks of occupational brucellosis from 2013 to 2015 in the pharmaceutical manufacturing industry.¹ All the infected seven patients showed joint pain, undulant fever, and two of them with vertebral abscess. No patients showed lymphadenopathy and hepatosplenomegaly. It has been described that more than 80% of patients exhibit fatigue, headache, chill, back and joint pain, fever, and night sweat.² Because the workers failed to wear the effective personal protective equipment,¹ they were likely to be easily exposed to the pathogen derived from as many as 120 tons of sheep placenta. Aborted placental and fetal membrane tissues from cattle, swine, sheep, and goats are well-documented sources of human exposure. The typical incubation period takes 1–6 weeks,² so that they should more describe in details when the symptoms appeared after the processing of sheep placenta. A serum agglutination test (SAT) was used to confirm the diagnosis by the authors,¹ but microplate agglutination test can detect the specific antibody of a large number of patients simultaneously using much less amount of blood or bone-marrow samples as compared with SAT.³ Considering the absence of specific clinical manifestations other than the most common symptom of high “spikes” which usually occur in the afternoon, also referred to as abortus/undulant and intermittent fevers,² it is important to perform the pathogen isolation and/or polymerase chain-reaction (PCR) examinations that can amplify the genes-encoding BCSP31 and outer-membrane proteins OMP2/31.² Note that PCR test can be accurately positive only the period of bacteremia. As the first identification of *Micrococcus melitensis* (also known as *Brucella melitensis*) in the middle of 19th century after this infectious disease became popular among British soldiers of the Crimean War, there have been reported the following *Brucella* species; *B melitensis* (goat and sheep), *B suis* (pigs), *B abortus* (buffalo), and *B canis* (dogs).^{1,4} These species preferentially proliferate in the placenta and cause abortion in many kinds of animals, but not in human beings with no clear molecular machinery identified so far. In terms of definitive diagnosis, PCR examinations allow us to identify which species of *Brucella* is responsible for the disease.

In Japan, 13 cases of brucellosis have been documented from 1999 to 2008.³ Considering brucellosis was designated as Category IV Infectious Diseases according to the Japanese

Infectious Disease Law in 1999, it is likely that there are several cases underestimated in terms of the definitive diagnosis before 1999. Among 13 reported domestic cases, while four cases developed as imported infectious disease, nine cases were due to the infection of *B canis* from dogs, which is the typical zoonosis. Unlike China where the number of infectious patients with *B melitensis* rapidly increased to more than 20 000 each year, the rare reported cases occurred with infection with *B abortus* or *B canis* in our country.^{1,3} That is why it is crucial to ask the suspected patients about not only the travel history but also the history of contact with dogs and of consumption of potentially contaminated milk-derived food products. Remarkably, *Brucella* species can survive in the natural cheese for up to 3 months, as shown in Table 1.^{2,5}

Although they did not clearly mention the treatment,¹ the appropriate combination of antibiotics should be determined given the severe cases with endocarditis and sepsis due to *Brucella* infection. Approximately 5% of brucellosis patients died mainly with serious endocarditis when they did not receive the effective treatment.² Since 1986, the combination of doxycycline and rifampicin has been recommended by World Health Organization, but this antibiotics regimen should be replaced by the combination of doxycycline and streptomycin for the following two reasons: firstly, rifampicin can increase the clearance of therapeutically effective doxycycline from the blood; and secondly, the former regimen is not effective for the treatment of vertebral abscess.⁵ Furthermore, *Brucellae* are often sensitive to ampicillin and/or tetracyclines. Moreover, because this pathogen is aerobic, gram negative, and more importantly intracellular, the long-term administration of appropriate several antibiotics should be performed. Otherwise the recurrence is highly likely to occur in brucellosis.

To be sure, the authors emphasized the outbreaks of brucellosis in the occupational settings and the significance to protect workers from the occupational biological hazards in this novel report,¹ which is not familiar to us Japanese medical doctors. However, given how tightly connected we all are in the global international community, we have to recognize that this zoonosis can emerge in our country mainly among overseas travelers. In addition, because of 2020 Summer Olympics which is going to be held in Tokyo and the absence of useful vaccines available for the prevention of brucellosis,

TABLE 1 The persistence period of *Brucella* species

Food/environment	Survival period
Frozen meat	3-6 mo
Salt meat	3 mo
Milk	
(71.1°C)	5-10 s
(38°C)	Up to 9 h
(25-37°C)	24 h
(0°C)	18 mo
Raw cream (4°C)	6 wk
Butter (8°C)	3-4 mo
Natural cheese	10-90 d
Cheddar cheese	6 mo
Exposure to direct daylight	4-5 h
In the soil with 90% moisture	2-3 mo
In the sewage-laden water	3-5 mo
In the miscarried fetus	6 mo

there has been a growing social concern about the terrorist attacks using biochemical weapons including this easy-to-relapse zoonosis.

CONFLICTS OF INTEREST

There are no conflicts of interest to be declared about this letter.

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