Malaysian J Pathol 2019; 41(3) : 359 – 364

CASE REPORT

Cellulitis in human brucellosis: An atypical presentation

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Abstract

Introduction: Brucellosis is a zoonotic disease with variable clinical manifestations and atypical presentation in humans. Human brucellosis cases are not seen often in Malaysia. *Case Report:* This is a case report of 19 years old gentleman who presented with fever, lower limb redness, pain and swelling. He was initially treated as cellulitis. However, based on the recovery of *Brucella melitensis* from his blood culture, he was later diagnosed to have brucellosis. He had a history of consumption of fresh goat's milk and uncooked meat which could have been the possible modes of transmission. *Brucella* serology IgM and IgG were both positive, and anti-*Brucella* immunocapture agglutination test (BrucellaCapt) was also positive with a titer of 1:2560. He was treated with six weeks of oral doxycycline 100 mg twice daily and oral rifampin 450 mg twice daily. *Discussion:* This is a case of human brucellosis with atypical cutaneous involvement.

Keywords: Brucella melitensis, atypical, cutaneous, cellulitis, human brucellosis

INTRODUCTION

Brucellosis is a disease caused by *Brucella melitensis* which is a gram-negative, non-motile and rapidly urease-positive bacillus. Brucellosis can affect any system of the body and present with non-specific symptoms. Transmission to human occurs mainly via consuming unpasteurized contaminated goat's milk or soft cheese that had been infected with *Brucella melitensis*. Symptoms of brucellosis may appear within 1 to 4 weeks or even after months. A study done by Jama'ayah *et al*. showed that seroprevalence of brucellosis in Malaysia among those directly in contact with an infected animal is low which was 5.4%.[1] *Brucella* is also a potential weapon for bioterrorism in view of it is highly infectious via aerosolisation.[2] Here, a case report of human brucellosis in a young adult is depicted.

CASE REPORT

This is a case report of a 19 year-old-male, who presented with a one-week history of fever. The fever was low grade and not associated with chills or rigors. He also complained of bilateral lower limb redness, swelling and pain for six days. There was no relevant history of trauma or insect bite. He denies of any upper respiratory tract or urinary tract infection symptoms. He walked into a general practitioner's office five days prior to admission and was treated as lower limb cellulitis. He was given oral cloxacillin 1-gram four times a day, however, he only took the medication for three days. Premorbidly, he is obese and weighs 130 kilograms.

On admission, he was febrile with a temperature of 38°C and hemodynamically stable with blood pressure of 118/82 mmHg and pulse rate of 87 beats per minute. He was not tachypneic and oxygenation under room air was 99%. He was not septic looking and had a good hydration status. Cardiovascular and respiratory examinations were unremarkable. Examination of bilateral lower limb showed swelling, erythematous skin, warmth, and tenderness from ankle till mid-shin. The power and tone of bilateral lower limbs were good. The capillary refill times were less than 2 seconds.

Blood samples were obtained for investigation and he was started on intravenous (IV) cloxacillin 1-gram four hourly to cover for cellulitis. Laboratory investigation showed the total

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white cell count (WCC) was raised [12 x 10^9/L (reference range: 4-10)]. The C-reactive protein (CRP) level was also markedly raised [59.5 mg/L (<5.0)]. A raised WCC and CRP can point towards an infection.

Two sets of blood culture were sent for investigation. The first set of blood culture showed no growth after five days of incubation. A second set of blood culture obtained on day two of admission due to persistent temperature spiking was positive on day four of incubation. The gram stain showed small gram-negative coccobacilli. It was informed to ward, and IV ceftriaxone 2-gram stat and 1-gram daily started to cover for gram negative sepsis. At 24 hours of incubation, no growth was noted on blood agar, Mac Conkey agar and chocolate agar plates. After 48 hours of incubation, light growth of tiny colonies was seen on blood agar and chocolate agar. Urease was done, and it was rapidly positive. The plates were re-incubated in view of very tiny colonies. After 72 hours of incubation, heavy growth of small grey colonies without hemolysis (Fig. 1) was seen. Proceeded with VITEK 2 GN, the isolate was identified as *Brucella melitensis* with 99% identification. The identification of the isolate was confirmed by a reference laboratory via molecular method. However, the antimicrobial susceptibility testing was not performed for biosafety reason.

When the isolate was identified as *Brucella melitensis*, it was already nine days since admission. The patient was well, and he was already on day nine of IV cloxacillin and day five of IV ceftriaxone. His lower limb swelling, redness and pain had resolved on day three of IV ceftriaxone. Thus, picture of his lower limb cellulitis could not be obtained. Upon further investigation, he admitted to taking fresh goat's milk bought from a shop, in which, he was unsure of its pasteurisation status. He is a grilled skewered meat (satay) hawker and has to taste half-cooked meat while grilling to determine if the skewered meat is ready to be served to customers. Following the blood culture result, his blood was sent for *Brucella* serology, which showed positive *Brucella* IgM and IgG. An anti - *Brucella* immunocapture agglutination test (BrucellaCapt) was also performed and was positive with a high titer of 1:2560.

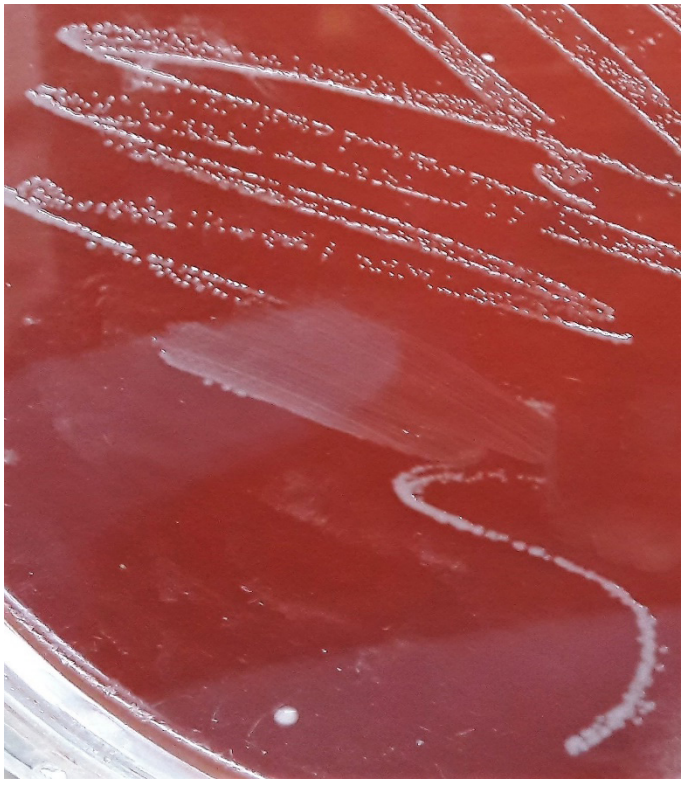

FIG. 1: *Brucella melitensis* colony after 72 hours of incubation on blood agar. Colony size around 1 mm, non-hemolytic, grey to whitish and glistening.

The infectious disease specialist reviewed the patient and he was discharged with six weeks of oral doxycycline 100 mg twice daily and oral rifampin 450 mg twice daily. Echocardiogram and ultrasound abdomen were done as outpatient procedures which were unremarkable. The patient was educated with full explanation regarding brucellosis and the importance of adherence to medication. The patient was given an appointment to be seen again in clinic in six weeks. Unfortunately, he defaulted the clinic follow-up. Upon a phone consultation follow-up, the patient claimed to be well and has completed his six weeks of oral medication as prescribed. A re-appointment was given to which he defaulted as well.

DISCUSSION

Human brucellosis can be caused by different species of *Brucella* with variable pathogenicity resulting in a variety of clinical course of the disease. Cutaneous manifestation in brucellosis is not specific to come to a definitive diagnosis.[3]

Brucellosis is a public health problem and most exposures are occupational related.[1] In Malaysia, reports of human brucellosis are rare. Data from the Report of Morbidity and Mortality for Patients for the year 2004 to 2008 shows that only 19 cases of brucellosis were admitted to Ministry of Health hospitals.[4] Further details of the patient characteristics or clinical presentations were not available. Hartady *et al*. reported a case of brucellosis in a research assistant in veterinary microbiology laboratory. The patient presented with febrile episodes and no skin manifestations noted.[5] Another study by Leong *et al*. reported a large outbreak involving 84 patients (the index patient is the owner of a goat farm, 79 of the patients are customers who consumed goat's milk bought from his farm and 4 patients were laboratory workers involved in handling of samples of the other patients).[6] In this outbreak report, most of the patients had constitutional symptoms, 3 patients had spondylitis, 2 patients had orchitis and 1 patient had infective endocarditis. There was no report of clinical human brucellosis with skin involvement. *Brucella* spp. is transmitted mainly via eating/drinking unpasteurised or raw dairy products.[7] A person could also be infected when they eat undercooked meat of an infected animal. Inhalation is also a route of infection but mainly this is a risk for laboratory workers[8] and those who work in slaughterhouse. Direct contact through skin wound or mucous membrane pose as a risk for those who work closely with animals or those who handle their meats. Infrequent modes of transmission such as via breast milk[9], blood transfusion[10], post bone marrow transplantation[11] and sexual transmission[12] were also reported.

The incubation period of *Brucella* is one to four weeks, but it could be prolonged up to several months. The clinical manifestations are variable and may pose significant issues in coming to a definitive diagnosis based only on history, symptoms, and signs. Clinical presentations may vary from asymptomatic to fatal illness. Patients may present with fever, night sweats, arthralgia, myalgia, malaise, fatigue, anorexia and even depression. The patient may also complain of abdominal pain, and cough. On clinical examination, splenomegaly, hepatomegaly, and lymphadenopathy may be evident. Around 30% of patients will have localised infection. Focal infections can involve musculoskeletal, genitourinary, gastrointestinal, pulmonary, cardiovascular, ocular and central nervous system. Hematological abnormalities could also be seen.[13]

In the literature, dermatological manifestations of brucellosis have been described either as the main presentation of the disease or as part of findings of a more generalised sign and symptoms as shown in Table 1. This is not an exhaustive list of all cases.

The cutaneous manifestation of brucellosis has no typical skin involvement that is pathognomonic. The skin involvement could range from maculopapular rash, morbilliform rash, eczematous rash, vasculitic lesion, ulcerative lesions, psoriatic-like lesion, erythema nodosum-like lesion and many more. However, maculopapular rash is the most commonly described skin manifestation of brucellosis. Brucellosis as an alternative diagnosis to a skin rash should be kept in mind especially in areas of high prevalence and particularly when there is a possible exposure.

In our patient, the only presentation of brucellosis was fever and bilateral leg cellulitis as evidenced by bilateral lower limb swelling, erythematous skin, warmth and tenderness. The diagnosis of brucellosis was not entertained initially until a positive blood culture of *Brucella melitensis* became available. This has led us to question the patient further which revealed more history of possible exposures including handling raw meats, consuming half cooked meat and drinking possibly unpasteurised milk. It is to be noted that the first blood culture obtained from this patient was negative. Bacteremia in

TABLE 1: Case series/report of brucellosis with cutaneous manifestation

Year	Author/ Type of study	Number of subjects	Age (gender)	Cases with skin involvement, n (%)	Types of skin involvement
1989	Ariza *et al*. (case series)[14]	436	-	27 (6%)	- Papulonodular eruption - Erythema nodosum-like lesion - Extensive purpura - Diffuse maculopapular rash
1996	Colmenero *et al*. (case series)[15]	530	-	18 (3.4%)	- Maculopapular or papulonodulary exanthema - Paniculitis
2001	Metin *et al*. (case series)[16]	103	-	14 (13.59%)	- Urticaria-like papules - Erythema nodosum - Primary inoculation abscess - Malar eruption - Psoriasiform lesion - Livedo reticularis - Malar eruption - Eczematous lesion - Palmar erythema
2007	Akcali *et al*. (case series)[17]	140	-	8 (5.71%)	- Maculopapular eruptions - Erythema nodosum–like lesions - Psoriasiform lesions - Palmar erythema - Malar eruption - Palmar eczema
1999	Nagore *et al*. (case report)[3]	-	22 (male)	-	- Leukocystoclastic vasculitis
2000	Milionis *et al*. (case report)[18]	-	49 (male)	-	- Maculopapular rash
2011	Karaali *et al*. (case report)[19]	-	49 (female)	-	- Leukocystoclastic vasculitis
2015	Shahcheraghi and Ayatollahi (case report)[20]	-	41 (male)	-	- Maculopapular lesion on leg
2018	Azadi *et al*. (case report)[21]	-	52 (male)	-	- Ulcerative lesion at dorsal aspect of fingers

brucellosis is unpredictable with isolation rates ranging from 29%[22] to 55.3%.[23] Bacteremia as an initial event of brucellosis is transient. Initial macrophage invasion is followed by a secondary bacteremia which could be either continuous or intermittent.[24] This may be the reason the blood culture was only positive after the subsequent culture. However, other known factors such as volume of blood sample collected could also have been a reason which was not investigated in this case.

Laboratory investigation is an important aspect in diagnosis of brucellosis because the symptoms and signs are variable and not specific. Serological, culture and molecular methods are the available options. Available serological methods include standard tube agglutination, enzyme-linked immunosorbent assay, Rose Bengal agglutination, Coombs test, immunocapture agglutination and 2-mercaptoethanol agglutination. Serological investigation does provide valuable impact

in the patient management. Immunocapture agglutination anti-*Brucella* (BrucellaCapt) test was shown to predict disease activity.[25] However, it was also noted that the reduction of titer slows down after a few months and around 20-25% patients with good clinical outcome still had positive titer after 12 – 18 months post therapy. In addition, rather than a single serological titer, a fourfold rise in *Brucella* antibody titer between acute and convalescent phase is more informative. Serology would be helpful in coming to a diagnosis in the presence of relevant history, symptoms and signs but as a stand-alone result, we cannot pinpoint brucellosis as the diagnosis because the test may remain positive for long. This would be difficult especially in endemic areas.

A definitive diagnosis could be obtained by recovering the organism from culture of blood, bone marrow, liver tissue or other body fluids or tissue. The gold standard of diagnosis is culture of bone marrow which yields higher rate of recovery of positive culture compared to blood. The mean of time to the detection in bone marrow culture is also significantly faster than blood and recovery of the organism is not affected by prior antibiotic use as compared to blood culture.[26] However, bone marrow culture is an invasive procedure and not often considered as first line investigation. Polymerase chain reaction (PCR) is a molecular method that is gaining popularity in past decade and it could be used to identify *Brucella* deoxyribonucleic acid (DNA). This method allows more rapid and sensitive identification of *Brucella* genus. However, PCR protocols lack standardisation and it is unable to differentiate between live and dead bacteria. PCR can detect DNA from dead or phagocytised cell and this should be considered when the results are interpreted. Hence, the result should be always interpreted with a clinical correlation.

In general, treatment for brucellosis requires extended time and an anti-bacterial agent with effective intracellular killing such as doxycycline, rifampicin. A short course of treatment is ineffective, and patient will relapse.[27] The first line recommended regime consist of six-week regimen of doxycycline combined either with streptomycin for 2–3 weeks, or rifampicin for six weeks. Gentamicin can be used to substitute streptomycin. Any other drug combination is considered as a second line treatment option.[28]

The patient in this case was diagnosed based on recovery of organism from blood culture, history of possible exposure, symptoms (fever and cellulitis), and further supported by the positive *Brucella* anti IgM and IgG. He was treated with oral antibiotics for 6 weeks as suggested in the treatment regime. No focal of disease was detected on echocardiogram and abdominal ultrasound. Unfortunately, monitoring of his general condition and the convalescent serology titer could not be done due to him defaulting. We were also unable to ascertain the compliance to the extended antibiotic treatment; hence, the risk of relapse or chronic brucellosis cannot be objectively determined.

CONCLUSION

Brucellosis poses a diagnostic dilemma in view of variable clinical manifestations even more so in an atypical presentation such as cellulitis. A combination of detailed history of possible exposure, high index of suspicion and reliable laboratory diagnostics are needed to come to a diagnosis of brucellosis to enable the appropriate treatment.

ACKNOWLDEGEMENT

We would like to thank the Director General of Health Malaysia for his permission to publish this article.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

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