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Clinical characteristics and outcome of *Brucella* endocarditis

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Background/aim: *Brucella* endocarditis, which is a rare condition, is the most common cause of death in human brucellosis, leading to severe cardiac complications. By collecting and analyzing clinical cases, we analyzed the clinical characteristics and outcome of *Brucella* endocarditis in endemic areas in China.

Materials and methods: Presented here are 5 cases of *Brucella* endocarditis, all managed uniformly. We present the clinical, serological, and echocardiographic features; the therapeutic approach; and the follow-up of five patients with *Brucella* endocarditis.

Results: There was a predominance of aortic involvement (4 cases) and a high incidence of left ventricular failure (5 cases). Polymerase chain reaction (PCR) testing was positive in all five patients. Diagnostic suspicion was essential in order to test blood cultures correctly, which in this series were positive in 3 patients. In the follow-up postoperative period of a minimum of 24 months, the patients suffered rare relapse in terms of either the infection or the dysfunction in terms of prosthesis after 3-month antibiotic therapy, with only one exception that died within that period.

Conclusion: We should pay attention to *Brucella* infections and strengthen public awareness and education. It is necessary to screen for and recognize *Brucella* endocarditis cases early and to provide adequate antibiotic treatment.

Key words: *Brucella* endocarditis, Clinical characteristics, outcome

1. Introduction

Infective endocarditis has an estimated annual incidence of 3 to 9 cases per 100,000 persons in industrialized countries, and it is a disease characterized by high morbidity and mortality (1–5). There are many pathogens that can cause endocarditis. Among these, gram-positive bacteria were shown to represent the predominant etiological agent (6). However, *Brucella* species, which are gram-negative bacilli, can also cause this disease and clinical manifestations are diverse. *Brucella* species are intracellular pathogens that are transmitted primarily through consumption of unpasteurized products. Complications due to *Brucella* infection develop in 25% to 35% of patients, most commonly involving the osteoarticular system, followed by the genitourinary, central nervous, and cardiovascular systems (6).

Here we describe the importance of considering *Brucella* as an etiological agent for endocarditis in Jilin Province, which is located in the northeastern part of China, which is a brucellosis-endemic region. We describe the clinical, serological, and echocardiographic features and our therapeutic approach as well as the follow-up of five patients with *Brucella* endocarditis.

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2. Materials and methods

We retrospectively identified 286 patients with suspected endocarditis (2003–2012) in the first hospital of Jilin University, Changchun city, Jilin Province. All patients suspected of suffering from endocarditis were examined by transthoracic echocardiography. Serological testing for brucellosis and blood cultures on routine liquid media were performed with patients who reported ingestion of unpasteurized milk and milk products from goats or cattle, or contact with secretions from these animals and their tissues. The diagnosis of brucellosis was made according to one of the following criteria: 1) isolation of *Brucella* spp. from blood or tissue samples; 2) brucellosis-compatible clinical manifestations and demonstration of specific antibodies at substantial titers (Wright's seroagglutination titer > 1:160 or a Coombs' antibrucella test titer > 1:320). Serological tests were performed in accordance with the World Health Organization recommendations (7).

Blood samples were cultivated using a nonradiometric system, Bactec 730 or 9240, which was half automatic. Based on the usual microbiologic skills, the blood cultures were thus processed (8). The maintenance for incubation lasted for 30 days, while the subcultures were conducted

with chocolate agar as well as the *Brucella* one after 10, 20, and 30 days. As for those subcultures, they were cultured at the temperature of 37 °C with a 5%~10% CO_2 environment, lasting for 3 days. Moreover, through such methods as morphology, oxidase, urease tests, and Gram staining as well as catalase and positive agglutination along with specific antiserum, suspect colonies have thus been recognized and identified. Furthermore, in the National Reference Laboratory situated in Valladolid, the isolated strains were finally identified before the biotyping.

The clinical diagnosis of endocarditis was made in accordance with the Duke criteria (9). Patients with both endocarditis and brucellosis were considered to have *Brucella* endocarditis. In the patients who experienced cardiac surgery, the diagnosis was confirmed in both a microbiological and/or histological way.

In the first 6 months, the patients would accept the monitoring every 2 months in the case of favorable disease course and no matter when it was necessary on the condition of the presence of complications. After that, the patients were monitored every 4 months, with a minimum observation period of 24 months.

3. Results

The reported rates of endocarditis after *Brucella* infection vary (10). In our study, 286 patients suspected of endocarditis were evaluated by using the above methods. Endocarditis was confirmed in 189 patients and *Brucella* was identified as the etiological agent in five patients (3%, 5/189). There were four male patients (80%, 4/5) and one female patient (20%, 1/5), with a median age of 41.8 years, ranging from 18 to 65 years (Table 1). All patients had a clear contact history such as exposure to their own or their neighbor's domestic sheep, or raw milk ingestion. Underlying cardiopathy was present in two patients (40%, 2/5): rheumatic cardiopathy in one and a bicuspid aortic valve in the other (Table 2). The endocarditis involved the aortic valve in four cases (80%, 4/5) and the mitral valve in one (20%, 1/5) (Table 2). All patients (100%, 5/5) had left ventricular failure at the time of diagnosis or shortly thereafter (Table 2).

The polymerase chain reaction (PCR) test was positive in all patients (100%, 5/5) (Table 3). The blood cultures were positive in three patients (60%, 3/5), with *Brucella* melitensis being isolated in all (Table 3). The two patients with negative blood cultures had received previous antibiotic therapy (Table 4). There was evidence of anti-*Brucella* antibodies in all cases, with high titers in at least one of the serologic tests used (Table 3).

Two of the 5 patients (40%, 2/5) were treated with doxycycline (200 mg/day) plus rifampicin (900 mg/day) for 3 months, with the incorporation of ciprofloxacin (1 g/day i.v.) during the first 6 weeks (Table 4). The other patient was not given ciprofloxacin because of an upset stomach, receiving instead doxycycline and rifampicin for 3 months (Table 4).

Table 1. The year of disease, sex, and age of 5 patients with *Brucella* endocarditis.

No.	The year of disease	Sex	Age (years)
1	2003	Male	18
2	2005	Male	58
3	2009	Male	26
4	2011	Male	65
5	2013	Female	42

Table 2. Main clinical features of 5 patients with *Brucella* endocarditis.

No.	Underlying cardiopathy	Valve	Left ventricular failure
1	None	Aortic	Yes
2	Rheumatic cardiopathy	Aortic	Yes
3	None	Aortic	Yes
4	Bicuspid aortic valve	Aortic	Yes
5	None	Mitral	Yes

Table 3. Main clinical diagnostic method in 5 patients with *Brucella* endocarditis.

No.	PCR	Serum agglutination test	Blood cultures
1	+	1/200	+
2	+	1/400	–
3	+	1/400	+
4	+	1/400	–
5	+	1/400	+

Table 4. Treatment method and clinical outcome of 5 patients with *Brucella* endocarditis.

No.	Antibiotic treatment	Surgery	Outcome
1	Doxycycline + rifampin	Yes	Died
2	Doxycycline + rifampin + ciprofloxacin	Yes	Favorable
3	Doxycycline + rifampin	No	Favorable
4	Doxycycline + rifampin	Yes	Favorable
5	Doxycycline + rifampin + ciprofloxacin	Yes	Favorable

One patient died during the immediate postoperative period (20%, 1/5). Four patients underwent surgery in addition to antibiotic therapy (80%, 4/5). The others were monitored for at least 2 years, with no evidence of relapse of infection or prosthetic dysfunction detected.

4. Discussion

While human *Brucella* infections have become an uncommon phenomenon in western countries, they still impose a significant burden on many Mediterranean, Middle Eastern, Asian, and South American countries (11). According to the Chinese Ministry of Health, until 1980 the incidence in China was highest in the provinces of Inner Mongolia, Jilin, and Heilongjiang, all of which are located in northeastern China. However, since 2000 the prevalence has been highest in the western central Chinese provinces of Shanxi, Hubei, and Henan. Tibet remains a region with increased endemicity (12). Notably, there is a steep increase in the annual incidence. Jilin Province is located in northeastern China, where stock breeding is one of the main economic resources.

Brucellosis has classically been categorized as acute, subacute, or chronic. Human brucellosis is traditionally described as a disease with various manifestations. Fever accompanied by rigors, malodorous perspiration, lymphadenopathy, hepatomegaly, and splenomegaly is often present.

Among the different manifestations of brucellosis, endocarditis remains the principal cause of *Brucella*-associated mortality. Endocarditis develops gradually and the time between infection and onset of endocarditis is unknown. Furthermore, it is unknown whether these bacteria can be eliminated. Among the cardiac complications associated with endocarditis are paravalvular leakage, ring abscess, congenital heart disease (ventricular septal defect), rheumatic heart disease, and acute valve malfunction. Extracardiac manifestations such as sepsis, septic shock, renal failure, pneumonia, blood disseminated pulmonary abscess, liver abscess, sacroiliitis, and encephalopathy were reported (13). Osteoarticular disease is universally the most common complication of brucellosis and the reproductive system is the second most common site of focal brucellosis. *Brucella*-associated hepatitis is also commonly observed. While according to most studies the central nervous system is affected in 5% to 7% of cases, respiratory complications of brucellosis are considered rare (14).

The diagnosis for brucellosis is not easy despite the high degree of suspicion. Moreover, there is lack of sufficient sensitivity for the blood culture, while for the serologic tests they are not completely specific despite the sensitiveness. Hence, there can be difficulty in terms of the interpretation in fields where the disease tends to be endemic. Furthermore, it could be negative in the early phase of the disease. When it comes to the diagnosis in terms of the focal forms concerning brucellosis, it may be extremely hard as it may not become a potential symptom for the physician, or that, there can be low production

of cultures acquired from both the blood and nonblood samples despite the consideration (15,16).

It is quite common for the young male to suffer frequent infection in brucellosis. Moreover, most of them would once be exposed to *Brucella* spp. For developed countries, brucellosis could be the only element affecting people concerned with the following professions, including farmers and people engaged in animal husbandry as well as veterinarians. However, not all patients are in related professions with high risks. In reality, the major infection route lies in drinking milk products (17), which could explain why there have been five patients contracting brucellosis by this route. Furthermore, as the only species isolated, *Brucella* melitensis could occur in other nations of the field (17).

As can be noted from this series, the aortic valve was predominantly involved, accounting for 80% (4/5) of the total, in which half the patients had potential cardiopathy. Nowadays, patients suffering from mitral endocarditis are prone to suffer from rheumatic cardiopathy, especially when *Brucella* spp. attack the valve (18,19).

The most popular complication is left ventricular failure. In our series, it happened in every case. This hemodynamic change results from long-time symptoms, which do great harm to the valve. Generally speaking, this hemodynamic change is identified when the disease is diagnosed or shortly after the diagnosis.

Several diagnostic tests are available for brucellosis, such as culture (whole blood or bone marrow culture), serodiagnosis (agglutination tests, enzyme-linked immunoassay, 2-mercaptoethanol test) and molecular detection (PCR). PCR testing was positive in all five patients (100%, 5/5). Compared with endocarditis resulting from other kinds of bacteria, *Brucella* endocarditis is usually related to a quite high ratio of negative blood cultures, as *Brucella* spp. reproduce slowly and demand proper culture medium. In addition, it is usually part of endocarditis with negative blood cultures caused by the pathogen (20). Nevertheless, two patients with negative blood cultures acquired the antibiotic therapy in advance. As a result, it is necessary to implement appropriate serologic tests to patients suffering from endocarditis as well as those with negative blood cultures.

A pathogen like *Brucella* spp. is prone to lead to fatal consequence only if it reproduces in the valvular endocardium. It is said that the unique method to get rid of infection related to a pathogen is combining medical with surgical treatment. Traditionally speaking, *Brucella* endocarditis is treated in the same way (21,22). Nevertheless, serious harm is likely to be caused not so much by the assumed poisonousness of the bacteria as by a late diagnosis.

Brucella endocarditis is very sensitive in the diagnosis of valvular ring abscesses, which calls for surgery at once. The constant finding during surgery for injuries not identified by transthoracic echocardiography will result in the traditional transesophageal echocardiography in cases of *Brucella* endocarditis.

At present, there is no definite method to deal with *Brucella* endocarditis. In the case of the antibiotic field, the best method to treat various kinds of brucellosis is to combine doxycycline with rifampicin (23). However, when it comes to endocarditis, ciprofloxacin is also included due to its great tissue distribution and great capacity to penetrate in valvular vegetations. In view of the embolic complications as well as late period of destruction concerning tissue in certain patients, our series produced good outcomes. It turns out that the triple antimicrobial therapy adopted is quite useful and is accepted well, and that the 3-month treatment is long enough, as no recurrence or periprosthetic infections happen.

In conclusion, the prospective series carried out helps to identify the traits of *Brucella* endocarditis in terms of diagnosis, clinics, and therapy. In the series, all the patients are treated in the same way. It turns out that much of the morbidity and mortality caused by *Brucella* endocarditis could be treated by medical as well as surgical method. Even though the valve can be replaced with regard to serious valvular failure, there is an effective medical method. In order to treat the disease effectively, it is necessary to identify and diagnose the disease as early as possible, especially in endemic areas.

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