Brucella endocarditis in prosthetic valves

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Human brucellosis is a multiple organ disease that presents with fever and is most often transmitted via contaminated, unpasteurized goat milk and cheese. In chronic cases, focal complications (eg, spondylitis, neurobrucellosis and endocarditis) are frequently seen. Although the disease may be severely debilitating, the mortality rate is low. Fatal cases are often due to endocarditis. Because *Brucella* endocarditis is a rare complication (2% to 5%), therapeutic considerations are based on single-case experiences only. Therapy includes long-term antibiotic treatment using combinations of various antimicrobial drugs and surgical valve replacement when required. A case of *Brucella* endocarditis complicated by the infection of two valvular prostheses implanted after involvement of the mitral and aortic valve due to rheumatic fever is described. The patient was successfully treated by a medical and surgical approach. Therapeutic strategies in *Brucella* endocarditis are discussed in light of the current literature.

Key Words: Antimicrobial therapy; *Brucella* endocarditis; Prosthetic valves; Valve replacement

Brucellosis is a common zoonosis in Mediterranean countries, transmitted to humans by direct contact with infected animals or by the consumption of contaminated food (eg, unpasteurized milk or dairy products, and raw meat) (1). Four of the six named species of the genus *Brucella* are human pathogens: *Brucella melitensis*, *Brucella abortus*, *Brucella suis* and *Brucella canis*. Human brucellosis is a severe systemic disease that may affect any organ and is characterized by focal complications, chronic courses, therapeutic failures and relapses. The case fatality rate is low (less than 1%). However, 80% of the fatal cases are caused by endocarditis (2). In endemic areas, *Brucella* endocarditis has been reported in 8.5% to 14.6% of all patients treated for endocarditis (3-5). A case of *Brucella* endocarditis on two valvular prostheses successfully treated in Charité – Campus Benjamin Franklin (Berlin, Germany) by a combined medical and surgical approach is described. Because *Brucella* endocarditis is a rare complication, general treatment recommendations do not exist for this potentially fatal complication. Therapeutic strategies in *Brucella* endocarditis are discussed.

CASE PRESENTATION

A 55-year-old Turkish woman was hospitalized primarily because of remittent fever up to 39.5°C, accompanied by night

Une endocardite à *Brucella* dans des valves prothétiques

La brucellose humaine est une maladie multiorganique qui se manifeste par de la fièvre et est surtout transmise par le lait de chèvre et le fromage non pasteurisés. Dans les cas chroniques, on remarque souvent des complications focales (p. ex., spondylite, neurobrucellose et endocardite). Bien que la maladie puisse être gravement débilitante, le taux de mortalité est faible. Les fatalités sont souvent causées par une endocardite. Puisque l'endocardite à *Brucella* est une complication rare (2 % à 5 %), les considérations thérapeutiques se fondent sur des expériences isolées. Le traitement inclut une antibiothérapie prolongée composée d'une association d'antimicrobiens et d'un remplacement valvulaire, au besoin. Est décrit un cas d'endocardite à *Brucella* compliqué par l'infection de deux valves prothétiques implantées après une atteinte des valves mitrales et aortiques imputable à un rhumatisme articulaire. Le traitement du patient a réussi, grâce à une démarche médicale et chirurgicale. Les stratégies thérapeutiques de l'endocardite à *Brucella* sont exposées à la lumière des publications courantes.

sweats and abnormal fatigue; she also suffered from left thoracic pain. Her medical history revealed an episode of rheumatic fever during childhood, followed by rheumatic disease of the heart valves. Because of combined mitral regurgitation and stenosis, a St Jude Medical prosthesis (St Jude Medical, USA) was implanted when the patient was 37 years of age. The aortic valve was also replaced due to insufficiency by the same type of prosthesis two years before admission to the hospital. Transesophageal echocardiography (TEE) did not show any vegetation on the two valves. However, Enterobacteriaceae were found in urine cultures. Urinary tract infection was suspected and the patient was treated with co-trimoxazole. Body temperature decreased to normal values, and her health improved markedly. Four weeks later, blood cultures taken before antibiotic treatment yielded *B melitensis* by 2. The isolates were identified by the German Reference Laboratory for brucellosis located at the Federal Institute for Risk Assessment (Berlin, Germany) following the standard laboratory procedures described by Alton et al (6). Rifampin and doxycycline were recommended for six weeks, but were only taken for two weeks because of noncompliance. A re-evaluation of the medical history did not reveal the probable source of infection, but the consumption of unpasteurized goat's milk and cheese during a family stay in Turkey seemed to be highly probable.

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Figure 1) Transesophageal echocardiography demonstrating a large inhomogeneous vegetation (white arrow) attached to the posterior rim of a St Jude Medical bileaflet prosthesis (black arrow, anteriorly oriented tilting disk) in the mitral position. LA Left atrium; LV Left ventricle

Approximately 9000 cases of human brucellosis (incidence of 14/100,000 population) were reported to the Turkish Ministry of Health every year during the past decade (1991 to 2000) (7).

The patient was rehospitalized two months later due to severe dyspnea caused by left heart failure. The patient had an oxygen saturation of 89%, heart rate of 130 beats/min and blood pressure of 130/70 mmHg. The patient's body temperature was 38.3°C. On admission, the patient's general status was reduced. A mitral systolic murmur (grade III) was audible and there were signs of severe left heart failure (New York Heart Association class III/IV) (ie, pulmonary edema and edema of the lower limbs). The liver and spleen were not enlarged on physical examination and no hemorrhages or petechiae were found.

Hematologically, a mild normocytic and normochromic anemia (97 g/L [normal: greater than 120 g/L]) and slightly decreased number of platelets (120,000 platelets/ μ L [normal range of 150,000 platelets/ μ L to 400,000 platelets/ μ L]) became obvious. White blood cell counts and the lymphocyte to neutrophil ratio were in the normal range. Both the C-reactive protein concentration (114 mg/L [normal concentration less than 5 mg/L]) and the erythrocyte sedimentation rate (70 mm/h [normal rate of 30 mm/h or less]) were elevated. Lactate dehydrogenase activity was high on admission (397 U/L [normal activity 120 U/L to 240 U/L]) and increased to a maximum of 1624 U/L. Because hemoglobin decreased to a minimum of 85 g/L at the same time, mechanical hemolysis of red blood cells was assumed, and the patient was given a transfusion. Liver enzymes and renal retention values were normal. Serum agglutination test showed increased anti-*Brucella* antibody titres (1:320) that were subsequently confirmed by the complement fixation test (1:320).

The electrocardiogram showed a tachycardic sinus rhythm with slight left axis deviation, complete right bundle branch block and positive voltage criteria for left ventricular hypertrophy. The chest x-ray revealed pulmonary edema and cardiomegaly with a cardiothoracic index of 0.55. The prosthetic valves were projected into the correct positions. TEE showed an echogenic mass (18 mm $\times$ 11 mm) attached to the posterior rim of the mitral prosthesis (Figure 1). At this edge, a small

leakage became visible during control examinations. After application of a diuretic drug, the patient rapidly improved. Because of the patient's previous history of incomplete treatment of brucellosis, *Brucella* endocarditis was already suspected on second admission and two blood cultures yielded *B melitensis* again. Although strongly advised, the patient refused thoracotomy and repeat valve replacement at that time. Hence, antibiotic treatment was started using a triple combination consisting of oral rifampin 900 mg once daily, oral doxycycline 100 mg twice a day and gentamicin 40 mg to 60 mg intravenously three times a day according to the drug levels measured every 24 h. Defervescence occurred within three days and C-reactive protein concentrations returned to normal values after six weeks of treatment. Rifampin and doxycycline were continued for three months. Because rifampin lowers the plasma levels of coumarin by induction of the hepatic cytochrome oxidases, low-molecular-weight heparin was used instead during antibiotic treatment. The patient was discharged after seven weeks of treatment. *Brucella* serum agglutination test titres were 1:160, and complement fixation test titres were 1:640.

Two months later, TEE showed a large, persistent vegetation at the posterior mitral prosthesis with moderate regurgitation due to impaired leaflet closure and periprosthetic leakage. Another small vegetation and an annular abscess cavity (5 mm $\times$ 5 mm) located toward the right ventricle with mild regurgitation was seen at the aortic valve prosthesis. The patient was subsequently convinced of the urgent need for operative replacement of the infected prosthetic valves. The echocardiography findings were confirmed during surgery. Both prosthetic valves were excised. After meticulous debridement of the aortic and the calcified mitral annulus, new St Jude Medical prostheses were implanted. Equine pericardial patch material was used to support the sutures of the mitral (31 mm) and aortic valve (23 mm) prosthesis. Rifampin 600 mg once daily by mouth, ampicillin 2 g three times, and gentamicin 160 mg twice a day intravenously were administered for four weeks after surgery. At the end of the therapy, the patient suffered from dizziness possibly due to vestibular toxicity of the aminoglycoside. Because doxycycline caused gastrointestinal complaints, amoxicillin in combination with rifampin was recommended for another four weeks after discharge. Antibody titres declined and the patient totally recovered. She is still doing well, without any signs of relapse two years after *Brucella* endocarditis on double valvular prosthesis and valve replacements.

DISCUSSION

Focal complications are found in one-third of all brucellosis patients, either initially or during the course of disease. However, cardiac complications (ie, pericarditis, myocarditis and endocarditis) occur in fewer than 2% of all cases (8-10). Despite its low frequency, *Brucella* endocarditis leading to congestive heart failure is responsible for the majority of deaths (11). Because endocarditis is a rare focal complication of brucellosis, most cases described in the literature are parts of small series or single reports. Therefore, no general treatment recommendations exist. Neither the combination of antimicrobial agents nor the duration of antibiotic therapy has been established. Additionally, the indication for surgery and its timing have not yet been precisely defined.

Approximately one-half of the patients with *Brucella* endocarditis suffer from underlying valvular damage (10). *Brucella* prosthetic valve endocarditis on mechanical and bioprostheses

has been described frequently (5,12-21). In endemic areas, such as Saudi Arabia, *Brucella* has established a high incidence (approximately 10%) among the causative agents of prosthetic valve endocarditis (12,15). However, to the best of our knowledge, only one case of *Brucella* endocarditis on double valvular prosthesis has been reported (19).

The aortic valve is predominantly affected (75%), and mitral valve, both mitral and aortic valves, and prosthetic valves are equally affected (8.3%) (10,11,22). The infection of a previously healthy valve most often involves the aortic valve, whereas secondary infections of predamaged valves preferably occur on mitral valves (20). *B. abortus* and *B. melitensis* are reported to be the most frequently isolated species. *B. suis* is rarely found (5% of cases) (11).

Agglutinating antibody titres are usually high in *Brucella* endocarditis. The duration of symptoms in our patient (more than three months before adequate antibiotic treatment) accompanied by anti-*Brucella* antibody titres just around diagnostic levels emphasizes the subacute or chronic character of the disease. We therefore cannot exclude that destruction of the aortic valve two years before admission to hospital was also caused by *Brucella*. *Brucella* endocarditis may take an insidious onset, and infections lasting for a year before a definitive diagnosis has been described (17,23). Valves affected by rheumatic fever appear to be susceptible to *Brucella* and clinical signs and symptoms of cardiac involvement may mimic rheumatic fever (24-27). Both acute rheumatic fever and brucellosis may present with fever, arthralgia or arthritis, as well as a high erythrocyte sedimentation rate.

Various complications are seen in the course of *Brucella* endocarditis. Some examples of these are myocardial abscesses and aneurysms (5,11); cusp perforation (25); ruptured chordae tendineae and detached leaflets (22); left ventricular failure; disseminated intravascular coagulation (28,29); and embolic phenomena (ie, mycotic aneurysms [15], transient ischemic attacks, myocardial and other organ infarctions [10,20,22,30]). Septic emboli dislodged from valve vegetations may cause infected infarcts of any organ, leading to relapse (21). However, the risk of embolism is not higher than in other types of endocarditis, although vegetations frequently present as a bulky mass, as in the present case. In a series of 44 necropsies on cases of fatal brucellosis, Peery and Belter (2) found myocardial abscesses in 43%. Abscess formation is more common in endocarditis caused by *Brucella* than other organisms (5). Intraoperatively, we also found an annular abscess cavity.

Electrocardiogram changes mainly include involvement of the cardiac conduction system (ie, right or left bundle branch blocks or atrioventricular blocks) (25,29,31). In the present case, a complete right bundle branch block was found.

In most reports, a combination of antimicrobial agents and early valve replacement or extensive surgical debridement are recommended for successful treatment of *Brucella* endocarditis (5,11,12,16,21-24,32,33). The authors of these studies claim that a medical and surgical approach is mandatory, especially in patients suffering from progressive heart failure secondary to severe aortic regurgitation due to valvular destruction. They also claim that the threat of embolism due to pedunculated, highly mobile vegetations should also lead to early surgical intervention (34). These indications for surgical therapy in *Brucella* endocarditis are in accordance with the guidelines of the American Heart Association for the management of infective endocarditis in general (35). Valve replacement can be

performed in spite of active disease, because the risk for recurrent infection of the newly implanted prosthesis seems to be low (10,13,18,25,33). However, valve replacement during the active phase of infection may lead to postoperative periprosthetic leakage (16).

There are some cases of *Brucella* native valve endocarditis that have been cured by medical treatment alone (10,13,27,28,30,36-39). However, not all of them were proven bacteriologically, and some of them have not been followed up long enough. Although isolation from tissue specimens is rarely successful (5,25), *Brucella* may still be found in cultures of infected valves after eight weeks of adequate antibiotic therapy (23). Because relapses may occur two years after a supposed cure, an attempt of medical treatment without surgical intervention absolutely requires careful monitoring under therapy, as well as strict and prolonged clinical and echocardiographic surveillance (21,37). Regarding these prerequisites, a conservative antibiotic treatment may be an appropriate alternative to surgery in selected patients, but in prosthetic valve endocarditis, surgical replacement is generally recommended (7,8,39). In brucellosis patients with a history of valvular heart disease, frequent echocardiographic studies are mandatory (12). TEE may be very helpful in establishing the diagnosis and for follow-up of *Brucella* endocarditis as more detailed information on valvular destruction, annular or myocardial abscesses, and the formation of aneurysms is provided (40).

In literature, only one case of mitral prosthetic valve endocarditis has been treated successfully without repeat valve replacement (15). In this case, however, diagnosis was based on rising titres of anti-*Brucella* antibodies. Cultures remained sterile. Ciprofloxacin (1000 mg/day), co-trimoxazole (2700 mg/day) and rifampin (600 mg/day) were administered for 12 months. Vegetations and perivalvular leakage completely disappeared and the patient showed no signs of relapse in a four-year follow-up period.

Our patient was advised to undergo cardiac surgery for removal of the infected prostheses at an early stage due to the recurrence of symptomatic disease and the echocardiographic evidence of valve vegetations after primary antibiotic therapy. Because she refused surgery at that time, we were able to observe the failure of broad and prolonged medical treatment alone. The recurrence of bacteremia after adequate antibiotic treatment of brucellosis in patients with prosthetic valves should always arouse suspicion for endocarditis (39).

In contrast with *Brucella* endocarditis in adults, either ending fatally or requiring emergency valve replacement, the disease does not show such a fulminant course in children and seems to carry a good prognosis. Children suffering from cardiac involvement promptly responded to medical treatment using a combination of oral tetracycline for three weeks, together with intramuscular streptomycin for two weeks (26). This antibiotic regimen is based on a former World Health Organization recommendation for the treatment of uncomplicated cases of brucellosis (41). In adults, however, triple or quadruple combinations in high dosages over a prolonged course (longer than 12 weeks) are necessary for successful treatment of *Brucella* endocarditis. Trimethoprim-sulfamethoxazole (trimethoprim 400 mg/day, sulfamethoxazole 2400 mg/day) and/or rifampin (600 mg/day to 900 mg/day) are used in addition to the traditional antimicrobial agents (ie, doxycycline [2 × 100 mg/day] in combination with an aminoglycoside [streptomycin 1 g/day or gentamicin 240 mg/day])

(5,7,8,11,24,39). Because no general recommendations exist for how long antimicrobial agents should be administered, clinical, serological and microbiological findings may help the physician to decide whether antibiotic treatment should be continued. The normalization of anti-*Brucella* titres is occasionally suggested to be the end point of an effective antibiotic therapy (24,39). In our opinion, prolonged postoperative antibiotic treatment was indicated in our patient to protect the newly implanted prosthetic valves.

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CONCLUSION

Long-term antibiotic treatment of *Brucella* endocarditis before surgery was insufficient to eradicate the infection in our patient with prosthetic intracardiac material. Repeat valve replacement seems to be mandatory in the management of *Brucella* prosthetic valve endocarditis to control acute disease, and to prevent complications and relapse. However, the timing of surgery remains controversial and should be based on the patient's clinical condition.