Brucella endocarditis of a prosthetic valve in a non-endemic region

Rik van den Biggelaar, Marvin AH Berrevoets, Marc P Buise, Anton G Buiting

ABSTRACT

Introduction: Brucellosis is a common bacterial zoonosis in endemic regions. Most cases of human disease are caused by contact with infected animals or consumption of contaminated animal products. In the Netherlands brucellosis in livestock had been eradicated so human disease is especially rare.

Case Report: We present a case of a 58-year-old female with a prosthetic valve endocarditis caused by Brucella melitensis. The patient had immigrated from an endemic region 12 months prior. She was treated with antibiotic triple therapy and valve replacement. The postoperative was complicated by multiple organ failure resulting in death.

Conclusion: Brucellosis has a wide spectrum of clinical manifestations and is poorly recognized in non-endemic regions. It should be considered in febrile patients whom had possible exposure at least up to a year prior. Delay of appropriate treatment could lead to potential life-threatening complications.

Keywords: Brucella melitensis, Brucellosis, Endocarditis, Prosthetic valve

INTRODUCTION

Brucellosis is a common zoonosis caused by a Gram-negative facultative intracellular coccobacilli of the genus Brucella, endemic in the Mediterranean basin, Middle East, Africa, western Asia, and Latin America. Humans acquire the disease mainly by ingestion of infected animal products such as unpasteurized milk, cheese, or raw meat. Contact with infected animals or inhalation of contaminated aerosols can also be a source of transmission [1].

The clinical presentation of human brucellosis varies widely. Patients often experience fever (78%), sweats (54%), chills (45%), and malaise (71%). Musculoskeletal-related manifestations such as arthralgia (65%), myalgia (47%), and back pain (45%) are common. Splenomegaly (26%) and hepatomegaly (23%) are less common. Epididymo-orchitis is found in 10% of males. Severe complications such as endocarditis and hepatitis are rare [2].

Human brucellosis in non-endemic regions is poorly recognized. In this paper we present a case of a patient, who had immigrated from an endemic region 12 months prior and developed a prosthetic valve endocarditis with Brucella melitensis. This case emphasizes the need to consider brucellosis as a diagnosis in febrile patients whom had possible exposure at least up to a year prior to prevent delay of appropriate treatment.
CASE REPORT

A 58-year-old Syrian female with a history of an ascending aorta prosthesis, mechanical aortic valve replacement and cerebral infarction, who had been living in the Netherlands for 12 months, presented herself with a three month history of intermittent fever, sweating, and weight loss. Physical examination revealed splenomegaly and inguinal lymphadenopathy. Cardiac auscultation was consistent with a mechanical valve prosthesis. Laboratory test results revealed a pancytopenia with Hb 5.2 mmol/L (normal range 7.5–10.0 mmol/L), leukocytes $2.3 \times 10^9/L$ (normal range $4.0–10.0 \times 10^9/L$), and thrombocytes $100 \times 10^9/L$ (normal range $150–400 \times 10^9/L$), the erythrocyte sedimentation rate (ESR) was 68 mm/h (normal range 0–30 mm/h), C-reactive protein 34 mg/L (normal range 0–10 mg/l), and creatinine 91 µmol/L (normal range 49–90 µmol/L). Electrocardiogram (ECG) showed a sinus rhythm with first degree atrioventricular (AV) block. The computed tomography (CT) scan showed a splenomegaly of 18 cm. Based on the pancytopenia, splenomegaly and fever, a hematological malignancy or chronic infection was suspected.

Gram-negative coccobacilli were isolated from the blood cultures three days after incubation with BACTEC FX (Becton Dickinson). The Gram stain is shown in Figure 1. Identification at the genus level was done by matrix assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry (Bruker Daltonics) according to database BDAL 8.0.0.0 + SR 1.0.0.0. Brucella agglutination test (Oxoid) was positive (titer $\geq 1280$). Further confirmation of identification and biotyping of the organism was done by the Center for Infectious Disease Research, Diagnostics and Laboratory Surveillance (IDS), and the National Institute of Public Health and the Environment (RIVM, Bilthoven, The Netherlands). Results were consistent with *Brucella melitensis*, biotype 3 (see Supplementary Material for comprehensive analysis).

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) has no clinical breakpoints for *Brucella* spp. so breakpoints of the Clinical and Laboratory Standards Institute (CLSI) were used [3]. Susceptibility is shown in Table 1. Minimal inhibitory concentration (MIC) breakpoints for rifampicin have not yet been established.

Initial empiric antibiotic treatment with cefuroxime was switched to doxycycline 2dd 100 mg and gentamicin 1dd 5 mg/kg. After the start of antibiotic treatment, multiple blood cultures were taken however none tested positive for *Brucella melitensis* when incubated for 12 days. A transesophageal echocardiography (TEE), shown in Figure 2, demonstrated a mechanical aortic valve with extensive abscess formation and a fistula to the left ventricle outflow tract causing moderate perivalvular leakage. No vegetations were seen on the mechanical valve. 18F-FDG positron emission tomography–computed tomography (PET/CT) revealed increased metabolism confined to the proximal ascending aorta and part of the aortic valve. According to the European Society of Cardiology (ESC) 2015 modified Duke criteria the suspicion of endocarditis could be confirmed based on two separate positive blood cultures and imaging positive for endocarditis (two major criteria).

Table 1: The MIC values for *Brucella melitensis*

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC (µg/mL)</th>
<th>Breakpoint (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>0.12</td>
<td>$\leq 1$</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0.5</td>
<td>$\leq 4$</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>0.064</td>
<td>$\leq 2/38$</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>1.0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Figure 1: *Brucella melitensis* staining predominately Gram-negative from positive blood culture ($\times 1000$).

Figure 2: Transesophageal echocardiography of patient showing prosthetic aortic valve (AVR) with multiple perivalvular cavities (indicated with white arrows). LA = left atrium, RA = right atrium, RVOT = right ventricle outflow tract.
Rifampicin 1dd 600 mg was added to the prior treatment and the patient was transferred to a cardiothoracic surgery center. There gentamicin was switched to co-trimoxazole 2dd 960 mg. The aortic valve and ascending aorta were surgically removed and replaced with a mechanical aortic valve prosthesis (St. Jude 21 mm) and ascending aortic prosthesis (Gelweave 26 mm). During surgery a dehiscence of the aortic valve prosthesis and abscess formation of the left coronary cusp was found. Sequencing of perioperative material was positive for Brucella melitensis, bacterial cultures however remained negative. The postoperative course was complicated by cardiogenic shock leading to severe ischemic necrotizing pancreatitis, followed by ischemic hepatitis and acute kidney failure due to distributive shock. The patient developed multiple organ failure and died eight days after surgery.

DISCUSSION

Human brucellosis can be caused by four species of the genus Brucella which each differ in their preferred host, namely B. abortus (bovine), B. melitensis (goats and sheep), B. suis (pigs), and B. canis (dogs). Veterinarian control of B. abortus has been successfully achieved in the Netherlands being officially eradicated since 1999. While B. melitensis was never determined in small ruminants in the Netherlands, the last case of B. suis was identified in 1973 [4].

Brucellosis in the Netherlands is rare, with on average four cases a year. Incidental cases of human brucellosis are mostly due to classical risk factors such as travel and/or consumption of infected animal products [4]. Laboratory-acquired brucellosis is frequently reported due to Brucella spp. being aerosolized during routine handling and low infectious dose [5]. Handling of the patient samples led in this case to high risk exposure to contaminated aerosols of six laboratory professionals. According to the Centers for Disease Control and Prevention (CDC), risk exposure is defined as direct contact with Brucella, work on an open bench with an isolate or within 5 feet of such work, or presence in a laboratory during an aerosol-generating event [6]. Post-exposure prophylaxis (PEP) consisting of doxycycline 2dd 100 mg and rifampicin 1dd 600 mg is advised in high-risk exposure [4]. After careful consideration PEP was not given. Follow-up was done by agglutination test at 2, 4, 6, and 24 weeks after exposure. No seroconversion of exposed personnel had occurred after 24 weeks.

Because brucellosis has become rare, it is often not recognized by clinicians. The most frequent symptoms are arthralgia, fever, and fatigue. Common clinical findings are fever, hepatomegaly, and/or splenomegaly and peripheral arthritis [7]. The disease should be suspected in febrile patients who travelled or immigrated from endemic regions up to several months prior due to the prolonged incubation period [8]. In our case the time from exposure to diagnosis was 12 months.

Focal complications of brucellosis, such as osteoarticular complications are common [9, 10]. Endocarditis, however, is rare being only reported in 0.8% of cases [11]. Although overall mortality is low, endocarditis is responsible for the majority of deaths. Prior to the introduction of open heart surgery, mortality was more than 80% [12]. Since then, a combination of medical and surgical therapy has reduced mortality to 6.7% [13]. Due to limited clinical studies the optimal treatment of Brucella endocarditis remains unknown.

The World Health Organization (WHO) recommends a combination regimen of doxycycline 2dd 100 mg and an aminoglycoside (streptomycin 1dd 1 g or gentamicin 1dd 5 mg/kg), with rifampicin 1dd 600–900 mg or co-trimoxazole 2dd 480 mg. Prolonged treatment of at least eight weeks is recommended [14]. The duration of the aminoglycoside is not specified. In addition, a study found that rifampicin decreases the plasma levels of doxycycline which is likely to result in lower therapeutic efficacy [15].

CONCLUSION

The diagnosis of brucellosis should be considered in patients presenting with fever of an unknown origin, who have been in an endemic region up to 12 months prior. Although endocarditis is a rare complication, additional echocardiography should be performed to rule out endocarditis given the high mortality rate. A lower doxycycline plasma level in patients treated with rifampicin due to drug interaction may result in a suboptimal therapeutic response. Increasing the dosage of doxycycline to 2dd 200 mg or substitution of rifampicin with co-trimoxazole may be a more favorable alternative.

REFERENCES

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Rik van den Biggelaar – Conception of the work, Design of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
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