A tale of four valves: outcome of Brucella endocarditis: a case series

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Background

Brucellosis is a zoonotic infection. Humans contract brucellosis through inhalation of aerosolized infected particles, or when they come in direct contact with infected animal parts, or on consuming unpasteurised dairy products. It can affect multiple organs and systems. Endocarditis is diagnosed late in the course of the disease with mostly aortic valve involvement with serious morbidity and mortality.

Case summary

We report a case series of four patients with Brucella endocarditis. The first patient presented with fever, malaise, and exertional breathlessness. He underwent aortic valve replacement for refractory heart failure and bulky vegetations after failed medical therapy. The second patient presented with fever, breathlessness New York Heart Association (NYHA) III, with arthralgia, myalgia, anorexia, and weight loss. In view of aortic abscess with impending rupture and compression of left main coronary artery, aortic valve replacement was performed on the 4th day of antibiotic treatment. The third patient presented with fever, fatigue, NYHA II, and developed peripheral embolization but responded to medical treatment alone. The fourth patient presented with intermittent fever for 7 months. During hospitalization, he suffered acute limb ischaemia and stroke with absence of left dorsalis pedis and posterior tibial pulsation. Brucella IgG ELISA was positive. Mitral valve replacement was done subsequently with unremarkable hospital course.

Discussion

Brucellosis is a challenging diagnosis to make. The diagnosis and treatment is often delayed as it presents with non-specific symptoms and signs. Cardiac involvement occurs in only 2% of the cases, but accounts for 80% of the mortality due to brucellosis. Brucella endocarditis should be suspected in cases of endocarditis with negative blood cultures and a risk of exposure. The most accepted treatment for Brucella endocarditis is a combination of antimicrobial therapy with surgery.

Keywords

Infective endocarditis • Brucella melitensis • Aortic abscess • Embolic phenomenon • Case series

Introduction

Brucellosis is a zoonotic infection. Humans contract brucellosis through inhalation of aerosolized infected particles, or when they come in direct contact with infected animal parts, or on consuming unpasteurised dairy products. It can affect multiple organs and systems that may be complicated by severe life-threatening entities: neurobrucellosis or endocarditis. Endocarditis is diagnosed late in the course of the disease with mostly aortic valve involvement and leads to serious morbidity and mortality. Brucella can affect both native or prosthetic valves.

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### Timeline

**Patient 1**

| Date          | Event Description                                                                 |
|---------------|----------------------------------------------------------------------------------|
| October 2017  | Fever and malaise × 1 month, exertional breathlessness × 1 month                  |
| 10 November 2017 | Hospital admission with acute heart failure, fever                               |
|               | Transthoracic echocardiogram: Severe aortic regurgitation (AR), moderate mitral regurgitation (MR), vegetation 2.6 × 2.0 cm attached to non-coronary cusp |
|               | Blood culture obtained                                                            |
|               | Empiric antibiotic: Ceftriaxone 2 g IV o.d., Gentamicin 3 mg/kg IV o.d.            |
| 11 November 2017 | Transoesophageal echo (TOE): Vegetations on both right and non-coronary cusp measuring 2.6 × 2.2 cm and 1.0 × 0.6 cm, respectively with severe aortic and moderate mitral regurgitation |
| 15 November 2017 | Blood culture negative                                                             |
| 15 November 2017 | No improvement. Fever and heart failure persisting                                |
| 16 November 2017 | Serology for Brucella obtained in view of occupation and bulky vegetation         |
| 26 November 2017 | Dyspnoea New York Heart Association IV, respiratory distress, heart failure, and mechanical ventilation |
| 27 November 2017 | The valve was excised together with the vegetation and replaced with a 23 mm St. Jude mechanical prosthetic valve |
| 5 December 2017 | Discharged home with antibiotics for 3 months. Stable at follow-up                |

**Patient 2**

| Date          | Event Description                                                                 |
|---------------|----------------------------------------------------------------------------------|
| August 2017   | Fever × 1 month, breathlessness × 15 days, anorexia, myalgia, arthralgia, and weight loss |
| 3 August 2017 | Admitted to the hospital Transthoracic echocardiogram: Severe AR, moderate MR, vegetation attached to right coronary cusp (RCC), and aortic root abscess with aneurysm |
|               | Computed tomography: Aneurysm arising from right sinus of Valsalva causing compression of the left main coronary artery |
|               | Blood cultures obtained                                                           |
| 3 August 2017 | Empiric antibiotic: Ceftriaxone 2 g IV o.d., Gentamicin 3 mg/kg IV o.d.            |
| 8 August 2017 | Blood culture confirmed Brucella melitensis                                       |
|               | Started on Doxycycline 200 mg/day, Rifampin 600 mg/day, and Co-trimoxazole 960 mg b.i.d. |

**Patient 3**

| Date          | Event Description                                                                 |
|---------------|----------------------------------------------------------------------------------|
| January 2016  | Fever and fatigue 2 months                                                        |
| 24 February 2016 | Admitted to the hospital. Transthoracic echocardiogram revealed vegetations attached to the RCC. Blood culture obtained. Empirically started on Ceftriaxone and Gentamicin |
| 25 February 2016 | Transoesophageal echo confirmed the presence of vegetation on RCC and non-coronary cusp measuring 1.0 × 1.0 cm and 0.4 × 0.6 cm, respectively |
| 1 March 2016  | Blood culture yielded B. melitensis                                               |
|               | Started on Doxycycline 200 mg/day, Rifampin 600 mg/day, and Co-trimoxazole 960 mg b.i.d. |
| 10 March 2016 | Peripheral embolization leading to acute limb ischaemia                           |
|               | Colour Doppler confirmed acute subtotal occlusion of left tibio-peroneal trunk    |
| 20 March 2016 | Repeat TOE demonstrated regression in vegetation size                              |
| 22 March 2016 | Discharged in stable condition on 3 months course of antibiotic treatment         |

**Patient 4**

| Date          | Event Description                                                                 |
|---------------|----------------------------------------------------------------------------------|
| 29 May 2018   | Fever × 7 months. Antibiotics given for 2 weeks before presentation               |
| 30 May 2018   | Total leucocyte counts were 23 450/mm³ with predominant neutrophils. Renal parameters were deranged. Echo examination revealed perforated anterior mitral leaflet (AML), severe MR with mobile vegetations attached to posterior mitral leaflet and AML and moderate tricuspid regurgitation. |
| 1 June 2018   | Acute limb ischaemia and stroke                                                   |
|               | Arterial Doppler revealed mixed echogenicity thrombus in right tibio-peroneal trunk, left proximal, and mid SFA suggestive of subacute embolism. Computed tomography brain revealed hypodensity in anteromedial aspect of the left thalamocapsular region suggesting infarction |
|               | Brucella IgG ELISA was positive. Antibiotics changed to Doxycycline, Rifampicin, and Co-trimoxazole with gradual improvement |
| 12 June 2018  | Mitral valve replacement was done. Recovery uneventful.                           |
Case presentation

Patient 1

A 38-year-old male farmer presented to us with a 1 month history of low-grade fever associated with sweating, exertional breathlessness of New York Heart Association (NYHA) Grade III, malaise, and arthralgia. There was no history of previous antibiotic use. His medical and surgical history were unremarkable.

On examination, he appeared unwell. His heart rate was 110 b.p.m., blood pressure was 100/60 mmHg, and temperature was 40°C. Cardiac auscultation revealed a left ventricular 3rd heart sound with an early diastolic murmur in the left 3rd intercostal space. There were no peripheral signs of infective endocarditis. Chest revealed bilateral basal crepitation. There were no sign of organomegaly.

The laboratory test revealed a haemoglobin of 9.8 g/dL (normal), total leucocyte count of 8000/mm³ (normal 4000–11 000/mm³), and platelet count of 69 000/mm³ (normal 150 000–400 000/mm³). Chest X-ray revealed a normal cardiothoracic ratio with hilar congestion. A transthoracic echocardiogram was performed in recumbent position, which revealed a large vegetation measuring 2.6 × 2.2 cm attached to the non-coronary cusp prolapsing from the aorta to the left ventricle (Figure 1, Supplementary material online, Video S1). There was evidence of severe aortic regurgitation (AR) and moderate mitral regurgitation (MR). Transthoracic echocardiogram confirmed the presence of vegetations on both right and non-coronary cusp measuring 2.6 × 2.2 cm and 1.0 × 0.6 cm, respectively (Figure 2, Supplementary material online, Video S2) with severe AR and moderate MR. The valves, however, were normal in structure.

Our patient was empirically started on Ceftriaxone 2 g with Gentamicin 3 mg/kg body weight. Meanwhile, three sets of blood cultures were obtained as per protocol. The patient’s occupation and presence of bulky vegetations raised our suspicion for brucellosis. Serology for Brucella came as positive with high titres. The antibiotics were changed to include Doxycycline (200 mg/day), Rifampicin (600 mg/day), and Co-trimoxazole (960 mg b.i.d.). During the subsequent 10 days, despite appropriate antibiotic treatment, the patient developed NYHA Class IV breathlessness requiring mechanical ventilation. Since the patient continued to be in NYHA Class IV and the vegetations did not show any sign of regression with the possibility of embolic complication, we proceeded to aortic valve replacement. Cardiopulmonary bypass was established with conventional mild hypothermia (34.0°C). Aortotomy revealed large vegetations in the right coronary cusp (RCC) and non-coronary cusp (Figure 3). The valve was excised together with the vegetation and replaced with a 23 mm St. Jude mechanical prosthetic valve.

The patient’s clinical state improved post-surgery. At follow-up after 1 month, our patient was doing well. Antibiotics were continued for 3 months thereafter.

Patient 2

A 35-year-old male farm labour, presented to us with fever since 1 month, breathlessness NYHA III since 15 days, with arthralgia, myalgia, anorexia, and weight loss.

On examination, the patient was febrile with a temperature of 38.2°C, pulse rate of 120 b.p.m., and blood pressure of 100/60 mmHg. Cardiac examination revealed an early diastolic murmur in the aortic area.

Transthoracic echocardiogram showed large vegetations attached to the RCC with severe AR with aortic root abscess extending into the interventricular septum. Aneurysm of sinus of Valsalva was evident (Figure 4, Supplementary material online, Video S3). There was moderate MR with anterior mitral leaflet (AML) perforation. Left to right shunt was noted through a patent foramen ovale. Computed tomography scan of aortic root and ascending aorta confirmed aneurysm arising from right sinus of Valsalva causing compression of the left main coronary artery (LMCA) (Figure 5).

Blood investigations showed mild anaemia. While awaiting blood culture we started empiric treatment with parenteral Ceftriaxone 2 gm per day and parenteral Gentamicin 240 mg IV per day. When blood culture grew Brucella melitensis antibiotics were changed to Doxycycline (200 mg/day), Rifampicin (600 mg/day), and Co-trimoxazole (960 mg b.i.d.). Valve tissue samples taken during surgery also showed growth of B. melitensis. In view of aortic abscess with
impending rupture and compression of LMCA, aortic valve replacement was performed on the 4th day of antibiotic treatment.
Recovery was uneventful. Antibiotics were continued for 3 months thereafter.

Patient 3
A 48-year-old male farmer presented to us with fever of 2 months duration with fatigue NYHA II.
On examination, the patient was febrile with a temperature of 38.8°C, pulse rate of 110 b.p.m., and blood pressure of 100/60 mmHg. Cardiac examination revealed an early diastolic murmur in the aortic area. During hospitalization, our patient had embolization to the left lower limb leading to acute limb ischaemia. Total leucocyte count was 14 800/mm³ (4000–11 000/mm³).
Transthoracic echocardiogram showed a large vegetation attached to the RCC with moderate AR (Figure 6, Supplementary material online, Video S4). Transoesophageal echo confirmed the presence of vegetation on RCC and non-coronary cusp measuring 1.0 x 1.0 cm and 0.4 x 0.6 cm, respectively. Colour Doppler of the lower limb revealed acute subtotal occlusion of left tibio-peroneal trunk which did not require intervention. Blood culture grew B. melitensis and antibiotics were changed to Doxycycline (200 mg/day), Rifampicin (600 mg/day), and Co-trimoxazole (960 mg b.i.d.). The total leucocyte counts normalized after treatment to 7000/mm³ (4000–11 000/mm³). The size of the vegetation reduced to 2 mm after antibiotic treatment with moderate AR. Recovery was uneventful with no mobility issues from the ischaemic limb. Antibiotics were continued for 3 months thereafter.

Patient 4
A 56-year-old diabetic male presented with history of intermittent fever for 7 months. He was diagnosed with mitral valve endocarditis elsewhere and treated with antibiotics for 2 weeks despite which patient had persistent fever and renal dysfunction and therefore was transferred to our specialist unit. On examination, patient was febrile, pulse rate of 116/min. Cardiac examination revealed a pansystolic
murmur at the apex. Total leucocyte counts were 23 450/mm³ (4000–11 000/mm³) with predominant neutrophils.

Blood urea was 78 mg/dL (15–45 mg/dL), serum creatinine was 2 mg/dL (0.6–1.2 mg/dL). Transthoracic echocardiogram revealed perforated AML, severe MR with large mobile vegetations attached to posterior mitral leaflet measuring 1.4 × 2.2 cm, to the base of AML measuring 0.8 × 1.8 cm and atrial surface of AML and moderate tricuspid regurgitation (Figures 7 and 8, Supplementary material online, Videos S5 and S6). During hospitalization, he suffered acute limb ischaemia with absence of left dorsalis pedis and posterior tibial pulsation and stroke with right hemisensory syndrome involving head, face, trunk, arm, and leg, accompanied by a right hemiparesis. Arterial Doppler revealed mixed echogenicity thrombus of right tibio-peroneal trunk, left proximal, and mid superficial femoral artery (SFA) with distal monophasic flow. Computed tomography brain revealed left sided 9 × 9 mm hypodensity in anteromedial aspect of thalamocapsular region suggesting infarction. Brucella IgG ELISA was positive. Antibiotics were changed to Doxycycline (200 mg/day), Rifampicin (600 mg/day), and Co-trimoxazole (960 mg b.i.d.) with gradual improvement. Mitral valve replacement was done subsequently with unremarkable hospital course.

All the patients are doing well on follow-up with no residual symptoms, and follow-up echocardiogram were unremarkable.

Discussion

Brucellosis is a zoonotic infection that transmits to humans due to contact with infected animal parts or consumption of unpasteurised dairy products. It is endemic to Middle East, Mediterranean, South Asia, and South America. Human infection usually is caused by one of the three species of Brucella: B. melitensis, Brucella abortus, or Brucella suis.

The most common presentation is pyrexia of unknown origin with night sweats, arthralgia, malaise, and asthenia. Cardiovascular involvement most commonly manifests as infective endocarditis but is seen in only 2% cases of brucellosis. However, it accounts for nearly 80% mortality in brucellosis infections. Most commonly the aortic valve is affected (75%), followed by equal involvement of mitral valve alone, aortic and mitral valve and prosthetic valve 8.3% each. The native aortic valve is preferentially involved but if the valves are damaged, then the predilection is for mitral valve. Brucella endocarditis may be complicated by myocardial abscess, heart failure, disseminated intravascular coagulation, and embolic phenomenon. Myocardial abscess may complicate as many as 43% cases of brucellosis. Abscess is more common in Brucella endocarditis than with any other organism.

Blood culture is the gold standard diagnostic test to diagnose brucellosis, but the sensitivity is 15–70%. Serology is being used...
increasingly and is a major criteria in Duke’s criteria. Wright’s agglutination titres of one in 160 is very specific and sensitive.\textsuperscript{12}

The most accepted treatment for Brucella endocarditis is a combination of antimicrobial therapy with surgery.\textsuperscript{13} Antibiotic regimen recommended is a combination of Rifampicin 300–600 mg/24 h, Co-trimoxazole 960 mg/12 h, and Doxycycline 200 mg/24 h for 3–6 months orally.\textsuperscript{14}

**Conclusion**

Brucella endocarditis is a lethal complication of Brucellosis. A high degree of suspicion should be entertained to diagnose this entity. Antibiotic therapy alone may not suffice and may require surgical intervention.

**Supplementary material**

Supplementary material is available at European Heart Journal - Case Reports online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case series including image(s) and associated text has been obtained from the patients in line with COPE guidance.

Conflict of interest: none declared.

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