CASE REPORT

Brucella endocarditis in a non-endemic area presenting as pyrexia of unknown origin

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SUMMARY

A 67-year-old man with type 2 diabetes mellitus and hypertension since 7 years presented with a 3-month history of low-grade fever and malaise. Cardiac auscultation revealed the presence of an ejection systolic murmur in the primary aortic area. Most of the investigations for febrile illness were reported normal. His two-dimensional (2D) echocardiogram revealed a calcified aortic valve with mild aortic stenosis. In view of the prolonged fever and calcified aortic valve with mild aortic stenosis, a transoesophageal echocardiogram was performed, which showed small vegetation noted on right coronary cusp about 2.2 mm with free independent mobility. Blood culture was positive for *Brucella* spp from all the three venepuncture sites. Medical therapy for brucellosis was given with ciprofloxacin, doxycycline, co-trimoxazole and streptomycin, resulting in complete recovery. Brucella endocarditis is a rare, mostly ignored and missed clinical infection. It requires a high index of clinical suspicion for prompt diagnosis and treatment.

BACKGROUND

The actual presentation of the patient was pyrexia of unknown origin, the commonest causes of which are infections or malignancy. Among the infections most common causes is tuberculosis, though in our patient it turned out to be brucella endocarditis affecting degenerative/atherosclerotic mild aortic stenosis in an atypical manner.

Brucella endocarditis is one of the rarest, most ignored and missed clinical infections. It requires a high degree of clinical suspicion for prompt diagnosis and treatment.

CASE PRESENTATION

A 67-year-old Indian man presented with a 3-month history of low-grade fever with malaise.

The onset was insidious and intermittent in nature and not associated with chills, rigours, rash, joint pain, decreased appetite or weight loss.

There was neither history of respiratory or cardiac symptoms, nor of tuberculosis; nor was there history of contact with animals. There was a history, however, of ingestion of fresh unpasteurised milk within the past few months; the exact date of ingestion was not known. There was no history of previous use of antibiotics and no significant surgical history. On general examination, the patient was febrile, with a temperature of 101°C. His pulse rate was 88/min R; blood pressure was 150/80 mm Hg. Cyanosis, clubbing, icterus, oedema or lymphadenopathy were not present.

On cardiac auscultation, ejection systolic murmur grade 3/6 in aortic area was conducted with the same intensity to both carotids. No signs of congestive cardiac failure or infective endocarditis were noted. Rest of the systemic examination was normal.

The patient was admitted to hospital thrice during the course of illness.

INVESTIGATIONS

On first admission his labs included:

- ▶ Haemoglobin: 11.4 g/dL
- ▶ Red blood cells: normocytic normochromic
- ▶ White cell count: 7000/mm³
- ▶ Platelet count: 0.3 million/mm³
- ▶ Rapid diagnostic test (RDT) for vivax and falciparum malaria was negative. Malarial parasites were not seen on peripheral blood smear.
- ▶ Erythrocyte sedimentation rate: 21 mm/h
- ▶ Blood sugar level fasting: 101 mg/dL, postprandial: 110 mg/dL
- ▶ Total bilirubin: 0.4 mg/dL
- ▶ Direct bilirubin: 0.2 mg/dL,
- ▶ Aspartate aminotransferase: 39 U/L
- ▶ Alanine transaminase: 34 U/L
- ▶ Alkaline phosphatase: 34 U/L
- ▶ Total protein: 7.6 g/dL
- ▶ Albumin: 4.5 g/dL
- ▶ Globulin: 3.1 g/dL
- ▶ Urea: 35 mg/dL
- ▶ Creatinine: 1.4 mg/dL
- ▶ Sodium: 136 mmol/L
- ▶ Potassium: 4.3 mmol/L
- ▶ HIV/HBsAg: negative
- ▶ Blood widal and dengue NS1 and IgM: negative
- ▶ Blood and urine culture: negative
- ▶ BMA and culture: no significant abnormality detected
- ▶ Chest X-ray: normal
- ▶ Ultrasonography (USG) of the abdomen and pelvis: normal
- ▶ ECG: within normal limit

2D echo: Moderate concentric hypertrophy of left ventricle, degenerative changes of aortic valve with mild aortic stenosis, ejection fraction 55%. No clots and no vegetations.

The patient was treated with ceftriaxone 2 g intravenously per day for 7 days keeping in mind the possibility of typhoid fever. He still showed an occasional mild rise of temperature. He was discharged after 7 days with advice to continue oral cefixime 400 mg once daily.

His fever bounced back within 48 h of discontinuation of intravenous ceftriaxone and he was readmitted.

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On second admission, the patient had the same symptoms, with no other clinically significant signs except temperature 100°C. Lab parameters were normal.

Other investigations included:

- ▶ Antinuclear antibody blot assay normal
- ▶ Chest X-ray and USG of the abdomen and pelvis normal
- ▶ MRI of the abdomen and pelvis normal
- ▶ Upper gastrointestinal endoscopy done in view of persistent anorexia did not show significant changes
- ▶ CT of thorax revealed no significant pulmonary pathology
- ▶ C reactive protein (CRP) positive (quantitative analysis was not available at our institute)
- ▶ Right atrium factor/antistreptolysin O/Venereal Disease Research Laboratory were negative
- ▶ RDT/dengue NS1, IgM and IgG were negative
- ▶ Thyroid functions were normal
- ▶ On 2D echo, the patient had concentric left ventricular hypertrophy (LVH) with grade 1 diastolic LV dysfunction and sclerotic aortic valve. No vegetations were noted. Rest of the valves and pulmonary artery pressure were normal, EF 55%.
- ▶ Cardiac MRI revealed LVH with mild aortic valvular stenosis.
- ▶ Blood cultures of three samples from three different venepuncture sites, each 1 h apart, on three separate occasions with intervals of 1 day revealed no growth.
- ▶ Brucella tube agglutination test was negative.

At this point, the possibility of culture negative infective endocarditis (strong clinical suspicion) was kept in mind as the patient had pre-existing cardiac lesion, although transesophageal echocardiography (TEE) was not done as the patient was not willing.

Cultures for other culture-negative organisms were not done as our institute had no facility for providing them.

The patient was started on empirical antibiotic treatment by vancomycin (30 mg/kg intravenously in two divided doses) and ceftriaxone (2 g intravenously daily) for 5 weeks.

After completion of antibiotic treatment, the patient was admitted third time with similar episodes of fever.

Routine laboratory reports were normal.

This time patient was free of all antibiotics for 1 week during hospitalisation.

Two sets of blood samples at an interval of 1 day were drawn from three different venepuncture sites, each 1 h apart, which revealed *Brucella melitensis* growth in all the blood samples; this was also confirmed by Bact/Alert 3D and VITEK 2 system.

A brucella tube agglutination test was again negative (it might have been falsely negative). The test was repeated with increasing dilutions and was strongly positive with 1:1280 titres; this was considered to be due to prozone phenomenon.

In view of calcific aortic stenosis but no vegetations on 2D echo, transoesophageal echocardiography was performed, which revealed small vegetation on right coronary cusp about 2.2 mm with free independent mobility (figures 1 and 2) with no paravalvular abscesses noted (figure 3) with new onset mild aortic regurgitation (figure 4).

Since Duke's diagnostic criteria were met in this patient, a diagnosis of infective endocarditis due to *B. melitensis* was established.

DIFFERENTIAL DIAGNOSIS

- ▶ Subacute bacterial endocarditis
- ▶ Brucellosis infection
- ▶ Tuberculosis
- ▶ Chronic malaria

Figure 1 Transesophageal echocardiography image showing 2.2 mm of vegetation on the right coronary cusp of aortic valve.

- ▶ Typhoid fever
- ▶ Connective tissue disorder
- ▶ Occult malignancy

TREATMENT

When blood culture revealed *B. melitensis*, antibiotics were changed to streptomycin 0.75 g intramuscular injection once daily for 2 weeks, doxycycline 100 mg orally twice daily, co-trimoxazole 800+160 mg orally twice daily, rifampicin 600 mg orally once daily.

Within 5–6 days the patient was displaying severe dyspeptic symptoms associated with deranged liver function tests so rifampicin was stopped and ciprofloxacin 500 mg orally twice daily started.

OUTCOME AND FOLLOW-UP

Follow-up TEE on 15th day of definitive therapy showed no evidence of endocarditis vegetations.

The patient was followed at weekly intervals with good compliance to doxycycline, co-trimoxazole and ciprofloxacin with no other symptoms.

He completed 3 months of therapy, which has now been discontinued.

He gained weight and appetite and was free of all constitutional symptoms.

He was offered the option of surgical treatment, which he declined.

Figure 2 Transesophageal echocardiography image showing vegetation is slightly in a different anatomical position to indicate it is mobile vegetation.

Figure 3 Transesophageal echocardiography image showing aortic semilunar valve with vegetation on the right coronary cusp without paravalvular abscess.

DISCUSSION

Brucellosis is a systemic infectious disease caused by Gram-negative, aerobic, non-capsulated coccobacilli of the genus *Brucella*.

Almost every organ gets involved to different degrees by this disease.

They are the commonest cause of zoonotic infections worldwide.^{1 2}

Brucellosis continues to be reported from Mediterranean and Middle Eastern countries.^{3 4}

Ten per cent to 15% of patients have complicated brucellosis.⁴

Although endocarditis is seen in less than 2% of the cases, it is responsible for half of the deaths due to brucellosis.¹

Direct contact with the infected tissue or blood, consumption of infected dairy products, unpasteurised milk or milk products and inhalation of infectious aerosol particles can transmit the disease.^{3 4}

The clinical presentation varies widely from asymptomatic and mild-to-severe disease so it is often challenging for diagnosis and often delays the appropriate treatment. The diagnosis is relatively easy, however, in endemic areas such as Mediterranean

and Middle Eastern countries; high suspicion is needed when the incidence of brucellosis is low.

Brucellosis is a systemic infection that can affect any organ: the spleen, liver and bone marrow, rich in reticuloendothelial cells, are the most frequently involved sites.

Cardiovascular, gastrointestinal, osteoarticular, urogenital, haematological, skin and neurological complications may arise.⁵

Vascular involvement is quite rare and includes arterial aneurysm formation in different vessels, peripheral arteritis, arterial thrombosis, cutaneous vasculitis, deep venous thrombosis and cerebral vein thrombosis.^{6–11}

Cardiovascular complications occur in less than 2% of cases, but 80% of deaths from this disease are due to the onset of endocarditis.^{12 13}

Brucella endocarditis was first reported in 1906.⁴

Generally, aortic valve invasion is most commonly seen.

Brucella endocarditis appears with a long-lasting subfebrile body temperature and a delayed (3–11 months afterwards) severe dysfunction occurring in the aortic valve.¹⁴

In our case, the aortic valve, right coronary cusp had 2.2 mm vegetation.

Brucella is able to infect endothelial cells and causes a powerful inflammatory response, leading to possible cardiovascular complications.

Endothelial activation in response to *Brucella* infection, with upregulation of adhesion molecules and secretion of proinflammatory chemokines, may play an important role.¹⁵

Endocarditis of native or, more often, prosthetic valves is the most common presentation of cardiovascular involvement.^{16 17}

Diagnosis of infective endocarditis on clinical basis is often challenging.

Up to 90% of patients present with fever often associated with chills, decreased appetite and weight loss.

Heart murmurs are found in up to 85% of patients.

Thirty per cent of patients present with vascular and immunological phenomena.

In febrile patients, diagnostic suspicion may be strengthened by laboratory signs of infection, such as elevated CRP or sedimentation rate, leucocytosis, anaemia and microscopic haematuria. However, they lack the specificity.¹⁸

Figure 4 Transesophageal echocardiography with colour Doppler study showing vegetation on the aortic valve with mild (grade 1) aortic regurgitation with no paravalvular complications.

Atypical presentation is common in the elderly or immunocompromised patients.¹⁹

In suspected cases at least three sets of blood culture from three different venepuncture sites should be drawn half an hour apart, each containing 10 mL of blood.²⁰

Blood culture constitutes the only specific test and is considered the gold standard diagnostic test in for brucellosis; its sensitivity, however, varies from 17% to 85%, depending on the conditions of the culture, the antibiotic treatment and the time lapse between the onset of symptoms and the diagnosis.

However, *Brucella*-positive blood culture is equivalent to endocarditis when relative predisposing factors co-exist.

Currently available tests for diagnosis of brucella endocarditis include blood culture, serology, immunohistology and PCR of surgical material.

As blood culture has a relatively low diagnostic yield shown in a recent study by Esmailpour *et al*, only 22.2% of cases of brucella endocarditis had positive blood culture; serological tests are of great importance in diagnosis of brucella endocarditis with higher sensitivity.²¹

Role of echocardiography in infective endocarditis are as below.

Transthoracic echocardiography is recommended as a first-line imaging modality in suspected infective endocarditis (IE).

Transoesophageal echocardiography is recommended in patients with high clinical suspicion of IE and a normal transthoracic echocardiography.²²

The sensitivity of transthoracic echocardiography ranges from 40% to 63% and that of TEE from 90% to 100%.²³

A surgical approach as a treatment modality was only introduced in 1964.⁴ Immediate surgery after medical treatment is very important because a delay may lead to complications that are difficult to repair.³

Conventionally, IE is managed by a combined medical and surgical approach.²⁴

Surgery mainly involves valve replacement and infected tissue debridement.

The absence of congestive heart failure or of a prosthetic valve, the relatively mild extravalvular involvement and the shorter course of the disease until the start of treatment have been proposed as characteristics of those patients who are responding in a satisfactory way to conservative treatment.²⁵

Despite the administration of properly adjusted pharmaceutical treatment on a case-by-case basis, brucella endocarditis calls for emergency or immediate heart surgery, in the majority of cases, due to inability to control the infection and the progressive shift to congestive heart failure.²⁶

Many studies showed better outcome with the surgical treatment.

However, recent studies showed many selected patients, who could be managed successfully with antibiotics alone, usually required a longer duration of antibiotic treatment, with careful monitoring of response, disease-related complications and need for surgical management.

Generally, brucellosis is treated with a combination of aminoglycosides or rifampicin and doxycycline.

European Society of Cardiology guidelines for treatment of infective endocarditis recommend:

- ▶ Doxycycline (200 mg/24 h) plus co-trimoxazole (960 mg/12 h) plus rifampin (300–600 mg/24 h)
- ▶ For ≥3 months duration orally.
- ▶ Addition of streptomycin (15 mg/kg/24 h in two divided doses) for the first few weeks is optional.
- ▶ Treatment success defined as an antibody titre <1:60.

During the acute phase of IE without any complications such as left atrial thrombosis, venous thromboembolism, atrial fibrillation, routine use of antithrombotic medications are not recommended.²⁷

Learning points

- ▶ *Brucella* endocarditis should be suspected in patients with negative blood cultures who have prolonged fever not responding to routine antibiotics; history of exposure to infected animals; or consumption of infected milk or other dairy products.
- ▶ Suspected patients should undergo both transthoracic echocardiography and transesophageal echocardiography; if initial results are negative and there is strong clinical suspicion, repeat both after 7–10 days.
- ▶ Diagnosed patients should be closely monitored for relapse, disease-related complications and need for urgent surgical intervention.
- ▶ *Brucella* endocarditis usually requires a longer duration of treatment with better patient compliance to treatment.

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Competing interests None.

Patient consent Obtained.

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