Reminder of important clinical lesson

Culture negative endocarditis: a diagnostic and therapeutic challenge!

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Summary

Infective endocarditis remains a diagnostic and therapeutic challenge. The authors report an older male who presented with a lower extremities rash and signs of cardiac failure. Echocardiography showed vegetations attached to the bio-prosthetic aortic valve, however, with negative blood cultures. Further investigation revealed positive *Bartonella* serologies. The patient was diagnosed with *Bartonella* endocarditis affecting the prosthetic valve and started on appropriate antibiotics. Valvular surgery was refused by patient secondary to age and medical co-morbidities. The patient presented 10 days later with intracerebral haemorrhage and progression of the endocarditis as demonstrated on echocardiogram. Valve replacement was contraindicated at this occasion due to the intracerebral bleed. The patient had poor prognosis and a decision to withdraw care was made by the family. The authors demonstrate a case of complicated infective endocarditis caused by *Bartonella* species leading to multisystem involvement. This case highlights the need for urgent valve replacement in the setting of *Bartonella* endocarditis.

BACKGROUND

Infective endocarditis remains a diagnostic challenge. Aetiological diagnosis is critical to select appropriate treatment because death rate remains high.¹ The diagnosis of infective endocarditis is currently based on the modified duke criteria. This requires evidence on echocardiogram or blood culture prior to antibiotic administration. The duke criteria may not be perfect for blood culture-negative infective endocarditis as patients may be chronically ill, afebrile, or may lack valvular vegetations.

Blood culture-negative infective endocarditis refers to endocarditis without aetiology after three blood samples inoculated on standard media. *Bartonella* species are fastidious gram-negative rods that comprise 2% of cases of blood culture-negative infective endocarditis.² Although most *Bartonella* species affect native valves, there are some case reports demonstrating their effect on prosthetic valves causing vegetations and valvular insufficiency.^{3–5} We describe a case of *Bartonella* endocarditis causing vegetations on a bio-prosthetic valve.

CASE PRESENTATION

A 66-year-old white male noted a rash on the anterior aspects of both lower extremities 2–3 days prior to presenting to the emergency room (ER) of a peripheral hospital. The rash was reddish, not raised and not associated with itching or pain. In the ER, the patient had elevated serum creatinine of 7.3 mg/dl (baseline 1.3 mg/dl) and chest x-ray suggestive of fluid overload. The patient was thus transferred to our hospital for further care. Transthoracic echocardiography showed evidence for a mobile mass attached to the aortic valve.

The patient had (1991) medical history of mechanical aortic valve replacement secondary to congenital bicuspid aortic valve. He developed methicillin-sensitive

Staphylococcus aureus bacteremia and an abscess around the prosthetic valve. The prosthetic valve was replaced by a homograft valve in 2007. Other significant medical history included diabetes mellitus, hypertension, hyperlipidemia and atrial fibrillation. There were no drug allergies known to the patient.

The patient stayed in southern Illinois all his life. There was no history of any recent travel or of recent exposure to pets or ticks. He used to work in a cemetery digging graves. He retired 2 years back. There was no history of any alcohol, tobacco, or illicit drug use.

He was febrile (38.1°C) on examination. He was haemodynamically stable. His cardiac examination revealed a loud S2. However, no murmurs, rubs, or gallops were appreciated. Both his lower extremities revealed multiple darkish 2–5 cm lesions over the anterior aspect of his shins. The soles and palms were not involved. There was a small subconjunctival haemorrhage in his left eye.

INVESTIGATIONS

The patient had evidence of pancytopenia with haemoglobin of 7.8 g/dl, white blood cell count of 3300/mm³ and platelet count of 81000/mm³. His serum creatinine was 7.9 mg/dl and glomerular filtration rate was seven. Urine analysis revealed proteinuria and haematuria.

The patient had four sets of blood cultures which were negative. A trans-oesophageal echocardiogram (TEE) showed evidence for two small (6 mm and 8 mm) vegetations attached to the bio-prosthetic valve.

DIFFERENTIAL DIAGNOSIS

The patient was diagnosed with culture negative endocarditis considering the above clinical picture. Non-infective causes of endocarditis such as rheumatic endocarditis, systemic lupus erythematosus and other autoimmune

conditions were considered. His rheumatoid factor was 29 IU/ml (normal <14 IU/ml), however other rheumatological titres such as antinuclear antibody, anti-neutrophil cytoplasmic antibodies, antismooth muscle antibodies and anticardiolipin antibodies were all negative.

Various infective causes of culture negative endocarditis such as the HACEK (*Haemophilus aphrophilus*; *Actinobacillus actinomycetemcomitans*; *Cardiobacterium hominis*; *Eikenella corrodens*; and *Kingella kingae*) group of organism and other epidemiologically relevant organisms such as *Bartonella* spp., *Coxiella Burnetii*, *Chlamydophila* spp., *Brucella* spp. and *Rickettsia* spp. were considered. Blood cultures incubated for prolonged duration to facilitate growth of fastidious HACEK group of organisms remained negative. The serologies for *Bartonella henselae* (IgG=1:8192, IgM <1:20) and *Bartonella quintana* (IgG=1:2048, IgM <1:20) were positive. Serological markers for the all other stated organisms were negative. Titres >1:256 have been recommended to suggest active or recent infection. In a previous case series, all but one patient with *Bartonella* endocarditis had titres ≥1:1600 using a microimmunofluorescence test; the positive predictive value of the test was 0.88.⁶

TREATMENT

The patient was diagnosed with *Bartonella* endocarditis affecting the prosthetic valve. The patient was started on intravenous ceftriaxone 2 g daily, intravenous gentamycin 1 mg/kg with each dialysis and oral doxycycline 100 mg twice a day according to the 2005 American Heart Association guidelines for treating 'culture-negative' endocarditis due to suspected *Bartonella* infection.⁷ Considering a case of prosthetic valve endocarditis, surgery was discussed with the patient to prevent future embolisation. The patient because of his age and other medical co-morbidities refused a high risk surgery. The patient was continued on the same antibiotic regimen and he remained stable and afebrile throughout the hospital course. Haemodialysis was started for his acute renal failure. The patient was discharged to complete a 42-day course of same antibiotic regimen at home.

OUTCOME AND FOLLOW-UP

The patient presented 10 days later to the emergency department with altered mental status and blurring of vision. Neurological examination revealed right homonymous haemianopia with left gaze preference, right haemiplegia and global aphasia.

The computed axial tomography scan of the brain revealed a 5.5 cm left temporo-parietal intraparenchymal haemorrhage. Repeat serologies showed *Bartonella henselae* IgG >1:16384 (normal <1:128) and *Bartonella quintana* IgG 1:2048 (normal <1:128). The follow-up TEE showed progression of the aortic bio-prosthetic valve endocarditis. There was increase in the number of vegetations with prolapse of the bio-prosthetic aortic valve. Valve replacement at this time was contraindicated due to his intracerebral bleed. The patient had very poor prognosis and a decision to withdraw care was made by the family.

DISCUSSION

Bartonella species are fastidious gram-negative rods that comprise around 2% of cases of blood culture-negative

endocarditis.² Preexisting valvular disease or history of valvular surgery are the major risk factors for *Bartonella* endocarditis, which often presents subacutely with fever, and acute renal insufficiency as in our patient.⁸ There have been isolated case reports and a case series of 22 patients that suggest *Bartonella* endocarditis is associated with high frequency of vegetations and embolism.^{6 9 10}

There has also been case reports suggesting occurrence of glomerulonephritis associated with *Bartonella* endocarditis.^{9 11 12} All the patients described had a pattern consistent with immune complex-mediated necrotising and crescentic glomerulonephritis. The findings of low serum complement levels, circulating anti-*Bartonella* IgG antibodies and positive rheumatoid factor in our patient with acute renal failure could suggest the diagnoses of glomerulonephritis secondary to immune-complex deposition.

We present a 66-year-old male with a bio-prosthetic aortic valve who presented with acute renal failure and evidence of bio-prosthetic valvular vegetations. The patient's repeated blood culture remained negative, however he had serologies positive for *Bartonella* species. He was promptly started on ceftriaxone, gentamycin and doxycycline for treatment of culture-negative endocarditis according to the 2005 American Heart Association guidelines. Approximately 80% of patients with *B. henselae* endocarditis require valve replacement because of the destructive nature of the pathogen.⁸ Our patient who refused surgery had further progression of his endocarditis including prolapse of his bio-prosthetic valve.

We demonstrate a case of complicated infective endocarditis caused by *Bartonella* species leading to multisystem involvement. The patient had acute renal failure from possible glomerulonephritis secondary to immune-complex deposition and later an intracerebral bleed which could have been secondary to development of a mycotic aneurysm or embolic phenomena. This case gives light to the need for urgent valve replacement in the setting of *Bartonella* endocarditis.

Learning points

- The diagnosis of infective endocarditis is currently based on the modified duke criteria. This requires evidence on echocardiogram or blood culture prior to antibiotic administration.
- Blood culture-negative infective endocarditis refers to endocarditis without aetiology after three blood samples inoculated on standard media. *Bartonella* species are fastidious gram-negative rods that comprise 2% of cases of blood culture-negative infective endocarditis.
- The duke criteria may not be perfect for blood culture-negative infective endocarditis as patients may be chronically ill, afebrile, or may lack valvular vegetations.
- Approximately 80% of patients with *Bartonella* endocarditis require valve replacement because of the destructive nature of the pathogen.
- Benefit is greatest in the early phase of infective endocarditis, when embolic rates are highest especially when it involves prosthetic valves.

Competing interests None.

Patient consent Obtained.

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