CASE REPORT

The Hidden Pathogen: *Bartonella* as a Cause of Blood Culture-negative Endocarditis (BCNE)

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ABSTRACT

This case illustrates *Bartonella* spp as a recognized cause of blood culture-negative endocarditis (BCNE). This is a case of a 48-year-old woman presenting with heart failure and had echocardiography findings of infective endocarditis (IE). Her blood culture showed no growth after five days incubation for all three sets. *Bartonella* serology was sent because of exposure to cats, and revealed positive *Bartonella henselae* IgM and IgG with titre > 1: 512; which strongly suggestive of infection with *B. henselae*. Her echocardiogram showed presence of severe aortic regurgitation and CT Angiogram showed features of aortic valve endocarditis. She was planned for aortic valve replacement; however, unfortunately, patient decided not to proceed with the surgery. She was given oral doxycycline and rifampicin to complete for three months and six weeks respectively. Her outcome of this disease remains unknown since she defaulted her clinic appointment after requesting to be discharged at own risk.
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INTRODUCTION

Bartonella are fastidious gram-negative pleomorphic bacteria. It belongs to the alpha-2 subgroup of the Proteobacteria and closely related to the genera Brucella and Agrobacterium. Human *Bartonella* infection has a variety of clinical manifestations such as *Bartonellosis*, bacillary angiomatosis, endocarditis, bacterial peliosis and cat scratch disease. Through a search in the literature, no case report for human *Bartonella* endocarditis is available yet in Malaysia. This case report aims to highlight *Bartonella* as a recognized cause of blood culture-negative endocarditis (BCNE).

CASE REPORT

A 48-year-old lady with underlying late-onset bronchial asthma on MDI Budesonide 2 puffs BD and MDI Salbutamol PRN, was referred from another tertiary center to our Cardiology Clinic for presumed infective endocarditis (IE). Her initial symptoms included bilateral lower limb swelling and reduced effort tolerance for two months. She also had fever but did not seek treatment. She denied any chest pain, palpitations, or syncope.

On examination, the patient had a blood pressure of 101/65 mmHg and a heart rate of 110 beats per minute. Her SpO_2 was 100% on room air, lungs were clear and cardiovascular examination revealed a diastolic murmur. Abdominal examination showed a soft, non-tender abdomen with palpable splenomegaly. An echocardiogram revealed severe aortic regurgitation, with the aortic valve appear thickened and calcified. There was also a suspected aortic root abscess with possible dissection. The initial impression was aortic valve endocarditis with aortic root abscess/dissection, with systemic lupus erythematosus (SLE) considered as a differential diagnosis. She was subsequently admitted to our cardiology ward for further evaluation.

Her blood investigations in the previous tertiary center were as follows: haemoglobin 7.2 g/dL, white cell count 3.1 x 10^9/L, platelet 90 x 10^9/L; anti-nuclear antibodies (ANA) and extractable nuclear antibodies (ENA) were

sent to rule out autoimmune diseases and the result were negative, with low C3 and C4. Her renal profile were sodium 124 mmol/L, potassium 5.2 mmol/L, urea 10.5 mmol/L and creatinine 217 µmol/L. Her 24-hour urine protein was normal (2.3g/day); and ultrasound KUB showed increased echogenicity and no focal renal lesion.

In the ward, the patient was co-managed by the Rheumatology, Nephrology, and Infectious Disease teams. Her obstetric history revealed two successful pregnancies in 1998 and 1999. However, she experienced multiple intrauterine deaths in 2005, 2007, and 2015, as well as a miscarriage in 2014. She also mentioned having many kittens at home. Given this history, *Bartonella* serology was ordered for further investigation. The team administered oral doxycycline and rifampicin to cover for *Bartonella* endocarditis and continued IV Rocephine, which was already started by the previous hospital. Blood culture was sent in three sets from three different locations as per IE guideline. CT angiogram (CTA) showed features of aortic valve endocarditis and aortic root pseudoaneurysm (Figure 1 and Figure 2). An aortic valve replacement with aortic root repair was planned.

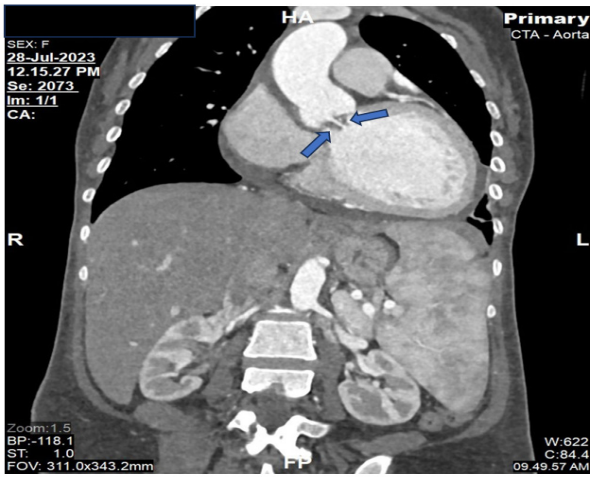

Figure 1: CT Angiogram showing the aortic valve leaflets are thickened (arrow) and calcified with few nodular hypodense lesions extending to the left ventricular outflow tract suggestive of vegetation.

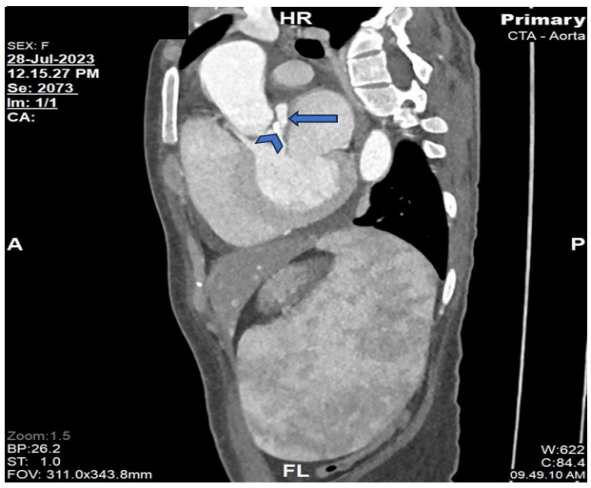

Figure 2: Focal contrast-filled outpouching (arrow) seen arising from the posterior aspect of the aortic root and located anterior to the left atrium consistent with aortic root pseudoaneurysm. There are also vegetation and calcification (arrowhead) adhere to the aneurysm extending to the annulus.

Her blood culture showed no growth after five days of incubation for all three sets. *Bartonella* serology result came back as positive *B. henselae* IgM and IgG with titre > 1:512, which was strongly suggestive of *Bartonella* infection. In addition to that, *B. quintana* IgG titre was 1:512, and IgM was negative. C-reactive protein (CRP) was decreasing in trend from 167 mg/L to 40.6 mg/L. Her ESR was > 120 mm/hr. Her haemoglobin level ranging from 6.9 to 9.5 g/dL. She had 1 pint packed cell transfused when her haemoglobin level was 6.9 g/dL. She remained thrombocytopenic throughout the admission with the highest platelet level of 89 x 10^9/L. Her renal profile showed persistent hyponatraemia with increased urea and creatinine levels.

Throughout the admission, she was well, hemodynamically stable, saturating well on room air and afebrile. She refused surgery and subsequently requested discharge against medical advice on day 13 of admission. She was discharged with a diagnosis of *Bartonella* aortic valve IE and aortic root abscess. Upon discharge, she was prescribed oral doxycycline (to

complete for three months) and rifampicin (to complete for six weeks). She was given clinic appointment in one month time, which, she defaulted.

DISCUSSION

This is a case of a 48-year-old woman presenting with heart failure and had echocardiography findings of IE. Investigation showed positive *B. henselae* IgM and IgG with titre > 1:512; with negative blood culture.

Bartonella spp. are recognized cause of BCNE. Of the six species reported, over 95% of cases are due to *B. quintana* or *B. henselae*. The three key *Bartonella spp* causing human disease are *B. bacilliformis, B. quintana*, and *B. henselae*.

Human *Bartonella* infection presents with various clinical manifestations, most commonly as cat scratch disease (CSD). CSD typically appears as localized cutaneous and regional lymphadenopathy but can also spread to organs like the liver, spleen, eyes or central nervous system. While localized cases usually resolve on their own, disseminated cases can lead to severe, life-threatening complications.

The patient's contact with cats, having many kittens at home, is a key risk factor for acquiring this disease. Physical examination revealed findings consistent with IE, including a murmur, clubbing, and splenomegaly, though peripheral stigmata such as Janeway lesions, Roth spots, splinter hemorrhages, and Osler nodes were absent. The echocardiogram showed valvular vegetations and a thickened aortic valve, aligning with Didier Raoult et al.'s study, which found that about 90% of *Bartonella* endocarditis patients have valvular vegetations on echocardiography, with 60% involving the aortic valve [1]. Common laboratory abnormalities, also seen in this patient, are elevated inflammatory markers like ESR, anemia, thrombocytopenia, and signs of renal failure. The mechanism behind *Bartonella*-induced thrombocytopenia is unknown. It may result from direct damage to megakaryocyte limiting platelets production or an autoimmune destruction of platelets causing immune thrombocytopenia [2]. Kidney disease commonly complicates IE, affecting 40% to 50% of patients with issues like parenchymal infarction, hematuria, or glomerulonephritis. In a previous study, 45% of *Bartonella* endocarditis cases led to kidney failure [3].

For this patient, SLE is part of the differential diagnosis as she had three episodes of intrauterine death. However, despite having a high ESR and low C3 and C4 levels, markers often associated with SLE; her ANA and ENA tests were negative. She also lacked typical SLE symptoms like rashes, synovitis, oral ulcers, or neurological symptoms. With an SLE score of 2 on the Systemic Lupus International Collaborating Clinics (SLICC) criteria, where 4 out of 17 criteria are needed for an SLE diagnosis, SLE is unlikely.

The DUKE criteria, first introduced in 1994 and revised in 2000, assist clinicians in diagnosing IE. The 2023 update by the Duke-International Society for Cardiovascular Infectious Diseases (ISCVID) added new major criteria for detection of fastidious pathogen. These include using PCR or other nucleic acid techniques to identify *Coxiella burnetti, Bartonella spp*, or *Tropheryma whipplei* from blood, and employing indirect immunofluorescence assays (IFA) to detect IgM and IgG antibodies to *B. henselae* or *B. quintana*, with an IgG titer >1:800. This highlights *Bartonella* as a significant cause of BCNE.

Physicians should have a high index of suspicion of *Bartonella* endocarditis in patients with clinical and echocardiographic findings of endocarditis, especially when traditional blood cultures are negative and there are risk factors, such as cat exposure. Early diagnosis is essential for effective treatment and management, which can help prevent complications like heart failure or embolic events. Embolic events in endocarditis occur in 10% to 50% of cases, with a higher risk in those with aortic valve involvement.

The mainstay treatment for *Bartonella* endocarditis is antimicrobial therapy, though some patients may also require surgical intervention. A study by Eloy E. Odaya et al. on 1-year outcomes in 15 patients with *Bartonella* endocarditis found that of the six patients who received combined surgical and medical treatment, five showed clinical improvement. Among the nine patients initially treated with medical therapy alone, four had good outcomes, while four were readmitted for valve replacement due to relapsed or persistent disease. One patient, who was initially managed medically, developed multiorgan failure and died before undergoing valve replacement [4].

For this patient, the Infectious Disease team planned to send an intraoperative valve tissue sample for 16S RNA analysis, as PCR-based tests on cardiac valvular tissue are crucial for diagnosing *Bartonella* endocarditis. A French review of 106 cases found PCR testing to have a sensitivity of 92% for valvular biopsy specimens, compared to 36% for serum and 33% for blood samples [5]. However, the patient ultimately decided not to proceed with the surgery.

Mortality rates for *Bartonella* endocarditis range from 7% to 30%, though more recent studies indicate lower rates, likely reflecting improvements in diagnosis, treatment, and surgical techniques. This patient was prescribed doxycycline for three months and rifampicin for six weeks, but since she missed her follow-up appointments, the outcome remains unknown. Nevertheless, prior to her discharge, she was counseled regarding the importance of compliance to antimicrobial therapy to

ensure eradication of the organism.

CONCLUSION

This case emphasises *Bartonella* as a recognized cause of BCNE, advocating the clinician to have a heightened awareness, a detailed history taking, early diagnosis and tailored therapeutic interventions to improve patient outcomes. Patient education is equally important in managing this fatal zoonotic disease.

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