



Blood culture–negative endocarditis caused by *Bartonella henselae*: a case report

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Abstract

Bartonella henselae is well known as a causative organism of cat scratch disease. Although this bacterium infrequently involves the heart, the diagnosis is difficult to confirm. A 75-year-old woman who had a pet cat presented with pancytopenia, hepatosplenomegaly, and low-grade fever. Echocardiography depicted sessile nodules on the aortic valve. C-reactive protein concentration was low, and leukocytosis was not seen. Two sets of blood culture turned out negative. However, elevated *B. henselae* immunoglobulin G titer led us to the diagnosis of infective endocarditis. Minocycline was administered orally in combination with intravenous administration of gentamicin as an antimicrobial treatment. The patient underwent aortic valve replacement 2 months after her initial visit. Warthin–Starry silver staining did not show any bacterial bodies. The culture of the vegetation tissue was negative. Polymerase chain reaction testing of the excised valve tissue detected the deoxyribonucleic acid of the organism. The postoperative course was uneventful, and the patient was discharged home.

Keywords *Bartonella henselae* · Endocarditis · Aortic valve · Serology · Polymerase chain reaction

Introduction

Bartonella henselae is well known as a causative organism of cat scratch disease (CSD). Although this bacterium infrequently becomes the etiologic agent of infective endocarditis, it is difficult to confirm the diagnosis. Herein, we describe a case of blood culture–negative endocarditis (BCNE) caused by *B. henselae*.

Case report

A 75-year-old woman was referred to the division of hematology in our institution because of pancytopenia, general fatigue, low-grade fever, and lower leg edema (day 0). The patient had a history of diabetes mellitus as well as hypertension and was keeping a cat, which used to be a stray.

She had not taken any antibiotics before presentation to our institution. Blood analysis at the initial visit was as follows: white blood cell, 4600 / μ L (segmented cell, 70%); hemoglobin, 8.2 g/dL; platelet, 70.0×10^3 / μ L; aspartate aminotransferase, 21 IU/L; alanine transaminase, 9 IU/L; creatinine, 0.71 mg/dL; blood urea nitrogen, 20.2 mg/dL; C-reactive protein (CRP), 3.46 mg/dL; immunoglobulin (Ig) G, 1975 mg/dL; IgA, 90 mg/dL; and IgM, 29 mg/dL. The urine test was positive for protein. On auscultation, slight systolic murmur was audible. Transthoracic echocardiogram revealed sessile nodules on the right coronary cusp (18×8 mm) as well as on the left coronary cusp (6×6 mm) (Fig. 1a). The ejection fraction was 55%, and mild to moderate aortic regurgitation was detected. Computed tomography showed moderate hepatosplenomegaly (Fig. 1b). Although bone marrow aspiration was performed for possible lymphocytic leukemia, no atypical cells were observed. The two sets of blood culture submitted on day 0 came out negative. On day 7, furosemide (20 mg/day) was started as a treatment for lower leg edema. On day 12, in consideration of BCNE, *Bartonella* antibody test using immunofluorescence assay (IFA) (Focus Diagnostics, Cypress, CA, USA) was carried out. Minocycline (200 mg/day) was initiated on the same day as a diagnostic therapy. On day 35, elevated *B. henselae* IgG titer (1:1024) was reported. IgM titer was low. On

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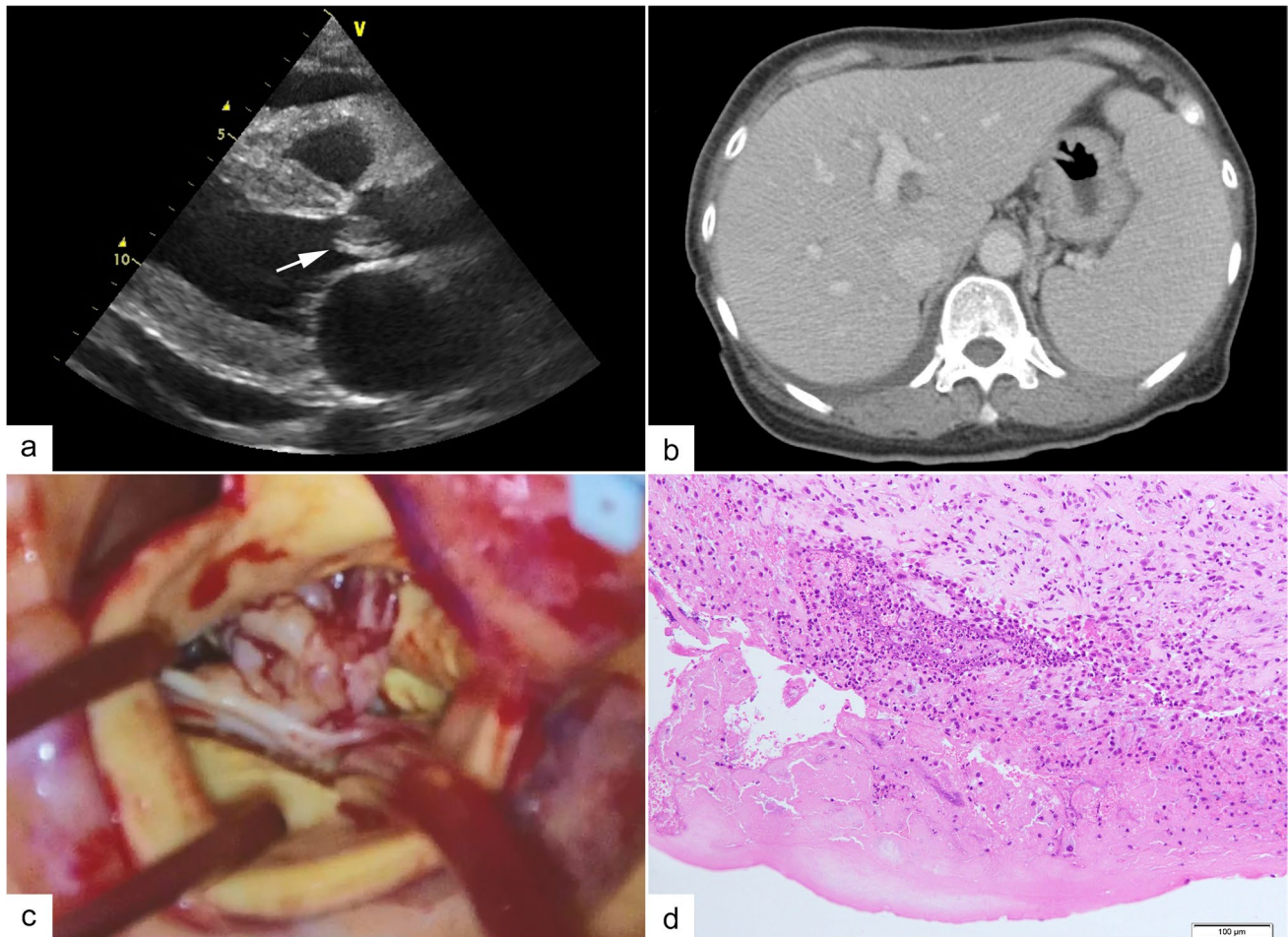


Fig. 1 **a** Long-axis view of transthoracic echocardiogram. The arrow shows the vegetation on the aortic valve. **b** Computed tomography. Hepatosplenomegaly is observed. **c** Intraoperative image. Two fragile vegetations were noted on the ventricular side of the right and left

coronary cusps. **d** Histopathological image. Infiltration of neutrophils and lymphocytes as well as fibrin precipitation is recognized. Original magnification $\times 200$

day 56, the patient complained of dyspnea on exertion. The second echocardiogram revealed no change in size of the vegetation, exacerbation of aortic regurgitation (moderate), reduced ejection fraction (45%), and pericardial effusion. The patient was admitted to the cardiovascular surgery ward, and a continuous infusion of intravenous furosemide was started. On day 59, gentamicin was administered intravenously (initially 120 mg/day, later decreased to 60 mg/day based on therapeutic drug monitoring) in addition to minocycline given orally, considering *B. henselae* as the target organism. Although the blood *B. henselae* polymerase chain reaction (PCR) test (Genesig PCR Kit by Primerdesign Ltd, Camberley, England) was negative, BCNE caused by the organism was strongly suspected. After taking gradual exacerbation of aortic regurgitation and left ventricular function into consideration, we concluded that the infection had not been controlled despite minocycline administration. Surgery was carried out on day 69.

Following median sternotomy, extracorporeal circulation was established by ascending aortic return and bicaval drainage. On opening of the aorta, fragile vegetations on the ventricular side of right and left coronary cusps were observed (Fig. 1c). Neither the annulus nor the mitral valve was involved. The leaflets were excised carefully, and a 21-mm Inspiris Resilia bioprosthesis (Edwards Lifescience, Irvine, CA, USA) was implanted in the supra-annular position.

Histopathology of the valve tissue stained with hematoxylin and eosin revealed infiltration of neutrophils and lymphocytes as well as precipitation of fibrin, which were consistent with infective endocarditis (Fig. 1d). Warthin–Starry silver staining did not show any bacterial bodies. The culture of the vegetation tissue was negative. However, PCR analysis of the vegetation was positive, detecting deoxyribonucleic acid (DNA) of *B. henselae*.

On day 75, gentamicin was discontinued. The postoperative course was uneventful, and the patient was discharged

on day 87. Blood test results were as follows: white blood cell, 3700 μL ; hemoglobin, 11.1 g/dL; platelet, 153×10^3 μL ; and CRP, 0.17 mg/dL. On day 96, minocycline was stopped to complete the treatment.

Discussion

B. henselae, formerly *Rochalimaea*, is a bacterium that is the causative agent of CSD. Humans usually get infected through scratches or bites of infected cats. Canine to human transmission is anecdotally reported. The disease is typically characterized by regional lymphadenopathy and fever. Although the heart involvement is known, the diagnosis is often difficult to confirm. *Bartonella* species account for 9–10% of BCNE [1, 2]. Houpiikian et al. [3] reported that among 71 cases of *Bartonella* endocarditis, *B. quintana* was responsible for 53 (75%) cases and *B. henselae* for 17 (24%) cases. The clinical presentations in the *B. henselae* group were as follows: fever (100%), body weight loss (40%), heart failure (53%), splenomegaly (40%), hepatomegaly (7%), arterial embolism (47%), leukocytosis (38%), anemia (55%), thrombocytopenia (33%), renal failure (50%), and elevated erythrocyte sedimentation rate (83%) [3].

B. henselae is a Gram-negative rod, which is culturable on chocolate agar or blood agar in 5% CO_2 incubator at 35–37°C [4]. However, owing to its fastidious nature, 2–3 weeks is required for incubation. Thus, the bacterium cannot be easily isolated from clinical specimens. Blood culture methods have a sensitivity as low as 20% for diagnosing *Bartonella* endocarditis, while tissue culture of excised valves has a similarly low sensitivity of 30% [3]. Histopathologically, Warthin–Starry silver staining has frequently been employed and reveals black-stained bacteria in the affected valve tissue. The reported sensitivity in *Bartonella* endocarditis is 46% [5]. However, this staining method also detects *Helicobacter pylori*, *Legionella pneumophila*, spirochetes, and *Klebsiella* species, but does not provide a definitive diagnosis.

For the above reasons, serological as well as PCR testing is essential to confirm *B. henselae* infection. IgM and IgG antibodies are measured by commercially available IFA. In the kit used, the cutoff indicating acute-phase infection was as follows: (1) IgM titers $\geq 1:20$ or IgG titers $\geq 1:256$, (2) initial specimen IgG titer $\geq 1:64$ and $< 1:256$, and (3) second specimen (drawn 10–21 days after) titer $\geq 1:256$ or a fourfold increase. Fournier et al. [6] reported that IgG titer of $\geq 1:800$ was highly indicative of current infection in patients with endocarditis. The specificity and sensitivity of serological analysis vary significantly across the literature probably due to cross-reactivity and between-kit variability [7]. By contrast, PCR test can identify the DNA of *B. henselae*. According

to Edouard et al. [5], among patients with endocarditis caused by *B. henselae* or *B. quintana*, the sensitivity was 33% and 92% in blood samples and surgically resected valve specimens, respectively. PCR testing of the valve tissue appears to be most useful in confirming the diagnosis, as was in the presented case. Notably, the modified Duke criteria, which mainly rely on blood culture positivity, show a lower accuracy for early diagnosis of endocarditis caused by *Bartonella* species.

Bartonella species are considered to evade the host immune system because of their intra-erythrocytic propagation and biofilm formation [8]. Thus, the use of at least two antibiotics has been advocated. The Sanford guide [9] recommended 200 mg/day of doxycycline for 6 weeks combined with 3 mg/kg/day of gentamicin for 2 weeks in patients with endocarditis. Since doxycycline was unavailable in our institution, minocycline was employed as an alternative. As regards its intractability to antimicrobial treatment, surgical resection of the infected valve tissue should always be considered.

Delayed diagnosis of endocarditis may cause further destruction of the valve, aggravation of heart failure, and annular abscess, which result in poor surgical outcomes. In our case, CRP before starting antimicrobial treatment remained low between 0.94 and 3.46 mg/dL, and no leukocytosis was detected. Ribeyrolles et al. [10] reported that CRP at admission was < 2 mg/dL in 13 (2.8%) of 469 patients with endocarditis. Not all patients with endocarditis present with elevated CRP or leukocytosis. Moreover, especially in patients with BCNE, the use of transesophageal echocardiography may help identify the progression of valve destruction and aortic regurgitation.

In conclusion, when an echocardiogram shows a mass on the valve leaflet, whereas blood culture is negative, serological as well as PCR testing should be carried out to screen for infection caused by fastidious bacteria, including *Bartonella* species.

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Declarations

Ethics approval Ethical approval was waived by the local Ethics Committee of Ichinomiya Municipal Hospital in view of the retrospective

nature of the study and all the procedures being performed were part of the routine care.

Informed consent Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Conflict of interest The authors declare no competing interests.

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