Case report

*Bartonella henselae* infective endocarditis with dissemination: A case report and literature review in Southeast Asia

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**ABSTRACT**

*Bartonella* is among the most common causes of culture-negative infective endocarditis, with *B. henselae* being one of the most frequently reported species. The clinical presentation of *Bartonella* endocarditis is similar to that of subacute bacterial endocarditis caused by other bacteria and the diagnosis can be challenging since the organism is difficult to isolate using standard microbiologic culture techniques. In clinical practice, *Bartonella* endocarditis is usually diagnosed based on serology. To date, only a handful of cases of infective endocarditis caused by *Bartonella* have been reported in Thailand. Here, we report the case of 51-year-old Thai male with *B. henselae* endocarditis with dissemination to the lungs, bones, subcutaneous tissue, epididymis, and lymph nodes with a successful outcome.

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**Introduction**

*Bartonella* species are small, fastidious, intracellular Gram-negative hemotropic bacilli that are transmitted by arthropod vectors. The infections caused by *Bartonella* species have a broad clinical spectrum ranging from asymptomatic self-limited infections to severe disease with high morbidity and mortality rates [1]. These species are among the most common etiologic agents of culture-negative infective endocarditis, with the prevalence varying from 0.1% to 4.65% of all cases of endocarditis [1]. To date, only a handful of cases of *Bartonella* endocarditis have been reported in Southeast Asia [2].

Here, we report the case of a 51-year-old Thai man with *B. henselae* endocarditis and disseminated infection and review the English language literature published in Southeast Asia.

**Case report**

A 51-year-old Thai man, living in Bangkok, presented with low-grade fever for 3 months. The patient was doing well until 3 months prior to admission when he had fever and back pain over the thoracic and lumbar areas. One month prior to admission, he developed dyspnea with a dry cough. He also noticed a tender nodule (2 cm in diameter) in the left chest wall and reported tenderness of the left testicle. He was admitted to a private hospital with the diagnosis of community-acquired pneumonia and treated with ceftriaxone and azithromycin; however, the patient showed no improvement. He was then referred to our hospital, King Chulalongkorn Memorial Hospital, Bangkok, Thailand. During the period of this illness, the patient lost 8 kg in weight.

On admission, the examination revealed a chronically ill patient with mildly pale conjunctivas, consolidation signs in left lower lung region, a mildly tender subcutaneous nodule (2 cm in diameter) in the lower left anterior chest wall, mild tenderness at the midline of the back from the mid-thoracic to lumbar areas, and tenderness of the left testicle. There were no heart murmurs or embolic and vascular phenomena of infective endocarditis.

Complete blood count analysis revealed a white blood cell (WBC) count of 7600 cells/mm\(^3\) (77.8% neutrophils, 15.4% lymphocyte, 5.8% monocyte), a hemoglobin concentration of 11.6 g/dL, and a platelet count of 382,000 cells/mm\(^3\). Blood chemistry values were normal, with the exception of alkaline phosphatase of 182 U/L and lactate dehydrogenase of 467 U/L. The patient tested negative for anti-HIV antibodies. Chest X-rays revealed linear opacities in both lower lung zones. Chest and abdominal computed tomography scanning revealed a mass-forming lytic lesion at the left anterior sixth rib, multiple lymphadenopathy (0.8–3.4 cm in size) at the right supraclavicular, bilateral internal iliac, para-aortic, precaval, and retrocaval areas, and multiple lytic lesions over the whole spinal and pelvic areas.

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(Fig. 1). Transesophageal echocardiograms exhibited a vegetation at the aortic valve leaflet (0.9 × 0.5 cm in size) (Fig. 2).

The patient was diagnosed with native valve infective endocarditis with disseminated infection; however, all three blood culture specimens were negative for bacteria despite incubation for 3 weeks. Because of lymphadenopathies, multiple osteolytic lesions, and a subcutaneous nodule, we suspected the infection was caused by a less common organism. The patient’s blood was tested for the presence of *Bartonella* and *Coxiella burnetii* using the molecular polymerase chain reaction (PCR) technique. Total DNA was extracted from patient’suffy coat using the QIAamp® DNA FFPE Tissue Kit (Qiagen, Hilden, Germany). The *pap31* gene of *B. henselae* was then amplified by the PCR using GoTaq® Flexi DNA polymerase (Promega, WI, USA) and the specific primers PAP31F and PAP31R [3]. The corresponding PCR product amplified from DNA obtained from another patient with proven *B. henselae* infective endocarditis was used as a positive control and a non-*Bartonella* bacterium (Streptococcus pneumoniae) was used as negative control. Direct DNA sequencing of the PCR product showed 99% homology with the *B. henselae* *pap31* gene (Fig. 3); however, serological testing for Bartonella spp. was not performed.

The patient was diagnosed with *B. henselae* endocarditis with dissemination to the lungs, bones, subcutaneous tissue, epidermis, and lymph nodes. A retrospective history revealed that the patient had been admitted to our hospital on several occasions during the past 5 years with a diagnosis of atypical pneumonia that was dramatically responsive to azithromycin or levofloxacin. Seven years previously, he also had experienced an acute fever with tender and enlarged epitrochlear lymph nodes, and had been successfully treated with azithromycin. He reported having four cats in his house.

The patient was then treated with a combination of levofloxacin, azithromycin, doxycycline, and gentamicin. His lung, bone, epideridymis and subcutaneous lesion was gradually improved and was discharged 23 days after his initial hospitalization.

**Discussion**

*B. henselae* was first isolated in 1992 from an HIV-infected patient who presented with prolonged fever [4]. *B. henselae* is globally distributed in domestic and feral cats (*Felis catus*), although most infected cats are asymptomatic despite a very high bacterial load [5]. The major arthropod vector is the cat flea (*Ctenocephalides felis*). *B. henselae* is the main etiologic agent of cat-scratch disease and is the second most common *Bartonella* species known to cause endocarditis as well as bacteremia and bacillary angiomatosis in immunocompromized patients. *B. henselae* (Chiangrai) and *B. vinsonii* subsp. *arupensis* (Khon Kaen) have been reported as the *Bartonella* species causing human infections (mainly acute fever of unknown etiology) in Thailand [6]. *B. henselae* endocarditis occurs mainly in individuals with pre-existing heart valve lesions, particularly those who have been exposed to cats or cat fleas [6].
Many Bartonella species, including *B. henselae*, *B. elizabethae*, *B. alsatica*, *B. koehlerae*, *B. quintana*, *B. vinsonii* subspecies berkoffii, and *B. mayonimonensis*, have been recognized as the causative agent of culture-negative infective endocarditis in humans, with *B. quintana* and *B. henselae* being the two most frequently reported species [1]. *B. henselae* and *B. quintana* account for over 90% of the cases of Bartonella endocarditis [7,8].

The clinical presentation of Bartonella endocarditis is similar to that of subacute bacterial endocarditis caused by other bacteria. Non-specific symptoms, including fever, fatigue, and weight loss are observed in most patients [7,9]. The diagnosis of Bartonella endocarditis is challenging since the organism is difficult to isolate using standard microbiologic culture techniques [11,12] and serologic tests are usually used in clinical practice. In a case series comprising 740 patients with blood culture-negative endocarditis in France, *Bartonella* infections were identified in 80 (22.5%) patients by indirect immunofluorescence assay of IgG antibodies against *B. quintana* and *B. henselae* (titers $\geq 1: 800$) [10]. In another recent cases series, also from French, reported on 106 patients with Bartonella endocarditis, PCR analysis of Bartonella in blood, serum, and cardiac valves was positive in 20 of 60 (33%), 25 of 70 (36%) and 48 of 52 (92%) patients, respectively [9,10]. In our study, we identified *B. henselae* infection by PCR amplification of the short fragment (151 bp) of the *pap31* gene using specific primers, which provide greater sensitivity for the detection than those specific for the 16S rDNA gene [3].

The treatment of Bartonella endocarditis usually requires a combination of antimicrobials [11]. Most guidelines recommend the use of at least two antibiotics, usually aminoglycoside and doxycycline [12].

A summary of the cases of Bartonella endocarditis reported in Southeast Asia is shown in Table 1. Seven cases have been reported, with a male: female ratio of 6:1 and a median age of 57 [interquartile range(IQR): 51, 62] years. Five patients were from Thailand (2 from the Northeast (Surin and Khon Kaen), and 3 from Bangkok), and two patients were from Laos. The duration of illness before diagnosis ranged from 5 to 270 days. Three (42.8%) patients had pre-existing valvular heart disease. The aortic heart valve being the most common site [7 (100%)]. The other metastatic organs included, lung, liver, spleen, bone, subcutaneous nodules and lymph node [1 (14.3%) each]. The diagnosis was made by PCR assay of the tissue valve or blood [4 (57.1% and 1 (143%), respectively], serology [3 (42.8%)], and Warthin–Starly silver staining of valves tissues [3 (42.8%)]. Surgical treatment was performed in four patients (57.1%) and patients were treated with amoxicillin, gentamicin, ceftriaxone, levofloxacin, doxycycline and azithromycin. The mortality rate was 0%.

The first case of Bartonella endocarditis in Thailand was reported in 2011. The patient, a man with pre-existing chronic rheumatic heart disease, presented with fever, generalized myalgia, and shortness of breath for 5 days. The transthoracic echocardiogram revealed a large mobile vegetation in the aortic and mitral valves and serum *B. henselae*-specific IgG was detected with a titer of 1: 512 by indirect immunofluorescent assay. The patient received amoxicillin and gentamicin, and underwent heart valve replacement. The valve tissue tested positive for *B. henselae* by immunohistochemical (immunoalkaline phosphatase) and PCR analyses [13]. The second case was a 53-year-old man with chronic aortic regurgitation who presented with intermittent low-grade fever for 9 months. Although the patient was treated empirically with amoxicillin/subbactam and gentamicin, he showed no improvement. A transesophageal echocardiogram revealed a large mobile mass (2 x 0.7 cm in size) at the right coronary cusp with a paravalvular abscess. Sequencing of the PCR product using primers specific for 16S rDNA gene revealed 99% identity with that of *Bartonella* species [14]. The third case was a 62-year-old man with atrial septal defect (ASD) and a prothestic pulmonic valve who presented with fever for 5 weeks. The diagnosis was made by the demonstration of rod-shaped bacteria in the heart valve by Warthin–Starley staining, in association with a 4-fold increase in the titer of *B. henselae*-specific IgG from 1: 200 to 1: 1600 and positive PCR amplification of the *pap31* gene of *B. henselae* from

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**Table 1**

A summary of seven reported case of *Bartonella* endocarditis in Southeast Asia.

| Sex and age (years), Province, year reported | Pre-existing disease | Duration of illness | Diagnosis (serology, PCR, culture) | Organ involved apart from IE complications | Treatment: surgery and medication | Outcome, follow-up period |
|--------------------------------------------|---------------------|-------------------|-----------------------------------|------------------------------------------|-------------------------------|-------------------------|
| M 57 Y Khon Kaen 2011 [15]                 | AS with AR, MS with MR (RHD) | 5 days | PCR of valve, IHC staining of valve and serology | – | AVR and MVR, ampicillin, gentamicin | Improved over 2 months but died suddenly from anticoagulant-associated complications |
| M 53 Y Surin 2013 [16]                    | AR                | 9 months | PCR of 16S rRNA gene, sequencing of valve and WSS staining of valve | | – | Improved, follow-up duration unknown |
| M 62 Y Bangkok 2016 [17]                  | ASD, AR, TR and bioprosthetic pulmonic valve | 5 weeks | Serology, PCR (*pap31* gene) of tissue valve and WSS staining of valve | Liver and spleen | AVR, PVR TVR, ceftriaxone, gentamicin, doxycycline | Improved over 9 months |
| M 49 Y Bangkok 2017 [18]                  | –                | 2 months | PCR (*16S–235 rRNA intergenic region*) and WSS staining of valve | | – | Improved over 6 weeks |
| M 51 Y Bangkok (our case) 2017            | –                | 5 months | PCR (*pap31* gene) of serum | Lung, bone, epididymis, lymph nodes | Levofoxacin, azithromycin, doxycycline, gentamicin | Improved over 7 months |
| M 57 Y Pakse, Laos 2012 [19]             | –                | 1 month | Serology | – | Ceftriaxone, gentamicin | Improved over 12 months |
| F 69 Y Xayseththa, Laos 2008 [19]        | –                | 2 months | Serology | – | Ceftriaxone | Improved but died due to gastric perforation |

M: male; F: female, AS: aortic stenosis, AR: aortic regurgitation, MS: mitral stenosis, MR: mitral regurgitation, PS: pulmonic stenosis, TR: tricuspid regurgitation, ASD: atrial septal defect, CHD: congenital heart disease, RHD: rheumatic heart disease, IE: infective endocarditis, AVR: aortic valve replacement, MVR: mitral valve replacement, TVR: tricuspid valve replacement, PVR: pulmonic valve replacement, IHC: immunohistochemical staining, WSS: Warthin–Starly silver.
paraffin-embedded heart valve tissue [17]. The fourth case was a 49-year-old without any underlying disease who presented with fever and dyspnea for 2 months. Transthoracic echocardiograms revealed severe aortic regurgitation with a large vegetation although the results of all three sets of aerobic blood cultures were negative. The diagnosis was made by demonstration of the presence of pleomorphic bacilli by Warthin–Starry staining and B. henselae-positive PCR analysis of valve tissues [18]. In the neighboring country, Laos, two cases of B. henselae endocarditis were diagnosed by Western blot analysis [19].

In conclusion, here, we have reported the case of an adult patient with B. henselae endocarditis with dissemination to the lung, bone, epididymis, and lymph nodes. The patient had a history of cat exposure and was previously diagnosed with cat-scratch disease. The patient gradually improved following treatment with levofloxacin, azithromycin, doxycycline, and gentamicin.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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