Bartonella Endocarditis

Chatiros Choorat, M.D.[1], Amornrut Leelaporn, Ph.D. (Microbiol)[2], Tuenjai Chuangsuwanich, M.D.[3], Susan Assanasen, M.D.[1]

[1]Division of Infectious Disease and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

[2]Department of Microbiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

[3]Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

ABSTRACT

We report a case of 53-year-old male with blood culture-negative endocarditis, who presented with low grade fever for 9 months and progressive dyspnea for 1 month. Transesophageal echocardiography revealed severe aortic regurgitation and a large mobile mass at right coronary cusp and paravalvular abscess adjacent to the left coronary cusp. *Bartonella* spp. was demonstrated in the heart valve tissue by Warthin Starry stain and 16S rDNA sequencing. After aortic valve replacement and appropriate antimicrobial therapy, the patient showed a significant clinical improvement. (*J Infect Dis Antimicrob Agents 2014;31:29-35.*)

Note: This case had been presented and discussed in the Interhospital Case Conference on Infectious Diseases (ICCID), 21 March 2013, Bangkok, Thailand.

INTRODUCTION

Blood culture-negative endocarditis (BCNE) is a term used to describe cases of infective endocarditis for which there is no bacterial growth in three independent blood samples cultured on standard aerobic media after seven days of incubation.[1] Incidence of blood culture-negative endocarditis is 2.5%–31% of all cases of endocarditis.[2] In the literature, the common etiologies of BCNE are *Coxiella burnetii, Bartonella* species, and *Streptococcus* species.[3] Due to limitation of molecular and serological diagnosis for the detection of fastidious agents, there is no large epidemiologic study of BCNE in Thailand. Consequently, there have been only a few reports on *Bartonella* endocarditis in Thailand.[4,5]

CASE REPORT

A 53-year-old Buddhist monk with 15-year history of aortic regurgitation presented with intermittent low grade fever for 9 months. He had no history of dental procedure, intravenous drug use, or weight loss. The patient rarely exposed to stray cats and dogs in the temple. He denied a history of scratches or bites from the animals and did not notice any flea or tick bites. Seven months before admission, he was diagnosed with leptospirosis at a community hospital in Surin (one of the north-eastern provinces in Thailand) and was prescribed

Keywords: *Bartonella,* endocarditis, culture-negative endocarditis

Corresponding author: Susan Assanasen, M.D., Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Prannok Road, Bangkoknoi, Bangkok 10700, Thailand.
E-mail: susan.ass@mahidol.ac.th

doxycycline for 2 weeks. Fever initially improved but recurred within 2 weeks. One month prior to admission, he developed progressive dyspnea and orthopnea.

On physical examination, temperature was 38°C, pulse rate was 90/min, respiratory rate was 16/min, and blood pressure was 129/54 mmHg. The patient was alert, not pale, no jaundice, no edema, no Osler's node, no Janeway lesion, no splinter hemorrhage, and no Roth's spot. Cardiovascular examination revealed bounding pulse, water hammer pulse, bisferiens pulse, loud P2, grade 3/6 to-and-fro murmur at left upper sternal border. The remainder of examination was unremarkable.

Complete blood count revealed a hemoglobin level of 10.1 g/dL, white blood cell count of 8,260 cells/mm^3 with 53% neutrophil, 36.8% lymphocyte, 9.3% monocyte, 0.5% eosinophil, 0.4% basophil and platelet count of 133,000/mm^3. Blood urea nitrogen was 14.1 mg/dL, serum creatinine was 1.27 mg/dL. Urine examination revealed RBC 5-10/High power field, WBC 2-3/High power field and a trace amount of protein. HIV serology was negative. Chest X-ray demonstrated increased cardiothoracic ratio and no definite pulmonary infiltrations. Three sets of aerobic blood culture were negative. Transthoracic echocardiography (TTE) revealed severe aortic regurgitation with a 0.7 cm mobile mass attached to the right coronary cusp and mild mitral regurgitation.

The patient was eventually diagnosed with blood culture-negative endocarditis and was empirically treated with intravenous ampicillin/sulbactam 3 g every 6 h and gentamicin 60 mg (1 mg/kg) every 8 h. However, his symptoms did not show any improvement. Ten days after antimicrobial therapy, transesophageal echocardiography (TEE) was performed to evaluate the cause of persistent fever. The study revealed a large (2 cm × 0.7 cm) mobile mass at right coronary cusp and a 1.4 cm × 0.56 cm paravalvular abscess adjacent to the left coronary cusp.

Due to uncontrolled infection, he underwent emergency aortic valve replacement and the antibiotics were changed to intravenous ceftriaxone 2 g every 24 h and levofloxacin 750 mg every 24 h. Gentamicin 60 mg every 8 h was still continued for 4 weeks. Intraoperative findings showed a destructive aortic valve with 1.5 cm vegetation (Figure 1). After surgery, all clinical symptoms were remarkably improved.

Figure 1. Gross pathology of the surgically removed aortic valve from a 53-year-old monk shows aortic cusp destruction and vegetation.

Histological examination of heart valve tissue after Gram staining, GMS, and Warthin-Starry silver staining showed bacterial cells with marked degeneration (Figure 2). Conventional aerobic culture of vegetation was no growth. The result obtained from 16S rRNA gene sequencing revealed that DNA sequence of approximately 1,300 bp of the organism from the vegetation shared ≥ 99%

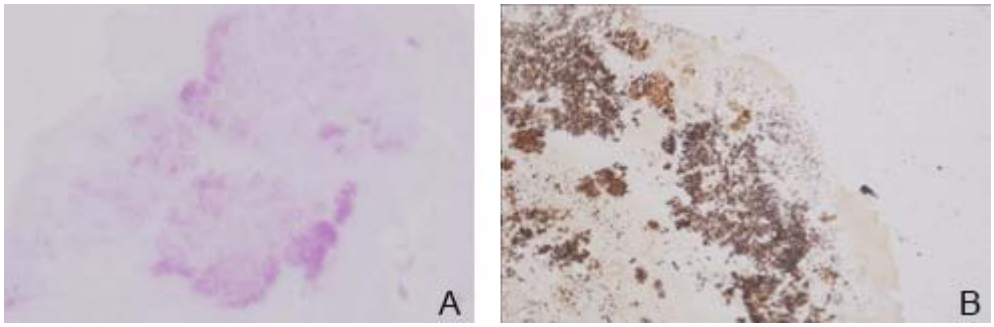

Figure 2. Light microscopy of the vegetation from aortic valve with *Bartonella* spp. infection.

(A) Faintly stained gram-variable organism within the vegetation (Gram stain, magnification × 100).

(B) The cluster of small, dark-staining organism within the vegetation (Warthin-Starry silver stain, magnification × 400).

sequence similarity to those of several species of *Bartonella,* such as, *B. henselae, B. koehlerae, B. vinsonii, B. capreoli ,B. tribocorum, B. grahamii, B. washoensis, B. queenslandensis, B. volans,* etc., indicating a strong association to the genus *Bartonella*. After 4 weeks of intravenous antimicrobial therapy, doxycycline 200 mg/day was prescribed for another 6 weeks.

DISCUSSION

Bartonella is a fastidious hemotropic gram-negative coccobacillus with a worldwide distribution. The reservoir hosts of *Bartonella* are mammals, such as cats, humans, rats, mice, voles, dogs, and squirrels. *Bartonella s*pecies usually have a specific mammalian species as a host, in which they can cause a chronic infection within the red blood cells. Cats are major reservoir hosts of *B. henselae, B. clarridgeiae,* and *B. koehlerae*, whereas humans are primary reservoir of *B. quintana* and *B. baciliformis*.

In Thailand, the prevalence of *Bartonella* spp. infection in animals varies depending on geographic region, type, and category of animals (e.g. domestic, stray, feral, etc.) and may be as high as 50% in cats, 41.5% in rodents, 35.8% in stray dogs, and 32% in cat fleas.[6-10] *B. henselae* and *B. clarridgeiae* were isolated from 83-96% and 4-12% of the *Bartonella*-positive cats, respectively.[6,8-11]

Bartonella are transmitted to humans either by the bite or saliva-contaminated scratch of chronically bacteremic mammals or by blood-sucking arthropods, such as fleas, lice, sand flies, ticks, and mosquitoes. The seroprevalence of *Bartonella* infection among Thai population also varies from 10% to 18%.[5,12-17]

Due to subacute onset, more than half of patients may not recall a traumatic animal contact or insect bites. In this case, stray dogs, cats, and rodents in the temple may serve as possible reservoirs for *Bartonella* spp. and the patient may acquire the organism by unrecognized flea and/or tick bites.

Bartonella has unique abilities to cause either acute or chronic infection. *Bartonella* infections have a wide range of clinical diseases, such as Carrión′s disease, trench fever, cat-scratch disease,

chronic lymphadenopathy, bacillary angiomatosis, peliosis hepatis, chronic paucisymptomatic bacteremia, meningoencephalitis, myelitis, osteomyelitis, myocarditis, and endocarditis.

Bartonella was first described as a cause of endocarditis in two separate reports in 1993 and subsequently has become appreciated as a significant cause of culture negative endocarditis.[18,19] Six *Bartonella* species, including *B. quintana, B. henselae, B. elizabethae, B. vinsonii, B. koehlerae,* and *B. alsatica,* have been reported to cause infective endocarditis in humans. *B. quintana* and *B. henselae* are the two most common etiological agents of *Bartonella* endocarditis in humans.[2] *B. quintana* endocarditis is associated with homelessness, alcoholism and exposure to body lice, whereas *B. henselae* endocarditis is associated with exposure to cats and previous valvulopathy.[20] Although the result of 16S rRNA gene sequencing could not exactly identify the species of *Bartonella*, the possible etiologic agent of endocarditis in this patient should be *B. henselae* due to a history of aortic regurgitation and cat exposure in the temple. To identify *Bartonella* into speices level, the target sequences in 16S-23S rDNA spacer region and/or riboflavin synthase gene may be employed. Patients with *Bartonella* endocarditis have clinical manifestations similar to other patients with subacute bacterial endocarditis.[20] Approximately 60 percent of patients with *Bartonella* endocarditis have aortic valve involvement. Embolic phenomena have been reported in 41% of patients.[20] Due to insidious onset, the diagnosis *Bartonella* spp. is usually delayed, which may explain why most patients present with heart failure.

The diagnosis of *Bartonella* endocarditis is usually established by inoculation of blood or resected valve tissue into blood agar or tissue culture, serologic testing, Warthin-Starry silver staining of bacteria in the vegetation, and molecular detection. Fresh agar plates are recommended to be used for *Bartonella* culture. The plates will be incubated in 5% CO_2 at 35-37°C for a minimum of 21 days.[21] However, the sensitivities of blood culture and valve tissue culture are only 20% and 31%.[2] IFA and ELISA are two most commonly used serologic methods for *Bartonella* infections.[1] A serum sample with an IgG antibody titer to *Bartonella* species of 1:800 or more has been demonstrated to be 95.5% predictive of *Bartonella* endocarditis.[2] Valvular tissue stained with hematoxylin and eosin shows mildly inflamed connective tissue with focal granulation tissue reaction.[22] Typically, Warthin-Starry silver staining may reveal masses of small dark-staining bacteria.[23] Molecular detection of gene fragments from valvular tissue has been demonstrated to have a higher sensitivity than culture, between 72% and 98%.[23,24]

The best treatment regimen for *Bartonella* endocarditis remains unknown because no randomized controlled trial (RCT) has been published. In vitro study, telithromycin, macrolides, doxycycline and rifampicin were effective agents against *Bartonella* spp.[25] Ceftriaxone probably has some activity against *Bartonella*, especially if combined with aminoglycosides. Benefits from aminoglycoside therapy was suggested in a retrospective analysis of 101 patients with endocarditis.[26] Patients who receive β-lactam antibiotics that include at least 14 days of aminoglycoside had greater likelihood of achieving full recovery and of survival than those treated only with doxycycline.[27]

According to American Heart Association guidelines, the treatment regimens for suspected *Bartonella* endocarditis are ceftriaxone 2 g/d IV/IM

once daily for 6 weeks plus gentamicin 1 mg/kg/d IV/IM every 8 hours for 2 weeks with/without doxycycline 100 mg/kg/d IV/PO twice daily for 6 weeks.[28] European Society of Cardiology (ESC) guidelines also recommend ceftriaxone 2 g/d IV or ampicillin 12g/d IV or doxycycline 200 mg/d PO for 6 weeks plus gentamicin 3 mg/kg/d IV or netilmicin for 3 weeks.[29]

Although this patient received the appropriate antimicrobial therapy during admission, his condition had not improved at day 10 of hospitalization. In prospective and retrospective studies, the sensitivity of TTE for detecting perivalvular abscess is low (18-63%), whereas the sensitivity of TEE is high (76-100%).[28] A possible explanation for uncontrolled infection is a failure of the TTE to early detect perivalvular extension of IE, a frequent cause of urgent valvular surgery. However, the patient improved rapidly following surgery.

CONCLUSION

Bartonella infection should be considered in patients who presented with culture negative endocarditits. Although the definite diagnosis of *Bartonella* endocarditis needs more sophisticated investigation, including serological test, polymerase chain reaction (PCR), and DNA sequenced-based testing, pathologic examination of the resected valve *tissue* using special staining such as Warthin-Starry silver stain may lead to the diagnosis.

References

1. Raoult D, Casalta JP, Richet H, et al. Contribution of systematic serological testing in diagnosis of infective endocarditis. J Clin Microbiol 2005;43: 5238-42.
2. Houpikian P, Raoult D. Blood culture-negative endocarditis in a reference center: etiologic diagnosis of 348 cases. Medicine (Baltimore) 2005;84:162-73.
3. Fournier PE, Thuny F, Richet H, et al. Comprehensive diagnostic strategy for blood culture-negative endocarditis: a prospective study of 819 new cases. Clin Infect Dis 2010;51:131-40.
4. Pachirat O, Kosoy M, Bai Y, et al. The first reported case of *Bartonella* endocarditis in Thailand. Infect Dis Rep 2011;3:e9.
5. Kosoy M, Morway C, Sheff KW, et al. *Bartonella tamiae* sp. nov., a newly recognized pathogen isolated from three human patients from Thailand. J Clin Microbiol 2008;46:772-5.
6. Assarasakorn S, Veir JK, Hawley JR, et al. Prevalence of *Bartonella* species, hemoplasmas, and Rickettsia felis DNA in blood and fleas of cats in Bangkok, Thailand. Res Vet Sci 2012;93:1213-6.
7. Foongladda S, Inthawong D, Kositanont U, Gaywee J. *Rickettsia, Ehrlichia, Anaplasma*, and *Bartonella* in ticks and fleas from dogs and cats in Bangkok. Vector Borne Zoonotic Dis 2011;11:1335-41.
8. Bai Y, Kosoy MY, Boonmar S, Sawatwong P, Sangmaneedet S, Peruski LF. Enrichment culture and molecular identification of diverse *Bartonella* species in stray dogs. Vet Microbiol 2010;146:314-9.
9. Bai Y, Kosoy MY, Lerdthusnee K, Peruski LF, Richardson JH. Prevalence and genetic heterogeneity of *Bartonella* strains cultured from rodents from 17 provinces in Thailand. Am J Trop Med Hyg 2009; 81:811-6.
10. Inoue K, Maruyama S, Kabeya H, et al. Prevalence of *Bartonella* infection in cats and dogs in a metropolitan area, Thailand. Epidemiol Infect 2009;137:1568-73.
11. Maruyama S, Sakai T, Morita Y, et al. Prevalence of *Bartonella* species and 16s rRNA gene types of *Bartonella henselae* from domestic cats in Thailand. Am J Trop Med Hyg 2001;65:783-7.
12. Bai Y, Kosoy MY, Diaz MH, et al. *Bartonella vinsonii*

subsp. arupensis in humans, Thailand. Emerg Infect Dis 2012;18:989-91.

13. Bhengsri S, Baggett HC, Peruski LF, et al. *Bartonella* seroprevalence in rural Thailand. Southeast Asian J Trop Med Public Health 2011;42:687-92.
14. Colton L, Zeidner N, Lynch T, Kosoy MY. Human isolates of *Bartonella tamiae* induce pathology in experimentally inoculated immunocompetent mice. BMC Infect Dis 2010;10:229.
15. Kosoy M, Bai Y, Sheff K, et al. Identification of *Bartonella* infections in febrile human patients from Thailand and their potential animal reservoirs. Am J Trop Med Hyg 2010;82:1140-5.
16. Paitoonpong L, Chitsomkasem A, Chantrakooptungool S, Kanjanahareutai S, Tribuddharat C, Srifuengfung S. *Bartonella henselae*: first reported isolate in a human in Thailand. Southeast Asian J Trop Med Public Health 2008;39:123-9.
17. Maruyama S, Boonmar S, Morita Y, et al. Seroprevalence of *Bartonella henselae* and *Toxoplasma gondii* among healthy individuals in Thailand. J Vet Med Sci 2000;62:635-7.
18. Spach DH, Callis KP, Paauw DS, et al. Endocarditis caused by *Rochalimaea quintana* in a patient infected with human immunodeficiency virus. J Clin Microbiol 1993;31:692-4.
19. Daly JS, Worthington MG, Brenner DJ, et al. *Rochalimaea elizabethae* sp. nov. isolated from a patient with endocarditis. J Clin Microbiol 1993; 31:872-81.
20. Brouqui P, Raoult D. Endocarditis due to rare and fastidious bacteria. Clin Microbiol Rev 2001;14: 177-207.
21. La Scola B, Raoult D. Culture of *Bartonella quintana* and *Bartonella henselae* from human samples: a 5-year experience (1993 to 1998). J Clin Microbiol 1999;37:1899-905.
22. Spach DH, Kanter AS, Daniels NA, et al. *Bartonella* (*Rochalimaea*) species as a cause of apparent "culture-negative" endocarditis. Clin Infect Dis 1995;20:1044-7.
23. Raoult D, Fournier PE, Drancourt M, et al. Diagnosis of 22 new cases of *Bartonella* endocarditis. Ann Intern Med 1996;125:646-52.
24. Fournier PE, Lelievre H, Eykyn SJ, et al. Epidemiologic and clinical characteristics of *Bartonella quintana* and *Bartonella henselae* endocarditis: a study of 48 patients. Medicine (Baltimore) 2001;80:245-51.
25. Dorbecker C, Sander A, Oberle K, Schulin-Casonato T. In vitro susceptibility of *Bartonella* species to 17 antimicrobial compounds: comparison of Etest and agar dilution. J Antimicrob Chemother 2006; 58:784-8.
26. Raoult D, Fournier PE, Vandenesch F, et al. Outcome and treatment of *Bartonella* endocarditis. Arch Intern Med 2003;163:226-30.
27. Foucault C, Raoult D, Brouqui P. Randomized open trial of gentamicin and doxycycline for eradication of *Bartonella quintana* from blood in patients with chronic bacteremia. Antimicrob Agents Chemother 2003;47:2204-7.
28. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation 2005;111:e394-e434.
29. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of

Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J 2009;30:2369-413.