CASE REPORT
Infectious Diseases, Microbiology & Parasitology

JKMS

http://dx.doi.org/10.3346/jkms.2012.27.11.1433 • J Korean Med Sci 2012; 27: 1433-1435

First Case of *Bartonella quintana* Endocarditis in Korea

Min Hee Lim[1], Doo Ryeon Chung[1], Wook-Sung Kim[2], Kyung Sun Park[3], Chang-Seok Ki[3], Nam Yong Lee[3], and Sang Min Kim[4]

[1]Division of Infectious Diseases, Department of Internal Medicine; [2]Department of Thoracic and Cardiovascular Surgery; [3]Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; [4]Division of Cardiology, Department of Internal Medicine, Chungbuk National University Hospital, Cheongju, Korea

Received: 11 April 2012
Accepted: 3 July 2012

Address for Correspondence:
Doo Ryeon Chung, MD
Division of Infectious Diseases, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea
Tel: +82.2-3410-0323, Fax: +82.2-3410-0064
E-mail: drchung@skku.edu

Since microbial gene sequencing was utilized for etiologic diagnosis of culture-negative endocarditis, cases of *Bartonella* endocarditis have been reported in various countries. Herein we report the first case of *Bartonella quintana* endocarditis, which was confirmed for the first time in Korea by 16S rRNA gene sequencing from the excised valve. A 75-yr-old woman was hospitalized due to dyspnea. Echocardiography demonstrated large oscillating vegetation at the aortic valve. Blood culture was negative. She underwent valve replacement and sequencing of the 16S rRNA gene from excised valve identified *Bartonella quintana*. She was successfully treated with combined use of ceftriaxone and gentamicin.

Key Words: Infective Endocarditis; *Bartonella quintana*; 16S rRNA; Gene Sequencing

INTRODUCTION

Etiologic diagnosis of infective endocarditis is very important for appropriate treatment, however culture-negative endocarditis has accounted for a substantial proportion of all endocarditis cases (1). Recent efforts to demonstrate the etiologic microorganisms of culture-negative endocarditis by use of the serologic tests and 16S rRNA gene sequencing of the valves identified *Bartonella* species as one of important causes in culture-negative endocarditis (2). Cases of endocarditis caused by *Bartonella* species have been reported from several countries; however there has been no report from Korea to date. Herein, we report the first case of *Bartonella* endocarditis confirmed by 16S rRNA gene sequencing in Korea.

CASE DESCRIPTION

A previously healthy 75-yr-old Korean woman was hospitalized with a 7-day history of exertional dyspnea and fever on August 16, 2011. She had not raised any pet dogs or cats. On admission, her vital signs showed body temperature 38.3°C, blood pressure 147/63 mmHg, heart rate 86/min, and respiratory rate 18/min. On physical examination, a grade 3 diastolic heart murmur was detected at left upper sternal border. Her complete blood count showed WBC 7,910/μL (neutrophils 90.8%, lymphocytes 7.5%), hemoglobin 12.7 g/dL and platelet 71,000/μL. Chemistry profiles showed total bilirubin 0.8 mg/dL, AST 16 IU/ L, ALT 4 IU/L, alkaline phosphatase 79 IU/L, total protein 6.1 g/dL and albumin 2.8 g/dL. BUN 17.1 mg/dL, creatinine 0.87 mg/dL and CRP 1.4 mg/dL. Arterial blood gas analysis showed pH 7.537, pO_2 65.9 mmHg, pCO_2 31.3 mmHg, O_2 saturation 92.2%, and HCO_3 26 mM. Urinalysis revealed microscopic hematuria and microalbuminuria. A chest radiograph and electrocardiogram showed no abnormality. Echocardiography demonstrated the presence of oscillating vegetation (0.46 × 1.77 cm) attached to the aortic valve, as well as moderate aortic regurgitation. Ceftriaxone was empirically given in a dose of 2 g/day after repeated blood cultures. On hospital day 2, she underwent urgent valve replacement surgery due to the risk of embolization. Intraoperative findings revealed 0.5 × 1.5 cm sized oscillating mass on left coronary cusp. Blood cultures obtained prior to antibiotic administration were all negative. Microbiological examination of the excised aortic valve and vegetation revealed no organism on the Gram stain and the culture grew no organism. Histology revealed fibromyxoid valvulopathy and chronic active inflammation with vegetation, which were consistent with infective endocarditis. Empirical ceftriaxone treatment was continued under the diagnosis of culture-negative endocarditis.

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pISSN 1011-8934
eISSN 1598-6357

Bacterial DNA was extracted from surgically excised valve tissue and vegetation, directly. A 16S rRNA fragment was amplified with the universal primers 4F (5´-TTGGAGAGTTTGATCCTGGCT-3´), 534R (5´-TACCGCGGCTGCTGGCAC-3´), 27F (5´-AGAGTTTGATCMTGGCTCAG-3´), and 801R (5´-GGCGTGGACTTCCAGGGTATCT-3´).

The 16S rRNA gene sequence showed 100% (707/707) similarity to that of the *Bartonella quintana* strain (accession no. BX897700 and AJ250247) in the GenBank database (http://blast.ncbi.nlm.nih.gov/). The next closest sequences were those of *Bartonella henselae*, and it showed 98.7% (699/708) similarity (accession no. DQ645426 and BX897699). Identification to the *Bartonella* species can be accepted if there is a ≥ 99% match with the 16S rRNA gene sequence and a difference of greater than 0.8% between those of other different species, according to the Clinical and Laboratory Standards Institute (CLSI) guideline MM18-A (3). *B. quintana* was also only the best-matched strain in the BIBI database (http://pbil.univ-lyon1.fr/bibi/). Based on the molecular identification using GenBank and BIBI databases, we concluded that *B. quintana* was the best matched species.

In addition, serologic testing with the indirect fluorescent antibody (IFA) method, which was performed at the Korea Center for Disease Control and Prevention showed an IgG titer of 1:512 to *Bartonella* spp. After she was finally diagnosed with *B. quintana* endocarditis, gentamicin was added to ceftriaxone in a dose of 1.7 mg/kg q8h. She was discharged after ceftriaxone treatment for 4 weeks in combination with gentamicin for the last 2 weeks.

DISCUSSION

This is the first reported case of *B. quintana* endocarditis in a healthy adult, which has been confirmed for the first time in Korea by using serologic test and 16S rRNA gene sequencing. Successful treatment of infective endocarditis requires timely and effective antibiotic therapy based on microbiological identification of causative microorganism. However, sometimes microbiological diagnosis remains difficult, and blood culture-negative endocarditis (BCNE) accounts for 2.5% to 31% of all cases of endocarditis (4, 5). Slow-growing or fastidious organisms such as the HACEK group, anaerobes, *Abiotrophia* spp., *Brucella* spp., *Bartonella* spp., *Legionella* spp., and *Mycoplasma* spp., or obligate intracellular organisms such as *Coxiella burnetii* had been reported as causes of BCNE (4). Microbiological identification of those pathogens in patients with endocarditis was very difficult until PCR-based sequence analyses have been adopted in clinical practices. Two prospective studies in French reference center from 1983 to 2001 and from 2001 to 2009, in which the etiology of BCNE was determined using a multimodal strategy including molecular methods, revealed that *C. burnetii* (37.0%-48.0%) and *Bartonella* spp. (12.4%-28.4%) were the most frequent microorganisms causing BCNE (2, 5).

Cases of endocarditis caused by *Bartonella* spp. have also been reported from other countries. An overview of published detailed cases of *Bartonella* endocarditis in Europe from 2000 to 2007 was presented, and the cases were reported from France, UK, Germany, Spain and the Netherlands (6). In addition, there have been reports of *Bartonella* endocarditis from Asian countries including India, Thailand and Japan as well as Australia (7). In contrast, in Korea, there has been no report of *Bartonella* endocarditis to date. However, recent reports have shown that *Bartonella* spp. were detected from the ticks and wild rodents in Korea (8), and *B. henselae* and *Bartonella clarridgeieae* were highly prevalent in Korean cats and dogs (9). In addition, there has been a paper reporting possible cases of cat scratch disease based on the seropositivity against *B. henselae* or *B. quintana* (10) and a report of cat scratch disease confirmed by molecular methods in Korea (11). These suggest that there is a possibility that cases of endocarditis by *Bartonella* spp. in Korea have not been diagnosed due to lack of suspicion. In fact, in many hospitals in Korea serologic tests for *Bartonella* spp. or gene sequencing from excised valves have not been generally performed for etiologic diagnosis for cases of culture-negative endocarditis.

Bartonella species are small fastidious Gram-negative rods, facultatively intracellular bacteria associated with a broad spectrum of diseases in humans, including cat scratch disease, trench fever, bacillary angiomatosis, chronic bacteremia, and endocarditis (12). Among various *Bartonella* species, *B. quintana* and *B. henselae* are the predominant human pathogens causing infective endocarditis (6, 12). Patients with *B. henselae* endocarditis frequently have a previous valvulopathy, and disease is associated with cat bites or scratches and cat flea exposure (13). In contrast, *B. quintana* endocarditis mostly develops in persons without any previous valvular injuries, and usually occurs in immunocompromised patients (12). Its other known risk factors include chronic alcoholism, homelessness, and body lice infestation (13). However, our patient did not have any alleged risk factors for *B. quintana* endocarditis.

Because of the fastidious nature of *Bartonella* spp., culture of these bacteria from clinical specimens remains very difficult. Therefore, serologic testing and/or molecular methods are necessary for *Bartonella* spp. identification. Previous study on a review of published cases of *Bartonella* endocarditis in Europe reported that pathogen identification was carried out by molecular methods and/or serologic testing in 16 out of 18 cases (6). In only two cases, *Bartonella* pathogens could be identified by culture methods. Currently, indirect immunofluorescent assay and enzyme-linked immunosorbent assay (ELISA) can be used for the serodiagnosis of *Bartonella* infection. Indirect immunofluorescent assay has a positive predictive value for *Bartonella* infection of 95% for an immunoglobulin G (IgG) titer to *B. henselae* and/or *B. quintana* of ≥ 1:800 in patients with endocarditis

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(13). However, serologic tests may not distinguish reliably between antibody responses to *B. quintana* and *B. henselae* (14). Furthermore, cross-reactions may occur at a low level with *C. burnetii* and significantly with *Chlamydia* spp. (14-16). In contrast, the molecular method using 16S rRNA gene sequencing or *Bartonella* species-specific 16S-23S rRNA intergenic region sequencing could resolve these problems and determine the species level of *Bartonella*.

Bartonella spp. are susceptible to most antimicrobial agents, including penicillins, cephalosporins, aminoglycosides, tetracyclines, macrolides, rifampicin, fluoroquinolones, and cotrimoxazole (17). However, only aminoglycosides have a bactericidal effect and it has been recommended to use aminoglycosides for minimum 2 weeks in combination with other class of antibiotics (12, 17, 18).

This report indicates that *Bartonella* endocarditis should be included in differential diagnosis of culture-negative endocarditis in Korea. Molecular genetic screening and serological testing methods for detection of *Bartonella* are necessary in cases of culture-negative endocarditis.

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