**BRIEF REPORT**

**Bartonella** as a Cause of Blood Culture-Negative Endocarditis. Description of 5 Cases

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**INTRODUCTION**

*Bartonella* is a Gram-negative bacterial genus that is difficult to culture. These bacteria produce a wide range of infectious diseases, including blood culture-negative endocarditis. Due to improvements in culturing and molecular biology techniques, 5 species have been recognized as causing infective endocarditis in humans (*B. quintana*, *B. henselae*, *B. elizabethae*, *B. vinsonii*, and *B. koehlerae*), although most cases are produced by the first 2. According to recent reports, *Bartonella* accounts for 1% to 17% of all cases of endocarditis. A Spanish review by Oteo et al described 6 cases published in the past 10 years. The purpose of the present article is to analyze cases of endocarditis caused by *Bartonella* diagnosed at a tertiary hospital and to determine the importance of this pathogen as a cause of endocarditis in our setting.
METHODS

This is a descriptive study based on a retrospective review of the medical records of patients diagnosed with Bartonella endocarditis between January 1995 and December 2006. The minimum basic data set (MBDS) was used to identify all patients who had been coded at discharge according to the International Classification of Diseases, Ninth Revision, as infective endocarditis or Q fever endocarditis, because no specific code exists for Bartonella endocarditis. The diagnosis of endocarditis was considered to be definitive or probable if the patient fulfilled the modified Duke criteria, and the infection was considered to be caused by Bartonella when the Bartonella immunoglobulin (Ig) G antibody titer was higher than 1/800 by indirect immunofluorescence (Focus Diagnostic) or Bartonella DNA screening by polymerase chain reaction (PCR) (amplification of the 16S ribosomal RNA [rRNA] gene and intergenic spacer region, performed at Centro Nacional de Majadahonda, Madrid, Spain).

The following variables were analyzed: age, sex, risk factors, epidemiologic history, clinical picture, valvular and extravalvular involvement, microbiologic data, treatment, and clinical progress.

RESULTS

During the period of 1995 to 2006, there were 140 cases of infective endocarditis, 10 of which yielded negative blood cultures (7% of all cases of endocarditis). Of these 10 cases, 2 had been caused by Coxiella burnetii, 4 by Bartonella species, and 1 by both Bartonella and C burnetii; 1 case was considered Loeffler endocarditis, another was tuberculous endocarditis, and in 2, an etiologic diagnosis was not established.

The main characteristics of the cases of Bartonella endocarditis are summarized in Table.

All 5 cases of Bartonella endocarditis occurred in men between 30 and 72 years of age; 4 had a history of contact with cats and 1 was infected with HIV. Only 2 patients had previous valve disease. The aortic valve was affected in all cases. The mean time to diagnosis was 143 days (range, 7-540). The predominant symptoms were fever and constitutional syndrome. Three patients presented with acute heart failure secondary to valve regurgitation and 1 with cerebral infarction. Three patients had embolic infarctions of splenic, mesenteric, and cerebral regions, and 1 patient with a prosthetic aortic valve presented aortitis of the aortic root and postinfectious glomerulonephritis with secondary renal failure. Serologic testing was positive for Bartonella in all 5 patients, with antibody titers above 1/800. PCR study of valve tissue was performed in 3 patients with positive results, although the species (B henselae) was determined in only 1 patient. Pericardial fluid culture yielded Bartonella in 1 patient. In addition, serology was positive for Chlamydia phila in 2 patients and for C burnetii in 2 others (coinfection was confirmed by PCR of valve tissue in only 1). All required valve replacement, but the clinical progress was favorable, and only 1 had residual chronic renal failure. Bartonella antibody titers were subsequently negative or reduced in all patients except 2, who continued with antibiotic therapy at the time of writing.

DISCUSSION

The incidence of blood culture-negative endocarditis varies from 3% to 31% of all cases of endocarditis, according to the series. Although the main reason is prior administration of antibiotics, endocarditis caused by zoonosis and bacteria transmitted by arthropods (mainly C burnetii and Bartonella) is prevalent in the Mediterranean countries, a fact that should be taken into account.

In the present study, culture-negative endocarditis accounted for 7% of all cases of endocarditis, and the Bartonella genus was implicated in 3.6% of endocarditis cases and 50% of culture-negative endocarditis. These findings are consistent with the results of other authors, such as Raoult et al who reported 22 cases of blood culture-negative endocarditis, 9 of them caused by Bartonella (3% of all the infective endocarditis cases) and the French National Reference Center for Rickettsial Diseases study, which reported 348 cases of culture-negative endocarditis between 1993 and 2001, with 48% of cases caused by C burnetii and 28% by Bartonella species.

Bartonella endocarditis may be difficult to diagnose because it presents a subacute clinical course with nonspecific symptoms, such as fever (not always present and often intermittent), weight loss, and asthenia. Embolic phenomena are not unusual and immune-complex glomerulonephritis has been described as a complication of Bartonella endocarditis that can lead to chronic renal failure.

Serology techniques are used for the diagnosis. An IgG antibody titre ≥1/800 has a positive predictive value of 95% for the detection of Bartonella infection among patients with culture-negative endocarditis. Cross-reactions with Chlamydia and C burnetii species that can lead to diagnostic error have been reported. PCR study of valve tissue is useful for the diagnosis; however, despite a high specificity (around 100%), its sensitivity to identify the pathogen in culture-negative endocarditis varies between 40% and 60%, probably due to prior use of antibiotics.
The technique can also help to identify the causative agent in patients who additionally have elevated titers of *Chlamydia* or *C. burnetii* and to rule out mixed disease. Moreover, PCR can often establish the species of *Bartonella*. Therefore, in patients who require valve replacement, valve tissue should be sent to the reference laboratory for analysis. A real-time PCR technique has been developed for the specific diagnosis of *Bartonella*, but it has a low sensitivity (58%). It may, however, be useful when *Bartonella* endocarditis is suspected and only serum samples are available. Nonetheless, the role of the technique in the diagnosis of nonsurgical endocarditis requires further study.13

There are no randomized studies on the treatment of *Bartonella* endocarditis, and the recommendations are based on series of case studies. Doxycycline is probably the best option for long-term therapy.

### TABLE. Characteristics of Patients with *Bartonella* Endocarditis

<table>
<thead>
<tr>
<th>Age, y/Sex</th>
<th>Risk Factor</th>
<th>Days to Diagnosis</th>
<th>Affected Valve</th>
<th>Extracardiac Involvement</th>
<th>Bartonella Serology</th>
<th>Microbiology</th>
<th>Antibiotic Therapy/Duration</th>
<th>Follow-Up Serology</th>
<th>Progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>30, male</td>
<td>Contact with cats, HIV</td>
<td>20 days</td>
<td>Aortic</td>
<td>IgM (+), IgG 1/2048</td>
<td><em>Bartonella</em></td>
<td>PCR (+), pericardial fluid culture (+), <em>Chlamydia psittaci</em> serology (+)</td>
<td>Initial: ampicillin, ciprofloxacin, gentamicin. Maintenance: doxycycline, ciprofloxacin. 7 months</td>
<td>6 months. <em>Bartonella</em>: IgG 1/512</td>
</tr>
<tr>
<td>Patient 2</td>
<td>54, male</td>
<td>None</td>
<td>60 days</td>
<td>Aortic</td>
<td>IgM (–), IgG 1/2048</td>
<td><em>Chlamydia pneumoniae</em></td>
<td>serology (+)</td>
<td>Initial: cloxacillin, gentamicin. Maintenance: cloxacillin, azithromycin. 6 months</td>
<td><em>Bartonella</em>: IgG 1/256</td>
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<tr>
<td>Patient 3</td>
<td>56, male</td>
<td>Contact with cats, alcoholism</td>
<td>7 days</td>
<td>Aortic</td>
<td>IgG 1/1024</td>
<td><em>Bartonella</em></td>
<td>PCR (–)</td>
<td>Initial: vancomycin, cefazidime, tobramycin. Maintenance: doxycycline, ciprofloxacin. 12 months</td>
<td><em>Bartonella</em>: IgG (–), IgG 1/256</td>
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<tr>
<td>Patient 4</td>
<td>72, male</td>
<td>Contact with cats, aortic regurgitation</td>
<td>90 days</td>
<td>Aortic</td>
<td>IgM (+), IgG 1/4096</td>
<td><em>Bartonella henselae</em></td>
<td>PCR (+), <em>Coxiella</em> PCR (+), <em>C. burnetii</em> serology: Phase I, IgG (–), IgG 1/16384; Phase II, IgM (–), IgG 1/16384</td>
<td>Doxycycline, ciprofloxacin. Still under treatment</td>
<td><em>Bartonella</em>: IgG (–), IgG 1/4096. <em>C. burnetii</em>: Phase I, IgG (–), IgG 1/16384; Phase II, IgM (–), IgG 1/16384</td>
</tr>
<tr>
<td>Patient 5</td>
<td>52, male</td>
<td>Cat scratch, aortic prosthesis</td>
<td>540 days</td>
<td>Aortic</td>
<td>IgM (+), IgG 1/8192</td>
<td><em>Bartonella</em></td>
<td>PCR (+), <em>C. burnetii</em> serology: Phase I, IgG 1/9192; Phase II, IgG 1/512</td>
<td>Initial: ampicillin, gentamicin, doxycycline. Maintenance: doxycycline, ciprofloxacin. Still under treatment</td>
<td><em>Bartonella</em>: IgG (–), IgG 1/256. <em>C. burnetii</em>: Phase I, IgG (–), IgG 1/128; Phase II, IgM (–), IgG 1/128</td>
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</table>
Treatment should be maintained between 3 and 6 months, although most patients require valve replacement.

In summary, Bartonella should be considered an important etiologic agent of culture-negative endocarditis in our setting. It is probably underdiagnosed and, because the clinical picture is nonspecific, the risk factors for this zoonosis should be investigated and serology tests should be performed in all blood culture-negative endocarditis. Cross-reactions with C burnetii and Chlamydophila are common, hence, PCR study of valve tissue may be useful to confirm the diagnosis if surgery has been performed.

REFERENCES