CASE REPORT

Afebrile Multi-valve Infective Endocarditis Caused by
*Lactococcus garvieae*: A Case Report and Literature Review

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Abstract

*Lactococcus garvieae* is considered to be a rare pathogen with low virulence in humans. We herein experienced an unusual case of multi-valve infective endocarditis caused by *L. garvieae* in an elderly woman who had undergone bioprosthetic mitral valve replacement due to severe mitral stenosis with rheumatic etiology. The patient was successfully treated with cardiac surgery after teicoplanin antimicrobial therapy failure followed by ceftriaxone treatment. *L. garvieae* was confirmed as the pathogen through 16S rRNA sequencing. To the best of our knowledge, this is the first case to indicate an effective treatment for infective endocarditis caused by *L. garvieae* in the Republic of Korea.

Key words: *Lactococcus garvieae*, endocarditis, heart valve prosthesis, bacteremia

(Intern Med 55: 1011-1015, 2016)
(DOI: 10.2169/internalmedicine.55.5935)

Introduction

In 1985, *Lactococcus garvieae*, formerly grouped with *Streptococcus*, was re-classified as *Lactococcus* based on a genetic analysis; it is one of eight species of facultative anaerobic, catalase-negative, Gram-positive cocci (1). This organism is well known in aquaculture as a fish pathogen, however, there are few reports in the literature of infections caused by *L. garvieae* in both immunocompromised and immunocompetent humans, including patients with infective endocarditis (2-18), osteomyelitis (19-21), liver abscess (22), cholecystitis (23), and peritonitis (24). Based on its low virulence in humans, *L. garvieae* has generally been considered to be an opportunistic pathogen in immunocompromised hosts.

However, its role in human clinical settings has not been clearly defined; an increasing numbers of patients in the clinical setting are immunocompromised due to acquired immune deficiency syndrome, cancer chemotherapy, organ transplants, and old age. Furthermore, due to insufficient clinical data about the efficacy of antimicrobial agents, therapeutic antibiotic options have not been established and there are currently no guidelines for standardized antibiotic susceptibility breakpoints for *L. garvieae* isolates. We herein describe what we believe to be the first reported Korean case of a patient with infective endocarditis caused by *L. garvieae* who was successfully treated with antibiotics and cardiac surgery.

Case Report

A 75-year-old woman presented to our hospital with a three-day history of dyspnea [New York Heart Association (NYHA) class III]. She had a history of a mitral valve replacement three years prior due to severe mitral stenosis with rheumatic etiology. Her current medications included cilostazol, amiodarone, digoxin, and warfarin. Of note, she ate fresh seafood several times per month. She was admitted for progressive heart failure without a fever or chills. On admission, her heart rate was 84 beats/min, blood pressure was 120/80 mmHg, and her body temperature was 36.9°C. The patient’s body weight was 44 kg and body mass index was 18.6 kg/m². A physical examination revealed a previously

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Received for publication June 8, 2015; Accepted for publication July 23, 2015

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undiagnosed III holosystolic murmur at the apex and her lung fields had bilateral rales in both bases. No Osler’s nodes, Janeway lesions, or splinter hemorrhages were observed. Initial laboratory results showed a hemoglobin level of 8.0 mg/dL, a white blood cell count of 17,980/μL with 87.0% neutrophils, and a platelet count of 68,000/μL. Serum biochemistry indicated a blood urea nitrogen level of 33.3 mg/L and creatinine level of 1.28 mg/dL (creatinine clearance 27.5 mL/min). Because her C-reactive protein (CRP) level was 87.0 mg/L, blood cultures were collected on the first day of hospitalization. A chest radiograph showed cardiomegaly and increased interstitial markings suggestive of pulmonary edema. All blood culture bottles drawn from three different sites yielded growth of a Gram-positive coccus. L. garvieae was identified as the causative organism in the blood cultures, using a VITEK II system (bioMérieux, Hazelwood, USA), with a probability of 98.0%. Transthoracic echocardiography (TTE) revealed pedunculated echogenic material 16 mm in diameter on the prosthetic mitral valve. For the first two days of hospitalization, before the blood culture Gram staining results were available,ceftriaxone (2 g/day), gentamicin (45 mg per 8 h), and rifampin (600 mg/day) were prescribed as empirical antibiotic therapy. After receiving the staining results, the patient was started on teicoplanin (400 mg/day) after an initial loading dose of 400 mg/12 h administered three times. However, therapeutic drug monitoring (TDM) data for teicoplanin were unavailable because teicoplanin TDM is not routinely performed in our hospital. A MicroScan MICROSTREP plus panel was used to determine antimicrobial susceptibility and measure the minimum inhibitory concentrations (MICs), revealing susceptibility to penicillin (0.12 μg/mL), amoxicillin/clavulanate (0.5/0.25 μg/mL), ceftriaxone (0.25 μg/mL), ceftaxime (0.25 μg/mL), meropenem (0.06 μg/mL), vancomycin (1 μg/mL), and levofloxacin (1 μg/mL) and resistance to clindamycin (>0.5 μg/mL). Antimicrobial susceptibility testing using Etest strips (bioMérieux, Marcy 1’Etoile, France) revealed the following values: penicillin 0.75 mg/L, ceftriaxone 0.38 mg/L, and teicoplanin 0.125 mg/L. Because the Clinical Laboratory Standards Institute (CLSI) has not yet established Lactococcus MIC breakpoints for antibiotic susceptibilities, susceptibilities were presumed based on the CLSI recommendations for viridans streptococci (25). To further confirm the identity of this isolate, sequencing of a 1,500-basepair 16S rRNA gene fragment according to CLSI recommendations revealed 99% identity to L. garvieae strain American Type Culture Collection (ATCC) 49156 and 89% identity to S. sanguinis strain ATCC 10556 (26).

Under the clinical diagnosis of infective endocarditis, intravenous teicoplanin (400 mg, once daily) was administered for 14 days. However, pulmonary edema visible on chest X-rays steadily worsened and her serum CRP levels increased to 134.0 mg/L. The patient required intravenous furosemide. Follow-up TTE showed increased echogenic material 35 mm in diameter on the prosthetic mitral valve. Follow-up blood cultures taken after three days of antibiotic therapy were negative for L. garvieae. On the 17th day of admission, the patient underwent cardiac surgery (aortic and mitral valve bioprostheses replacement). The intra-operative findings showed fresh vegetation that had invaded three leaflets of the bioprosthetic mitral valve (Figure A). Vegetation 3 mm in diameter was attached to the ventricular side of the left coronary cusp of the native aortic valve. A pathologic examination of the mitral valve revealed a thickened prosthetic valve containing vegetation with numerous polymorphonuclear leukocytes (Figure B). Gram staining of the tissue revealed paired clusters of Gram-positive cocci and coccobacillary forms within vegetation on both the mitral and aortic valves. However, tissue cultures of the valves were sterile, presumably due to the preceding 17 days of antibiotic therapy. According to these findings, the patient was started on ceftriaxone (2 g/day) immediately after cardiac surgery. The patient was discharged after completing the 26-day intravenous ceftriaxone treatment. At the 6-month follow-up visit after completion of antibiotic therapy, the patient was free of L. garvieae endocarditis.

**Discussion**

Over the last decades, *L. garvieae* has progressively spread in numerous countries and has been identified as the causative agent of lactococcosis outbreaks in several fish species (27, 28). Due to improved molecular methodologies, these strains were revealed to originate not only in fish and
dairy products, but also in meat products, vegetables, and cereals (29). Along with this spread, _L. garvieae_ has also been identified as a clinical pathogen in patients with infective endocarditis.

Including our case, a total of 19 cases of infective endocarditis caused by _L. garvieae_ have been reported in the literature (2-18). Eleven patients (57.9%) were men, and 15 (78.9%) were sixty years of age or older. Thirteen cases (68.4%) involved the native valve. Six patients (31.6%) underwent cardiac surgery due to infective endocarditis. Of these 19 cases, 4 (21.1%) died due to multi-organ failure, heart failure, or cerebral hemorrhage (Table). None of these 19 cases, including 4 patients with multi-valve infective endocarditis, involved a total of 23 valves, including mitral (n=14), aortic (n=8), and tricuspid valves (n=1). Among these, native valves included 11 (78.6%) mitral and 4 (50.0%) aortic valves.

Previous reports speculated that _L. garvieae_ infections might result from ingestion of contaminated food, especially raw fish, in patients with modified gastrointestinal tracts (13, 17, 18, 21, 23). Our case was also exposed to raw fish and had underlying gastritis. Among the 19 reported cases, nine (47.4%) were associated with fish exposure, and 12 (63.2%) had gastrointestinal disorders (Table). All previous cases, except a single German case, were reported from cities or countries on a peninsula or island or with contact with the sea.

There is little data on antimicrobial susceptibility of _Lactococcus_ species, and formal CLSI interpretive criteria for _Lactococcus_ do not currently exist. According to the criteria

### Table. Clinical Characteristics and Treatment Outcomes of 19 Cases of Infective Endocarditis due to _Lactococcus garvieae_.

<table>
<thead>
<tr>
<th>Ref</th>
<th>Country</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Fever</th>
<th>GI-related factors</th>
<th>Risk factors</th>
<th>Antimicrobial therapy</th>
<th>Cardiac surgery</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>USA</td>
<td>84 F</td>
<td>No</td>
<td>NMV</td>
<td>Use of PPI</td>
<td>-</td>
<td>Ampicillin+gentamicin, cefazolin+vancomycin, ceftriaxone after surgery</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>4</td>
<td>France</td>
<td>86 F</td>
<td>Yes</td>
<td>PAV</td>
<td>Small bowel obstruction by hernia, duodenal ulcer, use of PPI</td>
<td>-</td>
<td>Amoxicillin+gentamicin</td>
<td>No</td>
<td>Survival</td>
</tr>
<tr>
<td>5</td>
<td>Canada</td>
<td>80 M</td>
<td>Yes</td>
<td>NAV</td>
<td>Malignant colon polyps</td>
<td>-</td>
<td>Amoxicillin</td>
<td>Yes</td>
<td>Survival</td>
</tr>
<tr>
<td>6</td>
<td>Taiwan</td>
<td>72 M</td>
<td>Yes</td>
<td>NMV</td>
<td>Gastric ulcer, epigastralgia</td>
<td>Eating fish</td>
<td>Penicillin, gentamicin</td>
<td>No</td>
<td>Survival</td>
</tr>
<tr>
<td>7</td>
<td>Hong Kong</td>
<td>67 F</td>
<td>Yes</td>
<td>NMV</td>
<td>Eating fresh seafood</td>
<td>-</td>
<td>Ampicillin</td>
<td>Yes</td>
<td>Survival</td>
</tr>
<tr>
<td>8</td>
<td>Taiwan</td>
<td>41 M</td>
<td>No</td>
<td>NMV</td>
<td>Cook</td>
<td>Eating fresh seafood</td>
<td>Penicillin+gentamicin</td>
<td>Yes</td>
<td>Survival</td>
</tr>
<tr>
<td>9</td>
<td>France</td>
<td>64 F</td>
<td>Yes</td>
<td>PMV</td>
<td>Colon polyps</td>
<td>-</td>
<td>Amoxicillin+gentamicin</td>
<td>No</td>
<td>Survival</td>
</tr>
<tr>
<td>10</td>
<td>Japan</td>
<td>55 F</td>
<td>Yes</td>
<td>NMV</td>
<td>Grocery market worker Eating fish and white cheese</td>
<td>-</td>
<td>Benzylpenicillin+gentamicin, ceftriaxone+gentamicin</td>
<td>No</td>
<td>Survival</td>
</tr>
<tr>
<td>11</td>
<td>Brazil</td>
<td>58 F</td>
<td>Yes</td>
<td>PMV</td>
<td>Gingival perforation</td>
<td>-</td>
<td>Vancomycin</td>
<td>No</td>
<td>Survival</td>
</tr>
<tr>
<td>12</td>
<td>Germany</td>
<td>55 M</td>
<td>Yes</td>
<td>PTV</td>
<td>Chronic periodontitis</td>
<td>Fish farmer</td>
<td>Co-trimoxazole, gentamicin+vancomycin+rifampicin, levofloxacin+amoxicillin+clavulanic acid</td>
<td>No</td>
<td>Survival</td>
</tr>
<tr>
<td>13</td>
<td>Italy</td>
<td>63 M</td>
<td>Yes</td>
<td>NMV</td>
<td>Diverticulosis, dental procedure</td>
<td>-</td>
<td>Vancomycin+gentamicin, ampicillin</td>
<td>No</td>
<td>Survival</td>
</tr>
<tr>
<td>14</td>
<td>USA</td>
<td>68 M</td>
<td>Yes</td>
<td>NMV, PAV</td>
<td>-</td>
<td>Eating fish</td>
<td>Ampicillin+gentamicin, vancomycin</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>15</td>
<td>USA</td>
<td>64 M</td>
<td>No</td>
<td>NAV, NAV</td>
<td>Colorectal cancer surgery</td>
<td>-</td>
<td>Vancomycin</td>
<td>Yes</td>
<td>Survival</td>
</tr>
<tr>
<td>16</td>
<td>Spain</td>
<td>77 F</td>
<td>Yes</td>
<td>NMV, NAV</td>
<td>-</td>
<td>-</td>
<td>Amoxicillin+gentamicin</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>17</td>
<td>Spain</td>
<td>70 F</td>
<td>No</td>
<td>NMV</td>
<td>Rectal diverticulum</td>
<td>-</td>
<td>Amoxicillin+clavulanic acid+gentamicin, vancomycin</td>
<td>Yes</td>
<td>Survival</td>
</tr>
<tr>
<td>18</td>
<td>Sweden</td>
<td>81 M</td>
<td>Yes</td>
<td>NMV, PAV</td>
<td>Total esophagectomy due to esophageal adenocarcinoma</td>
<td>Eating fish</td>
<td>Ceftriaxone, gentamicin</td>
<td>No</td>
<td>Survival</td>
</tr>
<tr>
<td>19</td>
<td>Israel</td>
<td>76 F</td>
<td>Yes</td>
<td>PAV</td>
<td>-</td>
<td>-</td>
<td>Cefditoren, daptomycin+ampicillin+ceftriaxone, gentamicin</td>
<td>No</td>
<td>Death</td>
</tr>
</tbody>
</table>

for *Streptococcus* species, clindamycin resistance is a feature of *L. garvieae*; this feature can be used to distinguish it from other *Lactococcus* species (30). Of the previous 19 cases, 15 (78.9%) were administered b-lactams and aminoglycoside antibiotic therapy. Of these 15 patients, 11 survived. The remaining 4 patients received antibiotic mono-therapy, including vancomycin (n=2) or ampicillin (n=2) without mortality. Among these 4 patients, 3 (75%) underwent cardiac surgery. In our case, initial empirical antibiotic therapy for the prosthetic infective endocarditis was composed of ceftriaxone, gentamicin, and rifampin according to the clinical guideline (31). After the staining results indicated infection with Gram-positive cocci, the patient was started on teicoplanin (400 mg/day) upon consideration of the patient’s decreased renal function, in expectation of infection with *Streptococcus* and *Enterococcus* species. After *L. garvieae* was identified, teicoplanin was maintained continuously, because 5 of the previous 7 cases who received glycopeptides recovered from an illness in the literature review. However, the initial teicoplanin monotherapy resulted in treatment failure. This treatment failure might have been due to insufficient therapeuetic blood levels. After cardiac surgery, the patient was started immediately on ceftriaxone (2 g/day), because no adjustment in the ceftriaxone dose is needed in renal impairment. It was also chosen based on the susceptibility test using an E-test.

Six (31.6%) patients of the previous 19 cases required surgical intervention. All those who underwent the surgical intervention after antibiotic treatment made satisfactory progress. Our patient required cardiac surgery upon admission due to heart failure and mobile vegetation >10 mm. However, she did not initially wish to undergo cardiac surgery. After persistent recommendation from our team, she finally agreed.

The clinical presentations of infective endocarditis might not include a fever over 38°C. Of the previous 19 cases, five (26.3%) were afebrile. This observation might be associated with old age, underlying disease, or less virulent and opportunistic pathogens.

In conclusion, *L. garvieae* should be considered as a causative pathogen of afebrile infective endocarditis in immunocompromised patients. With improved molecular tests and continued development of aquaculture, an increasing number of clinical cases of *L. garvieae* infection are expected. Furthermore, clinical guidelines for the treatment of *L. garvieae* infection should be established based on the standard criteria for antimicrobial susceptibility.

The authors state that they have no Conflict of Interest (COI).

References