ABSTRACT

Lactococci are Gram-positive cocci that occur in short chains or pairs and are traditionally considered to be of low virulence in human. Most species are not associated with human disease. There are few reports regarding Lactococcus isolation in humans and the clinical significance of this rarely-encountered genus is unknown. Here, we report a case of infectious spondylitis due to Lactococcus garvieae confirmed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOFMS). A 77-year-old man was admitted to our hospital with back pain that had lasted 5 days. He had diabetes mellitus, hypertension, and histories of pulmonary tuberculosis and endovascular aneurysm repair due to an abdominal aortic aneurysm. Magnetic resonance imaging of his spine revealed paravertebral enhancement on T8-9 and a compression fracture on the lower endplate of T8. On blood cultures, L. garvieae was identified by MALDI-TOF MS. To our knowledge, this is the first report of spondylitis caused by L. garvieae in Korea. In this context, we reviewed non-endocarditis cases due to L. garvieae reported in the English-language literature to summarize its clinical features and outcomes.

Keywords: Lactococcus garvieae; Spondylitis; Bacteremia

INTRODUCTION

Lactococci are Gram-positive, catalase-negative, facultative anaerobic cocci that occur in short chains or pairs and which are traditionally considered to be of low virulence to humans [1]. In 1985, based on genetic evidence of DNA-DNA and DNA-RNA relatedness, the genus Lactococcus was separated from that of Streptococcus. Most species are not associated with human disease. There are few reports regarding Lactococcus isolation in humans and the clinical significance of this rarely-encountered genus is unknown. Among the eight species and subspecies, L. garvieae is responsible for the majority of reported cases of opportunistic human infections in the literature. The most well-recognized clinical syndrome of human L. garvieae infection is infective endocarditis [2-4]. Other reported cases included liver abscess, secondary peritonitis, diverticulitis, catheter-related urinary tract infection...
and infectious spondylitis associated with endocarditis [5-8]. Here we report a case of infectious spondylitis with septicemia due to \textit{L. garvieae} that was confirmed by MALDI-TOFMS (bioMerieux, Marcy l’Étoile, France). To our knowledge, this is the first report in Korea of spondylitis caused by \textit{L. garvieae}.

**CASE REPORT**

A 77-year-old man was admitted to our hospital with back pain that had lasted for 5 days. He had diabetes mellitus, hypertension, and histories of pulmonary tuberculosis and endovascular aneurysm repair due to an abdominal aortic aneurysm. On examination, his vital signs included the following: temperature 36.5°C, blood pressure 120/80 mmHg, pulse rate 62/min, and respiratory rate 19/min. Laboratory evaluation revealed a white blood cell count of 6,840/mm³ (neutrophil 87.3%), C-reactive protein of 3.75 mg/dL, blood urea nitrogen of 17 mg/dL, creatinine of 0.99 mg/dL, aspartate aminotransferase of 12 IU/L, alanine aminotransferase of 13 IU/L. Magnetic resonance imaging (MRI) of the spine revealed paravertebral enhancement on T8-9 and a compression fracture on the lower endplate of T8 (Fig. 1). No specific finding was observed in the chest and abdominal computed tomography. Two sets of blood cultures of samples drawn from two different peripheral sites were collected on admission. Two sets of blood cultures from the date of admission yielded growth of Gram-positive cocci in chains. \textit{L. garvieae} was identified by MALDI-TOF MS. Antimicrobial susceptibilities were determined by disk diffusion tests. Because the Clinical Laboratory Standards Institute (CLSI) has not yet established \textit{Lactococcus} minimum inhibitory concentration (MIC) breakpoints, the susceptibilities were determined based on the CLSI recommendations for viridans streptococci. The isolate was susceptible to cefotaxime, cefepime, erythromycin, levofloxacin, and vancomycin were susceptible, and was resistant to penicillin and clindamycin (Table 1). The vertebral biopsy was not performed. A transthoracic echocardiogram showed normal heart valves without vegetation. Ampicillin/sulbactam was started as an empirical antibiotics (3 g every 6 hours). After confirmation of the susceptibilities, the antibiotics was changed to 2 g ceftriaxone, administered every 24 hours. A follow-up blood culture sample drawn on hospital day 6 was negative. Intravenous ceftriaxone was administered for 2 weeks and was then switched to oral cefditoren (100 mg three times daily). After 4 months of oral antibiotic administration, his back pain and laboratory findings were improved, and the patient stopped taking medication. One month later, his back pain was aggravated. Two sets of blood cultures of samples drawn from two different peripheral sites were collected on admission. \textit{L. garvieae} bacteremia was again identified. The susceptibilities of antibiotics were same as previous. A spine MRI revealed vertebral enhancement on T6-7 and L4-5 as well as anterior epidural enhancement on L5-6 (Fig. 2A). Positron emission tomography-computed tomography (PET-CT) showed diffuse FDG uptake on L5-S2, and no evidence of graft infection on the abdominal aorta. A transesophageal echocardiogram showed normal heart valves without vegetation. Cefepime was started after confirmation of \textit{L. garvieae} bacteremia. Intravenous cefepime was administered for 1 month and was then switched to oral levofloxacin (750 mg once a day). After 6 months of oral levofloxacin, follow-up MRI revealed improvement of the previous lesions as compared to the previous MRI findings (Fig. 2B). The antibiotics were stopped and the patient remained well at follow-up 4 months.

**Table 1. Antibiotic susceptibilities of \textit{Lactococcus garvieae} isolate in this case report**

| Antimicrobial agent | Inhibition growth diameter (mm) | Susceptibility |
|---------------------|-------------------------------|----------------|
| Cefotaxime          | 28                            | S              |
| Clindamycin         | 6                             | R              |
| Erythromycin        | 24                            | S              |
| Levofloxacin        | 20                            | S              |
| Penicillin          | 10                            | R              |
| Vancomycin          | 18                            | S              |
| Cefepime            | 26                            | S              |

S, susceptible; R, resistant.

**Figure 1.** T1-weighted magnetic resonance imaging of the spine at first admission showing abnormal contrast enhancement in the paravertebral enhancement on T8-9 and a compression fracture on the lower endplate of T8.
The genus Lactococcus was separated from that of Streptococcus in 1985. It was first isolated from bovines with mastitis and then from fish and human specimens [9]. In summer, the higher water temperature is most suitable for breeding prawns, trout, and mullets, which carry the highest risk of lactococcosis [10]. In recent years, L. garvieae has been recognized as an emerging zoonotic pathogen, due to the increasing number of cases of human infections.

The suggested points of entry for L. garvieae are anatomic or physiologic defects of the gastrointestinal tract or the use of acid-suppressing medications; however often, no source of entry is identified. Wang et al. [5] suggested that the consumption of raw seafood during the summer by patients with underlying gastrointestinal diseases may be a potential predisposing factor for L. garvieae infection. The acid pH of the stomach, pancreatic enzymes, bile and intestinal secretions, peristalsis and the integrity of epithelial cells are important antimicrobial factors that prevent infection through the oral gastrointestinal route [5]. In addition, skin wounds can be a site of entry leading to L. garvieae infection [11]. Contaminated milk and unpasteurized dairy products can also be sources of infection. Moreover, L. garvieae have also been isolated in manufactured food due to their use in food products [12]. Our patient was exposed to raw fish. However, he did not suffer from any gastrointestinal disease and had not taken acid-suppressing medication. He denied any consumption of unpasteurized dairy products.

L. garvieae can be easily misidentified as Enterococcus species. Automated microbial identification systems such as the VITEK-2 have been helpful for identification but the results should be confirmed with a different method, such as MALDI-TOFMS or 16S rRNA sequencing [2].

A previous report of L. garvieae spondylitis identified by percutaneous bone biopsy had L3-4 involvement without bacteremia. The clinical symptoms improved after 6 weeks of intravenous ampicillin. However, our patient was switched to oral antibiotics after 2 weeks of intravenous ceftriaxone. Back pain was aggravated one month after antibiotic termination, and the bacteremia recurred with worsening of the spondylitis. The cause of worsening was likely the short duration of intravenous antibiotics and more data are required to evaluate the prognosis of L. garvieae spondylitis. Including our case, a total of 10 cases of L. garvieae infection except for endocarditis have been reported in the English-language literature [5-7, 10-14]. Intraabdominal infection was the most common source (5/10, 50.0%), followed by bone and joint infection (4/10, 40.0%). Half of the cases had bacteremia. Seven cases (70.0%) had risk factors including gastrointestinal disease or history of exposure to raw fish. Only one patient died. Of L. garvieae endocarditis cases, 84.2% had risk factors for L. garvieae infection and the mortality rate was 21.1% [4]. The mean ages were 63.3 ± 13.6 and 68.7 ± 11.4 years in non-endocarditis and endocarditis patients, respectively.

**DISCUSSION**

Figure 2. (A) T1-weighted magnetic resonance imaging of the lumbar spine at the second admission showing bone marrow signal abnormality and enhancement in T6-7 and L4-5 vertebral bodies as well as L5-6 anterior epidural enhancement. (B) Follow-up T1-weighted magnetic resonance imaging after 1 month of cefepime and 6 months of oral levofloxacin treatment, showing improvement of the previous lesions as compared to the previous image findings.
Non-endocarditis cases had a lower incidence of risk factors and mortality rate but more data and studies are needed for statistical significance (Table 2).

In conclusion, the number of human infections by *L. garvieae* is expected to increase. *L. garvieae* should be considered a causative pathogen of spondylodiscitis, especially in cases of gastrointestinal disorder or exposure to raw fish. Additional tests such as MALDI-TOFMS or 16S rRNA sequencing are required for the identification of *L. garvieae*.

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**Ethics statement**

This study was approved by the Institutional Review Board at the Keimyung University Dongsan Hospital (IRB No. 2020-08-027). This research was approved for a waiver of consent by the IRB as it used retrospective data.

**Conflict of Interest**

No conflicts of interest.

**Table 2. Characteristics of patients with infections other than endocarditis due to *Lactococcus garvieae***

| Clinical syndrome     | Age | Sex | Site     | Raw fish | Underlying disease                                | Treatment                          | Outcome | Reference |
|-----------------------|-----|-----|----------|----------|---------------------------------------------------|------------------------------------|---------|-----------|
| Diverticulitis        | 56  | F   | Blood    | None     | Small bowel diverticulosis                        | Cefazolin, gentamicin → cotrimoxazole | Survival | [5]       |
| Peritonitis           | 47  | M   | Ascite   | Yes      | Small bowel perforation                           | Piperacillin, amikacin             | Survival | [5]       |
| Osteomyelitis         | 56  | F   | Blood    | UK       | AS s/p AVR                                        | Vancomycin → teicoplanin           | Survival | [6]       |
| Liver abscess         | 68  | F   | Blood    | None     | Cholangiocarcinoma                               | Amoxicillin, netilmicin, metronidazole | Death    | [7]       |
| PD peritonitis        | 38  | M   | IP effluent | None    | IgAN s/p steroid on PD                            | IP cefazolin                       | Survival | [10]      |
| Prosthetic hip joint infection | 71  | F   | Joint fluid | UK    | HTN, DM, IHD, osteonecrosis s/p THR               | Ceftriazone, levofloxacin          | Survival | [11]      |
| Spondylodiscitis      | 70  | M   | Bone     | UK       | Gastritis (long administration of H2 blocker)     | Ampicillin                         | Survival | [12]      |
| Primary bacteremia    | 81  | M   | Blood    | UK       | VHD CHF s/p MVR, AVR, pacemaker, HTN, CKD, diverticulitis, reflux esophagitis | Piperacillin/ tazobactam → ampicillin, gentamicin | Survival | [13]      |
| Acute cholecystitis   | 69  | M   | Gall bladder | Yes    | Gastric ulcer perforation s/p gastrectomy         | Cefminox → cefaclor                | Survival | [14]      |
| Spondylodiscitis      | 77  | M   | Blood    | Yes      | HTN, DM, AAA s/p EVAR                             | Ceftriazone → cefidoren Cefepime → levofloxacin | Survival | Current case |

F, female; M, male; UK, unknown; AS, aortic stenosis; s/p, status post operation; AVR, aortic valve replacement; IgAN, immunoglobulin A nephropathy; PD, peritoneal dialysis; IP, intraperitoneal; HTN, hypertension; DM, diabetes mellitus; IHD, ischemic heart disease; THR, total hip replacement; VHD, valvular heart disease; CHF, congestive heart failure; MVR, mitral valve replacement; CKD, chronic kidney disease; AAA, abdominal aortic aneurysm; EVAR, endovascular aneurysm repair.

**Author Contributions**

Conceptualization: SYR, JYL. Writing - original draft: JYL. Writing - review & editing: SYR, JYL, MH, HAK.

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