Japanese Features of Native Valve Endocarditis
Caused by Coagulase-negative Staphylococci: 
Case Reports and a Literature Review

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Abstract

Although coagulase-negative staphylococci (CoNS) is a frequent cause of prosthetic valve endocarditis, native valve endocarditis (NVE) caused by CoNS is not commonly seen. Its high mortality is well known; however, there are no systematic reports published in Japan. We herein report the cases of two Japanese patients with CoNS NVE who were admitted to our hospital located in Tokyo and conduct literature searches on CoNS NVE in Japan from 1983 to March 2012 using PubMed and ICHUSHI WEB (Japan Medical Abstract Society). We also summarize the features of 22 Japanese patients with CoNS NVE, including our patients.

Key words: native valve endocarditis (NVE), coagulase-negative staphylococci (CoNS), Japanese, Staphylococcus epidermidis, Staphylococcus lugdunensis

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Introduction

Coagulase-negative staphylococci (CoNS), with over 40 recognized species and subspecies, are the most abundant microbes inhabiting normal human skin and mucous membranes (1). Although CoNS frequently cause prosthetic valve endocarditis, native valve endocarditis (NVE) caused by CoNS is rare, accounting for only 5-8% of all cases of NVE (1-4). It is known that CoNS NVE is a fatal disease and that the most common causative pathogen of CoNS associated with NVE is Staphylococcus epidermidis (3, 4). Staphylococcus hominis (5), Staphylococcus lugdunensis (6) and Staphylococcus capitis (7) are also reported to be typical pathogens of CoNS NVE. In major countries, systematic data of CoNS NVE are refined and maintained on an international-scale database (3, 4). These reports clarify the importance of CoNS as a cause of NVE and a potential cause of serious complications with CoNS NVE. CoNS NVE is rare in Japan, as in major countries. Although some case reports were written in Japan, no systematic reports exist in the Japanese literature. We herein report two cases of CoNS NVE and describe the features of these patients. We also conducted a literature review to analyze demographic characteristics, comorbidities, predisposing factors and outcomes of Japanese patients with CoNS NVE.

Case Reports

Case 1

A 78-year-old Japanese woman was admitted to our hospital presenting with a one-week history of a low-grade fever and abdominal pain. The patient was receiving acupunc-
tured twice a week regularly. She had been previously diagnosed with type C liver cirrhosis due to a blood infusion and was also diagnosed with depression. Other concomitant diseases included chronic kidney disease, moderate aortic stenosis and regurgitation. The patient had also undergone aortocoronary bypass surgery for unstable angina pectoris five months before admission.

On a physical examination performed on admission, the patient’s height was 150.0 cm and her body weight was 36.8 kg. Her temperature was 36.6°C, her blood pressure was 98/58 mmHg and her heart rate was 74 beats/min and regular. The lungs were clear. On heart auscultation, a Levine 3/6 to-and-fro murmur was heard at the left second intercostal space. No skin lesions such as Osler nodes or Janeway lesions were found. The initial blood examination showed the following results: WBC count: 17,100/μL, hemoglobin: 10.5 g/dL, platelet count: 43,000/μL, C-reactive protein: 7.4 mg/dL, blood urea nitrogen (BUN): 30 mg/dL, Cre: 1.28 mg/dL, total bilirubin: 1.18 mg/dL, aspartate aminotransferase: 58 IU/L, alanine aminotransferase: 26 IU/L, creatine kinase: 49 IU/L, and serum glucose: 152 mg/dL. The patient had been previously diagnosed with piperacillin-tazobactam at a dose of 4.5 g every eight hours and gentamicin at a dose of 30 mg every 12 hours intravenously on the next day of admission. Three days after admission, three sets of blood cultures obtained on admission revealed the presence of *S. epidermidis*. Afterwards, second consecutive positive blood cultures were identified. We confirmed the diagnosis of endocarditis due to CoNS NVE based on the Duke Criteria (8). After diagnosis, the piperacillin-tazobactam and gentamicin treatment was replaced with cefazolin at a dose of 2 g every 12 hours. Two days later, the sensitivity to cefazolin (MIC <=8) and ampicillin (MIC <=0.12) were revealed, and we changed the cefazolin to ampicillin at a dose of 2 g every six hours. Concerning the treatment strategy, antibiotic therapy was selected by both the patient and her family, although we thoroughly informed them of other treatment methods, including surgery.

After starting the antibiotic therapy, the C-reactive protein (CRP) value improved by degrees. On day 16, the CRP value improved to 1.7 mg/dL. On day 18, the patient suddenly lost consciousness due to a complete atrioventricular block and developed cardiopulmonary arrest. She died of sudden cardiac death due to complete atrioventricular block caused by CoNS NVE.

On autopsy, a spherical vegetation measuring 6×8 mm in size on the noncoronary cusp of the aortic valve was found (Figure). We believe that it caused the cardiac conduction abnormalities and fatal arrhythmia.

**Case 2**

A 52-year-old Japanese woman was admitted to our hospital presenting with a 10-day history of a low-grade fever and dyspnea on effort. Garenoxacin was administered approximately two weeks prior to admission. The patient had been diagnosed with a cerebral infarction, idiopathic thrombocytopenic purpura and carcinoma of the uterine cervix 45 years of age. She had also been diagnosed with systemic lupus erythematosus and antiphospholipid antibody syndrome 47 years of age and was treated with a dose of 10 mg of prednisolone and 5 mg of tacrolimus at an outpatient clinic. She had also been diagnosed with deep vein thrombosis of the right subclavian vein and treated with anticoagulation. Moderate mitral valve regurgitation was diagnosed at 49 years of age.

On a physical examination performed on admission, the patient’s height was 160.5 cm and her body weight was 51.9 kg. Her temperature was 36.5°C, her blood pressure was 132/78 mmHg, her heart rate was 98 beats/min and her SpO2 was 94% (ambient air). On heart auscultation, a Levine 5/6 holosystolic murmur was heard at the apex. The initial blood examination showed the following results: WBC count: 8,400/μL, hemoglobin: 8.9 g/dL, platelet count: 113,000/μL, C-reactive protein: 14.9 mg/dL, BUN: 38 mg/dL, Cre: 1.22 mg/dL, aspartate aminotransferase: 38 IU/L, alanine aminotransferase: 19 IU/L, Na: 3.0 mEq/L, K: 97 mEq/L, Cl: 152 mEq/L, and serum glucose: 30 mg/dL. ECG performed on admission showed a sinus rhythm with premature atrial contractions. Chest X-ray showed cardiomegaly (cardiothoracic ratio: 55%) and bilateral pleural ef-
After admission, the patient was treated with doripenem at a dose of 0.25 g every eight hours to treat a severe infection of unknown origin. Doripenem was replaced with minocycline at a dose of 100 mg every 12 hours due to a spike in fever. TTE performed on day 8 showed floppy vegetation on the mitral valve and severe mitral valve regurgitation. Two sets of blood cultures obtained on admission revealed the presence of *S. lugdunensis*. Susceptibility testing of the *S. lugdunensis* endocarditis to antibiotics showed the following results: penicillin G (MIC 8), ampicillin (MIC 4), vancomycin (MIC <=2), cefazolin (MIC <=2) and gentamicin (MIC <=1). We administered vancomycin at a dose of 0.5 g every 12 hours, gentamicin at a dose of 40 mg every 24 hours and cefazolin at a dose of 2 g every 12 hours to treat *S. lugdunensis* endocarditis caused by CoNS NVE. Afterwards, second consecutive positive blood cultures also were identified, and the diagnosis of endocarditis due to CoNS NVE was confirmed based on the Duke Criteria (8). On day 11, transesophageal echocardiography was performed, which revealed floppy vegetation on the anterior leaflet of the mitral valve measuring 5 mm in size. On day 27, atrial fibrillation occurred in association with heart failure due to severe mitral valve regurgitation. On day 29, atrial fibrillation converted to 2:1 atrial flutter. We conducted cardioversion for the atrial flutter because we predicted hemodynamic instability. We confirmed that surgical therapy was superior to therapy with antibiotics only. For surgical treatment, the patient was transferred to another hospital where she underwent mitral valve replacement and tricuspid annuloplasty. Her postoperative course was uneventful, and she was discharged from the hospital on the 10th day after surgery.

**Discussion**

We herein reported the cases of two Japanese patients with CoNS NVE who were admitted to our hospital located in Tokyo. To clarify the features of Japanese patients with CoNS NVE, we searched Japanese cases of CoNS NVE from 1983 to March 2012 using PubMed and ICHUSHI WEB (Japan Medical Abstract Society). The search strategy is shown in the appendix. Cases of infectious endocarditis fulfilling the Duke Criteria were included (8). Patients >=18 years of age were included.

As a result of the literature search, 20 cases of Japanese CoNS NVE were found. Table shows the characteristics of the 22 Japanese cases of CoNS NVE, including our two cases (14 men, age 57.9±14.7 years). In Table, healthcare-associated endocarditis was defined as receiving hospital services, home health care, home or clinic-based parenteral therapy or dialysis, residing in a nursing home or being hospitalized during the previous 90 days (4, 9). Patients who received acupuncture were classified as having healthcare-associated endocarditis.

The Japanese patients with CoNS NVE had a mortality rate as high as those in other major countries. In previous systematic reviews of CoNS NVE based on a large-sized database in major countries, the mortality rates of CoNS were 19% (19/99) (4) and 25% (32/128) (3). Our Japanese data (23%, 5/22) are similar to those of other major countries.

There are two possible reasons for the high CoNS NVE mortality rates: the delay in diagnosis, and the low efficacy of surgical treatment.

It is surmised that the cause of delay in diagnosis is related to the pre-existing comorbidities of patients. The mortality rate in patients with CoNS NVE is generally higher than that in patients with NVE due to the presence of the viridans group of streptococci. In the background of the high mortality rate lie advanced age, dialysis, diabetes, malignant tumors and the frequent use of immunosuppressants (3). It is also known that CoNS NVE is significantly related to healthcare-associated infection or the presence of long-term intravascular catheters (4). Patients with CoNS NVE, therefore, tend to be compromised hosts. It is surmised that compromised hosts are not diagnosed promptly because the symptoms of fever and increases in the inflammatory response on blood examinations do not often appear clearly in such cases.

In general, surgery is the basic treatment for patients with infectious endocarditis who exhibit the onset of congestive heart failure as a complication. A delay in surgery will worsen the prognosis of the patient, even if the patient is in the active phase of infection (11, 30, 31); however, it is known that the efficacy of surgery is low in patients with CoNS NVE (3, 32). The reason for the low efficacy in patients with CoNS NVE has not yet been clarified, and we believe that its clarification is an important issue for the future.

The characteristics of patients with healthcare-associated endocarditis have recently changed. The number of patients with staphylococci (NVE due to *S. aureus* or CoNS NVE) has noticeably increased in comparison to the number of patients with NVE caused by the viridans group of streptococci, and the mortality rate has been increasing consequently (33). In a highly aged society like Japan where the population is aging rapidly, the number of inhabitants of long-term care facilities is expected to increase, and the number of patients with CoNS NVE is expected to increase in the future as a result. We therefore think that making an early diagnosis and providing early intervention with treatment are most critical in order to reduce the mortality rate of patients with CoNS NVE.

According to our case reports and literature review, Japanese patients with CoNS NVE have a mortality rate as high as patients in other major countries. However, this hypothesis should be validated. The outstanding cases tend to be reported. In order to exclude publication bias and establish evidence regarding Japanese CoNS NVE, physicians must cooperate and create a prospective multi-center database of infectious endocarditis.
# Table. The Characteristics of 22 Japanese Case of CoNS NVE

<table>
<thead>
<tr>
<th>Ref</th>
<th>Age</th>
<th>Sex</th>
<th>Pathogen</th>
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<th>Other Primary Illness</th>
<th>Congenital Heart Disease</th>
<th>Place of Acquisition</th>
<th>Place of Vegetation</th>
<th>Heart Failure</th>
<th>Arhythmia</th>
<th>Surgery</th>
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<th>Other Complications</th>
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<td>-</td>
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<td>NS, NS</td>
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<td>+</td>
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<td>First Degree AV Block</td>
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<td>Septic Brain Embolism</td>
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<td>+</td>
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<td>+</td>
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<td>Post Transesophageal Angiography at the age of 64 years</td>
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<td>Community</td>
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<td>Atrial Fibrillation 2.3 Atrial Flutter</td>
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</table>

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

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Appendix

When we conducted literature searches with PubMed and ICHUSHI WEB using the following terms: (“coagulase negative staphylococcus” or “staphylococcus epidermidis” or “staphylococcus haemolyticus” or “staphylococcus lugdunensis” or “staphylococcus saprophyticus” or “staphylococcus auricularis” or “staphylococcus capitis” or “staphylococcus caprae” or “staphylococcus carnosus” or “staphylococcus cohnii” or “staphylococcus hominis” or “staphylococcus pasteuri” or “staphylococcus pettenkoferi” or “staphylococcus pulvereri” or “staphylococcus saccharolyticus” or “staphylococcus simulans” or “staphylococcus schleiferi” or “staphylococcus warneri” or “staphylococcus xylosus”) AND (endocarditis or “native valve endocarditis”). We focused only on case reports and original articles. After we obtained candidate literature, we checked the titles and abstracts to select appropriate Japanese cases of CoNS NVE.

References
