Three Fatal Cases of Rapidly Progressive Infective Endocarditis Caused by *Staphylococcus Aureus*

--- One Case With Huge Vegetation ---

Eri Miyata, MD; Shinji Satoh, MD; Kosuke Inokuchi, MD; Akemi Aso, MD; Yoshikuni Kimura, MD; Shinni Yokoyama, MD; Etsuo Mori, MD; Toshihiro Nakamura, MD; Takahiro Matsumoto, MD; Yusuke Fujino, MD; Yasuhiro Kishihara, MD; Ken Uda, MD; Koichiro Takemoto, MD; Toru Inoue, MD; Suguru Nakayama, MD; Ryozo Kobayashi, MD; Noriko Uesugi, MD; Koji Hiyamuta, MD

Staphylococcus aureus (*S. aureus*) infective endocarditis (IE) is a severe disease with a high mortality despite intensive therapy. Three cases of *S. aureus* IE had a rapidly progressive fatal clinical course despite intensive antimicrobial therapy. One case was methicillin-sensitive *S. aureus* IE, which formed rapidly growing a huge vegetation on a prosthetic mitral valve, complicated with multiple systemic emboli. The other 2 cases were methicillin-resistant *S. aureus* IE without any predisposing heart disease. (Circ J 2007; 71: 1488–1491)

**Key Words:** Infective endocarditis; Prosthetic valve; *Staphylococcus aureus*; Vegetation

Infective endocarditis (IE) caused by *Staphylococcus aureus* (*S. aureus*) is a serious septic disease that can be fatal unless effective therapy under correct diagnosis is initiated as soon as possible! Although diagnostic and therapeutic methods have improved and developed, the mortality rate for *S. aureus* IE is still higher than that caused by other pathogens. In addition, the prevalence of *S. aureus* IE is also becoming higher in Japan concurrent with an increase in predisposing factors such as use of intravascular devices and intravenous drugs! Here we report recent 3 cases of *S. aureus* IE that had a rapidly progressive fatal clinical course despite intensive antimicrobial therapy. One patient had a prosthetic mitral valve, which was infected with methicillin-sensitive *S. aureus* (MSSA), and the other 2 patients were infected with methicillin-resistant *S. aureus* (MRSA) on native valves. We review these cases and discuss the management of *S. aureus* IE in relation to current studies.

**Case Reports**

**Case 1**
A 64-year-old man, who had undergone replacement of a mechanical mitral valve 12 years ago in the USA, felt a general malaise and developed a high fever (>38°C) 3 days prior to admission to a community hospital where he was treated with intravenous flomoxef (2 g/day) followed by ampicillin (4 g/day). Transthoracic echocardiography on the second day revealed no definite vegetation or valve dysfunction. The high fever continued and on the third day of the clinical course, Osler’s nodes appeared. He was thus strongly suspected of having IE and was transferred to the Cardiology Department for further examination and treatment.

On admission, the patient was alert, with a temperature of 40.6°C, blood pressure of 120/60 mmHg, and pulse rate of 120 beats/min (irregular). Auscultation of the chest showed a grade II/VI holosystolic murmur that was maximal at the cardiac apex and there were normal vesicular respiratory sounds without rales. The chest X-ray revealed cardiomegaly (cardiothoracic ratio 66%) without lung consolidation. Electrocardiography (ECG) showed atrial fibrillation with tachycardia. Major blood chemistry findings were: hemoglobin 13.3 g/dl, white blood cell 13,000 /mm³, platelets 48,000/mm³, C-reactive protein (CRP) 16.11 mg/dl, INR 2.38, albumin 2.9 g/dl, total bilirubin 1.1 mg/dl, LDH 467 U/L, BUN 13 mg/dl, creatinine 0.9 mg/dl, Na 132 mmol/L, K 3.9 mmol/L, and brain natriuretic peptide 230 pg/ml. Transthoracic and transesophageal echocardiography revealed a vegetation of 10 mm in length on the prosthetic mitral valve, with a mild perivalvular leak. The diagnosis of IE was made. Relatively deep wounds in both hands because of enthusiastic golf practice a few months before the onset of the sickness were suggestive as the portal of entry of the microorganism. Because the antibiotics he had been administered at the previous hospital had been ineffective, we scheduled blood culture for the following day under antibiotic-free conditions and planned to start antibiotic treatment thereafter. That night he became uncon-
conscious (JCSIII-300) and emergency brain CT/MRI revealed multiple brain infarctions, probably caused by mycotic emboli. Because Gram-positive cocci grew in the blood culture, intravenous penicillin G (3×10^7 U/day) and gentamicin (150 mg/day) infusions were started immediately. After the microorganism was found to be MSSA and sensitive to cefalosporins, we changed penicillin G to cefazolin (8 g/day) in combination with 150 mg/day gentamicin. However, the high fever continued, and the vegetation was increasing in size daily to over 7 cm in length (Fig 1). Four days after admission to our hospital, the high fever continued and the vegetation was increasing in size daily to over 7 cm in length (Fig 1). Four days after admission to our hospital, a sudden aphasia and stupor appeared. Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain revealed multiple areas of high density and multiple areas of low signal intensity, respectively. Arterial blood gas analysis revealed a pH of 7.28, an oxygen saturation of 80%, and a bicarbonate concentration of 18 mmol/L. The patient died on hospital day 4.

Fig. 1. Transthoracic echocardiography showing rapidly growing vegetation in Case 1. Two-dimensional echocardiography at the parasternal long axis view is shown. Arrows indicate seaweed-like vegetation attached to the anterior portion of the prosthetic mitral valve. The vegetation was elongating day by day even under sensitive antibiotics therapy. Day X means the day after admission to our hospital.

Fig. 2. Pathological findings in Case 1. (A) Resected prosthetic mitral valve looked up from the left ventricular (LV) side. A seaweed-like vegetation attached to the mitral valve ring is shown (a white arrow). (B) Resected prosthetic mitral valve looked down from the left anterior (LA) side. Three tongue-like vegetations grew on the mitral valve ring are shown (white arrows). (C) Micrographic specimen prepared from the vegetation shown in A (*). Gram-positive cocci are seen. (D) Coronal section of the cerebrum hemispheres showing multiple infarctions with hemorrhage (*). (E) Abscess was formed in the cerebrum showing the infiltration of inflammatory cells including polymorphonuclear cells.
admission, follow-up head CT showed hemorrhagic infarction and subarachnoid hemorrhage. Although the antibiotics were continued, sepsis progressed to disseminated intravascular coagulation (DIC), resulting in death from multiple organ failure (MOF) on the 7th day after admission.

The autopsy revealed the following findings (Fig 2): the vegetation grew around the mitral valve ring, and there was a huge seaweed-like vegetation of which size was about 10 mm in width × 70 mm in length (Fig 2A). Three other tongue-like giant vegetations were also seen (Fig 2B). Gram stain showed gram-positive cocci in the vegetation (Fig 2C). The brain specimen showed multiple infarctions and hemorrhagic foci all over the brain (Fig 2D), and abscess was formed at several sites (Fig 2E). As regards the other organs, bilateral kidney and spleen showed multiple infarctions due to mycotic emboli (not shown).

**Case 2**

A 63-year-old man with an old cerebral infarction was admitted to the General Medicine Department because of productive cough and high fever. On, admission, MRSA was found in the sputum culture, but without active phagocytotic background. Blood culture was negative. ECG showed ordinary sinus rhythm and no significant ST-T changes. Heart sounds were clear. Transthoracic echocardiography showed normal left ventricular function with no organic valve lesions. He was diagnosed as having aspiration pneumonia and treated with cefotiam (1 g/day). A central venous line was inserted via the right internal jugular vein because of progressive renal dysfunction. MEPM (1 g/day) was restarted. On the 29th hospital day, he felt chest pain, but the ECG was normal. There was a diastolic murmur and transthoracic echocardiography revealed aortic valve regurgitation with a vegetation-like echo. Transesophageal echocardiography confirmed destruction of the aortic valve by a large vegetation. He developed left-sided heart failure because of acute aortic regurgitation and 24 h later became unconscious after a brain infarction. Even though intensive antibiotics therapy with TEIC + arbekacin supported by continuous hemodialysis was performed, he died from MOF on the 34th day after admission.

**Case 3**

A 68-year-old woman was admitted to the Brain Surgery Department because of hemorrhagic cerebral infarction with hemiplegia and dysphagia. On admission, ECG showed ordinary sinus rhythm and no significant ST-T changes. An ejection systolic murmur (Levine II/VI) was audible in the aortic valve area, but no regurgitant murmur was audible. Nutrition was controlled via a central venous line in the right neck. On the 20th day after admission, she developed a high fever and the white blood cell count was elevated despite no obvious focus, including negative blood culture. Although empirical antibiotic therapy was started, her clinical symptoms did not improve and 10 days later, MRSA was detected on blood culture. Based on the positive findings of gallium scintigraphy and magnetic resonance imaging, the diagnosis of suppurative lumbar spondylitis was made. We started vancomycin (VCM), but the high fever continued. On the 39th day after admission, a holosystolic murmur was noticed for the first time, and transthoracic echocardiography revealed a vegetation on the mitral valve with massive mitral regurgitation. The diagnosis of IE because of MRSA was made. Despite continued VCM followed by TEIC therapy thereafter because of insufficient effect of VCM, her general condition deteriorated and she died 2 weeks later from DIC.

We summarize the clinical features of these 3 cases in Table 1.

**Discussion**

Three cases of *S. aureus* IE were fatal despite intensive therapy including administration of sensitive antibiotics in
sufficient doses. The incidence of *S. aureus* IE has increased in Japan. In 2003, Nakatani et al performed a nationwide questionnaire survey and revealed that *S. aureus* was the causative microorganism in 31.7% cases of IE compared with 14.6% in a previous study reported by Katsu in 1980. Possible reasons for this increase include increased use of invasive procedures and intravascular devices, increased use of intravenous drug therapy, and improvements in diagnostic techniques!

Although there has been much development and improvement in both diagnostic and therapeutic methods, the mortality of *S. aureus* IE is still relatively high, ranging from 20% to 65%. Nadji et al compared *S. aureus* IE with that caused by other pathogens, and found that the 36-month actual overall survival rate was significantly lower for *S. aureus* IE than IE caused by other pathogens. This poor prognosis is because *S. aureus* is frequently resistant to antibiotics, and induces severe inflammation and systemic emboli in the early phase of sickness. Among cases of *S. aureus* IE, mortality is higher for MRSA than for MSSA, and for those with prosthetic valves than in cases involving native valves (range 25–59%). It appears that early valve replacement surgery for prosthetic valve endocarditis lessens mortality, even in the absence of intracardiac or extracardiac complications. However, that study may have been biased towards favorable outcomes in patients who underwent surgery, because patients in poor general condition may not have been selected for surgery. In fact, no randomized, controlled clinical trials have been performed to determine optimal antibiotic therapy or timing of surgery. In a recent study, limited to patients who were younger than 50 years, clinically stable, and who did not have cardiac or central nervous system complications, IE was cured with medical therapy alone? However, the general opinion at present is that all patients with *S. aureus* prosthetic valve endocarditis should be managed with a combined medical and surgical approach. In the present case 1, the prosthetic valve replacement surgery could not be performed because the patient was complicated with multiple cerebral emboli causing coma on the first day of admission. In addition, the vegetation became huge despite sufficient doses of sensitive antibiotics (8g/day cefazolin+150 mg/day gentamicin) in accordance with the Guidelines for the Prevention and Treatment of Infective Endocarditis of the Japanese Circulation Society 2003 indicating the treatment-resistant nature of this microorganism. We reiterate how important it is to rapidly confirm the diagnosis and start treatment, including surgery, in *S. aureus* IE.

Cases 2 and 3 tell us 2 important lessons: IE can occur in patients without predisposing heart disease, such as valvular heart disease, if they are otherwise compromised, and MRSA IE is resistant to intensive treatment, including sensitive antibiotic therapy. These 2 patients suffered from severe cerebral infarction, and their general condition was not good. We consider that the MRSA invaded through the central venous catheter in both cases. According to the Guidelines, prophylactic administration of antibiotics is not necessarily recommended for insertion of a central venous catheter; however, careful aseptic maneuver is important for prophylaxis of IE for the following reasons.

1. Nosocomical infection is increasing, so MRSA must be taken into account as a causative microorganism of IE in debilitated patients.
2. Recent studies indicate that the mortality rate for patients with IE caused by MRSA is significantly higher than that caused by MSSA. Therefore, in addition to appropriate medical treatment in sufficient doses, prompt diagnosis is very important. Unfortunately, IE was overlooked in both of the present cases during their early clinical course. In case 2, although MRSA bacteremia was diagnosed early and treated properly, TEIC had to be ceased because of progressive renal failure. In the meantime, MRSA bacteremia progressed to IE. In case 3, suppurative lumbar spondylitis was thought to be the focus of infection and IE was overlooked until a holo-systolic murmur was detected. Because neither of these cases was admitted to the Cardiology Department, careful periodic auscultation may not have been performed and could be a reason why the diagnosis of IE was delayed. Once MRSA IE was diagnosed, intensive antimicrobial therapy was begun according to the Guidelines; but was not effective. There was not enough time to use linezolid, which is reportedly effective against VCM-resistant species.

In conclusion, we report 3 cases of serious IE caused by *S. aureus*. Because the mortality rate is still high, we need more additional clinical studies to establish the optimal prophylaxis and treatment.

Acknowledgments

The authors express their gratitude to the co-medical staff in the Departments of Clinical Laboratory, Radiology, and Pathology, National Hospital Organization Kyushu Medical Center for their expert technical assistance.

References