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【 CASE REPORT 】

Prosthetic Valve Endocarditis Caused by ST8 SCC*mec*IVl Type Community-associated Methicillin-resistant *Staphylococcus aureus*

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Abstract:
The emergence of a Japan-intrinsic community associated methicillin-resistant *Staphylococcus aureus* strain (CA-MRSA/J) has been reported. A 70-year-old man with recurrent colon cancer and a history of mitral valve replacement was admitted to the hospital in a state of shock. He was diagnosed with prosthetic valve endocarditis (PVE) caused by MRSA and underwent cardiac surgery. The MRSA isolates belonged to multilocus sequence type 8 and carried staphylococcal cassette chromosome *mec* IVl and the genes of toxic shock syndrome toxin-1, enterotoxin C, and enterotoxin L. These characteristics indicated a CA-MRSA/J clone. This is the first reported case of PVE caused by CA-MRSA/J.

Key words: community-associated methicillin-resistant *Staphylococcus aureus*, septic shock, infectious endocarditis, multilocus sequence

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most common nosocomial pathogens worldwide. Since the 1990s, community-associated MRSA (CA-MRSA) has emerged in communities and has caused life-threatening infections, such as skin soft tissue infections (SSTI), pneumonia, and osteomyelitis, even in healthy individuals without risk factors (1, 2). Although the US Centers for Disease Control and Prevention have provided the epidemiological definition for CA-MRSA (3), CA-MRSA has been spreading rapidly in healthcare settings worldwide (2, 4). Therefore, the clear epidemiological classifications of CA-MRSA and healthcare-associated MRSA (HA-MRSA) remain unclear (2, 5).

CA-MRSA has a heterogeneous genetic background and is distinguished from HA-MRSA by molecular characteristics, such as multilocus sequence typing (MLST), and staphylococcal cassette chromosome *mec* (SCC*mec*) types (1, 2). CA-MRSA commonly carries SCC*mec* type IV or V, which are smaller than SCC*mec* type I, II, and III found in HA-MRSA. CA-MRSA outbreaks have been reported worldwide, and successful clones are usually associated with a specific geographic location (1, 2). In the United States, CA-MRSA with the genotype ST8-SCC*mec*IVa, known as USA 300, is currently the most prominent clone. The USA300 strain has the Panton-Valentine leucocidin (PVL) gene and arginine catabolic mobile element (ACME) (6). In contrast, the prevalence of CA-MRSA with the PVL gene is low in Japan (7).

It was recently reported that the Japan-intrinsic ST8-SCC*mec*IVl CA-MRSA strain (CA-MRSA/J), which is negative for the PVL and ACME genes and differs from USA300, has emerged and caused severe invasive infections (8). However, few studies regarding CA-MRSA/J have been reported (8, 9), and data on whether or not CA-MRSA/J causes healthcare-associated infections are scarce. We

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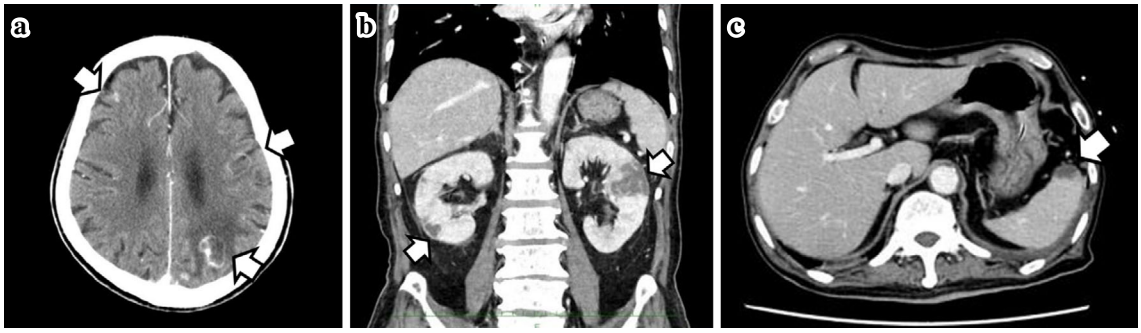

Figure 1. Enhanced computed tomography of the brain and abdomen obtained on day 6 showed multiple cerebral emboli with cerebral abscesses (a, arrows), bilateral renal infarctions with abscesses (b, arrows), and spleen infarction (c).

herein report a case of prosthetic valve endocarditis (PVE) caused by CA-MRSA/J.

Case Report

A 70-year-old man was transferred to the hospital because of rapid onset consciousness disorder and a fever with nausea and vomiting. He had a medical history of atopic dermatitis, colon cancer, mitral valve stenosis, and ischemic cardiomyopathy. Three years ago, he underwent resection of the sigmoid colon for sigmoid cancer and received adjuvant chemotherapy. Two years ago, mitral valve replacement with bioprosthetic valve and coronary artery bypass was performed for mitral valve stenosis and ischemic cardiomyopathy. Six months ago, local recurrence in the pelvis was detected. A totally implantable central venous access device was inserted, and chemotherapy was started.

On arrival at the hospital, he showed impaired consciousness (Glasgow Coma Scale, E3V4M5), and his vital signs were as follows: blood pressure 90/70 mmHg; heart rate, 120 beats/min (regular); respiratory rate, 24 breaths/min; oxygen saturation, 96% receiving 100% fraction of oxygen at 10 L/min using a reservoir mask; body temperature, 38.4℃. A physical examination revealed no rash or redness at the site of the totally implantable central venous access device.

Laboratory testing showed a state of high inflammation [white blood cells, 21,300/mm^3; C-reactive protein (CRP) 44.8 mg/dL, procalcitonin, 85.7 ng/mL], renal dysfunction (creatinine, 2.73 mg/dL; blood urea nitrogen, 56.7 mg/dL), liver dysfunction (total bilirubin 3.3 mg/dL; Aspartate transaminase 284 IU/L; Alanine transaminase 133 IU/L), disseminated intravascular coagulopathy [disseminated intravascular coagulation (DIC): platelet, $1.7\times10^4/mm^3$; D-dimer, 240 μg/mL; prothrombin time, 43%], and high lactate levels (11.2 mmol/L). Plain computed tomography (CT) of the chest and abdominal areas demonstrated unremarkable changes, and the local recurrence at the pelvis showed no change. Gram staining of the urine revealed Gram-positive cluster-forming cocci.

Antimicrobial therapy consisting of meropenem (500 mg every 24 hours, intravenously) and linezolid (600 mg every 12 hours, intravenously) was initiated. The patient required large amounts of intravenous fluids and norepinephrine for hypotension and mechanical ventilator support and was thus admitted to the intensive-care unit (ICU). On day 2, the totally implantable central venous access device was removed, and no abscess was found at the surgical site. Although prosthetic valve endocarditis (PVE) was suspected, transthoracic echocardiograms performed did not reveal any typical signs of PVE. On day 3, MRSA was detected in two sets of blood cultures and a urine culture obtained upon admission. Despite the intensive care, the patient exhibited a prolonged state of shock and multiple organ failure, including renal, hepatic, hematologic, and central nervous system. The antimicrobial therapy was changed to linezolid and clindamycin (600 mg every 8 hours, intravenously), and intravenous immune globulin was administered. A transesophageal echocardiogram (TEE) performed on day 3 revealed vegetation at the prosthetic mitral valve, and the patient was diagnosed with PVE caused by MRSA. Based on the diagnosis of PVE, the antimicrobial therapy was changed from linezolid to daptomycin (6 mg/kg every 48 hours, intravenously) on day 4. However, due to the persistent fever and the elevation of CRP, whole-body enhanced CT was performed on day 6, which showed multiple cerebral emboli with cerebral abscesses, bilateral renal infarctions with abscesses, and spleen infarction (Fig. 1). The antimicrobial therapy was changed from daptomycin to linezolid (600 mg every 12 hours, intravenously) once more. On day 8, the patient recovered from his state of persistent shock and was weaned off mechanical ventilation.

Although his body condition improved, a TEE performed on day 11 showed enlargement of the vegetation (22 mm in the major axis) and abscess around the prosthetic valve (Fig. 2). Therefore, surgery for PVE was required. He was transferred to the hospital where he had undergone mitral valve replacement. Mitral valve re-replacement with a bioprosthetic valve was performed on day 13. The intraoperative valve culture was positive for MRSA. Antimicrobial therapy with linezolid was continued following the surgery.

The patient showed cerebral infarction on day 28, and a

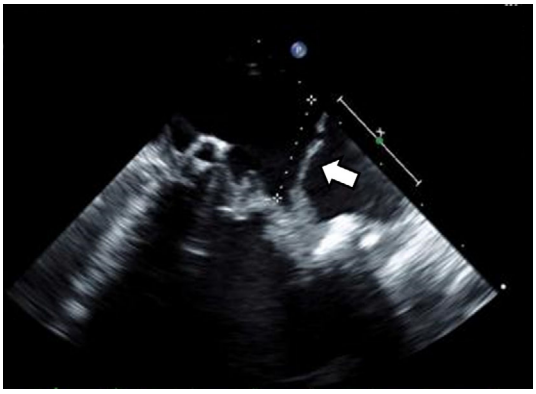

Figure 2. A transesophageal echocardiogram obtained on day 11 showed the vegetation (arrow) and abscess around the prosthetic mitral valve.

TEE revealed vegetation on the mitral valve; thus, the patient was diagnosed with recurrent PVE. The antimicrobial therapy was changed to vancomycin (750 mg every 24 hours, intravenously) and rifampicin (150 mg every 8 hours, orally). All blood cultures obtained after surgery were negative. Intravenous antimicrobial therapy was continued for four weeks and then changed to oral sulfamethoxazole/trimethoprim and rifampicin. The patient became almost permanently bedridden and was transferred to a long-term-care sanatorium.

The antibiotic susceptibility pattern of MRSA obtained from the patient's blood, urine, and vegetation was the same for all strains and included the following characteristics: resistance to gentamycin and sensitivity to clindamycin, minocycline, levofloxacin, sulfamethoxazole/trimethoprim, vancomycin, teicoplanin, linezolid, and daptomycin. The minimum inhibitory concentrations (MICs) of antimicrobial agents were determined by a broth microdilution method. The results were interpreted following the Clinical and Laboratory Standards Institute (CLSI) recommendations (10).

The following tests were conducted using methods that have previously been described. MLST was conducted (11), and the ST type was obtained from the MLST website (http://www.mlst.net/). The detection of the accessory gene regulator (agr) typing (12), coagulase (Coa) typing (13), and SCC*mec* typing (14) were conducted using polymerase chain reaction (PCR). The diagnosis of SCC*mec*IVl was performed using PCR-based detection of the *sasL* gene and SCCmecIV (15, 16). PCR of various virulence genes was conducted (16-25).

All of the MRSA isolates belonged to ST8, *agr* l, SCC*mec* type IVl, and CoaIII and were negative for PVL- (*lukS-PV* and *LukF-PV*) and ACME-related genes (*arcA* and *opp-3C*). The patterns of positive pathogenic factors were also the same, showing positivity for the genes of toxic shock syndrome toxin-1 (*tst-1*), staphylococcal enterotoxin C (*sec*), and staphylococcal enterotoxin L (*sel*). This strain has no other virulence genes; Staphylococcal enterotoxin (*sea, seb, sed, see, seg, seh, sei, selj, sek, sem, sen, seo, sep, seq, selr, ses, set, sey, se1*), Exfoliative toxin (*eta, etb, etd*), or epidermal cell differentiation inhibitor toxin (EDINs; *ednA, ednB, ednC*). Based on these results, it was concluded that the CA-MRSA/J strain caused the PVE in the present patient.

Discussion

The emergence of CA-MRSA infections is increasingly recognized as a life-threating problem (2). The emergence of CA-MRSA/J has recently been reported and is associated with severe invasive infections in Japan (8). One major genotype of CA-MRSA/J is ST8 /*spa*606(t1767)/agrl/SCC*mec*IVl/CoaIII. CA-MRSA/J has the superantigenic toxin-encoding *S. aureus* pathogenicity island (SaPI) carrying the *tst-1, sec,* and *sel* genes. The increased production of TSST-1 may contribute to the pathogenesis of CA-MRSA/J (8).

In the current case, CA-MRSA/J caused PVE, kidney and brain abscesses, DIC, and septic shock. Similar to previously reported CA-MRSA/J strains (8), the CA-MRSA/J strains isolated in this case harbored *tst-1*, *sec*, and *sel.* It was reported that 66.7% of CA-MRSA/J strains are positive for *sep* (8), and the CA-MRSA/J JH4899 strain possessed the plasmid pJSA01 carrying the *se1* and *edinA* gene (18). However, the CA-MRSA/J strains isolated in this case were negative for *sep, se1*, and *edinA*.

Recently, CA-MRSA strains have begun emerging as a cause of healthcare-associated infections, and hospital outbreaks have occurred worldwide (2). Based on the epidemiological definition (3), the CA-MRSA/J strains previously reported were predominantly classified as a CA-MRSA (8, 9), and only one case of postsurgical infection caused by a CA-MRSA/J variant strain has been reported as a healthcare-associated infection (8). The CA-MRSA/J strains isolated in this case were classified as HA-MRSA, as the patient had a totally implantable central venous access device and a history of surgery in the previous 12 months preceding the culture (3). This is the first reported case of PVE caused by CA-MRSA/J, suggesting that CA-MRSA/J may be spreading to healthcare settings.

Severe infections caused by CA-MRSA/J have been reported (8, 9). Indeed, the present patient showed a prolonged state of shock and multiple organ failure. However, combination therapy of vancomycin and rifampin is recommended for PVE caused by MRSA (26, 27). Therefore, not only the virulence factor of CA-MRSA/J but also the initial antimicrobial therapy of linezolid for PVE caused by MRSA may have been associated with the severe condition of the present patient.

In Japan, the increased prevalence of CA-MRSA strains in healthcare settings has been reported (28, 29). However, epidemiological information regarding the epidemic CA-MRSA clones identified in healthcare settings is limited. Surveillance of CA-MRSA in both community and health-

care settings focusing on specific epidemic clones in Japan is necessary in order to develop strategies to prevent and control MRSA infections.

In conclusion, we herein report a case of severe PVE caused by CA-MRSA/J. This report suggests that CA-MRSA/J may be spreading within healthcare settings. Further investigations of the epidemiology of CA-MRSA in healthcare settings are needed.

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

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