Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.6902-20
Intern Med 60: 3251-3255, 2021
http://internmed.jp

【 CASE REPORT 】

Infective Endocarditis from Furuncle with Meningitis Complication Caused by Methicillin-resistant *Staphylococcus aureus*

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Abstract:
Infective endocarditis (IE) may be acquired in the community as community-acquired (CA) IE or in the healthcare setting. In Japan, cases of CA-methicillin-resistant *Staphylococcus aureus* (MRSA) infection as skin infection have been increasing. CA-MRSA strains, including the USA300 clone, have higher pathogenicity and are more destructive to tissue than healthcare-associated MRSA strains because of the toxins they produce, including arginine-catabolic mobile element (ACME) and Panton-Valentine leukocidin (PVL). However, only a few IE cases induced by USA300 have been reported. We herein report a 64-year-old man who developed CA-IE from a furuncle caused by USA300 MRSA producing PVL and ACME, which resulted in complications of meningitis.

Key words: USA300, PVL, ACME

(Intern Med 60: 3251-3255, 2021)
(DOI: 10.2169/internalmedicine.6902-20)

Introduction

Infective endocarditis (IE) remains a severe health problem, with an in-hospital mortality rate of about 15-20% (1). IE may be community-acquired (CA) or healthcare-associated (2). In Japan, streptococci have been a common cause of CA-IE, while staphylococci have been a common cause of healthcare-associated IE. However, the prevalence of CA-IE caused by *Staphylococcus aureus* has increased in recent decades, as shown in the United States and European countries (1).

The prevalence of CA-methicillin-resistant *S. aureus* (MRSA) skin infection has increased in Japan (3). CA-MRSA strains, including the USA300 clone, have higher pathogenicity and are more destructive to tissue than healthcare-associated MRSA strains because of the toxins they produce, including arginine-catabolic mobile element (ACME) and Panton-Valentine leukocidin (PVL) (4). However, few IE cases caused by USA300 have been reported. Acute subarachnoid hemorrhaging and septic emboli have been reported as complications of IE caused by PVL- and/or ACME- producing IE (5); however, no report has described IE caused by USA300 complicated with meningitis.

We herein report a case of CA-IE caused by USA300 MRSA producing PVL and ACME, which resulted in com-

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Received: December 9, 2020; Accepted: March 4, 2021; Advance Publication by J-STAGE: April 19, 2021
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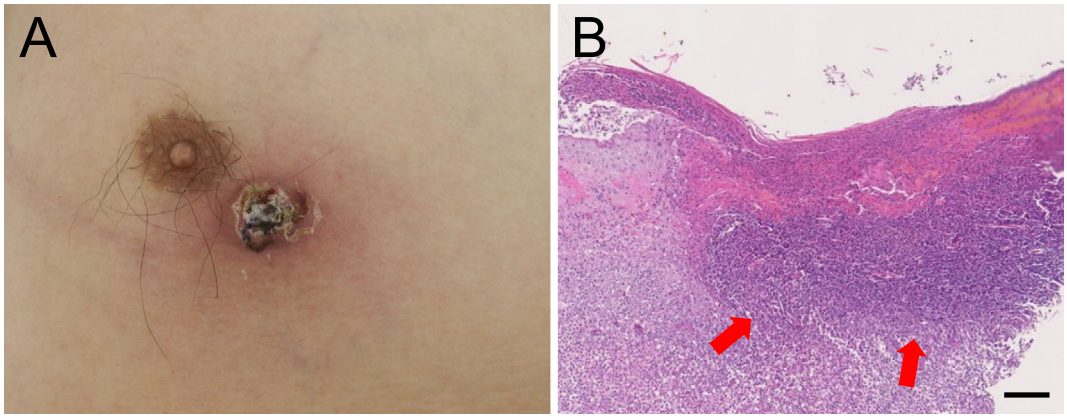

Figure 1. **Gross image showing a furuncle on the right breast (A) and Hematoxylin and Eosin staining of the biopsy from the furuncle showing abscess (B: arrows) with infiltration of inflammatory cells, including small lymphocytes.**

plications of meningitis.

Case Report

A 64-year-old man who received mitral valve plasty due to mitral prolapse a year ago noticed an eruption on the left thigh and visited a dermatologist. The patient had no other risk factors for MRSA infection, including skin injury, recent use of antibiotics, or a history of MRSA colonization or infection. The eruption was diagnosed as a furuncle, and the pus culture from the incisional drainage was positive for MRSA. Levofloxacin (once daily 500 mg) was prescribed for 7 days, and the furuncle gradually improved.

After 25 days, he felt general fatigue, had a high fever over 39℃, and noticed another eruption on the right breast (Fig. 1A), so he took levofloxacin (once daily 500 mg). Histology of the skin showed neutrophil and lymphocyte infiltration in the dermis, indicating skin abscess (Fig. 1B). Three days later, he was rushed to our hospital by an ambulance because of a fall after losing consciousness and was admitted.

The consciousness level was improved, but he claimed nuchal pain on admission. No abnormal neurological or objective findings of the head were noted aside from a stiff neck. His blood pressure was 118/80 mmHg, pulse was 113 bpm, and body temperature was 39.3℃. A physical examination revealed a diastolic murmur (Levine III/VI) on the third left sternum border. A chest radiograph and 12-lead electrocardiogram showed no significant changes. Laboratory data showed slight leukocytosis (7,500/μL) with elevated C-reactive protein (20 mg/dL) and serum creatinine (1.1 mg/dL) levels. Lumbar puncture revealed elevated cerebrospinal fluid (CSF) levels of white blood cells (89/μL, 90% polymorphs) and CFS protein (56 g/L) with normal CSF glucose levels (78 g/dL), indicating meningitis.

Transthoracic echocardiography revealed mild aortic regurgitation, but no vegetation was detected; however transesophageal echocardiography showed an abnormal mobile structure on the left coronary cusp of the aortic valve (Fig. 2A) that was strongly suspected of being a vegetation. Blood culture revealed MRSA of the same antibiotic sensitivity profile as the previous pus culture (Table); thus, a diagnosis of IE due to furuncle complicated with meningitis was made. An antibiotic sensitivity test showed that the bacteria were sensitive to vancomycin, linezolid, and daptomycin.

Tissue-destructive CA-IE from skin infection and USA 300 strain MRSA were suspected of having caused IE. To confirm this, we extracted chromosomal DNA from the colonies on agar plates using Cica Geneous® DNA Extraction Reagent (Kanto Chemical, Tokyo, Japan) and conducted multiplex polymerase chain reaction (PCR) using the Cica Geneus® Staph POT KIT (Kanto Chemical) (6) confirming the MRSA to be the USA300 strain. The PCR-based open-reading frame typing method (7) revealed the strain to be PVL-gene-positive, and a protein assay showed that the strain produced PVL. In addition, we revealed the strain to be ACME-positive.

MRSA was sensitive to vancomycin, but the minimum inhibitory concentration (MIC) was 2 mg/L, which was relatively high. Thus, linezolid (twice daily 600 mg) was administered. Blood culture results three days after the treatment revealed persistent positivity for MRSA. Therefore, daptomycin (once daily 350 mg) was added to linezolid. Despite dual-sensitive antibacterial therapy, blood culture results five days after the start of daptomycin still showed positivity for MRSA. Furthermore, during the antibiotic treatment, diffusion magnetic resonance imaging revealed multiple high-intensity spots, suggesting embolic stroke. Enhanced computed tomography revealed low density in the spleen and right kidney, suggesting renal and splenic emboli. However, he showed no symptoms of these issues (Fig. 2B-D).

We decided to perform surgery to remove the vegetation and replace the aortic valve due to uncontrolled bacteremia and thrombosis nine days after the antibiotic treatment. A 10-mm vegetation and a perforation at the left coronary cusp during the operation were observed by fiberscope (Fig. 3). After aortic replacement and antibiotic treatment with line-

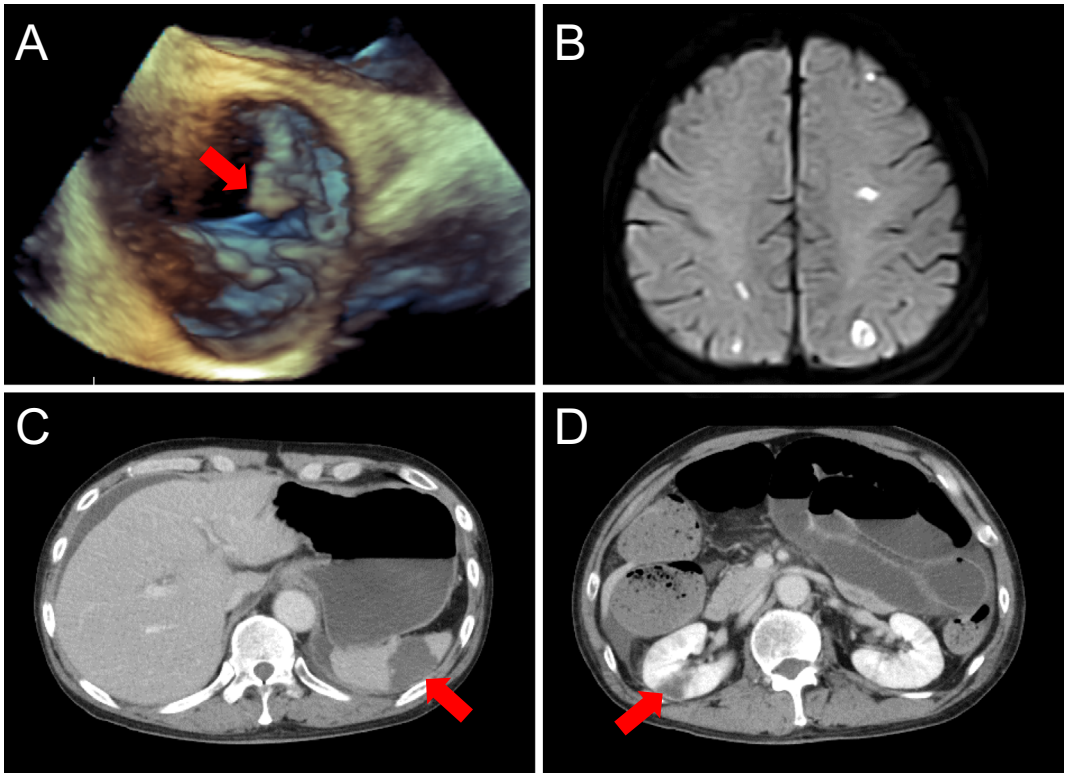

Figure 2. **Transesophageal echocardiographic image showing the vegetation on the left coronary cusp of the aortic valve (A: arrow), diffusion magnetic resonance image showing multiple cerebral infarctions, and computed tomography showing splenic infarction (C: arrow) and right renal infarction (D: arrow).**

zolid and daptomycin, he gradually recovered from his fever. Four weeks after the surgery, linezolid was withdrawn due to thrombocytopenia, but daptomycin was continued until six weeks after the surgery. He was discharged 39 days after admission without any disability.

Discussion

We reported a case of CA-IE caused by USA300 MRSA with a very high pathogenicity in a 64-year-old man who recovered after aortic valve replacement and antibiotic treatment with linezolid and daptomycin. The pathogenicity caused by the toxins produced, including ACME and PVL, resulted in complication with meningitis.

MRSA is a nosocomial pathogen in the hospital setting; however, the emergence of MRSA exhibiting high virulence in healthy individuals in the community has been reported since the late 1990s (8). CA-MRSA strains have higher pathogenicity than healthcare-associated MRSA strains because of the presence of virulence determinants and colonization factors, such as ACME and PVL (4). In Japan, *S. aureus* accounts for 21% of causes of IE, and MRSA contributes to 36% of IE cases caused by *S. aureus* (9). In cases of purulent skin soft-tissue infection, first-generation cephalosporins, amoxicillin/clavulanate, or clindamycin are recommended for empirical antibiotic treatment (10). The use of antibiotics against MRSA infection is suggested in cases at high risk of MRSA infection and those with a history of MRSA infection, a history of MRSA colonization, and failed primary treatment (10, 11). Thus, identifying the precise profile of MRSA is crucial for determining the appropriate treatment.

The USA300 clone, which is characterized as a sequence-type (ST) 8-staphylococcal cassette chromosome (SCC) *mec* type IV (ST8-IV), is a particularly virulent strain among *ACME-arcA*- and *lukS/F-PV*-positive clones and has spread rapidly in communities in the United States since it was first identified in 1999 (12).

In Japan, the number of reported IE cases provoked by USA300 is still low; however, the expected prevalence may increase in the future, as the prevalence of skin and soft tissue infection cases caused by USA300 has been increasing (13). In the US, PVL-positive USA300 clones reportedly account for 98% of skin infections of CA-MRSA (14).

The virulence of MRSA depends on the pathogen-producing genetic diversity of the accessory genome. The accessory component comprises approximately 25% of the total *S. aureus* genome. It consists of mobile genetic elements such as pathogenicity islands, bacteriophages, chromosomal cassettes, transposons, and plasmids acquired by horizontal transfer between strains (15). USA300 has multiple additional virulence determinants acquired through mobile genetic elements. Two of the most studied are ACME and PVL (16). The acquisition of ACME coding arginine

Table. Results of Drug Sensitivity from Furuncle Pus and Blood Culture.

Antibiotics	MIC	Criteria of CLSI
Penicillin G	>8	R
Oxacillin	>2	R
Ampicillin	>8	R
Sultamicillin	8	R
Ampicillin-sulbactam	8	R
Cefoperazon-sulbactam	8	R
Cefazolin	2	R
Ceftazidme	16	R
Ceftriaxone	16	R
Cefepime	4	R
Cefozopran	1	R
Ciprofloxacin	>8	R
Cefmetazole	4	R
Cefaclor	16	R
Flomoxef	4	R
Imipenem	0.25	R
Meropenem	0.5	R
Cefpodoxime Proxetil	>4	R
Gentamicin	<0.5	S
Arbekacin	<0.5	S
Erythromycin	>4	R
Clarithromycin	>4	R
Clindamycin	<0.25	S
Minocycline	<1	S
Vancomycin	2	S
Teicoplanin	<0.5	S
Fosfomycin	<4	S
Ciprofloxacin	>2	R
Levofloxacin	>4	R
Sulfamethoxazole-trimethoprim	<5	R
Rifampicin	<0.25	R
Linezolid	1	S
Azithromycin	>4	R
Cefdinir	2	R
Piperacillin-tazobactam	>8	R
Daptomycin	0.25	S

MIC: minimum inhibitory concentration, CLSI: clinical and loboratory standards institute, S: sensitive, R: resistant

deiminase is primarily restricted to USA300, and it precedes the rapid spread of this strain. ACME is posited to inhibit mononuclear leucocyte invasion and proliferation, leading to the suppression of the immune system and an improved survival in the low-pH environment of the skin (14, 15). Furthermore, PVL is a pore-forming toxin that targets polymorphonuclear leukocytes and macrophages. It induces cell death via necrosis or apoptosis by releasing cytotoxic lysosomal granule contents from lysed neutrophils (17). Thus, PVL-positive CA-MRSA may cause severe diseases, such as skin and soft tissue infections, necrotizing pneumonia, and bacteremia leading to IE (13). In the present case, we postulated that ACME contributed to the patient's prolonged survival under antibiotic therapy, leading to drug resistance, and PVL contributed to the tissue-destructive effects, such as valve penetration and meningitis.

S. aureus-induced IE is accompanied by neurological complications, including ischemic/hemorrhagic complications and encephalitis/meningitis (18), as MRSA can adhere to and invade the blood-brain barrier through the membrane-anchored lipoteichoic acid (19). The presence of meningitis due to *S. aureus* should suggest the possibility of concomitant *S. aureus* endocarditis. IE was reportedly diagnosed in 21% of *S. aureus* meningitis cases (20). Thus, when presented with patients with meningitis caused by *S. aureus*, IE should only be ruled out through repeated echocardiography, including transesophageal echocardiography.

Although data on the treatment efficacy of meningitis caused by MRSA are insufficient, vancomycin has been the first-line therapy for MRSA bacteremia and IE for decades. It has a poor CSF penetration of approximately 5% in patients complicated with meningitis. In addition, vancomycin may become less effective when the MIC reaches 2 mg/L (21). Linezolid and daptomycin are reasonable options when vancomycin cannot be used or is ineffective. Linezolid has a good CSF penetration of approximately 66%, and daptomycin has a moderately good CSF penetration of 5% with the achievement of adequate concentrations (21). Based on previous case reports and series of patients with central nervous system infections caused by MRSA, linezolid (600

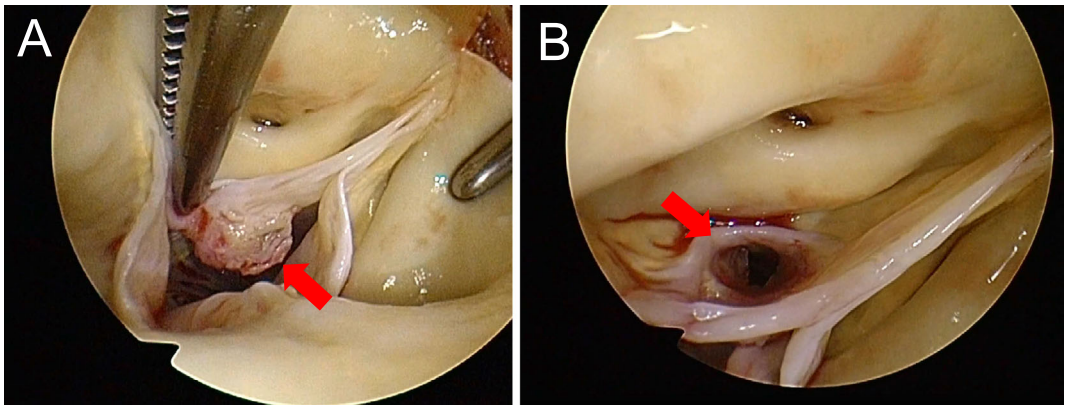

Figure 3. Fiberscopic image of the aortic valve during operation, showing vegetation on the left coronary cusp (A) and perforation through the left coronary cusp (B).

mg intravenously, twice daily) and daptomycin (6 to 10 mg/kg intravenously, once daily) might be viable alternatives to vancomycin. However, further studies are needed to establish the benefit of these agents in treating meningitis (21).

To our knowledge, this is the first report showing that ACME- and PVL-producing MRSA can cause IE complicated with meningitis.

In conclusion, physicians should be aware that cases of CA-MRSA IE caused by the USA300 clone have been increasing in Japan and that drug-resistant life-threatening IE may be caused by skin infection of ACME- and PVL-positive MRSA. Thus, appropriate timing of antibiotics against MRSA is critical, and early surgical treatment should be considered in cases of IE caused by USA300.

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

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