INTERNAL MEDICINE

□ CASE REPORT □

Necrotizing Pneumonia due to Femoral Osteomyelitis Caused by Community-acquired Methicillin-resistant *Staphylococcus aureus*

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Abstract

A chest X-ray of a young healthy African-American man with acute respiratory failure revealed bilateral multiple nodular shadows in the lungs, while community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) was detected in blood and sputum cultures. Magnetic resonance imaging showed osteomyelitis of the left thigh, and computed tomography revealed bilateral cavitary lesions in the chest, indicating necrotizing pneumonia with pulmonary embolism caused by osteomyelitis as a result of infection with CA-MRSA. CA-MRSA should be suspected as a causative agent of severe community-acquired pneumonia, even in Japan, among patients who belong to communities at high risk of CA-MRSA infection.

Key words: community-acquired methicillin-resistant *Staphylococcus aureus*, necrotizing pneumonia, osteomyelitis

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Introduction

Infection with methicillin-resistant *Staphylococcus aureus* (MRSA) became clinically important in the USA during the 1960s (1). This organism was recognized to be a nosocomial pathogen because such infections were often acquired by patients in hospitals, intensive care units and nursing homes (2). However, the first community-acquired MRSA (CA-MRSA) infections in the USA were reported in 1981 and have since become a matter of increasing concern (3).

The most common manifestations of MRSA infection are skin and soft tissue infections (4), while the prevalence of MRSA as the etiology of community-acquired pneumonia (CAP) remains around 2%, with a range from 0% to 5% depending on the site (5). A recent case series indicated that CAP caused by MRSA can cause fatal pneumonia in previously healthy young individuals (6) and typically occurs as a superinfection in patients with influenza, although it remains rather rare among patients with CAP (5), especially in Japan. However, the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) guidelines for CAP treatment state that CA-MRSA will become an emerging problem in CAP treatment (7). Some reports have indicated that the mortality rate of CA-MRSA pneumonia is 56%-63% (8, 9).

A few instances of CAP caused by CA-MRSA infection in Japan have been reported (10). We herein describe the case of a young American man who developed necrotizing pneumonia due to septic pulmonary embolism caused by osteomyelitis with CA-MRSA in Japan.

Case Report

A 31-year-old African-American man arrived at the emergency room of our hospital with a high fever and sudden

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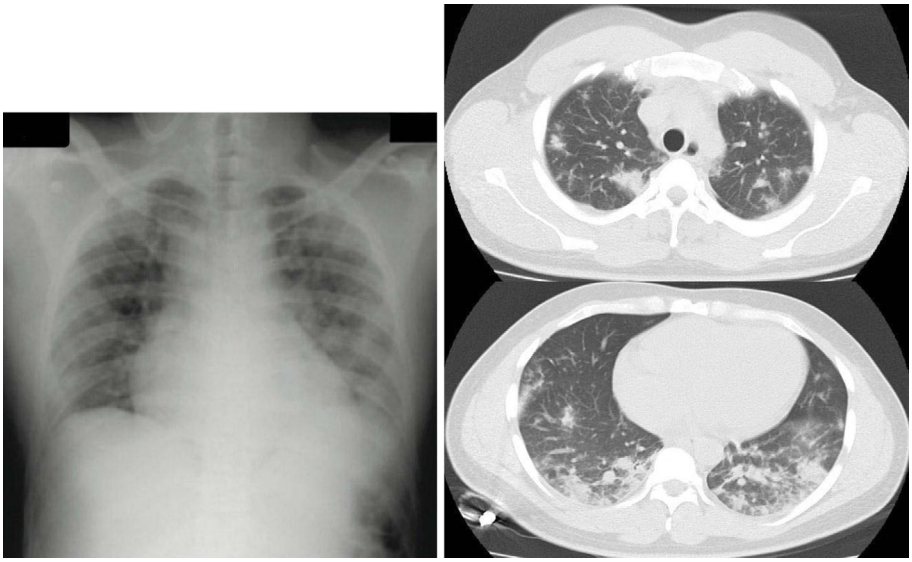

a b

Figure 1. Chest X-ray and computed tomography images of the patient upon admission. Chest X-ray showing cardiomegaly, multiple nodular shadows in both lungs and an obscured left costophrenic angle (a). Chest CT image showing multiple nodular shadows primarily right under the pleura of both upper lobes in addition to infiltration of both lower lobes (b).

dyspnea. He was an American naval serviceman with no medical history. One week before admission, he had fallen and bruised his left knee, and an impaired left tibial collateral ligament was diagnosed. On admission, a physical examination revealed the following: height, 183 cm; weight, 106 kg; body temperature, 39.2°C; blood pressure, 132/81 mmHg; heart rate, 105 beats/min and regular; and respiratory rate, 34/min. Auscultation revealed bilateral mild end-inspiratory coarse crackles; however, no cardiac murmurs were observed. The patient had no signs of either neurological impairment or superficial lymphadenopathy. His left knee joint was slightly reddish and swollen, suggesting the presence of an infectious site, in spite of apparent surface injury. Joint infection was negative because puncture of the joint disclosed no signs of infection. The laboratory findings revealed obviously increased levels of inflammatory markers, such as white blood cells ($13.11\times10^3/mm^3$), serum C-reactive protein (CRP; 36.3 mg/dL) and procalcitonin (3.65 ng/mL). Arterial blood gases determined on five liters of O_2 administered nasally were as follows: PaO_2 73.2 Torr; $PaCO_2$ 42.6 Torr; pH 7.44; HCO_3 24.1 mmol/L. The levels of aspartate aminotransferase (46 IU/L), alanine aminotransferase (49 IU/L) and lactate dehydrogenase (296 IU/L) were slightly elevated, while renal function data, that is blood urea nitrogen (10.8 mg/dL) and creatinine (0.83 mg/dL), were within the normal ranges. A chest X-ray (Fig. 1a) and computed tomography (CT) (Fig. 1b) revealed bilateral multiple nodular shadows essentially at the peripheral sides of the lungs, which suggested pulmonary embolization, and consolidation of the bilateral lower lobe. A physical examination and repeated transthoracic echocardiography did not identify any causes of vascular embolization, arguing against infective endocarditis. Gram staining of sputum samples did not identify any pathogens, and urinary *S. pneumoniae* and *L. pneumophila* antigens were negative. Therefore, imipenem/cilastatin (0.5 g every six hours) plus clindamycin (600 mg every 12 hours) were immediately administered in the emergency room to treat severe community-acquired pneumonia of unknown etiology. However, the patient's respiratory condition gradually deteriorated, and MRSA was detected in blood and sputum cultures on day 3 after admission. We added vancomycin considering that the initial regime had been ineffective, and adjusted the dose based on drug monitoring. At that time, the patient fulfilled the diagnostic criteria for disseminated intravascular coagulation (DIC), having a platelet count of $6.1\times10^4/mm^3$, a PT (INR) of 1.39 and an fibrinogen degradation products (FDP) level of 29.6 μg/mL (11). Therefore, gabexate mesilate was also administered. After two weeks of intravenous antibiotic therapy, the patient's oxygenation status resolved, and inflammatory markers, including the leukocyte count and serum levels of C-reactive protein and procalcitonin, gradually improved (Fig. 2).

Antimicrobial tests of this strain using broth microdilution according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) (12) revealed susceptibility to clindamycin, trimethoprim/sulfamethoxazole, minocycline hydrochloride and levofloxacin, in addition to anti-MRSA drugs, such as vancomycin. The minimum inhibitory concentration (MIC) for imipenem/cilastatin was 2 mg/L, which reflected the frequent tendency towards low imipenem/cilastatin MIC values in patients with CA-MRSA (13).

Type IV staphylococcal cassette chromosome *mec* (SCC*mec* IV) and genes encoding Panton-Valentine leuko-

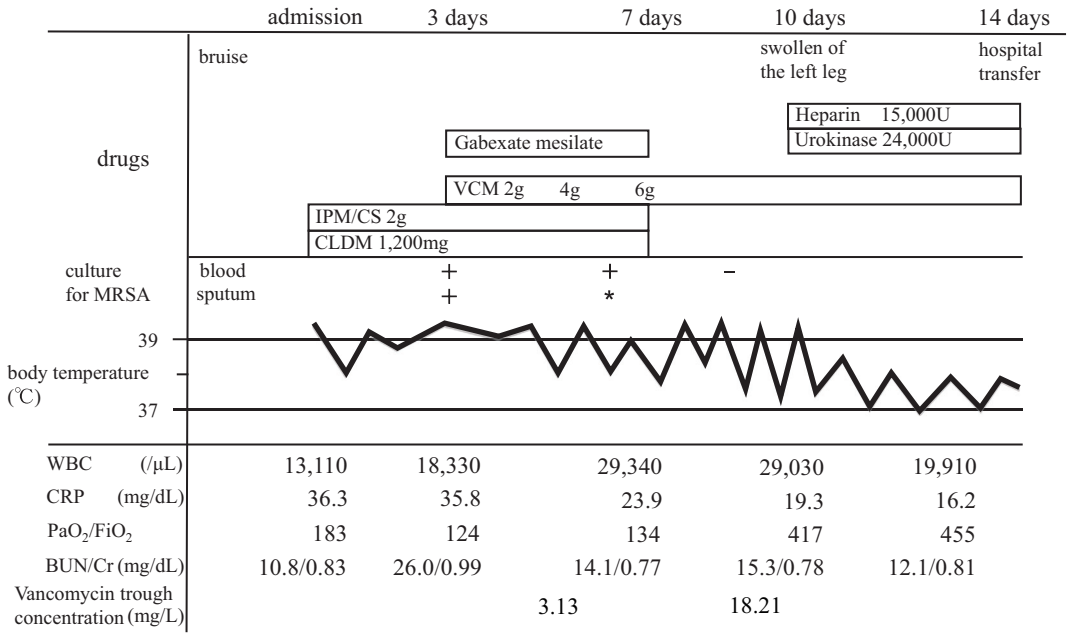

Figure 2. **Clinical course of the patient. CLDM: clindamycin, IPM/CS: imipenem/cilastatin, VCM: vancomycin, *not expectorated**

Table. **Molecular Characteristics and Exotoxin Gene Profiles of the CA-MRSA Strain**

	sputum	blood
SCC mec	Type IV	Type IV
PVL	+	+
sec	-	-
TSST-1	-	-
etb	-	-

PVL: Panton-Valentine leukocidin, etb: exfoliative toxin-B, SCC *mec*: staphylococcal cassette chromosome *mec*, sec: staphylococcal enterotoxin C, TSST-1: toxic shock syndrome toxin-1

cidin (PVL) were detected on polymerase chain reaction (PCR) of MRSA isolates obtained from the patient's sputum and blood. This molecular characteristic of the strain was also compatible with CA-MRSA (Table).

However, on day 10 of admission, the patient's left lower leg began to swell. Computed tomography and magnetic resonance imaging revealed osteomyelitis of the left thigh with femoral vein thrombosis due to surrounding inflammation (Fig. 3a and b). Thrombolytic therapy was immediately started, and antibiotic therapy was continued without surgical drainage in consideration of the patient's good clinical course. At that point, chest CT showed that most of the multiple nodular shadows in the lungs had become cavitary lesions (Fig. 4). Figure 2 summarizes the clinical course of this patient. We concluded that necrotizing pneumonia was induced by septic pulmonary embolism due to the osteomyelitis accompanying CA-MRSA. The patient was transferred to the American naval hospital when his respiratory status improved because long-term therapy was required for the osteomyelitis.

Discussion

Since the late 1990s, CA-MRSA has emerged as a worldwide pathogen associated with skin and soft tissue infections and occasionally fatal systemic infections, such as sepsis, necrotizing pneumonia and osteomyelitis (14). On the other hand, deep tissue infections with CA-MRSA are clinically associated with bacteremia and septic pulmonary embolism in children and young adults in some countries (15-17). Similarly, in our patient, a septic pulmonary embolus may have arisen from the primary deep tissue infection, namely osteomyelitis of the left thigh, considering that the area may have become infected after the patient's fall. Therefore, searching for deep tissue infections is recommended when septic pulmonary embolism and CA-MRSA bacteremia are present without right-sided endocarditis or thrombophlebitis.

In 2000, the US Centers for Disease Control and Prevention (CDC) Active Bacterial Core surveillance (ABCs) sites issued a standardized definition of epidemiological CA-MRSA (18). However, considering the possibility of clonal CA-MRSA spread between community and hospital (19), strains should be verified using microbiological and molecular methods (20). In our case, the strains retained the same susceptibility to various antibiotics, except for β-lactams, and phage open-reading frame typing determined that the strains isolated from the blood and sputum cultures were genetically identical (Fig. 5) (21, 22). However, the roots of these strains could not be determined because they were not the most common endemic CA-MRSA clones in the USA, namely USA300, and the strains did not match the Japanese

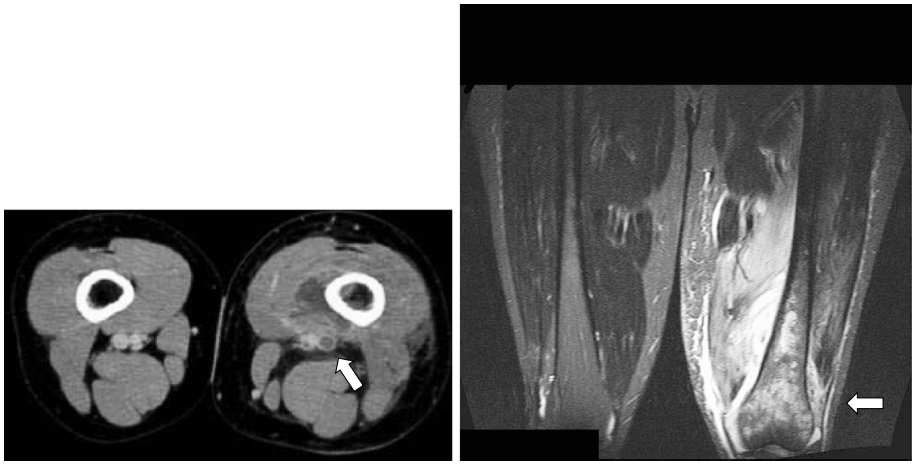

Figure 3. **Contrast-enhanced computed tomography (a) and magnetic resonance (b) imaging of the lower extremities. Inflammation had spread around the left femoral bone, and thrombosis was evident in the left femoral vein (arrow, a). Magnetic resonance image showing osteomyelitis of the left thigh and spreading inflammation (arrow, b).**

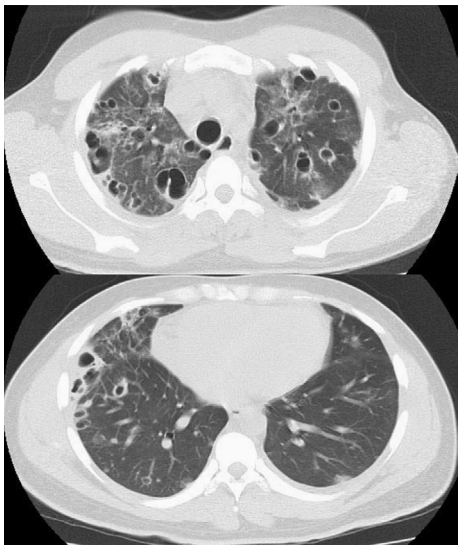

Figure 4. **Chest computed tomographic findings obtained on day 10 of admission. Most of the multiple nodular shadows were cavitary lesions. Infiltration of both lower lobes had diminished.**

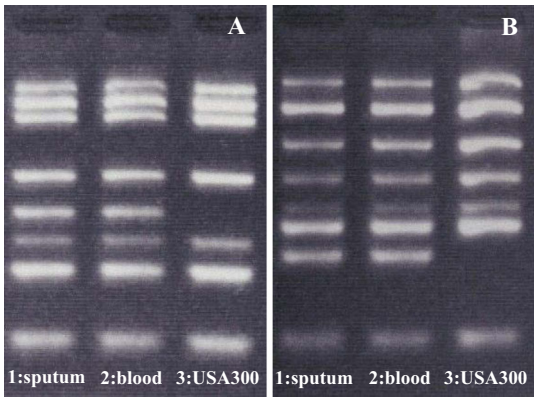

Figure 5. **Phage open-reading frame typing. Strains from the blood and sputum cultures are identical and not USA300. A and B, reaction mixtures a and b, respectively; 1, 2 and 3 are strains from the sputum, blood and strain USA300, respectively.**

endemic clone in view of producing PVL, as only 2.3% of SCCmec type IV strains in Japan have PVL (23).

Staphylococcus aureus strains can express many virulence factors. In particular, CA-MRSA strains tend to possess many exotoxin gene profiles. However, in the strains isolated from our patient, PCR detected only PVL (Table). PVL is a powerful cytolytic factor for human polymorphonuclear leukocytes (24) and is regarded to be a principal determinant of CA-MRSA virulence (25). On the other hand, conflicting reports have arisen recently (26, 27). One report found that tissue damage is most prominent in young mice and not significant in older mice, irrespective of cytolytic activity (28); therefore, the host reaction against PVL may contribute to the severity of infection (29), which may explain why our patient suffered from fatal necrotizing pneumonia.

Considering that CA-MRSA has been established to be a pathogen responsible for rapidly progressive and frequently fatal disease, some guidelines state that specific treatment for this pathogen, that is, the empirical administration of vancomycin or linezolid, should be started as soon as possible if the medical history is typical (30-32). In our case, we administered vancomycin (VCM) after MRSA was isolated, and clindamycin (CLDM) was used continuously due to its potential to inhibit toxin synthesis (33). Early linezolid administration was also considered; however, we increased the dose of VCM because the patient exhibited a slow clinical response in spite of receiving an inadequate concentration of VCM, and the susceptibility of MRSA to VCM was

MIC≦1 mg/L (34). Additionally, considering the presence of thrombocytopenia due to DIC, linezolid was not used for fear of myelosuppression. Meanwhile, there are several reasons why our patient did not initially respond to clindamycin. Inducible resistance, in addition to the insufficiency of the dose of CLDM, may explain this phenomenon because the MRSA strains isolated from our patient were clindamycin-susceptible and erythromycin-resistant (35).

We conclude that CA-MRSA pneumonia should be suspected, even in Japan, particularly when young otherwise healthy patients belonging to communities at high risk of CA-MRSA infection present with rapidly progressive necrotizing pneumonia. Clinicians should consider the empirical administration of anti-MRSA drugs.

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

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