

Pacemaker-associated infection caused by ST81/SCCmec IV methicillin-resistant, vancomycin-intermediate *Staphylococcus aureus* in Japan

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Abstract

A 76-year-old Japanese man was admitted to hospital for treatment of fever and skin lesion at the implantation site of his pacemaker. During his hospitalization, vancomycin-intermediate *Staphylococcus aureus* (MIC 4 µg/mL) with reduced susceptibility to daptomycin was isolated from venous blood. This isolate was identified as methicillin-resistant *S. aureus* with SCCmec IV and was genotyped as sequence type 81, *coa* VIIa and *spa* type t7044, harbouring *bla_Z*, *aac(6′)-aph(2′′)* and enterotoxin(-like) genes *sea*, *seb*, *sek*, *sel*, *selx* and *selw*. The patient was successfully treated with daptomycin, minocycline and sulfamethoxazole/trimethoprim. We describe the identification of sequence type 81/SCCmec IV vancomycin-intermediate *S. aureus* from pacemaker-associated septicaemia.

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a leading cause of nosocomial infections worldwide. MRSA has a genetic element SCCmec in its chromosome which has been classified into several types. Generally, SCCmec of hospital-acquired MRSA is mostly assigned to types I to IV, while community-acquired MRSA is assigned to types IV and V [1]. A glycopeptide antibiotic, such as vancomycin (VCM), is one of the representative anti-MRSA drugs and is frequently used as first-choice therapy to treat MRSA infections. However, VCM intermediate-resistant *S. aureus* (VISA) was first reported in Japan in 1996 [2]. VISA is defined as *S. aureus* showing VCM MIC of 4 to 8 µg/mL, according to Clinical and Laboratory Standards Institute criteria [3]. Despite its low incidence, VISA has been detected worldwide, and it poses a growing public health concern [4]. Occurrence of VISA is considered to be related to persistent infections and prolonged hospitalization with the provision of VCM [5]. In Japan, although prevalence is extremely low, VISA has been identified for SCCmec II-MRSA [6], SCCmec IV–sequence type (ST) 8 MRSA [7] and SCCmec IV-ST72 MRSA [8]. Here we report the detection of VISA with SCCmec IV-ST81 from a case of pacemaker-associated septicaemia.

Case report

A 76-year-old Japanese man was transferred to our hospital. He was suspected to have bacteraemia and pacemaker-associated infection. Because he had fever (temperature 39.2°C) associated with redness and swelling that appeared in the skin of the pacemaker implantation site on the left chest wall, ceftriaxone and VCM had been administered by a former doctor, although no bacterial examination had been performed. The patient had had a pacemaker implanted when he was 72 years old for bradycardic atrial fibrillation, and haemodialysis had been performed for chronic renal failure.

At admission (day 1), physical examinations showed the following: blood pressure 116/83 mm Hg, body temperature 37.5°C, respiratory rate 20 breaths/min, heart rate 86 beats/min (arrhythmia/self-pulse), SpO₂ 92%, clear consciousness (JCS0, GCSI5), no rale in breathing sound, flat and soft abdomen and no muscular defense. Blood tests revealed an increase in white blood cell count (11.7 × 10⁹/L), C-reactive protein (13.34 mg/dL) and procalcitonin (27.66 ng/mL).

MRSA was isolated from venous blood on days 1 and 2, as well as from the pacemaker (surface in contact with wounded

part, atrial and ventricular lead wires) on day 9, when the pacemaker was removed. Treatment with ceftriaxone and VCM was continued, but ceftriaxone was discontinued on day 6 after hospitalization, and VCM was administered until day 27. Blood culture results were negative on day 21. Surgery to reimplant the pacemaker was carried out on day 42; the postoperative course was uneventful, but slight fever persisted. On day 48, the patient had a temperature of 38.4°C, and blood culture revealed the presence of MRSA. Therefore, VCM was readministered on day 50. However, the patient's platelet count decreased, and MRSA isolated from blood samples taken on day 50 showed VCM MIC 2 µg/mL. VCM was changed to daptomycin (DAP). On day 61, increased VCM MIC, to 4 µg/mL, was observed for the MRSA isolate grown from blood taken on day 58, so minocycline and sulfamethoxazole/trimethoprim were added to the treatment. On day 63, negative blood culture was confirmed; DAP and minocycline were discontinued on day 73. Because the inflammatory reaction continued, teicoplanin (TEC) was administered for 12 days from day 81. Thereafter the patient fully recovered, without recurrence for 3 months.

The MRSA isolated on day 61 (strain HV2019-1) was confirmed to be VISA by MIC measured by broth microdilution test using Dry Plate 'Eiken' (192 plate), E-EP02 (Eiken Chemical, Tokyo, Japan). This strain exhibited slightly higher MICs than TEC and DAP (2 µg/mL each) than those isolated at admission (day 1) until day 9 (Table 1). Accordingly, this strain was judged to be nonsusceptible to DAP. The VISA strain was resistant to penicillin, cephalosporins, aminoglycosides and quinolones while being susceptible to macrolides, clindamycin, linezolid and sulfamethoxazole/trimethoprim. Except for VCM, TEC and DAP, strain HV2019-1 showed the same susceptibility pattern to those of MRSA isolated on days 1 and 9. The *SCCmec* type of strain HV2019-1 was identified as IV according to multiplex PCR by using previously published primers and conditions [9]. Strain HV2019-1 belonged to ST81 (clonal complex (CC) 1) based on the scheme of multilocus sequencing typing [10], coagulase genotype (*coa*) VIIa, *spa* type t7044 and *agr* type III. Virulence determinants and drug resistance genes were detected by uniplex/multiplex PCR as described previously [11]. Although PVL genes (*lukS-PV-lukF-PV*) and ACME (arginine catabolic mobile element)-*arcA* were negative, this strain harboured the enterotoxin(-like) genes *sea*, *seb*, *sek*, *sel*, *selx* and *selw*, as well as epidermal differentiation factor A gene (*edin-A*) and *blaZ* and *aac(6')-aph(2'')*.

Discussion

In the present study, genetic information of early MRSA isolates (days 1, 2 and 9) were not available. However, these MRSA

TABLE 1. Genotypes, antimicrobial susceptibility, virulence factors and other genetic traits of VISA strain HV2019-1

Characteristic	Value
Genotype	
<i>coa</i> type	VIIa
MLST	ST81, CC1 (allelic profile: 1-1-1-9-1-1-1)
<i>spa</i> type	t7044 (repeat profile: 07-23-21-16-34-33-20-13)
<i>agr</i>	III
<i>SCCmec</i>	IV, subtype-nontypeable (class B-mec, <i>ccrA2B2</i>)
Susceptibility pattern	
Resistant	β-Lactams, ^a AMK, GEN, LVX, CIP
Susceptible	ABK, ERY, CLR, ATM, CLI, MIN, TEC, GRX, FOF, SXT, LZD
MIC (µg/mL), MRSA/VISA ^b	
VCM	<0.5–1/4
TEC	≤0.5/2
DAP	0.25–1/2
Virulence factor ^c	
Haemolysin	<i>hla</i> , <i>hlb</i> , <i>hld</i> , <i>hlg</i>
Enterotoxin	<i>sea</i> , <i>seb</i> , <i>sek</i> , <i>sel</i> , <i>selx</i> , <i>selw</i>
Leukocidin	<i>lukDE</i>
Other	<i>edinA</i> , <i>sak</i>
Adhesin genes ^d	<i>cna</i> , <i>eno</i> , <i>fnbA</i> , <i>fnbB</i> , <i>ebpS</i> , <i>fib</i> , <i>clfA</i> , <i>clfB</i> , <i>sdrC</i> , <i>sdrE</i>
Resistance genes ^e	<i>icaA</i> , <i>icaD</i>
	<i>blaZ</i> , <i>aac(6')-aph(2'')</i>

ABK, arbekacin; AMK, amikacin; ATM, azithromycin; CC, clonal complex; CIP, ciprofloxacin; CLI, clindamycin; CLR, clarithromycin; DAP, daptomycin; ERY, erythromycin; FOF, fosfomicin; GEN, gentamicin; GRX, garenoxacin; LVX, levofloxacin; LZD, linezolid; MIN, minocycline; MLST, multilocus sequence typing; MRSA, methicillin-resistant *Staphylococcus aureus*; SXT, sulfamethoxazole/trimethoprim; TEC, teicoplanin; VCM, vancomycin; VISA, vancomycin-intermediate *S. aureus*.

^aβ-Lactams included: amoxicillin/clavulanic acid, ampicillin/sulbactam, cefaclor, cefazolin, cefdinir, cefepime, cefmetazole, cefotaxime, cefotiam, cefoxitin, cefpodoxime, ceftazidime, ceftriaxone, flomoxef, imipenem, meropenem, penicillin G, oxacillin, piperacillin/tazobactam, sulbactam/cefoperazone.

^bData shown as MRSA (days 1–9)/VISA (day 61). MRSA was isolated from venous blood (day 1, day 2) and pacemaker (surface in contact with wounded part and lead wires) (day 9). MRSA (VISA) was isolated from venous blood.

^cNegative for *lukF-PV/lukS-PV*, *lukM*, *sec-see*, *seg-sej*, *sem-seu*, *sey*, *selz*, *seI27*, *seI28*, *eta*, *etb*, *etd*, *tst-1*, *edinB*, *bap*, *scn*, *chp*.

^dNegative for *sdrD*, *bbp*.

^eNegative for *tetK*, *tetL*, *tetM*, *erm(A)*, *erm(B)*, *msrA*, *ant(4')-Ia*, *ant(6)-Ia*, *aph(3')-IIIa*.

isolates showed the same susceptibility patterns (except for VCM, TEC and DAP) to that of VISA strain HV2019-1, thus suggesting that HV2019-1 might be derived from the early MRSA isolated from blood and pacemaker, which presumably remained in any part of patient's body after treatment with VCM. Occurrence of VISA and its precursor, hetero-VISA (h-VISA), has been an obstacle in chemotherapy of MRSA infections. Globally, the most prevalent genotype of methicillin-resistant VISA is *SCCmec* II and III, and ST239 and ST5 [5]. Although other STs—ST72, ST59 and ST900—have also been found as less common types in VISA or hVISA [5], ST81 (CC 1) has never been detected. Thus, our present study is to our knowledge the first to report ST81 VISA, which was associated with *SCCmec* IV, a minor *SCCmec* type among VISA. ST81 *S. aureus* is rarely detected in human clinical isolates [11–13]; there is only a single report of ST81 MRSA that had the same genetic traits (*SCCmec* IV, *coa*-VIIa/*agr*-III) and similar *spa* type (t127, repeat profile 07-23-21-16-34-33-13) [11] to that of our present VISA strain. In contrast, ST81 methicillin-susceptible *S. aureus* appears to be commonly distributed in cows with or without mastitis and in rats in Japan [14,15].

We noted that the DAP MIC of the strain HV2019-1 increased and became nonsusceptible (associated with the occurrence of VISA on day 61) shortly after the provision of DAP. Similarly, DAP nonsusceptibility was reported for ST72 VISA (MRSA-IV) in Japan [8]. Reduced susceptibility to vancomycin in *S. aureus* has been revealed to be generated by accumulation of mutations in various genes represented by *rpoB* [2]. In case of nonsusceptibility to DAP, point mutations in *mprF* are associated [16]. One study indicated that a single mutation in *mprF* was related to reduced susceptibility to both vancomycin and DAP *in vitro* [17], which was also observed for a clinical MRSA isolate [18]. Therefore, it may be necessary to pay attention to provide DAP to patients with VISA infection.

In conclusion, we here present the isolation of ST81 VISA (MRSA-IV) from pacemaker-associated septicaemia. The findings underscore the careful monitoring of susceptibility to vancomycin and DAP for MRSA frequently isolated from patients with underlying diseases.

Conflict of Interest

None declared.

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