Title	First outbreak of methicillin-resistant Staphylococcus aureus USA300 harboring the Panton-Valentine leukocidin genes among Japanese health care workers and hospitalized patients.
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Abstract

This report describes the first outbreak of methicillin-resistant *Staphylococcus aureus* USA 300 in a general hospital ward in Japan, involving six healthcare workers and four patients. This report emphasizes the need for healthcare personnel to be alert that MRSA harboring *pvl* poses a threat for both nosocomial and occupational infection.

Accumulating evidence indicates that community-associated methicillin resistant *Staphylococcus aureus* (CA-MRSA) isolates can readily produce outbreaks in hospitals, adding to the threat posed by these organisms (1-3). CA- MRSA is genetically heterogeneous, and includes a variety of clones such as the multilocus sequence (ST) 1 (USA400) and ST8 (USA300) types that emerged as major clones in the United States. The USA300 clone can replace preexisting MRSA clones, and it now represents the predominant CA-MRSA clone in the United States (4,5). Until now, CA-MRSA infections reported in Japan have been sporadic, and most strains did not harbor the Panton-Valentine leukocidin (*pvl*) genes (6).

In September 2009, we were notified that a cluster of skin infections had broken out among healthcare workers (HCWs) and hospitalized patients in a general ward. We document herein the first outbreak of MRSA harboring *pvl* genes belonging to the USA300 clone in a healthcare setting in Japan.

At the time of notification, 65 patients were being cared for by 96 HCWs in a general ward at the tertiary care, 1240-bed Kyoto University Hospital (Japan), where dermatological disorders were quite prevalent. We were notified that a cluster of skin infections had developed among four healthcare workers (HCW 1-4) and it seemed compatible with *S. aureus* infection. Two weeks later, one patient (Patient 4) developed a skin abscess in the left arm from which MRSA was isolated. The isolate was susceptible to erythromycin, clindamycin and gentamicin. The antimicrobial susceptibility pattern was distinct from that of healthcare-associated MRSA (HA-MRSA) strains in Japan, which were usually multidrug-resistant and of which MIC levels of β-lactams were high. Subsequently, skin abscesses relapsed on the legs and chest of HCW 1 and HCW 5 and developed on the legs and buttock of HCW 6.

Eventually MRSA isolates were recovered from HCWs.

Based on information derived from these cultures, we developed a case definition in which MRSA with a specific antibiogram was recovered from a clinical specimen. The case-defined antibiogram was susceptible to erythromycin, clindamycin and gentamicin, but resistant to levofloxacin and β-lactams with MIC levels below those of HA-MRSA. We reviewed the antimicrobial susceptibility profiles of MRSA strains from all adult and pediatric hospitalized patients who were under care at Kyoto University Hospital during 2009 to detect any unidentified MRSA. HCWs were screened in the ward using nasal swabs to identify MRSA carriers.

Clinical specimens were inoculated onto mannitol salt agar plates and examined after 48h. Susceptibility testing proceeded according to the Clinical and Laboratory Standards Institute. The *mec*A gene, PVL determinants and *arcA* gene on the arginine catabolite mobile element (ACME) were detected and SCC*mec* typing was performed by PCR (7-9). The typing procedure included PFGE using the restriction enzyme *Sma*I as described (5). Multilocus sequence typing proceeded as described and the nomenclature was specified as previously described. (www.MLST.net)

Patients 1 to 3 who became infected with MRSA were newly identified based on the antimicrobial susceptibility profile described in the case definition (Table 1). A review of the medical records revealed that the first MRSA infection occurred in March 2009. Patient 1 developed catheter-related bloodstream infection followed by pneumonia and required intravenous anti-MRSA drug administration. Six of nine skin and soft tissue infections (skin abscesses, folliculitis) were treated with antibiotics, whereas three were cured by drainage alone. Patient 1 as well as HCW 1 and 5 developed recurrent infections. No case patient had a history of visiting abroad recently. All MRSA

isolates recovered from the case patients contained SCC *mec* type IV, the *pvl* gene and ACME-associated *arc*A gene. PFGE-based findings identified all isolates as being identical to and indistinguishable from the USA 300 clone. MLST defined all of them as ST8.

Excluding the isolates recovered from the case patients, four of 825 strains of MRSA isolates at our institution in 2009 had the same antimicrobial susceptibility profile as the outbreak strain. Those isolates were recovered from swab specimens and the patients did not have a symptom of infection when the specimens were taken. Screening nasal swabs of HCWs did not identify any carriers of CA-MRSA USA 300 other than the case patients.

Discussion

To our knowledge, this is the first report to document an outbreak of healthcare-associated and -transmitted CA-MRSA USA300 in Japan. To date, outbreaks of PVL-positive CA-MRSA have been reported, especially in neonatal intensive care units and long term care facilities in the United states and European countries (1-3). However, no outbreaks of CA-MRSA in either community- or nosocomial settings in Japan have been described. Only one sporadic infection with the USA300 clone in Japan has been documented (10). We speculate that infected HCWs or unidentified PVL-positive MRSA carriers served as the source of infection for Patients 1 to 4, because all of them became infected while in hospital. In addition, we considered that the causative agent was community-associated because antibiograms of the outbreak strain were distinct from those of HA-MRSA strains. This was supported by a review of the antibiotic susceptibility of MRSA strains isolated at our institution during 2009; the case-defined antibiogram occurred in only 0.5% of isolates.

The findings of this investigation have considerable public health implications. Although HA-MRSA remains a serious threat to hospitalized patients, the introduction of CA-MRSA strains into tertiary care hospitals like our hospital represents an especially serious challenge. Many of the infections caused by these strains have been reported to cause serious infections among healthy adults and can be severer and more life-threatening to those who are highly immunocompromised. In this study, healthy HCWs suffered from skin abscesses, although most infections were mild and cured without parenteral anti-MRSA drugs. Considering that infection relapsed in some case patients, further investigations are needed to establish the management of PVL-positive MRSA carriers, especially when they are caregivers. Systematic studies involving healthcare settings are needed to reveal the transmission of such CA-MRSA isolates within the healthcare system. These would provide not only an accurate estimate of CA-MRSA prevalence, but would help monitor the emergence of more resistant and/or virulent clones and help with therapeutic infection control and patient management policies.

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146 Table 1 Characteristics of patients with CA-MRSA infections and their treatment, Kyoto

147 University Hospital, 2009

Case	Age, Sex	Underlying disease	Onset of infection	Type of infection	Site of infection	Antimicrobial drug treatment	Drainage
Pt 1	60,F	Inflammatory bowel disease	3/29	CRBSI	Blood-stream	TEIC	None
			8/27	Pneumonia	Lung	LZD	None
Pt 2	65,F	Decubitas ulcer	8/22	Skin abscess	Thigh	GEN	Spontaneous
Pt 3	42,M	Polyarteritis nodosa	10/19	Folliculitis	Legs	ST	Spontaneous
Pt 4	14,F	Decubitus ulcer	11/2	Skin abscess	Arm	GEN	Surgical,
HCW 1	31,F	none	9/19	Skin abscess	Arm	MINO	Surgical
			11/24	Skin abscess	Arm	CLI	None
HCW 2	27,F	none	9/21	Skin abscess	Arm	GEN	Surgical
HCW 3	27,F	none	9/21	Skin abscess	Leg	MINO	Surgical
HCW 4	25,F	none	9/21	Skin abscess	Leg	None	Surgical
HCW 5	27,F	none	11/20	Skin abscesses	Leg, Chest	CLI	Spontaneous
			12/14	Folliculitis	Arm, Finger	ST MUP	None
HCW 6	31,M	none	11/24	Skin abscess	Thigh	CLI	Spontaneous

148 TEIC, teicoplanin; LZD, linezolid; GEN, gentamicin(topical); ST,

149 Trimethoprim-sulfamethoxazole; MINO, minocyclin; CLI, clindamycin; MUP,

150 mupirocin (topical), CRBSI; catheter-related bloodstream infection