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CASE SERIES

Two Cases of Intrafamilial Transmission of Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Producing Both PVL and TSST-1 Causing Fatal Necrotizing Pneumonia and Sepsis

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Introduction: *Staphylococcus aureus* produces numerous toxins, such as toxic shock syndrome toxin 1 (TSST-1) and Panton–Valentine leukocidin (PVL). We isolated community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) strains producing both TSST-1 and PVL isolated from severe necrotizing pneumonia cases in a Nepali family. Detection of these CA-MRSA strains is rare in the world, and infection with these strains can take a rapidly progressive and lethal course. In this study, we traced the clinical course of this case and conducted a genetic analysis of the isolated strains.

Case Report: We described 2 familial cases (a 20-year-old male and 61-year-old female) of severe necrotizing pneumonia caused by CA-MRSA with the TSST-1 and PVL genes. A 20-year-old Nepalese male was admitted to our hospital after a 3-day history of high fever and coughing. Despite resuscitation efforts, he died of multiple organ failure. A 61-year-old Nepalese female was admitted to our hospital with a complaint of high fever and dyspnea for 1 day. She was the grandmother of the male subject and mostly stayed at his residence in Japan. We administered intravenous antibiotics, including anti-MRSA antibiotics, and she improved in 2 weeks. The sequence type of the isolates was ST22/SCCmec type IVa, and the spa type was t005. The virulence genes detected were as follows: PVL gene (lukSF-pv), TSST-1 gene (tst-1), sec, seg, sei, sel, sem, sen, seo, and seu. ST22 was not the dominant CA-MRSA clone type in Japan. Some of the reports demonstrated that PVL-/TSST-1-positive ST22-MRSA strains are prevalent in Nepal. Therefore, the MRSA strains were thought to be acquired from Nepal.

Conclusion: These cases highlight the emergence of TSST-1- and PVL-positive CA-MRSA infection and its association with life-threatening community-acquired necrotizing pneumonia. Clinicians should note the possibility of introducing MRSA strains from abroad and be aware of this illness to initiate appropriate treatment.

Keywords: community-acquired methicillin-resistant *Staphylococcus aureus*, CA-MRSA, toxic shock syndrome toxin 1, TSST-1, Panton–Valentine leukocidin, PVL, necrotizing pneumonia

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Introduction

Staphylococcus aureus is one of the most common pathogens causing various human infections, including skin, soft tissue, respiratory, bone, joint, and endovascular infections.[1] Methicillin-resistant *S. aureus* (MRSA) strains are also known to be hospital- or healthcare-associated pathogens [hospital- or healthcare-associated

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MRSA (HA-MRSA)].[2] Since the mid-1990s, the health-care system has reported many MRSA infections in patients lacking risk factors for exposure. This new MRSA strain is called community-associated MRSA (CA-MRSA).[3] Molecular typing studies have shown that CA-MRSA differs from HA-MRSA.[4] CA-MRSA belongs to distinct genetic lineages, and it usually carries smaller staphylococcal cassette chromosome mec (SCCmec) cassettes such as type IV SCCmec and specific virulence factors such as Panton–Valentine leukocidin (PVL).[5] PVL is a cytotoxin that causes leukocyte destruction and tissue necrosis, including severe necrotizing fasciitis and necrotizing pneumonia.[6–8] PVL is thought to be the important factor for the virulence of CA-MRSA. Among CA-MRSA, USA300 clone (ST8/SCCmec IV/PVL+) is a major CA-MRSA clone that is endemic in the United States and causes various types of infectious diseases, from skin and soft-tissue infections to more invasive diseases, such as pneumonia, bacteremia, and osteomyelitis.[5,9] Meanwhile, other CA-MRSA clones are prevalent in other parts of the world, such as the Southwest Pacific clone (ST30/SCCmec IV/PVL +), the Taiwanese clone (ST59/SCCmec IV or V/PVL +), and the European clone (ST80/SCCmec IV/PVL +).[4,5,10] In Japan, PVL-producing CA-MRSA is less common, while toxic shock syndrome toxin-1 (TSST-1)-producing CA-MRSA and exfoliative toxin (ET)-producing CA-MRSA have been found to be common. Analysis of CA-MRSA isolated from the skin showed that among SCCmec type IV-MRSA strains, 18.8% were PVL-producing strains, 7.9% were ET-producing strains and 43.2% were TSST-1-producing strains.[11] TSST-1 is a superantigen that causes toxic shock syndrome (TSS) characterized by high fever, erythematous rash, hypotension and multiple organ failure; it is commonly known as a toxin produced by the New York/Japan clone (ST5/SCCmec type II), a representative clone of HA-MRSA.[12] In summary, TSST-1-producing CA-MRSA is common in Japan, but the incidence of PVL-producing CA-MRSA is gradually on the rise.[11,13]

Recently, we obtained CA-MRSA strains producing both PVL and TSST-1 isolated from severe necrotizing pneumonia cases in a Nepali family. Detection of CA-MRSA with this characteristic is rare not only in Japan but also in the world. There has been a report that methicillin-sensitive *Staphylococcus aureus* (MSSA), which produces both toxins, has caused severe pneumonia; thus, this MRSA clone may be highly virulent.[14] Because we considered the experience of this case to be valuable and important, in this study, we traced the exact clinical course of this case and conducted a genetic analysis of the isolated strains.

Case Report

Case 1

A 20-year-old Nepalese male was admitted to our hospital after a 3-day history of a high fever and cough. He had been previously seen at another local clinic where he was diagnosed with influenza and treated with oral oseltamivir for the first 3 days. On the fourth day, he developed dyspnea and was admitted to our hospital on the same day. He did not have any relevant past history and had not been prescribed any medications. He came to Japan for employment almost five years ago with his parents and took his residence in Saitama Prefecture.

His vital signs on the day of admission were as follows: level of consciousness, E3V4M6/Glasgow Coma Scale; blood pressure, 100/72 mmHg; heart rate, 133 beats per minute; body temperature, 38.4 °C; respiratory rate, 24 breaths per minute; and peripheral capillary oxygen saturation level at an O_2 flow rate of 2 liters per minute, 94%. Physical examination revealed lower respiratory sounds, and a few moist rales were heard in both lungs on chest auscultation. Laboratory data revealed a white blood cell (WBC) count of 700/mm^3, a blood platelet count of 82,000/mm^3, a C-reactive protein (CRP) level of 23.2 mg/dl, a blood urea nitrogen (BUN) level of 26.3 mg/dl, and a serum creatinine level of 2.2 mg/dl. The results of liver function tests were normal except for a lactate dehydrogenase (LDH) level of 618 IU/l. A chest computed tomography (CT) scan showed infiltrative and nodular shadows with pneumatocele formation in the right upper lobe (Figure 1).

At first, we diagnosed severe bacterial pneumonia after influenza and septic shock and initiated the administration of lactate Ringer's solution, noradrenalin infusion, and intravenous tazobactam/piperacillin (TAZ/PIPC) (4.5 g, 4 times daily) and azithromycin (AZM) (500 mg, once a day). However, his vital signs did not improve, and he developed respiratory failure requiring mechanical ventilation support. After rapid deterioration of his arterial oxygenation level, we introduced veno-veno extracorporeal membrane oxygenation support. Because gram-positive staphylococci were detected from sputum and blood samples collected on admission, we added linezolid (600 mg,

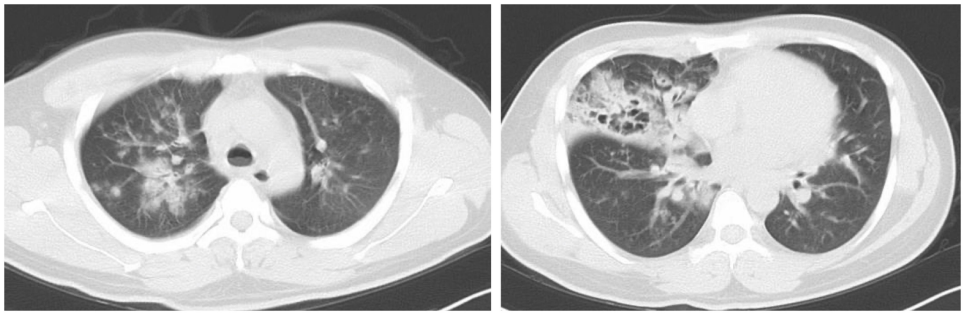

Figure 1 A chest computed tomography (CT) scan in Case 1 shows infiltrative and nodular shadows with pneumatocele formation in the right upper lobe.

2 times daily, intravenously) on day 2. On the same day, we performed a bronchoscopy, which showed diffuse inflammatory changes and easy bleeding (Figure 2). Therefore, we suspected necrotizing pneumonia caused by CA-MRSA. He underwent multidisciplinary treatment; however, his respiratory condition gradually worsened. Despite resuscitation efforts, he died of multiple organ failure on day 7. The isolates from the culture of blood and sputum samples on the day of hospital admission were MRSA strains TUM18988 and TUM18989. Additionally, his father, who lived with him in Japan, had a negative nasal swab test for MRSA.

Case 2

A 61-year-old Nepalese female was admitted to our hospital with a complaint of a high fever and dyspnea for 1 day. She was admitted 5 days later than the admission of Case 1. She did not have any relevant past medical history and had not been prescribed any medications, including antibiotics. She and her husband had come to tour Japan 3 months previously. She was the grandmother of Case 1 and mostly stayed at his residence.

Her vital signs on the day of admission were as follows: blood pressure, 139/86 mmHg; heart rate, 139 beats per minute; body temperature, 39.0 °C; respiratory rate, 35 breaths per minute; and a peripheral capillary oxygen saturation level on 3 liters of O_2 per minute, 96%. Laboratory data revealed a WBC count of 23,680/mm^3 and a CRP level of 43.2 mg/dl. A rapid test performed on a nasal swab was negative for influenza virus. A chest CT scan showed irregular consolidations and ground glass opacity and bilateral pleural effusion (Figure 3).

First, we suspected pneumonia associated with *S. aureus* because we had information about the medical history of Case 1. We started intravenous ceftriaxone (1 g, 2 times daily) and linezolid (600 mg, 2 times daily). On day 2 of admission, we changed the linezolid to vancomycin (1 g, 2 times daily, intravenously) due to allergy complications. She improved in 2 weeks and was discharged on day 13. She then flew back to Kathmandu-Nepal and had a full recovery.

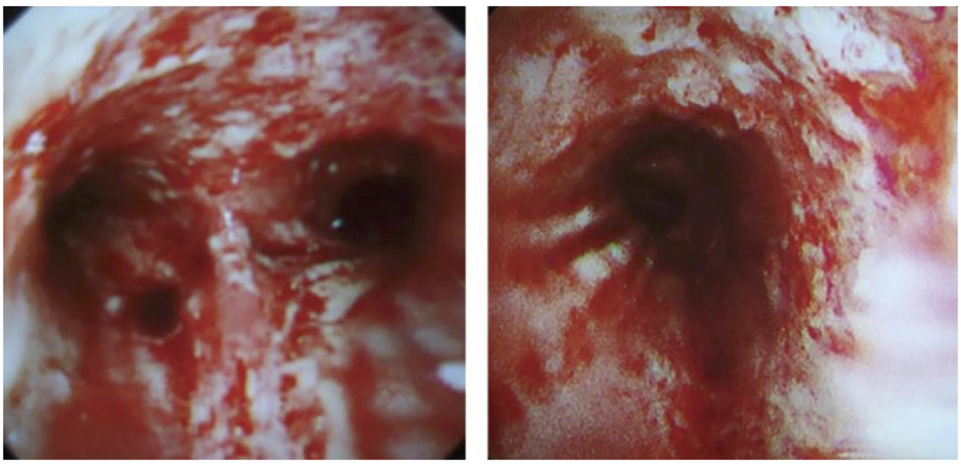

Figure 2 Bronchoscopy in Case 1 shows diffuse inflammatory changes and easy bleeding.

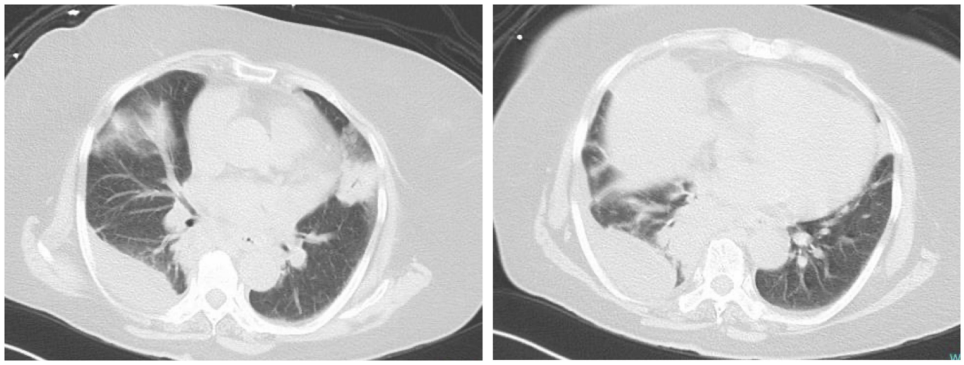

Figure 3 A chest CT scan in Case 2 shows irregular consolidations, ground glass opacity and bilateral pleural effusion.

Microbiological Test

Strain TUM18988 and strain TUM18989 were identified as *S. aureus* using the VITEK 2 system with the GP ID card panel (bioMérieux Japan Ltd., Tokyo, Japan). Determination of the minimum inhibitory concentration (MIC) of each antibiotic for the isolated strain was performed using a MicroScan WalkAway 96 Plus system with the Pos MIC 3.3J panel (Beckman Coulter, Inc., Brea, California, USA) according to the CLSI guidelines (2016).[15] Strain TUM18988 and strain TUM18989 were resistant to oxacillin (MIC >2 mg/l), penicillin (MIC >8 mg/l), ampicillin (MIC >8 mg/l), meropenem (MIC =8 mg/l), cefazolin (MIC =16 mg/l), gentamicin (MIC >8 mg/l), erythromycin (MIC >4 mg/l), clindamycin (MIC ≤0.5 mg/l), and levofloxacin (MIC >4 mg/dl), but susceptible to minocycline (MIC ≤1 mg/l), arbekacin (MIC ≤1 mg/l), vancomycin (MIC =1 mg/l), teicoplanin (MIC ≤2 mg/l), linezolid (MIC =1 mg/l), and trimethoprim/sulfamethoxazole (MIC ≤0.5 mg/l). The isolate from the culture of sputum samples of Case 2 was also MRSA (strain TUM18990) and showed the same properties as strain TUM18988 and strain TUM18989.

The Genetic Features in These Cases

Bacterial genomic DNA of strain TUM18988 and strain TUM18990 were extracted using the DNeasy Blood & Tissue Kit (Qiagen, Aarhus, Denmark) with lysostaphin (Wako) as previously described.[16] Genomic DNAs were used as a template for whole-genome sequencing by next-generation sequencing (NGS) using MiSeq (Illumina, San Diego, CA, USA). DNA-libraries for NGS were prepared with Nextera XT DNA sample preparation kits (Illumina) in accordance with the manufacturer's protocol. The read data from each strain were assembled using CLC Genomics Workbench v 12.0 software (Qiagen, Aarhus, Denmark), and the obtained contigs were analyzed using the SCCmecFinder service, multilocus sequence typing (MLST) service, spaTyper service, Resfinder service, and VirulenceFinder service on the Center for Genomic Epidemiology website.[17] The sequence type was ST22/SCCmec type IVa, and the spa type was t005. The virulence genes detected were as follows: PVL gene (lukSF-pv), TSST-1 gene (tst-1), sec, seg, sei, sel, sem, sen, seo, and seu (Table 1.). Furthermore, reads from each strain were mapped to the sequence of the EMRSA-15 strain (accession no. CP007659.1, the same sequence type strain as TUM18988; ST22), and the mutations between each isolate were identified by comparing the mapping sequence using CLC Genomics Workbench software. Only four SNPs were detected between TUM18988 and TUM18990 in a whole-genome comparison. The sequence data for strain TUM18988 and strain TUM18990 were deposited in the DNA Data Bank of Japan (DDBJ) under BioProject Accession number PRJDB8964.

Discussion

We present a case of intrafamilial transmission of CA-MRSA infection with severe pneumonia in a healthy person with no medical history. The genotype of both strains isolated from this case was ST22/SCCmec typeIV/TSST-1+/PVL+, which was unique in that it harbored both the TSST-1 and PVL genes. ST22 is the same clone type as the EMRSA-15 clone, which is known as the HA-MRSA clone in Europe.[18] The EMRSA-15 clone was PVL-negative/TSST-1-negative, suggesting that the isolates in this study were different from the EMRSA-15 clone. Furthermore, ST22 clones are rarely isolated in Japan. ST22/SCCmec type IV clones have been detected from familial infection in Japan;[19] however, ST22 was not the dominant CA-MRSA clone type in Japan,[11] and this clone

Table 1 Genetic Characteristics and Virulence Factors in Two Isolates in This Study

Isolates	Genotype					Resistant Gene		Antimicrobial Susceptibility (μg/mL)							
	SCCmec	MLST	spa	coa	agr	Virulent Gene	Acquired	Mutations	EM	CLDM	LVFX	MINO	ST	ABK	VCM	LZD
TUM18988 and TUM18990	IVa	ST22	t005	XIa	I	*lukSF-pv, tst-1, sec, seg, sei, sel, sem, sen, seo, seu*	*blaZ, mecA, aadD, aac (6')-aph(2'')*, *erm(C), tem(M)*	*grlA* (S80F), *gyrA* (S84L)	>4	≤0.5	>4	≤1	≤0.5	≤1	1	1

was PVL-positive but TSST-1-negative. Furthermore, MRSA isolates harboring PVL genes were demonstrated in Nepal and classified into ST22/SCCmec type IV and ST772/SCCmec type V.[20] Some of these ST22-MRSA strains were reported to be harboring TSST-1 genes. ST22/SCCmec type IV-MRSA strains have been isolated from domestic swine and wild macaques residing in Nepal.[21] Therefore, the ST22/SCCmec type IV-MRSA strain that is positive for PVL-/TSST-1 can be one of the prevailing clones in Nepal. The MRSA strains obtained from Case 1 and Case 2 were the same clones based on whole-genome comparisons. Because Case 1 who lived in Japan and developed symptoms after Case 2 from Nepal visited him, the MRSA strain was thought to be brought from Nepal and transmitted to the grandson (Case 1) from the grandmother (Case 2). Clinicians should note the possibility of introducing MRSA strains from abroad, even if the strains are not prevalent in their country, as in these cases.

In Australia, an increasing incidence of CA-MRSA infections has resulted in the addition of vancomycin to standard empiric therapy in patients with suspected CA-MRSA bacteremia.[22] Because skin infection caused by CA-MRSA is common in the United States, vancomycin, trimethoprim/sulfamethoxazole in combination with rifampin, and linezolid are thought to be the first line of antimicrobial therapy for cutaneous abscesses.[23] Particularly after influenza infection, MRSA pneumonia may occur even in healthy adults without any immunological abnormality.[24] Our clinicians should consider the administration of anti-MRSA antibiotics to patients with suspected necrotizing pneumonia, even if it is a community-acquired infection. PVL toxin produced by CA-MRSA is not associated with superantigenic toxins, and TSST-1 genes are thought to be rarely found in PVL-positive strains.[25] Although the prevalence of PVL- and TSST-1-positive MSSA/MRSA, such as in our cases, is still rare, there have been some reports in recent years.[26] Most MSSA/MRSA is generally detected in skin infections.[27] However, there is a report describing a fatal case of necrotizing pneumonia due to both TSST-1- and PVL-positive MSSA. This report indicated that early diagnosis and appropriate antimicrobial treatment are crucial to achieve positive results in patients infected with TSST-1 and PVL-positive MSSA.[14] Linezolid is recommended for the treatment of necrotizing pneumonia caused by MRSA as it can inhibit exotoxin production.[28] In our cases, we had clinical information about the culture of the sputum and blood samples

of Case 1, and we could administer anti-MRSA antibiotics for Case 2 at an earlier phase.

Finally, it is important to emphasize that the association between PVL and TSST-1 genes and particular clinical manifestations requires further research because other combinations of exotoxin genes could also be important pathogenic factors. However, clinicians should know about CA-MRSA with PVL and TSST-1 as a possible cause of life-threatening community-acquired necrotizing pneumonia.

Conclusion

In conclusion, we described 2 familial cases of severe necrotizing pneumonia caused by CA-MRSA with TSST-1 and PVL genes in Japan. This MRSA strain was thought to be brought from Nepal. CA-MRSA necrotizing pneumonia should be considered in the differential diagnosis of severe community-associated pneumonia, particularly in healthy adults. Additionally, the CA-MRSA strains can be brought from abroad, even if they are not prevalent in one's own country, as in our cases. Appropriate early treatment with antibiotics, including anti-MRSA antibiotics such as vancomycin or linezolid, should be initiated when severe necrotizing pneumonia is suspected.

Abbreviations

MRSA, methicillin-resistant *Staphylococcus aureus*; HA-MRSA, hospital- or healthcare-associated MRSA; CA-MRSA, community-acquired MRSA; SCCmec, staphylococcal cassette chromosome mec; PVL, Panton–Valentine leucocidin; TSST-1, toxic shock syndrome toxin 1; MSSA, methicillin-sensitive *Staphylococcus aureus*; WBC, white blood cell; CRP, C-reactive protein; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; CT, computed tomography; TAZ/PIPC, tazobactam/piperacillin; AZM, azithromycin; MIC, minimum inhibitory concentration; DNA, deoxyribonucleic acid; MLST, multilocus sequence typing.

Ethical Approval and Consent for Publication

Informed consent has been obtained from patient one's father and patient two. And written consent (including for the accompanying images) has been obtained for publication in an online journal. The institutional approval was not required to publish the case details.

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Disclosure

The authors report no conflicts of interest for this work.

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