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Retropharyngeal abscess caused by community-acquired MRSA USA300 clone in a Japanese child

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Title: Retropharyngeal abscess caused by community-acquired MRSA USA300 clone in a Japanese child

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Running head: Retropharyngeal abscess caused by CA-MRSA in Japan

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Abstract

We describe a domestic case of retropharyngeal abscess (RFA) in a child caused by a community-acquired Methicillin-resistant *Staphylococcus aureus* (CA-MRSA) isolate that was genetically proven to be USA300 clone (ST8-SCC*mec* IVa- Panton-Valentine leukocidin (PVL)). USA300 generally has a PVL gene, epidemiologic association with severe and recurrent skin and soft tissue infection, and is the leading cause of RPA in the United States. A 1-year-old previously healthy girl visited the emergency department for fever, sore throat, and refusal to move her neck. There was no recent medical exposure or history of travel abroad. An enhanced computed tomography revealed bulky low-density area with ring enhancement on retropharyngeal space and right parapharyngeal space. MRSA was isolated from the pus obtained from surgical drainage, and antibiotics were continued for a total of 21 days. The MRSA was analyzed by whole genome sequencing and compared with the representative USA300 isolates. The strain was typed as ST8-t9829-SCC*mec* IVa with PVL and ACME, and the sequence was 99.8 % identical to USA300 isolates. The present case supports the possibility that USA300 is potentially spreading in the Japanese community, and raises alarm for the possibility of USA300 invasive infections without a clear route of infection.

Text

In 1981, community acquired Methicillin-resistant *Staphylococcus aureus* (CA-MRSA) was first reported in the United States (1). Thereafter, skin and soft tissue infection, necrotizing pneumonia, retropharyngeal abscess (RPA) and severe sepsis caused by CA-MRSA have been reported (2-5). MRSA is classified by sequence type (ST) and staphylococcal cassette chromosome *mec* (SCC*mec*). ST8-SCC*mec* IVa is the most predominant CA-MRSA strain in the United States. USA300, which is known to have epidemiologic association with severe and recurrent skin and soft tissue infection, is ST8-SCC*mec* IVa and generally characterized by the presence of Panton-Valentine leukocidin (PVL) gene and arginine catabolic mobile element (ACME) (2, 3). In the United States, USA300 is the leading cause of RPA, and the incidence had risen to 2.8-fold over the past 11 years (between 1993-2003 and 2004-2010) (4). In Japan, the first case of impetigo caused by CA-MRSA emerged in 2004 (6). Since then, some cases with serious cutaneous and subcutaneous infection associated with CA-MRSA have been reported. However, to the best of our knowledge, no case of retropharyngeal abscess caused by CA-MRSA, especially USA300, has been reported in Japan. Herein, we report the first case of RPA in previously healthy children caused by CA-MRSA USA300 clone (ST8-SCC*mec* IVa-PVL/ACME positive) by whole genome sequencing in Japan. The study was approved by the institutional review board at the National Center for Child Health and Development (NCCHD-1554) and the patient's parents agreed to publication.

In 2017, a 1-year-old previously healthy girl visited a primary care clinic for fever with sore throat and snoring while sleeping. Pharyngitis was suspected and faropenem was prescribed, however, these symptoms did not improve. She visited the emergency department for 3 days of fever, severe sore throat, and refusal to move her neck. There was no access to daycare, no

underlying disease, no recent medical and antimicrobial exposure, and no travel history abroad. Her general appearance was not toxic, and vital signs were as follow: a body temperature of 38.8°C, a heart rate of 140 /min, a respiratory rate of 45 /min, a SpO₂ of 99% (on room air), and blood pressure of 86/44 mmHg. Physical examination revealed right cervical swelling (3 × 2 cm) with tenderness, and bulging of the right posterior pharyngeal wall. White blood cell count (22,800/μL with 77 percent of neutrophils) and C-reactive protein (8.79 mg/dL) was elevated. A neck enhanced computed tomography (CT) revealed a bulky low-density area with ring enhancement on retropharyngeal space and right parapharyngeal space (**Figure 1**). She was diagnosed with retro and parapharyngeal abscess and was admitted to the pediatric intensive care unit after surgical drainage of the abscess. She was intubated for 2 days, considering the risk of developing airway obstruction. Gram-positive cocci in clusters were observed from the pus, ampicillin/sulbactam and vancomycin was initiated. MRSA was isolated from the pus, and ampicillin/sulbactam and vancomycin was replaced with clindamycin on the 5th day as a definitive therapy based on the susceptibility. She was continued on antibiotics for a total of 21 days and discharged on the 22nd day of hospitalization without any sequelae.

The Centers for Disease Control and Prevention defined a CA-MRSA case as a patient with an MRSA infection and no history of the following: surgery, hospitalization, or residence in a long-term care facility within the year before infection, presence of a percutaneous device or indwelling catheter, dialysis within the previous year, hospitalization >48 hour before MRSA culture, or previous MRSA infection or colonization (7). Therefore, the MRSA was categorized as community-acquired MRSA (CA-MRSA), and was suspected to have been acquired domestically based on her medical and travel history. Furthermore, her family had no travel history to the United States, no recent medical exposure and no history of recurrent skin and soft

tissue infection. The MRSA isolate designated as JICS104 was analyzed by whole genome sequencing using Miseq (Illumina, California, USA), followed by molecular typing via Center for Genomic Epidemiology website <<http://www.genomic-epidemiology.org/>> (accessed on January 8th, 2020) as previously described (8). Comparison of the whole genome sequence with the representative USA300 isolates FPR3757 and TCH1516 was also performed via Genome-to-Genome Distance Calculator 2.1 website <<https://ggdc.dsmz.de/ggdc.php#>> (accessed on January 8th, 2020) (9). The strain JICS104 was typed as ST8-t9829-SCC*mec* IVa with PVL and ACME (**Table 1**), and the sequence was 99.8 % identical to both of FPR3757 and TCH1516. Based on these results, the strain JICS104 was identified as USA300 clone.

The present case supports the possibility that USA300 is potentially spreading in the Japanese community, and raises alarm for the possibility of USA300 invasive infections without a clear route of infection. The domestic epidemiological data had shown that CA-MRSA accounted for only 4% of all MRSA isolates from 2008 to 2009 (10). While SCC *mec* IV was the predominant SCC*mec* type in Japan, ST8 SCC*mec* IV/J has become successful as a native clone (11). However, most ST8 SCC*mec* IV/J was negative for the PVL *gene*, different from USA300 (11). Five cases of infection caused by PVL-positive CA-MRSA were reported from 2000 to 2008 in Japan, these strains were ST30-SCC*mec* IVa (10). USA300 was first isolated in 2007 from a 3-month-old Indian girl who was born in the United States and moved to Japan (11). In 2008, USA300 was isolated from 11-month-old Japanese girl who had no travel history and contact history with foreigners (11). More recently, several reports suggesting the spreading of USA300 in certain areas of Japan. A 2014 to 2016 survey in a neonatal intensive care unit reported that a third of the MRSA isolates were USA300 suggesting a wider distribution of this clone (12). Furthermore, an investigation for the nasal carriage rate of USA300 among adult

outpatients in the western area of Tokyo in 2016-2017 showed a high carriage rate of 20.5% (13). The route of USA300 transmission in this case was unknown. Nasopharyngeal culture and skin carriage status of her family was not investigated. Thus, we were unable to assess whether USA300 was transmitted by family members or not. However, since she and her parents had no obvious history of travel abroad and medical exposure, this most likely represents transmission in the Japanese community. In fact, reports on the transmission of USA300 in the Japanese community has been increasing (12, 13). Therefore, the possibility of CA-MRSA, especially USA300, should be considered when serious Gram-positive cocci infection is suspected, even in the absence of history of travel abroad or medical exposure. The USA300 clones are known to be the dominant cause of deep neck and lung abscess in the United States and when such infections are observed, a close examination of the strains may be worth considering.

An abscess formation may be preceded by upper respiratory tract infection, pharyngeal trauma or foreign body ingestion, but a substantial proportion appears to be idiopathic in origin. Most cases (96%) occur in children <6 years of age because the retropharyngeal lymph nodes usually recede after this age and 50% of cases occur in patients between 6 and 12 months of age (4). Most retropharyngeal abscesses are polymicrobial in origin, *Streptococcus pyogenes* and anaerobic bacteremia in the oral cavities was the common causative organisms of RPA in Japan (14). Whereas, in the United States, USA300 has become a common organism of RFA accounting for 79% (26/33 cases) of cases necessitating empiric coverage for MRSA (4, 15). To the best of our knowledge, this is a rare case of RPA caused by USA300 in Japan and does not suggest a need to change empirical antibiotics for RFA. However, we may need to consider MRSA coverage for severe infection with abscess formation depending on future epidemiological data.

Conflict of interest: We have no COI to disclose.

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Figure legends

Figure 1. An enhanced computed tomography for the retropharyngeal and right parapharyngeal abscess

The abscess was detected as low-density area with ring enhancement on retropharyngeal space and right parapharyngeal space (White arrow in A, B).

The abscess disappeared after incision drainage and 3 weeks of antibiotic (C, D).

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Table 1. The result of molecular types and pathogenicity genes of the MRSA

Molecular types		
Sequence type	8	
<i>spa</i> type	t9829	
SCC <i>mec</i> type	IVa	
Pathogenicity genes (Products)		
Host-immunity modulators	ACME (arginine catabolic mobile element) gene	
	<i>sak</i> (staphylokinase)	
	<i>scn</i> (staphylococcal complement inhibitor)	
Exoenzymes	<i>aur</i> (aureolysin)	
	<i>splA</i> (serine protease splA)	
	<i>splB</i> (serine protease splB)	
	<i>splE</i> (serine protease splE)	
Toxins	<i>hlgA</i> (gamma-hemolysin chain II precursor)	
	<i>hlgB</i> (gamma-hemolysin component B precursor)	
	<i>hlgC</i> (gamma-hemolysin component C)	
	<i>lukD</i> (leukocidin D component)	
	<i>lukE</i> (leukocidin E component)	
	<i>lukF-PV</i> (Panton Valentine leukocidin F component)	
	<i>lukS-PV</i> (Panton Valentine leukocidin S component)	
	<i>sek</i> (enterotoxin K)	
Drugs-resistant genes	<i>seq</i> (enterotoxin Q)	
	<i>ant(6)-Ia</i>	Resistant to aminoglycoside
	<i>aph(3')-III</i>	Resistant to aminoglycoside
	<i>blaZ</i>	Resistant to beta-lactam
	<i>mecA</i>	Resistant to beta-lactam
	<i>mph(C)</i>	Resistant to macrolide
	<i>msr(A)</i>	Resistant to macrolide, lincosamide, streptogramin B
	<i>gyrA</i> mutation: S84L	Resistant to fluoroquinolone
	<i>griA</i> mutation: S80Y	Resistant to fluoroquinolone

Figure 1. An enhanced computed tomography for the retropharyngeal and right parapharyngeal abscess