



Case Report

Psoitis and multiple venous thromboses caused by Pantone Valentine Leukocidin-positive methicillin-sensitive *Staphylococcus aureus* in a 12-year-old girl: A case report[☆]



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ABSTRACT

Panton Valentine Leukocidin (PVL) is one of the many toxins produced by *Staphylococcus aureus*. In Japan, PVL-positive *S. aureus* strains are mainly methicillin-resistant *S. aureus* (MRSA). Data regarding PVL-positive methicillin-sensitive *S. aureus* (MSSA) are scarce. In this report, we describe a case of severe infection by PVL-positive MSSA. A 12-year-old healthy girl was admitted with high fever and pain in the lower back. Computed tomography revealed a diagnosis of psoitis and multiple venous thromboses. Blood cultures obtained after admission revealed infection with MSSA. Her fever continued despite adequate antibiotic therapy. On the fifth hospitalization day, she developed bladder dysfunction, and an abscess was noted near the third lumbar vertebra. She underwent an emergency operation and recovered. Bacterial analyses revealed that the causative MSSA was a PVL-producing single variant of ST8 (related to USA300clone), of sequence type 2149. PVL is known to cause platelet activation. This case demonstrates the need for detailed analyses of the causative strain of bacteria in cases of *S. aureus* infection with deep vein thrombosis, even in cases of known MSSA infection.

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1. Introduction

Staphylococcus aureus (*S. aureus*) causes various types of infections including pneumonia, bacteremia, and skin and musculoskeletal infections [1]. *S. aureus* is divided into two broad groups depending on their sensitivity to methicillin: methicillin sensitive *S. aureus* (MSSA), and methicillin resistant *S. aureus* (MRSA) [1]. MRSA had originally gained prominence as a pathogen among hospitalized patients. However, the first community associated MRSA (CA-MRSA) infections were reported from the United States

in 1981, and the numbers have increased since the 1990s. CA-MRSA is a major pathogen affecting the skin in children, and young adults, occasionally causing severe infections. The type of CA-MRSA that causes severe infections produces Pantone Valentine Leukocidin (PVL), which is one of the toxins produced by *S. aureus*. PVL-positive *S. aureus* was initially believed to belong to the MRSA group, recent reports suggest, however, that they may also be MSSA [2–4]. The prevalence of PVL positive MSSA among all clinical isolates varies from country to country. Although only 13% of the MRSA produce PVL, most of the PVL-positive *S. aureus* in Japan belong to the MRSA group [5]. Data on the prevalence of PVL-positive MSSA in Japan is scarce, and its clinical outcome in children is poorly understood. In this report, we will be discussing the case of a 12-year old girl having psoitis, bacteremia, and multiple venous thromboses, caused by PVL-positive MSSA.

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Abbreviations

ACME	arginine catabolic mobile element;
CA-MRSA	community associated methicillin resistance <i>Staphylococcus aureus</i>
CC	clonal complex
CRP	C-reactive protein
CT	computed tomography
DVT	deep vein thrombosis
ET	exfoliative toxin
HNP	human neutrophil peptide
IVIG	intravenous immunoglobulin
MRI	magnetic resonance imaging
MRSA	methicillin resistance <i>Staphylococcus aureus</i>
MSSA	methicillin sensitive <i>Staphylococcus aureus</i>
PCR	polymerase chain reaction
PVL	Panton Valentine Leukocidin
SE	staphylococcal enterotoxin
SLV	single-locus variant
ST	sequence type
STIR	Short T1 inversion recovery
TSST-1	toxic shock syndrome toxin-1.

2. Case report

A 12-year-old previously healthy girl was referred to our hospital with fever, limping, and multiple thrombi of the inferior vena cava. She pursued a form of Korean martial art, named taekwondo.

The patient initially had low back pain, and slight dysesthesia of the left leg, without fever. Five days later, she developed high fever, with severe low back pain, and was admitted to a regional hospital.

Although urinalysis was unremarkable, the transabdominal ultrasound showed swelling, and increased echogenicity of the left kidney. Based on these results, the patient was diagnosed with bacterial nephritis. Antibiotic therapy with ampicillin and cefotaxime was initiated after obtaining samples for blood cultures. The blood culture reports available the following day were positive for *S. aureus*. Contrast-enhanced computed tomography (CT) scan of the thorax, abdomen, and pelvis, performed to search for the infective focus, showed increased CT values suggestive of panniculitis of the left retroperitoneal region, and swelling of the left iliopsoas (Fig. 1). Multiple vein thromboses of the inferior vena cava (Fig. 2) were noted, in addition to multiple nodular shadows in the



Fig. 1. Contrast-enhanced CT scan of the pelvis (axial section). The arrow indicates the low-density area in the left iliopsoas.

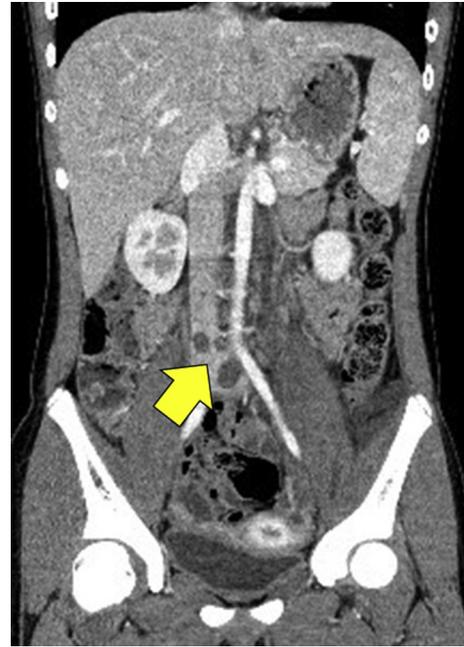


Fig. 2. Contrast-enhanced CT scan of the pelvis (coronal section). Some venous thromboses are seen in the inferior vena cava. The arrow indicates the thromboses.

lungs (Fig. 3). However, no low-density areas with ring enhancement were noted in her iliopsoas. She was transferred to our hospital on the same day.

On presentation at our hospital, her body temperature was 39.3 °C, her blood pressure was 112/56 mmHg, and the pulse and respiratory rates were 130 beats per minute and 18 breaths per minute, respectively. The oxygen saturation was noted to be 99% while breathing ambient air. She felt pain in the back, on leg movement. The rest of the clinical examination was unremarkable, with symmetrical full range of motion noted on passive movement. The results of the laboratory tests revealed the white blood cell count to be 3200/μL, with 40.0% neutrophils, the platelet count to be 120,000/mm³, and serum CRP level to be 22.1 mg/dL. Short T1 inversion recovery (STIR) contrast magnetic resonance imaging (MRI) of the spine showed hyperintensity around the left iliopsoas.

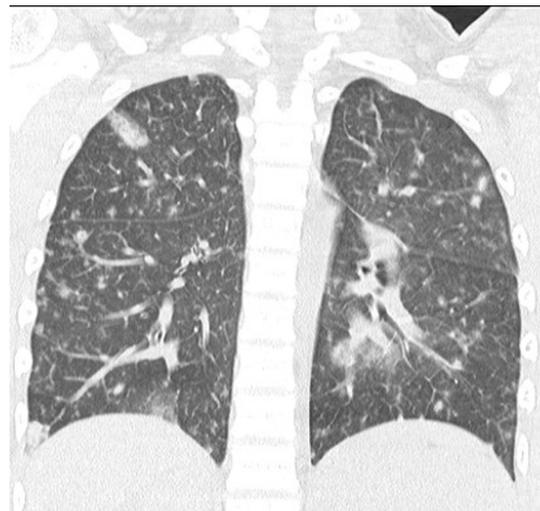


Fig. 3. Normal CT scan of the thorax (coronal section). Many multiple nodular shadows are seen in the lungs.

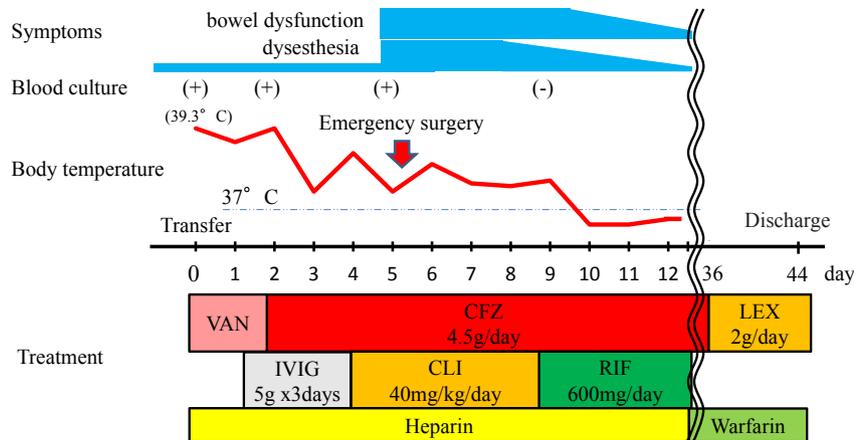


Fig. 4. Clinical course of the patient. The horizontal line shows the days of hospitalization. The broken horizontal line shows 37 °C. CFZ, cefazolin; LEX, cefalexin; CLI, clindamycin; IVIG, intravenous immunoglobulin; RIF, rifampicin; VAN, vancomycin.

However, MRI revealed no spondylitis. Based on the findings of the clinical examination and the laboratory tests, we diagnosed her as having pyomyositis with bacteremia caused by *S. aureus*, multiple venous thromboses of the inferior vena cava, and septic pulmonary embolism. She was started on vancomycin. On the second hospitalization day, the report on the antimicrobial susceptibility of the bacteria isolated from the blood culture, revealed MSSA infection. We switched over from vancomycin to cefazolin (100 mg/kg/day q8h, intravenously). Although her general condition improved and the CRP levels decreased, the fever persisted for the next three days. Clindamycin was accordingly added (40 mg/kg/day q8h). On the midnight of the fifth hospitalization day, dysfunctions of the bladder and bowel were noted, and the dysesthesia of the left leg worsened. On the next morning, the MRI of the lumbar spine showed an epidural soft tissue swelling around the L 3–4 vertebral level, which displaced the cauda equina, and caused an effusion in the left L 3–4 zygapophyseal joint. Additionally, osteomyelitis was noted in the L 4 vertebral body. Emergency surgical care was considered on the same day. A unilateral posterior approach was adopted, at the L 2–4 vertebral level. An abscess was found overlying the L 3–4 vertebrae, containing pus, which was cloudy and bloody in appearance. An inflammatory thickening of the ligamentum flavum, displacing the cauda equina, was also noted. The facet joint was opened and thoroughly debrided.

Since MSSA was isolated from this abscess on the fourth postoperative day, clindamycin was changed to rifampicin (600 mg/day q24h, orally). However, rifampicin was stopped on the 22nd postoperative day due to drug fever. We continued with cefazoline for a total of 5 weeks, until her CRP levels normalized. The clinical progression was satisfactory, with complete afebrile and recovery of bladder and bowel dysfunction. The dysesthesia was relieved, and the affected leg regained active mobility. She was discharged on the 39th postoperative day. The detailed clinical course is shown in Fig. 4.

To investigate the severity of her infection, a screening test was performed to assess her immunocompetence, and coagulation. Results of these tests showed normal values. Multilocus sequence typing, and *S. aureus*-specific staphylococcal protein A (*spa*) typing was performed by sequencing to identify the strain isolated from the blood culture. Tests for coagulase typing, and *S. aureus* toxin identification were also performed. The tests intended to identify the following toxins: the toxic shock syndrome toxin –1, exfoliative toxin, PVL, staphylococcal enterotoxin (SE), and the arginine catabolic mobile element by polymerase chain reaction (PCR). These tests revealed that the sequence type (ST) was 2149 (a single-locus

variant (SLV) of ST8), the *spa* type was t008, and the coagulase was of type III. In addition, the strain tested positive for PVL, and SEa (Table 1). The patient and her guardian provided written consent for reporting this case.

3. Discussion

Iliopsoas pyomyositis and abscess are classified as primary and secondary diseases, respectively [6]. Primary disease occurs due to the hematogenous or lymphatic dissemination of a pathogen from a distant focus, while secondary disease occurs as a result of the direct inflammatory infiltration from neighboring organs [6]. The iliopsoas muscle has a rich blood supply and is in close proximity to the retroperitoneal lymphatic pathways. Infectious diseases may therefore spread to the iliopsoas from distant foci via the blood circulation. *S. aureus* is the most frequently isolated organism in primary iliopsoas infections [6]. Muscle strain facilitates the occurrence of bacterial pyomyositis [7]. In this case, we speculate that the iliopsoas muscle was strained during taekwondo, allowing infection with *S. aureus*.

After cefazoline administration, although CRP levels decreased, fever persisted for the next three days. Judging that the therapeutic effect was insufficient, we added clindamycin. Nevertheless, she needed to have an emergent operation two days after clindamycin was first administered. Although her fever gradually improved after the operation, MSSA was isolated from the abscess collected at the operation on the fourth postoperative day. As bacterial growth was observed during clindamycin administration, we replaced clindamycin with rifampicin. Some reports suggested that rifampicin adjunctive therapy for *Staphylococcus aureus* is good for osteomyelitis, because rifampicin can penetrate biofilms [8,9].

In this case, MSSA with ST2149 was detected from the blood culture. Only one ST2149 strain, which was detected in Australia in 2010, is registered in the MLST database [10,11]. According to some reports, the PVL-positive ratio among clinically isolated MSSA

Table 1
The results of bacterial analyses.

<i>mecA</i>	negative	TSST-1	negative
sequence type (ST)	2149	ET-A, ET-B	negative
clonal complex (CC)	8	PVL	positive
<i>spa</i> type	t008	SEa	positive
coagulase type	III	SEb, SEc, SEd, SEe	negative
		ACME- <i>arcA</i>	negative

clones vary by ST; no PVL-positive ST2149 clone has been reported [12–15]. ST2149 clones are SVT of ST8. PVL-positivity is higher in the USA300 clones, with the incidence of disease complications being higher in ST8 clones [14,16]. To the best of our knowledge, this is the first case report of severe infection caused by PVL-positive MSSA of the ST2149 clone. Further epidemiological studies are needed to reveal the relationship between severity of infection and ST.

The *S. aureus* strain detected in this case had tested positive for PVL. PVL is a β -barrel pore-forming toxin, also named LukS-PV and LukF-PV. On being released, these two toxins organize a pore-forming heptamer on neutrophil membranes, which lead to neutrophil lysis [2]. In general, PVL relates to community-acquired MRSA (CA-MRSA) infections [2,17]. However, recent reports suggest that MSSA clones can carry PVL genes as well [2]. Skin and soft-tissue infections caused by PVL-positive *S. aureus* are more likely to need surgical treatment than those caused by PVL-negative strains. In adults, the relationship between disease severity and PVL positivity in various infections including pneumonia, musculoskeletal disease, and bacteremia, has not been clearly established [2]. In the case of children, there may be important differences between PVL-positive and PVL-negative infections [2]. PVL-positive musculoskeletal infections in children are associated with a higher frequency of surgical drainage, and complications such as deep vein thrombosis (DVT), chronic osteomyelitis, and longer hospitalization as compared with PVL-negative clones [16–19]. Gonzalez et al. showed that the infection in 7 of 9 children with staphylococcal osteomyelitis and DVT, were caused by PVL-positive *S. aureus* [16]. Martinez-Aguilar et al. reported that 5 of 33 PVL-positive *S. aureus* musculoskeletal infections in children were associated with DVT, while none of 23 PVL-negative cases had DVT [18]. In these reports, musculoskeletal infections with DVT were mainly caused by MRSA or by the USA300 clone. In our case, the detected strain was PVL-positive and was of the ST 2149-t008-coaIII strain, which was similar to the USA300-t008-coaIII clone in terms of ST. This factor may have been responsible for the disease severity, and DVT in this case.

PVL also leads to lysis of neutrophils, and the secretion of antimicrobial α -defensins, named human neutrophil peptides (HNPs), and myeloperoxidase [20–22]. HNPs are an important trigger of sequential platelet activation [23]. PVL-positive infection is associated with production of substances such as HNPs, and with the lysis of enormous neutrophils accumulated at the site of osteomyelitis, both of which are closely related to platelet activation. This sequence of events may trigger the development of thrombosis [24]. Antibodies in the human plasma may prevent PVL related neutrophil lysis [22]. Patients having a high antibody titer against PVL are protected against some complications associated with PVL-positive *S. aureus* infections. The statistical probability of clinically significant antibody titers against PVL in children is likely to be low, owing to the low prevalence of PVL-positive clones in many countries [24].

In this case, PVL positive MSSA infection with ST2149 caused a severe infection, associated with DVT. This case demonstrates that in cases of *S. aureus* infections with DVT, clinicians may need to request a detailed analysis of the causative bacteria, including the production of PVL and ST, even in cases caused by MSSA. Although the analysis of toxin productivity and MLST of the isolated bacterial strain is cumbersome, it has some clinical benefits. First, the severity of the case can be better gauged through analysis. Failure to judge the severity of the case via bacterial analysis could lead to suspicious of underlying immune conditions of the host. Furthermore, detailed bacterial analysis can help to clarify the existence of emerging bacteria in our country and the relevance of emerging strains outside our country.

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Conflicts of interest

The authors confirm that there are no conflicts of interests to declare.

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