Multi-Site Infections Caused by Methicillin-Resistant *Staphylococcus Aureus* in a Six-Year Old Girl: A Rare Case Report

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Case report

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Abstract

Background

Community-associated Methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is an emerging pathogen that leads to severe outcomes, especially in pediatric patients with multiple site infections.

Case presentation:

We report a case of a multiple organ and life-threatening infection caused by CA-MRSA in a 6-year-old girl who manifested sepsis, myelitis, purulent arthritis, purulent meningitis, hydropericardium, pneumonia, and empyema. The girl exhibited good response to the combination therapy of linezolid and rifampicin after treatment with vancomycin failed due to delay in achieving target serum concentration. We performed pleural effusion and hydropericardium effusion drainage and treated left lower limb infection using interdisciplinary approaches.

Conclusion

This case highlights the need to be aware of CA-MRSA infection, which requires accurate diagnosis, identification of site infection, appropriate antibiotic treatment, and surgical debridement.

Background

Staphylococcus aureus (*S. aureus*) is one of the main pathogens of community- and hospital-acquired infections and can cause a wide variety of infectious diseases, including mild skin and soft tissue infections, endocarditis, osteomyelitis, and fatal pneumonia [1, 2]. Moreover, based on the sensitivity to antibiotic drugs, *S. aureus* can be categorized into methicillin-resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA). Based on the original source, MRSA is classified into community-acquired MRSA (CA-MRSA) and hospital-acquired MRSA (HA-MRSA) [3, 4]. MRSA infections lead to higher mortality than MSSA [5, 6] and delay in active antimicrobial therapy further worsens the outcomes. In the last decade, rates of CA-MRSA infection have increased steadily, while HA-MRSA infection rates have generally declined [7]. CA-MRSA typically presents as skin and soft tissue infection, but invasive infection such as septicopyemia may also occur, which can lead to serious or even fatal consequences, especially in children. Patients with CA-MRSA infections tend to be younger, and often, are otherwise healthy. Notably, CA-MRSA can acquire drug resistance genes, and its resistance has increased over time, making CA-MRSA treatment challenging. In a retrospective study based on 208 cases of community-acquired *S. aureus* mediated septicopyemia, 136 cases had CA-MRSA infection and 12 deaths were attributed to the CA-MRSA infections [8].

MRSA prevalence is estimated at < 50% in most countries, with several countries reporting prevalence of < 25%. However, the prevalence and epidemiology of MRSA have been constantly changing, with novel MRSA clones being reported in different geographical regions. MRSA prevalence has been increasing since the early 2000s and several reports have come from different countries [9]. Even with the ongoing development of new antibiotics and advances in infection prevention, MRSA remains a challenging pathogen with persistently high mortality [10]. The mortality rate of systemic infection caused by MRSA is more than 50%, which has become a worldwide problem in clinical and community anti-infective treatment [3, 11]. It has been estimated that the treatment failure rate of complicated MRSA bloodstream infections is as high as 40% [12]. The prognosis of a single site MRSA infections is relatively better. However, multiple site infections caused by MRSA are rare, are difficult to treat, and lead to high mortality rates. Here, we report a pediatric patient who suffered from sepsis, myelitis, purulent arthritis, purulent meningitis, hydropericardium, pneumonia, and empyema. The child exhibited good response to the therapy and had a good recovery.

Case Presentation

The patient was a 6-year-old girl without a family history of immunodeficiency. The girl suffered from left anklebone fracture due to trauma and received plaster fixation on January 14, 2019. Two days later, she was febrile with the temperature of 38.0 °C, accompanied by systemic pain, cough, dyspnea, chest tightness, headache, and pain in left foot. She had local swelling and was unable to walk. Blood and hydropericardium cultures were positive for MRSA and she was treated with intravenous meropenem combined with vancomycin. However, the treatment was not effective and the condition of the patient gradually aggravated. She was transferred to our hospital for further treatment in pediatric ICU on January 24, 2019.

After admission, the child presented dyspnea, which could not be alleviated by nasal catheter oxygenation. Chest-enhanced Computed tomography (CT) revealed bilateral pneumonia and large amount of pleural effusion (Fig. 1a-b). Closed thoracic drainage was performed, and specimens were sent for culture. Chest tube was removed after seven days. Further auscultation revealed weakened pulmonary moist rales and cardiac sound, while echocardiography revealed moderate amounts of hydropericardium and cardiac insufficiency. We performed pericardiocentesis and found hydropericardium to have yellow turbidity with flocs. Approximately 100 mL pericardial fluid was drained daily during the first two weeks, and the volume decreased gradually. The pericardial drainage tube was removed on the 26th day and pericardial fluid was sent for culture. Before administering anti-infective treatment, blood and bone marrow were also sent for culture. The child had been suffering from high fever with a temperature of 40°C and had headache. Investigations at the other hospital showed that cerebrospinal fluid (CSF) had 1233×10^6 leukocytes/L, glucose under 1.1 mmol/L, protein at 1470 mg/L, and chloride at 116.3 mmol/L. Investigation revealed purulent meningitis. After admission to our hospital, CSF investigation on January 27, 2019 showed 12.0×10^6 leukocytes/L, glucose at 2.5 mmol/L, protein at 500 mg/L, and chloride at 130 mmol/L. CSF culture showed absence of bacteria or fungi. However,

next-generation sequencing (NGS) analysis revealed presence of *S. aureus* (Fig. S1). Purulent meningitis was under control due to the administration of anti-infection treatment at the other hospital. As a result, the examination of nervous system did not show any obvious abnormalities, and the magnetic resonance imaging (MRI) of the cranium was normal. However, the laboratory findings including complete blood cells count revealed high level of white cells (white blood cell count of $13.9 \times 10^9/L$, with 78.3% neutrophils, 16.4% lymphocytes, and 3.7% monocytes), while the C-reactive protein (CRP) was 111 mg/L. Therefore, antibiotic treatment of vancomycin (15 mg/kg per dose every 6 hours) combined with rifampicin was administered. Once vital signs leveled off, MRI of the lower extremity was performed, which demonstrated osteomyelitis (Fig. 1c-d). Results of marrow, blood, pleural effusion, and hydropericardium cultures eventually confirmed MRSA infection after one week. Next, multi-locus sequence typing (MLST) and *S. aureus*-specific staphylococcal protein A (*spa*) typing were performed to identify the strain. Tests for Staphylococcal cassette chromosome *mec* (SCC*mec*) typing and MRSA toxin identification were also performed. The test results revealed that the sequence type (ST) was ST-59, the *spa* type was t437, and the SCC*mec* typing was type IV. In addition, the strain tested positive for panton-valentine leukocidin (PVL) and staphylococcal enterotoxin genes, including *seb*, *sek*, and *seq*.

On day 8 after hospitalization, the child still had fever and the inflammatory index including CRP and procalcitonin (PCT) remained significantly higher than normal. Meanwhile, left foot and knee had tenderness with obvious local swelling, increased local temperature, and restricted movement. Orthopedists performed debridement of the left ankle (Fig. 3a-d) and left knee, retained drainage after the surgery (Fig. 1d), and changed dressing regularly *per* the orthopedic recommendations. After the operation, the child still had a high fever; complete blood count showed WBC of $16.5 \times 10^9/L$, while CRP was 122 mg/L, revealing that the infection was not under control even on day 11 of antibiotic treatment. Vancomycin trough was routinely monitored, with a concentration of up to 7.4 $\mu g/mL$, which did not reach the effective range. Hence, vancomycin was discontinued and treatment with linezolid combined with rifampicin was started (Fig. 2b). Thus, the patient was treated for 45 days with intravenous linezolid combined with rifampicin following vancomycin treatment. The patient's condition gradually improved and WBC count and CRP level returned to normal, indicating that clinical treatment was effective (Fig. 2a). The chest CT showed a significant improvement in bilateral pneumonia, pleural effusion, and hydropericardium (Fig. 1c-d). MRI of left lower extremity showed that wide T2WI high signal had not improved, but cystic fluid was absorbed (Fig. 1g-h). Eventually, the patient was discharged on the 57th day of admission. The child and her guardian provided written consent for reporting this case.

Discussion

MRSA has become one of the most important pathogens of recent time. The organism is transmitted in both healthcare and community settings and is the leading cause of bacteremia, endocarditis, skin and soft tissue infections, bone and joint infections, and hospital-acquired infections. Studies have reported that MRSA can cause psoriasis, multiple venous thromboses [13], empyema necessitans [14], acute epiglottitis [15], fatal necrotizing pneumonia [16], sepsis with bilateral pneumonia, osteomyelitis, and

septic arthritis of the knee [17], all of which achieved good therapeutic results after relevant treatment. However, treatment of multi-system infections caused by MRSA is difficult, and therefore, its mortality rate remains high. No case reports have described MRSA infections leading to sepsis, osteomyelitis, purulent arthritis, hydropericardium, septic meningitis, pneumonia, and empyema. Here, we report a child who suffered from all clinical symptoms mentioned above and yet exhibited good response to the therapy. Such a typical case of MRSA infection has never been reported in literature. Here, we share our experience for clinicians to improve the success rate of treatment in future similar clinical scenarios.

We explored the reasons which may have caused the severe infections in this child. The causative strain was identified as ST59- SCCmec IV- t437, which was the most common CA-MRSA increasing in Shanghai, China [18–20]. Rates of CA-MRSA infections have increased significantly during the past 30 years worldwide. *S. aureus* can produce several types of exotoxins with varying effects. PVL is one of the synergohymenotropic exotoxins produced by *S. aureus* and belongs to pore-forming toxin family. Most CA-MRSA carry the gene encoding PVL. The association of PVL with an enhanced inflammatory response, pus-forming lesions, necrotizing pneumonia, skin infections, and other severe infections that often require surgical intervention is well documented in otherwise healthy children [21]. In our case, we confirmed that the strain was PVL-positive, which also explained the potential cause of the severe infection in the child.

MRSA is not only resistant to β -lactam antibiotics, but also to other antimicrobial agents such as aminoglycosides, quinolones, and macrolides. Infections caused by MRSA have been regarded clinically challenging and have attracted extensive attention from domestic as well as foreign experts. Vancomycin has long been considered the first-line antibiotic treatment for invasive MRSA infection, including both HA-MRSA and CA-MRSA. However the use of vancomycin is limited because of its shortcomings such as the slow bactericidal activity, increased minimum inhibitory concentrations (MICs), reduced activity against biofilm-forming pathogens, and poor tissue penetration [22]. Several researchers have shown that subtherapeutic trough vancomycin concentration is the main reason of treatment failure. Vancomycin treatment failed in our patient due to the delay in achieving target serum concentration. we monitored the vancomycin trough dynamically up to 7.4 $\mu\text{g/mL}$, while the guideline recommends the trough level to be 15–20 $\mu\text{g/mL}$, which could not be reached in our case. Since vancomycin is mainly excreted in urine, renal function is the most important determining factor for vancomycin pharmacokinetics. Augmented renal clearance (ARC) is associated with reduced β -lactam plasma concentrations and Yang Chu et al showed its impact on clinical outcomes [23]. Creatinine clearance (CL_{Cr}) of more than 130 $\text{mL}\cdot\text{min}^{-1}$ is termed high CL_{Cr} [24]. ARC patients are significantly younger, and exhibit a higher CL_{Cr} and glomerular filtration rate. The patients with high C_{cr} show significantly lower trough vancomycin concentrations in the same dosing regimen. Here, our patient was young and showed the CL_{Cr} within 120–130 $\text{mL}\cdot\text{min}^{-1}$. We speculate that the reason of low vancomycin valley concentration may be related to CL_{Cr}. Clinical practice guidelines for the treatment of refractory MRSA bacteremia and vancomycin treatment failure lack consensus. We started linezolid after vancomycin treatment failed. A previous study [25] showed that linezolid had the highest inhibitory effect on *S. aureus*. On the 7th day after starting linezolid

treatment, inflammatory biomarker CRP decreased from 120 to 85 mg/L and the body temperature also decreased significantly. Further, pulmonary inflammation and pericardial effusion were evidently absorbed, indicating that antibiotic treatment was effective. Finally, the child was discharged 57 days after admission. We followed up the child after discharge. While movement of her left leg has a slightly limp, the child is otherwise normal.

Conclusion

In summary, since clinical practice guidelines for the treatment of refractory MRSA bacteremia and vancomycin treatment failure lack consensus, antibacterial treatment should be adjusted according to the clinical efficacy; moreover, timely control of focal infection is the key to successful clinical outcome.

Declarations

Disclosure statement

No potential conflict of interest is reported by the authors.

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Pei Xiao, Jing Liu, and Xue Yang contributed equally to this work; Pei Xiao, Jing Liu, and Xue Yang designed and wrote the report; Gangfeng Yan and Guoping Lu reviewed the manuscript for intellectual content and revised the entire work; all authors have read and approved the final manuscript.

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Figures

Figure 1

a. The mediastinal window shows lung consolidation (red arrow), pleural effusion (green arrow) and hydropericardium (yellow arrow). b. The pulmonary window shows multiple nodules in both lungs (blue arrow). c-d. TSE T2WI FS sequence sagittal (c) and transverse (d) show extensive T2WI hypersensitivity in intramedullary and calf soft tissue, Suprapatellar bursa effusion. e. The mediastinal window shows pleural effusion and hydropericardium significantly reduced. f. The pulmonary window shows multiple nodules in both lungs obvious absorption. g-h. extensive T2WI hypersensitivity in intramedullary and calf soft tissue did not improve, suprapatellar bursa effusion absorption.

a

b

c

d

Figure 2

a-d show obvious local swelling of left foot, Orthopedists operated debridement of the left ankle, retained drainage after the surgery.

Figure 3

a shows the body-temperature curve (blue line) and C-reactive protein (red line); b shows the change in the mainly treatment and culture of bone marrow, blood, hydropericardium and pleural effusion.

Supplementary Files

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