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Community-acquired necrotizing pneumonia caused by methicillin-resistant *Staphylococcus aureus* producing Panton–Valentine leukocidin in a Chinese teenager: case report and literature review

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SUMMARY

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) has now been established as an important community-acquired pathogen. Although necrotizing pneumonia caused by community-acquired MRSA (CA-MRSA) strains producing Panton–Valentine leukocidin (PVL) has been reported with increasing frequency in many countries, it has been reported in only a few children younger than 1 year of age in Mainland China.
Methods: We describe a case of life-threatening necrotizing pneumonia due to PVL-positive CA-MRSA in a 15-year-old previously healthy female who presented with high fever, shivering, a dry cough, and dyspnea. Details of the clinical outcomes, microbiological data, and therapies for this patient were collected and compared with those of cases reported in the literature on CA-MRSA.
Results: Computed tomography (CT) findings showed cavitary consolidations in both lungs and bilateral pleural effusion. MRSA strains isolated from the patient's sputum and pleural fluid were susceptible to most non-β-lactam antimicrobial agents except for clindamycin and erythromycin. Both of these isolates tested positive for the *mec*A gene as well as PVL genes, and were identified as ST59-MRSA-SCC*mec* type IV-spa type t437. The patient was treated successfully with linezolid, fosfomycin, and teicoplanin.
Conclusions: To our knowledge, this is the first report from Mainland China of necrotizing pneumonia due to PVL-positive CA-MRSA among those aged older than 1 year. CA-MRSA necrotizing pneumonia should be considered in the differential diagnosis of severe community-acquired pneumonia, particularly in previously healthy individuals.

1. Introduction

Although traditionally regarded as a purely nosocomial pathogen, methicillin-resistant *Staphylococcus aureus* (MRSA) has now emerged as a community-acquired pathogen, affecting healthy people without recognized risk factors for MRSA acquisition.[1,2] In contrast to traditional healthcare-associated MRSA (HA-MRSA), these novel MRSA strains, termed community-acquired MRSA (CA-MRSA), carry smaller staphylococcal chromosomal cassette *mec* (SCC*mec*) elements (type IV or type V) and retain susceptibility to a wider range of antimicrobial agents, except for β-lactams.[1–4] Additionally, CA-MRSA strains are more likely than HA-MRSA strains to carry the Panton–Valentine leukocidin (PVL), a strong cytolytic factor with a unique ability to create pores in the cell membranes of human neutrophils and induce the release of chemotactic factors, although its role in the pathogenesis of CA-MRSA infections is controversial and PVL-negative CA-MRSA clones have been reported worldwide in recent years.[1,2,5,6]

CA-MRSA is primarily associated with skin and soft tissue infections (SSTIs) in previously healthy individuals;[2,7] however, it may occasionally cause invasive and severe infections like necrotizing pneumonia, necrotizing fasciitis, pyomyositis, osteomyelitis, and sepsis.[1,6] As one of the most severe illnesses caused

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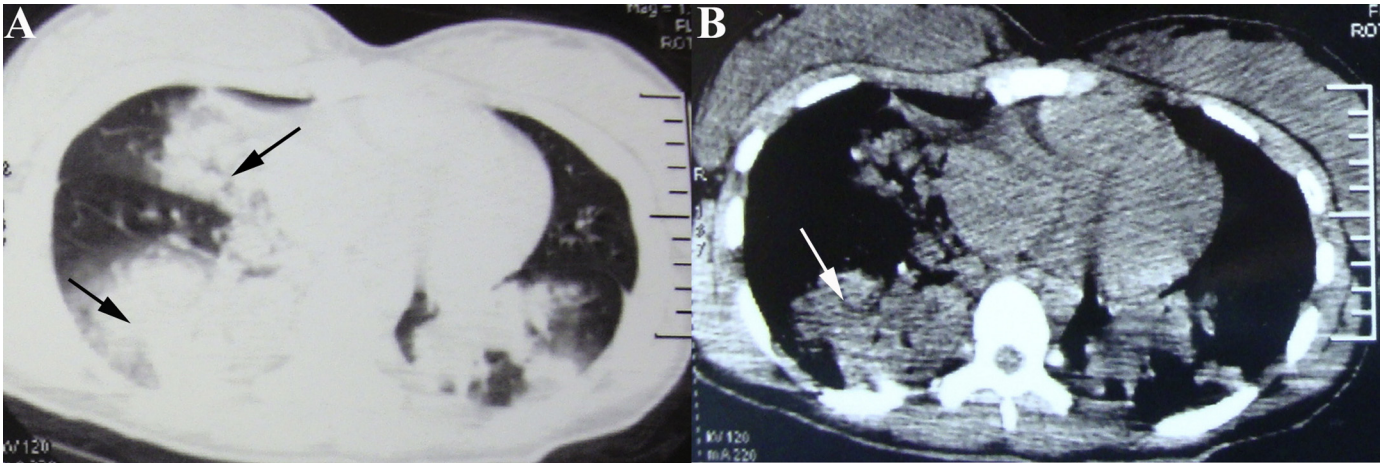

Figure 1. CT images at 5 days after the onset of pneumonia, showing irregular consolidations with interspersed small lucent areas in both lungs: A, black arrows; B, white arrow.

by CA-MRSA strains producing PVL, necrotizing pneumonia has been reported with increasing frequency in many countries and has a high mortality rate of 56–63%.[1,8] In China, data regarding CA-MRSA are limited and necrotizing pneumonia caused by PVL-positive CA-MRSA has been reported in only a few infants.[9]

Herein, we present a case of life-threatening pneumonia caused by CA-MRSA with a favorable outcome in a 15-year-old previously healthy teenage girl. To the best of our knowledge, this is the first report from Mainland China of necrotizing pneumonia due to PVL-positive CA-MRSA among those aged older than 1 year. We also review the literature related to CA-MRSA pneumonia.

2. Case report

A 15-year-old previously healthy female presented to the Chinese People's Liberation Army General Hospital with a 5-day history of high fever, sore throat, and a dry cough, as well as a 1-day history of shivering and dyspnea. She had been diagnosed with community-acquired pneumonia (CAP) and treated with intravenous azithromycin in a local hospital for the first 4 days. However, her clinical condition deteriorated rapidly. On the fifth day, she developed dyspnea requiring oxygen support, accompanied by shivering and a high fever of 41 °C. A chest computed tomography (CT) scan showed irregular consolidations with interspersed small lucent areas in both lungs (Figure 1).

Her vital signs on admission revealed a temperature of 39.9 °C, heart rate of 102 beats/min, and blood pressure of 140/85 mmHg. Physical examination showed pharyngeal hyperemia and swelling of the tonsils. On chest auscultation, lower respiratory sounds and a few moist rales were heard in the base areas of both lungs. Initial blood investigations revealed a white blood cell count (WBC) of 10.1×10^9/l with 94.7% neutrophils and normal hemoglobin and platelets. Arterial blood gas analysis showed a pH of 7.411, a partial pressure of carbon dioxide ($PaCO_2$) of 32.9 mmHg, and a partial pressure of oxygen, arterial (PaO_2) of 84.4 mmHg at 9 l/min inspired oxygen with a partial rebreathing mask. Serum C-reactive protein (CRP) and procalcitonin (PCT) were both markedly elevated at 14.2 mg/dl and 26.68 ng/ml, respectively. A PCR test performed on a nasal swab was negative for influenza virus. The patient underwent drainage of the pleural cavity and received a preliminary diagnosis of empyema. Pleural fluid examination revealed yellowish purulent features: WBC 2.88×10^9/l with 90% neutrophils, lactate dehydrogenase (LDH) 1302.2 IU/l, total protein (TP) 39.1 g/l, adenosine deaminase (ADA) 33.7 IU/l, glucose 2.4 mmol/l, and chloride 106 mmol/l.

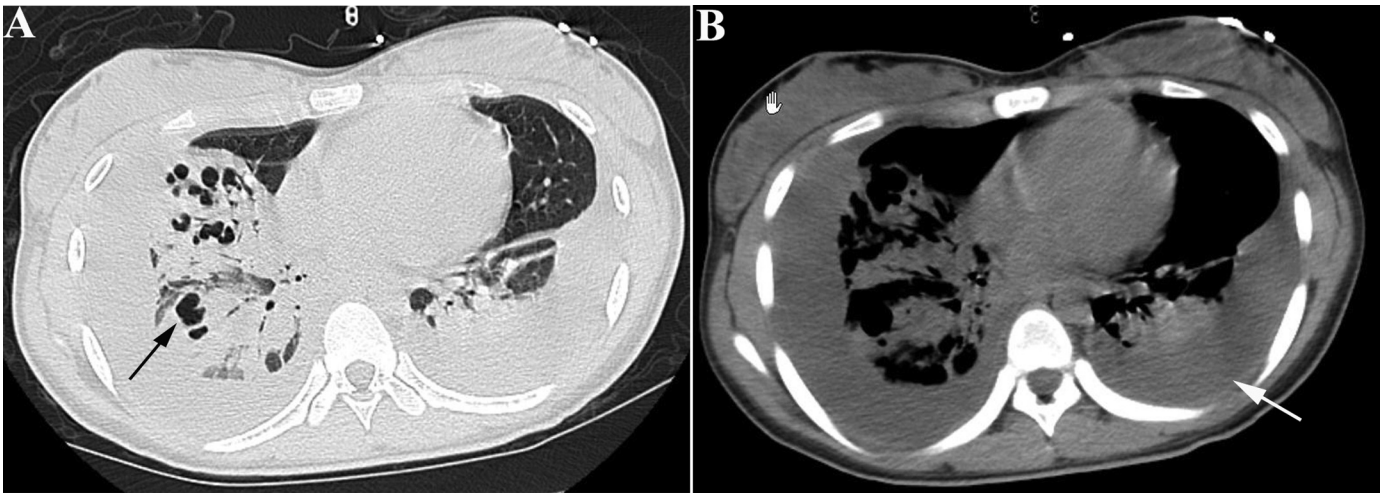

Figure 2. CT images at 8 days after the onset of pneumonia, showing multiple cavitary lesions in both lungs (A, black arrow) and bilateral pleural effusion (B, white arrow).

Since the patient was allergic to β-lactams, empirical therapy with tigecycline was initiated. Three days later, although the serum CRP and PCT had decreased to 8.3 mg/dl and 1.6 ng/ml, respectively, the patient still had a fever of 39.5 °C and a chest CT scan revealed multiple cavitary lesions in both lungs and bilateral pleural effusion (Figure 2). Cultures of sputum and pleural fluid samples obtained on the day of hospital admission yielded *S. aureus*.

3. Methods

Antimicrobial susceptibility testing was performed by broth dilution method and the results interpreted in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines. Characterization of SCC*mec* types and detection of the *luk*F/*luk*S genes encoding PVL were performed as described previously.[9] Typing of Staphylococcus protein A (spa) and multilocus sequence typing (MLST) were performed using established protocols, as described in the web-based electronic databases http://www.ridom.de/doc/Ridom_spa_sequencing.pdf and http://saureus.mlst.net/misc/info.asp.

4. Results

Both of the isolates were resistant to oxacillin (minimal inhibitory concentration (MIC) ≥4 mg/l), clindamycin (MIC ≥256 mg/l), and erythromycin (MIC ≥256 mg/l), but susceptible to vancomycin, teicoplanin, linezolid, tigecycline, tetracycline, fosfomycin, levofloxacin, gentamicin, rifampin, and trimethoprim–sulfamethoxazole (TMP–SMX). On the basis of culture results, antimicrobial therapy was changed to intravenous linezolid (600 mg, every 12 h) and fosfomycin (4 g, every 8 h). Other supporting therapy was also given to the patient. Twenty days after the treatment with linezolid and fosfomycin, the patient showed a significant improvement, although she still had an intermittent fever of 37.5–38 °C. Her CRP decreased to 2.6 mg/dl, PCT became negative, and leukocyte count was normal. Antimicrobial therapy with teicoplanin and fosfomycin was continued for 6 more weeks until her temperature and CRP became normal. At follow-up 3 months post-discharge, the patient remained in good health and a CT scan revealed only cord shadow in the lower part of both lungs. Both of the isolates tested positive for the *mec*A gene as well as PVL genes, and were identified as ST59-MRSA-SCC*mec* type IV-spa type t437, which is one of the predominant CA-MRSA clones in Asian countries.[9,10]

5. Discussion

MRSA was first identified among hospitalized patients in 1960[11] and remained a purely nosocomial pathogen causing serious infections only in individuals with healthcare-associated risk factors until the late 1980s.[6,11] During the 1990s, however, novel MRSA strains, termed community-acquired MRSA or community-associated MRSA, began to be reported in community settings, affecting healthy people without recognized risk factors for MRSA acquisition.[4,6,10] In 2000, the US Centers for Disease Control and Prevention (CDC) proposed an epidemiological definition of CA-MRSA that was based on the timing of the first MRSA isolate relative to hospital admission and the lack of recognized risk factors for MRSA acquisition.[1,4,12] According to the CDC definition of CA-MRSA, MRSA must be identified in the outpatient setting or at less than 48 h after hospital admission in an individual with no medical history of MRSA infection or colonization, admission to a healthcare facility, dialysis, surgery, or the insertion of an indwelling device in the past year.[4,12] The epidemiological definition of CA-MRSA has been adopted worldwide and has been useful for differentiating CA-MRSA strains from HA-MRSA strains in the past.[4] However, as the microbiology and epidemiology of CA-MRSA have evolved in recent years, purely epidemiological definitions of CA-MRSA are breaking down.[4,12] Combining epidemiological factors, clinical presentation, the antimicrobial susceptibility pattern, SCC*mec* typing, and genotyping to infer the likely origin of the MRSA may be the best way to define CA-MRSA strains at the current time.[4] In the present study, we combined the clinical features, epidemiology, genotyping, and SCC*mec* typing to define the strains isolated from a Chinese teenager as CA-MRSA.

The presence of CA-MRSA has been reported in many countries and in different populations, but the prevalence of CA-MRSA varies geographically.[8,13] In some countries and areas, such as the USA, Taiwan, Canada, and Australia, cases of CA-MRSA infection have become common.[13] A CDC study estimated that in 2005, there were 94 360 cases of culture-confirmed invasive community-onset MRSA infections in the USA, with an incidence rate of 31.8/100 000 population.[14] However, CA-MRSA remains an uncommon cause of CAP even in the USA. According to a recent investigation involving 12 American university-affiliated emergency departments, the prevalence of MRSA as the identified etiology of CAP was 2.4%, ranging from 0% to 5% by site.[15] In Taiwan, CA-MRSA isolates accounted for 34.8% of community-associated *S. aureus* infections according to the ANSORP (Asian Network for Surveillance of Resistant Pathogens) study.[10] However, in other countries and areas, CA-MRSA infections have been reported only as part of small outbreaks or case series, and it is usually suspected to have been imported from regions where the disease is endemic.[1]

In China, CA-MRSA has not yet become a common pathogen in the community setting.[16] According to surveys on community-associated SSTIs caused by *S. aureus*, the prevalence of CA-MRSA was only 4% among children[17] and 3% among adults.[18] A recent study on invasive MRSA infections among hospitalized patients in Beijing Children's Hospital (age ≤14 years), demonstrated that the incidence of invasive CA-MRSA infections was only 2.43 per 10 000 admissions in 2011.[16] In Mainland China, patients with CA-MRSA pneumonia were first reported in 2010.[9] Among 55 children with CA-MRSA pneumonia collected from eight Chinese hospitals countrywide, only five aged from 4 to 12 months were diagnosed with necrotizing pneumonia caused by PVL-positive CA-MRSA.[9] In 2011, Li et al.[19] reported a case of severe *S. aureus* CAP carrying the PVL genes with a favorable outcome in a Chinese adult, however it did not appear to be an MRSA. To our knowledge, the patient presented here is the first case of necrotizing pneumonia caused by a PVL-positive CA-MRSA among Chinese school children.

According to their genotypic characteristics, more than 20 CA-MRSA clones have been reported worldwide, with five globally predominant CA-MRSA clones: ST1-IV (USA400), ST8-IV (USA300), ST30-IV (South West Pacific clone), ST59 (Taiwan clone), and ST80 (European clone).[1,2,17] ST1-IV (USA400) was the predominant clone of CA-MRSA in North America in the late 1990s,[1,2] and was replaced by USA300 after 2000.[1] In recent years, PVL-negative ST1 strains have mainly circulated in Australia and England.[1,20] ST8-IV (USA300) is the most prevalent CA-MRSA clone in the USA today and has been isolated repeatedly in many countries across five continents.[1] ST30-IV has frequently been isolated all over the world since it was first reported in Australia, New Zealand, and West Samoa.[1,17] In Australia, Asia, South America, Europe, and the Middle East, ST30-IV is currently among the predominant clones of CA-MRSA.[1,17,21] ST80 is the most common clone of CA-MRSA in many Western European countries, and has also occasionally been found in other parts of the world, including Australia, Kuwait, Tunisia, and Malaysia.[1,17] ST59 is the primary CA-MRSA clone in Taiwan and several other Asian countries, and has also been recovered from patients in Australia, Europe, and the USA.[1,10,17]

Both of the CA-MRSA strains isolated from our patient belonged to the ST59-MRSA-SCC*mec* type IV-spa t437 clone. A recent ANSORP study involving eight Asian countries or regions demonstrated ST59-MRSA-SCC*mec* type IV-spa t437 to be the predominant clone in Taiwan, Hong Kong, Vietnam, and Sri Lanka.[10] ST59-MRSA-SCC*mec* type IV-spa t437 has also been verified to be the most prevalent CA-MRSA clone among children with SSTIs or uncomplicated pneumonia in Mainland China.[12,17,22] However, ST59-MRSA-SCC*mec* type IV-spa t437 has never before been reported to cause severe necrotizing pneumonia in Mainland China. Among five Chinese children with necrotizing CA-MRSA pneumonia reported in 2010, there were three clones responsible for the CA-MRSA infections, including ST910-MRSA-SCC*mec* type IV-spa t318, ST398-MRSA-SCC*mec* type V-spa t034, and ST1409-MRSA-SCCmec type IV-spa t653.[12]

In comparison with HA-MRSA strains, CA-MRSA strains are typically susceptible to most non-β-lactam antimicrobial agents in many countries. However, increasing non-β-lactam resistance among CA-MRSA strains has been reported repeatedly in recent years.[22] Some studies have shown the resistance rates of CA-MRSA isolates to non-β-lactam agents to vary between countries and clones.[1,23] In the USA, USA300 strains are usually resistant to erythromycin, while USA400 strains are often resistant to both erythromycin and clindamycin.[23,24] In Europe, ST80-IV strains are typically resistant to tetracycline and fusidic acid.[23,25] In Australia, the three predominant CA-MRSA clones, including ST30-MRSA-IV, ST93-MRSA-IV, and ST1-MRSA-IV, are often uniformly susceptible to almost all non-β-lactams.[20,23] In Asia, ST30-MRSA-SCC*mec* type IV-spa type019 strains and ST72-MRSA-SCC*mec* type IV-spa type t324 strains are often susceptible to non-β-lactams, but ST59-MRSA-SCC*mec* type IV-spa type t437 strains have shown multiple resistance to several non-β-lactam agents, including erythromycin, clindamycin, tetracycline, and gentamicin.[12,22,23]

Although severe necrotizing pneumonia caused by CA-MRSA is still rare in Mainland China, invasive CA-MRSA infections have increased significantly in recent years.[16] Clinicians should be aware that CA-MRSA can lead to lethal pneumonia even in previously healthy people. Necrotizing pneumonia is one of the most severe manifestations of CA-MRSA infection and has a rapidly progressive and fatal course.[8,26] Early recognition of this life-threatening infection and appropriate antimicrobial treatment are crucial for improving the prognosis.[26,27] It is well established that CA-MRSA should be suspected as the cause of pneumonia if the following specific features are present: an influenza-like prodrome; severe respiratory symptoms with a rapidly progressive pneumonia evolving to acute respiratory distress syndrome; fever >38–39 °C; hemoptysis; hypotension; leukopenia; chest radiograph showing multi-lobular infiltrates, which may have cavitated; known colonization with CA-MRSA or recent travel to an endemic area, such as North America, and recent contact with CA-MRSA; belonging to a group associated with increased rates of colonization with CA-MRSA; previous history or family history of recurrent furuncles or skin abscesses.[28] Appropriate cultures of blood, sputum, and pleural fluid specimens are essential for prompt diagnosis and should be performed prior to the initiation of empirical antimicrobial therapy.[29] Although CA-MRSA isolates are often susceptible to many non-β-lactam agents in vitro, the Infectious Diseases Society of America (IDSA) recommends vancomycin, linezolid, or clindamycin as first-line drugs for the treatment of CA-MRSA and HA-MRSA pneumonia.[30] However, since high resistance rates to clindamycin in CA-MRSA strains have been reported repeatedly in China,[12,16,17] clindamycin should not be used alone in the treatment of CA-MRSA pneumonia in China unless a CA-MRSA strain susceptible to clindamycin has been isolated from the patient.

To our knowledge, this is the first report from Mainland China of necrotizing pneumonia due to PVL-positive CA-MRSA among those aged older than 1 year. Since invasive CA-MRSA infections have increased significantly in China in recent years, CA-MRSA necrotizing pneumonia should be considered in the differential diagnosis of severe CAP, particularly in previously healthy individuals.

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Ethical approval: The case was studied and is presented here with the official permission of the individual.

Conflict of interest: We have no competing interests to declare.

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