

# Severe community-acquired pneumonia due to methicillin resistant *Staphylococcus aureus*, carrying SCCmecIV and PVL genes

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**Key words:**

- Community-acquired pneumonia
- MRSA
- PVL
- Necrotizing pneumonia

**SUMMARY.** The case is presented of a young woman suffering from necrotizing pneumonia caused by community acquired methicillin resistant *Staphylococcus aureus* (CA-MRSA), carrying the Staphylococcal Chromosome Cassette mecIV (SCCmecIV) and Panton-Valentine-Leukocidin (PVL) gene (ST80 clone). She developed acute respiratory distress syndrome (ARDS) and remained under mechanical ventilatory support for 49 days. Finally, she improved and was discharged from the ICU on the 55th day and from the hospital on the 84<sup>th</sup> day.

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## CASE REPORT

A 44 year-old female was admitted to the Pulmonary Medicine Department of the local hospital on a Greek island complaining of high fever (40°C), chills, dry cough, blood-stained sputum, tachypnoea (35 breaths/min), and tachycardia (heart rate 110/min). These symptoms had started three days earlier at home and the patient had not received antibiotics. She had suffered from a “flu-like” syndrome a few days prior to the onset of these symptoms. She was not a smoker and she had never travelled outside Greece. She did not consume alcohol or drugs. She was apparently immunocompetent.

The patient’s condition deteriorated despite the empirical administration of antimicrobial treatment (ceftriaxone 1 g 12 hourly i.v., azithromycin 500 mg/day, i.v.) at the local hospital, and four days later she was transferred to a tertiary hospital in Athens, where because of her severe condition she was admitted to the intensive care unit (ICU). On ICU admission the patient had a fever of 39.0 °C, sinus rhythm with heart rate 120/min, and tachypnoea (32 breaths/min). She was breathing spontaneously with exogenous administration of oxygen by means of a re-breathing mask. Arterial blood gas testing showed PaO<sub>2</sub>/FiO<sub>2</sub> 170, arterial pH 7.44, and PaCO<sub>2</sub> 28 mm Hg. The patient was haemodynamically stable (arterial pressure 160/75 mm Hg) with a central venous pressure of 6 mmHg, and urine output was approximately 100 ml/h. Physical examination revealed crackles over the bases of both

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lungs. Routine laboratory testing showed white blood cell count 20,400/mm<sup>3</sup>, neutrophils 92%, C-reactive protein (CRP) 39 mg/dl, Hb 10.8, Hct 33%, platelets 434,000/mm<sup>3</sup>, erythrocyte sedimentation rate (ESR) 96 mm/1<sup>st</sup> hour, and normal serum levels of creatinine, urea, transaminases, and bilirubin. Procalcitonin was above 2 ng/ml. Gram stain and cultures of bronchial secretions were negative. Two specimens for blood culture taken from different peripheral veins were also negative. Urine antigens for *Legionella pneumophila* and *Streptococcus pneumoniae* were also negative. Serum antibodies for *Chlamydia pneumoniae*, *Mycoplasma*, *Cytomegalovirus (CMV)*, *Epstein-Barr*, *Rickettsiae*, and *Coxiella burnetii* were negative. No serum *Influenzae* antibodies were detected.

Chest X-rays on admission to the ICU showed infiltrates in both lungs (Figure 1). Based on all these findings the diagnosis of community-acquired pneumonia (CAP) was made. Based on the Pneumonia Severity of Illness Scoring System the patient was rated at risk class IV (99 points), fulfilling the criteria for severe CAP. Intravenous antimicrobial treatment with ceftriaxone (1 g 12 hourly), moxifloxacin (400 mg daily) and linezolid (600 mg 12 hourly) was started on the first day in the ICU. The next day, the patient developed bronchospasm, and the arterial hypoxaemia deteriorated, and for this reason she was intubated. She remained febrile (38.5 °C) with significant arterial hypoxaemia (PaO<sub>2</sub>/FiO<sub>2</sub>=170). Bronchoscopy revealed blood stained secretions, but Gram stain and culture of specimens from bronchoalveolar lavage (BAL) fluid were negative. Because of a pneumothorax in the left hemithorax a chest drainage tube was inserted. A chest CT scan revealed extensive infiltrates and abscesses

(pneumatocoeles) in both lungs (Figure 2). The diagnosis of CAP due to *Staphylococcus* was the most possible diagnosis and for this reason rifampicin (900 mg/day) was added. Pleural fluid analysis showed a white cell count of 2,440/mm<sup>3</sup>, neutrophils 85%, protein 3.2 g%, LDH 1004 u/l, and glucose 70 mg/dl. The culture of the pleural fluid grew methicillin-resistant *Staphylococcus aureus* (MRSA). Analysis of this pathogen revealed that this MRSA strain carried the Panton-Valentine-Leukocidin (PVL) genes *lukF* and *lukS*, and specifically the type Staphylococcal Chromosome Cassette *meclIV* (SCC*meclIV*). The CA-MRSA strain isolated from the patient was susceptible to linezolid, vancomycin, clindamycin, rifampicin, and trimethoprim-sulfamethoxazole. A combination of three antistaphylococcal antibiotics (linezolid, clindamycin, and rifampicin) and intravenous immunoglobulins (IVIg) were prescribed, based on the current bibliography.<sup>1</sup>

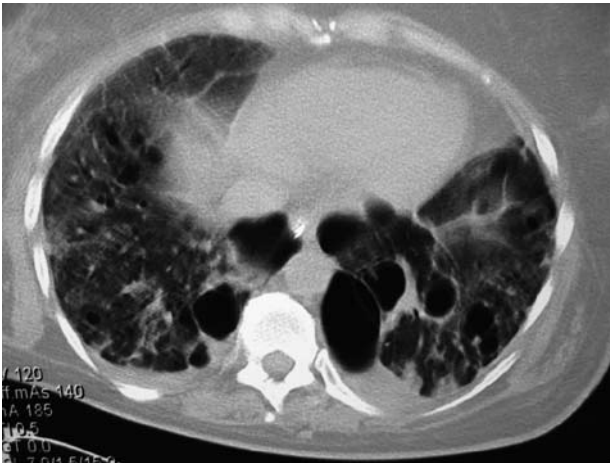
Despite the continuous i.v. administration of antibiotics the patient remained febrile for the following days, while she remained under mechanical ventilatory support. On ICU day 7, she developed bilateral pneumothorax and acute respiratory distress syndrome (ARDS), and suffered from severe recurrent episodes of bronchoconstriction, although she had no previous history of bronchial asthma or chronic bronchitis. On ICU day 10, all cultures (i.e., blood: 8, bronchial secretions: 6, urine: 1) were negative. On ICU day 11 the patient underwent percutaneous tracheostomy. On ICU day 15, all cultures (blood, bronchial secretions, and urine) were negative. On ICU days 23 and 31, repeated CT scan revealed many abscesses, cavities (pneumatocoeles) and recurrent pneumothorax in both lungs (Figure 3). Even after 40 days in the ICU her CT scan



FIGURE 1.

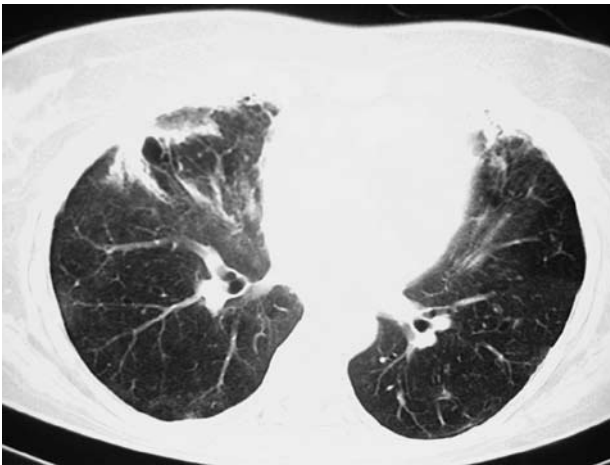


FIGURE 2.



**FIGURE 3.**

showed cavities in the lung parenchyma, evidence of lung necrosis. The patient was mechanically ventilated for 49 days. Finally, her condition improved and she was discharged from the ICU on the 55<sup>th</sup> day. She was discharged from the hospital on the 84<sup>th</sup> day, free of respiratory symptoms, and with normal chest X-ray and blood gases. Figure 4 shows the patient's lung CT scan few days before hospital discharge.



**FIGURE 4.**

## DISCUSSION

This is a case-report of a young healthy married woman with no soft tissue or skin infection who presented with necrotizing pneumonia caused by community-acquired CA-MRSA carrying the SCCmecIV and the PVL gene.

To our knowledge this is the second case of CA-MRSA pneumonia to be published in Greece, and the first case from the western part of the country (specifically the Eptanisa islands).

The genetic investigation of the CA-MRSA by Pulse Field Gel Electrophoresis (PFGE) showed the presence of the sequence type (ST) clone ST80. The PVL positive strains of *Staphylococcus aureus* have been associated with rapidly progressive haemorrhagic necrotizing pneumonia in young immunocompetent patients.<sup>1,2</sup> The binding of PVL toxin to neutrophils induces the release of chemotactic factors, and IL-8 and leukotriene B4 among other inflammatory mediators. The combination of neutrophilic chemotaxis and release of inflammatory mediators promotes tissue necrosis and abscess formation.<sup>3</sup>

Most patients have a history of a preceding "flu-like" syndrome.<sup>4</sup> The association between influenza and severe staphylococcal pneumonia is well recognized. The constellation of findings which strongly suggests the diagnosis of CA-MRSA pneumonia are dyspnoea, productive cough, haemoptysis, acute respiratory failure and hypotension, associated with multilobar infiltrates accompanied with cavitation on the chest X-ray, leucopenia, a very high CRP and Gram-positive cocci on a Gram stained sputum specimen. Non specific findings of a "flu-like" illness (fever of >39 °C, and tachycardia) may be present. The mortality rate of necrotizing pneumonia is approximately 75%.<sup>1,4</sup>

MRSA is one of the most common pathogens causing pneumonia in the ICU situation.<sup>6</sup> It accounts for more than 40%-50% of nosocomial staphylococcal infections (hospital-acquired MRSA; HA-MRSA). However, during the past decade the prevalence of MRSA in the community has increased and it is now a significant community pathogen too.<sup>7,8</sup> CA-MRSA generally causes skin and soft tissue lesions (abscesses and cellulitis), and rarely necrotizing pneumonia, in fit young patients with no risk factors, such as immunosuppression, chronic illness, and previous hospital admission.<sup>1,9,10</sup> CA-MRSA tends to be more virulent than HA-MRSA. CA-MRSA grows faster than HA-MRSA in vitro and through this rapid growth it achieves successful colonization and infection.<sup>11</sup>

The CA-MRSA strains causing necrotizing pneumonia are characterized by the presence of SCCmecIV element and PVL genes.<sup>1,2,12,13</sup> Almost exclusively, SCCmecIV clones carry the PVL genes.<sup>13</sup> SCCmecV clones have also been reported to carry these genes.<sup>14</sup> The small size of SCCmecIV (20-25 kb) increases its mobility and the propensity for transfer to diverse *Staphylococcus aureus* genetic backgrounds. SCCmec carries the mecA gene

which encodes a peptidoglycan transpeptidase, the penicillin binding protein (PBP2a) which has a low affinity to  $\beta$ -lactams.<sup>15,16</sup> In this way, *mecA* genes allow MRSA to grow and divide in the presence of methicillin and other  $\beta$ -lactam antibiotics.

PVL genes code the production of toxin that causes cell death by producing pores (punch holes) in the cellular membranes of leucocytes.<sup>15-17</sup> This is a bicomponent cytotoxin which is encoded by two genes; *lukS-PV* and *lukF-PV*.<sup>15,16</sup> SCCmecA I, II, III are found only in HA-MRSA which rarely carry the PVL genes.<sup>16,18</sup> PVL genes are associated with CA-MRSA carrying the SCCmecIV in a variety of genetic backgrounds.<sup>19-21</sup> SCCmecIV is associated with at least 11 STs.<sup>19,20</sup> PVL is a potent inflammatory mediator linked to bacterial spread in tissues and necrotizing infections.<sup>22</sup> Postmortem histopathological examination of the lungs shows extensive necrotic ulcerations of the tracheal and bronchial mucosa and massive haemorrhagic necrosis of interalveolar septa. Less than 5% of *Staphylococcus aureus* strains produce the PVL cytotoxin.<sup>23</sup>

The PVL genes are rarely found in HA-MRSA infections and to a lesser extent among methicillin-susceptible *Staphylococcus aureus* (MSSA) infections.<sup>2,10,24</sup> CA-MRSA SCCmecIV PVL (+) spread easily between persons in close contact and may cause community outbreaks of MRSA infections (primarily skin infections and severe pneumonia) in distinct populations and different countries (e.g., USA, Europe). For this reason, clinicians must learn to identify risk factors for CA-MRSA and facilitate prevention strategies to limit its transmission. It is well known that the Southern European countries have the highest rate of MRSA among the EU members.

In Greece, in a surveillance was conducted during the years 1999-2004, the proportion of *Staphylococcus aureus* that was resistant to methicillin was 45%.<sup>25</sup> The number of MRSA isolates reported per year ranged from 192 to 609 isolates.<sup>25</sup> These data mainly originate from university hospitals (30%) and general hospitals (57%), and the geographic distribution of the survey covered the whole country, with with the participation mainly of ICUs and Internal Medicine departments.<sup>25</sup> Data from the years 2001-2003 showed a significant increase in PVL strains of *Staphylococcus aureus*, most of which were MRSA.<sup>26</sup> Of the CA-MRSA, 72% carried the PVL genes but only 5% of the HA-MRSA were PVL positive, all of which concerned skin and soft tissue infections.<sup>26</sup> The proportion of MRSA found in ICU patients during the years 1999-2005 in Greece was approximately 60%.<sup>25</sup>

Anecdotal data identify the first CA-MRSA pneumonia case in 2004, in a young athlete with necrotizing pneumonia. The patient was admitted to the ICU of an Athens general hospital where he was treated for a few weeks and discharged a couple of months later. CA-MRSA SCCmecIV PVL positive was the clone isolated from this patient. In 2005, 20 new CA-MRSA strains were isolated in an Athens paediatric hospital. All isolates were from skin and soft tissue infections. PFGE revealed ST80, which has been isolated in many other European countries is considered to be the predominant CA-MRSA clone. These data suggest that, as in other areas in the world CA-MRSA seems to be a new emerging infection in Greece also.

In conclusion, the incidence of CA-MRSA pneumonia is still rare. However, if the prevalence of this pathogen continues to increase MRSA will soon become an important consideration in the differential diagnosis of severe CAP. In such a case, the current recommendations for empirical antimicrobial therapy may be inadequate. CA-MRSA strains are resistant to all  $\beta$ -lactams; agents with appropriate activity against CA-MRSA strains should therefore be considered early. A high level of suspicion, rapid institution of multiple antistaphylococcal antibiotics and in-vitro susceptibility testing constitute the cornerstone of treatment.

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