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*Casi clinici*

*Case reports*

# Necrotizing pneumonia caused by Panton-Valentine leukocidin-producing methicillin-susceptible *Staphylococcus aureus* (MSSA)

## *Polmonite necrotizzante causata da* Staphylococcus aureus *meticillino sensibile produttore di leucocidina di Panton-Valentine (MSSA)*

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## INTRODUCTION

*Staphylococcus aureus* is a major cause of respiratory, skin, bone, joint, and endovascular infections. These infections mostly occur in people with known risk factors such as cardiovascular disease, malignancy or diabetes mellitus. *S. aureus* is responsible for at least 10% of cases of nosocomial pneumonia but only for 2% of community-acquired pneumonia [1].
*Staphylococcus aureus* has a variety of different virulence factors. Among these, there are haemolysins and leukocidins. It has the capacity to produce a wide array of virulence factors, which are responsible for several clinical syndromes [2]. A minority of *S. aureus* strains carry the Panton-Valentine leukocidin. Its genes, lukS-PV and lukF-PV, are encoded on prophages and can be found in diverse genetic strains of *S. aureus*.
Panton-Valentine leukocidin (PVL) is a pore-forming cytotoxin *inducing* leukocyte lysis [3]. It has been associated with diverse clinical syndromes, including primary and secondary skin infections, abscesses and deep sites of infections such as necrotizing pneumonia. Necrotizing pneumonia due to PVL-positive *S. aureus* is usually severe and often fatal, it involves primarily young and healthy patients, and carries a mortality rate up to 75% despite intensive medical treatment. It was first described in 1932 by Panton and Valentine and is therefore known as Panton-Valentine leukocidin, or PVL. In recent years the incidence of PVL-positive *S. aureus* infections seems to be increasing with elevated morbidity and mortality. However, PVL is common not only in methicillin-resistant *S. aureus* (MRSA) but also in methicillin-susceptible *S. aureus* (MSSA) [4].

## CASE PRESENTATION

In April 2010 a previously healthy, 49-year old man, weighing 75 kg, without any predisposing factors, was admitted to our hospital in an ordinary ward. He used to travel frequently from Italy to the North of France. During his last trip he referred flu-like symptoms associated with bilateral hip pain, unresponsive to NSAIDs. These symptoms were associated with dyspnea, fever (39°C) and weakness associated with worsening bilateral hip pain. He denied being an illicit drug user.
Physical examination revealed tachypnea, diffusive tenderness of the abdomen, severe pain

to the hip and groin. No pathological signs were found during chest and heart examination. For these reasons several blood samples for microbiological cultures were collected. Laboratory data revealed only a mildly elevated leukocyte count of $11.9\times10^3/\mu L$ (normal range 4-10 x $10^3/\mu L$), a rise in D-Dymer levels, inflammatory markers including VES >20 mm/h (normal range 1-15 mm/h), C-reactive protein 12 mg/dl (normal range <0.8 mg/dl), creatinine of 1.27 mg/dl (normal range 1 mg/dl). Tests for Type B, Type C hepatitis and HIV were negative. Community-acquired pneumonia was diagnosed and an association of piperacillin/tazobactam 4.5 g i.v. every 8 hours and levofloxacin 500 mg/die i.v. was administered in the medical ward. A chest X-ray was performed (Figure 1), while a CT scan of the chest showed diffuse bilateral alveolar infiltrates (Figure 2). A few hours later the patient required oxygen administration for his dyspnea and elevated levels of blood I-Type Troponin required a cardiologic consult. On the day after his admission a trans-thoracic echocardiography showed no abnormal findings, in particular absence of valvular vegetations and regurgitation suggestive of infective endocarditis. He became critically ill, white blood cells increased: 16 x $10^3/\mu L$ (normal range 4-10x$10^3/\mu L$) and was transferred, initially, to the Coronary Care Unit (CCU). Blood cultures were positive for MSSA. The patient still suffered from high fever and severe dyspnea. The empiric antibiotic therapy with levofloxacin and piperacillin/tazobactam was stopped and changed to rifampicin 600 mg

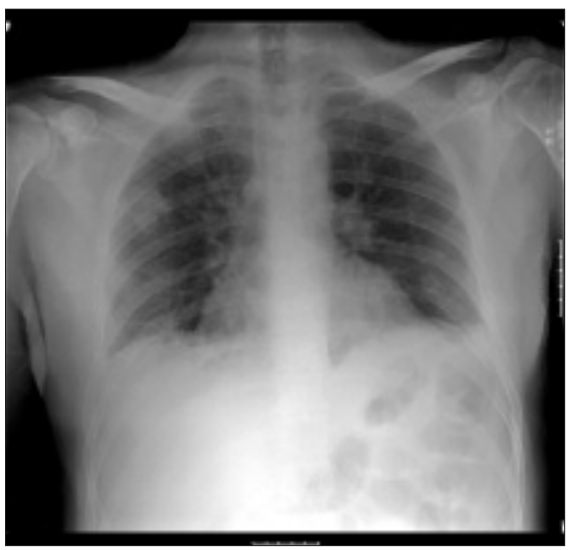


**Figure 1 -** Chest X-Ray at the admission.

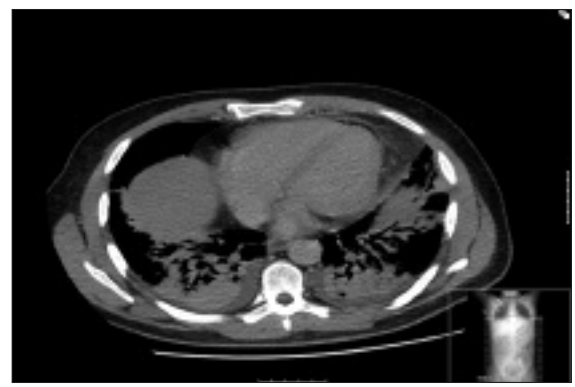
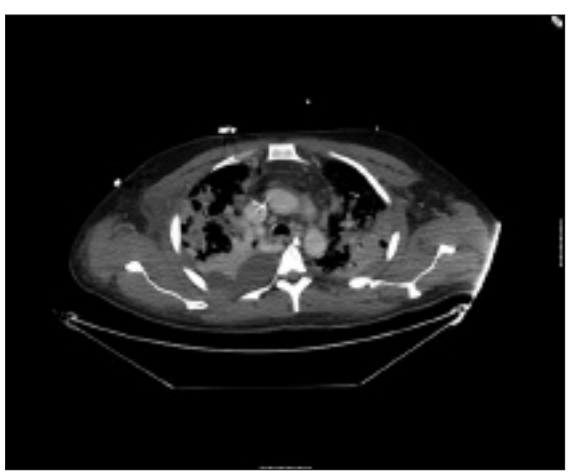


**Figure 2 -** Chest CT scan at the admission: diffuse bilateral alveolar infiltrates.



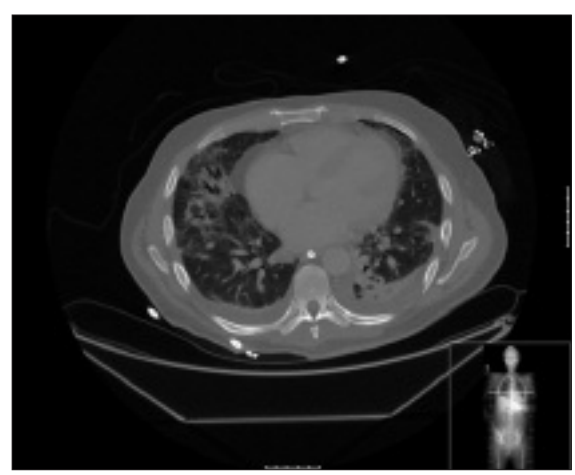


**Figure 3 -** Chest CT scans during ICU stay: extensive bilateral pleural effusions diffuse bilateral alveolar infiltrates and nodular opacities with cavity forming consistent with necrotizing pneumonia.

every 12 hours and oxacillin 12 g die, as recommended by the ID consultant. Within the first 24 hours after CCU admission, severe sepsis with coagulopathy was diagnosed [5]. Because of a respiratory distress syndrome with $PaO_2/FiO_2$ ratio <150, CPIS >7 and Lung Injury Score (LIS) >3, the patient was admitted to the Intensive Care Unit (ICU) and mechanically ventilated [6, 7]. Three days after, a CT scan of the chest revealed newly emerged extensive bilateral pleural effusions with diffuse bilateral alveolar infiltrates and nodular opacities with cavitations, a picture suggesting a necrotizing pneumonia (Figure 3). An immediate exploratory drainage of the chest was performed and the fluid confirmed the presence of MSSA. Surgical exploratory inspection and drainage of the right hip was performed after a computed tomography scan which revealed an abscess around his right hip; during the operation 200 ml of a purulent collection was drained. It was confirmed to be MSSA. However, our patient's condition worsened and a new chest X-ray was suggestive of severe acute respiratory distress syndrome (ARDS) with a $PaO_2/FiO_2$ ratio <100. Antibiotic therapy with oxacillin was stopped and changed to meropenem 1 g every 6 hours and rifampicin 600 mg every 12 hours. As he required inotropes, we started a systematic prone positioning to reduce hypercapnia and improve the effects of mechanical ventilation.

**Table 1 -** Antimicrobical susceptibility test result of MSSA producing PVL gene leukocidin.

| *Drug* | *MIC (µg/mL)* | *Interpretation* |
|---|---|---|
| Ampicillin | <1 | S |
| Amoxicillin/clavulanic acid | <1 | S |
| Cefazolin | <2 | S |
| Ciprofloaxacin | <2 | S |
| Clindamycin | <0.5 | S |
| Erithromycin | <0.5 | S |
| Gentamicin | <2 | S |
| Imipenem/Meropenem | <0.5 | S |
| Levofloxacin | <1 | S |
| Oxacillin | <0.5 | S |
| Penicillin | >1 | R |
| Piperacillin/tazobactam | <0.5 | S |
| Rifampin | <0.5 | S |
| Teicoplanin | <0.5 | S |
| Trimethoprim/ sulfamethoxazole | <0.5/9.5 | S |
| Vancomycin | <1 | S |
| S = Susceptible; R = Resistant | | |

Microbiological and molecular analysis of bacterial isolates from blood and pus yielded growth of *S. aureus* identified by Gram stain, catalase and coagulase reactions. MSSA was susceptible to rifampicin and meropenem (Table 1). On day 9, suspecting a PVL toxin-secreting strain, polymerase chain reaction (PCR) amplification of the lukS-lukF genes was performed and confirmed the presence of the PVL gene in all the available *S. aureus* strains. The isolates from blood specimens were further analysed using spa typing: Locus agr type IV, spa type 159, Clonal Complex (CC) 121. Antibiotic therapy was switched to linezolid 600 mg every 12 hours, clindamycin 600 mg every 6 hours and daptomycin 12 mg/kg/die. We also started intravenous immunoglobulin infusions for six days, 600 mg/kg/day [8]. The condition of the patient progressively improved: he rapidly became afebrile and arterial blood gases, inflammatory markers, VES and C-reactive protein, returned into their normal range. The total duration of linezolid, clindamycin and daptomycin treatment was respectively 25, 25 and 12 days, while rifampicin treatment was stopped after 7 days. The patient was successfully weaned after 35 days of mechanical ventilation and transferred to the medical ward on day 41. Subsequently he prolonged his hospital stay 3 weeks later until his discharge. The follow-up examination after one year showed no residual respiratory symptoms.

## DISCUSSION

This case offers the opportunity of an unusual severe clinical presentation: the patient was a young immunocompetent man with no apparent risk factors who sustained severe community-onset necrotizing pneumonia and extensive pleural effusions. The finding of lung necrosis was consistent with the production of PVL, confirmed by PCR.

Staphylococcal infection positive to Panton-Valentine leukocidin typically causes life-threatening infection of bone and soft-tissues; this infection may also lead to necrotizing pneumonia. During the last ten years there has been an increase in the incidence of an associated devastating pneumonia affecting healthy young people with a very high mortality rate. The literature contains less than 100 cases, with widely differing antimicrobial therapies with the occasional use of other adjunctive therapies, such as intravenous immunoglobulin, activated protein C and extracorporeal membrane oxygenation [9].

Panton-Valentine leukocidin is a synergohymenotropic toxin assembled from a two-component protein, a cytotoxin produced by 5% of the *S. aureus* strains; PVL has been associated with primary skin infections and severe necrotizing pneumonia, may lyse white blood cells and cause extensive tissue necrosis and chronic, recurrent or severe infection. The clinical role of this toxin, the possible impact on its virulence and the possible synergistic effects are not yet understood [10]. PVL has a potent virulence factor, especially regarding skin and/or soft tissue infections and pneumonia [11].

The true incidence of PVL-associated pneumonia is unknown, since the number of cases published is likely to be underestimated: the risk of superadded infection by PVL-producing *S. aureus* strains may be increased by the flu [12]. Indeed, the incidence of documented *S. aureus* coinfection increased 5-fold in the United States during the 2004-2007 influenza seasons compared to the incidence in inter-epidemic periods (13). Kallen et al. identified 51 cases of community-acquired *Staphylococcus aureus* pneumonia in 19 American states during the 2006-2007 flu season, of which 79% involved methicillin-resistant strains and 51% were fatal (14). In a study by Hageman et al., PVL genes were detected in 85% of community-acquired *S. aureus* strains causing pneumonia during the 2003-2004 flu season [15]. Besides its occurrence in methicillin-susceptible *Staphylococcus aureus* (MSSA), PVL is more often identified in community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) [16].

Gillet et al. compared the clinical features of PVL-positive pneumonia with PVL-negative pneumonia and found significant differences: PVL-positive patients were younger without risk factors for infection. They presented more often haemoptysis, high fever, tachycardia, tachypnea and developed diffuse bilateral infiltrates and pleural effusion. Mortality was significantly higher in PVL-positive compared to PVL-negative infections [17]. As described by Lina et al., an association with furuncolosis and community-acquired pneumonia correlate with PVL toxins producers MSSA [18]. Sequences, such as "quorum sensing" system, linked to the "agr" gene expression, seemed to regulate the exaggerate toxin production by *Staphylococcus aureus* [19, 20]. There are no evidence-based guidelines to consult for the management of PVL-associated staphylococcal pneumonia [9].

In the case report described here we observed a clear relationship between different antibiotic regimens and clinical conditions of the patient: the ß-lactams were associated with worsening of respiratory function and pulmonary infiltrates, whereas the resolution of pneumonia was achieved only after starting the toxin-suppressing agents: clindamycin, linezolid and daptomycin [21]. Daptomycin may be considered in case of metastatic soft tissue infections. Primarily it should not be used for treatment of pneumonia because of the inactivation by pulmonary surfactant; moreover rapid administration of antitoxinic therapy with clindamycin, linezolid and immunoglobulin (IVIg) may improve the outcome of PVL-associated staphylococcal necrotizing pneumonia, even when aggravating factors are present.

The main reasons that explain why ß-lactams may fail in infections associated with toxin-producing organisms are that these cell wall-active agents, in contrast to protein-synthesis inhibitors, do not suppress toxin-production, and that the lysis of the bacteria increases the release of intracellular toxins [22, 23]. These data suggest that treating the infections due to the extra-cellular toxins, produced by MRSA and MSSA, linezolid, clindamycin and daptomycin demonstrate a clear advantage over ß-lactams and vancomycin. Moreover, linezolid has an excellent lung tissue penetration, which is approximately six times higher than that of vancomycin [24].

## CONCLUSION

Less than 5% of all *S. aureus strains* harbour PVL genes. In our opinion, it is crucial that PVL-positive staphylococcal infections should be included early on in differential diagnosis when a young immunocompetent patient develops

necrotizing pneumonia, which may rapidly become lethal. PVL is overexpressed in the presence of β-lactams, but its expression can be blocked by combining a toxin-suppressing agent, such as clindamycin, linezolid, or rifampicin, with bactericidal antibiotics acting on the cell wall. In addition, intravenous immunoglobulin (IVIg) blocks the lytic effect of PVL on polymorph nuclear cells in vitro [8]. Early appropriate antibiotic treatment is considered essential to ensure a favourable outcome.

Various minor infections can precede this life-threatening syndrome, such as septic shock; flu-like prodrome and skin and soft tissue infections increase mortality [25]. In the Clinical Practice Guidelines an antibiotic treatment with bactericidal antistaphylococcal agents is recommended, and invasive surgical procedures may become necessary. However, the protein synthesis inhibitors (e.g., clindamycin and linezolid) and IVIg are not routinely recommended, but only in adjunctive therapy for the management of MRSA and MSSA diseases. Some experts, however, may consider these agents in selected scenarios (e.g., necrotizing pneumonia or severe sepsis) [26].

The outcome of patients with necrotizing pneumonia may be poor in most cases even if appropriate antibiotics are administered. In addition, intensive supportive care has a key role for improving the outcome in these severe infections. Susceptibility tests, moreover, need to be performed urgently in order to assess the efficiency of the therapy and to rule out PVL-MRSA and MSSA.

*Keywords*: Panton-Valentine leukocidin, pneumonia, *Staphylococcus aureus.*

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## SUMMARY

*Staphylococcus aureus* harboured by Panton-Valentine leukocidin (PVL) is emerging as a serious problem worldwide. There has been an increase in the incidence of necrotizing lung infections in otherwise healthy young people with very high mortality rate associated with these strains. This report documents a confirmed case of necrotizing pneumonia due to methicillin-susceptible *S. aureus* (MSSA) harbouring Panton-Valentine leukocidin genes. An apparently healthy 49-year old man was admitted to our hospital for dyspnea and he quickly developed acute respiratory distress syndrome. MSSA harbouring Panton-Valentine leukocidin genes were cultured from the abscess fluid and from multiple blood specimens. Aggressive antibiotic therapy was started and intensive supportive care led finally to a complete recovery. Rapid identification of Panton-Valentine leukocidin in MSSA samples should be supposed when a young, immunocompetent patient, develops a necrotizing pneumonia. Bactericidal antistaphylococcal antibiotics are recommended for the treatment as soon as possible to avoid the potentially devastating consequences of this kind of *S. aureus.*

## RIASSUNTO

*L'infezione da* Staphylococcus aureus *produttore di leucocidina di Panton-Valentine è un'emergenza mondiale. Epidemiologicamente si è registrata una tendenza all'incremento di infezioni polmonari necrotizzanti da tossina di Panton-Valentine in pazienti giovani. Questo caso tratta di un paziente di 49 anni con una documentata infezione da* S. aureus *meticillino-sensibile produttore di leucocidina di Panton-Valentine il cui riconoscimento ha permesso di instaurare una terapia antibiotica mirata che, associata al trattamento intensivo e allo sbrigliamento e drenaggio chirurgico della lesione muscolo-cutaneo iniziale, ha portato al buon esito clinico. Una rapida identificazione del germe, soprattutto in pazienti giovani e senza fattori di rischio, permette una impostazione terapeutica antimicrobica tanto efficace quanto precoce in modo da evitare le devastanti conseguenze dell'infezione stessa, la cui mortalità è dell'ordine del 75%.*

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