Community-Acquired Necrotizing Pneumonia due to Panton-Valentine Leukocidin-Producing Methicillin-Sensitive *Staphylococcus aureus*

Pneumonia Necrotizante Adquirida na Comunidade por *Staphylococcus aureus* Produtor de Leucocidina de Panton-Valentine

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Abstract:

The Panton-Valentine leukocidin (PVL), produced by *Staphylococcus aureus* (SA) strains, is a potent virulence factor associated with severe invasive disease. One of the most serious clinical presentations, necrotizing pneumonia, affects disproportionally more young healthy individuals than other causes of necrotizing pneumonia. However, PVL presence is not routinely tested, and strong clinical suspicion should guide clinicians, since appropriate antimicrobial therapy, with the association of agents capable of PVL production inhibition, is crucial. The authors hereby present a case report of a young, previously healthy adult male, admitted to an Intensive Care Unit due to acute hypoxemic respiratory failure. The patient evolved with a severe necrotizing pneumonia due to methicillin-susceptible *Staphylococcus aureus* (MSSA) and *Klebsiella pneumoniae* requiring two beta-lactam antibiotic therapy and invasive mechanical ventilation. Persistent clinical deterioration led to the clinical suspicion of an underlying PVL-producing SA strain. The patient evolved favourably with the association of linezolid and laboratory testing subsequently confirmed PVL-producing MSSA.

Keywords: Bacterial Toxins; Leukocidins; Methicillin-Resistant Staphylococcus aureus; Pneumonia, Necrotizing; Staphylococcal Infections.

Resumo:

A leucocidina de Panton-Valentine (PVL), produzida por algumas estirpes de *Staphylococcus aureus* (SA), é um potente fator de virulência associado a formas graves de doença invasiva. Uma das apresentações clínicas mais graves, a pneumonia necrotizante, afeta indivíduos jovens, previamente saudáveis, de forma desproporcionalmente mais frequente que outras causas de pneumonia necrotizante

No entanto, a presença de PVL não é pesquisada de forma rotineira, e a forte suspeita clínica deve alertar para a necessidade da sua pesquisa, uma vez que a terapêutica antimicrobiana adequada, incluindo a associação de agentes capazes de inibir a produção de PVL, é essencial.

Os autores apresentam o caso clínico de um jovem adulto, previamente saudável, admitido em Unidade de Cuidados Intensivos (UCI) por insuficiência respiratória aguda hipoxémica. O doente evoluiu com pneumonia necrotizante grave com isolamento de *Staphylococcus aureus* sensível à meticilina (MSSA) e *Klebsiella pneumoniae*, motivando terapêutica antibiótica com dois beta-lactâmicos e ventilação mecânica invasiva.

A persistência de deterioração clínica motivou a suspeição de uma estirpe de SA produtora de PVL. Após a introdução de linezolida, a evolução foi favorável e os exames laboratoriais confirmaram, posteriormente, a presença de Staphylococcus aureus sensível à meticilina, produtor de PVL.

Palavras-chave: Infecções Estafilocócicas; Leucocidinas; Pneumonia Necrotizante; Staphylococcus aureus Resistente à Meticilina; Toxinas Bacterianas.

Learning Points

1. PVL presence is not systematically analysed, and therefore, the current prevalence of PVL-producing SA strains and incidence of PVL pneumonia is probably underestimated.
2. Clinicians should have an adequate understanding of underlying risk factors for PVL MSSA and the knowledge that PVL toxin is detected by PCR/molecular methods, often on specific request.
3. PVL production can be stimulated by beta-lactam antibiotics if these do not attain the respective MIC in targeted tissues.
4. The association of antimicrobial agents capable of toxin production inhibition, such as clindamycin or linezolid, can prevent PVL production stimulation.
5. In the absence of timely PVL toxin identification, clinical suspicion of PVL-SA (pneumonia with shock or signs of toxaemia, difficult to treat SA infection, difficult to treat necrotising pneumonia or history of SA skin infections) should motivate adequate antimicrobial therapy implementation.

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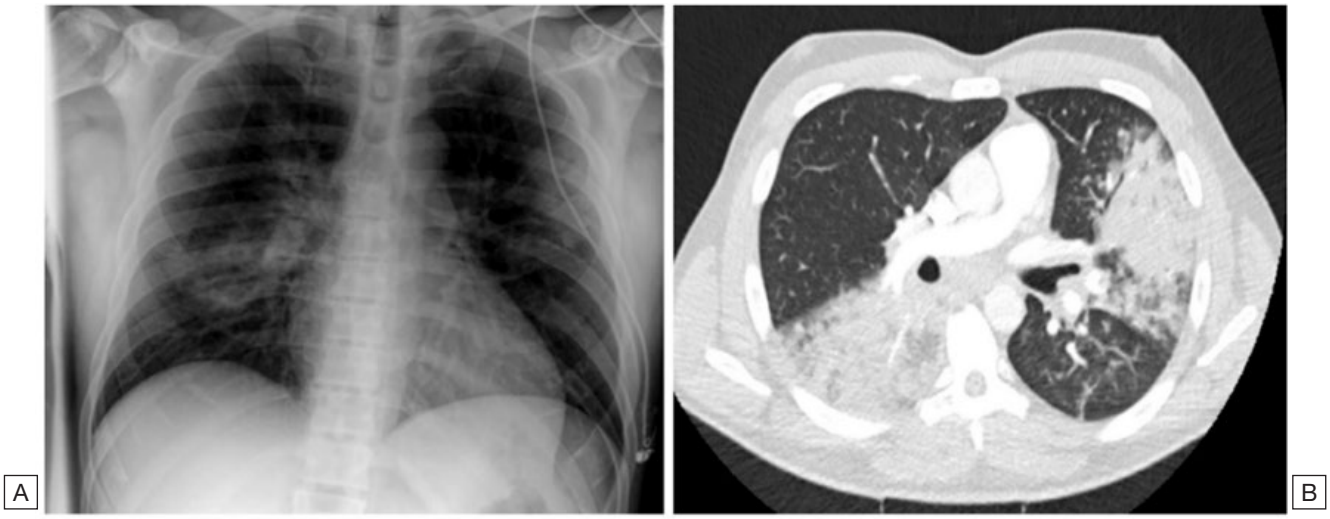

Figure 1: Admission imaging tests: **[A]** - Chest radiograph; **[B]** – Chest computed tomography.

Introduction

In recent decades, there has been an increase in severe infections associated with Panton-Valentine leukocidin (PVL)-producing *Staphylococcus aureus* (SA) strains.[1,2] However, PVL is not routinely tested in microbiology laboratories. Consequently, this leukocidin is largely underreported. One of the most serious clinical presentations of PVL-producing SA infections is necrotizing pneumonia in previously healthy children and young adults associated with high mortality.[3-5] We present a case report of PVL-methicillin-sensitive *Staphylococcus aureus* (MSSA) necrotizing pneumonia requiring intensive care unit (ICU) admission in a young and immunocompetent adult patient with no underlying risk factors.

Case Report

A 46-year-old male patient presented to the emergency department with a dry cough, fatigue, fever, pleuritic chest pain, and blood-tinged sputum. His medical history included allergic rhinitis and frequent physical activity. Recent travel and contact with family members from abroad was excluded. There were no recent symptoms suggesting viral infection.

On examination, the patient had a fever (38.6°C), polypnea at rest, and normotensive values. No signs of skin infection were observed. Arterial blood gas analysis revealed mild hypoxemia and normal lactate levels. Laboratory tests showed a white blood cell count of 8.2x10^3/µL, C-reactive protein of 1.83 mg/dL, procalcitonin of 0.18 ng/mL, and normal renal and hepatic function. Urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1 were negative. Initial sputum microbiology was performed, and radiologic findings were not suggestive of acid-fast bacilli (note that tuberculosis in Portugal should be considered). PCR testing detected human metapneumovirus and excluded SARS-CoV-2. HIV testing was negative.

Chest radiograph (CXR) on admission (Fig. 1-A) showed heterogeneous opacity in the right hilar region. A presumptive diagnosis of community-acquired pneumonia (CAP) was made, and antimicrobial therapy (AMT) was initiated with amoxicillin/clavulanic acid (1.2g q8h) and clarithromycin (500 mg q12h).

The patient's condition rapidly worsened, leading to respiratory failure. Chest computed tomography (CT) revealed bilateral micronodular and centrilobular alveolar consolidation with reactive mediastinal adenopathies (Fig. 1-B).

He was admitted to the ICU, started on high-flow nasal cannula (HFNC), but progressed to severe acute respiratory distress syndrome requiring invasive mechanical ventilation, neuromuscular blockade, and prone positioning. No additional organ dysfunctions were observed. Methicillin-resistant SA screening was negative.

Due to MSSA isolation from the admission sputum sample, flucloxacillin (12 g/day) was initiated, and clarithromycin was discontinued. Radiological deterioration on CXR (Fig. 2-A) prompted a new chest CT on day 5, showing extensive consolidations with bilateral air bronchogram and fluid-filled cavitations (Fig. 2-B), consistent with bilateral necrotizing pneumonia.

AMT was escalated to piperacillin-tazobactam and linezolid. *Klebsiella pneumoniae* was isolated from bronchoalveolar lavage (BAL) collected on the day of intubation, leading to a switch from linezolid to amoxicillin/clavulanic acid based on antimicrobial susceptibility testing. Despite this, clinical improvement was not observed.

On day 9, chest CT (Fig. 3) showed extensive necrosis and abscesses.

A new BAL on day 9 yielded MSSA, prompting the addition of linezolid to ongoing AMT. Genetic sequencing for the PVL gene and phenotyping of *K. pneumoniae* were requested, but further testing was not possible.

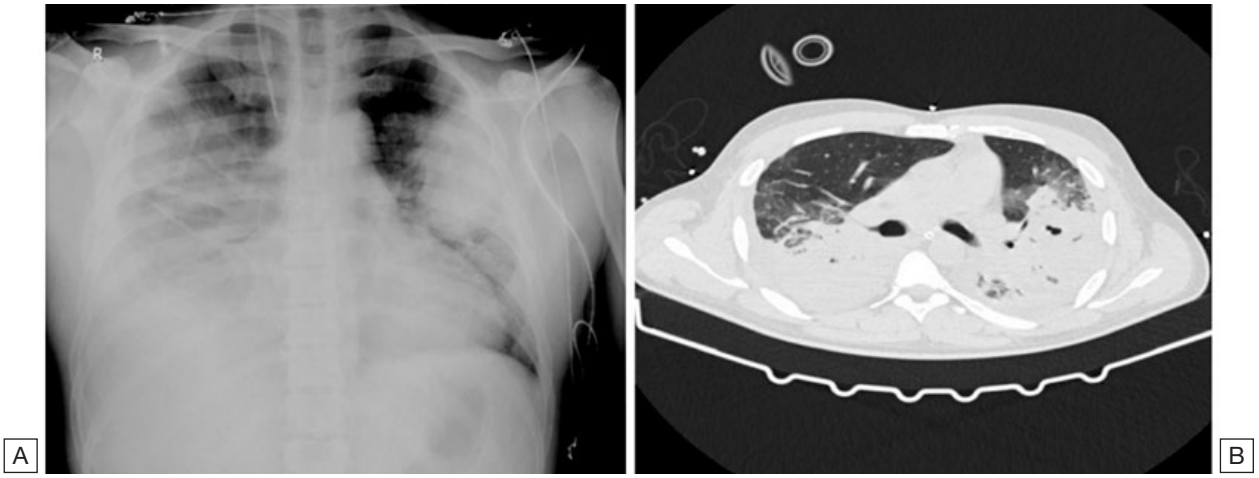

Figure 2: Chest imaging on the 5th day of admission. **[A]** - Chest radiograph; **[B]** – Chest CT.

Following the reintroduction of linezolid, the patient showed favourable progress with resolution of fever, improvement in respiratory failure, and normalization of inflammatory biomarkers (Fig. 4). Blood cultures remained negative throughout the ICU stay.

SA isolates were characterized for the PVL gene and protein A sequence (spa typing), revealing the presence of the PVL gene and spa type t355, associated with ST152 strains.

The patient was extubated on day 15 and transferred to the Pulmonology ward on day 17. Chest CT on day 20 showed significant improvement, and he was discharged home on day 34.

Since hospital discharge, the patient has been observed in a follow-up outpatient clinic. Almost complete resolution of chest CT findings has been documented, and he has recently completed his one-year post-ICU follow-up. Although he has resumed professional and sports activities with no exertional dyspnoea, he manifests complaints of psychological distress. Collaboration with the Psychology department has been prioritized.

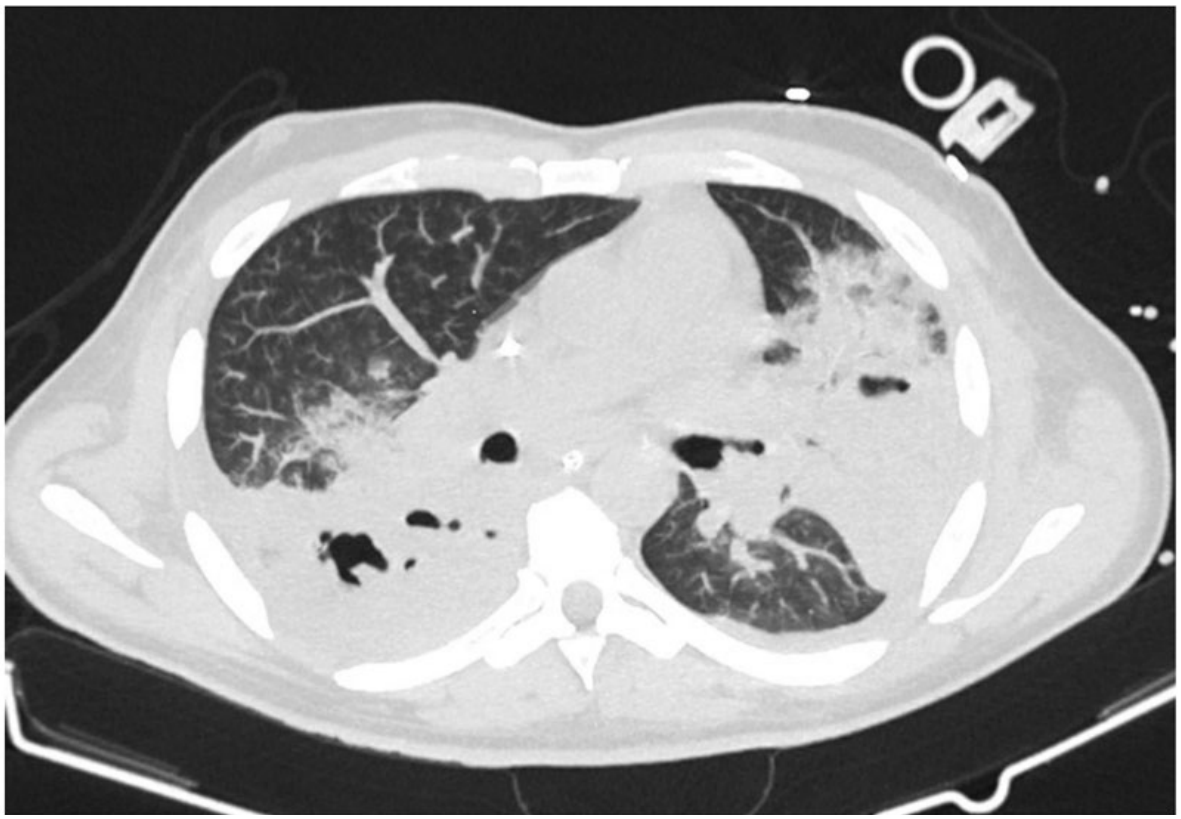

Figure 3: Chest CT on the 9th day.

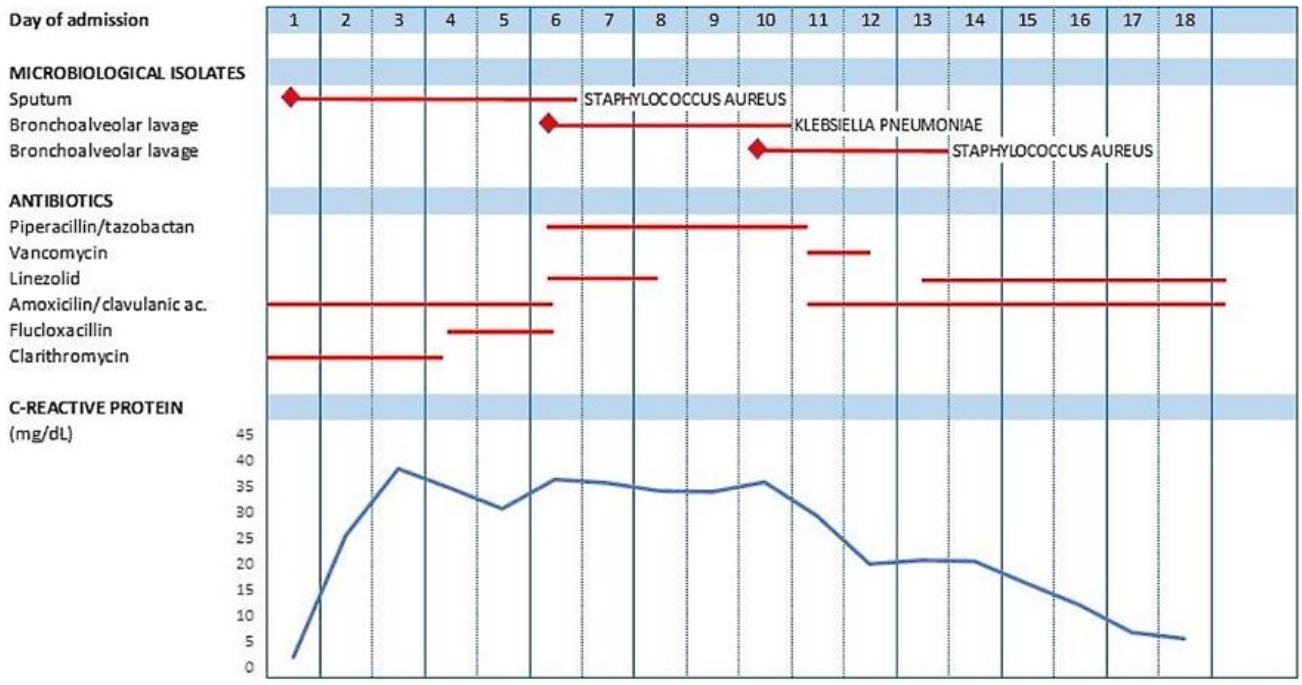

Figure 4: Graphic representation of microbiological isolates and C-reactive protein with simultaneous display of antimicrobial strategies throughout ICU admission.

Discussion

This case describes a young, immunocompetent adult with no known risk factors for MDR pathogens who developed severe necrotising pneumonia secondary to a PVL-producing MSSA, requiring ICU admission. There was no relevant travel history or known contact with endemic regions.

PVL is a cytotoxin produced by some SA strains, implicated in recurrent skin and soft tissue infections. Rarely, fulminant necrotising pneumonia, especially in healthy individuals, can occur.[3,4,6-9]

It was initially discovered by Van deVelde in 1895 due to its ability to lyse leukocytes and it was named in 1932 after the work of Sir Philip Noel Panton and Francis Valentine.[10]

It is a 2-component pore-forming leukocidin,[11] with very potent cytotoxic effect on human neutrophils,[12] coded by bacteriophage genes *lukS* and *lukF* (which could explain its association with recent viral infections, especially influenza).

Although more prevalent in community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA), PVL is also present in MSSA strains.[3,13,14]

There is controversy regarding the impact of the PVL genes on disease severity and clinical outcome in CAP and ventilator-associated pneumonia, with clinical studies showing conflicting results.[1,7,15-17]

The isolate in this case belonged to sequence type ST152, one of the clones previously identified in Portugal,[18] predominantly in skin and soft tissue infections. In this case report, it caused rapidly progressive pulmonary disease.

Notably, co-infection with *Klebsiella pneumoniae* complicated early management, prompting dual beta-lactam therapy (flucloxacillin and amoxicillin/clavulanic acid), which may have worsened the clinical course.[10]

The patient deteriorated under beta-lactam treatment, with clinical improvement only after initiating linezolid (600 mg IV 12-hourly). This supports the role of protein synthesis inhibitors in suppressing PVL production. Clindamycin and linezolid are preferred due to their ability to inhibit exotoxin synthesis and excellent tissue penetration, particularly of pulmonary compartments.[19] Vancomycin lacks this inhibitory effect on toxin production.[20] Rifampicin was not used because of its high potential to promote bacterial resistance.

Beta-lactams may increase PVL production[21] and act on the cell wall leading to bacterial lysis, resulting in the release of intracellular toxins.[22]

UK recommendations[23] suggest empirical use of clindamycin, linezolid, and rifampicin in suspected PVL-associated pneumonia. Though evidence remains limited, adjunctive intravenous immunoglobulin may be considered in severe cases.[24] In this case, given the absence of shock or other evidence of toxaemia, immunoglobulin was not used.

Given the rarity of PVL-SA in Europe, routine testing is often overlooked. However, its presence should be considered in severe necrotising pneumonia, particularly among young patients without comorbidities. Prompt recognition is essential to guide appropriate AMT. Travel history, recent viral illness (e.g., influenza), or recurrent skin infections may suggest PVL-SA involvement.

This case emphasizes the potential severity of PVL-MSSA pneumonia, even in healthy individuals, and highlights the need for clinician awareness, appropriate diagnostic investigation, and early targeted therapy. ■

Contributorship Statement

VM, PM and PP – Conceptualization, design, writing, and editing of the manuscript.

All authors approved the final version to be published.

Declaração de Contribuição

VM, PM e PP – Conceção, design, redação e edição do manuscrito.

Todos os autores aprovaram a versão final a ser publicada.

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Patient Perspective

I was admitted to the intensive care unit (ICU) on the same day that I arrived at the hospital. I felt unwell during the night with reddish expectoration and lack of energy. I went to the hospital, where my health seemed to deteriorate while under observation in the emergency room.

Realizing that my illness could be serious, I became increasingly anxious. I did not expect to be there so abruptly, let alone to be hospitalized directly in the ICU.

The entry into the ICU was very scary, involving painful procedures. As my entry into the ICU was presented as a precaution, I became more anxious as the days passed with the realization that my condition was always worsening.

Fortunately, my wife visited me regularly and was the light of my day. As soon as she left, there was only emptiness and a huge silence. I began to have a lot of difficulty sleeping, as my dreams invariably involved chases by bizarre and frightening characters. I had a lot of pain and difficulty breathing, despite all the medication and medical equipment.

At a certain point, I thought I was already in another country receiving treatment. I don't know if this happened in my "sleep" during induced coma or before. Truly traumatic was the communication, by the medical team, that I would be intubated and induced into a coma. I was devastated, and I know I pleaded not to do it because I feared for my life. I recall being informed by the medical team of the absolute necessity of that procedure, without remembering exactly what was said. I also know that I spoke with my wife and that, finally, I "accepted".

Fortunately, I woke up on a sunny day, under the gaze of my older brother. It seemed like I had had a rejuvenating sleep, and everything had happened in a matter of minutes or hours, but it hadn't. I was in this induced coma state for 9 days, and the worst was feared.

I was transferred a few days after waking up to the pneumology ward. The experience of passing through the ICU due to severe bilateral bacterial pneumonia was traumatic because it was very intense and in a very short period.

I think psychological support during and after this type of illness should be a priority.