

Clinical Feature: Community-acquired Pneumonia Caused by Panton-Valentine Leukocidin-positive *Staphylococcus aureus*

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Introduction

Panton-Valentine leukocidin (PVL), first verified in 1932, is one type of exotoxin secreted by *Staphylococcus aureus* (SA). A significant feature of this toxin is that it has two components, LukS-PV (33 kDa) and LukF-PV (34 kDa), which express high specificity to leukocyte for cytolytic activity. They assemble on the surface of polymorphonuclear leukocytes (PMNs) and macrophages to create pores in the membranes of target cells. A high concentration of secreted PVL into cells leads to cytolysis and activates inflammatory cytokines and reactive oxygen species, which cause tissue necrosis, whereas a low concentration activates the cytochrome caspase-activated PMN apoptosis pathway (**Figure 1**) [1]. Two opinions regarding SA virulence factors conflict with one another. In a study on a sepsis and abscess mouse model infected with methicillin-resistant SA (MRSA) either carrying or not carrying PVL strains, Voyich et al. concluded in 2006 that PVL was not the major virulence factor [2]. On the other hand, Labandeira-Ray and colleagues elucidated that PVL is a SA virulence factor of necrotizing pneumonia, which enhanced inflammation in the lung parenchyma and bronchial epithelium in cooperation with Staphylococcal protein A. They also claimed that the expression of PVL induced cell wall-anchored and secreted proteins' genes at the transcriptional level [3]. In addition, Diep et al. showed that PVL directly affected the peripheral lung tissue in a rabbit model, in which PMN sensitivity is more similar to that of humans than the rodent model [4]. Although the pathogenicity of PVL in humans has not yet been demonstrated, PVL is regarded as a predictive virulence manifestation in pulmonary infections.

Epidemiology

The strain of SA encoding PVL is believed to have begun spreading in the 1950s as a skin and soft tissue infection (SSTI) and propagated all over the world while mutating. In the late 1990s, an accumulation of fatal cases of PVL-MRSA, especially invasive pneumonia in healthy young adults and children [5], contributed to a perceived danger of related diseases as a public health concern. After this event, the dangers of MRSA, which is transmitted not only in the hospital but also in the community, received recognition again. Detection of a PVL-positive SA strain related generally less to cases of hospital-acquired pneumonia

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(HAP) than cases of community-acquired pneumonia (CAP), especially in primary infection.

Since more cases of PVL-SA pneumonia than expected were seen in the 2012/13 influenza season, Public Health England (PHE) enhanced their investigation of PVL-SA. During this period, 54 patients were identified, 18 of whom died within 21 days. This surveillance showed that about 70% (20/29) of patient's flu tests were positive for the toxin. PHE had to encourage clinicians to be aware of potential influenza co-infection in cases of severe pneumonia caused by PVL-SA [6].

MSSA and MRSA

PVL-SA-related diseases have spread all over the world. The proportion of SA strains carrying PVL genes is about 2%, including

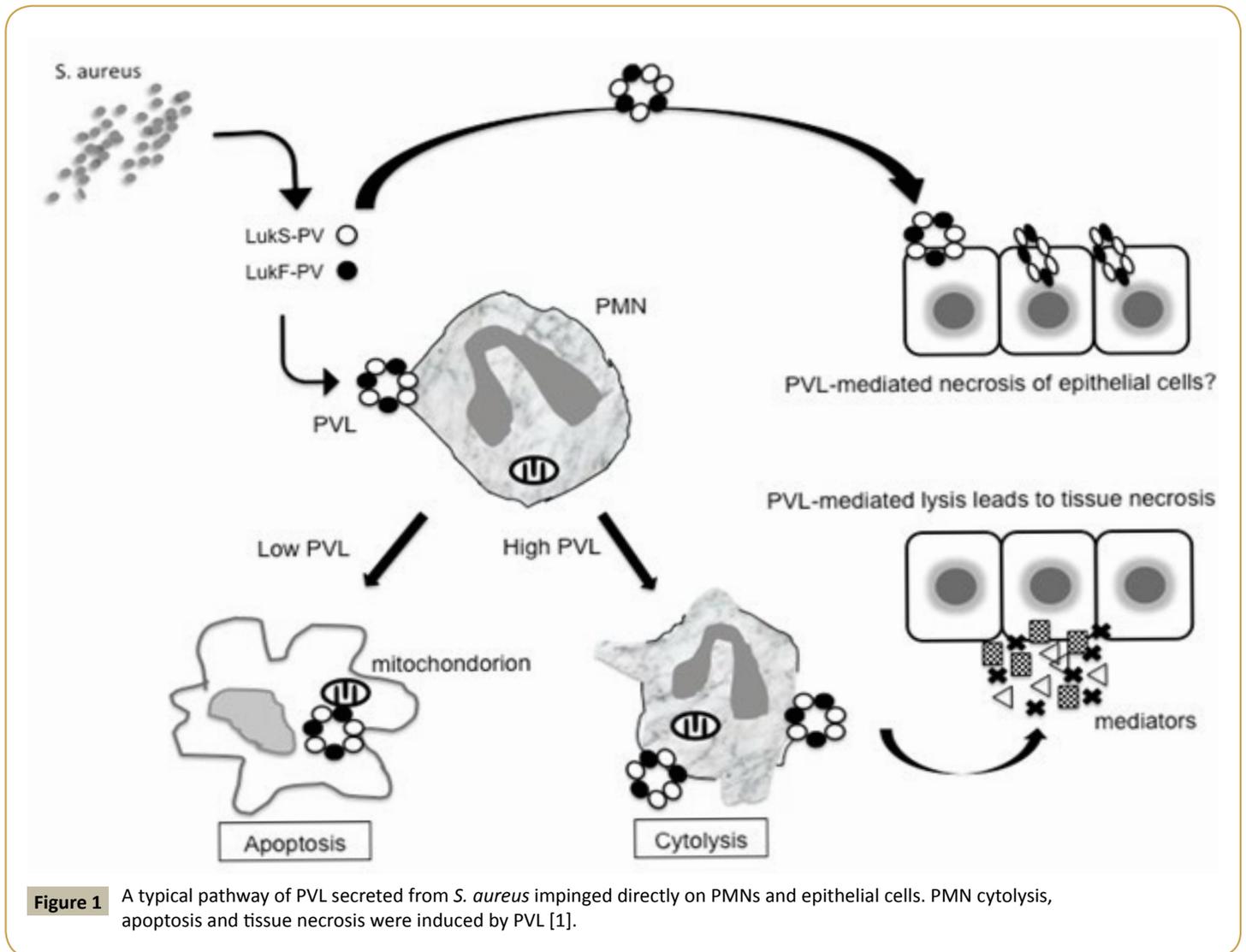


Figure 1 A typical pathway of PVL secreted from *S. aureus* impinged directly on PMNs and epithelial cells. PMN cytolysis, apoptosis and tissue necrosis were induced by PVL [1].

both MRSA and methicillin-sensitive SA (MSSA) [7]. About 60% of PVL-SA-related diseases are caused by MSSA and about 40% are caused by MRSA [8].

SA builds tolerance by acquiring staphylococcal cassette chromosome *mec* (*SCCmec*), which has the *mecA* gene for methicillin. MRSA, a major pathogen of nosocomial infection, occupied over 60% of SA isolated from inpatients in the 1990s; nevertheless, the percentage of MRSA isolation has been declining in recent years according to infectious disease control measures. MRSA is generally classified into two types: community-acquired MRSA (CA-MRSA) and hospital-acquired MRSA (HA-MRSA). The characteristics of HA-MRSA are that *SCCmec* type II is the major type, drug resistance against β -lactam agents, clindamycin, quinolone, and aminoglycoside have already progressed, many kinds of exotoxins are secreted, and the majority of bacilli carriers are elderly people. Patients with HA-MRSA are quarantined 48 hours after admission. Risk factors for HA-MRSA infection are as follows: 1. hospitalization or surgery; 2. long-term stay in some institutions other than the hospital; 3. hemodialysis; and 4. catheter placement and medication history of antibiotics. In cases of CA-MRSA, *SCC* type IV is the main type. Compared to *SCC* type

II, antibiotic sensitivity is still maintained and PVL secretion is a distinctive feature. Healthy young adults and children without established risk factors of severe disease are contaminated easily in their usual living environment. Vardakas et al. reported that the mortality rates of PVL-positive MSSA and MRSA were similar, even though small differences in clinical features, such as airway hemorrhage, acute respiratory distress syndrome (ARDS) (MSSA>MRSA), and gastrointestinal symptoms (MRSA>MSSA), were recognized [9].

Clinical Symptoms

Invasive diseases, such as septic arthritis, necrotizing fasciitis, necrotizing pneumonia, osteomyelitis, and purpura fulminans, are less common than with SSTIs. Shallcross et al. revealed meager evidence that infection with the PVL-positive strain was associated with negative outcomes (Table 1) [10]. Pneumonia-associated SA, however, has a low morbidity (about 2%) among patients with CAP; also, pneumonia caused by PVL-positive SA is more likely to be rare, so PVL might not be detected. Gillet and colleagues reported that lethality is high because of ARDS caused by lung inflammation, which is induced by the pore-forming toxin

Table 1 Outcome studies.

Location	Dates	Study Setting	Inclusion criteria	Cases (n)	Rate of MRSA	Age	Clinical outcome	Virulence of PVL	Art.
France	1986-98	76 hospitals	PVL-SA pneumonia patient defined by symptoms of respiratory tract.	16	6.3% (1/16)	14.8	The PVL-positive patient's survival rate 48h after admission: 63% (94% for PVL-negative patients)	Yes	[11]
France	1986-2005	39 hospitals	PVL-SA pneumonia patient defined by symptoms of respiratory tract.	50	12% (6/50)	14.5	Mortality rate of PVL-SA: 56%. Median survival time: 10 days. Airway bleeding and leukopenia related to mortality	Uncertain	[12]
Singapore	2004	Single hospital	SA specimens from adults	30	47% (14/30)	33	Mortality rate of PVL-SA infection: 5.3% (1/19)	No	[19]
Thailand	2006-07	Single hospital	Pneumonia patients defined	11	NA	NA	Mortality rate of PVL-SA pneumonia: 80% (4/5). PVL did not affect outcome.	No	[20]
China	2006-08	8 hospitals	Children diagnosed CA-MRSA pneumonia	55	100%	10M	1 patient died: 1.8%. No difference in rate of necrotizing pneumonia due to PVL presence	No	[21]
Australia		2 hospitals	CA-SA pneumonia patients	22	45% (10/22)	35	30 days mortality rate of PVL-SA: 40% (2/5)	No	[22]
USA	2001-09	Single hospital	SA-pneumonia children (not VAP)	117	74% (87/117)	10.8M	1 patient with PVL-MRSA died: 0.85%	Uncertain	[23]
USA	2008-10	4 hospitals	MRSA HAP or VAP patients	109	100%	53	PVL-MRSA HAP/VAP mortality rate: 10.3% (3/29)	No	[24]

PVL: Pantone-Valentine Leucocidin; SA: *Staphylococcus aureus*; CA: Community-Acquired; MRSA: Methicillin-Resistant SA; VAP: Ventilator Associated Pneumonia; HAP: Hospital Acquired Pneumonia; NA: Not Available; Art.: Article. This table reorganized reference D10.

reaction to PMNs [11]. Early diagnosis of necrotizing pneumonia might be difficult, but a past history of skin lesions caused by PVL-SA might help the diagnosis. The most important and distinctive clinical sign is bleeding from the respiratory tract and also hypotension, tachycardia (>140 beats/min), and digestive symptoms like nausea, vomiting, and diarrhea. On chest X-ray, multilobar infiltrates, which are apt to develop later cavitation, are often present. In addition, while leukopenia, a high level of serum creatine kinase and C-reactive protein (>200 g/L), and a negative pneumococcus and Legionella antigen test can make invasive disease doubtful, it is simple and useful for physicians to estimate the pathogen by examining sputum Gram stains and verifying grape-like clusters. The characteristic feature of rapid progression to fatal pneumonia is hemoptysis, alveolar hemorrhage, leukopenia, hypoxia, and influenza-like illness, mainly in young adults and healthy children [12].

Treatment

Drainage is the basic treatment for SSTI caused by PVL-SA, taking precedence over antibiotic administration. In cases of severe sepsis or septic shock due to pneumonia, however, it is important for physicians to intervene as soon as possible to detect the causative pathogen while obtaining blood culture and specimen samples. Empirical antimicrobial administration therapy, which is recommended for CAP, should start and antibiotic combination therapy should also be considered if SA infection was suspected due to Gram stain or co-infection with influenza. A targeted therapy using a narrower spectrum agent (de-escalation) after finding the infected organism is usually recommended. In cases of fulminant pneumonia associated with PVL-SA, not only adequate antibiotics, but also clindamycin, linezolid, and rifampicin might

be used in expectation of toxin production, although the dosage and administration course are still unclear. Combinations of vancomycin with clindamycin or rifampicin and linezolid or clindamycin with rifampicin were reported to successfully treat PVL-MRSA pneumonia, but single administration of rifampicin should be avoided, as drug resistance is easily acquired. Furthermore, intravenous immunoglobulin (IVIg) effectiveness still has not been verified, but might be considered for adjuvant therapy, since IVIg is expected to neutralize PVL pore formation and PVL's cytopathic effects [13]. The recommended dosage of IVIg following necrotizing pneumonia as well as the severe condition of staphylococcal toxic shock syndrome is 2 g/kg and repeated at 48 h if treatment failure is suspected. Respiratory management with a mechanical ventilator is surely necessary for fatal pneumonia patients. If adjusting and setting ventilators are difficult to prevent ventilator induced lung injury, barotrauma, and severe hypoxia, physicians need to decide immediately whether extracorporeal membrane oxygenation (ECMO) might be considered [14] and whether or not to transfer the patient to a specialized institute for induction of ECMO. The efficacy of ECMO for ARDS in adult patients has been revealed in recent years. With corresponding high frequency oscillatory ventilation, the lung protective strategy was reported in two large trials to have no significant effect on adult ARDS.

Administration of corticosteroids is recognized to have a positive effect on severe CAP, not only showing a shorter median time to clinical stability [15], but also showing a reduction in the risk of treatment failure [16]. It has been pointed out that an inflammatory cytokine excessively produced by immune cells at the initial response to antigen affected progressing ARDS.

Corticosteroid is expected to suppress inflammatory cytokine production and the excessive inflammatory immune response. Some complications, such as hyperglycemia and bleeding in the gut, have been reported.

Prevention

Risk factors are described as the “5 Cs”: cleanliness (poor hygiene), close contact, crowding, contaminated shared items (e.g., razors, towels), and cuts and other compromised skin integrity. Groups at risk are often the healthy and young and include confined communities with close contact, close contact sports (e.g., judo, rugby, wrestling), prisons, gyms, and military training camps. Outbreaks can easily occur in the community setting; personnel dealing with a PVL-SA related patient in the hospital setting need to pay careful attention to infectious disease control with isolation in a single room using personal protective equipment, proper hand hygiene, and environmental cleaning.

Care managers may carry out important tasks including standard infection control precautions, environment and general cleaning, and laundry facilities, to reduce spread of PVL-SA in care homes or households. Physicians need to consider decolonization of the patient and preventing contact with the patient after the primary infection has resolved and educate patients on how to prevent further transmitted infections. In addition, seeking a specialist’s advice and intervention are important through the whole admission course for the patient to take personal measures to improve clinical conditions and occupational situations [17, 18].

Conclusion

Critical CAP-associated PVL-SA has developed worldwide, especially in healthy young adults and children without any risk factors. All physicians should note the clinical signs and symptoms, should not overlook the dangers, and also should investigate the role of PVL in disease, colonization, and clinical outcomes for public health.

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