Panton-Valentine Leukocidin

Venkata Meka, M.D.

Panton-Valentine leukocidin (PVL) is a synergohymenotropic toxin, i.e., it acts through the synergistic activity of 2 non-associated secretory proteins, component S and component F (6). This toxin activates human neutrophils before creating lytic pores sensitive to monovalent cations, thereby damaging the cellular membrane. Injection of purified PVL induces a release of histamine from human basophilic granulocytes, enzymes (such as β-glucuronidase and lysozyme), chemotactic factors (such as leukotriene B4 and interleukin 8), and oxygen metabolites from human neutrophilic granulocytes (5). In animal studies, injection of purified PVL intradermally in rabbits resulted in severe inflammatory lesions with capillary dilation, chemotaxis, polymorphonuclear (PMN) infiltration, PMN karyorrhexis, and skin necrosis (10).

PVL is encoded by two contiguous and cotranscribed genes, lukS-PV and lukF-PV; and were found in a prophage segment integrated in the S. aureus chromosome (5). Different PVL-positive S. aureus strains have been shown to carry differing phage sequences, and one of the PVL-carrying phages (φSLT) has been shown to infect PVL-negative S. aureus strains, resulting in PVL production (7).

Clinical Significance

PVL production was initially linked to furuncles, cutaneous abscesses, and severe necrotic skin infections (8). Subsequently, a French study found that the PVL genes were present more frequently in S. aureus strains that caused primary skin infections and primary community-acquired pneumonia (versus S. aureus strains that caused secondary infections after skin injury or hospital-acquired pneumonia). The PVL genes were detected in 23 of the 27 S. aureus strains causing primary community-acquired pneumonia in that study, and infection by 14 of these strains lead to death (6). Significant findings on autopsy included bilateral necrotizing hemorrhagic pneumonia, and histology showed necrotic lesions of the tracheal mucosa and alveolar septa with numerous clusters of Gram-positive cocci. The study also found that patients often had a predisposing viral infection, leukopenia (a known effect of PVL as described earlier), blood
cultures positive for *S. aureus*, and a chest x-ray with pneumatoceles or patchy infiltrates over the lungs (6).

Gillet, et al. compared the characteristics of eight cases of community-acquired pneumonia due to PVL-positive *S. aureus* strains and eight prospective cases of PVL-positive *S. aureus* pneumonia to 36 cases of PVL-negative *S. aureus* pneumonia. The PVL-positive patients were younger (median 15 years) when compared to PVL-negative patients (median age 70 years). PVL-positive patients were significantly more likely to have temperature greater than 39°C, tachycardia above 140 beats per minute, hemoptysis, pleural effusion, and leukopenia. Mortality 48 hours after admission was significantly higher for the PVL-positive patients as compared to the PVL-negative patients. Histology from three autopsies of PVL-positive cases showed extensive necrotic ulcerations of the trachea and bronchial mucosa with massive hemorrhagic necrosis of the interalveolar septa (5).

The observation that 75% of patients with PVL-positive necrotizing pneumonia often followed an influenza-like infection was a striking clinical point. Gillet, et al. hypothesized that this was related to the attachment of the staphylococci; an initial viral lung infection could have led to desquamation of ciliated and secretory cells, thereby allowing bacterial adhesion to basal epithelial cells (5).

Recently, PVL-positive *S. aureus* strains and PVL-negative *S. aureus* strains were compared for their binding characteristics to extracellular matrix proteins, primary human airway epithelial cell cultures, and damaged human airway mucosa. Compared with PVL-negative strains, PVL-positive strains had a higher affinity for damaged airway epithelium, especially exposed basement membrane. Also, this finding was found to be due to a stronger affinity for type I and IV collagens and laminin, which was associated with the presence of the *cna* gene (present in 88% PVL-positive strains versus 25% PVL-negative strains) (2). Expression of most *S. aureus* exoproteins (including toxins such as PVL and enzymes) is controlled by the quorum-sensing system, *agr* (accessory gene regulator), which induces their gene expression at high organism density. De Bentzman, et al, hypothesized that in necrotizing pneumonia, the high affinity of PVL-positive *S. aureus* strains for type I and IV collagens and laminin led to a higher number of organisms adhering to damaged airway epithelium, which in turn triggers *agr* activation through the quorum-sensing mechanism and induction of exoprotein production. Among these exoproteins, PVL may contribute to extending tissue damage and affecting leukocyte response (2).
Epidemiology

Given these potentially serious effects, the PVL gene attained added significance with the worldwide emergence of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) infections. These infections are caused by *S. aureus* strains acquired in the community, without the usual risk factors for MRSA acquisition. Baba et al. sequenced the entire genome of a CA-MRSA isolate from North Dakota (designated MW2) and found the presence of a novel smaller variant of the methicillin-resistance locus (designated SCC\textit{mec} IVa) and the locus for PVL (1).

In a survey of 117 CA-MRSA isolates from the United States, France, Switzerland, Australia, New Zealand, and Western Samoa, all CA-MRSA strains carried a type IV SCC\textit{mec} cassette and the PVL locus (9). And, in San Francisco, 70% of MRSA which were isolated from jail inmates or patients requiring surgical treatment at an outpatient clinic specializing in skin and soft-tissue infections carried PVL (3).

Therapy

Given the potential complications associated with the PVL toxin, intravenous immunoglobulin (IVIg) has been considered as an adjunct in the treatment of necrotizing pneumonia. Commercial preparations of IVIg contain antibodies against PVL and these antibodies were shown to neutralize both leukocyte pore formation and the cytopathic effect of recombinant PVL and *S. aureus* culture supernatants. Possible mechanisms for this inhibitory effect of IVIg include antigen-specific antibodies and non-specific blockade of PMN receptors (4). This raises the possibility that the use of IVIg alone or with an antibiotic capable of inhibiting protein synthesis may reduce the expression of PVL and attenuate the potential cytotoxic effects.

REFERENCES


