Case Report

Purpura fulminans in a child secondary to Pantón–Valentine leukocidin-producing *Staphylococcus aureus*Abid Hussain,¹ Gisela Robinson,² Joanne Malkin,¹ Mark Duthie,² Angela Kearns³ and Nelun Perera¹

Correspondence

Nelun Perera

nelun.perera@uhl-tr.nhs.uk

¹Department of Clinical Microbiology, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester LE1 5WW, UK²Department of Child Health, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester LE1 5WW, UK³Staphylococcal Reference Laboratory, Laboratory of Healthcare Associated Infection, Health Protection Agency, Colindale, London NW9 5EQ, UK

Received 2 May 2007

Accepted 6 June 2007

A case of purpura fulminans (PF) in a child secondary to infection with meticillin-sensitive *Staphylococcus aureus* (MSSA) encoding the Pantón–Valentine leukocidin (PVL) toxin genes is presented. Occasional cases of PF have been documented secondary to *S. aureus* infection in adults, but, to the authors' knowledge, not in children. Here the first UK case of MSSA-PVL leading to PF is presented.

Case report

A 10-month-old girl presented to her local emergency department in profound septic shock. She had been unwell for 10 days with a coryzal illness and had been pyrexial for 72 h. Initial blood results were: total white cell count $3.0 \times 10^9 \text{ l}^{-1}$, platelet count $114 \times 10^9 \text{ l}^{-1}$, international normalized ratio 1.7 and fibrinogen $>4.5 \text{ mg l}^{-1}$.

On arrival, she had a capillary refill time of 5 s with a heart rate of $170 \text{ beats min}^{-1}$ and grunting respirations. Examination revealed a widespread, macular erythematous rash, with three punctate petechiae on her shoulder. Suspecting meningococcal septicaemia, she was commenced on intravenous ceftriaxone, fluid resuscitated, intubated and ventilated by 3 h post-presentation.

Despite 100 ml kg^{-1} fluid boluses and maximal inotropic support, she remained acidotic, at which point teicoplanin was added. The rash became bullous, spreading rapidly and affecting the lower limbs (Fig. 1).

In view of the atypical progression of the rash, clindamycin was added. Bacterial cultures of the fluid from the bullae correlated with initial blood cultures, confirming invasive *Staphylococcus aureus* infection, which was resistant to penicillin, but sensitive to flucloxacillin, erythromycin, tetracycline, vancomycin, clindamycin and rifampicin. The isolates were sent to the Staphylococcus Reference Laboratory, Health Protection Agency (HPA), Colindale,

London, for toxin gene profiling and were confirmed as encoding the Pantón–Valentine leukocidin (PVL) genes.

Over the next 48 h she remained critically ill on maximal intensive care support. She developed acute respiratory distress syndrome, multiorgan failure and disseminated intravascular coagulopathy requiring significant blood product support. After an initial ventilatory improvement, she deteriorated on day 8 secondary to a pneumothorax.

She continued to develop multiple pneumothoraces and abscesses requiring bilateral chest drains and she was eventually weaned off respiratory support 5 weeks after the initial presentation. The chest X-rays remained abnormal with bilateral, multiple pneumatoceles which were eventually managed with a surgical pleurectomy.

Blood and endotracheal cultures remained positive for *S. aureus* until day 36. Throughout this time, she was treated with multiple courses of antibiotics including clindamycin, imipenem and rifampicin. Despite multiple debridements and early intervention by the vascular surgeons, she underwent a right forefoot and a left mid-tibial amputation. Investigations for immunodeficiency and protein C deficiency were unremarkable.

Follow-up magnetic resonance imaging scans of the left femur demonstrated extensive osteomyelitis. This required further revision and prolonged treatment with antibiotics. At the present time, the child is clinically well.

Screening of household contacts for *S. aureus* carriage could not be performed because the parents and extended family were not resident in our local area.

Abbreviations: PF, purpura fulminans; PVL, Pantón–Valentine leukocidin.

Fig. 1. Purpura fulminans of the lower limbs.

Discussion

PVL is a phage-encoded, 2-subunit exotoxin. This cytotoxin is formed from two synergistic proteins, LukS-PV and LukF-PV. In combination, an octameric protein is formed which results in pore formation in the cell membrane of leukocytes, allowing an influx of calcium. This effect appears to be concentration-dependent, with apoptosis occurring at low levels and necrosis at higher levels. The toxin is encoded by <5 % of clinical isolates of *S. aureus*, almost half of which are meticillin-resistant (Morgan, 2005).

PVL-*S. aureus* is mainly associated with necrotic suppurative skin lesions, but it has also been isolated from patients with severe community-acquired necrotizing pneumonia with a mortality rate of 75 % (Kravitz *et al.*, 2005).

The incidence of PVL-*S. aureus* infections is difficult to assess accurately. A recent study from the HPA confirmed that 1.6 % of the isolates submitted to the laboratory carried the PVL genes (Holmes *et al.*, 2005). Purpura fulminans (PF) is not a notifiable syndrome in the UK and there is a tendency to assume that PF is synonymous with meningococcal sepsis.

Due to the severity of PF and the growing appreciation that several organisms are associated with this syndrome, initial treatment should include broad-spectrum antibiotics (including adequate cover for meticillin-resistant *S. aureus*) (Morgan, 2005; Kravitz *et al.*, 2005). In dealing with confirmed PVL-*S. aureus* infection, several studies have reported the value of combination therapy (McCartney *et al.*, 2006) including two or more of vancomycin, clindamycin, linezolid, rifampicin or co-trimoxazole (Klein *et al.*, 2003; Wargo & Eiland, 2005).

A recent report suggests that with appropriate treatment protocols the outcome of PF amongst children can be improved (Gürgey *et al.*, 2005). In this recent series, 43 % of the paediatric cases presented with a severe bacterial infection (seven cases), of which 57% (four cases) were secondary to sepsis caused by *S. aureus*. None of the

isolates were tested for PVL. All of these patients survived, albeit with varying degrees of amputation.

There are conflicting thoughts with regard to the use of intravenous immunoglobulin (IVIG) in the treatment of PF due to PVL-*S. aureus*. There are *in vitro* data demonstrating neutralization of the PVL toxin (Gauduchon *et al.*, 2004) but there are no comparative clinical studies. Several authors recommend the use of IVIG for its antitoxin properties (Morgan, 2005; Kravitz *et al.*, 2005) although this mechanism has yet to be firmly established (Chambers, 2005).

This is the first report of PF secondary to PVL-meticillin-sensitive *S. aureus* sepsis in a child in the UK. It illustrates the dramatic evolution of infection caused by PVL. Our aim is to alert clinicians to consider PVL-*S. aureus* in conjunction with meningococcaemia when dealing with a clinical case of PF and respond promptly with appropriate therapeutic strategies, which may be a combination of antimicrobial, immunological and surgical methods. In our view, the initial choice of antimicrobials should be broad and include adequate anti-staphylococcal cover, including cover for meticillin-resistant *S. aureus*. These decisions should be made in conjunction with a microbiologist, pending the identification and susceptibility profiles of isolates. Screening for PVL genes in *S. aureus* isolates should be considered in patients with haemorrhagic necrotizing skin, soft tissue and pulmonary infections to inform clinicians on the appropriate management and prognosis.

Given the evidence of spread of PVL-*S. aureus* via skin-to-skin contact (Morgan, 2005), we suggest that in cases of serious, life-threatening disease, consideration must be given to screening of close contacts.

References

- Chambers, H. F. (2005). Staphylococcal purpura fulminans: a toxin-mediated disease? *Clin Infect Dis* **40**, 948–950.
- Gauduchon, V., Cozon, G. & Vandenesch, F. (2004). Neutralisation of *Staphylococcus aureus* Pantone Valentine leukocidin by intravenous immunoglobulin *in vitro*. *J Infect Dis* **189**, 346–353.
- Gürgey, A., Aytac, S., Kanra, G., Secmeer, G., Ceyhan, M. & Altay, C. (2005). Outcome in children with purpura fulminans: report on 16 patients. *Am J Hematol* **80**, 20–25.
- Holmes, A., Ganner, S., McGuane, S., Pitt, T. L., Cookson, B. D. & Kearns, A. M. (2005). *Staphylococcus aureus* isolates carrying Pantone Valentine leukocidin genes in England and Wales: frequency, characterization, and association with clinical disease. *J Clin Microbiol* **43**, 2384–2390.
- Klein, J. L., Petrovic, Z., Treacher, D. & Edgeworth, J. (2003). Severe community-acquired pneumonia caused by Pantone Valentine leukocidin-positive *Staphylococcus aureus*: first reported case in the United Kingdom. *Intensive Care Med* **29**, 1399.
- Kravitz, G. R., Dries, D. J., Peterson, M. L. & Schlievert, P. M. (2005). Purpura fulminans due to *Staphylococcus aureus*. *Clin Infect Dis* **40**, 941–947.
- McCartney, C., Cookson, B., Dance, D., Day, C., Duerden, B., Elston, T., Kearns, A. & Morgan, M. (2006). *Interim Guidance on Diagnosis and*

Management of PVL-Associated Staphylococcal Infections in the UK. Health Protection Agency PVL Working Group. http://www.dh.gov.uk/AboutUs/MinistersAndDepartmentLeaders/ChiefMedicalOfficer/Features/FeaturesArticle/fs/en?CONTENT_ID=4133761&chk=oW8s4w. Accessed 5 September 2006.

Morgan, M. (2005). *Staphylococcus aureus*, Panton-Valentine leukocidin, and necrotising pneumonia. *BMJ* **331**, 793–794.

Wargo, K. A. & Eiland, E. H. (2005). Appropriate therapy for community acquired methicillin resistant *Staphylococcus aureus* carrying the Panton-Valentine leukocidin gene. *Clin Infect Dis* **40**, 1376–1377.