Panton-Valentine leukocidin-secreting Staphylococcus aureus causing severe musculoskeletal sepsis in children

A NEW THREAT


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Panton-Valentine leukocidin secreted by Staphylococcus aureus is known to cause severe skin, soft tissue and lung infections. However, until recently it has not been described as causing life-threatening musculoskeletal infection. We present four patients suffering from osteomyelitis, septic arthritis, widespread intravascular thrombosis and overwhelming sepsis from proven Panton-Valentine leukocidin-secreting Staphylococcus aureus.

Aggressive, early and repeated surgical intervention is required in the treatment of these patients.

The Panton-Valentine leukocidin toxin not only destroys host neutrophils, immunocompromising the patient, but also increases the risk of intravascular coagulopathy. This combination leads to widespread involvement of bone with glutinous pus which is difficult to drain, and makes the delivery of antibiotics and eradication of infection very difficult without surgical intervention.

Panton-Valentine leukocidin is a bacterial exotoxin that leads to leukocyte destruction and tissue necrosis. Its toxic effects result from the synergistic action of two distinct exoproteins, coded for lukS-PV and lukF-PV genes carried on bacteriophages within the staphylococci. It is generally associated with infections of the skin and soft tissues, and necrotising pneumonia. As a result, the orthopaedic community has had little exposure to Panton-Valentine leukocidin-producing staphylococcal infection. However, recently cases of musculoskeletal infection by these strains have been reported.

Panton-Valentine leukocidin can be secreted by staphylococcal strains that are either methicillin sensitive (MSSA) or methicillin resistant (MRSA). In Britain, this is secreted by 1% to 2% of Staphylococcus aureus isolates. In 2006, a small number of cases of osteomyelitis or septic arthritis caused by Panton-Valentine leukocidin-secreting staphylococci were published in the USA, France and Australia. Recently, reports from Tennessee and Michigan suggest that this threat is increasing. The Panton-Valentine leukocidin toxin not only destroys host neutrophils, immunocompromising the patient, but also increases the risk of intravascular coagulopathy. This combination leads to widespread involvement of bone with glutinous pus which is difficult to drain, and makes the delivery of antibiotics and eradication of infection very difficult without surgical intervention.

Case 1

A nine-year-old boy was admitted to hospital with pain and swelling of the left leg, inability to bear weight, and a fever of 37.7°C. The symptoms had started three days previously. Two days prior to the onset of his symptoms he had fallen on to his left leg, but had not sustained serious injury. On admission, he was in septic shock with a C-reactive protein (CRP) of 275 mg/dL, and a total white blood cell count of $2.0 \times 10^9/L$. He required full intensive-care support with inotropes and artificial ventilation.

His left thigh was markedly swollen. Imaging showed multiple abscesses in the lungs, in the retroperitoneal space and in the muscles of the left thigh. There was also an effusion in the left hip. He developed rhabdomyolysis and required haemofiltration for renal failure. Methicillin-sensitive Panton-Valentine leukocidin-secreting Staph. aureus was grown from blood cultures and the hip aspirate. Duplex ultrasound identified large thrombi in the left common femoral vein, both internal jugular veins, and the right brachial vein.

Treatment was started with high-dose intravenous antibiotics (vancomycin, clindamycin and ceftriaxone). Because of his severe respiratory, renal, and clotting problems, he was initially unfit for surgery. On the fifth day, he was sufficiently stable to be taken...
Case 1

A six-year-old boy complained of ‘pain in his legs’. Two days earlier he had grazed his left leg when playing football. He was taken to the local A & E department where a diagnosis of ‘pulled’ muscles was made and he was discharged. Two days later he had developed a fever as well as the pain in his legs, and was taken to his GP who diagnosed a urinary tract infection and prescribed trimethoprim. A further two days later he developed a blanching maculopapular rash, was hallucinating, complaining of headaches, and became progressively more unwell. He attended another A & E department, where a provisional diagnosis of meningitis was made. He had a thready pulse of 150/min and his peripheral circulation was shut down, but he was maintaining his blood pressure. He was transferred to our intensive-care unit and started on antibiotics and dexamethasone. His white cell count was 2.8 × 10^9/L, inflammatory markers were grossly raised, and blood cultures grew a Panton-Valentine leukocidin-toxin-producing strain. He developed infected emboli in her left foot. She required further drainage and debridement of the tibia, but improved and was extubated on day 26. On regaining consciousness she was found to have aphasia with a dense right hemiplegia, shown on CT to be due to a cerebral infarct. An echocardiogram demonstrated infective endocarditis, with vegetations on the mitral valve. She was treated with a prolonged course of intravenous and then oral antibiotics (clindamycin and rifampicin) for one year. The tibia healed well, but she has other significant complications of the infection, including speech impairment, altered behaviour, mild right hemiparesis, convulsions, and a damaged mitral valve which will require surgical repair in the near future.

Case 2

A nine-year-old girl presented three days after a fall from her scooter in which she sustained minor damage to her left ankle. Plain radiographs were normal and she was discharged. However, five days later she complained of severe pain in the leg and feeling unwell. She was febrile with a cough. Plain radiographs suggested osteomyelitis of the left tibia. Drainage of the tibia was planned, but later the same day she collapsed with signs of septic shock. She required full paediatric intensive care with artificial ventilation, inotropes and antibiotics. Once her condition had stabilised the tibia was drained. Her white cell count fell to 2.1 × 10^9/L. Blood cultures grew Staph. aureus, later shown to be a Panton-Valentine leukocidin-toxin-producing strain. She developed infected emboli in her left foot. She required further drainage and debridement of the tibia, but improved and was extubated on day 26. On regaining consciousness she was found to have aphasia with a dense right hemiplegia, shown on CT to be due to a cerebral infarct. An echocardiogram demonstrated infective endocarditis, with vegetations on the mitral valve. She was treated with a prolonged course of intravenous and then oral antibiotics (clindamycin and rifampicin) for one year. The tibia healed well, but she has other significant complications of the infection, including speech impairment, altered behaviour, mild right hemiparesis, convulsions, and a damaged mitral valve which will require surgical repair in the near future.

Case 3

A six-year-old girl presented three days after a fall from her scooter in which she sustained minor damage to her left ankle. Plain radiographs were normal and she was discharged. However, five days later she complained of severe pain in the leg and feeling unwell. She was febrile with a cough. Plain radiographs suggested osteomyelitis of the left tibia. Drainage of the tibia was planned, but later the same day she collapsed with signs of septic shock. She required full paediatric intensive care with artificial ventilation, inotropes and antibiotics. Once her condition had stabilised the tibia was drained. Her white cell count fell to 2.1 × 10^9/L. Blood cultures grew Staph. aureus, later shown to be a Panton-Valentine leukocidin-toxin-producing strain. She developed infected emboli in her left foot. She required further drainage and debridement of the tibia, but improved and was extubated on day 26. On regaining consciousness she was found to have aphasia with a dense right hemiplegia, shown on CT to be due to a cerebral infarct. An echocardiogram demonstrated infective endocarditis, with vegetations on the mitral valve. She was treated with a prolonged course of intravenous and then oral antibiotics (clindamycin and rifampicin) for one year. The tibia healed well, but she has other significant complications of the infection, including speech impairment, altered behaviour, mild right hemiparesis, convulsions, and a damaged mitral valve which will require surgical repair in the near future.

Fig. 1

Coronal T2 MR scan of the hips and thighs, demonstrating effusion in the left hip with lateral subluxation, oedema in the proximal femoral metaphysis and shaft, myositis in the thigh, and abscesses in the adductor compartment.
in both sites. He remained pyrexial but his general condition improved. Plain radiographs of his right femur showed extensive osteomyelitis, and a repeat MRI on day 22 showed a loculated collection around the femur with intramedullary infection. Further drainage was carried out. His hip was very stiff and was treated with traction. Plain radiographs showed osteopenia in the greater trochanter extending up to the femoral head. After 15 weeks the inflammatory markers had settled and he was mobilised without weight-bearing and discharged. He has 2 cm shortening of the right leg and a stiff right hip, with destruction of the femoral head.

Case 4

A 13-year-old boy of Asian extraction presented to the A & E department with increasing pain and swelling of the right knee six days after hitting his knee against the side of his bed. He was unable to bear weight on his right leg. There was tenderness over the patellar ligament, and he could not straight leg raise. The knee joint was not warm or erythematous.

Ultrasound of the knee indicated a longitudinal partial tear of the patellar ligament, with a surrounding haematoma and a possible fracture of the tibial apophysis.

Later that evening he developed a fever of 39°C and a pulse rate of 120/min. On the next day his knee was warm and swollen, with no active movement and only 15° of passive flexion. An arthroscopy of the right knee revealed pus in the joint which was washed out, and he was started on intravenous ceftriaxone. Staph. aureus was grown on blood culture and from the aspirate and synovial tissue from the knee. He was given clindamycin every six hours, four times a day, and continued for six weeks intravenously.

On the fifth day, as he was continuing to have daily fevers, a further arthroscopic washout of the knee was performed and the right tibia drilled. On the sixth day an MR scan suggested no evidence of osteomyelitis in the femur or proximal tibia, but signs of significant fluid collections in the subcutaneous fat and intermuscular planes. A radiograph of the chest showed several focal opacities within the lung, thought to be septic emboli, with patchy consolidation at the right lung base. He was started on a prophylactic dose of enoxaparin for septic deep-vein thrombosis. The strain of Staph. aureus was confirmed as secreting Panton-Valentine leukocidin.

On days 7, 9, 14 and 17 he had further arthroscopic washouts and wound debridement.

On day 20 an open arthrotomy was performed and thick, yellow, globular pus was removed piecemeal, the knee was thoroughly washed out and the wound debrided.

He had further knee washouts and debridements on days 23, 27, 30, 32 and 35. On these occasions, no organisms were grown from the washout or synovial biopsies. At no time did his white cell count fall below 5.4 x 10⁹/L. He remained well throughout, although he became anaemic with a haemoglobin of 6.9 g/L and required blood transfusion on day 18.

Discussion

These four patients suffering from musculoskeletal infection caused by Panton-Valentine leukocidin-secreting Staph. aureus appear to be the first to be published from Britain in the orthopaedic literature. Regardless of whether the strain of staphylococcus is methicillin-sensitive or methicillin-resistant, it is the Panton-Valentine leukocidin that is of particular concern because of its tendency to destroy the patient’s leukocytes, and to impair the phagocyte immune response. Previously, Panton-Valentine leukocidin-secreting Staph. aureus has been reported mainly to affect soft tissues, with the production of deep-vein thromboses. These patients demonstrate that this infection can affect not only soft tissues but also bones and joints, where the associated intravascular coagulation makes it particularly difficult to treat as the pus rapidly becomes loculated, gluttonous, and difficult to drain. Early MRI is very useful to demonstrate the extent of bony involvement, which is often more extensive than is clinically apparent. It is most important that the joints infected by Panton-Valentine leukocidin-secreting organisms are aggressively and repeatedly washed out, and the bones drilled and debrided thoroughly and repeatedly if necessary. In this situation intravenous antibiotics alone are not sufficient and surgical eradication of all infected tissue is essential.

Recently Hensinger stated that the orthopaedic community must be aware of the dangers of musculoskeletal infection associated with community-acquired MRSA. Panton-Valentine leukocyte Staph. aureus-associated osteomyelitis and septic arthritis usually occur in very sick children with septic shock, disseminated infection and coagulopathy. Despite the severe systemic symptoms in these patients, early orthopaedic involvement and surgical intervention is important to debride poorly-vascularised areas of infection. Repeated surgical intervention may be required as well as prolonged antibiotic treatment with anti-staphylococcal drugs. We favour the combination of clindamycin and rifampicin to maximise soft tissue and bone penetration. Treatment is continued for many months until the infection is cleared and bone healing well established.

We would encourage orthopaedic surgeons to request the Panton-Valentine leukocyte status of all Staph. aureus isolates from their patients with osteomyelitis, as this will alert them to the need for early surgical intervention and prolonged intravenous therapy. In addition, decolonisation therapy with nasal mupirocin and chlorhexidine washes may be of benefit in eradicating Panton-Valentine leukocyte Staph. aureus colonisation in affected patients and their close household contacts.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.
References


