

Toxic shock syndrome caused by hospital-acquired methicillin-resistant *Staphylococcus aureus* in a patient with pancytopenia

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Staphylococcal toxic shock syndrome (TSS) is an acute illness characterised by fever, rash, hypotension, multiorgan failure and desquamation.¹ Non-menstrual TSS has been described in a variety of clinical settings, and methicillin-resistant *Staphylococcus aureus* (MRSA) has been identified as the cause in more recent cases.^{2,3} Community-acquired MRSA (CA-MRSA), distinct from hospital-acquired MRSA (HA-MRSA), is more commonly associated with TSS.⁴ The clinical manifestations of TSS are caused by bacterial exotoxins that act as, and induce massive release of, cytokines, resulting in a systemic inflammatory response.⁵ Intuitively, the mechanism of TSS requires an intact immune system. We report a case of non-menstrual TSS caused by HA-MRSA in a patient with pancytopenia after chemotherapy, which to our knowledge has not been previously reported in the medical literature.

Clinical record

A 44-year-old, previously healthy man presented to hospital with low-grade fevers, bilateral loin pain and epistaxis. His blood count showed thrombocytopenia, and blast cells were seen on a peripheral blood film. After investigations, including bone marrow biopsy, he was diagnosed with acute myeloid leukaemia. As no focus of infection was identified, the patient was treated empirically with broad-spectrum antibiotics (piperacillin plus tazobactam and gentamicin). The leukaemia was treated with chemotherapy with the ICE protocol (idarubicin, high-dose cytarabine and etoposide). The patient rapidly developed pancytopenia; he was treated with blood products to correct anaemia and thrombocytopenia, granulocyte-colony stimulating factor to correct neutropenia, and fluconazole as antifungal prophylaxis.

By Day 3 of chemotherapy, the patient developed high-grade intermittent fevers with rigors. As no focus of infection could still be identified, the antibiotic therapy was empirically changed on Day 5 to meropenem, vancomycin and amphotericin. However, the patient continued to have intermittent fevers and also developed an erythematous rash over the upper body and episodes of vomiting and diarrhoea by Day 7.

ABSTRACT

Toxic shock syndrome is an uncommon condition in patients with neutropenia. We describe a 44-year-old man who developed toxic shock syndrome caused by hospital-acquired methicillin-resistant *Staphylococcus aureus* while pancytopenic after chemotherapy. He died of multiorgan failure despite high-level intensive care support and treatment with appropriate antibiotics and intravenous immunoglobulin. This case illustrates the need for a high index of suspicion for toxic shock syndrome in patients with febrile neutropenia, and also highlights the lack of high-quality evidence for the various treatment modalities used in this syndrome.

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The rash was initially thought to be an adverse drug reaction but did not resolve on withdrawal of the suspected causes (vancomycin and meropenem). By Day 12, the patient's clinical condition had worsened, with severe sepsis with septic shock and acute renal failure, necessitating his admission to the intensive care unit. The rash had become confluent over the upper torso, with a sunburn appearance (Figure 1). Culture of blood taken on Day 13 showed *S. aureus* in two separate samples. All other investigations for a source of the sepsis gave negative results.

By Day 13, the patient also developed respiratory failure requiring mechanical ventilation, in addition to the requirement for continuous renal replacement therapy and high-dose vasopressors. His condition met all five clinical criteria for a diagnosis of TSS (fever, rash, hypotension, desquamation and multisystem involvement), as well as laboratory criteria (all cultures negative for all organisms except *S. aureus*).¹

Considering the severity of the disease, we decided to administer intravenous immunoglobulin (IVIG) in addition to changing the antibiotic therapy to linezolid, aztreonam, metronidazole and amphotericin to cover for the possibility of vancomycin-intermediate *S. aureus* (VISA) and other

Figure 1. Patient's rash on Day 13 of chemotherapy

By Day 13 of chemotherapy, the erythematous rash was confluent over the upper body with a sunburn appearance, but spared the hands and feet.

multiresistant organisms. Two doses of IVIG (2 g/kg) were given at an interval of 48 hours; the dose was derived from the UK guidelines for severe staphylococcal infections.⁶ There was a transient reduction in vasopressor requirements after the first dose. Subsequent blood cultures did not grow any organisms.

Further testing of the staphylococcal isolate from Day 13 showed it was resistant to methicillin but sensitive to vancomycin. Staphylococcal enterotoxin A gene was identified by polymerase chain reaction (PCR) testing. Toxic shock syndrome toxin 1 (TSST-1) and Pantone–Valentine leukocidin genes were not identified. DNA fingerprinting by pulsed field gel electrophoresis and multilocus sequence typing identified an HA-MRSA strain (ST293-MRSA-III).

The patient's clinical condition continued to deteriorate, and he died of multiorgan failure on Day 19. An autopsy was not performed in accordance with the wishes of his family.

Discussion

Staphylococcal TSS was first described in a paediatric case series in 1978,⁷ but a large number of case reports of menstrual TSS brought it to public attention in the early 1980s.⁸ The Centers for Disease Control and Prevention (CDC) in the United States define TSS as a febrile illness with multiorgan involvement and a diffuse macular erythematous rash that characteristically desquamates, particularly on the palms and soles, 1–2 weeks after the onset of illness.¹ The lack of a laboratory test for TSS means the diagnosis is clinical, and becomes possible only quite late in the disease process.

Although menstrual TSS accounts for three-quarters of all reported cases, non-menstrual TSS has been reported in a range of clinical settings: surgical and postpartum wounds, mastitis, respiratory tract infections, burns, osteomyelitis and cutaneous non-surgical lesions (especially in children).^{2,3,9} Recent case reports have identified CA-MRSA as the cause in many of these cases,^{2,3} but HA-MRSA has not been commonly associated with TSS.

TSST-1 was the exotoxin initially isolated from *S. aureus* isolates implicated in TSS in 1981.⁸ This toxin is produced by 90%–100% of *S. aureus* strains associated with menstrual TSS, but only by 40%–60% of strains associated with non-menstrual cases. Non-menstrual TSS is associated with staphylococcal enterotoxins A to E and G to I rather than TSST-1.¹⁰

Our patient met the CDC criteria for TSS,¹ but we also considered the possibility of severe sepsis with a drug rash. However, we found no temporal relation between administration of any of the suspect drugs and the onset of the rash, and the rash did not resolve with cessation of the suspect agents. Identification of the gene encoding staphylococcal enterotoxin A in the *S. aureus* strain isolated from the patient helped confirm the diagnosis of TSS.

S. aureus exotoxins cause disease because they are superantigens — molecules that activate large numbers of T cells (often up to 20% of all T cells at a time), resulting in massive cytokine production.^{5,11} Superantigens do not need to be processed by an antigen-presenting cell before binding with the Class II major histocompatibility complex, possibly accounting for TSS developing in a patient with neutropenia. We hypothesise that, despite pancytopenia, sufficient T cells were present in lymph nodes and other lymphoreticular tissue to produce a superantigen response.

The high mortality in non-menstrual TSS has been assumed to be due to delayed diagnosis. However, our patient's condition deteriorated despite treatment with appropriate antibiotics from early in the disease. Meropenem and vancomycin are the second-line antibiotics for febrile neutropenia in our institution, but these cell-wall active agents may fail in infections associated with toxin-producing organisms as — unlike protein synthesis inhibitors — they do not suppress toxin production.¹² We hypothesise that linezolid might be more beneficial than vancomycin in treating MRSA TSS.

MRSA produces substantially more exotoxin than methicillin-sensitive *S. aureus*.¹³ As antibiotics are unable to inactivate the toxins, the systemic toxic symptoms may persist even after elimination of the organism. Also anti-exotoxin antibody may not be produced immediately after an MRSA infection.¹⁴

Human-origin IVIG neutralises TSST-1 and staphylococcal enterotoxin A in vitro.¹² Several observational studies show

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a mortality and morbidity benefit with the use of IVIG in streptococcal TSS,^{15,16} and a European randomised controlled trial, although inadequately powered, showed similar trends.¹⁷ However, we were able to find only a single case report on the use of IVIG in staphylococcal TSS.¹⁸ We decided to use IVIG because of concerns that the patient's pancytopenia meant exotoxins were unlikely to be neutralised, and because his clinical condition was deteriorating. There was an initial response to IVIG, with a 50% reduction in vasopressor requirement, but this proved transient. More evidence is required before the routine use of IVIG in this setting.

Conclusion

The possibility of TSS should be considered in patients with febrile neutropenia. TSS can be produced by both community- and hospital-acquired MRSA. If there is a high index of clinical suspicion for TSS, then protein synthesis inhibitors, such as linezolid, may be considered to treat MRSA TSS rather than cell wall-active agents, such as vancomycin. The role of IVIG in staphylococcal TSS is unclear and requires further evaluation.

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References

- Centers for Disease Control and Prevention [US]. Case definitions for infectious conditions under public health surveillance. *MMWR Recomm Rep* 1997; 46 (RR-10): 1-55.
- Haddadin DW, Samnani IQ, Moorman JP. Drotrecogin alfa (activated) for nonmenstrual toxic shock syndrome associated with methicillin resistant *Staphylococcus aureus* infection. *South Med J* 2006; 99: 1295-6.
- Cui L, Kasegawa H, Murakami Y, et al. Postoperative toxic shock syndrome caused by a highly virulent methicillin-resistant *Staphylococcus aureus* strain. *Scand J Infect Dis* 1999; 31: 208-9.
- Fey PD, Said-Salim B, Rupp ME, et al. Comparative molecular analysis of community- or hospital-acquired methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2003; 47: 196-203.
- Li H, Llera A, Malchiodi EL, Mariuzza RA. The structural basis of T cell activation by superantigens. *Annu Rev Immunol* 1999; 17: 435-66.
- PVL Subgroup of the Steering Group on Healthcare Associated Infection. Guidance on the diagnosis and management of PLV-associated *Staphylococcus aureus* infections (PVL-SA) in England. 2nd ed. London: Health Protection Agency, 2008.
- Todd JK, Kapral FA, Fishaut M, Welch TR. Toxic shock syndrome associated with phage group 1 staphylococci. *Lancet* 1978; 2: 1116-8.
- Reingold AL, Hargrett NT, Shands KT, et al. Toxic shock syndrome surveillance in the United States, 1980 to 1981. *Ann Intern Med* 1982; 96: 875-80.
- Hajjeh RA, Reingold AL, Weil A, et al. Toxic shock syndrome in the United States: surveillance update, 1979-1996. *Emerg Infect Dis* 1999; 5: 807-10. <http://www.cdc.gov/ncidod/eid/vol5no6/hajjeh.htm>
- Lee VT, Chang AH, Chow AW. Detection of staphylococcal enterotoxin B among toxic shock syndrome (TSS)- and non-TSS-associated *Staphylococcus aureus* isolates. *J Infect Dis* 1992; 166: 911-5.
- Murray RJ. Recognition and management of *Staphylococcus aureus* toxin-mediated disease. *Intern Med J* 2005; 35: S106-19.
- Stevens DL, Ma Y, Salmi DB, et al. Impact of antibiotics on expression of virulence-associated exotoxin genes in methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*. *J Infect Dis* 2007; 195: 202-11.
- Schmitz FJ, Mackenzie CR, Geisel R, et al. Enterotoxin and toxic shock syndrome toxin-1 production of methicillin resistant and methicillin sensitive *Staphylococcus aureus* strains. *Eur J Epidemiol* 1997; 13: 699-708.
- Bonventre PF, Linnemann C, Weckbach LS, et al. Antibody responses to toxic-shock-syndrome (TSS) toxin by patients with TSS and by healthy staphylococcal carriers. *J Infect Dis* 1984; 150: 662-6.
- Kaul R, McGeer A, Norrby-Teglund A, et al. Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome — a comparative observational study. The Canadian Streptococcal Study Group. *Clin Infect Dis* 1999; 28: 800-7.
- Norrby-Teglund A, Muller MP, McGeer A, et al. Successful management of severe group A streptococcal soft tissue infections using an aggressive medical regimen including intravenous polyspecific immunoglobulin together with a conservative surgical approach. *Scand J Infect Dis* 2005; 37: 166-72.
- Darenberg J, Ihendyane N, Sjölin J, et al. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. *Clin Infect Dis* 2003; 37: 333-40.
- Cone LA, Woodard DR, Byrd RG, et al. A recalcitrant, erythematous, desquamating disorder associated with toxin-producing staphylococci in patients with AIDS. *J Infect Dis* 1992; 165: 638-43. □