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MRSA toxic shock syndrome associated with surgery for left leg fracture and co-morbid compartment syndrome

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ABSTRACT

We report the case of a 46-year-old Japanese man who was brought to the hospital with fever, hypotension and diffuse erythematous rash with multiple organ damage. Three weeks before he had undergone orthopaedic surgery for left leg fracture and comorbid compartment syndrome. Fasciorrhaphy was performed successfully 2 weeks before, but the next day he became feverish and hypotensive with signs of systemic low perfusion. He was referred to the hospital for further evaluation and treatment. On arrival, high fever, hypotension and diffuse erythroderma were observed. Lab results revealed multi-organ dysfunction. Clinical manifestations led to the diagnosis of toxic shock syndrome (TSS). The patient was treated with extensive hydration, local drainage and antibiotics. After 2 weeks of intensive care, he recovered and was successfully discharged from the hospital. A culture of the wound tissue revealed the presence of MRSA with positive TSST-1.

1. Introduction

The staphylococcal toxic shock syndrome (TSS) is a fatal infectious disease caused by the enterotoxins (toxic shock syndrome toxin-1 (TSST-1) and other toxins) released by *Staphylococcus aureus (S. aureus)*. The exotoxin serves as a superantigen, which directly interacts with the invariant region of the class II MHC molecule, thereby activating large numbers of T cells, often up to 20% of all T cells at a time. This results in massive cytokine production[1]. Released cytokines including interleukin (IL)-1, IL-2, tumour necrosis factors (TNF)-α and -β and interferon (IFN)-γ cause the symptoms of TSS. Clinical manifestations are often characterized by fever, rash (erythema)/desquamation (1-2 weeks after the onset of rash) and hypotension. Furthermore, TSS causes multisystem involvement including that of GI, muscular, mucous membrane, renal, hepatic, haematological and central nervous systems. The majority of cases of staphylococcal TSS are caused by methicillin-susceptible *S. aureus* (MSSA). However, as rates of infection due to methicillin-resistant *S. aureus* (MRSA) have increased, the number of cases of TSS due to MRSA have also increased[2,3].

Half of all TSS cases are not reported to be associated with menstruation[4,5]. Non-menstrual TSS has been observed in a wide variety of clinical settings including postoperative and postpartum wound infections, sinusitis, respiratory infections following influenza, mastitis, osteomyelitis, arthritis, burns, cutaneous/subcutaneous lesions and enterocolitis[6-13]. Postoperative cases increased from 14% in 1979-1986 to 27% in 1987-1996[14].

Patient fatalities have been attributed to cardiac problems (arrhythmias and cardiomyopathy), respiratory failure or DIC. Mortality due to non-menstrual TSS is higher than that in menstrual cases (5% versus 1.8%)[14,15]. Death usually occurs within the first few days, but in some cases it occurs 15 d after hospital admission[16,17].

2. Case report

A previously healthy 46-year-old baseball player with no remarkable past medical or family history, no known drug allergy and no prior medications was referred to our hospital by an orthopaedic surgeon. The patient presented

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with fever, hypotension and watery diarrhoea. He had smoked for 28 pack-years and consumed 500 mL of beer per day. Three weeks before, he had undergone orthopaedic surgery because of left fibular and tibial fracture during a baseball game. Open reduction and internal fixation (ORIF) and fasciotomy were performed to treat his fracture and the compartment syndrome that occurred concurrently. Two weeks before, fasciorrhaphy was performed successfully. However, the next day the patient passed loose brownish stools; his blood pressure dropped to 60 mmHg (systolic blood pressure), and fever rose to 39 ℃. Blood tests revealed BUN to be 50 mg/dL and Cr to be 2.5 mg/dL. The patient was referred to our hospital. He had taken cefazolin for 2 weeks after surgery.

On examination, the vital signs of the patient were as follows: blood pressure, 70/48 mmHg; heart rate, 107 beat per min; body temperature, 39.0 ℃; respiratory rate, 24 and SpO_2, 95% in ambient air. Diffuse macular erythema was observed on the trunk (Figure 1), extremities and face. The left leg was markedly swollen, with the presence of warmth and redness and the surgical scar (Figure 2). External Juglar vein collapse was evident even in the supine position. Other physical findings were unremarkable. His blood test results were as follows: WBC 189 800/μL, Hb 11.1 g/dL, Ht 30.5%, Plt 11.2×10^4/μL, T-P 5.1 g/dL, Alb 2.3 g/dL, AST 136 IU/L, ALT 71 IU/L, T-bil 1.5 mg/dL, LDH 452 IU/L, CPK 5 026 IU/L, ALP 43 IU/L, GGT 14IU/L, Amy 103 IU/L, UN 53 mg/dL, Cr 2.5 mg/dL, BS 121 mg/dL, Na 129 mEq/L, K 4.0 mEq/L, Cl 96 mEq/L, CRP 23.0 mg/dL, FDP 40.8 mg/dL, FIB 339 mg/dL, D-dimer 26.5 μg/mL. An X-ray of the left lower extremity revealed no gas collection beneath the soft tissue.

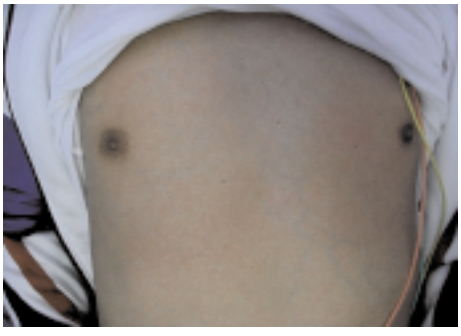

Figure 1. Diffuse macular erythema was found on his trunk.

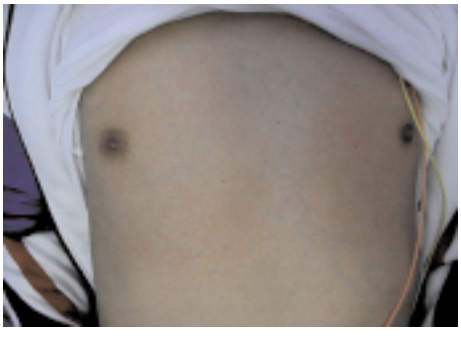

Figure 2. Left leg was markedly swollen with warmth and redness with surgical scar.

On the basis of his clinical manifestations, the patient was diagnosed with TSS. Aggressive fluid replacement therapy (infused fluid volume, 5-8 L/d for the first 3 d) with administration of vancomycin (1 g) and ceftriaxone (2 g) plus clindamycin (1 200 mg qd) were immediately initiated. Surgical inspection was performed, but no necrotic tissue was observed. Local drainage was performed.

After supportive antibiotic therapy, TSS symptoms resolved. One week later, desquamation was complete. Two weeks after the day of admission, the patient was stabilised and discharged from the hospital. A culture of the wound tissue revealed MRSA with positive TSST-1.

3. Discussion

Sex distribution was equal in a study of 130 TSS cases in which vaginal and postpartum-associated cases were excluded[18]. Patients with non-menstrual TSS are significantly older (mean age, 26.8 years versus 23 years in patients with menstrual TSS) and more often non-white compared with patients with menstrual TSS[5,11,18]. The case-fatality rate for non-menstrual TSS was reported to be 5% and did not decrease over time[14]. TSST-1 was the first exotoxin isolated from *S. aureus* in TSS in 1981[19,20]. It is found in over 90% of menstrual TSS cases and in 40%-60% of strains from non-menstrual cases. Our patient was a middle-aged Asian male suffering from postoperative TSS caused by TSST-1.

The diagnosis of TSS is established based on clinical presentation that satisfies the CDC case definition[21,22]: patients must have fever >38.9 ℃, hypotension, diffuse erythema, desquamation (unless the patient dies before desquamation can occur) and involvement of at least three organ systems. A probable case is defined as a patient who is missing one of the characteristics of the confirmed case definition. Our patient satisfied all the aforementioned criteria with GI, muscular, renal and hepatic involvement. Eighty to ninety percent of TSS patients have S. aureus isolated from mucosal or wound sites, while this is not required for the diagnosis of staphylococcal TSS[23]. On the other hand, *S. aureus* is rarely isolated (5%) from blood cultures compared with streptococcal TSS[18]. In our patient, *S. aureus* was isolated from the wound site, and not from blood cultures.

The mainstay of treatment for TSS is supportive, while the patient presents hypotension. Rapid fluid replacement and/or vasopressors are also necessary. In addition to supportive therapy, removal, drainage or debridement of any possible infectious focus is imperative. Exploration of surgical wounds is important for patients with postoperative TSS because signs of infection may be masked because of the decreased inflammatory response.

Whether antibiotics alter the course of acute TSS remains unclear although antibiotic therapy has been revealed to reduce the likelihood of recurrent TSS by eliminating the carrier state[23]. Clindamycin plus either vancomycin or linezolid may typically be administered to patients with TSS due to MRSA for 10-14 d even in the absence of overt *S. aureus* infection. Clindamycin is a pivotal and efficacious drug for a

drained postoperative infected focus, acting by suppressing bacterial protein synthesis[24]. Vancomycin and linezolid are effective drugs for treating MRSA. In our patient, vancomycin and ceftriaxone were administered in addition to clindamycin at the beginning of the therapy because it was uncertain whether the causative agent was *Streptococcus* or *Staphylococcus*. Hence, we covered both of the organisms since TSS is the fatal condition and the dual coverage should be required unless the causative organism is uncertain.

Intravenous immunoglobulin (IVIG) therapy has been suggested in severe cases that have been recognized early in their course and have not responded to supportive therapy[25]. However, no controlled trials of IVIG therapy in staphylococcal TSS have been conducted in humans[25,26]. On the other hand, IVIG treatment may be efficacious in streptococcal TSS[27,28]. A report from Sweden noted that culture supernatants containing the superantigen from *S. aureus* were less efficiently inhibited by IVIG than those from *S. pyogenes*[29]. Another additional therapy corticosteroid is not recommended because of the limited clinical evidence with this therapy. We did not use both of IVIG and corticosteroids in our case.

Conflict of interest statement

We declare that we have no conflict of interest

References

[1] Schlievert PM. Role of superantigens in human disease. *J Infect Dis* 1993; **167**: 997.

[2] Durand G, Bes M, Meugnier H, Enright MC, Forey F, Liassine N, et al. Detection of new methicillin-resistant *Staphylococcus aureus* clones containing the toxic shock syndrome toxin 1 gene responsible for hospital- and community-acquired infections in France. *J Clin Microbiol* 2006; **44**: 847.

[3] Fey PD, Saïd-Salim B, Rupp ME, Hinrichs SH, Boxrud DJ, Davis CC, et al. Comparative molecular analysis of community- or hospital-acquired methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2003; **47**: 196.

[4] Centers for Disease Control (CDC). Reduced incidence of menstrual toxic-shock syndrome--United States, 1980-1990. *MMWR Morb Mortal Wkly Rep* 1990; **39**: 421.

[5] Gaventa S, Reingold AL, Hightower AW, Broome CV, Schwartz B, Hoppe C, et al. Active surveillance for toxic shock syndrome in the United States, 1986. *Rev Infect Dis* 1989; **11**(Suppl 1): S28.

[6] Bartlett P, Reingold AL, Graham DR, Dan BB, Selinger DS, Tank GW, et al. Toxic shock syndrome associated with surgical wound infections. *JAMA* 1982; **247**:1448.

[7] Dann EJ, Weinberger M, Gillis S, Parsonnet J, Shapiro M, Moses AE. Bacterial laryngotracheitis associated with toxic shock syndrome in an adult. *Clin Infect Dis* 1994; **18**: 437.

[8] Ferguson MA, Todd JK. Toxic shock syndrome associated with *Staphylococcus aureus* sinusitis in children. *J Infect Dis* 1990; **161**: 953.

[9] Morrison VA, Oldfield EC 3rd. Postoperative toxic shock syndrome. *Arch Surg* 1983; **118**: 791.

[10]Paterson MP, Hoffman EB, Roux P. Severe disseminated staphylococcal disease associated with osteitis and septic arthritis. *J Bone Joint Surg Br* 1990; **72**: 94.

[11]Reingold AL, Hargrett NT, Dan BB, Shands KN, Strickland BY, Broome CV. Nonmenstrual toxic shock syndrome: a review of 130 cases. *Ann Intern Med* 1982; **96**: 871.

[12]Vuzevski VD, van Joost T, Wagenvoort JH, Dey JJ. Cutaneous pathology in toxic shock syndrome. *Int J Dermatol* 1989; **28**: 94.

[13]Kotler DP, Sandkovsky U, Schlievert PM, Sordillo EM. Toxic shock-like syndrome associated with staphylococcal enterocolitis in an HIV-infected man. *Clin Infect Dis* 2007; **44**: e121.

[14]Hajjeh RA, Reingold A, Weil A, Shutt K, Schuchat A, Perkins BA. Toxic shock syndrome in the United States: surveillance update, 1979 1996. *Emerg Infect Dis* 1999; **5**: 807.

[15]Broome CV. Epidemiology of toxic shock syndrome in the United States: overview. *Rev Infect Dis* 1989; **11**(Suppl 1): S14.

[16]Larkin SM, Williams DN, Osterholm MT, Tofte RW, Posalaky Z. Toxic shock syndrome: clinical, laboratory, and pathologic findings in nine fatal cases. *Ann Intern Med* 1982; **96**: 858.

[17]Paris AL, Herwaldt LA, Blum D, Schmid GP, Shands KN, Broome CV. Pathologic findings in twelve fatal cases of toxic shock syndrome. *Ann Intern Med* 1982; **96**: 852.

[18]Reingold AL, Dan BB, Shands KN, Broome CV. Toxic-shock syndrome not associated with menstruation. A review of 54 cases. *Lancet* 1982; **1**: 1.

[19]Bergdoll MS, Crass BA, Reiser RF, Robbins RN, Davis JP. A new staphylococcal enterotoxin, enterotoxin F, associated with toxic-shock-syndrome *Staphylococcus aureus* isolates. *Lancet* 1981; **1**: 1017.

[20]Schlievert PM, Shands KN, Dan BB, Schmid GP, Nishimura RD. Identification and characterization of an exotoxin from *Staphylococcus aureus* associated with toxic-shock syndrome. *J Infect Dis* 1981; **143**: 509.

[21]Centers for Disease Control (CDC). Repeat injuries in an inner city population--Philadelphia, 1987-1988. *MMWR Morb Mortal Wkly Rep* 1990; **39**: 1.

[22]Centers for Disease Control and Prevention. Case definitions for infectious conditions under public health surveillance. *MMWR Morb Mortal Wkly Rep* 1997; **46**(RR-10): 39.

[23]Davis JP, Osterholm MT, Helms CM, Vergeront JM, Wintermeyer LA, Forfang JC, et al. Tri-state toxic-shock syndrome study. II. Clinical and laboratory findings. *J Infect Dis* 1982; **145**: 441.

[24]Schlievert PM, Kelly JA. Clindamycin-induced suppression of toxic-shock syndrome--associated exotoxin production. *J Infect Dis* 1984; **149**: 471.

[25]Keller MA, Stiehm ER. Passive immunity in prevention and treatment of infectious diseases. *Clin Microbiol Rev* 2000; **13**: 602.

[26]Chesney PJ, Davis JP. Toxic shock syndrome. In: Feigin, RD, Cherry, JD. *Textbook of pediatric infectious diseases, 4th ed.* Philadelphia: WB Saunders Co; 1998, p. 830.

[27]Barry W, Hudgins L, Donta ST, Pesanti EL. Intravenous immunoglobulin therapy for toxic shock syndrome. *JAMA* 1992; **267**: 3315.

[28]Darenberg J, Ihendyane N, Sjölin J, Aufwerber E, Haidl S, Follin P, 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.

[29]Darenberg J, Söderquist B, Normark BH, Norrby-Teglund A. Differences in potency of intravenous polyspecific immunoglobulin G against streptococcal and staphylococcal superantigens: implications for therapy of toxic shock syndrome. *Clin Infect Dis* 2004; **38**: 836.