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Two patients with toxic shock-like syndrome are presented. Both patients had necrotizing cellulitis due to Streptococcus pyogenes, *and both patients required extensive surgical debridement. The association of* Streptococcus pyogenes *infection and toxic shock-like syndrome is discussed. (Henry Ford Hosp Med J 1989;37:69-72)*

Since 1978, toxin-producing strains of *Staphylococcus aureus* have been implicated as the cause of the toxic shock syndrome (TSS), which is characterized by fever and rash and followed by desquamation, hypotension, and multisystem involvement (1). Most cases subsequently reported have occurred in menstruating women in association with tampon use (2-6). However, TSS associated with *Staphylococcus aureus* infection has been described in numerous other clinical illnesses including use of contraceptive sponges (7), nasal packing (8,9), surgical wound infection (10), and nonsurgical infections at various sites including skin and subcutaneous tissue (11,12).

Cone et al (13) recently described a toxic shock-like illness in two patients with cellulitis due to group A beta-hemolytic streptococci (*Streptococcus pyogenes*). Several other reports have implicated *Streptococcus pyogenes* in TSS (14-16).

Two patients with necrotizing *Streptococcus pyogenes* infections associated with a toxic shock-like syndrome have been observed at our hospital in the past three years. These patients were admitted with streptococcal cellulitis with prominent necrosis of skin and subcutaneous tissue which required extensive surgical debridement to control the illness. One of the patients was also bacteremic with *Streptococcus pyogenes*. We report these cases to increase the awareness that *Streptococcus pyogenes* may produce a toxic shoek-like syndrome and that aggressive surgical treatment may be necessary to obtain an optimal result.

Case Reports

Case 1

A 76-year-old man suffered a superficial abrasion of his right elbow two days prior to admission. He was being treated with chlorthalidone and metropolol for hypertension but otherwise had been in good health. He was not diabetic. Over a two-day period the elbow area became progressively more erythematous, tender, and swollen. He was visited at home by a nurse who noted that he was confused and severely ill. He was noted to have a bright erythroderma over most of his body. He was brought to the emergency room where a physical examination revealed a temperature of 40.9°C (105.6°F), blood pressure of 98/72 mm Hg, respiration of 36 breaths/min, and a pulse of 72 beats/min. The skin showed a bright sunburn-type rash, most prominent over the trunk and face, but present over the entire body. Desquamation of skin of the upper and lower extremities, particularly the hands and feet, occurred later. A strawberry tongue was present, and there was prominent infection of both bulbar and palpebral conjunctivae. A 3 x 3 cm abrasion was noted over the right elbow. The surrounding skin was indurated, erythematous, and tender. Vesicles were present (Figure). The abraded area oozed serous drainage. The patient became more hypotensive, and a Swan-Ganz catheter was inserted for hemodynamic monitoring. Intravenous crystaloid infusions, albumin, and dopamine were administered to maintain adequate blood pressure. He received 2 g of nafcillin intravenously every six hours for 48 hours and subsequently 6 mU of penicillin intravenously every 24 hours for 19 days. He also received 500 mg of metronidazole intravenously every six hours from days 3 through 16 and 1 g of cefoperazone intravenously every 12 hours from days 3 through 13. He developed a rapidly rising creatinine (424 μmol/L [4.8 mg/dL] on admission), abnormal liver function, renal failure, and acute respiratory distress syndrome. Hemodialysis and ventilatory support were given. Blood cultures and cultures of drainage from the elbow area revealed *Streptococcus pyogenes*. The organism produced pyrogenic streptococcal type B toxin but not toxins A and C.§ His condition was further complicated by colonic distention, gastrointestinal bleeding due to gastritis, and cardiac arrhythmias. He developed rapidly progressive necrotic changes of the skin and subcutaneous tissue of the right arm and forearm, accompanied by hemorrhagic

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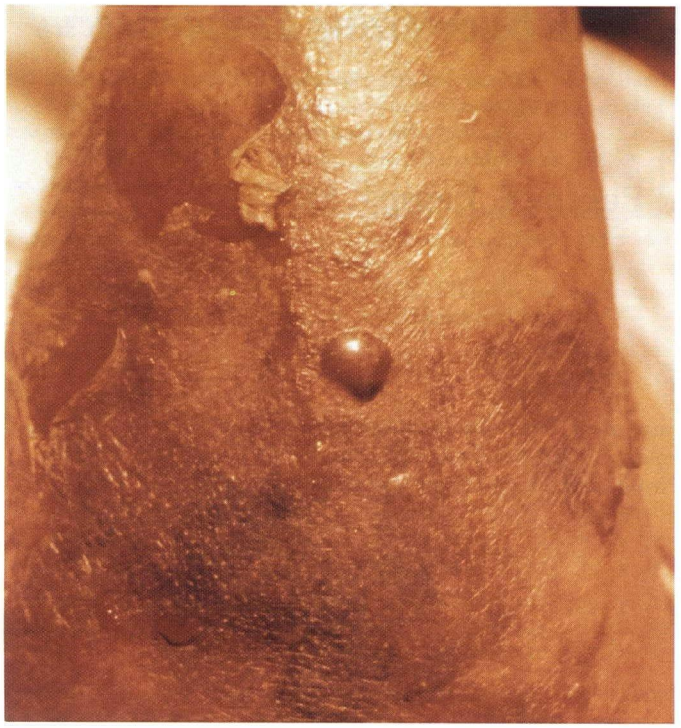

Figure—Dorsum of forearm with cellulitis with bleb formation.

Table
Laboratory Values in Two Patients with Streptococcal Necrotizing Cellulitis and Toxic Shock Syndrome

	Case 1		Case 2	
	12/15/87	12/18/87	4/29/86	5/1/86
WBC count (per μL)	11.0	14.6	21.4	14.6
Hemoglobin (g/dL)	17.6	12.8	11.8	10.4
Hematocrit (%)	53.7	36.2	35.4	30.8
Platelet count (per μL)	193	48	248	170
Creatinine μmol/L (mg/dL)	424 (4.8)	813 (9.2)	566 (6.4)	194 (2.2)
BUN mmol/L (mg/dL)	15.7 (44)	38.2 (107)	24.9 (70)	17.9 (50)
Bilirubin μmol/L (mg/dL)	27 (1.6)	72 (4.2)	67 (3.9)	123 (7.2)
Alkaline phosphatase μkat/L (U/L)	0.4 (22)	0.8 (45)	4.4 (261)	2.6 (153)
SGOT* μkat/L (U/L)	1.40 (84)	13.94 (836)	0.63 (38)	0.62 (37)
CPK†	2,417	2,386	319	509
Albumin g/L (g/dL)	29 (2.9)	32 (3.2)	30 (3.0)	30 (3.0)
Calcium mmol/L (g/dL)	2.20 (8.8)	1.60 (6.4)	1.87 (7.5)	1.77 (7.1)

*SGOT denotes aspartate aminotransferase.
†CPK denotes creatinine phosphokinase.

bullae. These changes required repeated extensive surgical debridement over a three-week period following admission. The infection was ultimately controlled, and skin grafting was performed prior to the patient's discharge from the hospital. Laboratory data are listed in the Table.

Case 2

A 22-year-old nulliparous woman noted erythema and tenderness of the right breast 72 hours prior to admission. She was obese but otherwise had been in excellent health. She was not diabetic. Her breast had not been injured. She had completed a normal menstrual period one week previously. She had not used tampons and had not been sexually active. She had not had any vaginal irritation or discharge. Twenty-four hours after her initial symptoms, she developed some vesiculation of the skin. She was seen by her physician who prescribed 500 mg of cephalexin every six hours. She developed some nausea and diarrhea the following day. Two days after antibiotics were started, she developed rapidly increasing erythema, swelling and induration of the breast, with necrosis of the skin and subcutaneous tissue with extensive eschar formation. She was noted to be confused and was brought to the hospital. Physical examination revealed an acutely ill woman. Her temperature was 38.9°C (102°F), blood pressure 90/70 mm Hg, and pulse 100 beats/min. She was confused. There was diffuse erythroderma of the skin of the trunk and extremities resembling a sunburn. There was considerable erythema, induration, and necrosis of the skin of the right breast. Extensive blister formation was also present. Desquamation of skin of the hands occurred later. Bulbar and palpebral conjunctival infection and a strawberry tongue were present. Muscles of the upper and lower extremities were markedly tender to palpation. She received 2 g of nafcillin intravenously every four hours for nine days and 900 mg of clindamycin intravenously every eight hours for three days. She was given an initial dose of 2 mg/kg of tobramycin intravenously with subsequent doses being adjusted for dysfunction. She received tobramycin for nine days. Although her serum creatinine initially was 566 μmol/L (6.4 mg/dL), dialysis was not necessary. Cultures from several areas of the inflamed breast grew *Streptococcus pyogenes*. Streptococcal pyrogenic toxin determinations were not performed, and the streptococcal isolate is not available. Cultures of the breast also revealed *Pseudomonas aeruginosa* and *Enterobacter cloacae*. Vaginal cultures revealed *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida albicans*. Blood and urine cultures were negative.

Extensive surgical debridement of skin and subcutaneous tissue of the breast was performed, with skin grafting to the breast accomplished later. Laboratory data are noted in the Table.

Discussion

Streptococcus pyogenes may cause numerous infections including pharyngitis, cellulitis, impetigo, erysipelas, puerperal fever, and bacteremia, as well as necrotizing cellulitis, fasciitis, or myositis. It may also be responsible for noninfectious illnesses including rheumatic fever, glomerulonephritis, and erythema nodosa. While *Streptococcus pyogenes* may produce toxins A, B, and C, recently type A toxin has been produced by far fewer strains than in previous years (17). Streptococcal toxins have diverse toxic properties that include pyrogenicity, enhancement of lethal endotoxin effects, and increased vascular permeability and skin reactivity, as seen in scarlet fever (18-21).

Willoughby and Greenberg (22) noted that *Streptococcus pyogenes* produced toxins with biologic features in common with toxins associated with staphylococcal TSS and suggested that these streptococcal toxins might also cause a toxic shock-like syndrome. Toxic shock syndrome toxin-I (TSST-1) (23-26),

previously termed staphylococcal enterotoxin F or pyrogenic exotoxin C, and staphylococcal enterotoxin B (27,28) are considered to be the staphylococcal products responsible for staphylococcal TSS.

It has been noted that streptococcal toxin A and staphylococcal toxin B are related structurally (29).

Both of our patients manifested symptoms characteristic of staphylococcal toxic shock. These features included diffuse erythroderma, conjunctival infection, strawberry tongue, hypotension, both hepatic and renal dysfunction, and desquamation of the skin.

The patient in Case 1 was bacteremic with *Streptococcus pyogenes*. His rash was that of a bright erythroderma and not the typical sandpaper rash of scarlet fever. Prominent conjunctival infection, strawberry tongue, and hepatic dysfunction were present. These features and the severe renal dysfunction requiring dialysis that occurred with mild hypotension strongly suggested a toxic shock-like syndrome rather than effects of streptococcal bacteremia. Both patients rapidly developed extensive necrotic changes of skin and subcutaneous tissue. Extensive surgical debridement was performed early in the course of both patients; repeated surgical debridement was required in Case 1. For this patient in particular, the effectiveness of debridement appeared to be correlated with clinical improvement, with clinical deterioration occurring when further necrosis of tissue developed.

The degree of skin involvement, mucous membrane manifestations, and degree of tissue destruction in this syndrome have been quite varied. Hribalova (15) reported a case of peritonitis with rash but no mucous membrane involvement. Two of the three cases described by Bartter et al (14) had erythroderma, but mucous membrane involvement and tissue destruction were not noted. Desquamation was noted in one patient. Both cases described by Cone et al (13) had erythema of the face and conjunctivitis, but a strawberry tongue was not noted. Desquamation did not occur, and tissue destruction was not noted. Tissue destruction was a prominent feature of the 20 cases described by Stevens et al (16), but generalized erythema was not noted. Two of their cases had a petechial rash, and two had maculopapular rash. Four of their patients had desquamation. These authors emphasized the role of erythrogenic toxin type A in their cases. Eight of the ten strains of *Streptococcus pyogenes* produced pyrogenic exotoxin A, three produced toxins A and B, one produced toxins A, B, and C, and one produced only toxin B.

Both of our cases had prominent erythroderma followed by desquamation, conjunctivitis, and strawberry tongue. Both also had prominent tissue destruction requiring extensive debridement. In Case 1 where tissue destruction was most marked, toxin analysis revealed the presence of exotoxin B but not toxins A or C. In a recent editorial, Stollerman (30) noted that all three erythrogenic toxins, types A, B, and C, of *Streptococcus pyogenes* possessed potent toxin properties with type A being the most potent. It is thus not surprising that TSS due to *Streptococcus pyogenes* may be associated with both toxins A and B and possibly toxin C as well, although type A appears to be the most prevalent.

It is important to recognize that TSS may be associated with various *Streptococcus pyogenes* infections, some clinically obvious and some occult, and that patients with prominent tissue destruction requiring extensive debridement comprise an important group of these infections.

References

1. Todd J, Fishaut M, Kapral F, Welch T. Toxic-shock syndrome associated with phage-group-1 staphylococci. Lancet 1978;2:1116-8.
2. Davis JP, Chesney PJ, Wand PJ, LaVenture M. Toxic-shock syndrome: Epidemiologic features, recurrence, risk factors, and prevention. N Engl J Med 1980;303:1429-35.
3. Shands KN, Schmid GP, Dan BB, et al. Toxic-shock syndrome in menstruating women: Association with tampon use and *Staphylococcus aureus* and clinical features in 52 cases. N Engl J Med 1980;303:1436-42.
4. Osterholm MT, Davis JP, Gibson RW, Mandel JS, Wintermyer LA, Helms NT. Tri-state toxic-shock syndrome study. I. Epidemiologic findings. J Infect Dis 1982;145:431-40.
5. Schlech WF III, Shands KN, Reingold AL, Dan BB, Schmid GP, Hargrett NT. Risk factors for development of toxic shock syndrome: Association with a tampon brand. JAMA 1982;248:835-9.
6. Kehrberg MW, Latham RH, Haslam BT, Hightower A, Tanner M, Jacobson JA. Risk factors for staphylococcal toxic-shock syndrome. Am J Epidemiol 1981;114:873-9.
7. Faich G, Pearson K, Fleming D, Sobel S, Anello C. Toxic shock syndrome and the vaginal contraceptive sponge. JAMA 1986;255:216-8.
8. Barbour SD, Shlaes DM, Guertin SR. Toxic-shock syndrome associated with nasal packing: Analogy to tampon-associated illness. Pediatrics 1984; 73:163-5.
9. Hull HF, Mann JM, Sands CJ, Gregg SH, Kaufman PW. Toxic shock syndrome related to nasal packing. Arch Otolaryngol Head Neck Surg 1983; 109:624-6.
10. Bartlett P, Reingold AL, Graham DR, Dan BB, Selinger DS, Tank GW. Toxic shock syndrome associated with surgical wound infections. JAMA 1982;247:1448-50.
11. Reingold AL, Dan BB, Shands KN, Broome CV. Toxic-shock syndrome not associated with menstruation: A review of 54 cases. Lancet 1982;1:1-4.
12. 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;96:871-4.
13. Cone LA, Woodard DR, Schlievert PM, Tomory GS. Clinical and bacteriologic observations of a toxic shock-like syndrome due to *Streptococcus pyogenes*. N Engl J Med 1987;317:146-9.
14. Bartter T, Dascal A, Carroll K, Curley FJ. "Toxic strep syndrome": A manifestation of group A streptococcal infection. Arch Intern Med 1988; 148:1421-4.
15. Hribalova V. *Streptococcus pyogenes* and the toxic shock syndrome (Letter). Ann Intern Med 1988;108:772.
16. Stevens DL, Tanner MH, Winship J, et al. Severe group A streptococcal infections associated with a toxic shock-like syndrome and scarlet fever toxin A. N Engl J Med 1989;321:1-7.
17. Schlievert PM, Bettin KM, Watson DW. Production of pyrogenic exotoxin by groups of streptococci: Association with group A. J Infect Dis 1979;140:676-81.
18. Watson DW. Characterization and pathobiological properties of group A streptococcal pyrogenic exotoxins. In: Parker MT, ed. Pathogenic streptococci. Proceedings of the Seventh International Symposium on Streptococci and Streptococcal Diseases. Chertsey, England: Reedbooks, 1979:62-3.
19. Schlievert PM, Bettin KM, Watson DW. Purification and characterization of group A streptococcal pyrogenic exotoxin type C. Infect Immun 1977; 16:673-9.
20. Barsumian EL, Cunningham CM, Schlievert PM, Watson DW. Heterogeneity of group A streptococcal pyrogenic exotoxin type B. Infect Immun 1978;20:512-8.
21. Kim YB, Watson DW. Streptococcal exotoxins; biological and pathological properties. In: Wannamaker LW, Matsen JM, eds. Streptococci and streptococcal diseases: Recognition, understanding and management. New York:

Academic Press, 1972:33-50.

22. Willoughby R, Greenberg RN. The toxic shock syndrome and streptococcal pyrogenic exotoxins. Ann Intern Med 1983;98:559.

23. 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;1:1017-21.

24. 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;143:509-16.

25. Bonventre PF, Weckbach L, Staneck J, Schlievert PM, Thompson M. Production of staphylococcal enterotoxin F and pyrogenic exotoxin C by *Staphylococcus aureus* isolates from toxic shock syndrome-associated sources. Infect Immun 1983;40:1023-9.

26. Schlievert PM. Biological properties of toxic shock syndrome exotoxin. Surv Synth Pathol Res 1984;3:54-62.

27. Garbe PL, Arko RJ, Reingold AL, Graves LM, Hayes PS, Hightower AW. *Staphylococcus aureus* isolates from patients with nonmenstrual toxic shock syndrome: Evidence for additional toxins. JAMA 1985;253:2538-42.

28. Schlievert PM. Staphylococcal enterotoxin B and toxic-shock syndrome toxin-1 are significantly associated with non-menstrual TSS. Lancet 1986; 1:1149-50.

29. Johnson LP, L'Italien JJ, Schlievert PM. Streptococcal pyrogenic exotoxin type A (scarlet fever toxin) is related to *Staphylococcus aureus* enterotoxin B. Mol Gen Genet 1986;203:354-6.

30. Stollerman GH. Changing group A streptococci: The reappearance of streptococcal "toxic shock" (Editorial). Arch Intern Med 1988;148:1268-70.