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NOTE

Dual Infections with *Staphylococcus aureus* and *Streptococcus pyogenes* Causing Toxic Shock Syndrome

Possible Synergistic Effects of Toxic Shock Syndrome Toxin 1 and Streptococcal Pyrogenic Exotoxin C

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We describe a 35-year-old woman with clinical, microbiologic, and serologic findings suggesting that the patient developed toxic shock syndrome as a result of dual infections caused by toxin-producing strains of Staphylococcus aureus *and* Streptococcus pyogenes. *Certain aspects of the pathogenesis of this toxin-related syndrome are reviewed.*

Toxic shock syndrome was originally described in association with infection caused by *Staphylococcus aureus* (Todd et al., 1978). This potentially life-threatening illness has been linked to toxin production, including toxic shock syndrome toxin 1 (TSST-1) (Marrack and Kappler, 1990; Schlievert, 1993). A toxic-shock-like syndrome has been recently associated with strains of exotoxin-producing *Streptococcus pyogenes* (Cone et al., 1987; Stevens, 1992; Stevens et al., 1989). We report a case of toxic shock syndrome in a woman with clinical, serologic, and microbiologic evidence of dual infections caused by toxin-producing strains of *S. aureus* and *Streptococcus pyogenes*.

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A 35-year-old woman who had previously been healthy developed generalized weakness, fever, and malaise 4 days before admission. The following day she developed watery diarrhea, nausea, vomiting, and diffuse abdominal pain. She also experienced a sore throat during the first 3 days of illness, which had improved by admission. Additional reported symptoms included headache, dysuria, and a sore mouth. The patient's menses began 5 days before admission, and she had been using tampons.

On initial physical examination the woman was oriented but appeared to be very weak. Her temperature was 37.8°C and her pulse rate was 128 beats/min with a blood pressure of 80/60 mm Hg. She had a confluent, erythematous rash in the axillary and suprapubic areas. The throat was markedly erythematous, but there was no exudate present. She had tongue papillae changes characteristic of strawberry tongue. The conjunctiva were injected. A moderate amount of purulent drainage from the vagina was seen following tampon removal.

Initial laboratory examination revealed the following levels: creatinine 4.1 mg/dl, potassium 2.9 mmol/liter, CO_2 17 mmol/liter, anion gap 18, creatine kinase 835 U/liter, aspartate aminotransferase

56 U/liter, alanine aminotransferase 43 U/liter, and total bilirubin 3.8 mg/dl with conjugated bilirubin 1.7 mg/dl. The peripheral white blood cell count was 19,000/mm^3 (67% segmented neutrophils, 24% band forms, and 9% lymphocytes), and the platelet count was 125,000/mm^3. Admission urinalysis showed 1+ bilirubin, 2+ protein, 6–8 white blood cells/high-power field, and 2–3 red blood cells/high-power field. Chest radiographs were normal.

The patient was admitted to an intensive care unit with a presumptive diagnosis of toxic shock syndrome. Fluid resuscitation, pressor agents, and nafcillin, 2 g intravenously every 4 h, were administered. Her rash progressed to a diffuse erythroderma and her temperature increased to 39.4°C. On the second hospital day, she complained of arthralgias and developed intermittent confusion. Lumbar puncture was performed and showed only four lymphocytes/mm^3 and nine red blood cells/mm^3. Glucose and protein levels were normal. The admission vaginal culture grew 3+ *S. aureus*, which was susceptible to oxacillin. Throat culture grew 3+ group A β-hemolytic streptococci.

The woman's diarrhea and arthralgia resolved within 3 days, and she continued to improve until hospital discharge. During the second week of hospitalization, she began to desquamate the distal portions of several fingers. Serologies for rubella, leptospirosis, and Rocky Mountain Spotted Fever were all negative. An antistreptolysin 0 titer obtained on the sixth hospital day was abnormally elevated to 300 IU/ml.

The staphylococcal isolate from the patient's vaginal swab produced toxic shock syndrome toxin 1 (TSST-1); the streptococcal isolate recovered from a throat swab produced streptococcal pyrogenic exotoxin C (SPE C). Results of acute serology drawn on hospital day 2 and convalescent serology drawn 36 days later are listed in Table 1. They demonstrate a fourfold rise in antibody titer of antibody to TSST-1 and an increase in antibody titer to SPE C.

TABLE 1 Results of Antibody Assays on the Acute and Convalescent Sera From the Present Case

Serum Tested	Antibody Titer[a]		
	TSST-1	SPE C	SEC[b]
Control TSS acute serum	10[c]	10	160
Pooled gamma globulin	640	80	1280
Patient 8/17/92 (acute)	10	<10	160
Patient 9/22/92 (convalescent)	40	10	160

[a]Measured by enzyme-linked immunosorbent assay.
[b]Staphylococcal enterotoxin C–unrelated toxin.
[c]For all of these tests, titers begin with a 1:10 dilution because lesser dilutions are uninterpretable as a result of background interference.

To our knowledge, this is the first reported case of toxic shock syndrome caused by dual infections resulting from *S. aureus* and group A β-hemolytic streptococci. Both microbiologic and serologic findings suggest that dual infections did occur. Both isolates produced exotoxins associated with the pathogenesis of toxic shock syndrome, and the paired antibody assays of the patient's acute and convalescent sera provide strong evidence for recent infections due to toxin-producing strains of *S. aureus* and *Streptococcus pyogenes*. The patient had a fourfold rise in antibody titer to TSST-1, indicating exposure to the toxin. Her convalescent antibody titer to TSST-1 was less than that of individuals who are considered resistant to the toxin. No antibody response or marginal antibody response is commonly observed in patients who develop toxic shock syndrome (Bonventre et al., 1984). The patient had no measurable antibody titer to SPE C acutely, and there was a minor increase in titer during her convalescence. This is consistent with SPE C being the least effective of all pyrogenic exotoxins to elicit an antibody response (Bohach et al., 1990). At the same time, the patient did not manifest a general antibody deficiency because she had a protective antibody titer to staphylococcal enterotoxin C (SEC).

We speculate that the clinical manifestations observed in this patient resulted from the synergistic effects of the TSST-1 and SPE C. Previous work (P.M. Schlievert, unpublished data) has shown that animals treated with two or more toxins belonging to the pyrogenic exotoxin family develop much greater than expected mortality than animals treated with a single pyrogenic exotoxin at the same additive dose. Toxin assay and mortality rates from 434 patients with confirmed or probable toxic shock syndrome suggest that the toxicity resulting from the combination of TSST-1 and staphylococcal enterotoxin C_1 (SEC1) is more potent than TSST-1 alone (Crass and Bergdoll, 1986). Finally, it is well recognized that TSST-1 and SPE C cause the release of interleukin-1 and tumor necrosis factor-α and dramatically enhance host susceptibility to lethal endotoxin shock (Stone and Schlievert, 1987), and that endotoxin in turn enhances interleukin-1 and tumor necrosis factor-α production by macrophages stimulated with TSST-1 (Beezhold et al., 1987).

Streptococcal toxic shock syndrome due to noninvasive pharyngitis has been infrequently reported, and in only one case has serologic documentation, based on seroconversion of antitoxin, been described (Chapnick et al., 1992). An otherwise healthy 14-year-old boy developed toxic shock syn-

drome due to group A β-hemolytic streptococcal pharyngitis in that case report. A culture of a throat specimen revealed heavy growth of *Streptococcus pyogenes*, which was found to produce SPE A, but not SPE B or SPE C. Multiple cultures of blood, sputum, urine, and cerebrospinal fluid obtained at admission were negative. Testing for antibody to type A exotoxin in acute and convalescent sera demonstrated an impressive rise in antibody titer from 1:40 to 1:1280. In another case report that lacked tests for antitoxin assays (Bradley et al., 1991), a pediatric patient developed pharyngitis with complicating toxic shock syndrome due to *Streptococcus pyogenes* isolated on throat specimen culture. This isolate produced both SPE A and SPE B.

Our case represents an initial description of toxic shock syndrome caused by dual noninvasive infections resulting from toxin-producing strains of *S. aureus* and *Streptococcus pyogenes*. In view of the increasing prevalence of severe pyogenic and toxemic illnesses produced by *Streptococcus pyogenes*, similar case presentations are likely, and clinicians must consider dual infections in the short-term and long-term management of these patients.

REFERENCES

Beezhold DH, Best GK, Bonventre PK, Thompson M (1987) Synergistic induction of interleukin-1 by endotoxin and toxic shock syndrome toxin-1 using rat macrophages. *Infect Immun* 55:2865–2869.

Bonventre PF, Linnemann C, Weckbath LS, et al. (1984) Antibody responses to toxic-shock syndrome (TSS) toxin by patients with TSS and by healthy staphylococcal carriers. *J Infect Dis* 150:662–666.

Bohach GA, Fast GJ, Nelson RD, Schlievert PM (1990) Staphylococcal and streptococcal pyrogenic toxins involved in toxic shock syndrome and related illnesses. *Crit Rev Microbiol* 17:251–272.

Bradley JS, Schlievert PM, Peterson PM (1991) Toxic shock-like syndrome, a complication of strep throat. *Pediatr Infect Dis* 10:790.

Chapnick EK, Grandon JD, Lutwick LI, Kim J, Levi M, Kim MH, Schlievert PM (1992) Streptococcal toxic shock syndrome due to noninvasive pharyngitis. *Clin Infect Dis* 14:1074–1077.

Cone LA, Woodward DR, Schlievert PM (1987) Clinical and bacteriological observations of a toxic shock like syndrome due to *Streptococcus pyogenes*. *N Engl J Med* 317:146–149.

Crass BA, Bergdoll MS (1986) Toxin involvement in toxic shock syndrome. *J Infect Dis* 153:918–926.

Marrack P, Kappler J (1990) The staphylococcal enterotoxins and their relatives. *Science* 248:705–711.

Schlievert PM (1993) Role of superantigens in human disease. *J Infect Dis* 167:997–1002.

Stevens DL (1992) Invasive group A streptococcal infections. *Clin Infect Dis* 14:2–13.

Stevens DL, Tanner MH, Winship J, Swarts R, Ries KM, Schlievert PM, Kaplan E (1989) Severe group A streptococcal infections associated with a toxic shock-like syndrome and scarlet fever toxin A. *N Engl J Med* 321: 1–6.

Stone RL, Schlievert PM (1987) Evidence for the involvement of endotoxin in toxic shock syndrome. *J Infect Dis* 155:682–689.

Todd J, Fishaut M, Kapral F (1978) Toxic shock syndrome associated with phage-group-I staphylococci. *Lancet* 2: 1116–8.