A Fatal Case Of Toxic Shock Associated With Group A Streptococcal Cellulitis

David M. Whittiker, M.D.

The patient in septic shock presents an imposing challenge to the physician's clinical skills; therapy must be initiated often before important data are obtained to assure optimal outcome for these very ill patients. For the past several decades the term *septic shock* has been virtually synonymous with gram-negative sepsis, as this syndrome is most frequently caused by the endotoxin sometimes expressed by gram-negative organisms. In susceptible individuals this endotoxin can cause hypotension, mental obtundity, decreased left ventricular function, acute renal impairment, vascular instability, severe hematological derangements, and, in 25 percent of cases, death.[1] The early 1980s introduced us to a relatively new player in sepsis: *Staphylococcus aureus* and the toxic shock syndrome. A series of cases was defined in relation to vaginal tampon use, but since then toxic shock has occurred also in the presence of other staphylococcal infections.[2] Recently another gram-positive bacterium has reportedly been associated with sepsis and shock. This organism is well known to office-based family physicians as the cause of many soft tissue infections thought until recently to be "routine": acute pharyngitis, otitis media, acute sinusitis, cellulitis, and erysipelas. The organism is group A β-hemolytic streptococcus (GABHS), and there is an increasing number of reports of sepsis and death occurring as complications of one of these so-called routine infections.[3-6] These findings are of great importance to office-based family physicians, because many affected patients have been young, otherwise healthy individuals without predisposing immune deficiency or debilitating illnesses. The following is a report of septic shock that recently occurred in my patient.

Submitted, revised, 10 December 1991.

From the Wichita Falls Family Practice Residency Program, Department of Family Practice and Community Medicine, University of Texas Southwestern Medical Center, Dallas, and The Southwest Medical Clinic, Wichita Falls, TX. Address reprint requests to David M. Whittiker, M.D., Six Eureka Circle, Wichita Falls, TX 76308.

Case Report

The patient was a 38-year-old woman, a reformed intravenous amphetamine user and former prostitute, who came to the office one morning complaining of an abrupt onset of weakness, diarrhea, left-sided abdominal pain, and difficulty breathing that began 48 hours earlier. Her history included bilateral breast implants 5 years previously, laser ablation of a rectal carcinoma 2 years before, a total abdominal hysterectomy and bilateral oophorectomy for persistently positive Papanicolaou smears 18 months before, and amphetamine abuse. Medications included regular injections of estrogens and a benzodiazepine for anxiety.

During a brief examination in the office the patient was exceedingly weak but awake and alert, unable to speak because of her weakness. Her blood pressure was 80/50 mmHg, pulse 110 beats per minute, respirations were 28/min, and her temperature was 35.5°C (96°F). Her throat was clear as were her lungs, and she had no heart murmur. Her abdomen was slightly tender in the left lower quadrant, but the bowel sounds were normal. There were bullous lesions on the dorsum of the right hand. She denied recent use of illicit drugs.

She was sent immediately to the intensive care unit in the local hospital for further evaluation and treatment. There her blood pressure was 80/50 mmHg, pulse 120 beats per minute, respirations 40/min and rectal temperature 35°C (95°F). There were no abnormal findings on a pelvic examination, but a rectal examination showed a stool grossly positive for occult blood. Though she continued to be weak, there were no lateralizing neurological signs. Her skin was mottled, and there was peripheral cyanosis. Her right hand was pale, cold, and painful.

Laboratory studies disclosed the following values: her white cell count was 15.9×10^9/L ($15{,}900/mm^3$) with 0.32 segmented neutrophils and 0.50 band forms. The hemoglobin was 10.7 mmol/L (17.2 g/L) and the hematocrit was 0.50;

platelets were 245 × 10^9/L (245,000/mm^3). The prothrombin time was 18 seconds with a control of 11 seconds. The sodium was 128 mmol/L (128 mEq/L), potassium 6.6 mmol/L (6.6 mEq/L), chloride 90 mmol/L (90 mEq/L), bicarbonate 8 mmol/L (8 mEq/L), blood urea nitrogen 14.6 mmol/L (41 mg/L), and creatinine 398 μmol/L (4.5 mg/L). The blood glucose was initially measured at 0.6 mmol/L (10 mg/L), but this value was judged clinically to be an artifact and a recheck had normal blood glucose readings. The urinalysis showed a specific gravity of 1.010, a large amount of blood, a pH of 5.5, protein 1 g/L (100 mg/L), and red cells and white cells too numerous to count, with frequent bacteriuria. Arterial blood gases on admission showed a pH of 6.94, pCO_2 4.4 kPa (33 mmHg), pO_2 14.3 kPa (107 mmHg), and base excess − 1.37 mmol/L (− 27 mEq/L). The aspartate aminotransferase was 3.22 μkat/L (3217 nmol/L/sec) (193 U/L), lactic dehydrogenase 11.55 μkat/L (11,550 nmol/sec/L) (693 U/L), urate 547 μmol/L (9.2 mg/L), and creatine kinase was 174.03 μkat/L (174,044 nmol/sec/L) (10,440 U/L). The fibrinogen was 3.14 g/L (314 mg/L), and fibrin split products were greater than 40 μg/mL. A Gram stain of the fluid in the right-hand bullae showed moderate gram-positive cocci in chains. Blood alcohol was not measurable, and the serum drug test showed only the benzodiazepine, but the urine drug test contradicted the earlier history of no recent drug use: there were amphetamines in the urine. When confronted with this evidence, the patient confirmed that she had been injected by others with intravenous amphetamine into her right hand. Other studies included an echocardiogram with normal findings, an electrocardiogram that showed only sinus tachycardia, a normal chest radiograph, and an analysis of her cerebrospinal fluid that showed her protein level was 0.31 g/L (3.1 g/L), but no other abnormality. Samples of the cerebrospinal fluid, blood, urine, and fluid obtained from the bullae on the dorsum of the right hand were sent for culture.

Despite early institution of intravenous fluids, pressor agents, broad-spectrum antibiotics, and bicarbonate, the patient's course deteriorated, and she died 6 hours after admission. Cultures of all fluids were negative except that from the bullae on the right hand, which grew GABHS in great amounts. The body was sent for an autopsy, where an "intense inflammatory infiltrate" and "large numbers of gram-positive cocci" in microscopic sections of the right-hand wound were found. The final autopsy diagnosis was death from complications of cellulitis caused by GABHS.

The culture specimen was sent to the laboratory of Dennis L. Stevens, M.D., at the Veterans Administration Medical Center in Boise, ID, for identification and assay for presence of exotoxin. The *Streptococcus* organism that was responsible for this patient's death was of M Type 22 and T Type 12, and it produced streptococcal pyrogenic exotoxin B.

Discussion

Gram-positive organisms were the most common cause of sepsis and shock at the beginning of this century. After the introduction of effective antibiotics in the 1930s and 1940s, the rate of serious suppurative and nonsuppurative complications of gram-positive infections declined to where such cases became the exception.[7] In the early 1980s the toxic shock syndrome was defined as a predictable "new" complication of staphylococcal infections in susceptible individuals.[2] There have been reports during the past few years of resurgent virulence displayed by certain group A streptococci.[3-5] In 1987 Cone, et al.[4] reported two cases of streptococcal cellulitis that were complicated by sepsis and shock. One patient died. In 1988 Bartter, et al.[5] reported three similar cases marked by the presence of streptococcal soft tissue infection, hypotension, and renal failure, and they coined the term *toxic strep syndrome*, postulating an exotoxin-mediated process that can go underdiagnosed and be confused with staphylococcal toxic shock. Stevens, et al.[3] reported in 1989 a series of 20 patients in the Rocky Mountain area who had streptococcal infections. Nineteen developed sepsis and shock, and 6 died. The patients in all these cases were young (aged 29 to 66 years) and otherwise healthy, and most complained of soft tissue infections, such as cellulitis, pharyngitis, myositis, or fasciitis. Such cases have now been described in Great Britain and in various regions of the United States, suggesting not only an increased rate but also a widespread occurrence of this dangerous organism.

The toxic strep syndrome is probably mediated by exotoxins produced by certain serotypes of GABHS.[7-9] These toxins, streptococcal pyrogenic exotoxin-A (SPE-A), SPE-B and SPE-C, have been analyzed and bear some structural similarities to the toxin produced by the staphylococci that cause toxic shock syndrome.[10] The serotypes associated with toxin production were more widespread before the 1950s, and SPE-A has been implicated as the causative factor of rheumatic fever, in decline since that time. It has further been proposed that a shift in the number of these virulent serotypes is responsible for the emergence of the toxic strep syndrome, as well as the recent increase in rheumatic fever reported in some areas.[7,9]

The syndrome can strike persons of any age. The most common complaint is an acute onset of skin or other soft-tissue infection, usually accompanied by fever, myalgias, weakness, and other symptoms referrable to the specific infection. Within hours multiorgan changes occur, producing hypotension, acute renal failure, mental status changes, decreased left ventricular function, severe acidemia, hematologic derangements, vascular instability, and eventually death. Poor prognosis is presaged by early onset of acute renal failure and hypotension. Laboratory findings are not specific to this syndrome but reflect the severe organ dysfunction that occurs. Blood cultures can be negative, as it is less the presence of the organisms themselves than the toxins they elaborate that cause the cellular changes leading to this syndrome.[11] Cultures of the infected tissues should grow GABHS, but the time required for such cultures to be completed limits their usefulness in the acute early stages of the illness. A Gram stain of infected tissues will often show the gram-positive cocci, giving weight to the diagnosis of sepsis or toxemia caused by GABHS. Caution should be used, as it is often difficult to distinguish between streptococcal and staphylococcal infections using Gram stain alone.

Effective treatment requires early suspicion for GABHS and prompt attention to the tissues that can harbor the toxin-producing organisms. Evaluation of patients with possible sepsis should include a complete examination of the skin and other soft tissues for evidence of infection. If such an infection is suspected, then débridement of the infected area is required, because only a small number of organisms can produce sufficient toxin to be clinically important. The toxins are not dialyzable, nor is there an antitoxin available. It might be wise, if GABHS infection is suspected, to include aqueous penicillin in addition to the broad-spectrum antibiotics usually prescribed.[8] The antistaphylococcal penicillins are active against GABHS also, though much less so than penicillin. Other supportive measures, such as intravenous fluid therapy, central venous pressure monitoring, acid-base management, and treatment of specific organ system dysfunction, are identical to such treatment rendered to patients with gram-negative or staphylococcal toxic shock.

Primary care physician awareness of the toxic strep syndrome is crucial, for treatment must be initiated often before appropriate consultation can be obtained. It has been postulated that the present generation, treated as they have been with effective antibiotics for common streptococcal infections, could be without actively acquired immunity and therefore could be more susceptible to this dangerous organism and its toxins.[9] If, as has been suggested, the rate of these virulent serotypes is increasing, then the role played by the well-informed family physician will be pivotal.

References

1. Root RK, Jacobs R. Septicemia and septic shock. In: Wilson JD, Braunwald E, Isselbacher KJ, Petersdorf RG, Martin JB, Fauci AS, et al., editors. Harrison's principles of internal medicine. 12th ed. New York: McGraw-Hill, 1991:502-7.
2. Chesney PJ, Davis JP, Purdy WK, Wand PJ, Chesney RW. Clinical manifestations of toxic shock syndrome. JAMA 1981; 246:741-8.
3. Stevens DL, Tanner MH, Winship J, Swarts R, Ries KM, Schlievert PM, 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.
4. 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.
5. 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.

6. Group A beta-hemolytic streptococcal bacteremia — Colorado, 1989. MMWR 1990; 39:3-6, 11.
7. Stollerman GH. Changing group A streptococci. The reappearance of streptococcal "toxic shock." Arch Intern Med 1988; 148:1268-70.
8. Sanderson P. Do streptococci cause toxic shock? BMJ 1990; 301:1006-7.
9. Schwartz B, Facklam R, Breiman RI. Changing epidemiology of group A streptococcal infection in the USA. Lancet 1990; 336:1167-71.
10. Marrack P, Kappler J. Staphylococcal enterotoxins and their relatives. Science 1990; 248:705-11.
11. Bisno AL. Group A streptococcal infections and acute rheumatic fever. N Engl J Med 1991; 325:783-93.