Case Report

Prolonged Course of Toxic Shock Syndrome Associated with Methicillin-Resistant *Staphylococcus aureus* Enterotoxins G and I

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Toxic shock syndrome (TSS), which may be life-threatening, is defined by clinical and laboratory evidence of fever, rash, hypotension, and multisystem abnormalities in the absence of other causes. Most cases are nonmenstrual in origin.†* Whereas *Staphylococcus aureus* TSS toxin-1 causes the vast majority of menstrual cases, it causes only about half of other cases." Staphylococcal enterotoxins (SEs) were implicated in nonmenstrual TSS cases shortly after the role of TSS toxin-1 was elucidated, and currently, SEs that are reported to be associated with TSS are SEs A, B, C, D, G, H, and I, with SE-B most commonly reported and SE-G and SE-I most recently reported, albeit the latter two with scant clinical details.2,4,6 The following case associated with SE-G and SE-I illustrates the consequences of these immunomodulatory pyrogenic toxin superantigens over a prolonged course, as well as pitfalls in their diagnosis and management.

CASE REPORT

A 57-year-old woman was transferred to Northridge Hospital Medical Center (NHMC) on October 3, 1997, for rehabilitation. She had sustained multiple traumata on May 2, 1997, which led to admission to an intensive care unit (ICU) in another hospital. She suffered a C2 odontoid fracture, intracranial bleeding, right hemothorax and lung contusion, and multiple fractures. She was initially quadriplegic and hypotensive; the serum creatinine was 1.7 mg/dL. The patient underwent multiple surgeries, received intravenous cefazolin and corticosteroids, developed adult respiratory distress syndrome (ARDS), and remained dependent on mechanical ventilation. She temporarily needed hemodialysis.

On hospital day 38, fever ensued (39.5°C) while the patient received intravenous vancomycin therapy for presumptive methicillin-resistant *S. aureus* (MRSA) pneumonia. Blood pressure dropped to 70 mm Hg systolic, and oliguria, hypotension, leukocytosis (white blood cell count [WBC] 19,400/mm³) followed. Ceftazidime therapy was added, but the patient remained febrile (39.7°C), the WBC rose further, and nonoliguric acute tubular necrosis secondary to hypotension and "occult sepsis" were diagnosed; an erythematous rash on the patient's back was ascribed to possible allergy to ceftazidime. The patient was transferred to the ICU of another medical center on June 12, 1997, for further management. She was febrile on admission while receiving intravenous ceftazidime and vancomycin, the latter of which was given for approximately 3 months. A consultant initially noticed "diffuse erythroderma," which suggested drug allergy, and omitted ceftazidime therapy. Purulent tracheal secretions continually yielded MRSA. Other antimicrobials were administered for finding of gram-negative bacilli in cultures from various sites, but infections there did not seem to have contributed to recurrent bouts of fever, hypotension, and leukocytosis. Color photographs documented persistent diffuse erythema. On day 7 empirical therapy with ceftazidine and amphotericin B was started, and fluconazole was also briefly administered to reduce fever (39.9°C). Dopamine treatment was needed, and leukocytosis (WBC 18,800/mm³) increased. Creatinine rose further, and hemodialysis continued. On day 11 a covering consultant administered intravenous immunoglobulin initially at 1 g/kg and then 0.5 g/kg thrice on alternate days after having considered a diagnosis of TSS; this intervention was not documented in transfer summaries, consultants' notes, or in telephonic communications in 1997. It led to a somewhat salutary response, including return of WBC to normal. Erythematous rash continued, and on day 37, fever recurred. Vancomycin and antibiotics directed against gram-negative
bacilli were given for "probable pneumonia," but fever and hypotension continued, requiring intravenous phenylephrine on day 47. The WBC rose to 37,900/mm³.

The patient slowly improved, but on day 80 she sustained another episode of fever, erythema, and leukocytosis. Amphotericin B was empirically administered, complicated by atrial fibrillation. On day 104 multiple antibacterials, including vancomycin, were given for treatment of fever. Pressors were required again; leukocytosis worsened. On day 130 "sepsis syndrome" was diagnosed, but blood cultures remained negative and no cultural confirmation was made. Imipenem, ciprofloxacin, and vancomycin therapy was given, and transfer to NHMC took place October 3, 1997.

On admission to rehabilitation service the patient had multiple decubitus ulcers, including on the occiput. Imipenem and ciprofloxacin were continued, despite no clear source of infection. Sputum culture yielded MRSA. Dialyses continued. On day 4, temperature rose to 39.2°C. Later cefazidime and gentamicin were given. Chest computed tomography (CT) showed pleural effusions, volume loss, atelectasis, and perihilar alveolar air space filling defect infiltrates. Cultures of tracheal aspirate and occipital decubitus ulcer yielded MRSA susceptible only to vancomycin, rifampin, and tetracycline. White blood cell count increased to 13,200/mm³. A consultant’s examination on day 5 showed tachypnea, tachycardia, diffuse erythema of the skin, multiple decubitus ulcers, and no exudate at the gastrojejunosotomy (G-J) site. Vancomycin and mupirocin were administered, along with local mupirocin at the G-J site and chlorhexidine. Leukocytosis worsened. On day 6, fever recurred, lethargy ensued, erythematous rash increased, leukocytosis increased further (WBC 16,900/mm³ with 35% immature forms); hypotension and tachypnea along with a heart rate of 156 beats per minute associated with atrial flutter with 2:1 block necessitated transfer to the ICU.

Fluid resuscitation and levaterenol were required to correct hypotension (BP 60/40 mm Hg), and the atrial flutter was converted. Other findings included obtundation, diffuse blanching erythema, and extensive occipital decubitus ulcers. Supportive care, including mechanical ventilation and vancomycin, continued; meropenem was given. Sepsis syndrome with toxic erythema was diagnosed. On day 7, mental status improved, but fever persisted (temperature 39.4°C) and WBC rose to 26,400/mm³. By day 10, fevers had somewhat abated, but pressors were still required, and the leukocytosis persisted; indium WBC scan was negative except for slightly increased activity at the occiput. Antibacterial therapy was continued, as was dialysis.

On day 15, erythema increased, leukocytosis worsened (WBC 38,600/mm³) and hypotension recurred; diphenhydramine and hydrocortisone were administered, and mupirocin and meropenem were omitted because of possible drug allergy. An "antibiotic holiday" followed, accompanied by some clinical improvement, although leukocytosis persisted, associated with new eosinophilia. Search for other infections, including fungal, was negative.

On day 31, with the finding of strawberry tongue and increased subconjunctival injection in both eyes, a tentative diagnosis of persistent, recurrent TSS was made. An isolate from tracheal aspirate of MRSA (isolate No. 1) was sent to a reference laboratory (MRL Reference Laboratory, Cypress, California) for TSS toxin analysis (later results showed that TSS toxin-1 and enterotoxin B were not produced), serum was sent for antibody detection against TSS toxin-1 (MRL Reference Laboratory; later result indicated antibody present) and for T-Cell analysis and quantitative serum immunoglobulin levels. Intravenous immunoglobulin, 0.35 g/kg, was given pending results. Five additional daily intravenous immunoglobulin infusions of 0.35 to 0.4 g/kg were given. CD4+ cell count was 2220/mm³ (normal, 400-1700) and CD8+ cells, 1812/mm³ (normal, 240-1220). Serum IgG level was 465 mg/dL (normal, 613-1245); IgM, 30 mg/dL (normal, 55-334); and IgA was normal. Fever decreased and the patient improved, although leukocytosis persisted. By day 44, the patient was more alert and able to be weaned from the ventilator. Erythema had decreased, and the WBC had decreased from 35,500/mm³ to 19,800/mm³ after the third dose of intravenous immunoglobulin. Audiogram showed profound sensorineural hearing loss in both ears. Cultures from the G-J tube site, trachea, and occult yielded MRSA. Mild subconjunctival injection, intermittent erythema, and low grade fevers again led to administration of a second course of five infusions of intravenous immunoglobulin on days 53 to 61. The WBC fell to normal and fever abated. Multiple nails were lost. Eradication measures against MRSA were again unsuccessful and led to rifampin resistance in MRSA.

On day 75, the G-J tube was removed. A long hospitalization followed with need for dialyses and breakdown of the former G-J tube site, with culture yielding MRSA. Intermittent unexplained leukocytosis occurred. The patient returned to the rehabilitation service on day 126.

Local surgical exploration, in March 1998, of the old G-J site showed a retained suture, which was removed. Urine output increased and the patient was changed to peritoneal dialysis. Tracheal aspirate cultures continued to show MRSA. In April 1998, levels of CD4+ and CD8+ cells were normal. The patient was discharged in a wheelchair on April 28, 1998. A nonhealing tracheocutaneous fistula, which along with the occipital ulcer was colonized with MRSA, was closed.

Several episodes of unexplained leukocytosis occurred, and the patient was briefly readmitted on November 30, 1998, for intravenous vancomycin therapy. Nonetheless, as dialysis continued, leukocytosis recurred (e.g., WBC 21,200/mm³) and intercurrent urinary tract infections were treated. Worsening of the occipital decubitus ulcer led to readmission February 8, 1999. Methicillin-resistant S. aureus (isolate 2) was present only in the occipital wound. Vancomycin was given again, and plastic
surgical débridement achieved good response. Serum was obtained for antibody determination. No intravenous immunoglobulin could be obtained. The patient died elsewhere in 2000 while dependent on dialysis.

Isolates Nos. 1 and 2 were analyzed by standard methods. A multiplex polymerase chain reaction (PCR) assay for 10 toxin genes currently known to be associated with staphylococcal TSS was performed. Results indicated that both isolates harbored the structural genes for SE-G and SE-I. Genes for TSS toxin-1 or other enterotoxins were not detected in either isolate. Antibody against SE-G was measured by enzyme-linked immunosorbent assay (ELISA) and found to be elevated at a titer of 1:1280 compared with 1:640 found in intravenous immunoglobulin, indicating past exposure.

**DISCUSSION**

The patient presented here exhibited multiple episodes of TSS (Table 1), including approximately six at two other institutions, before definitive management, which included repeated courses of intravenous immunoglobulin infusions, and subsequent resolution of focal infections controlled into intoxication. The nosology is not entirely clear as to whether the episodes were recurrences or variations on a continuum of chronic disease; certainly the patient showed a scarlet fever-like rash for more than 5 months and later had bouts of unexplained leukocytosis. The course of the rash was longer than that of previously described "late" rashes several weeks after a bout of TSS. Considerable morbidity included not just prolonged hospitalizations and attendant, almost assuredly unnecessary, use of antibacterial and antifungal agents with their toxicity (e.g., hearing loss and cardiac arrhythmias) but also years of continued dependency on renal dialysis. The elevated antibody titer to SE G found long after (about 1 year) administration of intravenous immunoglobulin reflected host response and certainly was not related to the distant intravenous immunoglobulin use. The prior antibacterial therapy and nosocomial acquisition are consistent with prior nonmenstrual cases of toxic shock syndrome, but the recurrences are not. Although not actively sought, no other nosocomial cases were noted, perhaps because of isolation procedures for MRSA.

Staphylococcal enterotoxins are moderate molecular weight protein toxins that not only produce emesis in some settings but, like TSS toxin-1 and the pyrogenic exotoxins of *Streptococcus pyogenes*, act as superantigens. Thus, they bind major histocompatibility complex (MHC) class II proteins, stimulate T lymphocytes dependent on the V_{β} of the T lymphocyte receptor, and cause their clonal proliferation; they also cause sustained release of cytokines, such as tumor necrosis factor, interleukins and interferon-γ, the last of which can suppress immunoglobulin secretion. Findings in this patient included compatible clinical features, and laboratory features of nonspecific clonal T-lymphocyte activation and depression of IgG and IgM levels, with possible incomplete inability to form potentially protective antibody. Serum immunoglobulin levels reverted to normal long after intravenous immunoglobulin therapy, but antibody against SE-G later was found. The patient's clinical course and the experimental finding of increased production of other toxins at 35° to 40°C suggest that the wound isolates were more significant than the sputum isolates. Although clonal typing of the isolates from the patient was not done, it is likely that they were the same.

The clinical manifestations of the staphylococcal toxins, including TSS toxin-1, SEs, and others, are protean. The interactions between the toxins and a diverse variety of hosts, including early neonates (TSS toxin-1), patients with acquired immunodeficiency syndrome (AIDS) (TSS toxin-1, SE-A, SE-B), human T-cell lymphotropic viral infections, and rarely, in children with Kawasaki syndrome-like illness (SE-B), lead to far-ranging clinical findings. In addition, Lina and colleagues recently suggested, based upon finding TST toxin-1 and SEs in cases of staphylococcal scarlet fever, that it may be an abortive form of TSS.

Staphylococcal enterotoxin-G and SE-I were originally isolated from a *S. aureus* from human nares and shown to have both emetic properties and those of a superantigen. Jarraud and colleagues recently used PCR to detect SE-G and SE-I genes in strains sent to a reference laboratory and, subsequently, found these isolates did not produce other known SEs, exfoliative toxins, or TSS toxin-1. They reported that 9 of 170 TSS cases were linked to SE-G and SE-I; only one was menstrual in origin, and no information on antibiotic susceptibility or nosocomial acquisition was given. Linkage to staphylococcal scalded skin syndrome was shown. The current requirement for laboratory confirmation of diagnosis lies in PCR amplification done in a reference laboratory, as in the present case and in the French study, illustrating the need for earlier diagnosis and presumptive therapy before laboratory confirmation. Moreover, the limited usefulness of the commercially available toxin analysis, especially in nonmenstrual TSS, is shown by the present case.
Therapy includes supportive measures, use of appropriate antibacterial therapy (with consideration of clindamycin use if the isolate is susceptible), drainage of focal infections, and in parallel with the convincing demonstration of its efficacy in treatment of streptococcal TSS and fasciitis, infusions of intravenous immunoglobulin. Although use of a single dose of intravenous immunoglobulin has been suggested, experience in streptococcal disease and in this patient suggests the need for multiple infusions or titration to clinical response. Commercial intravenous immunoglobulin may have nonspecific properties, but it has also been shown to contain high concentrations of antibodies to eight different staphylococcal superantigens and to inhibit T-cell activation by them. Assays for SE-G and SE-I were not done in that study or in preparations used for this patient, but the clinical response argues for their presence. Since the superantigens are bacterial virulence factors, experimental vaccine work with SE-A devoid of that property is one theoretic approach to protection.

CONCLUSION

Nonmenstrual TSS may be confused with other conditions, which in the nosocomial setting are, most importantly, sepsis itself and drug allergy. It has a higher case-fatality rate than does menstrual TSS, and is probably underdiagnosed. Toxic shock syndrome associated with SE-G and SE-I, which is certainly underdiagnosed, is probably similar to that caused by other staphylococcal toxins, but this case had a prolonged course with prominent erythroderma. Reliance on antibacterial agents alone is inappropriate, and appropriate acute management of TSS includes clinical suspicion, supportive care, administration of intravenous immunoglobulin, and careful attention to resolution of focal infection.

ACKNOWLEDGMENTS

The authors thank Dr. Jeffrey Weisel and the staff, particularly those of the microbiology laboratory, of Northridge Hospital Medical Center for assistance in the management of this patient, and Dr. Bernard Kubak for useful information.

REFERENCES