

CLINICAL REPORT

Two Men with Toxic Shock Syndrome Presenting with Targetoid and Spotty Skin Rashes

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Two previously healthy men who presented with hypotension, constitutional symptoms, and targetoid and discrete spotty erythematous plaques were diagnosed with toxic shock syndrome based on histopathological findings. Specifically, their biopsies revealed necrotic keratinocytes, neutrophils in the epidermis, and neutrophils surrounding dilated superficial vessels. In one case, the diagnosis of toxic shock syndrome was confirmed with rising titers to toxic shock syndrome toxin-1. Both patients recovered with supportive care and clindamycin administration. We suggest that patients with fever, hypotension, constitutional symptoms and rash should be started on clindamycin and have a skin biopsy as part of their initial evaluation. An understanding that toxic shock syndrome can strike anyone has manifold dermatological manifestations and defined histopathological findings is important for its early diagnosis and effective treatment. **Key words:** toxic shock syndrome; erythema multiforme; hypotension; clindamycin; superantigen; rash.

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First described in 1978 (1), toxic shock syndrome (TSS) combines fever, rash, hypotension, and desquamation (2) and multi-organ system dysfunction (3). Toxic shock syndrome toxin (TSST-1) produced by *Staphylococcus aureus* commonly causes TSS. A superantigen, TSST-1, binds class II major histocompatibility complex proteins of T-cells directly, stimulating them to release potent inflammatory mediators (4). Two types of TSS exist: menstrual TSS (mTSS) and non-menstrual TSS (nmTSS). mTSS was first described in 1980 among young, white, menstruating women using super-absorbent tampons. nmTSS affects both sexes and all age groups, is usually seen in burn victims and surgical patients, and a source is almost never found. Reducing the mortality of TSS requires early recognition of its

clinical and histopathological findings, despite atypical presentations, with prompt treatment prior to serious end organ damage.

CASE REPORT

Case 1

A previously healthy, 32-year-old Sri Lankan man presented with a 2-day history of headache, fever, malaise, productive cough, dizziness, sore throat, and an irregular, red rash. He complained of nausea, myalgias, malaise, moderate pruritus, and dysphagia. He denied neck stiffness, joint pain, photophobia, recent travel, sick family members, or a recent tick bite. Standard vaccinations were current. He was monogamous and only took acetaminophen. The patient was febrile (39.9°C), hypotensive, and tachycardiac. Skin examination revealed multiple 1–3 cm painless, erythematous annular plaques; many with non-blanching dusky centers distributed on the posterior trunk (Fig. 1). Blanching 0.5–1.5 cm erythematous macules and papules covered the anterior trunk extending bilaterally to the upper arms, thighs, and palms. The oral mucosa was uninvolved; the conjunctiva and pharynx were injected without exudate. There was no palpable lymphadenopathy. There was mild right upper quadrant tenderness without rebound or guarding, and the liver and spleen were not enlarged. Abnormal laboratory values included: white blood cell (WBC) count $13.6 \times 10^9/l$ ($4.5-10 \times 10^9/l$) with 41% bands (0–2%), prothrombin time (PT) 16.7 sec (11–13 sec), partial thromboplastin time (PTT) 33.6 sec (25–35 sec), fibrin split products 10–40 µg/ml (<10 µg/ml) fibrinogen 849 mg/dl (200–400 mg/dl), lactate

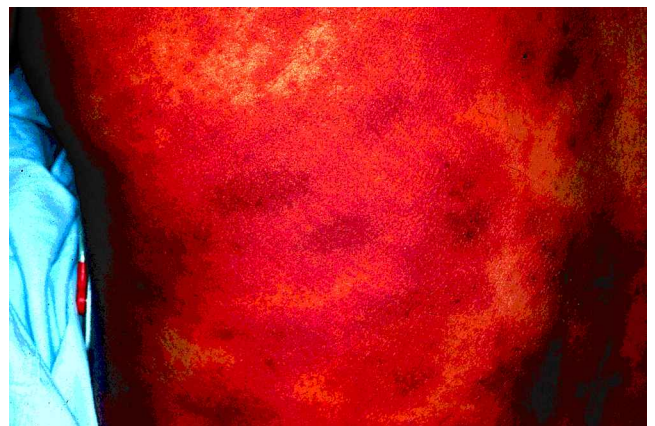


Fig. 1. Case 1: Multiple coalescing 1–3 cm erythematous plaques; many with non-blanching dusky centers distributed on back.

dehydrogenase (LDH) 275 U/l (50–240 U/l), alanine aminotransferase (ALT) 61 mg/dl (5–40 mg/dl), aspartate aminotransferase (AST) 51 mg/dl (5–40 mg/dl), blood urea nitrogen (BUN) 26 mg/dl (8–25 mg/dl), creatinine 2.0 mg/dl (0.5–1.5 mg/dl), and platelets $124 \times 10^9/l$ ($150\text{--}450 \times 10^9/l$).

The patient was pan-cultured and two skin biopsies revealed single necrotic keratinocytes, neutrophils trapped within the epidermis, striking dermal purpura, a perivascular infiltrate of neutrophils, and dilated superficial vessels saturated with neutrophils (Fig. 2) suggestive of TSS. Doxycycline was discontinued, and clindamycin and gentamycin were started. Blood samples were sent for TSST-1 antibody assay. On hospital day 3, the patient required triple vasopressors and mechanical ventilation but by day 5, the patient's condition had stabilized. On day 11, the patient's skin began to desquamate. He was discharged on day 16 with no apparent sequelae.

The diagnosis of TSS was confirmed by rising titers of TSST-1 antibodies that rose from 1:128 on hospital day 1, to 1:512 on day 7, and 1:1024 on day 14. The normal titer is $>1:1000$ and a baseline titer of $<1:100$ is thought to render a person susceptible to TSS. The patient had normal blood, urine, and CSF results for Rocky Mountain Spotted Fever (RMSF), Q fever, typhus fever, erlichiosis, anti-streptolysin, and Lyme disease, syphilis, anti-nuclear antibodies, and human immunodeficiency virus (HIV).

Case 2

A previously healthy 30-year-old African-American male presented with a 1-week history of headache, nausea, myalgias, sore throat, and 4 days of amoxicillin use. Standard vaccinations were current. He had a history of asthma, two bacterial pneumonias, and no sexually transmitted diseases. He denied neck stiffness, joint pain, photophobia, recent travel, sick family members, or a recent tick bite. The patient was febrile to 39.4°C , hypotensive, and tachycardiac. Dermatological examination revealed multiple 1–4 cm painless, erythematous plaques, some with non-blanching dusky centers coating the posterior trunk coalescing in the sacral area with similar but smaller plaques on the anterior trunk. Several plaques on the torso had a discrete spotty and targetoid appearance and a few bullae. A few erythematous macules and papules covered the anterior trunk extending to the upper arms and thighs bilaterally. His tonsils were slightly enlarged; his lips chapped, and his conjunctiva

and pharynx were injected without exudate. There was no palpable lymphadenopathy.

Skin biopsies revealed striking subepidermal edema and interface dermatitis with an infiltrate of lymphocytes, plasma cells, histocytes, and degranulated eosinophils (Fig. 3). Focal necrosis of epidermal keratinocytes was present. These findings suggested TSS.

The patient's laboratory values manifested multi-organ failure, specifically, BUN and creatinine 149 mg/dl and 9.5 mg/dl, AST and ALT 211 mg/dl and 103 mg/dl, WBC $45.8 \times 10^9/l$, PT 16.3 sec, PTT 46 sec, LDH 498 U/L, creatinine kinase (CK) 693 U/l (25–90 U/l), and decreased complement levels. Normal antibody levels were found for anti-streptolysin and Lyme disease. Tests for HIV, Epstein-Barr virus, hepatitis A, B, and C, chlamydia, syphilis, gonococcus, anti-nuclear, anti-DNA, anti-neutrophil cytoplasmic antibodies, cultures of blood, urine and cerebrospinal fluid were all negative. Computed tomographic scans of the head, neck, abdomen, and pelvis, a hepatobiliary immunodiabetic acid scan, and a bone marrow biopsy showed no infection. The patient experienced acute renal failure, received hemodialysis and intravenous norepinephrine, and spiked temperatures to 41.0°C .

Based on clinical and histological criteria, a diagnosis of TSS was made. No antibody titers were performed. Because the diagnosis of TSS took several days to define, and multiple infectious etiologies (including meningococcemia, rickettsial diseases and Gram-positive sepsis) were entertained, he received ceftriaxone, vancomycin, imipenem, clindamycin, and doxycycline. On day 10, the patient's skin began to desquamate (Fig. 4). On day 21, the patient defervescenced and was discharged 24 days after admission without sequelae.

DISCUSSION

These cases illustrate the sudden onset and dramatic presentation of TSS in previously healthy patients. Their initial differential diagnoses included: meningococcemia, erythema multiforme, rickettsial diseases (e.g. ehrlichiosis, RMSF), leptospirosis, viral exanthem (measles, varicella), drug reactions, immune complex vasculitis, TSS, and streptococcal toxic shock syndrome (STSS) caused by group A streptococcus (5). Dilantin

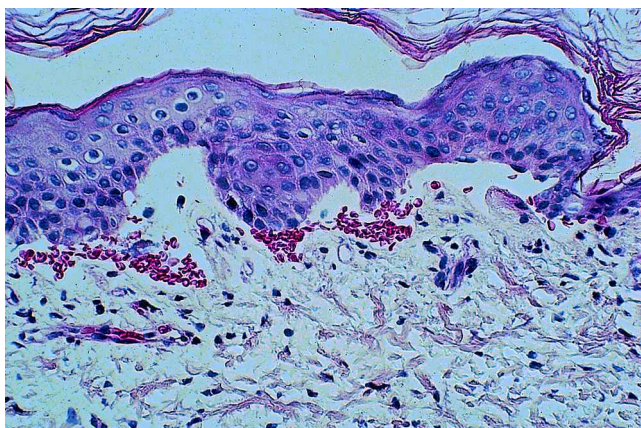


Fig. 2. Case 1: Single necrotic keratinocytes, neutrophils trapped within the epidermis, striking dermal purpura, a perivascular infiltrate of neutrophils, and dilated superficial vessels saturated with neutrophils (haematoxylin and eosin, original magnification $400\times$).

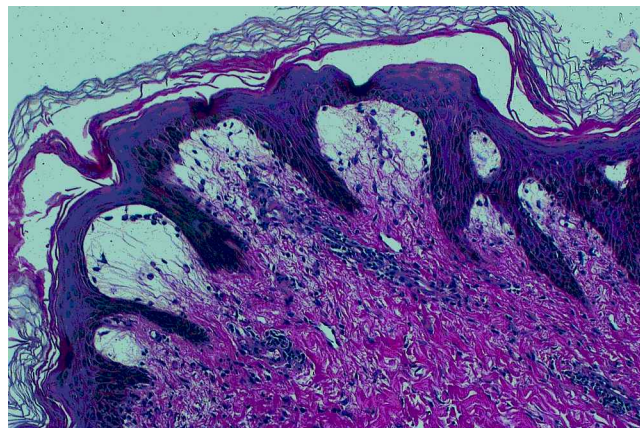


Fig. 3. Case 2: Striking subepidermal edema and interface dermatitis with an infiltrate of lymphocytes, plasma cells, histocytes and degranulated eosinophils (haematoxylin and eosin, original magnification $200\times$).

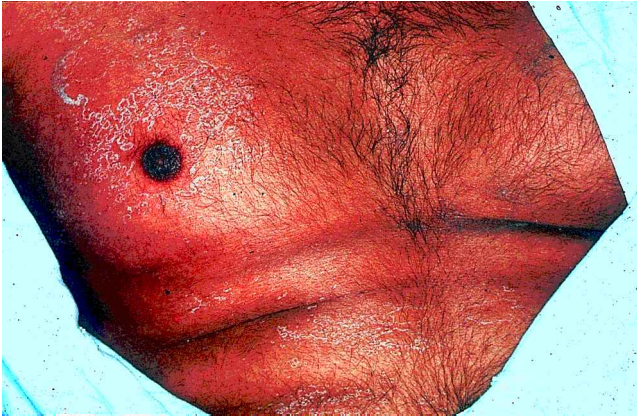


Fig. 4. Hospital day 10; desquamation on thorax, representing the convalescing phase of toxic shock syndrome in case 2.

hypersensitivity (6), adenovirus (7), erlichiosis (8), inhalational mercury poisoning (9), pseudoephedrine reaction (10), and severe measles infection (11) have also been reported to mimic the presentation of TSS. In both cases, the normal CSF findings eliminated meningococemia. The patients' high fever, hypotension, and vaccination history gainsaid viral infection. A marked neutrophilia with bandemia supported a bacterial or rickettsial etiology.

The failure to isolate a pathogen or to find significant antibody titers to any pathogen suggested a superantigen-driven process like TSS, because in TSS a pathogen is isolated in <15% of cases. In both cases, the Center for Disease Control clinical criteria of TSS were met because of the presence of hypotension, fever and rash and failure of more than three organs. Moreover, both cases had negative tests for RMSF, leptospirosis, measles, hepatitis B surface antigen, syphilis, and bacterial infections, criteria for the diagnosis of TSS.

The presentation of STSS resembles that of TSS; however, the disease course, sequelae, and treatment differ. The mortality rate of STSS is 30%, while that of TSS is 3–10% (12). Because in STSS blood cultures are positive in more than 50% of cases, negative cultures here suggested TSS. TSS and STSS's rashes classically manifest as "sunburn-like" erythroderma, but other findings occur as well (Table I). To our knowledge, there is no report of a targetoid-like rash or erythema multiforme-like lesions in TSS or STSS. Meningococemia or RMSF's purpuric lesions were not seen here.

Streptococcal scarlet fever, toxic epidermal necrolysis (TEN), staphylococcal scalded skin syndrome, and Kawasaki's disease are often included in TSS's differential diagnosis (13). Kawasaki's disease usually lacks hypotension, multi-organ involvement, and thrombocytopenia (14). Interestingly, an erythema multiforme-like rash has been reported in Kawasaki's disease (15). Staphylococcal scalded skin syndrome

Table I. *Dermatologic manifestations of toxic shock syndrome*

Mucous membrane	Skin
Early, days 1–4	
Eye	Erythroderma (termed "sunburn-like")
Scleral injection with photophobia	Diffuse of chest, back or abdomen and extremities (with or without papules, scaling or pustules)
Subconjunctival hemorrhages	Primarily lower abdomen and thighs
Discharge	Primarily extensor surfaces or joints
Ear	Petechiae
Inflamed tympanic membrane	Primarily on extremities
Oropharynx	Localized abscesses
Erythema, pain	Severe acne
Strawberry tongue	Infected extremity lesions
Vulva	Impetiginous lesions of mouth
Erythema, swelling	Lesion on neck or chin
	Perirectal involvement
	Erythema, Excoriations, Vesicles
	Nikolsky's sign
	Edema (generalized non-pitting edema)
	Bullae (Subepidermal bullae)
	Other
	Confluent spotty exanthem
	Maculopapular rash
Late, days 4–14	
Oropharynx	Maculopapular
Ulcers	Total body, pruritic
Swollen denuded tongue	Desquamation
	Palms, soles, tips of fingers and toes
Delayed, days 60–90	
None	Telogen effluvium
	Loss of hair and nails

Adapted with permission from ref. 2.

differs from TSS in that desquamation typically occurs during the acute illness as opposed to during convalescence. Furthermore, hypotension and multi-organ failure are usually absent.

Although subtle, the histology diagnosed TSS. Such histology includes necrotic keratinocytes, neutrophils in the epidermis, and purpura with neutrophils surrounding dilated superficial vessels (16). These findings distinguish TSS from TEN, which is marked by interface dermatitis and more widespread epidermal necrosis. Viral exanthems characteristically show perivascular infiltrates of lymphocytes in the superficial dermis without epidermal changes.

As positive blood cultures are present in <15% of cases of TSS, and the isolation of TSST-1 producing *S. aureus* from tissue is difficult, the antibody test for TSST-1 can confirm its diagnosis (4). A direct TSST-1 assay test has been reported but is not used (17). TSS's treatment benefits from the identification and elimination of its infection's source. Despite extensive testing, no focus of infection was identified in either case.

Most cases of nmTSS result from skin and soft tissue infection, although there are reported associations with endocarditis, osteomyelitis, endometritis, and

occult foci. Clindamycin is the first line agent in the treatment of TSS (18). It completely blocks production of TSST-1 by toxigenic strains of *S. aureus* at a concentration as low as 1/64 of the minimum inhibitory concentration (19). β -lactam antibiotics are only bactericidal in dividing bacteria and such dormant bacteria may continue to produce toxins, also known as the "Eagle effect" (20, 21).

High dose intravenous immunoglobulins (IVIG) have high levels of TSST-1 antibodies (22). A single dose of 400 mg/kg of IVIG over several hours has successfully cured TSS where broad-spectrum antibiotics and mechanical life support were failing. They were not used here because when these cases occurred such treatment was considered to be experimental. Systemic steroid administration during the acute phase of TSS may improve outcome but has not been demonstrated effective in a prospective controlled trial (23).

Despite systemic collapse, these patients survived TSS. Like a pair of Lazaruses, almost dead, once their superantigen-driven inflammatory cascades crested, with systemic support and proper medications their bodies righted themselves and they walked out of hospital alive. Accurate assessment of dermatological data facilitated their treatment. Their cases underline the manifold presentations of TSS's rashes and the value of knowing its histopathology.

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