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Toxic Shock Syndrome after Surgery: Case Presentation and Systematic Review of the Literature

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Background: Toxic shock syndrome (TSS) is an underrecognized but highly fatal cause of septic shock in postoperative patients. Although it may present with no overt source of infection, its course is devastating and rapidly progressive. Surgeon awareness is needed to recognize and treat this condition appropriately. In this paper, we aim to describe a case of postoperative TSS, present a systematic review of the literature, and provide an overview of the disease for the surgeon.
Methods: A systematic review of the literature between 1978 and 2018 was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines using the keywords "toxic shock syndrome" and "surgery." Variables of interest were collected in each report.
Results: A total of 298 reports were screened, and 67 reports describing 96 individual patients met inclusion criteria. Six reports described a streptococcal cause, although the vast majority attributed TSS to *Staphylococcus aureus* (SA). The mortality in our review was 9.4%, although 24% of patients suffered some manner of permanent complication. TSS presented at a median of 4 days postoperatively, with most cases occurring within 10 days.
Conclusions: Surgeons must maintain a high index of suspicion for postoperative TSS. Our review demonstrates that TSS should not be excluded despite young patient age, patient health, or relative simplicity of a procedure. Symptoms such as fever, rash, pain out of proportion to examination, and diarrhea or emesis should raise concern for TSS and prompt exploration and cultures even of benign-appearing postoperative wounds. *(Plast Reconstr Surg Glob Open 2020;8:e2499; doi: 10.1097/GOX.0000000000002499; Published online 29 May 2020.)*

INTRODUCTION

Septic shock is a serious condition, carrying a mortality of up to 50% and representing the second leading cause of deaths in noncardiac intensive care units (ICUs).[1,2] First reported in 1978, toxic shock syndrome (TSS) is a particularly insidious subtype of septic shock.[3] Although less well-known, it carries a significant mortality rate, higher even than meningococcal septicemia.[4] Unlike classic presentations of sepsis, patients with TSS often lack evidence of an overt infection or even bacteremia. Nonetheless, they may rapidly progress to shock and multiorgan failure. The systemic inflammatory response is predominantly caused by exotoxins and enterotoxins that are produced by pathologic strains of bacteria—most commonly SA and beta-hemolytic group A *Streptococcus* (GAS) species.[4]

Although there is some awareness of TSS among health-care professionals and even the general public, early reports have led to an association between TSS and the prolonged use of tampons. Changes in tampon manufacturing led to a decrease in the incidence of menstrual TSS, with menstrual TSS accounting for only 55% of TSS in women in the United States by 1986.[5] Indeed, 1 French surveillance study in 2008 demonstrated that 65% of staphylococcal TSS cases were nonmenstrual and that these carried a mortality of 22% compared to 0% in menstrual TSS.[6]

As the epidemiology of TSS has evolved over the recent decades, the relative rate of TSS has risen in postoperative patients.[7] Given the paucity of typical signs of sepsis in TSS, its rapid progression, and the high mortality conveyed by

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this condition, the aim of this paper is to provide an overview of this syndrome as it may present in patients after surgery. We present a case describing our experience with postoperative TSS and a systematic review of the literature.

Patient Presentation

A 57-year-old man with a history of hypertension and daily tobacco use first presented to our institution with a basal cell carcinoma of the frontal and parietal scalp (Fig. 1A). He underwent en bloc excision resulting in a significant calvarial defect requiring titanium mesh cranioplasty and anterolateral thigh (ALT) fasciocutaneous, perforator flap from the right thigh for soft tissue coverage (Fig. 1B and C). The ALT donor site could not be completely closed, so split-thickness skin grafts from the right medial thigh were used. The patient received 3 perioperative doses of cefazolin over the course of 24 hours. The donor site was dressed with Xeroform, Kerlix gauze, and a compressive wrap. The gauze and wrap was removed on postoperative day 5; the Xeroform was left in place over the split-thickness skin graft donor site until the skin reepithelialized. His postoperative course was unremarkable and on postoperative day 7 he was discharged.

On postoperative day 9, the patient presented to the emergency department with a 24-hour history of fevers, severe pain on the right lower extremity, and emesis. His mental status was at baseline. On physical examination, he was found to have a fever of 103°F and mean arterial pressures less than 65 mm Hg. Physical examination of the patient's ALT flap was unremarkable. The right thigh donor site demonstrated mild erythema and edema around the wound margins, but was without any purulent drainage or tissue necrosis. Hypotension was unresponsive to a total of 6 L of intravenous (IV) fluid. Blood cultures were drawn, and he was started on broad-spectrum IV antibiotics. He required emergent intubation in the emergency department and was admitted to the ICU where he required the maximum dose of vasopressors. His lactate peaked at 4.6 mmol/L; his white blood cell count (WBC) at the end of the day of his admission was 32×10^3 cells/μL (up from 10×10^3 cells/μL that same morning). Imaging demonstrated some soft tissue swelling in the right thigh but no fluid collections or evidence of gas along fascial planes. A bedside incision and drainage of his right thigh donor site revealed only viable muscle and subcutaneous tissue without evidence of purulent drainage.

Over the following days, the patient suffered 1 pulseless electrical activity arrest and significant multiorgan dysfunction: his WBC peaked at 51×10^3 cells/μL, urine production fell to 15 mL/h with rising creatinine (0.5 to 4.4 mg/dL), and creatine phosphokinase levels rose to 1,890 U/L. However, with supportive care and antimicrobial treatment, he gradually improved, and on the third day after admission was successfully weaned off vasopressors and extubated. Withdrawal of vasopressors resulted in return of the free flap Doppler signal and right foot (lost due to pressor requirements); however, the left foot remained ischemic.

Blood cultures were persistently negative for growth of organisms. The patient experienced desquamation of the palms of his hands (Fig. 2) and the soles of his feet on the 19th day after admission. He underwent a left below-knee amputation on the 25th day after admission. He was discharged 34 days after admission and was in good health at last follow-up.

METHODS

We performed a systematic review of the literature to assess reports of TSS after surgery. We searched the PubMed databased using the phrase "toxic shock syndrome" (title) and "surgery" (all fields). We also performed a manual search using the phrase "toxic shock syndrome after surgery." The criteria for "surgery" that were applied included any procedure that disrupted the epithelial/mucosal barrier by way

Fig. 1. Initial patient presentation and surgery. A, Preoperative image demonstrating fungating scalp mass. B, Defect following excision of mass and titanium mesh cranioplasty. C, Postoperative image demonstrating ALT flap coverage of defect with a single drain in place.

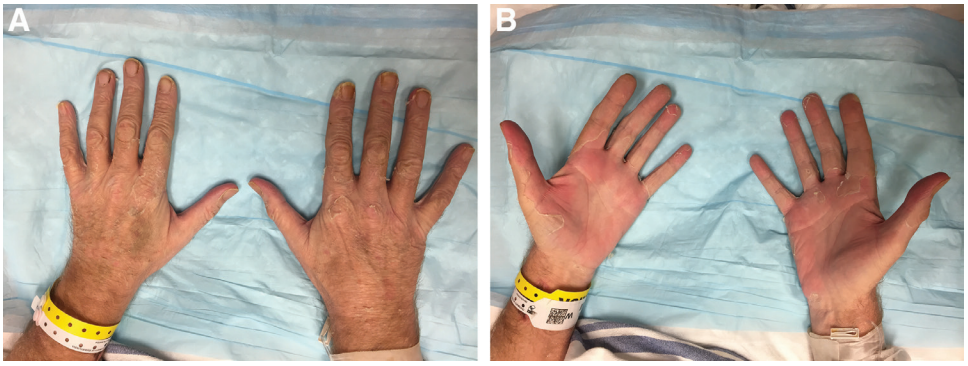

Fig. 2. Desquamation occurred approximately 19 days after surgery. A and B demonstrate the patient's hands with panel B showing desquamation of the palms. The patient had removed some of the desquamated skin on his palms when the pictures were taken.

of intentional instrumentation. Cases of TSS that occurred more than 60 days after surgery were excluded. Non-English language articles and commentaries were excluded. Cases of TSS due to the sole use of nasal packing, facial peels, or burns were excluded. Descriptive statistics and figures were generated using GraphPad Prism version 7.00 for Mac OS X, GraphPad Software, La Jolla, CA, USA.

RESULTS

Two hundred ninety-four titles were identified through PubMed. Four additional unique titles were identified through a manual search. All 298 titles were screened, and 222 titles were excluded based on predetermined criteria. The remaining 76 articles were reviewed in-depth. (**see Supplemental Digital Content 1**, http://links.lww.com/PRSGO/B271.) Nine titles were excluded following this in-depth review. Reasons for exclusion included the comorbid presence of necrotizing fasciitis, unclear timelines or outcomes, and unclear relation between TSS and a surgical procedure. A total of 67 articles describing 96 patients were included in our qualitative review (Fig. 3).

In our review series, 38 (39.6%) patients were men and 58 (60.4%) were women. The mean reported patient age was 34.1 years with an SD of 15.5 years and a range from 4 to 73 years; the most commonly reported age group was that between 26 and 30 years of age (Fig. 4A). The median number of postoperative days to onset of symptoms or hospital admission for TSS was 4 days, with an interquartile range of 6.75 days and a range from 1 to 44 days (Fig. 4B). Of the 96 patients, 73 (76%) did not suffer permanent complications. The remaining 23 (24%) patients suffered permanent complications, including additional procedures (eg, hysterectomy, cholecystectomy, skin grafting), amputations, reduced range of motion at a joint, or eventual death (Table 1). Nine (9.38%) patients in our review series eventually expired due to TSS (Table 1). The medical histories of 59 (61.5%) patients were considered noncontributory by the authors of their respective reports (Table 1). An even number of reports of postoperative TSS were published in the past 2 decades (excluding the case presented herein), 19 (28.4%) reports were published between 1990 and 1999, and 26 (38.8%) reports were published between 1980 and 1989 (Fig. 4C). Most of the surgical procedures preceding onset of TSS fell within the domain of plastic surgery, followed by orthopedic surgery and otolaryngology, respectively (Fig. 4D).

DISCUSSION

The mortality rate in our review (9.38%) is lower than that of other reports; this may reflect publication bias and advances in ICU care over time. The average time between TSS diagnosis/treatment and death was 6.78 days, with a range from 12 hours to 18 days. Mortality tended to occur early (<2 days) when due to the shock itself or late (>14 days) due to systemic complications such as cardiopulmonary arrest. Notably, the surgical procedures that most commonly preceded TSS were those that extensively involved the skin (plastic surgery, orthopedic surgery) or mucosal surfaces (otolaryngology), suggesting that sites colonized with toxin-producing bacteria may result in presentation only after disruption of the integrity of the epithelial or mucosal barrier.

Although our patient suffered TSS after extensive surgery, it is important to note that postoperative TSS may present even after relatively simple procedures. Two papers describe TSS in patients following the removal of skin lesions.[8,9] Suction-assisted lipectomy,[10,11] pilonidal cyst excision,[12,13] surgical biopsy,[13,14] arthroscopy,[15] and elective tubal ligation[16] represent just some of the procedures in our review. Furthermore, our review of the literature demonstrates that patients affected by postoperative TSS are often young and in otherwise good health.

The virulence factors responsible for TSS are produced mainly by Gram-positive organisms, especially SA and GAS. However, they are also known to be produced by some Gram-negative bacteria, *Mycoplasma* spp., and certain viruses.[4,17] In our series of postoperative TSS, most causative organisms, if identified, were GAS or SA—however, 2 reports described very virulent TSS following obstetrical procedures that led to the isolation of *Clostridium sordellii*.[18,19] One of these patients died.[19] Six reports included in our review reported cultures that grew beta-hemolytic *Streptococcus*.[14,16,20–23] Streptococcal

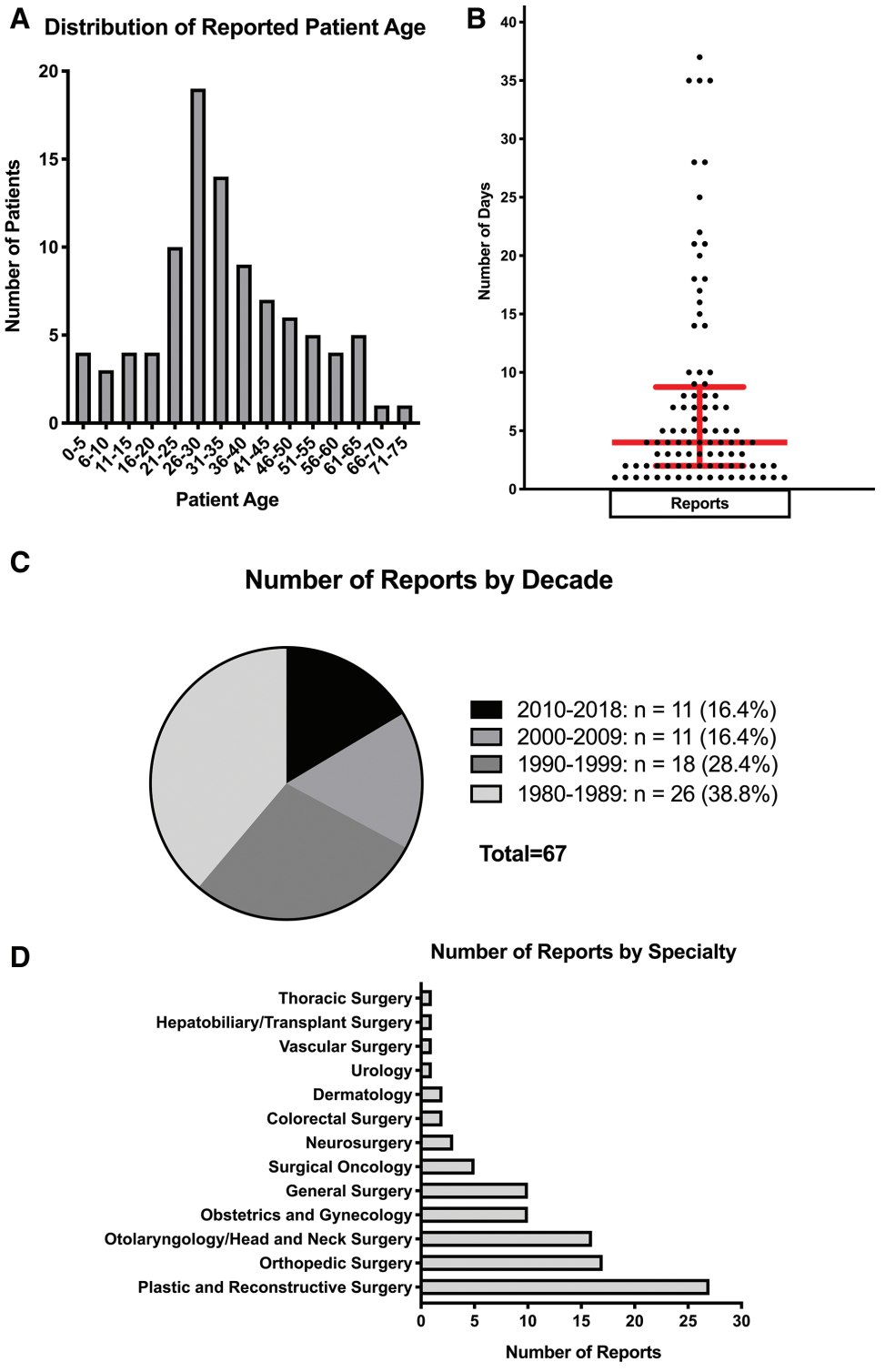

Fig. 3. Descriptive statistics of collected variables. A, Frequency distribution of patient age (in 5-year increments). Most patients were between 21 and 40 years of age. B, Distribution of days to onset of TSS symptoms or admission. The red bars represent the median (4 days) ± the interquartile range (6.75 days). C, Number of reports by decade. Most reports were published within the first decade since recognition of TSS. D, Frequency distribution of surgical procedure specialties preceding onset of TSS.

TSS carries a much higher mortality than staphylococcal TSS, with a mortality rate of up to 80% reported in some of the literature.[4,24]

Pathophysiology

Despite rapid deterioration, patients with TSS may not present with evidence of infection. This is because only a

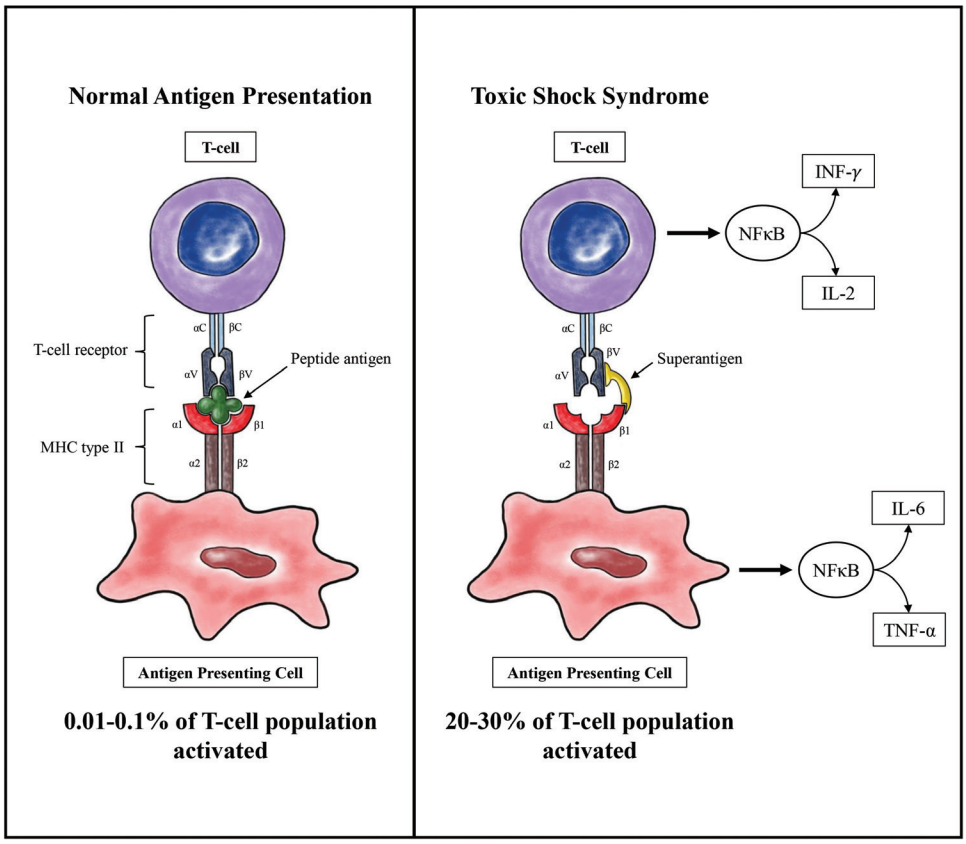

Fig. 4. Schematic of normal T-cell activation and abnormal T-cell activation induced by superantigen. Note that more inflammatory markers are secreted downstream than are shown in the figure.

critical mass of toxin-producing bacteria with concomitant epithelial or mucosal disruption is needed. It is the toxins produced by the bacteria that cause the presentation as opposed to a runaway infection by any 1 microorganism.

The word exotoxin refers to virulence factors that are genetically encoded and secreted. They are usually heat labile (but not always, eg, SEB, a type of bacterial superantigen[17]) and are highly toxic. The term enterotoxin refers to exotoxins that have an effect on the gastrointestinal (GI) tract, thereby producing GI symptoms (a prominent feature in most cases of TSS). The causative toxins behind TSS are usually referred to as "superantigens," a term first used in the 1980s to describe the mechanism by which streptococcal enterotoxin B stimulates T-cell populations.[25] Nearly all superantigens are exotoxins, and most are also enterotoxins.[26] Of note, the staphylococcal TSS toxin 1 (TSST-1) is responsible for nearly 95% of menstrual TSS and up to 50% of nonmenstrual TSS, making it the most common causative toxin.[4,27]

The pathogenicity of superantigens is due to the nonconventional activation of T-cells by antigen-presenting cells (APCs). Normally, APCs present processed peptide fragments to T-cell receptors (TCRs) by way of specific peptide-binding grooves in the major histocompatibility class II (MHC II) protein. This selective process results in the activation of only about 0.01% of the T-cell population.[4] By contrast, superantigens bind as unprocessed proteins to both the MHC class II protein and TCR (Fig. 4). They are thought to bind to the variable Vβ region of the TCR (although some bind to the α chain), and bind distant from the normal peptide-binding groove on the MHC II protein.[4,26,28] This results in the aberrant activation of up to 20%–30% of the T-cell population. Once a superantigen has cross-linked that T-cell and APC, there is a rapid increase in cytokine expression by both cell types. This is thought to be primarily due to the activation of nuclear factor κB.[29]

Superantigens are extremely potent, with human T-cell sensitivity noted at as little as 1 fg/mL in vitro.[17] GI symptoms have been noted with ingestion of less than 1 μg of staphylococcal enterotoxin.[30]

Clinical Presentation

It has been suggested that the onset of postoperative TSS most commonly occurs by the second postoperative day.[26,31] Our review demonstrated widespread variability in the timeline of postoperative TSS; though, Figure 3B shows that most cases became apparent within 10 days.

Of the 96 patients in our review, at least 52 were described as presenting with symptoms that included nausea, vomiting, or diarrhea. This highlights the enterotoxic nature of many superantigens. Furthermore, some manner of pain was frequently reported. For example, 2 reports described patients with severe hand and wrist pain following hand surgery, whereas another described nasal pain in a septoplasty patient.[32–34] The pain in TSS has been described as severe and relentless, making it a common impetus for patients to seek medical attention.[4]

Table 1. Select Variables from Case Reports Meeting Inclusion Criteria of Our Systematic Review

Study	Year	Patient Age	Patient Sex	Surgical Procedure	Days to Onset	Complications/ Additional Procedures	Mortality	Culture Results
Elkbuli et al[18]	2018	31	F	Cesarean section	17	Hysterectomy and bilateral salpingectomy	No	*Clostridium sordellii*
Tomura et al[8]	2017	35	M	Right lumbar melanoma excision	6	None	No	–
Komuro et al[61]	2017	33	F	Cesarean section	37	None	No	–
Suga et al[62]	2016	40	F	Mastectomy, SLNB, and immediate subpectoral implant-based reconstruction	10	None	No	–
		54	F	Mastectomy, SLNB, and immediate subpectoral implant-based reconstruction	8	None	No	–
Chan et al[63]	2015	5	F	Open reduction and K-wiring of lateral condyle fracture	14	None	No	Pin sites grew enterotoxin A, G, I, and TSST-1-producing SA
Rimawi et al[64]	2014	23	F	Cesarean section	7	Hysterectomy	No	Alpha-toxin-producing *Clostridium septicum*
Yadav et al[65]	2014	25	M	Inguinal hernia repair	2	None	No	–
Shimizu et al[66]	2014	46	M	ORIF and fasciotomy for left tibia/fibula fracture	21	None	No	–
Hung and Rajeev[20]	2013	24	F	Total thyroidectomy	2	None	No	–
Al-ajmi et al[16]	2012	39	F	Laparoscopic left salpingectomy	1	–	Yes	Blood grew GAS
		31	F	Elective tubal ligation	1	Bilateral salpingectomy	No	Intraperitoneal fluid grew GAS
Tare et al[67]	2010	36	F	Left mastectomy with DIEP flap reconstruction	8	–	Yes	Wound fluid grew TSST-1-producing MRSA
Vendemia and Rohde[43]	2009	55	F	Right tissue expander placement with AlloDerm	35	None	No	Periprosthetic wound culture grew TSST-1-producing SA
Shoji et al[68]	2007	61	M	Thoracotomy with mediastinal lymph node dissection	5	None	No	–
Jarrahy et al[69]	2007	47	F	Abdominoplasty	44	Anterior wall MI, heart failure, bilateral sensorineural hearing loss	No	Drain fluid grew SA
Kastl et al[70]	2007	35	M	Rectal mucosal biopsy	1	None	No	Rectal swab grew pyogenic exotoxin (SpeA, B, F, G, J)-producing GAS
Strenge et al[39]	2006	45	M	Excision of ganglion cyst	3	None	No	Wound cultures grew SA
Agerson and Wilkins[21]	2005	40	F	TRAM flap reconstruction of right breast; right salpingo-oophorectomy; left tubal ligation	15	None	No	Abdominal wall abscess grew GAS and *Klebsiella*
Goksugur et al[71]	2003	52	M	Laparotomy with lymph node sampling	2	None	No	Blood and wound cultures grew SA
Odom et al[72]	2001	56	F	L2 corpectomy with L1 to L3 interbody fusion and debridement of abscess	2	None	No	Abscess grew SA*
Gwan-Nulla et al[73]	2001	48	M	Sigmoid colectomy with end colostomy	18	None	No	Wound culture grew SA
Chadwell et al[41]	2001	47	M	Bilateral polypectomy, total ethmoidectomy, sphenoidotomy, frontal sinusotomy, and right antrostomy	18	None	No	Nasal stents and blood cultures grew TSST-1-producing SA
Umeda et al[11]	2000	27	F	Suction-assisted lipectomy	2	Meshed skin autograft over 22% TBSA due to repeat debridement	No	Wound cultures grew SA
Rutishauser et al[22]	1999	43	M	Elective herniotomy	2	Right orchiectomy	No	Wound cultures grew GAS
		55	F	Tetanus vaccine administration	4	None	No	Blood cultures grew GAS
Kato et al[74]	1999	23	F	Internal fixation of humerus fracture	4	Reduced elbow ROM	No	Wound grew enterotoxin C and TSST-1-producing SA
Birdsall et al[75]	1999	14	F	Closed reduction of proximal humerus and fixation with K wires	14	None	No	Blood and wound cultures grew TSST-1-producing SA
Kotlarz et al[76]	1998	62	F	Mastoidectomy	3	None	No	Wound cultures grew enterotoxin B-producing SA

(*Continued*)

Table 1. (*Continued*)

Study	Year	Patient Age	Patient Sex	Surgical Procedure	Days to Onset	Complications/ Additional Procedures	Mortality	Culture Results
Holm and Mühlbauer[44]	1998	58	F	Bilateral exchange of silicone implants (subglandular)	4	None	No	2-mL periprosthetic fluid grew SA
Bitti et al[19]	1997	29	F	Cesarean section	2	-	Yes	Intraperitoneal cultures grew *Clostridium sordellii*
Younis et al[77]	1996	5	M	Functional endonasal sinus surgery	10	None	No	Direct sinus cultures grew toxin-producing SA
		7	F	Functional endonasal sinus surgery	5	None	No	Direct sinus cultures grew toxin-producing SA
		32	M	Functional endonasal sinus surgery	35	None	No	Blood and sinus cultures grew toxin-producing SA
		8	M	Functional endonasal sinus surgery	7	None	No	Blood and sinus cultures grew toxin-producing SA
		27	M	Functional endonasal sinus surgery	10	None	No	Direct sinus cultures grew toxin-producing SA
Mills and Swiontkowski[23]	1996	29	M	Tibial hardware removal	2	-	Yes	Bullous fluid grew 3+ GAS
Grimes et al[78]	1995	4	F	Removal of Steinmann pins from iliac crest	9	-	Yes	Wound cultures grew SA
		4	F	Right femoral valgus osteotomy	22	None	No	Pin sites grew SA
Poblete et al[45]	1995	21	F	Elective augmentation mammaplasty (subglandular)	6	Bilateral transmetacarpal amputations; bilateral BKAs	No	Blood cultures grew enterotoxin B-producing SA
Graham et al[13]	1995	42	F	Oophorectomy	2	None	No	12 out of 12 patients had negative blood cultures
		64	F	Lumbar sympathectomy	2	None	No	
		15	M	Patellar realignment	5	None	No	
		40	F	Hysterectomy	4	None	No	
		28	M	Excision of navicular bone	4	None	No	
		45	F	Cholecystectomy	8	None	No	
		48	F	Cholecystectomy	9	None	No	
		26	M	Pilonidal cystectomy	5	None	No	
		61	F	Breast biopsy	2	None	No	
		26	F	Chest tube placemen	4	None	No	
		29	M	Nasal septoplasty	1	None	No	
		66	M	Percutaneous angioplasty	1	None	No	
Cederna[79]	1995	47	F	TRAM flap reconstruction of left breast	7	33% of TRAM flap lost; latissimus flap required for coverage	No	Small amounts of serous fluid from breast and abdomen grew SA
Miller[36]	1994	45	M	L1 laminectomy and discectomy	3	None	No	Serosanguinous fluid in deep tissue layer yielded light growth of SA
Rhee et al[10]	1994	36	F	Abdominoplasty with suction-assisted lipectomy	3	None	No	Wound and drain cultures grew SA
		43	F	Suction-assisted lipectomy	4	None	No	–
Abram et al[42]	1994	30	M	Functional endonasal sinus surgery	1	None	No	Nasal cultures grew SA
		32	F	Functional endonasal sinus surgery	1	None	No	Nasal cultures grew SA
		14	F	Second-stage endonasal clean-out	1	None	No	Nasal and throat cultures grew SA
		25	F	Functional endonasal sinus surgery	21	None	No	Throat cultures grew SA
		8	M	Second-stage endonasal clean-out	5	None	No	Nasal cultures grew SA†
Miller et al[80]	1994	61	F	Endoscopic bilateral ethmoidectomy, sphenoidotomy, maxillary antrostomy, and septoplasty	25	None	No	Sinus cultures grew SA
Bosley et al[9]	1993	14	F	Mole excision	1	Cardiac arrest, PE	Yes	Wound culture grew TSST-1-producing SA
Gosain and Larson[48]	1992	33	F	Bilateral breast reconstruction with latissimus dorsi musculocutaneous flaps; immediate silicone implants	28	None	No	–
Shlasko et al[12]	1991	29	M	Pilonidal cystectomy	3	None	No	–
Croall et al[81]	1989	27	M	MCL repair	8	None	No	Synovial fluid grew enterotoxin B-producing SA
Frame et al[82]	1988	17	M	Prominent ear correction	3	–	–	Wound cultures grew TSST-1-producing SA

(*Continued*)

Table 1. (*Continued*)

Study	Year	Patient Age	Patient Sex	Surgical Procedure	Days to Onset	Complications/ Additional Procedures	Mortality	Culture Results
Tobin et al[47]	1987	39	F	Left permanent prosthesis, right mastectomy with immediate implant-based reconstruction	5	None	No	Wound cultures grew TSST-1-producing SA
		57	F	L subpectoral tissue expander	3	None	No	–
		29	F	Herniorrhaphy and septorhinoplasty	1	None	No	Nasal cultures grew TSST-1-producing SA
Grayson and Saldana[32]	1987	20	M	Tenolysis of FDS and FDP	35	None	No	Wound fluid grew enterotoxin B-producing SA
Murphy et al[83]	1987	40	F	Lumpectomy	2	None	No	Wound discharge grew enterotoxin C-producing SA
Dreghorn et al[84]	1987	26	M	Repair of MCL	5	Reduced ROM at knee	No	Synovial fluid grew SA
Jacobson and Kasworm[33]	1986	27	F	Septoplasty	1	Right BKA, left Syme's amputation, Volkmann's contracture of left forearm	No	Vaginal and maxillary sinus cultures grew TSST-1-producing SA
		34	M	Septoplasty	1	None	No	–
		29	F	Septoplasty	1	None	No	Nasal cultures grew SA
Wagner and Toback[40]	1986	26	F	Septoplasty	2	None	No	Nasal cultures grew SA
Giesecke and Arnander[46]	1986	33	F	Bilateral primary augmentation mammoplasty (subglandular)	2	None	No	Periprosthetic fluid grew enterotoxin F-producing SA
Vanderheyden et al[85]	1986	30	F	Cesarean section	5	None	No	–
Smith et al[34]	1986	30	M	Extensor tenosynovectomy and side-to-side juncture (EDC ring to small finger)	4	None	No	Wound cultures grew TSST-1-producing SA
Shaffer et al[86]	1986	44	M	Orthotopic liver transplant and right adrenalectomy	16	None	No	Wound cultures grew SA
Farber et al[15]	1984	19	M	Arthroscopy	1	Cardiopulmonary arrest requiring bypass	Yes	Synovial fluid grew exotoxin C-producing SA
Beck et al[87]	1984	73	M	Cholecystectomy	28	–	Yes	Small sinus tract grew enterotoxin F-producing SA
Spotkov et al[88]	1984	21	F	Diagnostic laparotomy for bleeding cyst of corpus luteum	7	None	No	Wound drainage grew enterotoxin A, F-producing SA
Toback et al[89]	1983	21	M	Septorhinoplasty	1	None	No	Nasal cultures grew SA
Aganaba et al[35]	1983	26	M	Orchidectomy	4	None	No	Deep wound culture grew enterotoxin F-producing SA
Moyer et al[90]	1983	18	F	Patellar shaving procedure	3	None	No	Synovial cultures grew SA
		60	M	Arthrotomy and patellectomy	2	Cholecystectomy	No	Synovial cultures grew SA
Bresler[91]	1983	35	F	Removal of R breast implant	7	None	No	Periprosthetic fluid grew SA
Barnett et al[92]	1983	32	F	Right subglandular breast prosthesis exchange	7	None	No	Periprosthetic fluid grew SA
Thomas et al[93]	1982	25	F	Submucous resection and rhinoplasty	1	None	No	–
Bartlett et al[94]	1982	31	F	Removal of granulation tissue (bilateral augmentation incisions failed to heal)	1	–	Yes	–
		53	F	Vesico-urethral suspension	4	None	No	Suture abscess grew SA
McClelland et al[95]	1982	36	M	Wide excision with STSG	20	None	No	–
Knudsen et al[96]	1981	21	F	Bilateral primary augmentation mammoplasty	4	None	No	Right breast cavity grew SA
Silver et al[97]	1981	34	M	Amputation of left index finger due to trauma	3	None	No	0.25 cc serous fluid expressed from incision grew SA

*Blood cultures eventually grew SA, but this was too remote from onset of toxic shock symptoms.
†Stool testing was also positive for *Clostridium difficile* in the patient.
BKA, below-knee amputation; DIEP, deep inferior epigastric artery perforator; EDC, extensor digitorum communis; FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis; GAS, group A *Streptococci*; MCL, medial collateral ligament; MI, myocardial infarction; ORIF, open reduction, internal fixation; ROM, range of motion; SA, *Staphylococcus aureus*; SLNB, sentinel lymph node biopsy; STSG, split-thickness skin graft; TBSA, total body surface area; TRAM, transverse rectus abdominis myocutaneous.

A benign-appearing wound is another common feature of postoperative TSS, and this frequently leads to a delay in diagnosis.[4,26,28] Several case reports in our review explicitly noted the normal appearance of surgical wounds, even if these later grew the causative pathogen. For example, 1 report described a normal looking wound that eventually grew enterotoxin F-producing SA from deep swabs.[35] Another described an unremarkable wound that yielded "light" growth of SA from minimal serosanguinous fluid within the deep tissue layers.[36] Notably, the death of a 14-year-old girl was reported following TSS that developed after mole excision.[9] The authors note that although the surgical wound appeared dry and normal, debrided tissue eventually grew TSST-1 producing SA.[9]

After onset of symptoms, multiorgan failure can occur within as little as 8–12 hours.[4] Multiorgan failure is a prominent feature of the clinical case definitions proposed by the Centers for Disease Control and Prevention. These were first developed in 1980 and have undergone only slight modifications, with the most recent update occurring in 2011.[37] However, strict adherence to Centers for Disease Control and Prevention criteria may only identify the most severe cases of TSS. The authors noted that a changing understanding of TSS pathophysiology and presentation over time has demonstrated a wider range of severity than originally suggested and that advances in supportive care have likely begun to prevent the most severe manifestations of the disease.[37]

Less than 5% of staphylococcal TSS present with positive blood culture.[4,38] One series of 12 patients who developed postoperative TSS did not show a single patient with positive blood cultures.[13] Most commonly, SA was eventually isolated from the surgical wound,[11,34,39] and sometimes from nasal[40–42] or rectal[14] swabs. If foreign bodies were involved in the initial surgery, tissue or fluid around the foreign body frequently grew SA. For example, in cases that involved breast prostheses, SA was frequently isolated from periprosthetic fluid.[43–46] In contrast, streptococcal TSS more commonly presents with concomitant bacteremia.[4] This was the case for 2 out of 6 reports of streptococcal TSS in our review.[16,22]

Lastly, a late but characteristic feature of TSS is a peeling rash known as desquamation. This classically occurs on the palms of the hands or the soles of the feet (Fig. 2); however, several case reports indicated that it may also develop on the trunk or over regions affected by rash.[9,10] Although typically desquamation occurs within 10–21 days of symptom onset,[4] there was widespread variability in our report ranging from 3[47] to 35[48] days postoperatively. In the series of 12 postoperative TSS patients described earlier, 11 developed desquamation.[13]

Treatment

Treatment for TSS involves source control, supportive care, and antibiotic treatment. Source control is a principle that is particularly relevant to postoperative patients, as surgical wounds must be considered a potential source despite the lack of typical signs of infection.[4] Once sepsis is diagnosed, antibiotic treatment should be started within an hour,[26] and the requisite cultures should be acquired before this. We recommend that wound cultures accompany exploration of the wound early on in addition to standard blood cultures if a postoperative patient presents with symptoms suggestive of TSS. Initial surgical interventions should involve visual inspection for fascial involvement, debridement of any necrotic tissue, surgical biopsy for histopathology, and deep bacterial cultures.[49] If packing or any foreign objects are present, they should be removed. If suspicion for staphylococcal TSS is high, a nasal swab may be considered.

Appropriate initial antibiotic therapy has been shown to reduce mortality in sepsis,[50] and empiric therapy should be targeted at SA and GAS species. Given the potential for Methicillin-resistant Staphylococcus aureus (MRSA), vancomycin, or linezolid should be considered in cases of suspected staphylococcal TSS.[51] Linezolid has the added benefit of reducing exotoxin release, including TSST-1.[4,52] In cases of suspected streptococcal TSS, penicillin G remains an antibiotic of choice. This is because despite decades of use, *Streptococcus pyogenes* remains exquisitely sensitive to penicillin.[4,49,53] In addition to linezolid, clindamycin, erythromycin, rifampin, and fluoroquinolones have all been demonstrated to reduce bacterial exotoxin release by up to 90%.[51] Clindamycin is a common choice in combination with vancomycin or penicillin G.[4,51]

Resuscitation and supportive care should be performed according to current sepsis guidelines.[54] This includes maintaining a target mean arterial pressure of 65 mm Hg in patients requiring vasopressors and administering at least 30 mL/kg of IV crystalloid within the first 3 hours.[54]

The IV administration (usually 1–2 g/kg) of polyclonal, neutralizing intravenous immune globulin (IVIG) has long been proposed as a potential adjunct in the treatment of TSS. These immunoglobulins can block the activation of T-cells by both staphylococcal and streptococcal superantigens,[4] in addition to improving bacterial opsonization, phagocytosis, and destruction.[49,55] An observational cohort study in 1999 reported a mortality benefit conveyed by IVIG in cases of streptococcal TSS,[56] although this study may have been confounded by the fact that IVIG recipients were also more likely to receive surgery. Results from the INSTINCT trial, which was a randomized, double-blinded, placebo-controlled trial, were published in 2017. They demonstrated no significant difference between the placebo and intervention groups with regard to both functional status and mortality.[57] However, a recent meta-analysis demonstrated a reduction in mortality from 33.7% to 15.7% in patients with clindamycin-treated streptococcal TSS who received IVIG.[58] Therefore, there may be a role for IVIG in streptococcal TSS, although further evidence is needed. The utility of IVIG in staphylococcal TSS has been even less well determined. There is currently a European, multicenter, placebo-controlled, randomized trial underway that aims to assess the utility of IVIG in pediatric patients with TSS.[59] It hopes to enroll 156 patients and is expected to complete in 2022. Of note, the Infectious Disease Society of America has pointed to the heterogeneity between preparations of IVIG, which may result in variance between studies.[49,60]

CONCLUSIONS

TSS is a rapidly progressive, potentially fatal complication of surgery that frequently presents with a benign-appearing wound. As the incidence of gram-positive sepsis increases, and as MRSA colonization becomes more common in populations, surgeons must be aware of the potential subclinical presence of toxin-producing strains. Importantly, our review shows that TSS should not be excluded despite young patient age, patient health, or relative simplicity of a procedure. Symptoms such as fever, rash, pain out of proportion to examination, and diarrhea or emesis should prompt inclusion of TSS in the differential diagnosis. It is our hope that the case presented herein, and the systematic review, will aid surgeons in the earlier recognition and treatment of this dangerous syndrome.

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