Fulminant streptococcal toxic shock syndrome

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Abstract

We present a case of a previously healthy 37-year-old male who developed fever, nausea, vomiting, diarrhoea, and hypovolaemia. Within 5.5 h he presented with tachycardia, tachypnoea, became hypotensive and displayed a diffuse erythematous rash. In the following hours he developed persistent hypotension, acute respiratory distress syndrome, liver failure, kidney failure and disseminated intravascular coagulation. A diagnosis of toxic shock syndrome was made, but despite antibiotic therapy, immunoglobulin administration, and supportive measures, the patient died 50 h after presentation. ***Streptococcus pyogenes*** **was isolated from blood cultures.**

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Introduction

Streptococcal toxic shock syndrome (STSS) is one of the complications of invasive streptococcal disease. It is caused by the liberation of cytokines after the stimulation of the immune system by streptococcal toxins and is defined as the isolation of group A Streptococcus from a normally sterile site in the setting of shock and multi-organ failure.[1–4] Its high mortality rate (up to 70%)[5] makes it an entity that needs to be suspected and recognised early in order to provide patients with the appropriate treatment and support measures.

Case presentation

A previously healthy 37-year-old male presented to the Emergency Department (ED) with a history of sudden onset fever, nausea, and vomiting for the past hour. In the ED, he had 4–5 episodes of diarrhoea without mucus or blood. He looked acutely ill, was tachycardic (HR 110 beats/min), and appeared hypovolaemic (BP 100/60 mmHg). The rest of the physical examination was remarkable only for dry oral mucosa, increased bowel sounds, abdominal distension with mild diffuse tenderness, and right big toe paronychia. He was diagnosed with acute gastroenteritis with dehydration and was admitted to the ED for intravenous fluids.

Twenty-four hours before his symptoms started, the patient had returned from a 4 day trip to the northern coast of Peru. During his trip, he had eaten raw seafood and had been complaining of right big toe pain, for which he took acetaminophen and received topical therapy with a mixture of neomycin-polymixin B-bacitracin at a local healthcare facility.

Because of persistent fever and intense malaise, he was admitted to the General Medicine Ward after haemodynamic stabilisation (HR 86 beats/min, BP 110/70 mmHg, RR 20 breaths/min, temperature 37.7°C, and oxygen saturation (SO_2) 95% breathing room air). However, 1.5 h after admission (5.5 hours of illness), his status deteriorated: he became tachycardic (HR 120/min), tachypnoeic (RR 26/min), mildly hypotensive (BP 100/70 mmHg), febrile (38.6°C), with SO_2 88–92% breathing room air; a diffuse erythematous rash with intense conjunctival injection was noted. His initial laboratory results showed a haemoglobin of 13.9 g/L, WBC of 2630/µL (30% bands, 60% segmented neutrophils, and 10% lymphocytes, toxic granulations and vacuolar degeneration), and platelets 174,000/µL. Blood cultures were taken and ceftriaxone was started, which he received 6 h after admission (8 h after initial symptoms). Chest X-ray showed mild pulmonary congestion. Sepsis was suspected, the patient was transferred to the ICU, and broad antibiotic coverage was started with vancomycin and meropenem (9.5 h after start of illness).

Intense fluid resuscitation was attempted; however, the patient's haemodynamic condition worsened and 15 h after starting his symptoms he was found with increased HR (140 beats/min), RR (52 breaths/min), mean arterial pressure < 65 mmHg, decreased SO_2 (85%) breathing oxygen at FiO_2 = 100%, and oliguria. His laboratory results showed he was in acute kidney failure, liver failure and with disseminated intravascular coagulation: PT: 74.9 sec, INR: 6.98, PTT: > 200 s, TT: > 180 s, fibrinogen: < 80 mg/dL, glucose: 145 mg/dL (8.05 mmol/L), urea: 66 mg/dL (23.6 mmol/L), creatinine: 4.38 mg/dL (387 µmol/L), albumin: 1.3 g/dL

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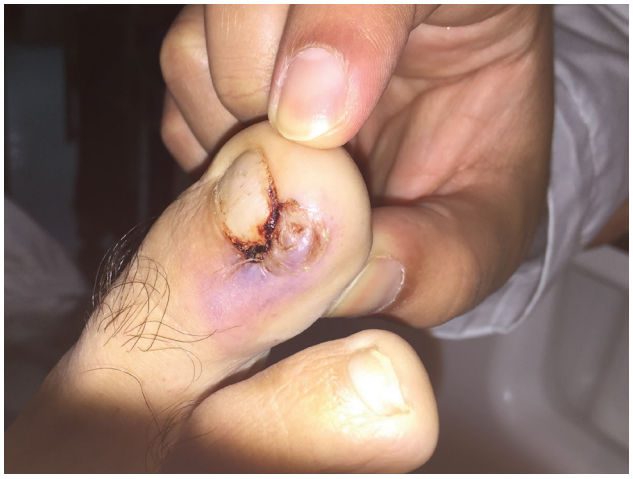
Figure 1 Right big toe lesion (paronychia)



(1.89 µmol/L), ALT: 1 065 U/L, AST: 506 U/L. At that time, the intensity of the rash had decreased. Fresh frozen plasma, cryoprecipitate and platelets were transfused. A diagnosis of toxic shock syndrome (TSS) was made with a possible portal of entry in the right big toe (Figure 1). Clindamycin was added and efforts to obtain immunoglobulin were undertaken.

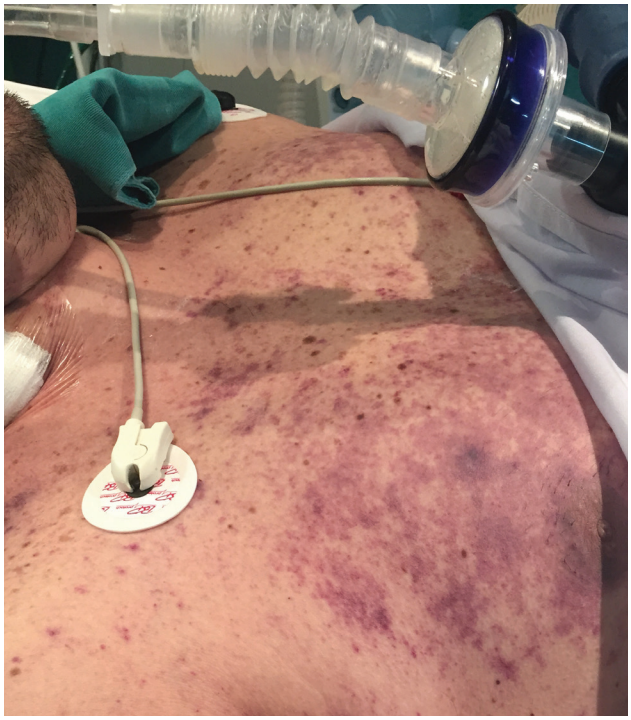
Seven hours after his admission to the ICU (16 h after starting his illness) the patient developed shock and hypothermia (35°C) and vasopressor therapy with norepinephrine was started. Intubation and mechanical ventilation was started shortly thereafter due to increased ventilator effort with pulmonary infiltrates compatible with acute respiratory distress syndrome. Three hours later, the patient was in refractory shock after showing no response to triple vasopressive therapy (norepinephrine, vasopressin, dopamine) plus hydrocortisone. A generalised purpuric rash with acrocyanosis was noted, with generalised oedema (Figure 2). Intravenous immunoglobulin (IVIG) at a dose of 1 g/kg weight on day 1 and 2 was added in an attempt to decrease the amount of circulating active toxin. He underwent conventional low flux haemodialysis but it was inefficient. The blood cultures started growing Gram-positive cocci. Despite all measures, the patient died 50 h after first symptoms. Further microbiologic testing identified the cocci as *Streptococcus pyogenes*. A fluid culture from the paronychia grew *Staphylococcus epidermidis*.

Discussion

TSS may be caused by toxin-producing strains of *Staphylococcus aureus* and *Streptococcus pyogenes* (group A Streptococcus). STSS is a clinical entity resulting from the excessive liberation of cytokines due to the presence of streptococcal toxins (superantigens), particularly exotoxin A.[1] It presents as a life-threatening illness and typically has a rapid clinical course with a high mortality rate. These characteristics make STSS a diagnosis that should be suspected very early in order to give patients the appropriate treatment and necessary support measures to avoid mortality.

STSS was first reported as a toxic shock-like syndrome in the 1980s due to its similarity to the TSS caused by

Figure 2 Purpuric rash



Staphylococcus aureus. Case series were published, the largest having 20 patients from the Rocky Mountain area who developed STSS after presenting with different types of infections, most commonly necrotising fasciitis (40%).[1] The case-fatality rate varies between 30–70%.[5] Usually STSS occurs sporadically although some clusters of cases have been reported.

Predominant strains isolated from patients with STSS belong to serotypes M1 and M3 that frequently produce the Streptococcal pyrogenic exotoxin A (SpeA), associated with the clinical manifestation of shock, organ dysfunction and rash,[6–8] and the presence of elevated levels of TNF-α and TNF-β,[9–11] indicators of T cell activation. Similarly, SpeB, a protease, has been found to play a role in the disease process by promoting inflammation.[12] Several studies have found a correlation between the presence of isolates carrying the SpeA gene with invasive disease and STSS, while the isolates predominantly found in patients with invasive disease but not STSS mostly carry the SpeC gene.[8] People who lack antibodies against these superantigens are at risk of developing TSS.[15]

Our patient presented to the ED with a gastroenteritis-like syndrome which is a common form of presentation in TSS.[1,2,5] Infection may begin at a site of minor local trauma in the skin,[5] like the toe lesion in this patient.

The multi-organ compromise presents rather early in the course of the disease.[3,4,13,14] In the 20 patient case series,[1] 80% had tachycardia and only 55% had a systolic BP below 110 mmHg at presentation. However, of the 9 patients who presented with a systolic BP above 110 mmHg, 8 developed marked hypotension and shock within 4 h. Skin changes (petechial rash, maculopapular rash or desquamation) were

present in 8/20 patients. Around 60% of patients with STSS have positive blood cultures, whereas in cases of staphylococcal TSS this is found in less than 5% of patients.[15]

A diagnosis of STSS is made by the presence of hypotension or shock and involvement of at least two organ systems: renal impairment defined by a creatinine ≥ 2 mg/dL, platelet count ≤ 100,000/μL or disseminated intravascular coagulation, elevation of transaminases or bilirubin at least twice the upper normal limit, acute respiratory distress syndrome, a generalised erythematous rash that may later desquamate, or soft-tissue necrosis. The diagnosis will be definite if group A Streptococcus is isolated from a sterile site, and probable if isolated from a non-sterile location.[4,15,16] Our patient presented with hypotension and later developed shock with acute respiratory distress syndrome; his laboratory results demonstrated elevated transaminases, disseminated intravascular coagulation and renal failure. He also presented a disseminated erythematous rash that later became purpuric with acrocyanosis. In this case, group A Streptococcus was isolated from the blood culture taken on admission, which makes STSS a definite diagnosis. Patients also present with hyperaemia of mucous membranes, especially of the conjunctivae, as our patient did.[17]

Recommended treatment includes clindamycin because, due to its protein synthesis inhibition, it decreases the production of the toxin and other virulence factors more potently than penicillin.[18] IVIG is recommended although evidence of its benefit from clinical trials is still lacking.[19] In vitro studies show that IVIG contains neutralising antibodies against the superantigens, therefore it inhibits the activation of T-cells via superantigen neutralisation, decreasing the production of cytokines (e.g. TNF-α, IL-1β, IL-6) and terminating the cytokine cascade associated with shock and multi-organ failure. The recommended dose of IVIG is 1 g/kg weight on day 1, and 0.5 g/kg weight on days 2 and 3.[20] Perhaps a larger dose would have a better response, as seen in Kawasaki disease where higher doses of IVIG (2 g/kg) have superior immunomodulatory effects.[19]

The present case exemplifies how rapidly this illness can lead to death. It is important to have a high index of suspicion for this condition in order to have the opportunity of starting early appropriate therapy. In this case, the early intense malaise, disproportionate for gastroenteritis, could have been a clue to an underlying serious process. The intense conjunctival injection with the rash should have alerted to the possibility of this life-threatening condition.

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References

1 Stevens DL, Tanner MH, Winship J 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.
2 Stevens DL. Streptococcal toxic-shock syndrome: specturm of disease, pathogenesis, and new concepts in treatment. *Emerg Infect Dis* 1995; 1: 69–78.
3 Cone LA, Woodard DR, Schlievert PM et al. Clinical and bacteriologic observations of a toxic shock-like syndrome due to Streptococcus pyogenes. *N Engl J Med* 1987; 317: 146–9.
4 Breiman RF. Defining the Group A Streptococcal Toxic Shock Syndrome. *JAMA* 1993; 269: 390–1.
5 Shalaby T, Anandappa S, Pocock NJ et al. Lesson of the month 2: Toxix shock syndrome. *Clin Medicine* 2014; 14: 316–8.
6 Talkington DF, Schwartz B, Black CM et al. Association of phenotypic and genotypic characterisitics of invasive Streptococcus pyogenes isolates with clinical components of streptococcal toxic shock syndrome. *Infect Immun* 1993; 61: 3369–74.
7 Yu C, Ferretti J. Molecular Epidemiologic Analysis. *Infect Immun* 1989; 57: 3715–9.
8 Ferretti JJ, Stevens DL, Fischetti V, editors. *Streptococcus pyogenes: Basic Biology to Clinical Manifestations*. Oklahoma City: University of Oklahoma Health Sciences Center; 2016.
9 Hackett S, Stevens D. Superantigens associated with staphylococcal and streptococcal toxic shock syndrome are potent inducers of tumor necrosis factor-beta synthesis. *J Infect Dis* 1993; 168: 232–5.
10 Hackett S, Stevens D. Streptococcal toxic shock syndrome: synthesis of tumor necrosis factor and interleukin-1 by monocytes stimulated with pyrogenic exotoxin A and streptolysin O. *J Infect Dis* 1992; 165: 879–85.
11 Stevens D, Bryant A, Hackett S, et al. Group A streptococcal bacteremia: the role of tumor necrosis factor in shock and organ failure. *J Infect Dis* 1996; 173: 619–26.
12 Norrby-Teglund A, Kotb M. Host-microbe interactions in the pathogenesis of invasive group a streptococcal infections. *J Med Microbiol* 2000; 49: 849–52.
13 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.
14 Conly J, Shafran S. Resurgence of virulent group A streptococcal infections – the streptococcal toxic shock syndrome. *Can J Infect Dis*; 3: 222–3.
15 Lappin E and Ferguson AJ. Gram-positive toxic shock syndromes. *Lancet Infect Dis* 2009; 9: 281–90.
16 Kiska DL. Staphylococcal and streptococcal toxic shock syndrome. *Clin Microbiol Newsletter* 1997; 19: 33–7.
17 Nelson C. Early recognition and treatment of staphylococcal and streptococcal toxix shock. *J Pediatr Adolesc Gynecol* 2004; 17: 289–92.
18 Mascini EM, Jansze M, Schouls LM et al. Penicillin and clindamycin differentially inhibit the production of pyrogenic exotoxins A and B by group A streptococci. *Int J Antimicrob Agents* 2001; 18: 395–8.
19 Curtis N. Toxic shock syndrome: under-recognized and under-treated? *Arch Dis Child* 2014; 99: 1062–3.
20 Shah PJ, Vakil N, Kabakov A. Role of intravenous immune globulin in streptococcal toxic shock syndrome and *Clostridium difficile* infection. *Am J Health Syst Pharm* 2015; 72: 1013–9.