CASE REPORT

No Epidermis: Is it the drug, COVID-19 or Something Else?

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Summary

Staphylococcal toxic shock syndrome (TSS) is a clinical disease with acute onset of fever, rash, hypotension and multi-organ system involvement. *Staphylococcal* scalded skin syndrome (SSSS), mostly described in neonate and children, is a superficial blistering disease caused by the exfoliative toxin of specific strains of *Staphylococcus aureus*. TSS and SSSS rarely occur concurrently in adults. We here describe a 35-year-old woman who was initially referred to dermatology team as toxic epidermal necrolysis. She presented with a rapid epidermal detachment without mucosal involvement, fever and shock, associated with acute kidney injury and transaminitis, severe metabolic acidosis, complicated by COVID-19 infection, and finally succumbed within 36 hours of hospitalization. Early recognition and prompt treatment are the key factors in the management as TSS itself can lead to mortality. *Staphylococcal* TSS and SSSS are important differential diagnosis to consider in acute epidermal detachment, as not all cases are drug-induced.

Key words: E*pidermal detachment, toxic shock syndrome, Staphylococcus aureus, Staphylococcal scalded skin syndrome*

Introduction

Staphylococcal toxic shock syndrome (TSS) is a life-threatening clinical condition characterized by the rapid onset of fever, hypotension, skin rashes (diffuse macular erythroderma, followed by desquamation 1-2 weeks later), with multisystem involvement.[1] At least three or more of the following systems are affected in TSS which include gastrointestinal symptoms (vomiting and watery diarrhoea), muscle (severe myalgia with raised muscle enzyme), central nervous system involvement (headache and confusion which may lead to delayed presentation, seizure, loss of consciousness, agitation), mucous membrane hyperemia (vaginal, oropharyngeal, or conjunctival), kidney and liver impairment, and thrombocytopenia.[1]

It was first described in paediatric patients in 1978 by Todd.[2] Subsequently there was a peak of cases when highly absorbable tampons were introduced in the 1980s.[3] However, the overall incidence of TSS remains low. The incidence of TSS is around 0.8 to 3.4 per 100,000 in the United States.[4] TSS has also been described in

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non-menstruating individuals, including in the paediatric population and male patients.[5] Non-menstrual cases are associated with higher mortality, earlier onset of fever and rash, with more pronounced renal and central nervous system complications, but less musculoskeletal involvement.[6]

Staphylococcal scalded skin syndrome (SSSS), also known as Ritter disease, is a cutaneous emergency mostly described in neonate and children.[7] It is caused by exfoliative toxin produced by specific strains of *Staphylococcus aureus*, resulting in rapid blister formation on a widespread tender erythroderma with tissue paper-like wrinkling of the skin at the periorificial or flexural area.[7] It typically spares the mucous membrane.[7] The initial source of *Staphylococcal aureus* infection is usually localized at upper respiratory tract, inner ear, conjunctiva, umbilical stump and others.[7]

Here we describe a young female who succumbed to *Staphylococcal* toxic shock syndrome with possible coexistent SSSS, who was initially referred to dermatology team as toxic epidermal necrolysis.

Case Report

A 35-year-old Myanmarese waitress, with no known medical illness or allergy, presented to the emergency department with a GCS of E3V5M6. Based on the history given by her housemate, she had severe painful skin peeling over bilateral lower limbs and suprapubic area for a week. She had history of swimming in seawater 2 days before she developed itchiness over the bilateral lower limbs. She denied any trauma, burn or bite. There was no known drug, supplement, or traditional medication exposure prior to the incident. She did not seek treatment for her symptoms. Instead, she used topical medications bought over the counter to the affected pruritic area. The painful rash followed by skin peeling developed rapidly and was associated with difficulty in ambulation.

There was no documented fever at home. She had no history of abdominal pain, vomiting or diarrhoea, limb weakness, numbness or muscle ache. There was no facial, eye, oral or genital involvement as well. She completed 2 doses of CoronaVac (Sinovac, China) vaccination and was unaware of any COVID contact. She did not smoke, consume alcohol or use recreational drugs. She had been living in Malaysia for more than 10 years. She was single with no significant sexual history. However, there was no information regarding her menstrual history and tampon practice. She had no pets.

On arrival, she was hypotensive with blood pressure of 53/28mmHg, tachycardic with a heart rate of 121/minute, and febrile with a temperature of 39.5°C. Oxygen saturation was 98% under room air. Her estimated body mass index was 25 kg/m^2. There was epidermal detachment over anterior and posterior aspects of bilateral lower thighs, extending to the knees and legs sparing the soles as shown in Figure 1(a) involving nearly 35% of body surface area. There was a small erosion over right labia majora. Confluent erythema associated with oedema was noted over lower abdomen and suprapubic region. No other skin lesions were seen. There was no enanthem and no mucosal erosions.

She had treatment-resistant hypoglycaemia, with glucometer readings ranging from 2.3 to 3.2mmol/l, and was oliguric. The patient was given aggressive fluid resuscitation followed by maximum inotropic support, boluses and maintenance dextrose solution. A dose of intravenous Cefuroxime 1.5g was given at 1 hour after presentation and sodium bicarbonate infusion was initiated. She was then intubated for respiratory support in view of severe metabolic acidosis (pH=7.23, bicarbonate 9.2mEq/L, lactate 4.9mmol/L).

Blood investigations showed microcytic hypochromic anaemia (haemoglobin 10.2 g/dL), leucocytosis (total white cell count 14.6 x10^9/L) with neutrophil predominant, thrombocytopenia (platelet 106 x10^9/L). She had acute kidney injury (urea 31.6 mmol/L, creatinine 416µmol/L), hyponatraemia (127mmol/L), elevated creatinine kinase (360

U/L), hypoalbuminaemia (15g/L), mildly raised total bilirubin (27μmol/L), transaminitis (ALT 175 U/L), and coagulopathy (PT 17.6sec, INR 1.6). C-reactive protein was markedly elevated at 263.5 mg/L. Her troponin T was raised as well 176 ng/L (normal <15). Her electrocardiograph showed sinus tachycardia, with no features of ischaemia. There were ground glass opacities seen over bilateral lungs on her chest X-ray as shown in Figure 1b. Her tracheal aspirate for 2019-NCoV PCR was detected, with CT value of 24.5.

Our provisional diagnosis was *Staphylococcal* Toxic Shock Syndrome (TSS) with COVID-19 co infection. Differential diagnosis such as *Staphylococcal* Scalded Skin Syndrome (SSSS), generalized bullous fixed drug eruption (GBFDE), toxic epidermal necrolysis, and COVID-19 multisystem inflammatory syndrome were also considered.

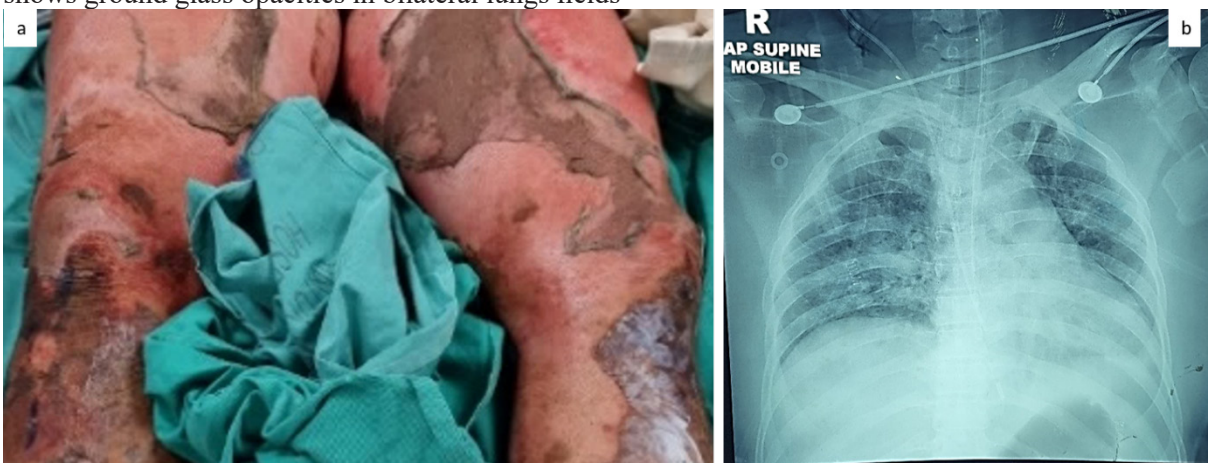
Intravenous piperacillin-tazobactam was later initiated with five doses given over the course of less than 2 days. Despite aggressive intravenous antibiotic administration, fluids resuscitation and inotropic support, the patient continued to deteriorate. She progressed to disseminated intravenous coagulopathy and succumbed 36 hours after admission. Her blood culture was later reported to grow *Methicillin-Sensitive Staphylococcus aureus* (MSSA).

Discussion

According to the United States Centre for Disease Control and Prevention (CDC), the clinical criteria for a confirmed case of *Staphylococcal* TSS includes fever with temperature ≥38.9ºC, hypotension with systolic blood pressure ≤90mmHg, diffuse macular erythroderma followed by desquamation one or two weeks later, involvement of ≥3 organ systems, positive cultures for *Staphylococcus aureus* and negative for alternative pathogens with serologic tests negative for other conditions.[8] Our patient's presentation fulfilled the clinical criteria for *Staphylococcal* TSS.

SSSS is characterized by oedematous erythema of the eyelids and nostril, generalized cutaneous pain, erythema, superficial blistering, and desquamation, associated with fever, with no mucous membrane involvement.[7,9] Although SSSS is more common in the paediatric population, adult SSSS has been reported at an annual incidence of 0.98 cases/million.[10] The three criteria that are required to make a diagnosis of SSSS include (1) a clinical pattern of erythroderma, desquamation or bullae formation; (2) histopathological evidence of intraepidermal cleavage through the stratum granulosum and (3) isolation of an exotoxin A (ETA) and/or exotoxin B (ETB) producing *Staphylococcus aureus* from the skin lesions.[11]

Figure 1. (a) confluent epidermal detachment over anterior and posterior aspect of bilateral lower limbs and lower abdomen leaving raw erosion involving 35% body surface area; (b) chest X-ray (supine, rotated film) shows ground glass opacities in bilateral lungs fields



There are only 5% of *Staphylococcus aureus* isolates produce exfoliative toxin ETA and ETB. These exfoliative toxins are serine proteases that target and cleave desmoglein 1 (Dsg1), which is a desmosomal cadherin maintaining keratinocytes adhesion. *Staphylococc*al exfoliative toxin results in hydrolysis of the amino-terminal extracellular domain of Dsg1. Hence, skin biopsy on a SSSS lesion typically shows splitting within the stratum granulosum without inflammatory cells or bacterial cocci.

Adult SSSS was associated with a higher mortality and complications.[12] Interestingly, about 60% of adults SSSS grow *Staphylococcus aureus* in the blood culture.[9] Co-existence of TSS and SSSS has been described rarely in adults and was associated with underlying renal impairment and immunosuppression.[13,14] Similar to children, adults with SSSS demonstrate a fever and lesions over the face.[7,12] Our patient, although presented with scalded like erosions over the lower abdomen and both thighs, she had no lesions over the face which is the primary affected site in SSSS.

Epidermal detachment could be a manifestation of generalized bullous fixed drug eruption (GBFDE) or drug-induced epidermal necrolysis which includes Steven Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or SJS/TEN overlap syndrome. In GBFDE, a history of similar eruptions at the same site with each exposure to a similar drug, with widespread blisters and erosions involving more than 10% BSA in at least three out of six sites (head and neck, anterior trunk, back, upper limbs, lower limbs and genitalia) should be elicited.[15] However; GBFDE has limited mucous membrane involvement. Drug induced epidermal necrolysis should be considered if it is accompanied with severe erosions at two or more mucous membranes.[16] There was, however, no prior history of drug exposure in this patient. In addition, she had minimal mucosal erosions (at the right labia majora only).

COVID-19 multisystem inflammatory syndrome might be considered as well, as this patient was diagnosed with COVID-19 infection via tracheal aspirate PCR, with multi-organ involvement. However, the most commonly reported cutaneous manifestations of COVID-19 were morbiliform rash, pernio-like acral lesions, urticaria, macular erythema, vesicular and/or papulosquamous eruption, and retiform purpura.[17] Epidermal detachment as the only manifestation of COVID-19 infection has not been described in the literature.

Interestingly, Yilin et al. reported a case of non-fatal TSS post-COVID-19. In that case, the patient presented with high grade fever, hypotension, erythematous and dusky-coloured plaques with bullae and superficial flaking, as well as yellow crusting, scaling, and widespread erosions which involved 40% of total body surface area. Although cultures were negative, skin biopsy was reported to favour TSS.[18] There was an interval between the COVID-19 infection and the rash onset in the case reported. However, our patient presented with skin lesions and was diagnosed to have COVID-19 concurrently. There were no respiratory symptoms reported prior to her presentation.

TSS can be caused by *Staphylococcus aureus* or *Streptococcus pyogenes.* Both are normal flora of skin and mucous membrane in humans. *Staphylococcus aureus* contributes to almost all menstrual TSS and half of non-menstrual TSS. *Streptococcus pyogenes* causes only non-menstrual TSS.[19] In addition to menstruating females, *Staphylococcal* TSS can occur in postpartum and postsurgical states especially when packings are used, in cases where barrier contraceptives are used, in *staphylococcal* pneumonia, sinusitis, and superinfected skin lesions.[20] *Streptococcal* TSS is preceded by trauma to the skin.

Staphylococcal TSS can be caused by both methicillin-susceptible or methicillin-resistant *Staphylococcus aureus* (MRSA), and is associated with mortality.[21,22] *Staphylococcus aureus* produces TSS toxin-1 (TSST-1), a type of exotoxin, which acts as a superantigen that can activate T cells, causing massive cytokine

production.[23] Insufficient antibody response to TSST-1 is found to be the cause of toxic shock syndrome.[24] Apart from exotoxin, enterotoxins produced by *Staphylococcus aureus* may play an important role in the disease manifestations. Inflammatory mediators including interleukin (IL)-1, IL-2, tumour necrosis factor (TNF)-alpha, TNF-beta, and interferon (IFN)-gamma are produced in large amounts.[25] Due to the presence of IL-1, high fever is noted. IL-1 is also involved in proteolysis of skeletal muscle; resulting in myalgia and high creatinine kinase.[25] This explains the raised creatinine kinase and Troponin T level in our patient. TNF inhibits polymorphonuclear leukocyte functions, hence purulence is not observed.[25]

To assist with the diagnosis, cultures from the blood, wound sites and mucosal sites including vaginal canal and nares, should be obtained. Any foreign material such as tampons, contraceptive sponges or intrauterine devices in vaginal canal should be promptly removed.[26] TSST-1 assays are useful in diagnosis, however the test is not available in our setting. It would have been important to perform a vaginal examination in this case to remove any foreign material and to take a vaginal swab for culture. Apart from that, to assess the possibility of concurrent SSSS, isolation of ETA and/or ETB producing *Staphylococcus aureus* from denuded skin as well as a skin biopsy would be helpful. Regrettably, our patient was intubated very soon on arrival before verbal consent could be obtained to examine the genitalia as well as skin biopsy. In addition, there was no next of kin who could give the consent on behalf of her.

The management of *Staphylococcal* TSS and SSSS involves aggressive treatment of shock, antibiotic therapy, intravenous fluids regimens, and surgical debridement of the primary source if indicated. Anti-*Staphylococcal* antibiotics are the mainstay of treatment and it is recommended to be administered within 1 hour upon recognition of septic shock.[27,28] Beta-lactam antibiotics, such as penicillin or cephalosporins should be combined with clindamycin for TSS due to MSSA, while vancomycin can be combined with clindamycin for TSS secondary to MRSA.[28] Vancomycin, clindamycin and piperacillin-tazobactam/cefepime/carbapenem can be started empirically if staphylococcal TSS is highly suspected. The rationale of adding clindamycin (bacteriostatic) to beta-lactams (bactericidal) is due to the lower effectiveness of beta-lactams on bacteria in stationary phase of growth, especially in large inoculations, where there are loss of several penicillin-binding proteins.[29] In addition, Clindamycin has the additional benefit of inhibiting bacterial toxins from *Staphylococcus aureus*. The duration of antibiotic treatment ranges from 10 to 14 days in cases without bacteraemia or other focus of infection.

The effectiveness of intravenous immunoglobulin (IVIG) in the treatment of TSS is debatable.[27] There are studies which are unable to draw a conclusion regarding the efficacy of IVIG in TSS.[27] However, there are observational studies that reported lower mortality rates with the use of IVIG in addition to antibiotic, compared with the use of antibiotics alone.[30] Since IVIG neutralizes the superantigens and halts the cytokine production, it can be accepted as an adjuvant treatment option in the management of TSS, after considering the side effects, which include transfusion reactions, thromboembolic events, kidney failure and aseptic meningitis.[31]

The use of systemic corticosteroids has been reported in TSS. A comparative retrospective analysis done by James et al in 1984 concluded that corticosteroids result in significantly reduced illness severity when given in the first 2 to 3 days of TSS.[2,32] Latest evidence suggested that hydrocortisone 200mg per day should be given intravenously to adults with septic shock, especially those who require norepinephrine or epinephrine dose of ≥0.25mcg/kg/min.[27] Our patient succumbed despite intensive management, likely due to advanced sepsis and concurrent COVID-19 infection.

Conclusion

We describe a COVID-19 infected female who succumbed to *Staphylococcal* TSS with possible concomitant SSSS that was initially referred to dermatology team as toxic epidermal necrolysis. *Staphylococcal* TSS and SSSS should be considered in patients who present with acute painful erythema followed by epidermal detachment, associated with high grade fever, and hypotension with multisystem involvement. Early recognition and prompt treatment are the keys points in the management especially in TSS, as it can lead to rapid fulminant deterioration resulting in mortality.

Conflict of Interest Declaration

The author have no conflict of interest to declare.

Acknowledgement

The authors would like to thank the Director General of Health Malaysia for the permission to publish this paper.

References

1. Wharton M, Chorba TL, Vogt RL, Morse DL, Buehler JW. Case definitions for public health surveillance. MMWR Recomm Rep 1990;39:1-43.
2. Todd JK. Toxic shock syndrome. Clin Microbiol Rev 1988;1:432-46.
3. Dugourd PM, Dupont A, Hubiche T, Chiaverini C, Alkhalifa A, Roudiere L et al. *Staphylococcal* toxic shock syndrome should be considered in the event of diffuse erythema with fever and shock. Ann Dermatol Venereol 2019;146:287-91.
4. Lappin E, Ferguson AJ. Gram-positive toxic shock syndromes. Lancet Infect Dis 2009;9:281-90.
5. Hajjeh RA, Reingold A, Weil A, Shutt K, Schuchat A, Perkins BA. TSS in the United States: Surveillance update, 1979-1996. Emerg Infect Dis 1999;5:807-10.
6. Kain KC, Schulzer M, Chow AW. Clinical spectrum of nonmenstrual toxic shock syndrome (TSS): Comparison with menstrual TSS by multivariate discriminant analyses. Clin Infect Dis 1993;16:100-6.
7. Ladhani S, Joannou CL, Lochrie DP, Evans RW, Poston SM. Clinical, microbial, and biochemical aspects of the exfoliative toxins causing *staphylococcal* scalded-skin syndrome. Clin Microbiol Rev 1999;12:224-42.
8. CDC National Notifiable Diseases Surveillance System. Toxic Shock Syndrome (Other Than Streptococcal) TSS. Available at https://ndc.services.cdc.gov/case-definitions/toxic-shock-syndrome-2011/ Accessed on 19th May 2022
9. Patel S, Cadwell JB, Lambert WC. Comparison of adult vs. paediatric inpatients with staphylococcal scalded skin syndrome: a retrospective database analysis. Br J Dermatol 2021;184:767-9.
10. Staiman A, Hsu DY, Silverberg JI. Epidemiology of staphylococcal scalded skin syndrome in US adults. J Am Acad Dermatol 2018;79:774-6.
11. Falk DK, King LE. Criteria for the diagnosis of staphylococcal scalded skin syndrome in adults. Cutis 1983;31:431-4.
12. Handler MZ, Schwartz RA. Staphylococcal scalded skin syndrome: diagnosis and management in children and adults. J Eur Acad Dermatol Venereol 2014;28:1418-23.
13. Brewer JD, Hundley MD, Meves A, Hargreaves J, McEvoy MT, Pittelkow MR. *Staphylococcal* scalded skin syndrome and toxic shock syndrome after tooth extraction. J Am Acad Dermatol 2008;59:342-6.
14. Rahmanian SD, Molenda M, Fox C, Zirwas M, Sood N. A 42-year-old man with fever, shock, and rash. Chest 2010;138:1256-9.
15. Anderson HJ, Lee JB. A review of fixed drug eruption with a special focus on generalized bullous fixed drug eruption. Medicina (Kaunas) 2021;57:925.
16. Lipowicz S, Sekula P, Ingen-Housz-Oro S, Liss Y, Sassolas B, Dunant A et al. Prognosis of generalized bullous fixed drug eruption: Comparison with Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol 2013;168:726-32.
17. Freeman EE, McMahon DE, Lipoff JB, Rosenbach M, Kovarik C, Desai SR et al. The spectrum of COVID-19-associated dermatologic manifestations: An international registry of 716 patients from 31 countries. J Am Acad Dermatol 2020;83:1118-29.
18. Feng Y, Armenti ST, Albin OR, Mian SI. Novel case of an adult with toxic shock syndrome following COVID-19 infection. Am J Ophthalmol Case Rep 2020;20:100843.
19. Reiss MA. Toxic shock syndrome. Prim Care Update Ob Gyns 2000;7:85-90.
20. Chan BC, Maurice P. Images in clinical medicine. *Staphylococcal* toxic shock syndrome. N Engl J Med 2013;369:852.
21. Contou D, Colin G, Travert B, Jochmans S, Conrad M, Lascarrou JB et al. Menstrual toxic shock syndrome: A French nationwide multicentre retrospective study. Clin Infect Dis 2022:74:246-53.
22. Durand G, Bes M, Meugnier H, Enright MC, Forey F, Liassine N et al. Detection of new methicillin-resistant *Staphylococcus aureus* clones containing the toxic shock syndrome toxin 1 gene responsible for hospital- and community-acquired infections in France. J Clin Micriobiol 2006:44:847-53.
23. Schlievert PM. Role of superantigens in human disease. J Infect Dis 1993;167:997-1002.
24. Bonventre PF, Linnemann C, Weckbach LS, Staneck JL, Buncher CR, Vigdorth E et al. Antibody responses to toxic-shock-syndrome (TSS) toxin by patients with TSS and by healthy staphylococcal carriers. J Infect Dis 1984;150:662-6.
25. Parsonnet J. Mediators in the pathogenesis of toxic shock syndrome: overview. Rev Infect Dis 1989;11:S263-9.
26. Silversides JA, Lappin E, Ferguson AJ. Staphylococcal toxic shock syndrome: Mechanisms and management. Curr Infect Diss Rep 2010;12:392-400.
27. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47:1181-247.
28. Annane D, Clair B, Salomon J. Managing toxic shock syndrome with antibiotics. Expert Opin Pharmacother

2004;5:1701-10.
29. Stevens DL, Gibbons AE, Bergstrom R, Winn V. The Eagel effect revisited: efficacy of clindamycin, erythromycin and penicillin in the treatment of *Streptococcal* myositis. J Infect Dis 1988;158:23-8.
30. Wilkins AL, Steer AC, Smeesters PR, Curtis N. Toxic shock syndrome – the seven Rs of management and treatment. J Infect 2017;74:S147-52.
31. Amreen S, Brar SK, Perveen S, Chaudhry MR, AlBabtain S, Khan S. Clinical Efficacy of Intravenous Immunoglobulins in Management of Toxic Shock Syndrome: An Updated Literature Review. Cureus 13:e12836.
32. Todd JK, Ressman M, Caston SA, Todd BH, Wiesenthal AM. Corticosteroid therapy for patients with toxic shock syndrome. JAMA 1984;252:3399-402.