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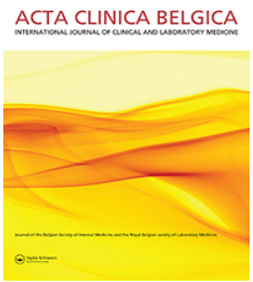

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CASE REPORT

Streptococcal toxic shock syndrome in a returning traveller

Stéphanie Note[a,b], Patrick Soentjens[c,d], Marie Van Laer[b], Philippe Meert[b] and Peter Vanbrabant[c,e]

[a]Medical Component, Royal Military Academy, Brussels, Belgium; [b]Emergency Department, Cliniques Universitaires Saint-Luc, Brussels, Belgium; [c]Center for Infectious Diseases ID4C, Military Hospital Queen Astrid, Brussels, Belgium; [d]Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium; [e]General Internal Medicine, University Hospitals Leuven, Leuven, Belgium

ABSTRACT

Background: A patient presenting with fever and purpura after a stay in the tropics tempts a physician to make a differential diagnosis mainly focusing on imported diseases. Although the importance of considering a tropical disease is obvious, the fact that cosmopolitan infections account for one third of the cases in a febrile returning traveler must not be overseen. Toxic Shock Syndrome is amongst the most notorious diseases due to the high mortality when inappropriately managed and the association with necrotizing fasciitis.
Methods : We present a 60-year old female with fever, shock syndrome and progressive appearance of painful purpura on the lower legs after a 2-week holiday in Zanzibar.
Results : The patient was diagnosed with Streptococcal Toxic Shock Syndrome. Treatment focusing on aggressive fluid resuscitation, prompt administration of antibiotics (ceftriaxon, doxycycline and one dose of amikacin) and adjunctive treatment by clindamycin and immunoglobulin was initiated. She was also immediately taken into surgery for a bilateral fasciotomy and surgical exploration of the lower legs. Histology appeared compatible with purpura fulminans, thereby excluding necrotizing fasciitis. No source of infection could be identified.
Conclusion: Toxic Shock Syndrome remains a challenging diagnosis and even more in a returning traveler with an extensive differential diagnosis containing both tropical and cosmopolitan diseases. Cornerstones for the treatment of Streptococcal Toxic Shock Syndrome are abrupt administration of antimicrobial therapy comprising beta-lactam antibiotics and clindamycin and surgical exploration to apply source control when indicated.

KEYWORDS
Toxic shock syndrome; streptococcus pyogenes; necrotizing fasciitis; purpura; returning traveller

Introduction

Toxic shock syndrome (TSS) is a severe illness resulting in multi-organ failure and even lethal outcome if not recognized and treated in an early stage. TSS is located at the end of a spectrum of diseases most frequently caused by the toxin-producing *Staphylococcus aureus* and *Streptococcus pyogenes* (Group A streptococcus [GAS]) [1,2]. This case report focusses on streptococcal TSS and the importance of raising a red flag of suspicion for necrotizing fasciitis at appearance of purpura and extensive pains.

Case

A 60-year-old woman without noticeable medical history or treatment presented at the emergency department (ED) immediately after return from Zanzibar, where she had spent 14 days on a beach holiday. About 2 days after her arrival abroad, she already experienced some nausea and pain at the throat, but did not notice any fever, chills or other systemic symptoms such as respiratory complaints, arthralgia or diarrhoea. She did not take any malaria prophylaxis, as it was deemed not indicated during a pre-travel consultation. No obvious trauma was reported during her stay. At the end of the holiday, she gradually lost her appetite and upon return home she suffered from vomitus and stupor, leading to the consult at the ED.

A rapid evolution into septic shock with renal failure (serum creatinine 3.07 mg/dL or eGFR 14 ml/min upon admission) and disseminated intravascular coagulation (DIC) followed, requiring an admission at an intensive care unit. Prompt antimicrobial treatment by ceftriaxon, doxycycline and one dose of amikacin was initiated. Besides adequate fluid resuscitation, concomitant vasopressor support was necessary. The presence of a deep vein thrombosis (DVT) at the right calf was diagnosed, but due to the presence of DIC no low molecular weight heparin were administered. Given her leg was already swollen during presentation at ED, flight-related venous stasis, rather than a complication of DIC, was assumed to be the cause of the DVT.

The thick peripheral blood smear for malaria came back negative, as did the evaluation for Dengue fever. The patient appeared immune for hepatitis A, cytomegalovirus and Epstein-Barr virus. HIV-screening was negative.

Blood cultures identified *Streptococcus pyogenes* as causal pathogen the day after admission. At that

CONTACT Stéphanie Note stephanie_note@msn.com, stephanie.note@mil.be Medical Component, Royal Military Academy, Brussels, Belgium

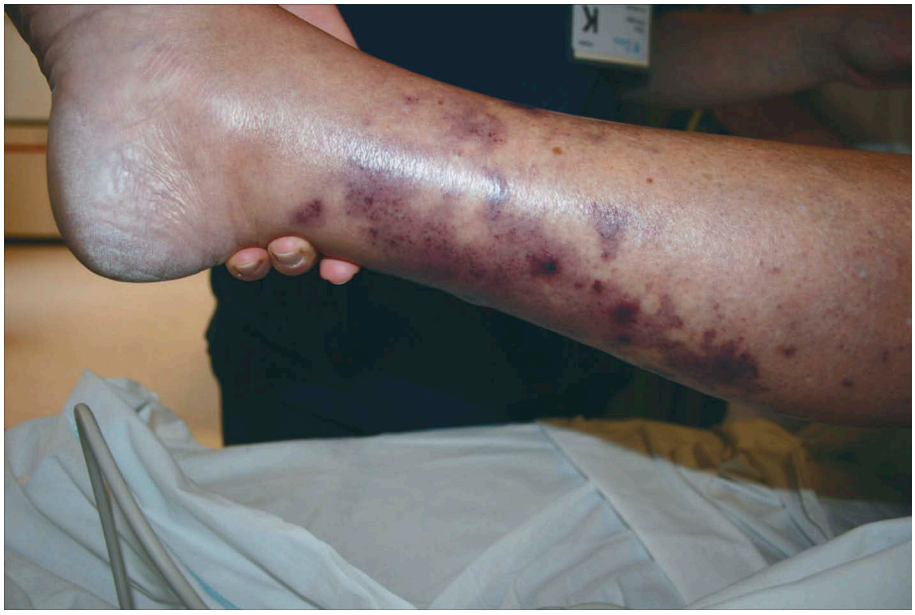

Figure 1. Purpura lower legs.

moment, the patient started to complain about bilateral lower limb pain and purpura appeared on the lower legs (Figure 1). This rose the suspicion of necrotizing fasciitis with streptococcal toxic shock syndrome (STSS) given the persistent hemodynamic instability. The patient was immediately taken into surgery for a bilateral fasciotomy and surgical exploration, but no apparent signs of inflammation were present. Histology results revealed a epidermal necrosis associated with diffuse thrombi at the superficial dermal vascular plexus, compatible with purpura fulminans.

As the criteria for STSS were met, clindamycin and intravenous immunoglobulins were added to the therapy, both for a period of 3 days. Concomitant corticosteroid therapy was also administered during these days. The extensive supportive therapy in the context of multi-organ system failure could be reduced over the following days. Dobutamin for the septic myocardial depression was stopped 24 h after initiation and mechanical ventilator support and CVVH could be stopped after 3 days. After the aggressive fluid resuscitation phase, guided by invasive hemodynamic monitoring, diuretics and human albumin were added to the therapy.

After five days, transfer to the medium care department was possible. In an attempt to find the infection focus, referrals to ENT, cardiology and orthopaedics were made. Respectively, no arguments for a retropharyngeal abscess, endocarditis or septic arthritis of the right knee, suspected due to a limited joint effusion, could be found. The treatment by ceftriaxon was terminated after 7 days. Three weeks after admission, a first surgical debridement of the necrotic purpura on the inferior limbs took placed, followed by a second intervention utilizing vacuum assisted closure (VAC) therapy 1 week later. After another 2 weeks, autografts were used to cover the wounds.

Discussion

The most common etiologic agents of TSS are *Staphylococcus aureus* and *Streptococcus pyogenes* (Group A streptococcus [GAS]), both with their more specific sources and clinical features [1,2]. If a Staphylococcus is the causal organism, a portal of entry, if found, is more likely to be superficial, such as surgical wounds, burns or a foreign body [2]. A specific subcategory, the menstrual staphylococcal TSS, was associated to highly absorbent tampon use in the eighties [3]. TSS may also arise from any focal staphylococcal infection (e.g. pneumonia) or even from colonization with *Staphylococcus aureus* [2]. In contrast, the streptococcal TSS occurs more often after viral infections (e.g. varicella and influenza), pharyngitis or trauma, haematoma or joint-effusion causing deep-seated infection [1]. TSS must be considered into the spectrum of invasive streptococcal infection, defined as the entry of GAS into usually sterile sites of the body. Whereas less severe forms (e.g. cellulitis and bacteraemia) are located at one end, diseases with high mortality rates (e.g. necrotizing fasciitis and TSS) are located at the other [4].

According to an epidemiologic study throughout Europe in 2008, skin and soft tissue were the most common foci of *Streptococcus pyogenes* infection, with 32 percent of patients having cellulitis and eight percent necrotizing fasciitis [5]. The overall 7-day case fatality rate was 19 percent, but rose to 44 percent among patients who developed streptococcal TSS, indicating the importance of early recognition and management [5].

The clinical features of the TSS are the result of toxin production in combination with symptoms from the infection focus [1,2]. These toxins react as superantigens, triggering massive and uncontrolled T-cell activation by bypassing conventional limiting inflammatory processes. This results in downstream activation of other cell types and subsequent cytokine avalanche [1,2,6,7]. A direct correlation between this cytokine response and the severity of clinical manifestation of TSS has been reported [8]. Furthermore, the magnitude of the inflammatory response is linked to interaction between the host an pathogen [1]. Host genetic factors such as human leucocyte antigen class II haplotype are involved. Whereas some HLA-types significantly increase the risk of TSS, others have proven to do the opposite [1,9]. Additionally, the lack of host antibodies against the superantigen appears to be a another key risk factor for TSS [1,7,10].

STSS is a clinical diagnosis, characterized by rapid-onset shock, multi-organ failure and isolation of *Streptococcus pyogenes* from a normally sterile body site [1,2,11]. The Center for Disease Control and Prevention (CDC) proposed the widely accepted clinical case definitions (Table 1) [11], although they hold some issues. The tool was designed for research, aiming for a high specificity at the expense of a high sensitivity as required for detection and diagnostics [2,12]. Furthermore, many cases only fulfil these criteria in retrospect or later in the disease course. Sometimes, they do not even meet the criteria at any stage of the illness at all. This indicates the necessary high index of suspicion and the consequential need for prompt initiation of treatment [2,12].

Cutaneous manifestation is a common finding in TSS. Typically, the rash will be a diffuse, macular, sometimes pruritic erythroderma, often present at onset of disease [2]. Desquamation of the palms and soles typically develops 1 to 3 weeks later. Superficial ulcerations may occur in severe cases. Non-pitting oedema due to capillary leak can be present [2]. If the pain exceeds what is expected based on clinical examination, and especially at appearance of purpura or ecchymotic plaques, necrotizing fasciitis needs to be suspected [13–15]. If further investigation appears negative, histology can guide into the direction of acute infectious purpura fulminans, as presented in this case. Purpura fulminans is a life-threatening syndrome marked by DIC and endovascular thrombosis, resulting in the characteristic pattern of cutaneous purpura, associated to multiple-organ failure [14–16]. Purpura fulminans can be related to an anticoagulant protein deficiency or a post-infectious context, but most commonly occurs as a severe complication in the acute phase of infection [15,16]. Typically, gram-negative bacteria are the causal organisms, but reports of association with a streptococcal infection were made [16–18].

Table 1. The clinical case definition of streptococcal toxic shock syndrome.

1 Isolation of group A β-haemolitic streptococci
a. From a normally sterile site – blood, CSF, peritoneal fluid, tissue biopsy
b. From a non-sterile site – throat, vagina, sputum
2 Clinical signs of severity
a. Hypotension – systolic blood pressure ≤ 90 mmHg in adults or less than the fifth percentile by age for children aged < 16 years
b. Two or more of the following signs
(i) Renal impairment – creatinine > 2 mg/dL (> 177 µmol/L)
(ii) Coagulopathy – platelets ≤ 100×10^9 or disseminated intravascular coagulation
(iii) Hepatic involvement – alanine aminotransferase, aspartate amino-transferase or total bilirubin twice the upper limit of normal
(iv) Adult respiratory distress syndrome
(v) Generalized, erythematous, macular rash that may desquamate
(vi) Soft-tissue necrosis – necrotizing fasciitis, myositis or gangrene
Case classification
Probable : a case that meets the clinical case definition in the absence of another identified ethology for the illness and with isolation of group A Streptococcus from a nonsterile site.
Confirmed : a case that meets the clinical case definition and with isolation of group A Streptococcus from a normally sterile site.

The treatment must be focussed on rapid and aggressive fluid resuscitation according to the current sepsis guidelines [1,2,12,19], often in an intensive care setting where hemodynamic and respiratory supportive therapy are available. Cornerstones are administration of antibiotics, adjunctive treatment by immunoglobulin and source-control [12].

As soon as STSS is diagnosed, antimicrobial treatment involving penicillin and clindamycin should be administered [1,12]. Since GAS remains sensitive to β-lactam agents, penicillin is a part of the first-line treatment [1,12]. Clindamycin is commonly added as it has shown to suppress superantigen production and possesses a better tissue penetration and longer post-antibiotic effect than penicillin, thereby improving survival [1,2,12,20,21]. Furthermore is clindamycin able to overcome 'the Eagle effect', e.g. the reduced effect of β-lactam antibiotics when large numbers of bacteria are present [12]. Monotherapy is not sufficient because of the increasing resistance of group A streptococci to macrolides and cross resistance is known [1,21].

The efficacy of intravenous immunoglobulin (IV Ig) in STSS has not been definitively established [1,2,12,22]. The rationale for immunoglobulin use is that antibodies are able to block T-cell activation by the superantigens *in-vitro*, but so far no study could demonstrate a significant *in-vivo* repercussion. One multicentre, randomized, double-blind, placebo-controlled trial was terminated prematurely due to shortfalls in recruitment. Although RCT data could not reach significance, treatment with IV Ig indicated a lower mortality and an improvement of organ failure, compared to the placebo group [23]. The Infectious Disease Society of America determined that existing evidence is insufficient for a strong recommendation and emphasized the need for further study [21,22].

This statement is followed by the UK Department of Health, stating that IV Ig may be added when the approach by antibiotics and source control have failed to elicit a response [1,24] .

Deep-seated soft tissue infections, including necrotizing fasciitis, myositis and cellulitis, are commonly the source of infection. Surgical exploration and debridement is therefore a priority. A thorough clinical search must be an indispensable part of the initial assessment [1,2,12]. Clinical examination may be supplemented by CT or MR imaging, yet delay in surgical assessment must be avoided [12,15].

As demonstrated above, TSS is an important yet challenging diagnosis to consider when encountering fever and purpura in a patient. Complicating the diagnosis further is the fact that many other potentially life-threatening diseases may present in a similar way, especially in a patient returning from tropical areas. This broad differential diagnosis includes for example Meningococcemia, Rickettsiosis, Leptospirosis, Dengue Fever and other haemorrhagic diseases [25]. If during history a patient turns out to be a returning traveller, this might direct the attention of the treating physician towards these imported diseases. Nevertheless, a study from Bottieau et al. demonstrated that in returning travellers consulting with fever at the hospital, only 39% were suffering from a tropical disease, whereas 34% had a cosmopolitan infection [26]. In the remaining 24%, the diagnosis remained unknown. 14% of these febrile patients were presenting dermatological signs as well [26]. By consequence, fever and rash in the returning traveller always prompt a cautionary assessment and often requires a hospital admission for observation and confirmation of the diagnosis [25].

Conclusion

When confronted with a returning traveller presenting with fever and purpura in the emergency department, a rapid diagnosis must be made, taking into account an extensive differential diagnosis containing both tropical and cosmopolitan diseases. Once the diagnosis of STSS has been established, prompt antimicrobial treatment (comprising beta-lactam antibiotics and clindamycin) is mandatory, often accompanied by surgical exploration to exclude or confirm necrotizing fasciitis.

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ORCID

Stéphanie Note http://orcid.org/0000-0002-9624-7619
Marie Van Laer http://orcid.org/0000-0002-1900-6117

References

[1] Lappin E, Ferguson AJ. Gram-positive toxic shock syndromes. Lancet Infect Dis. 2009;9(5):281–290.
[2] Gottlieb M, Long B, Koyfman A. The evaluation and management of toxic shock syndrome in the emergency department: a review of the literature. J Emerg Med. 2018;54(6):807–814.
[3] Davis JPCJ, Chesney PJ, Wand PJ, et al. Toxic-shock syndrome: epidemiologic feactures, recurrance, risk factors and prevention. N Engl J Med. 1980;303 (25):1429–1435.
[4] Walker MJ, Barnett TC, McArthur JD, et al. Disease manifestations and pathogenic mechanisms of group A Streptococcus. Clin Microbiol Rev. 2014;27 (2):264–301.
[5] Lamagni TL, Darenberg J, Luca-Harari B, et al. Epidemiology of severe Streptococcus Pyogenes disease in Europe. J Clin Microbiol. 2008;46(7):2359–2367.
[6] Bisno AL, Brito MO, Collins CM. Molecular basis of group A streptococcal virulence. Lancet Infect Dis. 2003;3(4):191–200.
[7] McCormick JK, Yarwood JM, Schlievert PM. Toxic shock syndrome and bacterial superantigens: an update. Ann Rev Microbiol. 2001;55:77–104.
[8] Norrby-Teglund A, Chatellier S, Low DE, et al. Host variation in cytokine responses to superantigens determine the severity of invasive group A streptococcal infection. Eur J Immunol. 2000;30(11):3247–3255.
[9] Kotb M, Norrby-Teglund A, McGeer A, et al. An immunogenetic and molecular basis for differences in outcomes of invasive group A streptococcal infections. Nat Med. 2002;8(12):1398–1404.
[10] Mascini EM, Jansze M, Schellekens JFP, et al. Invasive group A streptococcal disease in The Netherlands: evidence for a protective role of anti-exotoxin A antibodies. J Infect Dis. 2000;181(2):631–638.
[11] Centers for Disease Control and Prevention. Case definitions for infectious conditions under public health surveillance. MMWR Morb Mortal Wkly Rep. 1997;46(NoRR–10):33–34.
[12] Wilkins AL, Steer AC, Smeesters PR, et al. Toxic shock syndrome – the seven Rs of management and treatment. J Infect. 2017;74(suppl 1):S147–52.
[13] Dahl PR, Perniciaro C, Holmkvist KA, et al. Fulminant group A streptococcal necrotizing fasciitis: clinical and pathologic findings in 7 patients. J Am Acad Dermatol. 2002;47(4):489–492.
[14] Ramos-e-Silva M, Libia Cardozo Pereira A. Life-threatening eruptions due to infectious agents. Clin Dermatol. 2005;23(2):148–156.
[15] Karimi K, Odhav A, Kollipara R, et al. Acute cutaneous necrosis: a guide to early diagnosis and treatment. J Cutan Med Surg. 2017;21(5):425–437.
[16] Colling ME, Bendapudi PK. Purpura fulminans: mechanism and management of dysregulated hemostasis. Transfus Med Rev. 2018;32(2):69–76.
[17] Dhodapkar K, Corbacioglu S, Chang M. Purpura fulminans caused by group A ß-hemolytic Streptococcus sepsis. J Pediatr. 2000;134(4):562–567.

[18] Daskalaki MA, Boeckx WD, Demey A, et al. Toxic shock syndrome due to group A beta-hemolytic streptococcus presenting with purpura fulminans and limb ischemia in a pediatric patient treated with early microsurgical arteriolysis. J Pediatr Surg. 2013;48 (1):2013.

[19] Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43(3):304–377.

[20] Carapetis JR, Jacoby P, Carville K, et al. Effectiveness of clindamycin and intravenous immunoglobulin, and risk of disease in contacts, in invasive Group A Streptococcal infections. Clin Infect Dis. 2014;59 (3):358–365.

[21] Stevens D, Bisno A, Chambres H. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious disease society of America. Clin Infect Dis. 2014;59(2): e10–e52.

[22] Kadri SS, Swihart BJ, Bonne SL, et al. Impact of intravenous immunoglobulin on survival in necrotizing fasciitis with vasopressor-dependent shock: A propensity score-matched analysis from 130 US hospitals. Clin Infect Dis. 2017;64(7):877–885.

[23] Darenberg J, Ihendyane N, Sjölin J, et al. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. Clin Infect Dis. 2003;37(3):333–340.

[24] Provan D, Nokes TJC, Agrawal S, Winer J, Wood P, IVIg Guideline Development Group of the IVIg Expert Working Group. Clinical guidelines for immunoglobulin use. 2nd ed. London: Department of Health, 2008

[25] Kotlyar S, Rice B. Fever in the returning traveler. Emerg Med Clin North Am. 2013;31(4):927–944.

[26] Bottieau E, Clerinx J, Schrooten W, Van den Enden E. Etiology and outcome of fever after a stay in the tropics. Arch Intern Med. 2006;166(15):1642–1648.