

Staphylococcal Toxic Shock Syndrome in Returned Travellers

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ABSTRACT

Staphylococcal toxic shock syndrome (TSS) is a rare, but life-threatening systemic illness which occurs in diverse clinical settings. It commonly presents with symptoms of gastroenteritis and may mimic other febrile illnesses. Diagnosis rests mainly on clinical grounds. Early recognition and aggressive management of the syndrome will decrease the over-all morbidity and mortality. Clinicians should therefore be familiar with the manifestations of TSS and should consider the diagnosis in appropriate clinical settings. We describe two cases of Staphylococcal TSS presenting with diarrhoea and vomiting after travel abroad.

INTRODUCTION

Staphylococcal TSS is a toxin mediated systemic illness associated with *Staphylococcus aureus* infection. Despite numerous sporadic reports suggesting the existence of a syndrome since 1927,¹ it was only recognised as an important clinical syndrome after 1978 when Todd et al reported TSS as a clinical entity in a series of seven children.² It was initially associated with the use of super-absorbent tampons, but it is now known to occur in diverse clinical settings often mimicking common febrile conditions including gastroenteritis. With early recognition and treatment the serious consequences of TSS, namely organ failure, limb loss, and death can often be avoided. It is therefore extremely important that health professionals are familiar with the manifestations of TSS and consider the diagnosis in appropriate settings even if the patients have a travel history.

CASE REPORTS

Case No.1

A 26 year old lady was admitted to hospital with a one day history of profuse diarrhoea and vomiting. She had returned from a holiday in Tenerife six days prior to being admitted, and she had spilled some hot water over her left thigh the day after returning, suffering superficial burns. She was subsequently seen in the burns clinic, and was getting regular wound dressings as advised. On examination she was flushed and pyrexial with a temperature of 41°C. Her blood pressure was 110/60 mmHg and her pulse rate was 100 beats per minute. Her heart sounds were normal and her abdomen was soft and non-tender. Her chest was clear and she had evidence of superficial burns to the inner aspect of her left thigh which had been dressed with silver sulfadiazine 1% cream. Investigations on admission showed a white cell count of $17.1 \times 10^9/L$ with a neutrophilia, haemoglobin of 14.1 g dl^{-1} , and platelet count of $106 \times 10^9/L$. Renal function tests and clotting screen were within normal limits. She was initially admitted to the acute medical unit where a provisional diagnosis of gastroenteritis was made, taking the travel history into consideration. A few hours after admission, her condition deteriorated, and she became hypotensive. Her blood pressure dropped to 90/50 mmHg, and she developed a widespread rash. She was reviewed by the infectious diseases physicians when toxic shock syndrome was suspected. She was commenced on IV teicoplanin due to her history of penicillin allergy. She was also resuscitated with IV fluids aided by CVP monitoring. Her blood culture and stool culture results were all negative. Urinary legionella antigen and serum legionella antibody tests were negative. A chest x-ray showed clear lung fields. Swabs from left thigh showed a moderate growth of *Staphylococcus aureus*. Her CRP was 181 mg/L. She received a ten day course of antibiotics and all her symptoms including diarrhoea and vomiting resolved. She developed desquamation of her skin about twelve days after admission. It was later diagnosed by the national reference laboratory that the *S. aureus* isolated was a toxin producing strain producing Enterotoxin C and toxin shock syndrome toxin 1 (TSST 1).

Case No.2

A 35 year old housewife was admitted to hospital with a four day history of profuse diarrhoea, vomiting, confusion and high fever. She had returned from Pakistan ten days previously having

visited the mountainous areas there. She had taken malaria pr-phylaxis prior to travelling and during her five week stay. She had felt ill five days after returning, when she developed a widespread rash. She was initially diagnosed to be suffering from acute gastroenteritis by the admitting physician and was referred to the infectious diseases unit. On further inquiry the patient admitted to having her menstrual period seven days prior to admission and using tampons during this time.

On examination she was pyrexial with a temperature of 38.9 C. She had a blanching erythematous rash and conjunctival hyperaemia. She was hypotensive with a blood pressure of 60/40 mmHg, and was tachycardic with a pulse rate of 100 beats per minute. Her heart sounds were normal, and her chest was clear. Abdomen was soft with mild epigastric tenderness. She also had a vaginal discharge but there was no evidence of any tampons in situ on vaginal examination.

Investigations on admission showed a white cell count of $13.3 \times 10^9 \text{ L}^{-1}$ with a neutrophilia, haemoglobin of 9.8 g dl^{-1} , and platelet count of $126 \times 10^9 \text{ L}^{-1}$. Malaria films were negative and blood films showed toxic granulation with left shift in neutrophils. CRP was raised at 253 mg/L. She also had renal and hepatic impairment with a serum urea of 24.3 mmol/L, creatinine of 446 $\mu\text{mol/L}$, alkaline phosphatase of 512 U/L, albumin of 18 g/L, bilirubin of 33 $\mu\text{mol/L}$. Her chest x-ray showed clear lung fields. Urine tested negative for Legionella antigens.

Toxic shock syndrome was suspected. She was therefore treated with IV flucloxacillin and resuscitated with IV fluids aided by CVP monitoring. She was subsequently admitted to the intensive care unit as she required inotropic support to maintain her blood pressure. Her blood culture and stool culture results were later found to be negative. The vaginal swabs, however, showed a heavy growth of *Staphylococcus aureus* sensitive to flucloxacillin. This was later found to be an Enterotoxin A and toxic shock syndrome toxin 1 (TSST-1) producing strain by the national reference laboratory. All her symptoms including diarrhoea and vomiting settled with treatment. Eleven days after admission she developed desquamation of the skin on her hands and feet. CRP prior to discharge was $<10 \text{ mg L}^{-1}$.

DISCUSSION

Toxic shock syndrome is often confused with septic shock, although the clinical manifestations differ considerably.³ It is a rare but life threatening condition mediated by toxins, and the fatality rate may vary between 4 - 11%.¹³ TSS is generally associated with *S. aureus* and Group A Streptococci, but Group C Streptococci and *Pseudomonas* species have also been rarely associated with TSS.⁴

The diagnostic criteria for TSS include a high fever ($>38.9 \text{ C}$), diffuse macular erythroderma type rash, hypotension (systolic BP 90 mmHg), multisystem dysfunction (at least 3 of gastrointestinal, muscular, mucous membranes, renal, hepatic, haematological and neurological), desquamation characteristically around 1-2 weeks after the onset of the illness and evidence against alternative diagnosis.⁵ Blood cultures are usually negative for *S. aureus* but can occasionally be positive.

Colonisation or infection by a toxin producing strain of *S. aureus* is essential for initiation of the disease process. The toxin produced by the *S. aureus* is later absorbed and the subsequent intoxication leads to the full-blown syndrome. The cross sectional carriage rate of *S. aureus* is 15 - 40%. Common sites include the anterior nasopharynx, axillae, vagina and the perineum.⁶ About 25% of all *S. aureus* strains are toxigenic. Roughly 4 - 10% of normal people harbour toxigenic strains at any given time. Although these toxigenic strains have the genetic potential to produce toxins, they actually do so rarely, only at times when toxin production serves the bacterium's survival needs. The exact nature and environmental signals which trigger this are not fully understood.⁶

Toxic shock syndrome toxin 1 (TSST-1) formerly known as "Staphylococcal Enterotoxin F" is the toxin isolated in the majority of cases. This toxin is responsible for almost all cases ($>90\%$) of Staphylococcal TSS associated with menstruation. However, non-menstrual Staphylococcal TSS accounts for roughly 30-50% of all cases of Staphylococcal TSS, one third of which involve men. Even in this group TSST-1 accounts for 50 - 60% of cases.⁷ The remainder of the cases are mediated through Enterotoxin B and less commonly Enterotoxins A, C, D or E.⁸⁻¹⁰

Many adults, almost 80 - 90%, demonstrate protective antibody titres against TSS.^{11,14} TSS can occur whenever a non-immune person is exposed to a TSS toxin.¹¹ It is therefore common in younger people, acquisition of protective antibodies being a function of age. Clinical signs and symptoms of TSS are due to the effects of toxins mediated through the production of interleukin 1 (IL-1), interleukin 2 (IL-2), tumour necrosis factor (TNF) and interferon gamma (IFN- γ).⁷

TSS is said to be "menstrual" if it occurs during the menstrual period (may be associated with tampons) and non-menstrual when it occurs at other times. Non-menstrual TSS could be associated with barrier contraceptive use, septic abortions and non-obstetric, gynaecological surgery.⁶ It could be related to primary Staphylococcal infections (folliculitis, cellulitis, carbuncles and abscesses) or Staphylococcal superinfection of pre-existing lesions such as burns,¹³ insect bites, Varicella zoster infections and surgical wounds. Respiratory tract infections, osteomyelitis and septic arthritis could also lead to TSS. Post-operative TSS has been specifically associated with nasal packing, insertion of hardware, surgical drains, retained foreign materials and breaks in sterile techniques.^{12,15}

Treatment of TSS involves several key components. It is extremely important to identify and decontaminate the site of toxin production. This may involve draining and debriding lesions, removing foreign material and exploring surgical wounds. Aggressive fluid resuscitation is vital. Substantial amounts of fluid may be needed. Patients may require 10 to 20 litres of fluid in the first 24 hours to maintain blood pressure.

The next step involves anti-staphylococcal antibiotics. Semisynthetic penicillins have been widely used; however protein synthesis inhibitor clindamycin is thought to be more effective in this illness. The greater efficacy of clindamycin is likely multifactorial: first, it is a potent suppressor of toxin production by *S. aureus* in vitro; second, clindamycin facilitates bacterial phagocytosis; third, it is known to suppress synthesis of penicillin binding proteins which, in addition to being targets of penicillin, are also enzymes involved in cell wall synthesis and degradation; fourth, clindamycin also has a longer post-antibiotic effect than beta lactams such as penicillin; and lastly, its efficacy may also be related to its ability to modulate the immune response.¹⁷ Clindamycin could be used alone or in combination with a cell wall active agent (semisynthetic penicillin or vancomycin).⁶ The duration of antibiotic treatment need not exceed 10 to 15 days in the absence of bacteraemia or other complications (e.g. osteomyelitis).¹⁸

Often patients require intensive care monitoring with ventilatory and inotropic support, CVP monitoring, and dialysis/filtration support to manage rhabdomyolysis, renal dysfunction and coagulopathy. The role of intravenous immunoglobulins is ill defined.⁷ All commercial immunoglobulin preparations contain high levels of anti TSST-1 antibody levels, but whether this may exert any activity upon STSS in humans is unclear. Therefore it should be reserved for refractory cases.

A variety of differential diagnoses may have to be considered when returning travellers present with fever, shock and symptoms of gastroenteritis. This may include bacterial sepsis, malaria, dengue, Rocky Mountain spotted fever, and leptospirosis, to name a few. The cases described here presented with profuse diarrhoea and vomiting and were referred to the Infectious Diseases Unit with a presumed diagnosis of bacterial enteritis. Travel history partly contributed to the misdiagnosis. A careful history, examination and appropriate investigations later confirmed that the cases described fulfilled the criteria for TSS. Physicians should therefore consider the diagnosis of TSS in patients presenting with symptoms of gastroenteritis and marked hypotension with high fever,¹⁶ especially if the patients are younger, as individuals acquire protective antibodies with age.

CONCLUSION

Toxic shock syndrome is not always considered in the differential diagnosis of patients presenting with diarrhoea and vomiting although it commonly mimics gastroenteritis at presentation. Diagnosis of TSS should be seriously considered in patients with diarrhoea and vomiting associated with fever, marked hypotension and rapid decompensation. It is imperative that clinicians do not think of TSS as a disease only related to tampon use. The diagnosis of TSS is made on clinical grounds, thus a strong suspicion, early recognition and aggressive management of the syndrome will decrease overall morbidity and mortality.

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