Aches and pains with a shocking rash

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CASE PRESENTATION

A 10-year-old girl presented to the emergency department with a three-day history of fever and generalized rash. Eleven days earlier, she had been camping in Ontario. Activities while camping included sleeping in a tent, hiking in the forest and swimming in a lake. She sustained multiple mosquito bites that were pruritic and subsequently formed scabs. Ten days before presentation, she developed left hip and thigh pain, which progressed in severity over the next three days. She also developed severe generalized myalgia. Three days before presentation she developed a fever and an erythematous, nonpruritic rash. The rash was first noticed on the thigh but soon involved the upper limbs, palms and soles. There was no sore throat or contact with others with fever or rash. Her general practitioner suspected scarlet fever and she was started on amoxicillin. After no improvement over the following day, she presented to the emergency room.

On examination in the emergency department, the patient was febrile and her blood pressure was 100/50 mmHg. She had a generalized erythematous macular rash, bilateral injected conjunctiva, jaundice, peeling of the skin on the soles of her feet and multiple hyperpigmented crusted lesions on her legs. She had generalized myalgia with tenderness in the left hip and thigh region. Over the subsequent 6 h to 12 h, her blood pressure dropped to 85/37 mmHg and she had a peak temperature of 39.2°C. She was treated with fluid resuscitation and antimicrobials.

Her white blood cell count was 40.4×10^9/L with a left shift and her platelet count was 72×10^9/L. She was in renal failure (serum creatinine level 400 µmol/L) and had conjugated hyperbilirubinemia (serum conjugated bilirubin level 138 µmol/L) and mild transaminitis (alanine aminotransferase level 157 U/L, aspartate aminotransferase level 264 U/L). Ultrasound of the left hip showed no joint effusion. X-rays of the femur and lumbosacral spine were unremarkable.

What is the diagnosis?

DIAGNOSIS

At admission, on account of her camping exposure history and her presentation with shock, jaundice, macular rash, acute renal failure and scabbed skin lesions, the differential diagnosis included bacterial sepsis (group A streptococcus, *Staphylococcus aureus*), leptospirosis, rickettsial infections, other tickborne illnesses (babesia, ehrlichiosis, anaplasmosis) and hantavirus. She was empirically started on vancomycin, ceftriaxone and doxycycline.

On the fourth hospital day, her admission blood culture grew methicillin-sensitive *S aureus*. The antibiotics were changed to cefazolin and clindamycin. The polymerase chain reaction (PCR)/serology investigations for the other potential infections were subsequently negative.

A magnetic resonance imaging scan of the pelvis obtained on the fourth day of hospitalization revealed a multilobular fluid collection extending from the sacroiliac joint involving the psoas muscle, consistent with sacroiliitis and psoas abscess. There was abnormal T2 hyperintensity and T1 hypointensity in the adjacent sacral and iliac bone marrow suggestive of osteomyelitis. The hip joints were unremarkable. A contrast study was not performed due to renal failure.

The clinical presentation and imaging were consistent with pelvic (sacroiliac) osteomyelitis. In addition, she fulfilled the Centers for Disease Control and Prevention (Georgia, USA) criteria for a confirmed case of toxic shock syndrome (TSS) (Table 1) (1). Desquamation of her hands and feet progressed in the second week of admission. Her renal and liver parameters returned to normal with supportive care. Her psoas abscess resolved radiographically and her pain improved clinically after antibiotic treatment for subacute pelvic osteomyelitis.

PCR for staphylococcal toxins was performed at the National Microbiology Laboratory in Manitoba. The TSS toxin-1 (TSST-1) PCR was negative. *Staphylococcus* enterotoxins C, G and I, however, were positive.

DISCUSSION

Staphylococcal TSS is an acute multisystem disease that is characterized by fever, hypotension, rash and desquamation on hands and feet, with evidence of ≥3 organ systems involved. TSS associated with staphylococci was first described in 1978 (2) and is classified as either menstrual or nonmenstrual. After an initial epidemic of menstrual TSS in 1980 in the United States, the overall incidence has declined to 0.5 per 100,000 population. This has been attributed to public education and the discontinuation of high-absorbency tampons. Currently, nonmenstrual TSS accounts for 50% of all reported cases and has a marked female predilection. The median age of children with nonmenstrual TSS is 9.5 years (3,4).

In TSS, bacterial toxins act as superantigens that directly activate T cells. This leads to an overwhelming release of cytokines, causing the manifestations of TSS. The most common *Staphylococcus* toxin for both menstrual and nonmenstrual TSS is TSST-1 (1-3). The next most common toxins in nonmenstrual TSS are enterotoxins A, B and C (5).

The staphylococcal toxins identified in our patient were enterotoxin C, G and I. While enterotoxin C has been reported as the third most common toxin causing nonmenstrual TSS, enterotoxins G and I are less common. The first time enterotoxin G and I were reported as being linked to TSS was in 1999 (6). This article described *S aureus* strains isolated from nine patients with TSS who were all positive for both enterotoxin G and I by PCR. None of the cases were positive for the other known superantigenic toxins (TSST-1, *Staphylococcus* enterotoxin A to E and H), thus supporting the argument that enterotoxin G and I are toxins that can also lead to TSS.

The primary site of our patient's *S aureus* infection was pelvic osteomyelitis. Pelvic osteomyelitis, the fourth most common site of

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TABLE 1
Centers for Disease Control and Prevention (Georgia, USA) clinical case definition for staphylococcal toxic shock syndrome* and criteria fulfilled by the patient

Clinical criteria	Criteria fulfilled by the patient
Fever: temperature ≥102.0°F (≥38.9°C)	✓
Rash: diffuse macular erythroderma	✓
Desquamation: 1–2 weeks after onset of illness, particularly involving the palms and soles	✓
Hypotension:	
Systolic blood pressure ≤90 mmHg for adults or <5th percentile according to age for children <16 years of age; orthostatic drop in diastolic blood pressure ≥15 mmHg	✓
Orthostatic syncope or dizziness	
Multisystem involvement (≥3 of the following organ systems):	
Gastrointestinal: Vomiting or diarrhea at onset of illness	
Muscular: Severe myalgia or creatine phosphokinase level ≥2 times the upper limit of normal	✓
Mucous membrane: Vaginal, oropharyngeal or conjunctival hyperemia	✓
Renal: Blood urea nitrogen or creatinine ≥2 times the normal upper limit, or pyuria (≥5 leukocytes per high-power field) in the absence of urinary tract infection	✓
Hepatic: Total bilirubin, alanine aminotransferase enzyme or asparate aminotransferase enzyme levels ≥2 times the upper limit of normal	✓
Hematological: Platelets <100,000/mm^3	✓
Central nervous system: Disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent	
Laboratory criteria	
Negative results on the following tests, if obtained:	
Blood, throat or cerebrospinal fluid cultures (blood culture may be positive for *Staphylococcus aureus*)	✓
Negative serologies for Rocky Mountain spotted fever, leptospirosis or measles	✓

**Case classification: Probable: a case in which four of the five clinical findings are present. Confirmed: a case in which all five clinical findings are present, including desquamation, unless the patient dies before desquamation occurs. Adapted from reference 1*

TABLE 2
Osteomyelitis leading to staphylococcal toxic shock syndrome in children

Author	Year	Age, years/sex	Site of infection	Culture	Outcome	Toxin identified
Aranow and Wood (9)	1942	15/female	Left femur	Blood+ Pus+	Discharged	Erythrogenic toxin
Milner et al (10)	1983	10/female	Right humerus	Blood+ Pus+	Discharged	Phage 2 Enterotoxin B
		7/female	Right tibia	Blood+ Pus+	Discharged	Phage 2 Enterotoxin B
Jacobson and Baltimore (11)	1989	13/female	Left clavicle	Blood+ Pus+	Discharged	Toxic shock syndrome toxin-1

+ Positive

osteomyelitis in children, is typically observed among children seven to 14 years of age. It has a variable presentation including back, hip, thigh and/or buttock tenderness. The presentation may also include fever, decreased range of hip motion and refusal to weight bear. This variable presentation can lead to diagnostic delay. Plain films and bone scans may appear negative, while magnetic resonance imaging scans have a reported sensitivity of 97% (7).

There are scarce data regarding acute osteomyelitis presenting with staphylococcal TSS in children (8-11). A review of the English literature revealed four reported cases (Table 2). All four patients were girls between seven and 15 years of age. Also of note, all four cases involved the appendicular skeleton. Enterotoxin B was identified in two patients and TSST-1 was identified in one. Of note, the three toxins identified in our patient have not been previously described in osteomyelitis-associated TSS.

CONCLUSION

Osteomyelitis may be an occult cause for TSS in children. The variable presentation of pelvic osteomyelitis in children can lead to diagnostic delay, but should be considered in an older child who presents with hip, thigh or gluteal pain who may also be refusing to weight bear.

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REFERENCES

1. Case definitions for infectious conditions under public health surveillance. Centers for Disease Control and Prevention. MMWR Recomm Rep 1997;46(RR-10):1-55.
2. Todd J, Fishaut M, Kapral F, et al. Toxic-shock syndrome associated with phage-group-I *Staphylococci*. Lancet 1978;2:1116-8.
3. Hajjeh RA, Perkins BA, Reingold A, et al. Toxic shock syndrome in the United States: Surveillance update, 1976-1996. Emerg Infect Dis 1999;5:807-10.
4. Adalat S, Dawson T, Hackett SJ, et al. In association with the British Paediatric Surveillance Unit. Toxic shock syndrome surveillance in UK children. Arch Dis Child 2014 May 1 [Epub ahead of print].
5. DeVries AS, Lesher L, Schlievert PM, et al. Staphylococcal toxic shock syndrome 2000-2006: Epidemiology, clinical features, and molecular characteristics. PLoS One 2011;6:e22997
6. Jarraud S, Cozon G, Vandenesch F, Bes M, Etienne J, Lina G. Involvement of enterotoxins G and I in staphylococcal toxic shock

syndrome and staphylococcal scarlet fever. J Clin Microbiol 1999;37:2446-9.
7. Faust SN, Clark J, Pallett A, Clarke NM. Managing bone and joint infection in children. Arch Dis Child 2012;97:545-53.
8. Chuang YY, Huang YC, Lin TY. Toxic shock syndrome in children: Epidemiology, pathogenesis, and management. Paediatr Drugs 2005;7:11-25.
9. Aranow H Jr, Wood W Jr. Staphylococcic infection simulating scarlet fever. JAMA 1942;119:1491-5.
10. Milner LS, de Jager J, Thomson PD, Doehring RO. Toxic shock syndrome caused by staphylococcal enterotoxin B. A report of 2 cases in children. S Afr Med J 1983;63:822-4.
11. Jacobson RM, Baltimore R. Toxic shock syndrome associated with osteomyelitis in premenarcheal girl. Pediatr Infect Dis J 1989;8:125-6.