ORIGINAL ARTICLE

Unusual staphylococcal toxic shock syndrome presenting as a scarlet-like fever

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Abstract

Diagnosis of nonmenstrual staphylococcal toxic shock syndrome (TSS) is often challenging. A female medical colleague had a rare entity, a staphylococcal pharyngitis complicated by TSS. The diagnosis was confirmed by isolation of *tst*-positive *Staphylococcus aureus* in throat culture and by identification of a specific Vβ2 expansion pattern of her T lymphocytes. Recent improvements in microbiology can be of great help for the diagnosis of nonmenstrual TSS.

Keywords: Non menstrual TSS, scarlet fever, *Staphylococcus aureus*, StrepA rapid antigenic test, Vbeta T lymphocytes expansion
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Case description

We report the case of a healthy 32-year-old female colleague, who was admitted to our hospital in septic shock with high fever (40°C), tachycardia and hypotension, with no response to fluid resuscitation and antibiotic therapy. Her symptoms started 4 days before with isolated sore throat (no rhinitis or cough) followed by erythroderma (Fig. 1). The day before admission, her husband—an infectious disease specialist—prescribed her amoxicillin 1 g three times a day, suspecting *Streptococcus pyogenes* pharyngitis.

At admission, her main complaints were persistent severe throat pain, fever and onset of a generalized rash (Fig. 1(A)). She is a mother of two healthy children and had no other relevant contact history. Physical examination revealed erythrodermia, enanthema and pustular lesions of the oropharynx and posterior pillars bilaterally. Tonsils were erythematous, as was the hypopharynx and larynx. No oedema or abscesses were observed. A thorough systematic assessment did not reveal any other site of infection, in particular no sign of fasciitis or myositis, and no gynecologic symptoms (discharge, pain or menstruation) were present.

Direct antigenic StrepA detection tests were performed twice but remained negative despite our initial clinical suspicion of streptococcal scarlet fever. Throat swabs were performed and the samples cultured. Microscopic examination of the urine was normal, and blood cultures were performed.

Laboratory results were as follows: leukocyte count 9.5 g/L with 51% band forms and absolute lymphopenia (0.1 g/L). Hemoglobin was 129 g/L, and thrombocytes were 153 g/L. Blood smear revealed band forms and vacuolated neutrophils with Döhle bodies. C-reactive protein was elevated, at 483 mg/L, and procalcitonin was 2.97 µg/L. Serum creatinine was elevated, at 121 µmol/L, with an estimated (Modification of Diet in Renal Disease study equation) creatinine clearance of 44 mL/min/1.73 m^3. Liver function tests were normal. Coagulation prothrombin ratio was 62%, and partial thromboplastin time was 47 seconds.

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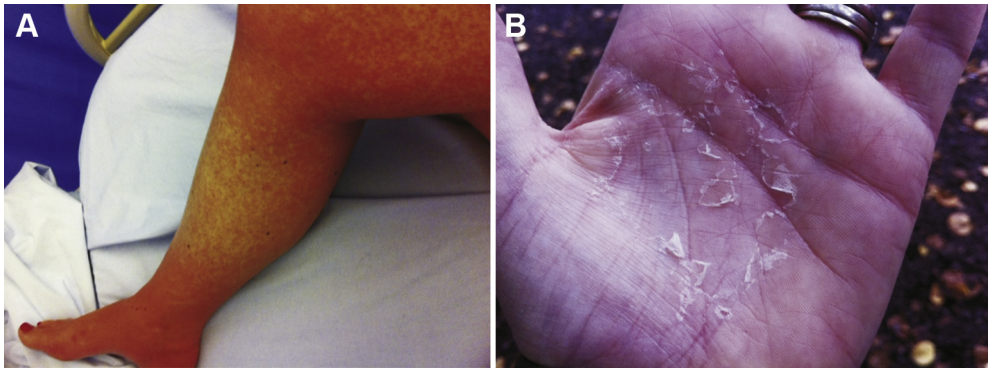

FIG. 1. Classical staphylococcal toxic shock syndrome rash (A) followed by palm desquamation at day 7 (B).

The patient initiated therapy with ceftriaxone 2 g delivered intravenously once daily in the emergency room. Intravenously administered clindamycin 900 mg TID (three times a day) was added 3 hours later when the patient was seen by the infectious disease specialist because of new instability. A switch from ceftriaxone to imipenem 750 mg four times a day (with clindamycin) was made in the intensive care unit while admitting the patient for refractory hypotension requiring aminergic (norepinephrine) support. The latter was needed for 12 hours only, as the patient rapidly improved.

The throat swab obtained at admission grew a methicillin-susceptible *Staphylococcus aureus* (MSSA), whereas all other cultures (blood and urine) remained negative. We suspected staphylococcal toxic shock syndrome (TSS) resulting from pharyngitis, and we tested the MSSA strain positive for *tst* encoding TSST-1 (toxic shock syndrome toxin 1). Analysis of the Vβ profile of T lymphocytes of the patient's blood was performed. The analysis covers the 24 more frequent Vβ profiles by IO Test Beta Mark and FACScan cytometry (Becton Dickinson, Franklin Lakes, NJ, USA). The results revealed a unique strong expansion of the Vβ2 subset of T lymphocytes (23%; normal range, 5.8–10.6%), confirming that TSST-1 was produced and was responsible for the clinical disease in our patient. Antistreptolysin O (ASLO) testing, performed in the context of the initial suspicion of scarlet fever, was measured at day 1 and 1 week later, and remained negative. A serologic panel for a "mononucleosis syndrome" was negative for HIV and cytomegalovirus (including viraemia) and positive for Epstein-Barr virus (previous infection). The patient strain of MSSA was resistant to clindamycin, and she was discharged with oral amoxicillin–clavulanate. Desquamation of her palms occurred at day 7 (Fig. 1(B)). Her recovery was complete, with disappearance of fever, throat pain and rash.

Discussion

We describe a rare case of staphylococcal pharyngitis complicated with TSS in a female colleague. The direct antigen detection kits for StrepA are known to be of moderate clinical sensitivity (70–90%) [1]. Throat culture remains the reference standard to diagnose group A *Streptococcus* (GAS) infections, with a sensitivity of 90–95% when performed properly [1]; both these tests remained negative for GAS.

Staphylococcal TSS was diagnosed as a result of the presence of a toxic shock and of a positive throat culture for a *S. aureus* encoding the *tst* gene. The Vβ2 lymphocytes' unique expansion pattern confirmed the signature of TSST-1 because Vβ's multiple other expansion patterns are generally observed with other staphylococcal or streptococcal superantigens [2,3]. Although the Vβ2 profile is not 100% specific (the SpeC toxin of *Streptococcus pyogenes* is responsible for a Vβ2 pattern), the combination of this Vβ2 subset, associated with the isolation of a *tst*-positive MSSA and the lack of ASLO, allowed us to conclude that this "scarlet fever" complicated by TSS was indeed due to MSSA. Because the patient presented desquamation 1 week after onset of symptoms, her disease met the US Centers for Disease Control and Prevention (CDC) diagnostic criteria for probable TSS: high fever, rash, desquamation, hypotension, only two organ failures (acute kidney injury, impaired coagulation), for 4/5 criteria. Nonmenstrual TSS (nmTSS) resulting from a staphylococcal pharyngitis was our final diagnosis. The molecular analysis of *S. aureus* strain was *tst* positive. The strain belonged to *agr* type 3 and was tested as *eta*/*etb* and *pvl* negative (encoding exfoliatins and Panton-Valentine leukocidin, respectively).

Clinical TSS was first described by Todd *et al.* in 1978 [4]. TSS became a public health issue in 1980 when a menstrual TSS

epidemic linked to the use of vaginal tampons arose; a systemic diffusion of TSST-1 occurred after *S. aureus* vaginal colonization. nmTSS are generally observed in the context of surgical site infection, postpartum or from cesarean section wound infection, burns, cutaneous lesions, arthritis or osteomyelitis, and is due to the systemic diffusion of TSST-1 or enterotoxins (the latter do not efficiently cross the mucosal barrier) [5]. Upper respiratory viral illness complicated by *S. aureus* TSS has been identified and is called postinfluenza TSS, although no specific tests were available at the time to confirm this diagnosis [6]. This severe condition has mainly been reported in association with suppurative tracheitis and pneumonia [7]. Of note, nmTSS could be a form of frontier between TSS and septic shock if the patient has a suppurative primary site of infection and/or if blood cultures grow *S. aureus.* (TSST-1 or enterotoxins participate in the inflammatory response with peptidoglycan and common staphylococcal toxins such as hemolysin α.) In children, TSS has already been described as a complication of staphylococcal rhinolaryngologic infections or surgery [8], and more rarely pharyngitis [3]. In children, staphylococcal scarlet fever has been used to describe incomplete, mild forms of TSS after *S. aureus* pharyngeal colonization; these cases generally lack hypotension and have rash as the predominant sign [9]. A similar mild form of nmTSS due to TSST-1 has also been described in neonates, called neonatal TSS-like exanthematous disease, which is associated with systemic diffusion of TSST-1 associated with the expansion of Vβ2 [10]. In adults, *S. aureus* pharyngitis complicated with TSS has not been described. This shows how exceptional it is compared to streptococcal TSS due to the TSS toxin–like superantigen of GAS.

The CDC have defined specific criteria for probable and definite TSS, including high fever, rash, hypotension, multisystem disease and desquamation in association with the absence of microbiologic criteria for alternative disease [11–13]. Although desquamation is probably the most specific clinical finding, it arises several days after the onset of the disease, so it is not useful for early diagnosis. Acute and convalescent antibody testing can help establish the diagnosis, although several series have shown an inability of some patients to increase serologic titles after the disease; this inability gives rise to recurrent TSS in some patients [14].

The CDC diagnostic criteria were established mainly for epidemiologic surveillance purposes, and no positive microbiologic or serological/immunologic criteria are included [13]. The isolation of a *S. aureus* strain carrying genes coding for superantigenic toxins, together with the identification of a specific Vβ T lymphocytes expansion pattern, are probably the most useful complementary tests to confirm the clinical suspicion of staphylococcal TSS in an acute setting. Availability of these results in 24 hours allows a prompt, decisive confirmation of the diagnosis and favours the addition of clindamycin in this type of clinical setting. Although the clinical CDC criteria remain the main pillars for the diagnosis of TSS, the addition of these microbiologic and immunologic diagnostic tests in defined situations can be of great help for the diagnosis of nmTSS.

Conflict of interest

GL has received research funding from Pfizer, bioMérieux and Basilea. DOA, TF, NS, CF, AC and SE have no potential conflict of interest to declare.

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