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Case Report

CASE REPORT

Intense, flu-like symptoms in women using menstrual devices: always think of staphylococcal Toxic Shock Syndrome

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Abstract

Staphylococcal Toxic Shock Syndrome (TSS) is an exceptionally rare, toxin-induced, life-threatening, clinical entity that has largely been associated with the use of tampons and other menstrual devices. We, here, report a case of menstrual TSS in a young, female patient who was successfully treated in our hospital. The patient was vaginally colonized with *Staphylococcus aureus* and *Escherichia coli* and the possible interactions between the two are discussed. An account of all the essential facts that physicians should be aware of with regard to TSS is subsequently included.

INTRODUCTION

Staphylococcus aureus is a Gram-positive opportunistic pathogen which is considered as the main culprit for a rare, exotoxin-induced clinical syndrome, the Toxic Shock Syndrome (TSS). Staphylococcal TSS was first recognized as a distinct clinical entity in 1978 whereas a sharp increase in reported cases occurred in the 1980s affecting primarily young, female patients. Tampons were then implicated and their withdrawal resulted in a decline in incidence from ~13.7 cases to 1 case per 100 000, remaining relatively stable over the following years [1].

CASE REPORT

A 29-year-old, female, Caucasian patient was referred by a local General Practitioner to the Emergency department of our hospital because of fever, vomiting and diarrhea. Her symptoms had started 4 days prior to presentation. Her medical history was noticeable for psychotic depression and she was on therapy with olanzapine. Since she was a tourist in Greece, she had been using a tampon for menstrual bleeding during the last 5 days in order to enjoy swimming in the sea. She, also, mentioned a yellowish vaginal secretion 24 h after the first tampon use.

The patient's clinical and laboratory findings upon initial evaluation were as follows: fever (40.3°C), hypotension (systolic blood pressure 80 mm Hg), sinus tachycardia (120 beats per minute), tachypnea (30 breaths per minute), elevated inflammation markers (12×10^3/μl leukocytes with 84% neutrophils, C-reactive protein (CRP) 30 mg/dl), thrombocytopenia (50×10^3/μl), azotemia (urea 88 mg/dl, creatinine 1.68 mg/dl) and high lactate levels (4 mmol/L). A generalized tenderness was noticed on abdomen's palpation. Multiple, ulcerative lesions were detected in the oral cavity. A chest X-ray did not reveal any abnormal findings. She was admitted to the Internal Medicine ward where

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the tampon was discontinued and urine, blood and vaginal samples were collected and sent for culture. Empirical treatment was initiated with ceftriaxone and clindamycin as well as supportive care with fluids and oxygen.

Despite the above therapeutic interventions, both her clinical status and laboratory parameters were deteriorating within hours (Table 1). She was remaining hypotensive, while signs of disorientation and severe hypoxemia (PaO_2 55 mm Hg) resistant to oxygen administration were observed. Furthermore, a second chest X- ray demonstrated bilateral infiltrates suggesting the development of Acute Respiratory Distress Syndrome. The patient was intubated and transferred to the Intensive Care Unit (ICU) where support with inotropes and low tidal volume ventilation was applied and treatment was switched to meropenem and clindamycin.

On Day 2, the vaginal culture was available for evaluation. The culture had grown a Gram-positive coccus and a Gram-negative bacillus that were later identified as *Staphylococcus aureus* and *Escherichia coli*, respectively, with Vitek 2 automated system (bioMérieux Inc., Durham, USA). It is worth emphasizing that Gram stain of both the initial vaginal specimen and the subsequent culture revealed a noticeable absence of the normal vaginal lactobacilli. In the meantime, no other routes of infection could be identified with urine and blood samples being negative for bacterial growth and no clinical signs of a skin and soft tissue infection. In view of the patient's history and clinical picture, molecular amplification of the TSST-1 gene was performed by polymerase chain reaction and turned positive. Susceptibility testing was conducted with Vitek 2 automated system and revealed a methicillin-susceptible *S. aureus* strain that was resistant to penicillin.

Since Day 2, the patient's condition showed no further signs of deterioration. On Day 5, the patient improved essentially enough to be successfully extubated. Shortly after, she was transferred to the ward where she remained for a week, completing an additional 7-day meropenem course. She was discharged in good clinical condition, with instructions for follow-up evaluation by an Infectious Disease specialist in her country.

DISCUSSION

Research has elucidated parts of the pathophysiology underlying the onset of TSS. It is currently considered to be triggered by particular exotoxins, which belong to the Pyrogenic toxin superantigen family. These encompass the Toxic Shock Syndrome Toxin-1 (TSST-1), most of the staphylococcal enterotoxins as well as the streptococcal pyrogenic toxins. One of their main common features is their capacity to induce polyclonal activation of T-helper cells through irregular bindings with both MHC-II and TCR receptors. It is noteworthy that up to 30% of T-helper cells could become activated while the usual proportion does not exceed a percentage of 0.001–0.01% [2]. This excessive immune activation leads to a cytokine storm responsible for the dramatic clinical course.

Nonetheless, only a minor subset of colonized patients will actually develop symptomatic disease. A prerequisite for that is lack of protective humoral immunity. Furthermore, the use of tampons, especially those made of polyester foam and carboxymethylcellulose, is regarded as an important co-factor for the onset of menstrual TSS. It has been hypothesized that their composition facilitates *S. aureus* replication in the mildly alkaline pH of the vagina during menstruation by providing a viscous medium for adherence and growth and by trapping O_2 and CO_2 inside the foam cubes [3]. The role of microbiota on TSST-1 expression has insufficiently been investigated. According to one study, lactobacilli play an inhibitory role while *E. coli* does not affect expression [4]. However, another pilot study mentions the presence of *E. coli* in vaginal cultures of seronegative cases in contrast with healthy, seronegative carriers [5]. Interestingly, our patient was colonized by both *S. aureus* and *E. coli* at an approximate ratio of 1:1 colony forming units. There is evidence in the literature that *E. coli* could promote TSST-1 production by providing essential nutrients [6]. Alternatively, it could be the source of molecules such as endotoxins that act synergistically with TSST-1 on exaggerating the immune response [7]. Indeed, a case–control study comparing menstrual TSS cases and healthy TSST-1-positive *S. aureus* carriers could uncover potential risk factors for symptomatic disease that have not, yet, been identified.

TSS diagnosis could be rather tricky due to the syndrome's rarity and due to its' non-specific signs and symptoms. The Center for Disease Prevention and Control (CDC) provides a case definition to assist diagnosis (Table 2). However, the aforementioned definition has been questioned for a lack of sensitivity [8]. TSS ultimately reflects the individual intensity of the host's immune response and prompt management could, also, shift its presentation. In support of this, studies implicate TSST-1-producing strains of *S. aureus* in abortive forms of febrile, exanthematous disease with no hemodynamic disturbance [9].

Our patient lacked the generalized rash and desquamation and, thus, does not fulfill the criteria of a confirmed case. However, her medical history and the fulminant clinical course supported by the available laboratory findings make alternative diagnoses highly unlikely. In fact, all other possible routes of infection were excluded by microbiological investigation and the vaginal swab was the only specimen that yielded a positive result indicating the presence of a TSST-1-producing *S. aureus* strain in a tampon-using menstruating female patient. Besides,

Table 1: Patient's main laboratory findings on admission to the Internal Medicine ward, on admission to the ICU and on discharge

Parameter in blood (units)	Admission to the Internal Medicine ward	Admission to the ICU (6 h after admission to the ward)	Discharge
CRP (mg/dl)	30	34.2	4.3
Platelets (10^3/μl)	50	35	440
Lactate (mmol/l)	4.0	4.7	1.3
International normalized ratio	1.77	1.89	1.10
Urea (mg/dl)	88	96	30
Creatinine (mg/dl)	1.68	1.94	0.70
Procalcitonin (ng/ml)	0.41	0.59	0.10

Worth pointing out the dramatic deterioration of the laboratory parameters during the very first hours of hospitalization, suggesting a fulminant presentation of STSS.

Table 2: The criteria provided by CDC for disease diagnosis

1. Fever: temperature greater than or equal to 38.9°C (102.0°F)
2. Diffuse macular erythematous rash
3. Desquamation within 1–2 weeks after the onset of rash
4. Hypotension: systolic blood pressure less than or equal to 90 mm Hg for adults
5. Involvement of three or more of the following organ systems:
   Gastrointestinal: vomiting or diarrhea
   Muscular: myalgias or twice than normal creatine phosphokinase
   Mucous membranes: vaginitis, pharyngitis, conjunctivitis
   Renal: twice than normal BUN or creatinine level or pyuria
   Hepatic: elevated total bilirubin, twice than normal aspartate aminotransferase and alanine aminotransferase
   Hematologic: platelets less than or equal to 100 000/mm^3
   Central nervous system: disorientation or altered level of consciousness without focal neurologic findings when fever and hypotension are absent
6. Negative throat or cerebrospinal fluid cultures (positive *Staphylococcus aureus* blood cultures do not exclude TSS)
7. Negative serology for Rocky Mountain spotted fever, leptospirosis, rubella

Confirmed cases fulfill all criteria, including desquamation, while probable cases lack one clinical criterion.

blood cultures are positive in only 5–15% of the patients with staphylococcal TSS, in contrast with streptococcal TSS where they can be positive in up to 50% of the cases [10]. Furthermore, we consider that the initial rapid deterioration of the clinical and laboratory parameters despite the administration of the starting empirical treatment is probably due to the action of the already synthesized exotoxin and not due to treatment failure. Prompt recognition of the syndrome is foremost essential for effective management. Clindamycin is generally the preferred agent because it interferes with exotoxin synthesis at the ribosomal level and, in addition, downregulates monocyte synthesis of tumor necrosis factor-α [11].

In conclusion, despite being rare, TSS should always be considered in cases of young patients presenting with intense, non-specific, flu-like symptoms with or without hemodynamic imbalance, especially when foci of infection suggestive of *S. aureus* are detected. Prompt etiological diagnosis will contribute to the optimization of treatment options and will minimize the case fatality ratio associated with the syndrome. The complex interactions of human microbiota and their potential contribution to the onset of TSS are interesting and insufficiently elucidated topics, which thus merit further research.

CONFLICT OF INTEREST STATEMENT

None declared.

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