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Two-consecutive cases of toxic shock syndrome from intravaginal traditional fertility treatment: a case report

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Abstract
Toxic Shock Syndrome (TSS) is a bacterium based super-antigen mediated disease that is potentially fatal. Its incidence has been waxing and waning; however in recent times there has been significant reduction in occurrence due to improvement in menstrual hygiene and withdrawal of highly absorbent tampons. This is a report of two consecutive cases of toxic shock syndrome following intra-vaginal traditional infertility treatment. Both were friends with long years of infertility who went for traditional fertility treatment and had a molded substance prescribed to be inserted into the vagina, "that the longer it stayed the more effective it would work". First case presented two days after insertion but remove it because of unbearable burning sensation while the second presented in coma from septic shock four days after insertion of the substance. This clearly showcases the fact that the duration of the offending substance in the vaginal predicts strongly the prognosis and severity of the disease and calls for women's education on vaginal hygiene, and to create awareness to alternative medical practitioners on the danger associated with traditional vaginal pessary. It may also suggest strongly the need for routine clinical enquiry for vaginal hygienic practices and pelvic examination in women with sudden febrile illness.

Keywords: toxic shock syndrome, infertility, traditional fertility treatment

Introduction
Toxic shock syndrome (TSS) is a bacterium based super-antigen mediated disease that is potentially fatal [1]. Bacterial toxins act as highly virulent super- antigens that trigger massive immune cells activation and release of cytokines, resulting in distributive shock and multi-organ failure. These super-antigens induce remarkable expansion of T-lymphocytes and bypass normal antigen presentation [2, 3]. Toxic shock syndrome is associated with a wide variety of clinical settings, such as menstruation, postpartum and postsurgical states, barrier contraceptive use, staphylococcal pneumonia, sinusitis, and infected skin lesions [1, 2]. In 95% of menstrual cases of TSS, staphylococcal TSST-1 is the causative agent [4]. Host antibody deficiency is a recognized important factor in the development of fulminant TSS [2, 4, 5], although almost anyone can develop TSS, menstruating women and women using barrier contraceptive devices (diaphragms and vaginal sponges) have a higher risk of developing TSS [1, 6]. Although in recent times with improvement in menstrual hygiene and withdrawal of highly absorbent tampons, the incident of TSS is on the downward trend, thus often considered late in the clinical course of the disease. Prompt diagnosis from high index of clinical suspicion is highly needed to avert fatality. Robust quality randomized controlled trials on the best management guidelines are lacking [7]. The principle of management of TSS includes; early diagnosis, targeted antibiotic therapy, source control, haemodynamic resuscitation and adjunctive immunomodulatory therapy.
Infertility is a great burden in our environment because of the quest for large family size and inheritance [8]. Infertility has far reaching psychosexual, cultural and emotional distress with women suffering most [8, 9]. Women with infertility are stigmatized in both western and non western cultures and child bearing is considered a hallmark of womanhood [8, 9]. Furthermore, child bearing is prized in Africa and it is an important yardstick for assessing marital success [8-10]. Women are most likely to suffer the social consequences of infertility; they suffer physical and mental abuse, neglect, economic deprivation and social ostracism as a result of their inability to bear children [8, 10, 11]. They can therefore seek all sorts of medical treatment both orthodox and non orthodox to achieve pregnancy irrespective of their cultural, religious, educational and socioeconomic status. This therefore poses a higher risk of morbidity and mortality [12].

Informed consent was obtained from the patient

Case report 1. A- 35 year old para o plus 4, civil servant with tertiary level of education who presented to the Emergency room with history of high grade fever, burning sensation on the vulva and vagina and a 7 year history of inability to conceive. Three days prior to presentation she visited a tradomedical centre with her friend who also had infertility. There she was given a molded substance described as a 'small irish potato' to insert into the vagina after her bath in the evening and kept in there for a long time to make it more effective. This she did, however with increasing pain and burning sensation she removed it after 48 hours. Following which she became febrile, with associated malaise. At presentation in the Emergency ward, the significant findings were high grade fever (T 39.5^{o}C), low blood pressure 90/50 mmHg. Her vulvae and vagina were hyperaemic. Initial laboratory test results are showed in Table 1

FBC
Hb - 13.5 g/dl
PCV -39 %
Total WBC 18 x 10^6 c/ml
Neut. 65%
Lymph. 25%
Platelet 200x 10^6 cell/ml
Urinalysis: Glu-Neg, Protein -Neg, Nitrites-Neg, Leucocytes-Neg.
Urine M/C/S: appearance- Amber colour, epithelia cell +, culture yielded no growth after incubation for 48 hours.
E/U/Cr Na+: 135mmol/l.
K+: 3.0 mmol/L
Cl-: 100mmol/L
HCO3: 22mmol/L
Urea: 4.2mmol/L
Creatinine: 165µmol/L

She was managed with intravenous fluids, parenteral Co-amoxiclav, tetanus toxoid, anti-tetanus serum and antipyretic. The vaginal was copiously irrigated with warm normal saline. She developed classical macular rashes on the limbs while on admission. Patient recovered satisfactorily and was discharged home.

Case Report 2. A 33 year old Para o plus 2 trader with tertiary level of education who presented to the Emergency ward of ISTH with high grade fever, loss of consciousness and convulsion following insertion of traditional fertility treatment into the vagina four days prior to presentation. She had a 5 year history of infertility. On examination she was acutely ill-looking, febrile temperature 39 ^{o}C, dehydrated and in respiratory distress-(spo_2 -90) and unconscious. Pulse rate was 120 beats / minute it was fast and thready. Blood pressure was 80/40mmHg and she had cold clammy extremities. While being resuscitated she had an episode of generalized tonic-clonic seizure but no focal neurologic deficit, seizure was promptly aborted with intravenous diazepam. She was anuric and had evidence of acute kidney injury at presentation. She was managed in the intensive care unit. Fluid resuscitation was commenced thereafter kidney was challenged with 80mg of frusemide and dopamine infusion, strict input and output monitoring was instituted. She re-gained consciousness after fluid resuscitation. Initial antibiotic was intravenous co-amoxiclav however she still had persistent high grade fever after 48 hours, this was changed to IV meropenem 500mg 8 hourly and intravenous hydrocortisone 100mg stat, then 50 mg 8 hourly for 48 hours was also given. Her temperature settled 24 hours after commencing IV meropenem there was also improvement in her renal status. She developed the classical maculopapular skin rashes and was transfered to the gynaecology ward. She had 10 days hospital stay and was discharged to be followed-up at the out-patient clinic.

Initial laboratory test
FBC
Hb - 12.5 g/dl
PCV -35 %
Total WBC 22 x 10^6 cells / ml
Neut. 75%
Lymph. 15%
Platelet 130 x 10^6 cell/ml
Urinalysis: Glu-Neg, Protein Neg, Nitrites-Neg, Leucocytes-Neg.
Urine M/C/S: appearance- Amber colour, epithelia cell +, culture yielded no growth after incubation for 48 hours.
E/U/Cr Na+: 145mmol/L
K+: 3.2 mmol/L "
Cl-: 110mmol/L
HCO3: 24mmol/L
Urea: 10.4mmol/L
Creatinine: 212µmol/L

Discussion

Toxic shock syndrome was first described in 1978 among children by Todd, but later from menstruating women [6]. It can result from none catamenia causes; however it has not been reported to be associated with traditional fertility treatment to the best of our knowledge. Use of vaginal pessary in medicine has also not been associated with such. Vagina is a highly vascular zone and these enhance easy treatment response with locally administered drugs. Most of these drugs are highly dispersible and not left as solid substances. The duration of the offending substance determine strongly the severity of the disease as such local control of source is a strategic principle in the treatment [1]. These two cases therefore highlight this fact. They were instructed to leave the substance in the vagina for a long period of time with the mind that the longer it stays the more effective the treatment. This directly epitomizes the worse clinical state of the second case. A high index of suspicion is crucial for early diagnosis and prompt intervention. In these cases, the first presented with suggestive symptoms and with high index of clinical suspicion the diagnosis was made, while the first patient was been treated at the Emergency ward the second case presented in coma and her relatives gave the history of the substance that was inserted they also identified the first patient as her friend who had similar traditional fertility treatment together. Toxic shock syndrome (TSS) is a severe febrile illness now confirmed to be caused by exotoxin-producing strains of *Staphyloccocus aureus* and *Streptococcus pyogene.* Toxic shock syndrome (TSS) is a toxin-mediated acute life-threatening illness, usually precipitated by infection with either *Staphylococcus aureus* or group A *Streptococcus* (GAS), and also called *Streptococcus pyogenes.* It is characterized by high fever, rash, hypotension, multi-organ failure (involving at least 3 or more organ systems), and desquamation, typically of the palms and soles, 1-2 weeks after the onset of acute illness. The clinical syndrome can also include severe myalgia, vomiting, diarrhea, headache, and non-focal neurologic abnormalities. In TSS the super antigens are able to trigger a remarkable expansion of the T-cells lymphocytes (over 20 %) by- passing the normal natural antigen presenting cells pathway [7]. More than 90% of menstrual cases of Staphylococcus aureus

exotoxin mediated TSS are caused by Toxic shock syndrome toxin type-1 (TSST-1), whereas a high percentage of non menstrual cases are caused by Staphylococcal enterotoxins B. [13, 14]. Factors influencing the expression of this toxin-mediated illness include host immunity status, host-pathogen interaction, and local factors (pH, glucose level and magnesium level). Bacterial toxins acts as highly virulent superantigens that trigger massive immune cell activation and cytokine release resulting in distributive shock and multi-organ failure [2, 13]. Superantigens are molecules that interact with the T-cell receptor in a domain outside of the antigen recognition site and hence are able to activate large number of T cells resulting in massive cytokine production [13, 14]. Cytokines implicated in TSS include interleukin 1 (IL-1) and tumour necrosis factor (TNF), furthermore, pyrogenic exotoxins induce human monoclear cells to synthesize TNF-alpha, IL- beta, and interleukin 6 (IL-6). [13, 15].

Diagnostic criteria are available to facilitate the diagnosis; however they should not be relied on for definitive diagnosis. Rather, specific situations should trigger consideration of this disease process as delay in making diagnosis can be lethal. Diagnostic criteria to facilitate diagnosis is illustrated in Table 3 below.

2011 Case Definition- Toxic Shock Syndrome (other than Streptococcal)

Clinical Criteria

An illness with the following clinical manifestation

1. Fever: temperature of ≥38.9°C (≥102°F)
2. Hypotension: systolic blood pressure of ≤90 mmHg or orthostatic hypotension (orthostatic drop in diastolic blood pressure by ≥15 mmHg, orthostatic syncope, or orthostatic dizziness)
3. Diffuse macular rash, with desquamation 1–2 weeks after onset (including the palms and soles)
4. Multisystem involvement (three or more of the following organ systems)

a. Hepatic: bilirubin or aminotransferase levels ≥2 times normal
b. Hematologic: platelet count ≤100,000/μL
c. Renal: blood urea nitrogen or serum creatinine level ≥2 times the normal upper limit or urinary sediment with pyuria (greater than or equal to 5 leucocytes per high-power field) in the absence of urinary tract infection.
d. Mucous membranes: vaginal, oropharyngeal, or conjunctival hyperemia
e. Gastrointestinal: vomiting or diarrhea at onset of illness
f. Muscular: severe myalgias or serum creatine phosphokinase level ≥2 times the normal upper limit
g. Central nervous system: disorientation or alteration in consciousness without focal neurologic signs and in the absence of fever and hypotension.

Laboratory Criteria for Diagnosis

1. Blood or cerebrospinal fluid cultures may be positive for Staphylococcus aureus
2. Negative serologic or other tests for measles, leptospirosis, and Rocky Mountain spotted fever.

Case Classification

Probable

A case which meets the laboratory criteria and in which four of the five clinical criteria described above are present.

Confirmed

A case which meets the laboratory criteria and in which all five of the clinical criteria described above are present, including desquamation, unless the patient dies before desquamation occurs [16].

The clinical picture in TSS is similar to septic shock hence the diagnosis of TSS depends on a constellation of findings rather than one specific finding and on a lack of evidence of other possible differential diagnosis. The principle of treatment involves early diagnosis, fluid resuscitation, control of the focus and antibiotic therapy targeted at the most likely causative organisms. The use of corticosteroids in TSS is uncertain, although steroids may decrease the inflammation and prevent complement mediated leukostaxis [17].

Control of focus is very important, in these cases warm normal saline was used used for copious washing and irrigation of the vaginal. Anti- tetanus serum (ATS) and tetanus toxoid were administered. They had the classical skin rashes with desquamation which were more on their palms and sole of the feet. Both cases responded well to treatment.

Conclusion

Toxic shock syndrome is indeed a life threatening febrile illness that requires early diagnosis and appropriate treatment to avert fatality. Improvement in menstrual hygiene and withdrawal of highly absorbent tampons has lead to reduction in its incidence however other sources can trigger same response. Pelvic examination should form part of full clinical examination in women with acute onset febrile illness. Alternative medical practitioner should be educated on the potential danger of traditional vaginal pessary insertion.

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Declaration

The authors declare no conflict of interest.

Limitations

Assay for C reactive protein, creatine phosphokinase and serologic screening for infectious diseases (like measles, leptospirosis and Rocky Mountain spotted fever) were not done because the facilities were not available at the study location.

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