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Case Report

Streptococcal toxic shock syndrome following group A streptococcal vulvovaginitis in a breastfeeding woman☆

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ABSTRACT

Streptococcal toxic shock syndrome (STSS) is a systemic, life-threatening illness usually caused by invasive respiratory tract or skin and soft tissue infections of *Streptococcus pyogenes* (group A streptococcus, GAS). We report the case of an adult woman with lactational amenorrhea and GAS vulvovaginitis progressing to STSS. She was admitted to our hospital because of fever, lethargy, and a 2-week history of vaginal discharge; she also had hypotension and multiple organ failure. Blood and urine cultures yielded gram-positive cocci and GAS. After 14 days of antimicrobial therapy, she fully recovered without any complications. The vulvovaginitis was most likely the portal of entry for GAS, which is rarely recognized as a causative pathogen of vulvovaginitis. Lactational amenorrhea is thought to be a risk factor for GAS vulvovaginitis. It is important for clinicians to recognize the possibility of GAS vulvovaginitis in breastfeeding women with vaginal symptoms and consider the necessity of prompt antibiotic treatment.

1. Introduction

Streptococcal toxic shock syndrome (STSS) is a toxin-mediated life-threatening illness which arises from invasive infection with *Streptococcus pyogenes* (group A streptococcus, GAS). STSS is defined by isolation of GAS from a normally sterile body site and by the presence of shock and organ failure such as renal failure, coagulopathy, liver failure, and acute respiratory distress syndrome [1]. The skin and soft tissue and respiratory tract are the most frequent clinical foci of invasive infections with GAS [2] although the vagina is uncommon. GAS is linked with vulvovaginitis in prepubertal girls but rarely in breastfeeding women.

In this case report, we describe a 32-year-old woman with STSS secondary to GAS vulvovaginitis.

2. Case report

A 32-year-old previously healthy Japanese woman was admitted to our hospital because of fever, lethargy, and vaginal discharge. She was in the period of lactational amenorrhea since vaginal delivery. She had no significant medical history and took no medication. Two weeks before admission, she visited a gynecology clinic with 2-day complaints of a profuse, watery, and yellow vaginal discharge accompanied by vulvar pruritus after having unprotected sexual intercourse with her husband. A gynecological examination revealed vaginal erosions. A vaginal swab was obtained for culture and metronidazole vaginal tablets were prescribed as treatment for bacterial vaginosis. Although the swab culture was positive for GAS, the result was considered as colonization by the gynecological physician. Two days before admission, she developed fever, chills, fatigue, urinary frequency and left back pain as well as vaginal discharge. The patient had no recent history of dermal or respiratory infection. Although her husband had noticed pruritus in his penis without any discharge or rash at the time of sexual contact with her, he had no symptoms after that. Her 7-month-old son was treated for a skin infection of the perineum caused by GAS 3 weeks before the onset of her symptoms.

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On examination, she was fully alert and oriented. Her temperature was 38.9 °C, blood pressure 110/57 mmHg, pulse 88/min, respiratory rate 16 breaths/min. There were no signs of pharyngeal or skin involvement. Examination of the other systems revealed no significant abnormalities. Laboratory results were normal, except for an elevated leukocyte count of 9900 cells/mm^3 and a C-reactive protein of 3.6 mg/dL. One dose of ceftriaxone (2 g) was administered after 2 sets of blood and urine cultures were obtained.

On the first hospital day, the patient became hypotensive with her blood pressure reduced to 77/48 mmHg. Laboratory tests revealed thrombocytopenia (90×10^9/L) and elevation of liver enzymes (aspartate aminotransferase 242 U/L, and alanine aminotransferase 505 U/L). Urinalysis revealed clear yellow urine with 1–4 red cells and 5 to 9 white cells per high-power field. On the second day, two sets of blood cultures taken on admission yielded gram positive cocci. Considering STSS based on these results in addition to the GAS isolation from the vaginal culture at the gynecology clinic, antimicrobial therapy was changed to a combination of clindamycin (900 mg every 8 hours) and ceftriaxone (2 g every 24 hours). Subsequently, her vital signs stabilized, and the vaginal discharge resolved. On the third day, a gynecological examination showed no cervical tenderness, vaginal discharge, or erythema. On the fourth day, GAS was isolated in both the aerobic and anaerobic blood cultures as well as from her urine sample (10^4 colony-forming units/mL) collected before starting antimicrobial treatment. Antimicrobial therapy was switched to ampicillin (2 g every 6 hours) based on the results of antimicrobial susceptibility testing and administration of clindamycin was discontinued. After 14 days of antimicrobial therapy, the outcome was favorable, and the patient was discharged home.

3. Microbiological analyses

We examined phenotypic and genotypic characteristics of the GAS isolates from the blood (strain M6-1) and urine (M6-2) of this patient. Phenotypic analyses were performed using colonial morphology on sheep blood agar plates and percent identification by numerical profile using the API-20 Strep system (SYSMEX; bioMérieux Co., Ltd., Tokyo, Japan). Genotypic analyses were performed using 16S rRNA gene sequencing, *emm* genotyping, and full-length *emm* sequencing [3]. Sequence type (ST) was determined using multilocus sequence typing (MLST) and the pubMLST website (http:/pubmlst.org/spyogenes/), and we also determined the exotoxin gene profile (*speA-speB-speC-ssa-smeZ*) to assess the relationship between the profile and onset of STSS and the tetracycline-class and macrolide/lincosamide-class resistance determinants [*tet(M)-tet(O)-tet(K)-tet(L)-tet(S) and erm(A)-erm(B)-mef(A)*] [3].

The phenotypic and genotypic characteristics, including antimicrobial susceptibility, results are shown in Table 1. The *emm* genotype (subtype) was *emm*76 (.0), and the full-length *emm* sequence (798 bp) was 100% similar to that of GAS JS105 strain (AF502094.1). The ST was 50 and the exotoxin gene profile was *speB* alone. The isolates from the blood and urine revealed the same phenotypic and genotypic features except for the biochemical property profiles based on the API-20 Strep system.

4. Discussion

We described a case of a breastfeeding woman with STSS secondary to GAS vulvovaginitis after having sexual intercourse with her husband. The isolates from the blood, urine, and vagina yielded a rare GAS strain (*emm76*/ST50).

This case showed GAS vulvovaginitis can occur in adult women during lactational amenorrhea after delivery. GAS vulvovaginitis is generally an uncommon condition among non-pregnant adult women. In some epidemiological studies for patients under the care of family doctors, GAS was isolated from about 1% of the vaginal samples of adult women complaining of vaginal discharge [4,5].

However, adult women are thought to be at high risk of vaginal GAS infection during lactational amenorrhea. Lactational amenorrhea may cause similar vaginal atrophy to the immature, hypoestrogenic vaginal environment found in prepubescent girls, who are more susceptible to GAS vulvovaginitis than adult women [6]. Lactation decreases estrogen levels, which leads to the loss of *Lactobacillus* species, known as a vaginal normal bacterial flora, and to the overgrowth of potentially pathogenic organisms [7]. Therefore, breastfeeding women are more likely to develop GAS vulvovaginitis. Several cases of GAS vulvovaginitis in breastfeeding women have been reported [8,9]. Furthermore, the patient in this case had other predisposing factors which have been previously reported as associated with GAS vulvovaginitis: 1) household or personal history of dermal or respiratory infection due to GAS, and 2) sexual intercourse [10].

Vaginal infection is considered an unusual cause of STSS. Our literature search discovered only two case reports of STSS occurring due to vulvovaginitis: two cases of STSS secondary to GAS vulvovaginitis in menopausal women [11] and one case of STSS and peritonitis due to an ascending vaginal infection [12]. The mechanism proposed for STSS secondary to GAS vulvovaginitis is that vaginal atrophy allows GAS to colonize the vagina [13], invade deeper tissues [14], and cause a bacterial translocation [11]. Although there was no evidence that her husband had GAS in his penis, sexual intercourse with her husband had the possibility of

Table 1
Phenotypic and genotypic features of *Streptococcus pyogenes* isolates from blood and urine of this patient.

Strain ID	M6-1 and M6-2
Clinical specimen	Blood (M6-1) and urine (M6-2)
Gross appearance of colonies on sheep blood agar plate	Non-mucoid beta-hemolytic white-colored smooth small colonies
Numerical profile using the API-20 Strep system (% probability)	0160414 (99.9) and 0161415 (99.9)
Similarity (%) of S. pyogenes type strain[a] using 16S rRNA sequencing (sequencing size, bp)	100 (1417)
emm type (subtype)	*emm76* (.0)
emm full-length (sequencing size, bp)	100% similarity to that of S. pyogenes JS105 strain[b] (798)
Sequence type (allelic profile: gki-gtr-murI-mutS-recP-xpt-yqiL)	50 (11-6-3-6-6-27-4)
Profile of exotoxin genes	*speB*
Antimicrobial agent resistance class[c]	Tetracyclines/Macrolides/Lincosamides
Profile of antimicrobial resistance genes	*tet*(M)+*erm*(B)

[a] *S. pyogenes* NCTC8198(T).
[b] Accession number is AF502094.1.
[c] Resistance to antimicrobials was determined by the broth microdilution method according to the Clinical and Laboratory Standards Institute document M100-S22.

transmitting GAS to her vulnerable vagina during the period of lactational amenorrhea.

In this case, we considered that the patient was more likely to develop STSS from vulvovaginitis than from urinary tract infection (UTI), and that the GAS bacteriuria was possible bacterial contamination associated with vulvovaginitis. The first symptoms of this case, vaginal discharge and vulvar pruritus, and the vaginal findings at the gynecology clinic suggest that the portal of entry was the vagina. GAS is generally considered a rare causative bacterium for UTI and the low urine culture bacterial counts without pyuria lowered the possibility of UTI. However, we could not completely rule out the possibility of febrile urinary tract infection as a complication of vulvovaginitis.

We examined the molecular epidemiological features of the GAS *emm76*/ST50 isolates from the blood and urogenital tract of our patient. According to the PubMLST database (https://pubmlst.org/bigsdb?db=pubmlst_spyogenes_isolates&page=query) of GAS isolates, there are five *emm76*/ST50 strains isolated from sterile specimens including blood ($n = 2$) and upper respiratory tract ($n = 3$) in the USA, Switzerland, the Czech Republic, and Japan (as of January 11th, 2019). Therefore, the incidence of GAS *emm76*/ST50 isolated from the urogenital tract seems to be very rare in clinical settings. The presence of GAS *emm76*/ST50 ($n = 1$) and *emm76*/ST378 [a single locus variant of ST50] ($n = 3$), which were isolated from the invasive infections, was reported from Romania [15]. One of the four isolates caused the STSS cases, suggesting the virulence of this *emm* type.

We reported the first case of STSS associated with vulvovaginitis in a breastfeeding woman. When breastfeeding women complain of vaginal symptoms, clinicians should consider GAS vulvovaginitis as one of the differential diagnoses that could necessitate appropriate antibiotic treatment to prevent progression to STSS.

Conflicts of interest

None declared.

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References

[1] Wu CMY, Noska A. Intrauterine device infection causing concomitant streptococcal toxic shock syndrome and pelvic abscess with Actinomyces odontolyticus bacteraemia. BMJ Case Rep 2016;2016. https://doi.org/10.1136/bcr-2015-213236.

[2] Ikebe T, Tominaga K, Shima T, Okuno R, Kubota H, Ogata K, et al. Increased prevalence of group A streptococcus isolates in streptococcal toxic shock syndrome cases in Japan from 2010 to 2012. Epidemiol Infect 2015;143:864–72. https://doi.org/10.1017/S0950268814001265.

[3] Sakai T, Taniyama D, Takahashi S, Nakamura M, Takahashi T. Pleural empyema and streptococcal toxic shock syndrome due to Streptococcus pyogenes in a healthy Spanish traveler in Japan. ID Cases 2017;9:85–8. https://doi.org/10.1016/j.idcr.2017.06.006.

[4] Morris CA, Morris DF. 'Normal' vaginal microbiology of women of childbearing age in relation to the use of oral contraceptives and vaginal tampons. J Clin Pathol 1967;20:636–40. https://doi.org/10.1136/jcp.20.4.636.

[5] Morris CA. Seasonal variation of streptococcal vulvo-vaginitis in an urban community. J Clin Pathol 1971;24:805–7. https://doi.org/10.1136/jcp.24.9.805.

[6] Stricker T, Navratil F, Sennhauser FH. Vulvovaginitis in prepubertal girls. Arch Dis Child 2003;88:324–6. https://doi.org/10.1136/adc.88.4.324.

[7] Martin HL, Richardson BA, Nyange PM, Lavreys L, Hillier SL, Chohan B, et al. Vaginal Lactobacilli, microbial flora, and risk of human immunodeficiency virus type 1 and sexually transmitted disease acquisition. J Infect Dis 1999;180:1863–8. https://doi.org/10.1086/315127.

[8] Meltzer MC, Schwebke JR. Lactational amenorrhea as a risk factor for group a streptococcal vaginitis. Clin Infect Dis 2008;46. e112–5, https://doi.org/10.1086/587748.

[9] Rahangdale L, Lacy J, Hillard PA. Group A Streptococcus vulvovaginitis in breastfeeding women. Am J Obstet Gynecol 2008;199:4–5. https://doi.org/10.1016/j.ajog.2008.02.045.

[10] Verstraelen H, Verhelst R, Vaneechoutte M, Temmerman M. Group A streptococcal vaginitis: an unrecognized cause of vaginal symptoms in adult women. Arch Gynecol Obstet 2011;284:95–8. https://doi.org/10.1007/s00404-011-1861-6.

[11] Hikone M, Kobayashi K ichiro, Washino T, Ota M, Sakamoto N, Iwabuchi S, et al. Streptococcal toxic shock syndrome secondary to group A Streptococcus vaginitis. J Infect Chemother 2015;21:873–6. https://doi.org/10.1016/j.jiac.2015.07.011.

[12] Iwata Y, Iwase S. Group A streptococcal peritonitis and toxic shock syndrome in a postmenopausal woman. Intern Med 2017;56:2523–7. https://doi.org/10.2169/internalmedicine.8552-16.

[13] Paraskevaides EC, Wilson MC. Fatal disseminated intravascular coagulation secondary to streptococcal cervicitis. Eur J Obstet Gynecol Reprod Biol 1988;29:39–40. https://doi.org/10.1016/0028-2243(88)90163-3.

[14] Ugurlu G, van der Houwen C, Brandenburg A, Schreuder I, Bogchelman D. Streptococcus pyogenes vaginitis in a postmenopausal woman. Eur J Obstet Gynecol Reprod Biol 2008;138:115–6. https://doi.org/10.1016/j.ejogrb.2007.02.022.

[15] Luca-Harari B, Straut M, Cretoiu S, Surdeanu M, Ungureanu V, Van Der Linden M, et al. Molecular characterization of invasive and non-invasive Streptococcus pyogenes isolates from Romania. J Med Microbiol 2008;57:1354–63. https://doi.org/10.1099/jmm.0.2008/001875-0.