Case Reports

Intrauterine fetal demise due to streptococcal toxic shock syndrome: a case report

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Summary

Background: Toxic shock syndrome caused by group A streptococci (GAS) is rare around the time of delivery, but it may predispose pregnant women to a life-threatening condition. *Case:* A 32-year-old primigravida at 21 weeks of gestation was taken to our hospital with acute severe abdominal pain following fever. On admission the fetus was found to be dead, and intrauterine fetal demise due to placental abruption was suspected. An emergency cesarean section found no sign of placental abruption. Soon after the surgery, the patient went into shock but was successfully treated with intensive care. Although repeated blood cultures failed to detect microorganisms, the patient was positive for streptococcal pyrogenic toxin A, which is a superantigen of GAS. *Conclusion:* Once GAS infection is suspected, regardless of negative blood cultures, supportive care in the intensive care unit is mandatory.

Key words: Pregnancy; Streptococcus pyogenes; Superantigen; Toxic shock syndrome.

Introduction

Despite recent advances in the use of antibiotics and support therapies, pregnant women and their fetuses are susceptible to serious and life-threatening infections.

Group A streptococci (GAS), such as *Streptococcus pyogenes,* cause uncomplicated pharyngitis, scarlet fever, impetigo, and acute rheumatic fever, and sometimes lead to severe manifestations, e.g., sepsis, necrotizing fasciitis, and toxic shock syndrome. In the field of obstetrics, infections with GAS have traditionally represented the most common cause of puerperal sepsis, although the incidence has decreased in recent years. Recently, the numbers of maternal and fetal deaths due to severe GAS infection before, during or shortly after delivery have been reported [1, 2]. We report on a case of intrauterine fetal demise at 21 weeks of gestation associated with streptococcal toxic shock syndrome.

Case Report

A 32-year-old Japanese primigravida developed a fever and presented to her primary obstetrician at 20 weeks of gestation. Her previous medical history was unremarkable, and the current pregnancy was otherwise uncomplicated. She was diagnosed as having influenza B and was given oseltamivir phosphate, which rapidly alleviated her fever. One week later, she became febrile again. Although she was administered an oral cephalosporin empirically, her body temperature was > 39°C the following day. She was hospitalized immediately, and a carbapenem was administered intravenously. The following morning, the patient complained of lower abdominal pain that rapidly increased in intensity, and she was taken to our hospital. On admission, the patient was conscious but appeared to be in anguish. Her body temperature was 37.8°C, blood pressure was 127/66 mmHg, and pulse rate was 133 bpm. Her abdomen was hard, and the uterus felt hypertonic with mild tenderness. Her cervix was 2.0 cm in length and dilated 1 cm with mild vaginal discharge. Ultrasonography revealed that the fetus was dead and that the placenta had thickened. The patient had the following clinicopathologic characteristics: white blood cell count, 18,500/mm^3, with 87.5% neutrophils; hemoglobin, 11.4 g/dl; platelet count, 17.6 × 10^4/mm^3; and C-reactive protein, 8.0 mg/dl. Activated partial thromboplastin time was prolonged to 39.1 seconds (control, 35.6 seconds), and fibrin/fibrinogen degradation products (FDP) and D-dimer were elevated to 200.7 and 57.8 g/ml, respectively. Placental abruption with intrauterine fetal demise and disseminated intravascular coaglopathy (DIC) was considered. Three hours after admission, an emergency cesarean section was performed, and a stillborn fetus weighing 456 g was delivered. Laparotomy produced no evidence of placental abruption, purulent myometritis or neighboring inflammation. Uterine contraction during surgery was fair, and blood loss was estimated to be 900 ml.

Soon after returning to the obstetric ward, the patient complained of dyspnea. Her blood pressure was 90/40 mmHg, and this was not increased by rapid fluid replacement. Laboratory data suggested a progression of DIC, with hemoglobin level of 6.2 g/dl, platelet count of 7.7 × 10^4/mm^3, FDP of 776.5 µg/ml, and D-dimer of 268.2 g/ml. The patient was admitted to the intensive care unit (ICU), and was treated for DIC with red blood cell and platelet transfusions, danaparoid sodium, and antithrombin. As septic shock or toxic shock syndrome was strongly suspected, meropenem was initiated intravenously at a dosage of 3 g/day. On the first day in the ICU, fluid replacement was administered up to 6,400 ml, to maintain blood pressure, but the patient did not show any response to diuretic agents. One day later, hydrocortisone was administered, and her condition gradually improved along with diuresis. In parallel with the supportive therapies, blood, vaginal, and urine cultures, and serological analyses were repeatedly performed during her hospitalization in an attempt to detect microorganisms. However, no infecting microorganisms were detected before her return to the obstetric ward day 7 and subsequent discharge on day 16 postsurgery.

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After the patient was discharged from the hospital, samples of her sera that had been stored at -20°C were evaluated for the presence of staphylococcal enterotoxins A, B, and C (SEA, SEB, and SEC), toxic shock syndrome toxin-1 (TSST-1), and streptococcal pyrogenic toxin A (SPEA), using enzyme-linked immunosorbent assays (ELISA) [3] (Table 1). On the day of her operation, the patient had a serum SPEA level of 19.2 pg/ml, which was higher than the cut-off value. On postoperative day 13, the level of SPEA was still high, while at two months post-surgery, it was below the level of detection. These findings indicate that the patient suffered from streptococcal toxic shock syndrome, which resulted in the death of the fetus.

Table 1. — *Changes in serum concentrations of superantigens over time*.

	Postoperative			Cutoff value (pg/ml)	
	Day 0	Day 13	2 months	positive	false-positive
SEA	2.66	N/D	0.24	8	6
SEB	0.77	N/D	0.00	50	30
SEC	53.0	N/D	N/D	70	50
TSST-1	0.00	0.27	0.00	25	15
SPEA	19.2	10.1	0.00	10	8

SEA, staphylococcal enterotoxin A; SEB, staphylococcal enterotoxin B; SEC, staphylococcal enterotoxin C; TSST-1, toxic shock syndrome toxin-1; SPEA, streptococcal pyrogenic toxin A; N/D, not determined.

Discussion

According to the definition of streptococcal toxic shock syndrome proposed by the Centers for Disease Control and Prevention of the United States [4], this patient could not be regarded as even a probable case, since GAS were not isolated. However, we believe that this patient had streptococcal toxic shock syndrome, based on several lines of evidence.

This case shared several clinical features with a definite case documented in our hospital in 1996 [5], in which abnormal uterine contraction, highly elevated FDP, and fetal heart rate abnormalities, which are common signs of placental abruption, were noted. It is noteworthy that the onset of streptococcal toxic shock syndrome is sometimes followed by a flu-like prodrome [1, 5]. Our patient was treated for influenza one week before the onset of the disease. Recent studies have shown that influenza virus infection can promote secondary bacterial infections, and that superinfection with influenza virus can cause a lethal GAS infection. Okamoto *et al*. reported that influenza virus infection enhanced adhesion and internalization of GAS and caused incremental increase of proinflammatory cytokines, interleukin-6 and tumor necrosis factor , in the alveolar epithelial cells in mice [6, 7]. Indeed, Harre et al. reported a fatal case of GAS myopericarditis following by influenza A infection [8]. Given the current concern about a global pandemic of influenza, physicians should consider the possibility that superinfections with influenza viruses and GAS may result in lethal, invasive GAS infections.

Although blood culturing is the most important diagnostic procedure for identifying microorganisms, culture-based microbiological identification procedures are comparatively slow and have limited sensitivities. An additional complication is that the blood cultures may be negative because the patient has already received antibiotics. Since severe GAS infections are associated with early onset and rapid progression [9], rapid and convenient detection systems for GAS are really needed. In the present case, we used ELISAs to test for five bacterial superantigens, SEA, SEB, SEC, TSST-1, and SPEA, which are responsible for staphylococcal or streptococcal toxic shock syndromes. GAS produces several superantigenic toxins, including SPEA, streptococcal pyrogenic toxin C, and streptococcal superantigen, and the release of these toxins causes streptococcal toxic shock syndrome. Among these toxins, SPEA is the most pyrogenic, and it can directly stimulate T cells to release massive amounts of proinflammatory cytokines [10]. Tanaka et al. reported a definite case of streptococcal toxic shock syndrome, in which the serum level of SPEA was remarkably elevated [11]. In the present case, serum SPEA was positive, although we failed to detect GAS in repeated blood cultures. We believe that the detection of superantigens is a helpful diagnostic tool for GAS infections.

Once streptococcal toxic shock syndrome is suspected, intensive therapy should be initiated immediately. However, a successful therapy for invasive GAS infection has not been established. The CDC recommends high-dosage parenteral penicillin and clindamycin for toxic shock syndrome. Clindamycin is considered to be effective in the reduction of toxin production through the inhibition of protein synthesis. Intravenous administration of human immunoglobulin G may also be useful in reducing mortality [1, 11]. In addition, the administration of a glucocorticoid may reduce the toxicity of T-cell activation and the specific responses to superantigens [12]. In the present case, the condition of the patient seemed to improve after hydrocortisone was administered.

In summary, severe GAS infection should be considered when a pregnant woman presents mimicking placental abruption following influenza infection. Once GAS infection is suspected, regardless of negative blood cultures, supportive care in an intensive care unit is mandatory.

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References

[1] Crum N.F., Chun H.M., Gaylord T.G., Hale B.R.: "Group A streptococcal toxic shock syndrome developing in the third trimester of pregnancy". *Infect. Dis. Obstet. Gynecol*., 2002, *10,* 209.

[2] Udagawa H., Oshio Y., Shimizu Y.: "Serious group A streptococcal infection around delivery". *Obstet. Gynecol.,* 1999, *94,* 153.

[3] Miwa K., Fukuyama M., Sakai R., Shimizu S., Ida N., Endo M., Igarashi H.: "Sensitive enzyme-linked immunosorbent assays for the detection of bacterial superantigens and antibodies against them in human plasma". *Microbiol. Immunol.,* 2000, *44*, 519.

[4] Defining the group A streptococcal toxic shock syndrome. Rationale and consensus definition. The Working Group on Severe Streptococcal Infections. *JAMA*, 1993, *269,* 390.

[5] Hirose Y., Shibuya H., Okazaki E., Aono K., Tokunaga A., Taguchi S., Haraguchi M., Honda H.: "Toxic shock-like syndrome with flu-like prodrome: a possible role of 'enhancing tissue focus' for streptococcal toxic shock". *J. Infect*., 2001, *42,* 195.
[6] Okamoto S., Kawabata S., Nakagawa I., Okuno Y., Goto T., Sano K., Hamada S.: "Influenza A virus-infected hosts boost an invasive type of Streptococcus pyogenes infection in mice". *J. Virol*., 2003, *77*, 4104.
[7] Okamoto S., Kawabata S., Terao Y., Fujitaka H., Okuno Y., Hamada S.: "The Streptococcus pyogenes capsule is required for adhesion of bacteria to virus-infected alveolar epithelial cells and lethal bacterial-viral superinfection". *Infect. Immun*., 2004, *72,* 6068.
[8] Harre B., Nashelsky M., Douvoyiannis M., Shulman S.T.: "Fatal group A streptococcal myopericarditis during influenza A infection". *Pediatr. Infect. Dis. J*., 2006, *25,* 660.
[9] Schuitemaker N., van Roosmalen J., Dekker G., van Dongen P., van Geijn H., Gravenhorst J.B.: "Increased maternal mortality in The Netherlands from group A streptococcal infections". *Eur. J. Obstet. Gynecol. Reprod. Biol*., 1998, *76,* 61.
[10] Fraser J.D., Proft T.: "The bacterial superantigen and superantigen-like proteins". *Immunol. Rev*., 2008, *225,* 226.
[11] Tanaka T., Matsubara K., Umemoto Y., Harada H., Ohyama A., Endo M., Katsukawa C.: "Successful treatment of both mother and infant in pregnancy-associated Group A streptococcal toxic shock syndrome". *Am. J. Infect. Dis*., 2007, *3*, 1.
[12] Gonzalo J.A., Gonzalez-Garcia A., Martinez C., Kroemer G.: "Glucocorticoid-mediated control of the activation and clonal deletion of peripheral T cells in vivo". *J. Exp. Med*., 1993, *177,* 1239.

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