Toxic Shock-like Syndrome Caused by T Serotype B3264 Streptococcus

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Abstract

A 45-year-old woman was transferred from a local hospital to our hospital because of shock-like manifestations in addition to septic polyarthritis and necrotizing cellulitis of the left leg. Since Streptococcus pyogenes was isolated from the blood culture examined one day before admission, the diagnosis of streptococcal toxic shock-like syndrome (TSLS) was made. Antibiotic treatment together with supportive care started at the time of admission, resulting in clinical improvement, although poststreptococcal acute glomerulonephritis occurred during the period. TSLS is a life-threatening disease, but early recognition of the disease and prompt initiation of appropriate treatment may lead to successful outcome.

(International Medicine 39: 266-269, 2000)

Key words: Streptococcus pyogenes, septic polyarthritis, necrotizing cellulitis, streptococcal pyogenic exotoxin

Introduction

Group A streptococcus (Streptococcus pyogenes) may cause a variety of illnesses ranging from very common, usually clinically mild conditions such as pharyngitis and impetigo to less common severe infections including septicemia (1). The organism has, moreover, long been the focus of intense clinical and investigative interest because of its association with two nonsuppurative sequelae: acute rheumatic fever and poststreptococcal acute glomerulonephritis (PSAGN) (2). In the past 10 years, there has been an increase in the incidence of invasive group A streptococcal infections called streptococcal toxic shock-like syndrome (TSLS) (3, 4). The most characteristic clinical finding of the disease is hypotension with associated multi-organ system involvement occurring early in the course of infection, such as shock, acute respiratory distress syndrome, renal failure, aggressive soft tissue destruction and coagulopathy (5). The mortality rate of such patients has been reported to be as high as 30–85% (3, 6). Here, we report a patient with TSLS followed by PSAGN who was successfully treated on the basis of early recognition of the disease.

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Case Report

A 45-year-old woman was admitted to a local hospital because of severe left leg pain. A laboratory examination at admission revealed marked leukocytosis. Blood culture was examined, although she did not have a fever. One day later, shock-like signs such as hypotension (80/54 mmHg), tachycardia and tachypnea in addition to polyarthritis developed, and she was transferred to our hospital for further examination and therapy. She had a past history of myoma uteri and iron deficiency anemia. On physical examination, the patient appeared pale. Her temperature was 37.2°C, and pulse was 110/min. The blood pressure was 88/62 mmHg. Fine crackles were audible in the right lower lung field. The heart sounds were normal. The abdomen was soft, and a hard mass corresponding to myoma uteri was palpable in the lower abdomen. Severe redness and tenderness were present on the left leg, and painful swelling was found in both wrist joints and the left knee joint. The white blood cell count was elevated at 40,000/mm³ with a left shift, and the platelet count was 67,000/mm³ (Table 1). C-reactive protein was markedly increased to 45.4 mg/dl. Liver dysfunction was revealed as total bilirubin 2.3 mg/dl, aspartate aminotransferase 126 IU/l and alanine aminotransferase 50 IU/l. Renal impairment was manifested by the elevated levels of blood urea nitrogen (BUN) 64 mg/dl and creatinine 2.6 mg/dl. Coagulation parameters were abnormal with a prothrombin time...
of 52% and fibrin degradative product of 107 µg/ml, which were, in conjunction with thrombocytopenia, suggestive of the presence of disseminated intravascular coagulation (DIC). On the first hospital day, antibiotic treatment with aminobenzylpenicillin 4 g/day and clindamycin 600 mg/day, and supportive care including anticoagulant therapy for DIC were started, since *Streptococcus pyogenes* was isolated from the blood culture examined one day before admission in a local hospital (Fig. 1). However, inflammation of the joints seemed to progress despite the initiation of treatment. The synovial fluid aspirated from the left knee joint disclosed a marked increase in the white blood cell count at 95,000/mm³, and T serotype B3264 streptococcus which produces streptococcal pyrogenic exotoxin (SPE)-B was isolated from the fluid. The daily doses of aminobenzylpenicillin and clindamycin were increased to 12 g and 2,400 mg, respectively, with subsequent clinical improvement. The titers of anti-streptolysin O (ASO) and anti-streptokinase (ASK) were not elevated at admission (ASO 23 U/ml and ASK 80x). However, the values increased 3–4 weeks after admission (ASO 305 U/ml and ASK 640x). For the skin lesion in the left leg, biopsy was performed on the 7th hospital day, revealing necrotizing cellulitis.

Urinalysis showed 1+ proteinuria and 3+ occult blood at admission; the amount of proteinuria was approximately 0.5 g/day and the urine sediment showed 5–10 erythrocytes and 0–5 leukocytes per high-power field without cellular casts. This was thought to result from bacterial infection- or bacterial toxin-associated direct renal involvement or a part of clinical manifestations of DIC or shock induced by streptococcal infection. In fact, the levels of serum BUN and creatinine were normalized within 1 week after the initiation of antibiotic treatment. However, during the clinical course of illness, the amount of proteinuria increased up to 3.5 g/day and the urine sediment revealed 50–100 erythrocytes per high-power field 2–3 weeks after admission, although other clinical manifestations were greatly improved at this time. The levels of serum C₃ were 43 mg/dl at admission and 40 mg/dl 3 weeks after admission. The decreased level of serum C₃ was thereafter followed by an increasing trend and returned to a normal value 4 weeks after admission in conjunction with the improvement of abnormalities in urinalysis. The level of serum C₄ was normal at admission, and the values were not significantly changed during the period. Autoantibodies including anti-nuclear antibody and anti-neutrophil cytoplasmic antibody were negative throughout the study. Ultrasonography-guided renal biopsy was performed on the 50th hospital day when only a trace amount of proteinuria was detected. The biopsy specimen showed mild mesangial proliferation in glomeruli without inflammatory cell infiltration by periodic acid-Schiff staining (Fig. 2A). Taken together, deposition of C₃ on glomerular basement membranes was found by immunofluorescent staining (Fig. 2B).

**Discussion**

TSLS is an uncommon but life-threatening disease caused by *Streptococcus pyogenes*, although recent studies have indicated a worldwide resurgence of the disease (3, 4). In Japan, Shimizu et al reported the first Japanese case of TSLS in 1993.
Figure 1. Clinical course of the patient. Antibiotic treatment with aminobenzylpenicillin (ABPC) and clindamycin (CLDM) improved clinical symptoms and signs, although proteinuria was transiently exacerbated during the period.

Figure 2. A renal biopsy specimen showed mild mesangial proliferation (panel A, periodic acid-Schiff staining, x400) and deposition of C3 on glomerular basement membranes (panel B, immunofluorescent staining, x600).

The epidemiologic and clinical features of TSLS have varied (8, 9). Cases have been reported in all age groups. The focus of initial infection has been the skin or soft tissues. However, the syndrome has followed infection of the upper respiratory and the female genital tract as well. In most instances, patients with TSLS do not have predisposing underlying disease.

TSLS is defined as the isolation of Streptococcus pyogenes, hypotension and multi-organ system involvement of at least two of coagulopathy, respiratory distress, generalized erythematous macular rash, soft-tissue necrosis, renal and hepatic damage. Clinical findings of the present case appeared to meet the provisional diagnostic criteria for TSLS (1).

The pathogenesis of TSLS is not fully understood. However, several investigators have suggested a pivotal role of SPEs in the pathophysiologic process of the disease (3, 10). SPEs belong to a family of bacterial proteins known as superantigens, which stimulate strong proliferation of T lymphocytes with
concomitant induction of excessive quantities of inflammatory cytokines. Each superantigen has a characteristic affinity to a set of T cell receptor Vβ elements and can therefore stimulate most T cells bearing those elements, resulting in either specific expansion or deletion of those T cells. This may account for the pathogenesis of TSLS characterized by rapid onset of hypotension and multi-organ failure, although the differences in the susceptibility and immunity are also involved in the severity of the infection. In addition, some groups have shown that certain serotypes of *Streptococcus pyogenes* are associated with TSLS (3, 9, 11). By the serotype analysis in Japan, expansion of T3 serotype strain in TSLS was implicated (12). Although the incidence of T3 serotype B3264 strain in this syndrome, which was isolated from the synovial fluid in the present case, seemed to be relatively low in Japan (12), the strain did produce SPEs. Thus, its infection can cause TSLS as seen in the present case.

Since the progression of the disease is quite rapid in TSLS, the case-fatality rate is 30–85%, even though most patients receive antibiotic therapy, surgical debridment and maximal supportive care (3, 6). In the present case, isolation of *Streptococcus pyogenes* and recognition of TSLS were achieved at an early stage of the disease. This resulted in prompt initiation of appropriate treatment. Previous reports also showed the importance of early recognition of the disease in the management of patients with TSLS (5). We should keep in mind that *Streptococcus pyogenes* is one of infectious agents causing a life-threatening disease with rapid progression.

PSAGN is known as a nonsuppurative consequence of group A streptococcal infection. In the present case, the amount of proteinuria increased 2–3 weeks after admission, although other symptoms and signs were markedly improved during the period. The level of serum C3 was relatively low at this time and proteinuria increased 2–3 weeks after admission, although other symptoms and signs were markedly improved during the period. The level of serum C3 was relatively low at this time and proteinuria increased 2–3 weeks after admission, although other symptoms and signs were markedly improved during the period. Furthermore, the histologic findings in the renal biopsy specimen taken on the 50th hospital day were consistent with those of PSAGN at a resolving stage. Several investigators have demonstrated the candidates for nephritogenic antigen, such as preabsorbing antigen (13), nephritis strain-associated protein (14) and nephritis plasmin binding protein (NPBP) (15). Among them, the N-terminal amino acid sequence of NPBP is identical to the sequence of SPE-B, indicating that NPBP is a precursor of SPE-B (15). The organism isolated in the present case produced SPE-B. It is possible that SPEs are relevant to the pathogenesis of not only TSLS but also PSAGN, although further studies are needed to elucidate the exact mechanisms of such conditions.

### References