감 염 제 32 권 제 6 호 2000년
Vol. 32, No. 6, 456~461

□증 례□

A Case of Streptococcal Toxic Shock Syndrome with Myonecrosis

Jin Kyoung Cho, M.D., Moon-Hyun Chung, M.D., Kwan Hee Lee, M.D.*
Young Chae Jo, M.D.† and Eui Chong Kim, M.D.‡

Department of Internal Medicine, Orthopedic Surgery, Anatomical Pathology†, College of Medicine, Inha University, Incheon, Department of Clinical Pathology‡, College of Medicine, Seoul National University, Seoul, Korea*

근괴사를 동반한 연쇄상구균 독성 쇽 증후군 1예

인하대학교 의과대학 내과학교실, 정형외과학교실*, 해부병리학과교실†, 서울대학교 의과대학 임상병리학교실‡

조진경 · 정문현 · 이관희* · 조영채† · 김의종‡

1980년대 중반부터 침윤성 연쇄상구균 감염증이 증가하기 시작했으며, 이 중 하나가 연부조직 괴사를 특징으로 하는 독성 쇽 증후군이다. 근괴사는 독성쇽 증후군에서 발생할 수 있지만 임상상에 대해서는 잘 알려져 있지 않다. 건강하던 38세 여자가 입원 하루 전부터 발생한 양측 하지의 통증과 종창을 주소로 입원하였다. 입원 6시간 후 하지 종창은 더 심해지고 멍이 든 것과 같이 자주색 반점들이 생기면서 출혈성 수포가 생겼다. 10시간 후에는 혈압이 떨어지고 범발성혈관내응고 소견들이 나타났으며, 다장기 부전으로 진행하였다. Clindamycin을 포함한 항균제, 괴사조직 절제, 정맥용 면역글로불린을 투여함에도 호전되지 않고 입원 4일 후 사망하였다. 혈액 배양과 수포액 배양에서 *Streptococcus pyogenes*가 배양되었고, 연쇄상구균 발열외독소 (*speA* gene)와 3형 M단백을 연쇄다중반응으로 증명하였다. 근조직의 병리 소견에서 근섬유의 괴사와 출혈을 관찰할 수 있었으나 백혈구 침윤은 없었다. (Korean J Infect Dis 32:456~461, 2000)

핵심용어 : *Streptococcus pyogenes,* Toxic Shock Syndrome Myonecrosis, Myositis

INTRODUDTION

The medical community has long recognized *Streptococcus pyogenes* as the cause of a broad spectrum of acute illnesses (e.g., pharyngitis, scarlet fever, impetigo, erysipelas, necrotizing fasciitis, myositis) and two nonsuppurative sequelae, i.e., rheumatic fever and poststreptococcal glomerulonephritis. Over the past 10 years, the manifestation known as streptococcal toxic shock syndrome (StrepTSS) has received increasing attention. Drastic disease progression, high mortality, and soft tissue necrosis are the main characteristics of StrepTSS. Necrosis usually involves fascia and carries a better prognosis than muscle necrosis. Necrosis of muscle is included as a diagnostic criterion for StrepTSS, but there is no relevant reference on the incidence, clinical difference, or relative prognosis of myonecrosis compared to necrotizing fasciitis.

StrepTSS is rather uncommon in Korea, compared to other developed countries and reported cases have all involved necrotizing fasciitis[1]. This report is the first case of StrepTSS with myonecrosis in Korea.

접수 : 2000년 8월 20일, 승인 : 2000년 9월 15일
교신저자 : 정문현. 인하대학교병원 내과
Tel : 032)890-2202, Fax : 032)882-6578
E-mail : mhchung@nownuri.net

CASE REPORT

A 33-year-old woman, previously well, having a 3 month history of alcoholism was hospitalized because of severe pain in her legs. The patient had received an unidentified gynecological procedure to treat uterine myoma 4 weeks prior to admission. Three days before admission, she suffered contusions to the chest wall and both legs after a fall. One day before admission, fever, chill, and myalgia had developed. On the day of admission the patient complained of severe pain and swelling in both legs which were progressively worsening.

On admission, the patient was alert. Vital signs were evaluated and were blood pressure 120/70 mmHg, pulse 100/minute, respiration 20/minute and temperature 36.5℃. Her legs were swollen and tender to palpation. The overlying skin and peripheral pulses were normal. Other physical findings were normal. Laboratory tests revealed a hemoglobin of 12.2 g/dL, WBC 1.9×10^3/mm^3, platelets 113×10^3/mm^3, prothrombin time 72%, partial thromboplastin time 48.7 seconds, glucose 178 mg/dL, BUN 11 mg/ dL, creatinine 0.5 mg/dL, and creatinine phosphokinase 7,295 IU/L.

Six hours later, well-demarcated violescent discoloration and hemorrhagic bullae had developed (Figure 1). A further ten hours later, the lesion had progressed rapidly toward the upper trunk and showed hemorrhagic discharge. Blood pressure dropped to 70/40 mmHg, the patient's level of consciousness declined and she became drowsy. Incision of the lateral aspect of her left calf showed marked edema, serosanguinous fluid, and darkly discolored muscle, but subcutaneous fat and fascia were relatively normal. Neither gas nor foul odor was present. Gram stain of fluid obtained from the bulla revealed short chain gram-positive cocci. Streptococcal myonecrosis was suspected and treatment was changed to cefazolin (1 g every 8 hours), clindamycin (900 mg every 8 hours), and intravenous gamma globulin (20 g/day for 3 days). It was not possible to excise all necrotic tissue because of rapid progression and wide involvement. The patient's condition worsened and the patient suffered respiratory failure and renal

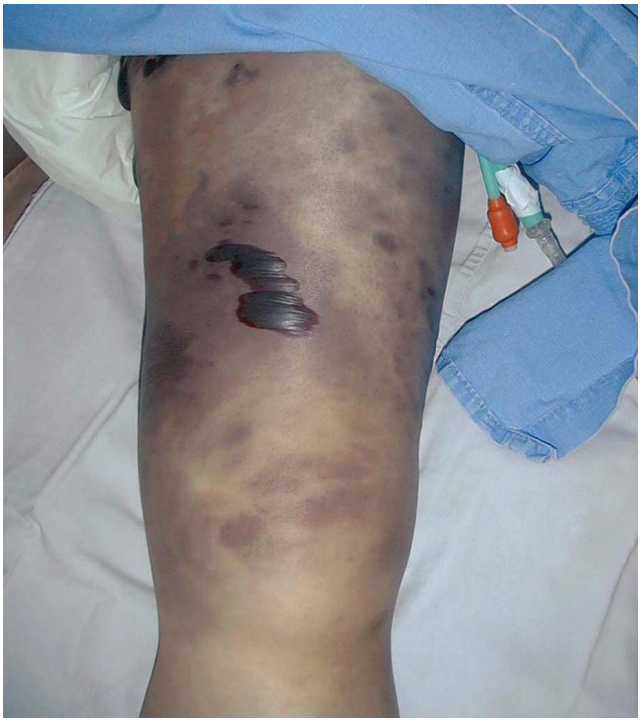

Figure 1. A photograph of the patient's right thigh shows bruise over nearly all areas of the thigh and two dark hemorrhagic bullae.

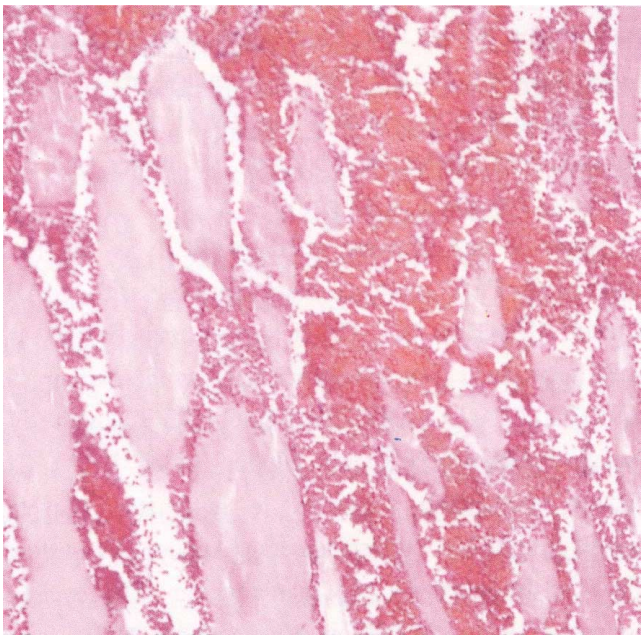

Figure 2. A microscopy of the incised muscle shows loss of normal striae of the muscle and extensive hemorrhage (H&E, ×100).

failure, and subsequently died of shock 4 days after hospital admission.

All blood cultures and an aspirate culture subsequently showed abundant growth of *S. pyogenes*. Genes for pyogenic exotoxin A (*speA*) and M-protein type 3 were detected using the polymerase chain reaction (PCR) (see below for the method). Microscopic examination of the affected muscles showed extensive muscle necrosis and hemorrhage without infiltration of leukocytes which were characteristics of myonecrosis rather than myositis (Figure 2).

METHODS

1. *emm* gene typing by sequence analysis

DNA of group A streptococci was prepared for PCR as described previously[2]. The bacteria were grown at 37℃ overnight in 10 mL of Todd-Hewitt broth and centrifuged. The pellet was washed with TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0), resuspended in 300 L of 0.85% NaCl and incubated for 30 minutes at 60 ℃. Cells were centrifuged and resuspended in 100 L of TE buffer containing 300 U of mutanolysin (Sigma, USA) per mL and 30 g of hyaluronidase (Sigma, USA) per mL for 30 min at 37℃. Samples were then heated at 100℃ for 10 minutes and briefly centrifuged to pellet the debris. The supernatant was transferred to a new tube and mixed with 2 volumes of 100% ethanol. DNA was precipitated out for 1 hour at -20℃ and then resuspended in 20 L of TE buffer and 1 L of DNase-free RNase (20 g/mL).

Primers 1 and 2 were used in PCR as described previously[3]. PCR products were purified with QIAEX II resin (QIAGEN Inc., USA). Approximately 100 ng of PCR products were sequenced using the primer (5'-TATTCGCTTAGAAAATTAAAAACAGG-3') with dye-labeled terminator PCR mix (Perkin-Elmer, USA). The products were then subjected to automated sequence analysis on a 373 autosequencer (Applied Biosystems, USA) as described by the manufacturer. The cycling parameters were 96℃ for 10 seconds, 50℃ for 5 seconds, and 60℃ for 4 minutes. DNA sequences were subjected to homology searches against the bacterial DNA database with the BLAST program (National Center for Biotechnology Information, USA).

2. PCR of *speA* gene

The PCR primers were used for detection of exotoxin *speA* gene as previously described[4]. Initial denaturation of DNA at 94℃ for 3 min was followed by 30 cycles of 94℃ for 1 minute, 50℃ for 1 minute, and 72℃ for 1 minute. The amplicon size for *speA* was 205 bp.

DISCUSSION

The reemergence of invasive group A streptococcal infections since the 1980s has been reported from most parts of the world. Many of these cases have been deep-seated infections causing shock and multiple organ failure (streptococcal toxic shock syndrome)[5]. In contrast to the findings of previous reports, patients between the ages of 20 and 50 are most commonly afflicted, and such patients often do not have predisposing underlying disease. The initial symptom is the abrupt onset of severe pain in the affected muscle which is usually located in the leg or thigh, but other locations (arm, neck, glutei) can be involved. Before the onset of pain, 20% of patients have had an influenza-like syndrome characterized by fever, chill, myalgia, and diarrhea. Fever, confusion, localized swelling and erythema are present on hospital admission and subsequently bullae, hypotension, renal dysfunction, and ARDS develop rapidly[6].

Correct differentiation of myositis from necrotizing fasciitis using imaging techniques (such as computer tomography or magnetic resonance imaging) or surgical exploration in streptococcal infection is prognostically important because mortality in streptococcal necrotizing fasciitis is about 30% but is 80～100% in streptococcal myositis. The terms streptococcal myositis or pyomyositis, streptococcal gangrenous myositis or necrotizing myositis have all been used, without a precise definition, to describe a condition of muscle inflammation caused by *Streptococus pyogenes*. Myonecrosis is a

term used to describe muscle necrosis not accompanied with infiltration of leukocytes, which is a typical pathology of gas gangrene. The case reported in this study did not show infiltration of leukocytes, so myonecrosis is a more appropriate diagnosis.

Necrotizing infection of fascia or muscle may be caused by group A streptococcus, *Clostridium perfringens*, *Clostridium septicum*, anaerobes, or polymicrobial infection. Distinguishing streptococcal myonecrosis from spontaneous gas gangrene caused by *C. septicum* or *C. perfringens* may be difficult, however the presence of crepitus or gas in the tissue tends to indicate clostridial infection. Microbiological identification is possible by aspiration of the affected area or by blood culture. If the culture is negative, anti-streptolysin O is sometimes a useful marker to confirm retrospectively an etiology in streptococcal toxic shock syndrome.

The portal of entry of streptococci cannot be ascertained in 45% of cases but the vaginal or pharyngeal mucosa is the portal of entry in the remaining cases[7]. Surgical procedures (such as suction lipectomy, hysterectomy, vaginal delivery, and bone pinning), minor local trauma, acupuncture, and varicella have provided a portal of entry in many cases. The patient in this case report had undergone an unidentified gynecological procedure 4 weeks before the onset of StrepTSS, however it is not certain that the procedure was a contributing factor to the streptococcal infection.

Pathogenesis is discussed in terms of the interaction between the GAS virulence factor and host defense mechanisms. The M surface protein has been strongly associated with the invasiveness of a given strain of streptococcus. The M1 and M3 surface proteins have been shown not only to greatly facilitate bacterial adherence to infected tissue, but also to have antiphagocytic properties directed against polymorphonuclear leukocytes. Pyrogenic exotoxins induce fever and shock. SPEA and SPEB exotoxins induce human mononuclear cells to synthesize not only tumor necrosis factor (TNF-α)[8] but also interleukin-6, suggesting that TNF-α could mediate the fever, shock, and tissue injury observed in patients with StrepTSS[8].

If necrotizing fasciitis or myonecrosis is suspected, prompt surgical consultation is necessary in addition to antibiotic therapy[9, 10]. In cases of necrotizing fasciitis caused by organisms other than streptococcus, surgical excision dramatically improves patient outcomes. The importance of surgical excision of necrotic tissue is the same in streptococcal necrotizing soft tissue infections, and intravenous gamma globulin may be an additional armament for the treatment of StrepTSS. A report by Perez and associates[11] suggests that intravenous gamma globulin (0.5 g/kg, with repetition of the dose the next day if no improvement is noted) may be efficacious in treatment of streptococcal toxic shock syndrome. Presumably, antibodies present in the preparation react to streptococcal toxins and so prevent the release of cytokines. If a patient develops irreversible shock and a broad surface of the body is involved, no surgical procedure is possible by the time of diagnosis. For these severe cases immediate administration of intravenous immunoglobulin may be helpful in reducing the incidence of mortality. Our case received three doses of intravenous gamma globulin, though, its beneficial effect was not noticed.

Penicillin is still the antibiotic of choice (2 to 4 million units intravenously every 6 hours)[9] for the treatment of streptococcal infection, though, in this case cefazolin was used. Staphylococcal toxic shock syndrome and streptococcal toxic shock share many clinical features, therefore presumptive antibiotics for such patients should include antibiotics effective against both staphylococcus and streptococcus. In this context cefazolin has a more ideal antimicrobial spectrum than penicillin. Clindamycin (600 to 900 mg intravenously every 6 to 8 hours) offers the theoretical advantage of inhibiting bacterial protein synthesis and, therefore, further toxin production. In addition, studies in animals[12, 13], have suggested that penicillin may lose effectiveness when large numbers of slowly dividing streptococci are present, as is the case in necrotizing fasciitis. This phenomenon, called the Eagle effect, is thought to occur because organisms that are present in high concentration produce decreased amounts of certain penicillin-binding proteins. Penicillin-binding proteins are the targets of penicillin, so decreased production of these pro-

teins results in diminished killing of streptococci. The action of clindamycin is independent of penicillin-binding protein, which may explain why it was more effective than penicillin in a mouse model of streptococcal myositis[10, 14] and also in a retrospective human study[15]. Whether clindamycin should be added to penicillin or used as a single agent instead of penicillin has not been proven in a controlled study. One concern regarding the use of clindamycin monotherapy is the resistance of streptococcus to macrolide antibiotics because resistance to erythromycin is often associated with resistance to clindamycin. A study conducted in a Korean hospital showed a 16% resistance rate to erythromycin and a 10% resistance rate to clindamycin[16].

Hyperbaric oxygen (HBO) therapy has been used for the management of several severe or necrotizing soft tissue infections, such as gas gangrene. However, reports on this modality are mostly uncontrolled and retrospective studies, so the exact role of HBO therapy in the treatment of necrotizing fasciitis or non-clostridial myonecrosis can not be ascertained. One report suggested that in all types of necrotizing fasciitis, hyperbaric oxygen reduced mortality and the need for additional debriments[17]. In an animal model, HBO shows a similar result, that HBO has an additive effect when used in combination with penicillin in decreasing bacterial counts and increasing a survival rate[18]. Based on this limited knowledge, the possible indication of HBO therapy in severe soft tissue infection is limited to cases where there is involvement of critical areas, such as the face, or necrosis of very extensive areas of tissue. The patient described in this case report may have been a candidate for HBO therapy, but regretfully it could not be performed, chiefly because the vital signs of the patient could not be monitored in the available HBO chamber.

Finally, only increasing awareness of the condition and immediate appropriate therapy can reduce the fatality rate of streptococcal toxic shock syndrome. Severe unexplained pain and edema, even in the absence of fever, leukocytosis, and skin change at the time of examination, should alert practitioners to the possible existence of an occult necrotizing bacterial infection of fascia or muscle.

ABSTRACT

Invasive infections by group A streptococci have reemerged as a global public health problem since the middle of the 1980s. Streptococcal toxic shock syndrome (StrepTSS) is one manifestation of invasive streptococcal infections, and it is characterized by necrotic infection of soft tissue. Myonecrosis can occur in StrepTSS, but the clinical features of this subset of StrepTSS are not clearly defined.

A previously healthy 38-year-old woman was hospitalized because of pain and edema of both legs, which had developed one day prior to admission. Six hours after admission, the swelling of the patient's left leg became more severe and areas of well-demarcated violescent discoloration of the skin and hemorrhagic bullae developed. A further ten hours later, she was in shock and exhibited signs of disseminated intravascular coagulation and multiple organ failure. Gram stain of an aspirate from the bulla revealed short chains of gram-positive cocci. *Streptococcus pyogenes* was isolated from blood culture and the presence of streptococcal exotoxins (*speA* gene) and M- protein type 3 were confirmed using the polymerase chain reaction. Muscle biopsy showed extensive myonecrosis and hemorrhage without infiltration of leukocytes. Despite intensive treatment with antibiotics (including clindamycin), debridement, and intravenous gamma globulin, the patient died four days after admission to the hospital.

REFERENCES

1) Seon Ju Kim, Kim MG, Hwang YS, Yang JW, Ku KH, Chung ST : *Two case of acute necrotizing fasciitis due to S. pyogenes. Korean J Infect Dis 28:185-190, 1996*
2) Beall B, Facklam R, Thompson T : *Sequencing emm-specific PCR products for routine and accurate typing of group A streptococci. J Clin Microbiol 34:953-958, 1996*
3) Whatmore AM, Kehoe MA : *Horizontal gene transfer in the evolution of group A streptococcal emm-like genes : gene mosaics and variation in Vir regulons. Mol*

Microbiol 11:363-374, 1994

4) Stanley J, Desai M, Xerry J, Tanna A, Efstratiou A, George R : *High-resolution genotyping elucidates the epidemiology of group A streptococcus outbreaks. J Infect Dis 174:500-506, 1996*
5) The Working Group on Severe Streptococcal Infection : *Defining the group A streptococcal toxic shock syndrome : rationale and consensus definition. JAMA 269:390-391, 1993*
6) Stevens DL, Tanner MH, Winship J, Swarts R, Ries KM, Schlievert PM, *et al.* : *Severe group A streptococcal infections associated with a toxic shock-like syndrome and scarlet fever toxin A. N Engl J Med 321:1-7, 1989*
7) Meleney FL : *Hemolytic streptococcus gangrene. Arch Surg 9:317-364, 1924*
8) Lancefield RC : *Current knowledge of type-specific M antigens of group A streptococci. J Immunol 89:307-313, 1962*
9) Stevens DL : *Invasive group A streptococcus infections. Clin Infect Dis 14:2-13, 1992*
10) Schattner A, Hay E, Lifschitz-Mercer B, Gorbacz S, Bentwich Z : *Fulminant Streptococcal myositis. Ann Emerg Med 18:320-322, 1989*
11) Perez CM, Kubak BM, Cryer HG, Salehmugodam S, Vespa P, Farmer D : *Adjunctive treatment of streptococcal toxic shock syndrome using intravenous immunoglobulin : case report and reviews. Am J Med 102:11-13, 1997*
12) Steven DL, Gibbons AE, Bergstrom R, Winn V : *The Eagle effect. Revisited : efficacy of clindamycin, erythromycin, and penicillin in the treatment of streptococcal myositis. J Infect Dis 1998:158:23-28, 1998*
13) Eagle H : *Experimental approach to the problem of treatment failure with penicillin. I. Group A strept. Infection. Am J Med 13:389-399, 1952*
14) Hause AR : *Streptococcal toxic shock. Postgrad Med 104:31-44, 1998*
15) Zimbelman J, Palmer A, Todd J : *Improved outcome of clindamycin compared with beta-lactam antibiotic treatment for invasive Streptococcus pyogenes infection. Pediatr Infect Dis J 18:1096-1100, 1999*
16) Jung HS, Park SE, Lee HJ, Kim EC, Kim JH : *Clinical features of infections caused by Streptococcus pyogenes in children and their antimicrobial susceptibility. Korean J Infect Dis 30:419-425, 1998*
17) Riseman JA, Zomboni WA, Curtis A, Graham DR, Konrad HR, Ross DS : *Hyperbaric oxygen therapy for necrotizing fasciitis reduce mortality and the need for debridements. Surgery 108:847-850, 1990*
18) Zamboni WA, Mazolewski PJ, Erdmann D, Bergman BA, Hussman J, Cooper MD, *et al.* : *Evaluation of penicillin and hyperbaric oxygen in the treatment of streptococcal myositis. Ann Plast Surg 39:131-136, 1997*