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Streptococcal Toxic Shock Syndrome Occurred during Postoperative Radiotherapy in a Cancer Patient with Preexisting Lymphedema and Chronic Illness
-Case Report-

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A case is reported of a man with malignant fibrous histiocytoma (MFH) in right thigh who developed streptococcal toxic shock syndrome (STSS) during postoperative radiotherapy. Before radiotherapy, a patient complained wax and wane lymphedema following wide excision of tumor mass which was confirmed as MFH. He took some nonsteroidal antiinflammatory drug (NSAID) for about one month. He suffered preexisting hepatitis C virus (HCV) infection, diabetes and well-controlled hypertension. The patient received conventional radiotherapy to right thigh with a total dose of 32.4 Gy at 1.8 Gy per day. At last radiotherapy fraction, cutaneous erythematous inflammation was suddenly developed at his affected thigh. At that time, he also complained of oliguria, fever and chills. The patient was consulted to internal medicine for adequate evaluation and management. The patient was diagnosed as suggested septic shock and admitted without delay. At admission, he showed hypotension, oliguria, constipation, abnormal renal and liver function. As a result of blood culture, Streptococcus pyogenes was detected. The patient was diagnosed to STSS. He was treated with adequate intravenous antibiotics and fluid support. STSS is one of oncologic emergencies and requires immediate medical intervention to prevent loss of life. In this patient, underlying HCV infection, postoperative lymphedema, prolonged NSAID medication, and radiotherapy may have been multiple precipitating factors of STSS.

Key Words: Malignant fibrous histiocytoma, Streptococcal toxic shock syndrome, Radiotherapy

Despite improvements in surgical and radiotherapeutic techniques for cancer patients, treatment-related lymphedematous complications are not uncommon.[1,2] The frequency varies between 1% and 50%. One of the most troublesome complications of long standing lymphedema is the propensity of recurrent soft tissue infection.[2,3] The clinical presentation of soft tissue infection in lymphedema can be variable from skin change without fever to rapidly progressive soft tissue infection with high fever and systemic toxicity. The time from completion of radiotherapy to the onset of soft tissue infection ranged from several days to several months. These complications are usually not life-threatening and only small number of patients are progressed to systemic toxicity.[2]

One of the serious forms of soft tissue infection with systemic toxicity is streptococcal toxic shock syndrome (STSS). In STSS, the bacteria is entering through the skin in about 80% of cases, with a soft tissue infection such as cellulitis, necrotizing fasciitis, or cutaneous wounds.[4] Most cases occur in persons with chronic underlying medical illness, especially adults with solid tumors, intravenous drug abusers, HCV infected patients, and HIV positive patients.[4~9] NSAID used against fever or lymphedema is also implicated in the pathogenesis of STSS.[11,12] However, STSS is an infrequent complication of moderate dose of radiotherapy for cancer patients.

This report presents a man who developed STSS after moderate dose of postoperative radiotherapy, before com-

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pletion of radiotherapy, on a lower extremity with preexisting postsurgical lymphedema.

Case Report

A 66-year-old male underwent repeated wide excision for malignant fibrous histiocytoma (MFH) of medial side of the right thigh at other hospital. He was referred to our hospital for postoperative radiotherapy. At presentation, he complained of mild swelling of his affected leg after wide excision, though surgical wound is clearly healed. He frequently took some NSAID medicine due to his leg swelling after operation. He had preexisting HCV infection, diabetes and well-controlled hypertension on his past medical history.

Radiotherapy started 5 weeks after surgery. He received radiotherapy 32.4 Gy at 1.8 Gy per day, Monday to Friday. The target volume of radiotherapy included the site of the primary lesion and those tissues that had involvement suggestive of microscopic disease. The field margins were specified to be 7 cm proximal and distal to clinically or radiologically evident sarcoma. The radial margins were 2 cm.

After weekend resting period, he suddenly presented complaining of chillness, dizziness, oliguria, constipation, erythematous rash and swelling of the affected thigh (Fig. 1). This patient was consulted to infection department of internal medicine. He was admitted urgently to suggested toxic shock syndrome (TSS).

One day after admission, vital signs showed body temperature of 38.6°C, pulse rate of 80 beats/min, respiratory rate of 20 breaths/min, and blood pressure of 90/60 mmHg. Laboratory values showed a white blood cell count (WBC) of 7,900/mm^3, hemoglobin of 15.4 g/dL, hematocrit of 42.2%, platelet count of 68,000/mm^3, neutrophil in WBC differentiation count of 88.5%, lymphocyte 3.5%, and other whole blood finding within normal limit. The prothrombin time was mildly prolonged to 12.5 second and fibrinogen level was elevated to 593.2 nm/dL. On liver and kidney function parameters showed somewhat deteriorated function. The serum aspartate transferase (SGPT) titer was 38.9 U/L, serum alanine transferase (SGOT) 97.0 U/L. The blood urea nitrogen was elevated to 34.8 mg/dL and creatinine to 2.33 mg/dL. C-reactive protein titer was elevated to 19.6 IU/mL at admission and rapidly decreased to 1.88 IU/mL after 14 day antibiotic therapy. Antistreptolycin-O titer was increased from 119 IU/mL to 880 IU/mL during 14 admission days and then rapidly decreased to normal range. Streptococcus pyogenes was detected on blood culture. M-typing of isolate was not done. No other organisms were isolated. Table 1 showed the criteria for defining STSS. This case is defined as a definite STSS.[5] Fig. 1 showed diffused erythematous swelling with focal scaling in the right extremity. Cellulitis was evident on his skin lesion. The erythema, swelling, and pain of the involved extremity significantly worsened. During admission, open wound on the scar was developed and drained pus

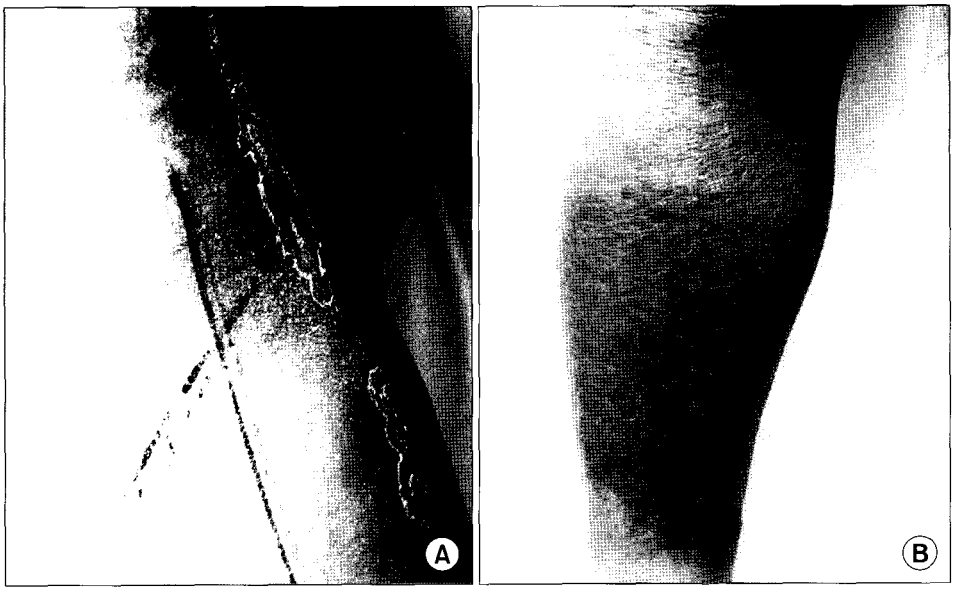

Fig. 1. Photograph of the right lower extremity of the patient, showing erythema, tense swelling, and focal dehiscence. (A) Above knee, (B) Below knee.

Table 1. Definition for the STSS[5]

Case definition*	Our case
I. Isolation of group A Streptoccus	
A. From a normally sterile site (ex. blood, cerebrospinal, pleural, peritoneal, fluid, tissue biopsy, surgical wound, etc)	Yes, from blood culture
B. From a nonsterile site (ex. throat, sputum, vagina, superficial skin lesion, etc)	No
II. Clinical signs of severity	
A. Hypotension: systolic blood pressure $\leq$90 mmHg and	Yes, 90 mmHg
B. $\geq$2 of the following signs	
1. Renal impairment: creatinine $\geq$2 mg/dL or greater than or equal to twice the upper limit of normal for age	Yes, creatinine 2.34 mg/dL
2. Coagulopathy: platelets $\leq$100,000/mm^3 or disseminated intravascular coagulation defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products.	Yes, platelets 68,000/mm^3
3. Liver involvement: alanine aminotransferase (SGOT), aspartate aminotransferase (SGPT), or total bilirubin levels greater than or equal to twice the upper limit of normal for age	Yes, SGOT 97.0 U/L
4. Adult respiratory distress syndrome defined by acute onset of diffuse pulmonary infiltrate and hypoxemia in the absence of cardiac failure, or evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal dffusions with hypoalbuminemia	Yes, pleural effusion with hypoalbuminemia
5. A generalized erythematous macular rash that may desquamate	Yes
6. Soft-tissue necrosis, including necrotizing fasciitis or myositis, or gangrene	No

*An illness fulfilling criteria IA and II can be defined as a definite case. An illness fulfilling criteria IB and II can be defined as a probable case if no other etiology for the illness is identified.

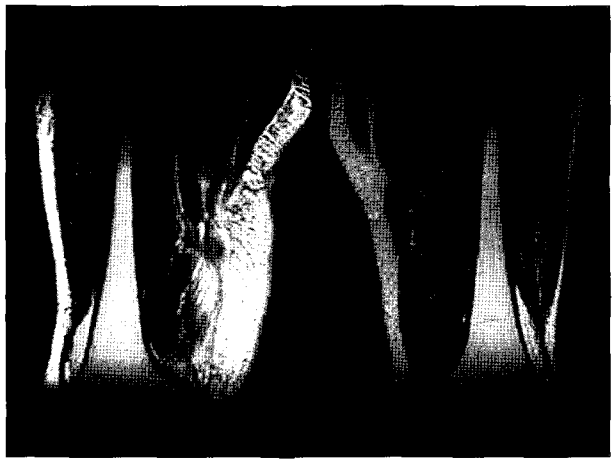

Fig. 2. MR image of the right thigh of the patient, showing swelling on fat layer of thigh, but no definitive necrotizing fasciitis.

throughout the admission days.

The diagnosis of STSS due to streptococcal pyogenes was made at 5th admission day. Chest X-ray showed mild pleural effusion in both lung fields. Abdominal sonogram showed the finding of liver cirrhosis with mild splenomegaly. Magnetic resonance (MR) image of the right thigh showed swelling on fat layer of femur, consistent with cellulitis, not necrotizing fasciitis (Fig. 2).

He was treated with first generation cephalosporin antibiotics for 9 days. Then antibiotics changed to Clindamycin because of cephalosporin drug eruption.

After 3 weeks of intensive medical treatment, this patient was discharged with an improved condition. After 6 months, the open wound was closed and leg edema was normalized.

Discussion

STSS is one of oncologic emergencies. The mortality rate of STSS is 15~70% despite overuse of antibiotics.[6,7] An oncologic emergency is a clinical condition resulting from a structural or metabolic change caused by cancer or its treatment that requires immediate medical intervention to prevent loss of life or quality of life.[5-15]

TSS was primarily associated with menstruation.[16] Menstrual TSS was caused by Staphlyococcus aureus. In 1980s, with increasing public awareness, major changes in tampon

composition, and a decrease in tampon absorbency, the frequency of menstrual TSS has decreased dramatically. Since late 1980s, nonmenstrual TSS has been associated with a variety of surgical procedures, soft tissue infections, etc.[5,6,13-15] Nonmenstrual TSS is caused by a pyrogenic exotoxin of Streptococcus pyogenes, better known as group A Streptococcs (GAS). Nonmenstrual TSS is known as STSS. GAS is not only a common source of pharyngitis and skin infections that are relatively easy to treat, but it can also cause invasive life threatening infections, such as necrotizing fasciitis and STSS.[17] M protein, a constituent of the streptococcal cell wall, has been known to be a virulence factor of GAS.[18]

The incidence of STSS is increasing due to advances in transplantation, aggressive cancer care, life-saving technology, more widespread antibiotic resistance, steroid use and the advancing age of the population.[19] By the Ontario group A streptococcus study group, the elderly and those with underlying chronic illness are at greatest risk for STSS and necrotizing fasciitis.[6] In the nationwide Japanese research, 80% of patients who died and 67% of survivors had multiple past illnesses with diabetes, injury, liver dysfunction, and hypertension.[7] The administration of NSAID should be avoided because it can contribute to sudden emergence of shock and organ failure, and inflammation.[11] This suggests that NSAID taken at the early stage of invasive GAS infection affects the cascade systems and decrease of the inflammatory signs and increase in production of cytokines.[11,12] We suppose that prolonged NSAID medication of this case could cause more aggressive infection.

There are some reports that systemic toxicity with soft tissue infection developed after completion of radiotherapy.[2,13] Patients who had undergone radiation for head and neck cancer often developed acute inflammation with cellulitis, abscess, or skin necrosis.[13] These complications were associated with extent of radiation field in the neck. However, the total radiation dose did not predict the complications. A report from Taiwan found solid tumor was an important predisposing underlying disease, especially in patients who had received radiotherapy.[14]

Considering this case, we suggest that postoperative lymphedema, underlying HCV infection, diabetes and radiotherapy are predisposing factor of STSS, although the surgical wounds are unremarkable.

STSS is characterized by sudden onset of fever, rash, vomiting, diarrhea, and hypotension followed by desquamation by recovery.[5,6,13,14] In patients with high fever and inexplicable musculoskeletal pain, the doctor should consider the possibility of a beginning of an infection by GAS. Table 1 shows definition for the STSS.[5] The first criterion for defining STSS is the isolation of GAS. A patient with GAS isolates from a normally sterile site (IA). The second requirement of the case definition is the presence of signs associated with severe infection, especially shock and multiorgan involvement (Table 1, IIA and B). In our case, streptoccus pyogenes was isolated from blood and the clinical features were included in this definition.

In STSS, the treatment should be started immediately because the infection develops in 2~3 days into systemic manifestations with high mortality rate.[13] Essential to survival of patients with this aggressive STSS is early diagnosis, initiation of appropriate antibiotics, and surgical removal of infected tissue.

Clindamycin is presently the drug of choice for treatment of STSS. The use of intravenous gamma globulin, despite good results, still deserves additional investigation.[19,20]

STSS is life-threatening. It occurs in a wide spectrum of medical conditions, and once suspected must be treated without delay.

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국문초록

수술 후 림프부종과 만성질환을 동반한 종양 환자에서 방사선치료 기간 동안 발생한 연쇄구균독소충격증후군 예

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67세 남자환자가 하지의 악성섬유조직구종으로 진단받고 광범위 절제술 후 방사선치료를 받는 동안 연쇄구균독소충격증후군이 발생하여 그 예를 소개하고자 한다. 환자는 수술 후 증감하는 부종이 있어 약 1개월간 비스테로이드소염제를 복용하였다. 환자는 C형 간염보균자였으며, 당뇨, 고혈압의 과거력이 있었다. 환자는 수술 후 방사선치료를 계획하여, 주 5회 조사하여 32.4 Gy를 치료받았다. 이틀간의 주말 치료중단이후 갑자기 방사선치료 받은 우측 대퇴부에 홍반성 염증이 발생하였고, 열, 오한, 소변감소증이 동반되었다. 환자는 즉시 감염내과에 의뢰되었고, 독소충격증후군이 의심되어 즉시 입원하였다. 입원당시 환자는 저혈압, 소변감소증, 변비, 비정상적인 신기능 및 간기능 소견을 보였다. 환자의 혈액 배양 결과 스트렙토콕쿠스 피오게네스균(Streptococcus pyogenes)이 검출되었다. 환자는 연쇄구균독소충격증후군으로 진단받고 적절한 항생제치료와 수액공급을 받았다. 연쇄구균독소충격증후군은 생명을 위협하는 종양학적 응급상황으로 즉각적인 처치가 필요하다. 본 예의 환자는 C형 간염보균, 수술 후 증감되는 부종, 지속적인 비스테로이드소염제 복용과 방사선치료가 연쇄구균독소충격증후군을 일으킨 인자들로 생각되어진다.

핵심용어: 악성섬유조직구종, 연쇄구균독소충격증후군, 방사선치료