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A Case that Developed Stevens-Johnson Syndrome as a Complication During Treatment for Methicillin Resistant *Staphylococcus aureus*

Kei Jitsuiki[1], Youichi Yanagawa[1]*, Hiromichi Ohsaka[1], Kouhei Ishikawa[1], Ikuto Takeuchi[1], Toshihiko Yoshizawa[1], Kazuhiko Omori[1], Takashi Yoshiike[2]

[1]Department of Acute Critical Care Medicine, Shizuoka Hospital, Juntendo University, Japan
[2]Department of Dermatology, Shizuoka Hospital, Juntendo University, Japan

***Corresponding author**
Youichi Yanagawa
Email: yyanaga@juntendo.ac.jp

Abstract: Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are both acute life-threatening rare dermatoses that are characterized by extensive epidermal sloughing at the dermoepidermal junction resulting from keratinocyte apoptosis. We herein report a case in which a complication of SJS occurred during treatment for methicillin resistant *Staphylococcus aureus* (MRSA) infection. A seventy-four-year-old male patient presented with fever, along with pain and swelling at the site of an implantable defibrillator. An infusion of vancomycin and amikacin was initiated, and the removal of the defibrillator was executed at a local medical facility. The patient's blood and wound cultures were positive for methicillin resistant *Staphylococcus aureus*. On the 8th day of hospitalization, the patient had fever and multiple erythema multiforme lesions were found on his body. Fur appeared in his oral cavity, both palms and scrotum and the fur changed into mucous membrane lesions, suggesting SJS. On the 11th day of hospitalization, his systolic blood pressure decreased, his respiratory function deteriorated, and his condition was complicated by thrombocytopenia and coagulopathy so that he was transported to our hospital. All of the medications that had been used were ceased. The patient received an infusion of methylprednisolone and immune-globulin. The patient underwent mechanical ventilation under tracheal intubation to allow for a massive infusion, a transfusion of platelets and fresh frozen plasma. After these treatments, the patient's vital signs, inflammatory markers, thrombocytopenia and coagulopathy improved. He was thereafter able to eat and was transferred to the dermatology ward on the 18th day of hospitalization. To obtain a favorable outcome in SJS/TEN, the timely recognition of the disease, the early cessation of the causative drug, and the immediate provision of critical intensive care are essential.
Keywords: Stevens Johnson syndrome; toxic epidermal necrolysis; intensive care.

INTRODUCTION

Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are both acute life-threatening rare dermatoses that are characterized by extensive epidermal sloughing at the dermoepidermal junction resulting from keratinocyte apoptosis [1]. Both conditions are mostly elicited by drugs and/or their metabolites and they form part of the spectrum of erythema multiforme (EM). The cutaneous lesions of Stevens Johnson syndrome are more extensive than erythema multiforme. In SJS patients, severe mucous membrane lesions appear on up to 10% of the body surface, including the oral, conjunctival and genital areas [2]. SJS/TEN are specific drug hypersensitivity reactions; cytotoxic T lymphocytes (CTLs) play a role in their initiation phase [3]. In addition to the direct cytotoxicity of CTLs, several soluble factors, such as tumor necrosis factor-a, nitric oxide, soluble Fas ligand, granulysin, and annexin A1 are now considered to mediate keratinocyte apoptosis [4]. In addition, specific HLA alleles are associated with a high risk of developing SJS/TEN, especially in Japanese individuals [4]. We herein report a case in which a complication of SJS occurred during treatment for methicillin resistant Staphylococcus aureus (MRSA) infection.

CASE PRESENTATION

A seventy-four-year-old male patient presented with fever, along with pain and swelling at the site of an implantable defibrillator, which had been inserted two months previously for ventricular fibrillation induced by hypertrophic cardiomyopathy. He was taking bisoprolol, amiodarone, frusemide, spironolactone and febuxostat. As the patient was positive for inflammatory markers, an infusion of vancomycin and amikacin was initiated, and the removal of the defibrillator was executed at a local medical facility after admission. The patient's blood and wound cultures were positive for MRSA. After these treatments, the patient obtained normothermia once. His renal function deteriorated due to antibiotics. The administration of amikacin was therefore stopped and the dose of vancomycin was decreased on the 7th day of hospitalization. On the 8th day of hospitalization, the patient had fever and multiple erythema multiforme lesions were found on his body.

On the 9th day of hospitalization, fur appeared in his oral cavity, both palms and scrotum; this was treated by an infusion of micafungin. The fur changed into mucous membrane lesions, suggesting SJS. On the 11th day of hospitalization, his systolic blood pressure decreased to 80 mmHg, his respiratory function deteriorated, and his condition was complicated by thrombocytopenia and coagulopathy. As he required intensive care for multiple organ failure, including SJS, he was transported to our hospital. On arrival, his Glasgow Coma Scale score was 15. His blood pressure was 130/60 mmHg with the use of noradrenaline and his heart rate was 60 beats per minute (BPM). The physiological finding was multiple erythema multiforme with mucous membrane lesions on his body with chemosis (Figure 1). A chest X-ray showed cardiomegaly with pulmonary congestion. An electrocardiogram showed premature venticular contraction. Whole body computed tomography did not show a focus of infection in the internal organs [5]. A complete blood count revealed the following findings: white blood cells, 4,800/mm^3 (neutrophil 60%, lymphocytes 24%, monocytes 9%, eosinophils 7%); hemoglobin, 11.9 g/dl and platelets, 0.8 x 104/mm^3. Serum biochemical analyses revealed the following findings: total bilirubin, 0.4 mg/dl; aspartate aminotransferase, 43 IU/L; alanine aminotransferase, 75 IU/L; total protein, 5.2 g/dl; glucose, 120 mg/dl; amylase, 138 IU/L; blood urea nitrogen, 73.4 mg/dl; creatinine, 2.39 mg/dl; creatine phosphokinase, 37 IU/L; sodium, 136 mEq/L; potassium, 3.9 mEq/L; chloride, 109 mEq/L; c-reactive protein, 6.1 mg/dl; prothrombin time, 13.1 (12.1) s; activated partial thromboplastin time, 103.1 (27.0) s; fibrinogen, 416 mg/dl; fibrinogen degradation product, 36.5 μg/ml; Herpes simplex virus immunoglobulin (Ig) M (-); Epstein-Barr virus IgM (-); Epstein-Barr virus IgG, ×160; Epstein-Barr nuclear antigen, ×160; Mycoplasma, ×4; β-D-Glucan, 5.0 (0-20) pg/mL; and procalcitonin 0.32 (<0.05) ng/mL. The patient underwent mechanical ventilation under tracheal intubation to allow for a massive infusion, a transfusion of platelets and fresh frozen plasma, and an infusion of recombinant thrombomodulin. The findings of an arterial blood gas analysis after mechanical ventilation (FiO_2, 0.35) revealed the following: pH, 7.40; $PaCO_2$, 29 mmHg; PaO_2, 121 mmHg; HCO_3^-, 17.7 mEq/l; and lactate, 1.1 mg/dl. All of the medications that had been used in the previous hospital were ceased. The patient received an infusion of methylprednisolone (1 g/day for 3 days, followed by 1 mg/kg/day) and immune-globulin (2.5 g/day for 3 days). After these treatments, the patient's vital signs, inflammatory markers, thrombocytopenia and coagulopathy improved. On the 9th day of hospitalization, the patient developed pneumonia, an infusion of tazobactam/piperacillin was administered with the continuation of steroid therapy. After the improvement of the patient's pneumonia, the tracheal tube was removed on the 14th day of hospitalization. He was thereafter able to eat and walk, and was transferred to another hospital to implant the defibrillator again.

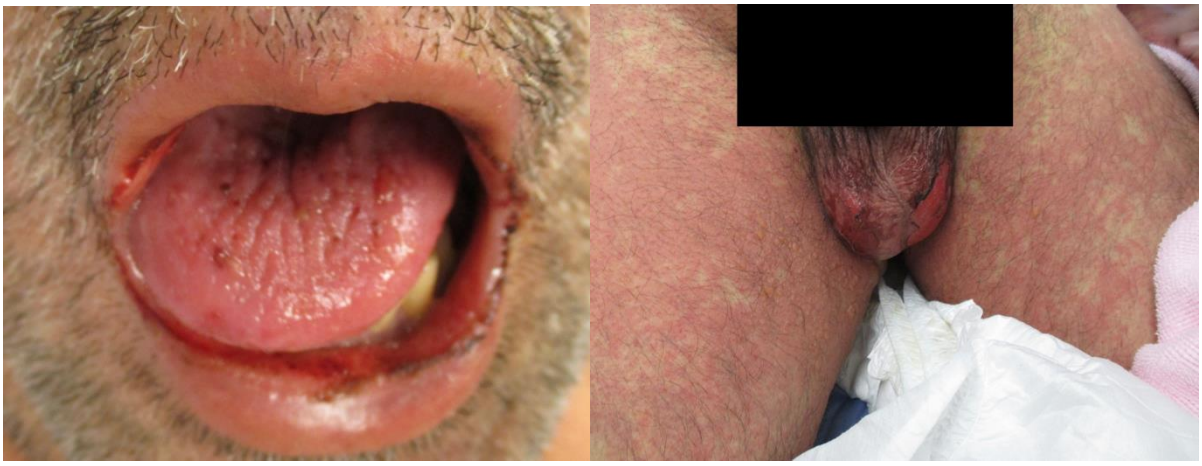

Fig-1: The patient's body surface on arrival

The patient's body surface had multiple erythema multiforme lesions with mucous membrane involvement.

DISCUSSION

Drugs are the assumed cause or are identified as the main cause in most cases of SJS/TEN; however, Mycoplasma pneumoniae and Herpes simplex virus infections are well-documented causes alongside rare cases in which the etiology remains unknown [3]. In the present case, mycoplasma and herpes simplex infections were ruled out based on the results of a biochemical analysis. Staphyloccocal scalded skin syndrome (SSSS) was previously one of the most important differential diagnoses; however, the incidence is currently very low (0.09 - 0.13 cases per one million inhabitants per year). SSSS is usually seen in infants and children and is rarely seen in adults. In addition, the patient's blood culture was negative for MRSA when he was transported to our hospital; thus, the possibility of SSSS was minimized in the present case. As drug exposure and a resulting hypersensitivity reaction is the

cause of SJS/TEN in a very large majority of cases, the drugs that were used in the previous hospital were thought to be the most likely cause. Allergological testing can help to identify the most likely candidate. However, the severity of SJS/TEN does not allow for re-challenge or intradermal testing with the culprit drugs due to the risk of re-inducing a second episode of SJS/TEN; thus, we did not try to specify the causative drug.

The Japanese guidelines recommend the systematic administration of steroids, an infusion of immune-globulin, and plasmapheresis as the 3 first-line treatments of choice [6]. In addition, Aihara *et al.* recently reported that the efficacy of an infusion of immune-globulin in addition to steroid therapy in SJS/TEN [7]. As plasmapheresis requires an invasive procedure, and serious side effects from the use of immune-globulin were not observed in their report, we selected an infusion of both steroids and immune-globulin after the cessation of all of the drugs that had been used in the prior hospital. SJS/TEN is a life threatening condition, thus supportive care is an essential part of the therapeutic approach [3]. A multicenter study showed that the survival rate of patients who were transferred to a burn unit within 7 days after the onset of disease was significantly higher in comparison to patients who were admitted after 7 days [8]. As our department also treated the patients with severe burns, the intensive care provided in our hospital may have also led to the favorable outcome in the present case.

CONCLUSION

To obtain a favorable outcome in SJS/TEN, the timely recognition of the disease, the early cessation of the causative drug, and the immediate provision of critical intensive care are essential.

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