Severe Obliterative Bronchitis Associated with Stevens-Johnson Syndrome

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Abstract

We report a case of Stevens-Johnson syndrome (SJS) in which the patient had been diagnosed with severe obliterative bronchitis. A 29-year-old woman was admitted with a high fever and a widespread vesicular rash. She was diagnosed with SJS and betamethasone administration was started. After one month, her vesicular skin rash improved; however, she developed respiratory failure and was assisted with mechanical ventilation. Computed tomography of the chest demonstrated a hyperlucent lung with narrowing of the peripheral vessels. Bronchoscopy revealed an occlusion of the bronchus when the patient exhaled. The flow-volume curve revealed a severe obstructive pattern. The patient was diagnosed with obliterative bronchitis following SJS. She was treated with a bronchodilator and steroids, but could not breathe adequately without the ventilator. During the following year, her PaCO₂ increased to 100 torr and her heart function also continued to worsen. Despite intensive treatment, she died one year and seven months after the onset of SJS. In SJS and toxic epidermal necrolysis (TEN) patients, chronic pulmonary complications are rare, but there is no effective therapy for obliterative bronchitis following SJS/TEN. Therefore, early awareness of this condition is needed and lung transplantation must be considered at an early stage of this disease.

Key words: obliterative bronchitis, Stevens-Johnson syndrome

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Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but severe diseases characterized by extensive detachment of the epidermis and mucous membrane involvement (1). It is generally accepted that SJS/TEN are usually adverse drug reactions, although various etiologic factors have been implicated as causes of SJS/TEN including infection, vaccination, drugs and systemic diseases (2, 3). The mortality rate is reported to be between 1-5% for SJS and 10-40% for TEN (4, 5).

SJS and TEN present as a febrile illness associated with erythematous macules and atypical target lesions followed

by skin detachment. Involvement of ocular, oral and genital mucosa occurs in both illnesses. SJS and TEN are currently considered to be a part of a spectrum of clinically and pathologically related diseases (1-3). Within this spectrum, TEN is the most severe type with epidermal detachment involving more than 30% of total body surface area (TBSA), while SJS is a milder type with less epidermal detachment (1). The pathogenesis of SJS/TEN is not understood, but it is well known that the basic epidermal and mucosal pathology in SJS/TEN is large-scale epidermal and mucosal death, which is the result of apoptosis (7).

SJS and TEN are often accompanied by visceral involvement, including pulmonary complications, hepatitis, gastrointestinal hemorrhage, and glomerulonephritis (7-10). Ac-

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Figure 1. A computed tomography of the chest demonstrated a hyperlucent lung with narrowing of the peripheral vessels on the 27th day (A). Bronchiectasis and atelectasis were observed in the right lower lung on the 189th day (B). Advanced bronchiectasis and atelectasis were observed on the 268th day (C).

cording to previous reports, pulmonary complications associated with SJS/TEN have been divided into two types: interstitial pneumonia in the acute phase and obliterative bronchitis or bronchiolitis in the chronic phase (9). However, there are only a few reports concerning chronic pulmonary complications in patients with SJS/TEN (11-23). We herein report a patient with SJS who had been diagnosed with severe obliterative bronchitis and died due to respiratory failure.

Case Report

A 29-year-old woman was admitted with a high fever and a widespread vesicular rash associated with erosions of the oral mucosa, conjunctivitis and laryngitis. She had been taking an antipyretic drug containing acetaminophen for several days for a slight fever and cough. She had no history of al-

lergic diseases or other previous illnesses.

On admission, epidermal detachment involved less than 10% of TBSA. Laboratory tests were normal except for the following: Blood data showed a WBC of 8,100/ μ L (band.3.0%, seg.77.5%, mono.12.5%, lym.6.5%), CRP 1.7 mg/dL, and liver dysfunction was observed (ALT 114 mU/mL, AST 657 mU/mL, LDH 600 mU/mL). Mycoplasma and chlamydia infections and other viral infections (herpes simplex virus, cytomegalovirus) were negative on serological tests.

Under a diagnosis of SJS, administration of betamethasone was started at 10 mg/day. The patient began to improve about one week after starting the treatment and betamethasone was reduced gradually over one month. However, she developed progressive dyspnea attacks, with wheezing and a respiratory rate of 24/min. Wheezing was audible in the bilateral chest, the oral mucosa was slightly dry, her skin was pigmented and conjunctival adhesion was observed.

An arterial blood gas examination performed on the 27th day of hospitalization revealed pH of 7.390, PaCO₂ of 62.3 torr and PaO₂ of 88.0 torr during FiO₂ of 0.6. Sputum culture revealed methicillin-resistant *Staphylococcus aureus* (MRSA). Chest CT showed bilateral hyperlucencies with narrowing of the peripheral vessels (Fig. 1A). The dyspnea attack was accompanied by wheezing and heavy sputum secretion.

The first time, her symptoms were thought to be caused by acute bronchitis. She was treated with intravenous aminophylline, a β_2 -stimulant inhaler and betamethasone 6 mg/day. Oral clarythromycin was also administered from her 61st day of hospitalization. However, her dyspnea worsened and PaCO₂ elevated to 100 torr. She developed CO₂ narcosis and required mechanical ventilation support on her 80th day of hospitalization. Her chest X-ray did not show any obvious abnormalities without hyperlucencies. Mechanical ventilation support was used with pressure support and end-expiratory pressure (PEEP). Intravenous aminophylline and prednisolone were administered with a β_2 -stimulant inhaler, beclomethasone inhaler, and antibiotics. With the ventilation support, her PaCO₂ improved to 60 torr, and we tried several times to wean her from the ventilator, but failed. We concluded that weaning was impossible and mechanical ventilation was continued.

Bronchoscopy performed on the 86th day of hospitalization revealed an occlusion of the fifth bronchus on exhalation (Fig. 2). A pulmonary function test was performed on the 104th day of hospitalization. The flow-volume curve revealed a severe obstructive pattern, suggesting the presence of an obstruction in the relatively central bronchus (Fig. 3). A biopsy of the bronchial mucosa was performed on the 86th day of hospitalization. Biopsied tissues from the right second carina showed squamous metaplasia (Fig. 4A), goblet cell hyperplasia and submucosal edema (Fig. 4B). These findings suggested remodeling of the bronchial membrane after severe erosive bronchitis as a result of SJS. Sputum

Figure 2. View of the right B8a by bronchofibroscopy on the 86th day. The upper photo (A) showed the bronchus on inspiration. The lower photo (B) showed the bronchus on expiration. These findings showed that the bronchus was completely obstructed on expiration.

culture was examined once a week, and it revealed MRSA intermittently.

Chest CT showed bronchiectasis and atelectasis (Fig. 1B). The atelectasis was improved by bronchial lavage, and many mucus plugs were observed in the lavage fluid. Finally, she was diagnosed with obliterative bronchitis following SJS. Despite all the medical treatment in combination with the mechanical ventilator, her PaCO_2 retention increased gradually, accompanied by heavy discharge requiring frequent suction. Chest CT showed advanced bronchiectasis and atelectasis (Fig. 1C). She suffered from repeated pneumothorax and pneumomediastinum during her clinical course, and she became emotionally disturbed and needed antidepressant drugs. Lung transplantation was considered the best treatment option; however, since she had undergone mechanical ventilation for several months and her general and mental conditions were poor, the lung transplant option was rejected.

One year after the onset of SIS, the patient continued on the mechanical ventilator, and her PaCO_2 was about 100–140 torr at pressure control ventilation of 28 mmH₂O with PEEP of 6 cmH₂O. Her heart function also continued to

Figure 3. The flow-volume curve showed air flow limitation and air trapping on expiration under conditions of PS 8 cmH₂O and PEEP 5 cmH₂O on the 104th day, suggesting the presence of an obstruction in the relatively central bronchus.

worsen. Moreover, she suffered from bilateral pneumothorax, and underwent bilateral thoracic drainage. Despite the intensive treatment, she died one year and seven months after the onset of SJS.

Discussion

The present patient experienced severe respiratory failure as a result of obliterative bronchitis following SJS. Pulmonary complications in the chronic phase of SJS/TEN are rare, and most of them are obliterative bronchitis or bronchiolitis (9). Fourteen cases of obliterative bronchitis or bronchiolitis following SJS/TEN have been reported (11–23). Two cases were thought to result from SJS brought on by mycoplasma infections (11, 12), and 11 cases were thought to have been related to SJS/TEN caused by drugs (13–19, 21–23). Six cases of severe respiratory failure, similar to that of the present patient, resulted in fatalities from 2 months to one and a half years after the onset of SJS/TEN (11, 12, 15, 20, 21, 23). One patient developed progressive respiratory failure due to obliterative bronchiolitis, and underwent a living-donor lung transplantation 6 months after the onset of SJS (22). The other patients were discharged, but they all had prolonged respiratory complaints (13, 14, 16–19). There are no reports of patients who have survived on mechanical ventilation due to obliterative bronchitis or bronchiolitis after SJS/TEN (11, 12, 15, 20, 21, 23).

The pathogenesis of SJS/TEN and its pulmonary complications are not well understood. It has been suggested that several pathways are implicated in the widespread apoptosis of keratinocytes in SJS/TEN (24–27). Involvement of cytotoxic T cells and the molecular cytotoxicity of Fas and cytotoxic enzymes, including granzyme B, perforin, and granulysin have been shown in SJS/TEN (25, 27). Cytokines including tumor necrosis factor alpha (TNF- α) and inter-

Figure 4. Biopsied tissues from the right second carina showed squamous metaplasia (A), goblet cell hyperplasia and submucosal edema (B) on the 86th day (Hematoxylin and Eosin staining, $\times 100$). These findings suggested remodeling of the bronchial mucosa after severe erosive bronchitis as a result of Stevens-Johnson syndrome.

feron gamma (IFN- γ) were found to be overexpressed in the lesional skin (24, 25, 28, 29). Wuepper et al demonstrated that immunocomplexes were detected in the serum and dermal/mucosal lesions of severely affected SJS patients (30), and those immunocomplexes were thought to be a possible cause of chronic pulmonary complications after SJS/TEN (23).

Secondary infections are also thought to be another cause of late pulmonary deterioration. In fact, MRSA was detected in the present patient's sputum culture. Although her infection was controlled by antibiotics, the secondary infection was thought to be a possible cause of her bronchitis.

In the present case, we assume that the remodeling of the bronchial mucosa in the form of fibrosis and scarring was the result of severe inflammation due to SJS, and also a cause of the obstructive changes. In fact, biopsied tissues from the bronchial mucosa revealed that there was little infiltration of inflammatory cells, while remodeling of the bronchial epithelium was observed. Two autopsy cases with obliterative bronchitis and bronchiolitis after SJS also showed loss of the bronchial epithelium, while the luminal space was totally replaced by fibrous granulation tissue (12, 15).

We think that the etiologic factor of SJS in our case was an antipyretic drug ingested before admission, although her drug-induced lymphocyte stimulation test (DLST) for traces of the drug using peripheral blood mononuclear cells was

negative. We cannot rule out the possibility that an infectious agent that we could not detect may have induced SJS, but the clinical course strongly suggests the antipyretic medicine was the etiologic factor. Yetiv et al reported that an allergic predisposition might have played a role in the development of SJS, and drugs and infections were especially suspect as etiologic agents in SJS (31).

Once the obstructive changes have been established, there is currently no curative therapy for obliterative bronchitis and bronchiolitis (32, 33). Steroids have been reported for the treatment of these conditions (15, 18, 23), but they only mitigate bronchial edema and improve the symptoms temporarily (15, 18, 23). In the present case, intravenous prednisolone and a beclomethasone inhaler were thought to be effective in reducing the bronchial mucosa edema and secretion to some degree. Our patient's breathing was disrupted by heavy bronchial discharge, and the use of influent suction and squeezing was effective in excreting the patient's sputum. Immunosuppressants such as cyclosporine are also used for the treatment of obliterative bronchiolitis, but the effect is uncertain (33, 34).

Lung transplantation is thought to be the only curative therapy for such a case (22). However, patients using mechanical ventilation for a long time, who have other complications and who cannot achieve total rehabilitation, are not candidates for lung transplantation. In SJS/TEN patients, chronic pulmonary complications are rare, but there is still no effective therapy for obliterative bronchitis and bronchiolitis following SJS/TEN. Therefore, early awareness of this condition is needed and lung transplantation must be considered at an early stage of this disease.

The authors state that they have no Conflict of Interest (COI).

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