

# Statistical Analysis of Stevens-Johnson Syndrome Caused by *Mycoplasma pneumoniae* Infection in Japan

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## ABSTRACT

**Background:** Stevens-Johnson syndrome (SJS) associated with *Mycoplasma pneumoniae* (*M. pneumoniae*) infection is mainly observed in children. In adults, drugs are a major cause of SJS, but some adult patients with SJS are infected with *M. pneumoniae*. We analyzed patients with SJS associated with *M. pneumoniae* infection to elucidate the differences between drug-induced SJS and *M. pneumoniae*-associated SJS and also to study differences between *M. pneumoniae*-associated SJS in children and adults.

**Methods:** This is a retrospective review of Japanese patients who have been reported as *M. pneumoniae*-associated SJS in medical Journals published from 1981 to 2009, compared with data of Japanese patients with drug-induced SJS reported from 2000 to 2009.

**Results:** Thirty-eight cases of *M. pneumoniae*-associated SJS and 78 cases of drug-induced SJS were analyzed in this study. Ocular lesions were observed more frequently in *M. pneumoniae*-associated SJS than in drug-induced SJS ( $p < 0.01$ ), and adult patients showed a higher ratio of sequelae in their eyes than did patients under 20 years of age ( $p < 0.01$ ). Sixty-six percent of adult patients with *M. pneumoniae*-associated SJS developed fever/respiratory symptoms and mucocutaneous lesions on the same day. In contrast, most of the patients under 20 years of age developed fever/respiratory symptoms before mucocutaneous involvement. This means that these adult patients were infected and immunized previously and developed allergic reactions to *M. pneumoniae* soon after the later infection.

**Conclusions:** In order to prevent ocular sequelae in adult patients when *M. pneumoniae* infection is suspected, more intensive treatment may be needed in adult patients than in younger patients.

## KEY WORDS

*Mycoplasma pneumoniae*, ocular involvement, sequelae, Stevens-Johnson syndrome, treatment

## INTRODUCTION

Stevens-Johnson syndrome (SJS) is a potentially fatal disorder characterized by high fever, widespread blistering exanthema of macules and atypical target-like lesions accompanied by mucosal involvement. It often advances to toxic epidermal necrolysis (TEN) characterized by widespread epidermal detachment.<sup>1</sup> SJS and TEN are usually related to medications, but some cases of SJS have been reported to be associ-

ated with infection by microorganisms such as *Mycoplasma pneumoniae* (*M. pneumoniae*).<sup>2,3</sup>

*M. pneumoniae* is a common respiratory pathogen that produces disease of varied severity, ranging from mild respiratory tract infection to severe atypical pneumonia.<sup>4</sup> This organism is also responsible for producing a wide spectrum of non-pulmonary manifestations, including neurological, hepatic, and cardiac diseases and erythema multiforme.<sup>5-8</sup> It may occur before, during or after pulmonary infection, as

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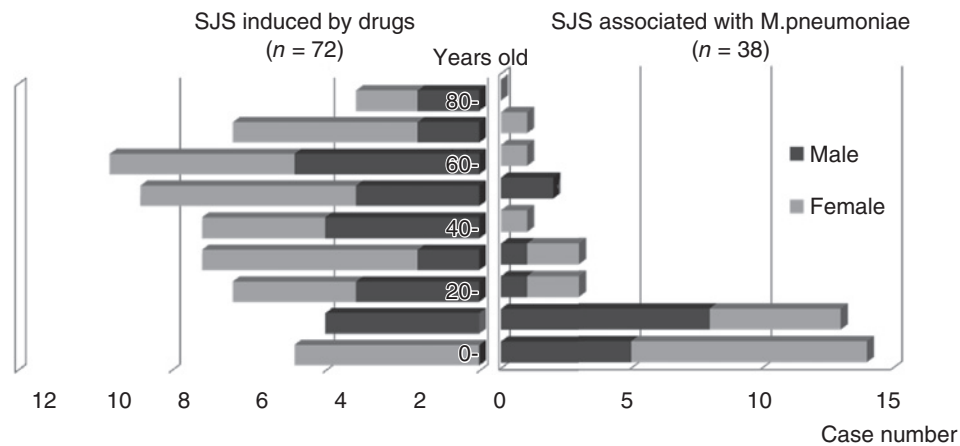


**Fig. 1** Age and sex. The patients with *M. pneumoniae*-associated SJS were much younger than those with drug-induced SJS.

well as in the absence of any pulmonary symptoms. *M. pneumoniae* is also known as a cause of SJS especially in childhood and adolescence. However only a few articles have reported on the clinical characteristics of SJS associated with *M. pneumoniae*.<sup>9-13</sup>

To elucidate the clinical characteristics of SJS associated with *M. pneumoniae* infection (*M. pneumoniae*-associated SJS), we retrospectively analyzed reports on Japanese patients with *M. pneumoniae*-associated SJS and compared them with reports on patients with drug-induced SJS. In addition, we studied the clinical differences between children and adolescent patients and adults.

## METHODS

Reports on Japanese patients with SJS published in medical journals were analyzed. Data on patients who had been diagnosed with *M. pneumoniae*-associated SJS were collected from 1981 to 2009 and those with drug-induced SJS were collected from 2000 to 2009 (published Yamane *et al.*<sup>14</sup> and additional reports from 2007 to 2009). Clinical reports were selected when enough information was available to make a credible diagnosis. Symptoms of SJS should include severe mucous membrane lesions (eyes, oral cavity and lips, genital area) and skin lesions (macules, atypical target-like lesions, bullae and erosion) with maximum skin detachment on less than 10% of the skin surface area. In order to exclude patients with erythema multiforme, patients were not included if they had slight or very mild mucous membrane lesions.

Diagnostic procedures associated with *M. pneumoniae* infection included serological findings, such as an increase of mycoplasma IgG antibody with or without positive mycoplasma IgM antibody, or clinical features and roentgenogram findings compatible with *M. pneumoniae* infection.

The collected and analyzed data were as follows:

Demographic information (age, sex), skin and mucous lesions, internal organ involvement, time interval between appearance of fever/respiratory symptoms and onset of skin/mucosal lesions, treatments, terms of hospitalization, sequelae and mortality. The data on patients with *M. pneumoniae*-associated SJS were divided into two groups according to age (less than 20 years old, and older) in order to clarify differences between the groups.

Data were compared using the chi-square test. A P-value less than 0.05 indicated a significant difference.

## RESULTS

### AGE AND SEX (Fig. 1)

Thirty-eight patients (17 males and 21 females, 1 : 1.2) with *M. pneumoniae*-associated SJS and 72 patients (30 males and 42 females, 1 : 1.4) with drug-induced SJS were analyzed in this study. The ages of patients with *M. pneumoniae*-associated SJS were between 1 and 74 years (mean, 15.3 years). Twenty-seven patients (71.1%) were less than 20 years old. In drug-induced SJS, the ages were between 2 and 89 years (mean, 46.6 years). The reason why patients with *M. pneumoniae*-associated SJS were much younger than patients with drug-induced SJS is thought to be that *M. pneumoniae* infections were more frequent in childhood and adolescence. There was no significant difference in the male to female ratio between *M. pneumoniae*-associated and drug-induced SJS.

### SKIN AND MUCOUS MEMBRANE INVOLVEMENT (Fig. 2)

Skin lesions were ranged from mild to severe in both *M. pneumoniae*-associated and drug-induced SJS. There was no remarkable difference between these groups, though the extent of the lesions was not always fully described in the reports.

The ocular lesions were observed in 94.4% of *M.*

## SJS Caused by Mycoplasma Pneumoniae

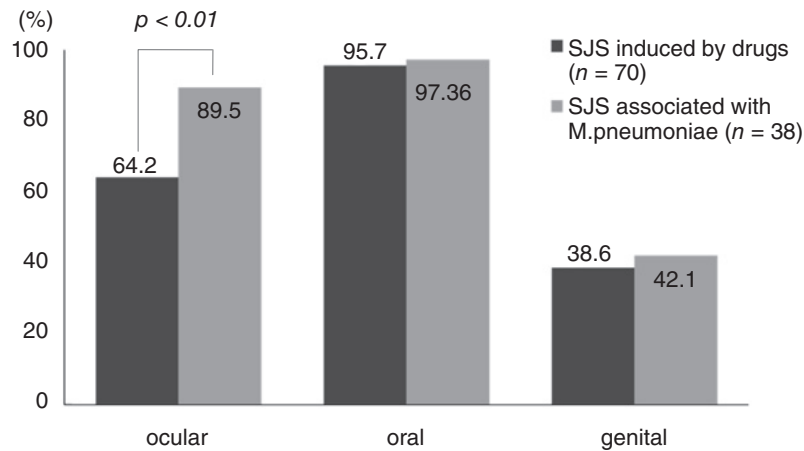


**Fig. 2** Symptoms of mucous lesions. Ocular lesions were observed in most of the *M. pneumoniae*-associated SJS patient but only in two-thirds of patients with drug-induced SJS.

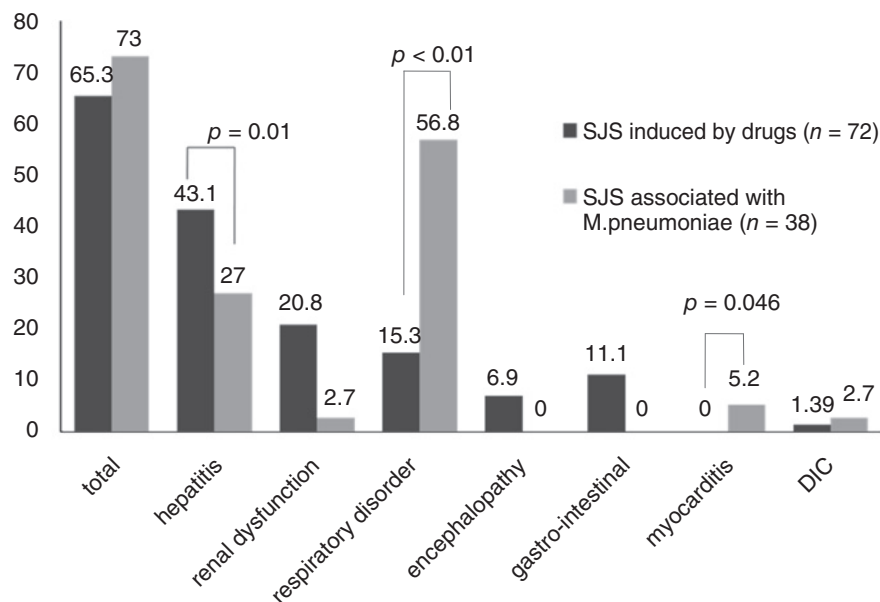


**Fig. 3** Internal organ involvement. Hepatitis was the most common complication in patients with drug-induced SJS, while respiratory disorders were more common in patients with *M. pneumoniae*-associated SJS ( $p < 0.01$ ).

*pneumoniae*-associated SJS and in 64.2% of drug-induced SJS, thus, a significantly higher percentage of these lesions was seen in *M. pneumoniae*-associated SJS ( $p < 0.01$ ). The oral lesions were observed in most of the patients in both groups. The genital lesions were observed in 38.6% and 42.1% of drug-induced SJS and *M. pneumoniae*-associated SJS, respectively ( $p = 0.72$ ). These results showed that in regard to mucous membrane involvement, ocular lesions appeared more frequently in *M. pneumoniae*-associated SJS than in drug-induced SJS.

### INTERNAL ORGAN INVOLVEMENTS (Fig. 3)

Internal organ involvement was shown in many SJS patients. Hepatitis was the most frequent complications in drug-induced SJS (43.1%). In contrast, respiratory disorders were most frequent in *M. pneumoniae*-associated SJS (56.8%), with a frequency that is significantly higher than the frequency of respiratory disorders in drug-induced SJS (15.3%) ( $p < 0.01$ ). This difference is probably due to an association of *M. pneumoniae* with respiratory tract infections. Respiratory disorders included pneumonia, hydrothorax, progressive respiratory failure and hypoxemia. However, abnormal shadows in roent-

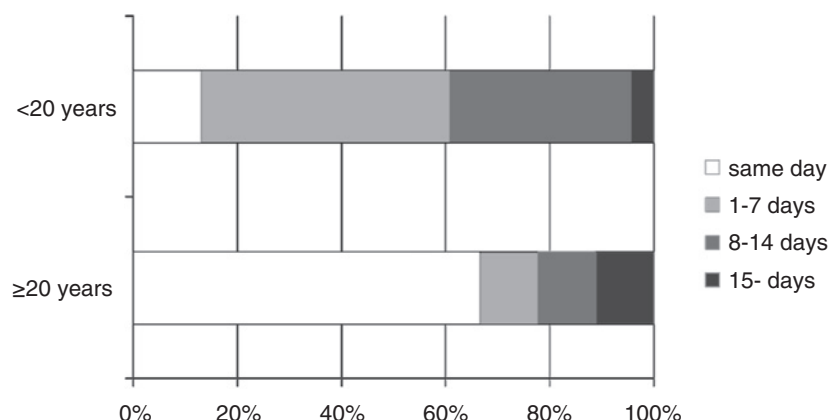


**Fig. 4** Time interval between appearance of fever/respiratory symptoms and onset of skin/mucosal lesions. The time interval between appearance of fever/respiratory symptoms and onset of skin/mucosal lesions was more than 1 week in 64% of patients under 20 years old. In contrast, 66% of older patients developed fever/respiratory symptoms and skin/mucosal lesions on the same day.

genograms were observed only in 21 patients (55.2%) with *M. pneumoniae*-associated SJS. Renal dysfunction was significantly higher in drug-induced SJS (20.8%) than in *M. pneumoniae*-associated SJS (2.7%) ( $p = 0.01$ ). Myocarditis was observed in a small number of patients with *M. pneumoniae*-associated SJS.

#### DURATION OF HOSPITALIZATION AND SEQUELAE

We compared the duration of hospitalization in the two groups, except in a deceased case. A total of 57% of *M. pneumoniae*-associated SJS and 51.8% of drug-induced SJS were discharged within 30 days. There were no significant differences between the two groups.

A total of 18% of patients in each group had chronic sequelae. Ocular complications, including corneal disorders, dry eyes, and loss of eyelashes, were observed in 13.5% and 12.5% of patients with *M. pneumoniae*-associated SJS and drug-induced SJS, respectively. Although *M. pneumoniae* infection itself presented with respiratory disorders, bronchitis as a sequela was only observed in 4.2% of patients with drug-induced SJS. Two patients died of drug-induced SJS. One 18-year-old male patient died of SJS that developed after *M. pneumoniae* infection, but he was administered acetaminophen before appearance of SJS symptoms. Therefore the cause of his SJS was not determined. He died of severe diffuse alveolar damage.

#### COMPARISON OF SYMPTOMS OF *M. pneumoniae*-ASSOCIATED SJS BETWEEN 2 GROUPS OF PATIENTS LESS THAN 20 YEARS OLD AND OLDER THAN 20 YEARS.

##### Time Interval between Appearance of Fever/Respiratory Symptoms and Onset of Skin/Mucosal Lesions (Fig. 4)

In *M. pneumoniae*-associated SJS, the time interval between appearance of fever/respiratory symptoms and onset of skin/mucosal lesions was compared between patients who were more than 20 years old and those who were less than 20 years old. The interval was less than 24 hours (the same day) in 13.0% and more than 1 week in 39.1% of younger patients. In contrast, 66.7% of older patients developed fever/respiratory symptoms and skin/mucosal lesions on the same day. According to these results, it seems likely that these adult patients were infected and immunized previously and then developed an allergic reaction to *M. pneumoniae* soon after the later infection.

##### Mucous Membrane Involvement and Internal Organ Involvement (Fig. 5)

The frequency of each type of mucous membrane involvement did not differ with age. Respiratory disorders and hepatitis were observed in 59.3% and 25.9%, respectively, of patients under 20 years old, and in 50.0% and 30.0%, respectively, of older patients. There was no significant difference between the frequencies of these disorders in the 2 groups. Renal dysfunction, myocarditis and DIC were observed only in the patients who were under 20 years old.

##### Treatments, Length of Hospitalization and Sequelae

Systemic treatment with antibiotics and corticosteroids was mainly used in *M. pneumoniae*-associated

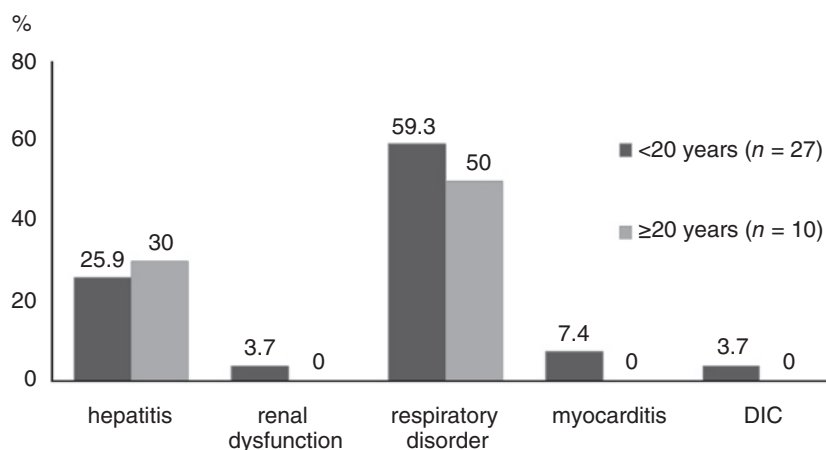


**Fig. 5** Internal organ involvement in *M. pneumoniae*-associated SJS. Hepatitis and respiratory disorders were more frequent in patients under 20 years old, although there were no significant differences between the two groups.

**Table 1**

|                                                                | Number of cases (%)   |                       |
|----------------------------------------------------------------|-----------------------|-----------------------|
|                                                                | <20 years<br>(n = 26) | ≥20 years<br>(n = 11) |
| No steroid and antibiotics therapy                             | 2 (7.7)               | 0                     |
| Steroid therapy                                                | 9 (34.6)              | 0                     |
| Steroid pulse therapy                                          | 1 (3.8)               | 1 (9.0)               |
| Steroid pulse therapy + Antibiotics                            | 1 (3.8)               | 0                     |
| Steroid pulse therapy + High dose immunoglobulin + Antibiotics | 0                     | 2 (18.1)              |
| High dose immunoglobulin + Antibiotics                         | 1 (3.8)               | 0                     |
| Antibiotics                                                    | 5 (19.2)              | 0                     |
| Antibiotics + Corticosteroids                                  | 6 (23.0)              | 8 (72.7)              |
| Semipulse therapy + Plasma exchange + Antibiotics              | 1 (3.8)               | 0                     |

SJS. Although all patients more than 20 years old were treated with corticosteroids, 8 patients (30.8%) younger than 20 years were treated without corticosteroids (Table 1). Steroid pulse therapy and high-dose immunoglobulin therapy were performed in some patients of both groups. Plasma-exchange was performed only in one patient (a 9-year-old boy) in combination with steroid pulse therapy.

Antibiotics were administered to 10 patients (90.9%) in the younger group and 14 patients (53.4%) in the older group. In the younger group, 5 patients were treated only with antibiotics.

Most of the younger patients (70.6%) could be discharged within 30 days. In contrast, 77.8% of adult patients were treated longer in hospitals (Fig. 6). The frequency of chronic sequelae was significantly

higher in adult patients than in younger patients, especially chronic ocular complications ( $p < 0.01$ ) (Fig. 7). Severe ocular lesions might be relevant to the longer hospitalization in adult patients.

## DISCUSSION

*M. pneumoniae* is the most common organism to cause SJS, especially in children and young adults.<sup>15,16</sup> Although the association of SJS with *M. pneumoniae* infection has been widely accepted, the clinical characteristics of *M. pneumoniae*-associated SJS have not been examined. In order to reveal the differences in clinical characteristics between *M. pneumoniae*-associated SJS and drug-induced SJS, we reviewed the reports published in the medical journals in Japan.

Patients with *M. pneumoniae*-associated SJS were much younger than those with drug-induced SJS. *M. pneumoniae* infected children in early childhood,<sup>17</sup> and the infection was repeated in young adults. This seems to be a major reason for the difference in the mean age of patients. Ocular involvement was more frequently observed in *M. pneumoniae*-associated SJS than in drug-induced SJS, but the difference was not significant. As *M. pneumoniae* infects the respiratory mucous membrane, respiratory disorders were observed more frequently in *M. pneumoniae*-associated SJS. However, bronchitis as a sequela was shown only in drug-induced SJS. This might suggest that serious lesions of epithelium in the respiratory tract are mainly induced by drug-induced SJS. Regarding other internal organ involvement, patients with drug-induced SJS showed hepatitis, renal dysfunction, encephalopathy and gastro-intestinal symptoms more frequently (significant difference in renal dysfunction,  $p = 0.01$ ). These results were compatible with results of a study reported by Wetter DA *et al.* They analyzed 27 SJS patients and concluded that *M. pneumoniae*-

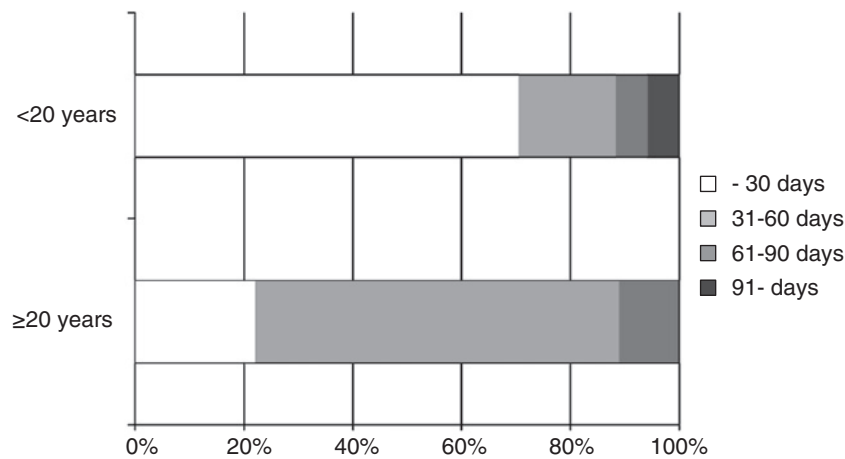


**Fig. 6** Length of hospitalization for patients with *M. pneumoniae*-associated SJS. Most patients under 20 years old could leave the hospital within 30 days. In contrast, many of the older patients remained longer in hospital.

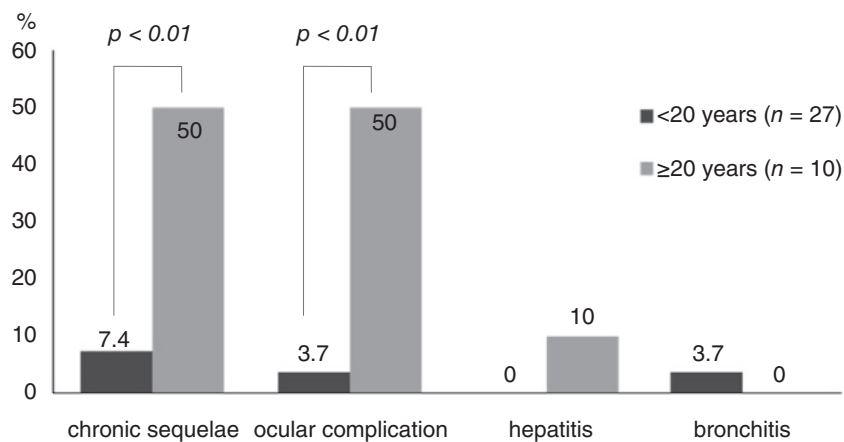


**Fig. 7** Sequelae in patients with *M. pneumoniae*-associated SJS. The incidence of chronic sequelae was significantly higher in patients under 20 years old than in older patients ( $p < 0.01$ ), especially chronic ocular complications ( $p < 0.01$ ).

associated SJS manifested less severely than drug-induced SJS, although only 6 patients with *M. pneumoniae*-associated SJS were included in the study.<sup>9</sup>

Next, we examined the differences in clinical manifestations between children and adult patients with *M. pneumoniae*-associated SJS. We divided the patients into two groups according to age: under 20 years old and older than 20 years. Respiratory disorders were present in 50-60% of both groups. Despite a relatively high frequency of internal organ involvement—except hepatitis—in younger patients, ocular sequelae appeared more frequently in the adult patients. This means that the adults patients developed more severe ocular lesions compared with the younger patients. Thus it might be one of the reasons why the duration of hospitalization was longer in the adult group.

The pathomechanisms of skin manifestations due

to *M. pneumoniae* infection remain unclear. Narita classified the extrapulmonary manifestation due to *M. pneumoniae* into three types: the first is a direct type in which inflammatory cytokines locally induced by lipoproteins contained in the bacterial cell membrane must play a role, the second is an indirect type in which immune modulation, such as autoimmunity, through cross-reaction between the bacterial cell components and human cells must play a role, and the third is a vascular occlusion type in which vasculitis and/or thrombosis with or without a systemic hypercoagulable state induced by the bacterium must play a role.<sup>18</sup> The author suggested that *M. pneumoniae*-associated SJS can be called a direct type because of *M. pneumoniae* isolation from blisters.<sup>19,20</sup> However, the isolation rarely succeeded. In this study, there was only one case report of *M. pneumoniae* isolation from a skin lesion of an SJS patient.

Thus the pathomechanism of *M. pneumoniae*-associated SJS is likely to involve immunological mechanisms, including cytotoxic T cells, similar to those shown in drug-induced SJS.<sup>21-23</sup>

Many adult patients with *M. pneumoniae* infection developed fever, respiratory disorders, and mucocutaneous lesions simultaneously, while many younger patients developed fever and respiratory disorders more than 1 week before the first manifestations of SJS appeared. This time difference may indicate the involvement of allergic mechanisms in *M. pneumoniae*-associated SJS. It seems likely that the adult patients were infected and immunized previously, and then developed an allergic reaction to *M. pneumoniae* soon after the later infection. In contrast, younger patients might need time for the immunization to take effect and therefore experienced an allergic reaction after the first infection.

In the treatment of *M. pneumoniae*-associated SJS, corticosteroids were used with or without antibiotics. Although the use of corticosteroids in *M. pneumoniae*-associated SJS is controversial, it was effective in the patients included in this study. No patient developed sepsis or severe organ involvement except one patient who died of severe diffuse alveolar damage after *M. pneumoniae* infection and acetaminophen administration.

In conclusion, patients with *M. pneumoniae*-associated SJS seem to show ocular manifestations more frequently than did those with drug-induced SJS, especially in adult patients. More intensive systemic treatment may be needed in adult patients than in younger patients with *M. pneumoniae*-associated SJS. The limitation of this study is that it was a retrospective review of cases from the literature and so a prospective study comparing the drug-induced SJS and *M. pneumoniae*-associated SJS is needed for further confirmation of the results.

## ACKNOWLEDGEMENTS

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## CONFLICT OF INTEREST

No potential conflict of interest was disclosed.

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