

## SHORT COMMUNICATION

Synergistic Effects of *Mycoplasma pneumoniae* Infection and Drug Reaction on the Development of Atypical Stevens-Johnson Syndrome in Adults

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*Mycoplasma pneumoniae* (Mp) is one of the most common causes of community-acquired pneumonia. It can induce a cellular immune response, leading to respiratory inflammation and injury. Mp infection is frequently accompanied by a variety of extrapulmonary manifestations, including arthritis, hepatitis, myositis, neurological involvement and cutaneous diseases. Cutaneous diseases, such as erythema nodosum, erythema multiforme, urticaria, vasculitis and Stevens-Johnson syndrome (SJS), develop in up to 25–33% of all Mp infections (1, 2). SJS associated with Mp infection is commonly observed in children, while adult SJS is caused mainly by drugs (3). Adult SJS associated with Mp infection has seldom been reported (4, 5). Here, we report 2 adult SJS patients with Mp infection and drug reaction, with possible synergistic effects on the development of SJS.

## CASE REPORTS

**Patient 1.** A 33-year-old man visited our hospital with ocular and oral lesions. He had a high-grade fever, general fatigue and nasal discharge, for which he had been prescribed diclofenac and L-carbocysteine by his doctor one day after the appearance of symptoms. On the following day, he had a painful throat and eyes, and was admitted to our hospital. Physical examination revealed hyperaemic conjunctivae, corneal erosions and pseudomembranous formation. Erosions on the buccal mucosa and ulcerations on the lips were also observed. No cutaneous lesions were seen. Laboratory tests revealed leukocytes  $13.3 \times 10^9/l$  and C-reactive protein (CRP) 7.1 mg/dl (normal  $<0.3$ ). Liver func-

tion tests were within normal limits. Human immunodeficiency virus (HIV) infection was negative and no adenovirus antigen was detected in the conjunctivae. Herpes simplex virus (HSV) antigen on the lip was negative. On admission, a titre of particle agglutination (PA) test for Mp was 1:320 (normal  $<40$ ). No abnormal findings were seen on chest X-ray. A skin specimen could not be obtained because the patient declined biopsy of the labial lesions. Atypical SJS without appearance of skin lesions was suspected. Lymphocyte transformation test (LTT) was performed to identify culprit drugs on admission (6, 7). The LTT for diclofenac was positive (stimulation index level 2.56 (positive  $>1.80$ )). The patient was treated with oral prednisolone, 40 mg daily, and a glucocorticoid eye drop. The prednisolone was tapered gradually. A 4-fold reduction in PA titre was found 4 weeks after onset.

**Patient 2.** A 59-year-old man was referred to our hospital because of a high-grade fever and mucosal lesions. He had been treated with loxoprofen and clarithromycin for fever and sore throat for 4 days before presentation. The symptoms persisted and he noticed labial and oral lesions. On examination, his temperature was 40°C, and bilateral conjunctivitis with pseudomembranous formation, corneal erosions (Fig. 1A), haemorrhagic appearance of the lips, and erosions on the buccal mucosa (Fig. 1B) were observed. Erosions were seen on the glans penis. Several scattered macules with bullae were also observed on the trunk and upper extremities (Fig. 1C). Laboratory findings on admission showed leukocytes  $6.3 \times 10^9/l$  and a CRP level of 18.0 mg/dl. Mild liver dysfunction was detected. A PA titre for Mp was 1:20,480 after admission, and then significantly decreased. Adenovirus antigens in the conjunctivae and HSV antigen on the lip were negative. Chest X-ray showed mild infiltrative shadowing on the right lower lung field. The LTT for loxoprofen was positive (stimulation index level 4.57)

(6, 7). Histological examination of a biopsy specimen of an erythematous macule on the abdomen revealed epidermal necrosis and a mild lymphocytic infiltration in the upper dermis (Fig. 1D). A diagnosis of atypical SJS was made, and treatment with oral prednisolone, 60 mg daily, and a glucocorticoid eye drop were initiated. The erythematous rash resolved, and then the oral lesions steadily improved. The infiltrative shadow on the chest

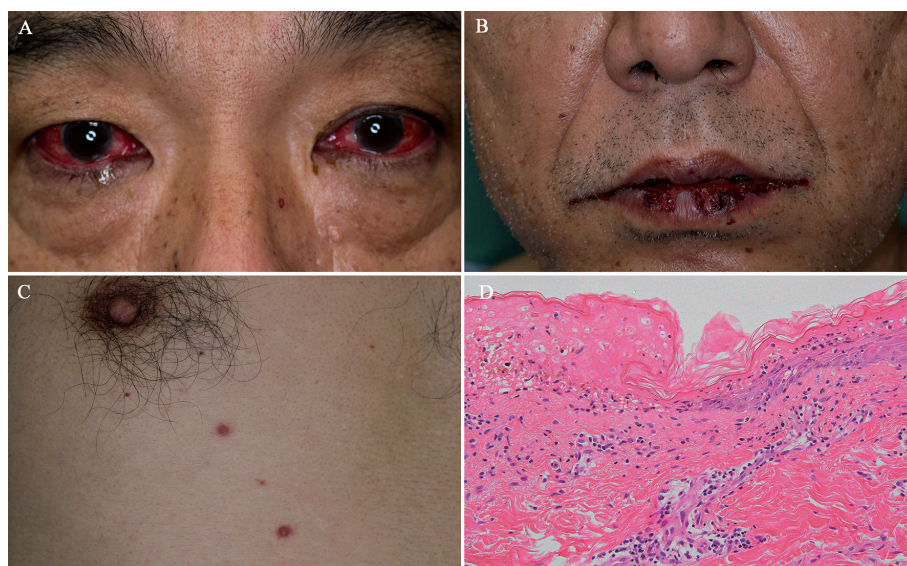


Fig. 1. Case 2 (A) Bilateral conjunctivitis with pseudomembranous formation. (B) Haemorrhagic scales on the lip. (C) Several scattered macules with bullae on the trunk. (D) Epidermal necrosis with a mild lymphocytic infiltration in the dermis (haematoxylin and eosin (H&E) stain; original magnification  $\times 100$ ).

X-ray disappeared. The LTT for loxoprofen became negative 6 months after disease onset (Table S1<sup>1</sup>). This case has been described in part elsewhere (8).

At the 1-year and 2-year follow-up of patients 1 and 2, respectively, no sequelae were detected.

## DISCUSSION

In adult SJS, drug reactions, rather than infections, have been emphasized as the main causative agent; therefore, intensive investigation for the culprit drug is carried out (9). The co-involvement of infectious agents might be overlooked in the clinical setting in adult patients with SJS. In children, Mp infection has been postulated as the most common implicated factor for the development of SJS (10). The characteristics of paediatric SJS associated with Mp infection are severe mucocutaneous involvements, such as oral ulcers, and keratoconjunctivitis, in the absence of skin lesions. In this regard, atypical SJS cases have been reported as Fuchs syndrome (4, 11), Mp-associated mucositis (12, 13), and incomplete SJS (14).

The clinical characteristics of our 2 patients were similar to those observed in paediatric SJS associated with Mp infection. The results of our serological examination showed significant alterations in Mp antibody titres in the 2 cases, with infiltrative shadowing on the X-ray in 1 case. Thus, it is clear that the preceding Mp infection contributed to the development of SJS in these 2 cases. In addition, drugs were given before the appearance of mucosal lesions in these 2 cases. LTT was performed to determine the causative drug and the results were positive in both cases. Therefore, the involvement of drug reactions was suspected in our atypical SJS adult patients. Although challenge tests could not be performed because the Committee of Severe Cutaneous Adverse Drug Reactions advises against the use of these tests, no positive LTT levels for diclofenac or loxoprofen in healthy individuals were observed with our method, which supports the involvement of a drug reaction in the present cases. Although LTT levels cannot predict whether sensitization leads to clinical symptoms, it has been shown that strong immune reactivity is frequently associated with clinical symptoms (6), and LTT needs to be carried out at the acute stage of SJS to avoid false-negative results (7). In the present cases, LTTs were performed at the acute stage. Therefore, it is likely that the interaction between Mp infection and drug reaction with the involvement of drug-specific T cells might have played an important role in the appearance of SJS in both patients.

Although the involvement of Mp infection in the appearance of SJS has not been clearly shown, Mp infection might affect the immune response in the initial

stage of development of SJS, thereby contributing to the atypical clinical manifestations of SJS. It remains unknown why SJS lesions in Mp-infected patients are confined to the mucous membranes in the immune-mediated process. The limited severe inflammatory cellular infiltration around the sites of infection might have prevented dissemination of the pathogens. In addition, molecular mimicry, with similarities between Mp proteinaceous adhesions and certain specific antigens in mucous membranes, has been hypothesized (1).

On the other hand, we showed previously that regulatory T cells (Treg) are profoundly impaired in SJS compared with those in other severe drug eruptions, such as drug-induced hypersensitivity syndrome (15). Given that Tregs recognize mycoplasma through toll-like receptor (TLR)-2 and modify their function, the suppressive function of Treg might be temporarily impaired in association with Mp infection (16, 17). The preceding Mp infection might provide a favourable milieu for the expansion of drug-specific effector T cells, thereby facilitating drug reactions despite the short-term drug administration. In support of this, the positive LTT that was performed at the initial stage of the disease became negative after complete resolution of the illness in the second case.

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