



# Multiple drug sensitization syndrome: A distinct phenotype associated with unrecognized *Mycoplasma pneumonia* infection

Yumi Aoyama, MD, PhD,<sup>a,b</sup> Fumihisa Sawada, MD,<sup>a,b</sup>  
Eiichi Makino, MD, PhD,<sup>a,b</sup> and Tetsuo Shiohara, MD, PhD<sup>c</sup>  
*Okayama, Kurashiki, and Tokyo, Japan*

**Key words:** adverse drug reaction; lymphocyte transformation test; multiple drug sensitization syndrome; *Mycoplasma pneumonia*.

## INTRODUCTION

Many adverse drug reactions (ADRs), including Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), are thought to be caused by delayed-type, cell-mediated immune reactions to a single drug or its related compounds. The term *multiple drug hypersensitivity syndrome* (MDHS) has been used to describe patients who show delayed-type, cell-mediated immune reactions to 2 or more chemically distinct drugs.<sup>1</sup> Despite the seemingly low prevalence of MDHS, these cases pose the fear of progressing to more severe and widespread forms of ADRs unless the culprit drugs are withdrawn. Thus, it is important to identify patient factors that could increase the risk of multiple drug hypersensitivity (MDH).

Although MDHS was initially defined based on a detailed case history alone or skin tests,<sup>2</sup> a recent study clearly shows that MDHS can be most efficiently proven by an *in vitro* lymphocyte transformation test (LTT).<sup>3,4</sup> Interestingly, sporadic case reports described that MDH or drug reactions were observed associated with *Mycoplasma pneumoniae* (MP) infection.<sup>5-7</sup> Indeed, there is mounting evidence suggesting that such infections create a favorable milieu for the initiation and progression of ADRs by abrogating regulatory T-cell (Treg) function.<sup>8,9</sup>

### Abbreviations used:

|          |   |
|----------|---|
| ADRs:    | adverse drug reactions                              |
| LTT:     | lymphocyte transformation test                      |
| MDH:     | multiple drug hypersensitivity                      |
| MDHS:    | multiple drug hypersensitivity syndrome             |
| MP:      | <i>Mycoplasma pneumoniae</i>                        |
| PA:      | particle agglutination                              |
| SJS/TEN: | Stevens-Johnson syndrome/toxic epidermal necrolysis |
| Tregs:   | regulatory T cells                                  |

We recently experienced a patient with MP infection who subsequently developed a morbilliform eruption 10 days after starting therapy. We also present a comprehensive review of all cases of MDHS previously described in the English- and Japanese-language literature.

## CASE SERIES

### Case 1

A 49-year-old woman with no medical history of drug eruptions presented with a 4-day history of erythematous rashes. Ten days before skin eruptions, therapy with loxoprofen sodium and garenoxacin was started for mild upper respiratory symptoms with low-grade fever. On day 4 of her medication use, the eruption began with pruriginous

From the Department of Dermatology, General Medical Center, Kawasaki Medical School, Okayama<sup>a</sup>; Department of Dermatology, Kawasaki Medical School, Kurashiki<sup>b</sup>; and Department of Dermatology, Kyorin University School of Medicine.<sup>c</sup>

Funding sources: This work was supported by a grant from the Ministry of Health, Labour and Welfare (Research for Intractable Diseases matching fund subsidy [H26-081]), and a Ministry of Education, Culture, Sports, Science and Technology.

Conflicts of interest: None declared.

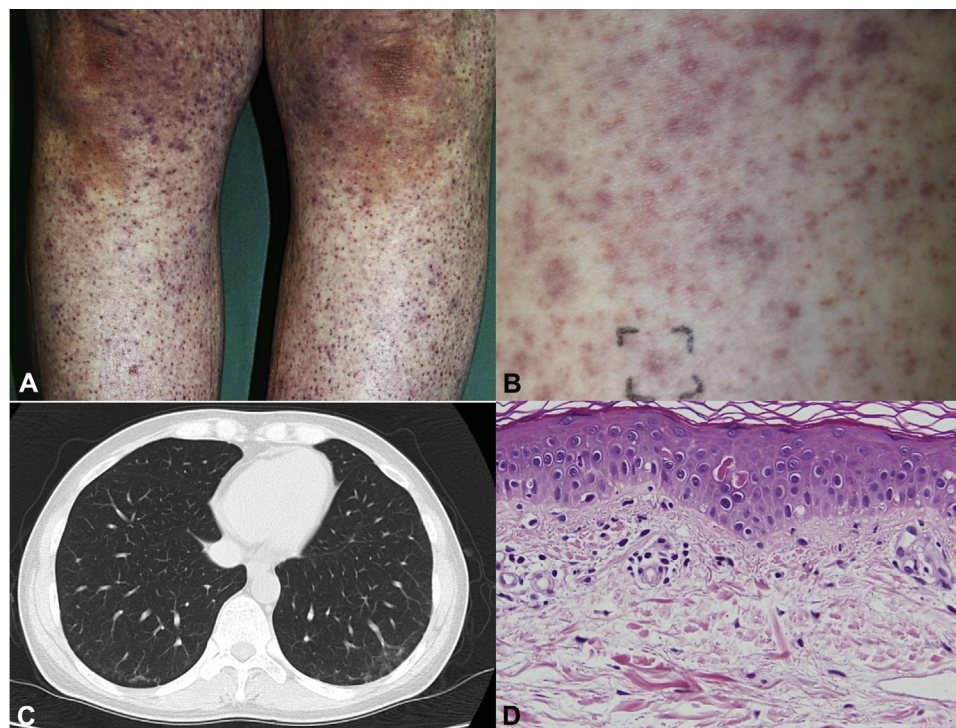
Correspondence to: Yumi Aoyama, MD, PhD, Dermatology, Kawasaki Medical Center, 2-6-1 Nakasange kitaku Okayama

City, Okayama 700-8505, Japan. E-mail: [ymaoyama@med.kawasaki-m.ac.jp](mailto:ymaoyama@med.kawasaki-m.ac.jp).

JAAD Case Reports 2017;3:301-5.  
2352-5126

© 2017 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<http://dx.doi.org/10.1016/j.jidcr.2017.03.005>



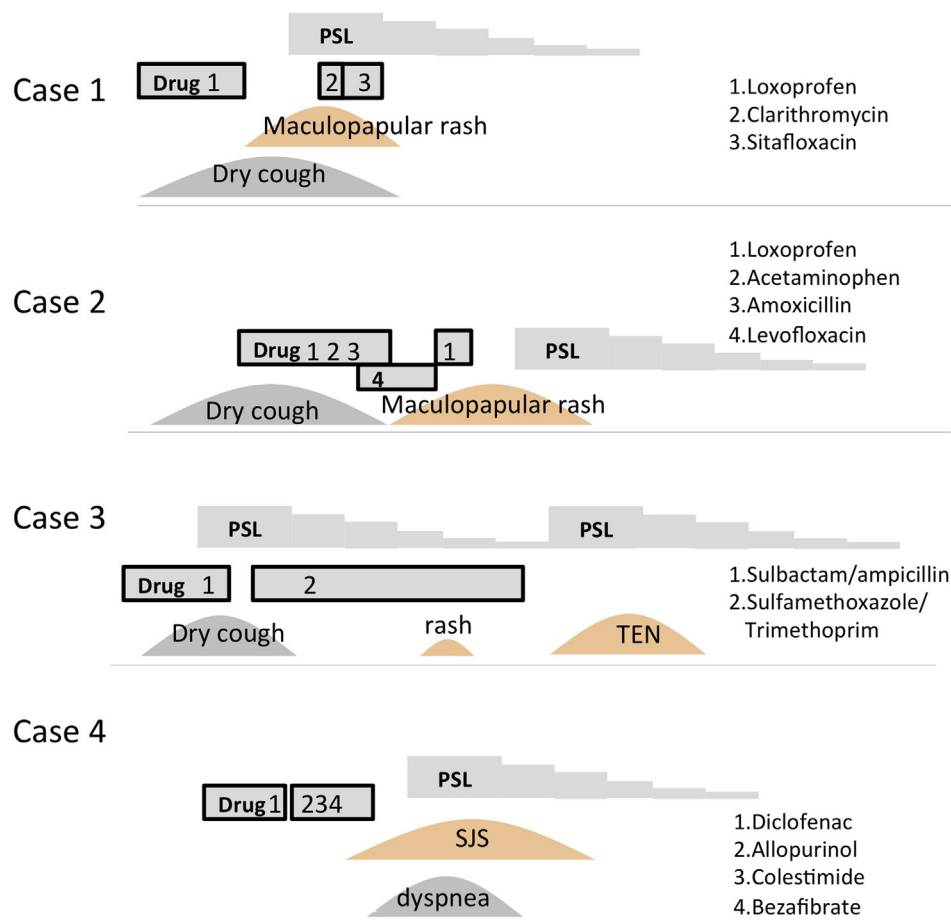
**Fig 1.** Clinical and histopathologic findings. **A**, Purplish erythema diffusely distributed to the lower extremities. **B**, Closer view of the purplish erythema. **C**, Computed tomography scan of the chest shows bilateral pulmonary homogeneous ground-glass opacity. **D**, Scant basal vacuolar change with focal necrosis of keratinocyte, dermal edema, and a mild superficial perivascular lymphocyte infiltrate. (**D**, Hematoxylin-eosin stain.)

morbilliform exanthema on her axilla and then spread to the entire body. The patient was admitted to our hospital under suspicion of drug eruptions, and these drugs were withdrawn. Physical examination found confluent, morbilliform, or purplish erythema on her cheeks, trunk, and proximal extremities (Fig 1, A and B) associated with painful lingual erosions. Laboratory data were as follows: white blood cell count of  $2620/\mu\text{L}$  with 39% of neutrophils and 50% of lymphocytes; platelet,  $11.1 \times 10^4/\mu\text{L}$ ; a titer of particle agglutination (PA) test for *MP*, 1:2560 (normal,  $<40$ ), suggestive of an acute infection with *MP*. Computed tomography scan of the chest was compatible with pulmonary involvement of *MP* infection (Fig 1, C). A skin biopsy found a mild perivascular infiltrate and scattered necrotic keratinocytes (Fig 1, D). A diagnosis was made of a morbilliform drug eruption associated with *MP* infection. The patient was treated with 40 mg/d of prednisolone because of the concern for progression to SJS. Prolonged pulmonary involvement was initially treated with clarithromycin, followed with sitafloxacin (Fig 2). Symptoms resolved completely within 14 days. Positive LTT reactions to loxoprofen sodium were repeatedly detected on the 21st day and

1.5 years after onset, whereas those to clarithromycin and sitafloxacin were only detected less than 100 days after onset.

#### Cases from review of the literature

In addition to these cases, a comprehensive MEDLINE and Japan Medical Abstract Society search covering the period from 2007 to 2016 was performed to identify published case reports displaying MDHS using the term *multiple hypersensitivity and skin rash with the exclusion of DiHS/DRESS (drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms)*. We identified 3 additional cases of MDHS in the literature<sup>5,10,11</sup>; several cases without available information on antecedent or underlying viral and *MP* infections were excluded. Detailed information and clinical course of the cases are shown in Table I and Fig 2. The most common symptoms were maculopapular rashes ( $n = 3$ ; 75%), SJS/TEN ( $n = 2$ ; 50%), fever ( $n = 4$ ; 100%), cough ( $n = 3$ ; 75%), and dyspnea ( $n = 3$ ; 75%). The site of involvement was the extremities in nearly all cases ( $n = 4$ ) and trunk in 3 cases, whereas mucous membrane was involved in 3 cases.



**Fig 2.** Clinical course of cases listed in Table I in relation to their drug intake. PSL, Prednisolone.

In case 4, the authors concluded that the SJS could be caused by allopurinol based on the positive LTT rather than an infectious process: both PA and complement fixation titers were negative at onset, but repeated measurements of PA found seroconversion (1:40) on day 31, which subsequently increased to 1:160 on day 86, suggesting that *MP* infection would have occurred at onset of drug eruption or near the day of the initial presentation.

Most importantly, all cases, except case 4, had antecedent *MP* infection in common, and rashes developed 4 to 20 days after drug ingestion. In all cases, *MP* infection was confirmed by a significant increase in PA and complement fixation titers for *MP*. Three of the 4 cases had at least 1 mucosal surface involved, with 1 case having 2 mucosal surfaces involved (case 4). The skin manifestations ranged from urticarial rashes to SJS/TEN: of note, 2 of the 4 cases progressed to severe ADRs, such as SJS/TEN, suggesting the significantly greater propensity to progress to severe ADRs. LTT was repeatedly

performed on different occasions in cases 3 and 4. Most of positive LTT reactions persisted within 100 days after onset. All cases received systemic corticosteroids at 30 to 50 mg/d, followed by the gradual dose reduction over 21 to 35 days in cases 1, 2, and 4 and 30 weeks in case 3. All cases made a full recovery without any short- and long-term sequelae.

## DISCUSSION

Skin manifestations are reported to occur in 8% to 33% of all patients infected with *MP*.<sup>7</sup> Because *MP* infection may itself present with fever, rash, and extracutaneous manifestations and, therefore, may confound the role of drug hypersensitivity in the development of skin manifestations, it is quite difficult to distinguish between *MP*-induced exanthema and drug-induced rash, solely on clinical grounds. Although still somewhat controversial, *MP* infection would serve to predispose individuals to develop drug hypersensitivity reactions by lowering the activation threshold of drug-specific effector T cells, probably owing to dysfunction of Tregs.<sup>12</sup>

Table I. Case characteristics

| Case no. | Age, y/sex              | Diagnosis/<br>antecedent<br>MP infection | Initial cutaneous<br>manifestations<br>(L or G)                           | Extracutaneous<br>manifestation        | Medication                        | Onset of skin<br>reaction after<br>culprit drug<br>intake | LTT (SI)<br>(positive >1.8) |        | Therapy for the<br>disease  | Disease<br>outcome    | Study                        |
|----------|-------------------------|--|---|--|-----------------------------------|---|-----------------------------|--------|---|-----------------------|------------------------------|
|          |                         |  |   |  |                                   |   | <100 d                      | >100 d |   |                       |                              |
| 1        | 49/F<br>present<br>case | Maculopapular<br>rash/yes                | Stomatitis (L),<br>Maculopapular<br>rash (G),<br>Purplish<br>erythema (L) | Fever, cough,<br>pneumonia             | Loxoprofen                        | 10 days   | 8.5                         | 2.4    | Oral prednisolone<br>40 mg/d  | Complete<br>remission | Current<br>case              |
|          |                         |  |   |  | Clarithromycin                    | NA*   | 2.6                         | 1.1    |   |                       |                              |
|          |                         |  |   |  | Sitafloxacin                      | NA*   | 2.5                         | 1.8    |   |                       |                              |
|          |                         |  |   |  | Garenoxacin                       | 10 d  | 1.7                         | NT     |   |                       |                              |
| 2        | 25/F                    | Maculopapular<br>rash/yes                | Urticaria (G),<br>Maculopapular<br>rash (G)                               | Fever, cough,<br>arthralgia            | Loxoprofen                        | 6 d   | 2.8                         | NT     | Oral prednisolone<br>30 mg/d  | Complete<br>remission | Takeo<br>et al <sup>10</sup> |
|          |                         |  |   |  | Acetaminophen                     | 5 d   | 12.2                        | NT     |   |                       |                              |
|          |                         |  |   |  | Amoxicillin                       | 5 d   | 1.9                         | NT     |   |                       |                              |
|          |                         |  |   |  | Levofloxacin                      | 4 d   | 3                           | NT     |   |                       |                              |
| 3        | 47/F                    | TEN/yes                                  | Maculopapular<br>rash (G),<br>Atypical target<br>lesion (G)               | Fever, cough,<br>dyspnea,<br>pneumonia | Sulbactam/ampicillin              | 20 d  | NT                          | 4.9    | Oral prednisolone<br>50 mg/d, plasma<br>exchange                        | Complete<br>remission | Gomi<br>et al <sup>11</sup>  |
|          |                         |  |   |  | Sulfamethoxazole/<br>Trimethoprim | 9 d   | 0.8                         | 3.8    |   |                       |                              |
|          |                         |  |   |  | Ceftriaxone                       | 12 d  | 1.1                         | NT     |   |                       |                              |
|          |                         |  |   |  | Ciprofloxacin                     | 12 d  | 0.8                         | NT     |   |                       |                              |
|          |                         |  |   |  | Diclofenac                        | 15 d  | 3.5                         | NT     |   |                       |                              |
| 4        | 37/M                    | SJS/serologically<br>positive            | Oral and genital<br>erosion (L),<br>Acral erythema and<br>bulla (L)       | None                                   | Allopurinol                       | 11 d  | 2.4                         | 1.9    | Steroid pulse<br>therapy<br>(1g × 3 d), oral<br>prednisolone<br>50 mg/d | Complete<br>remission | Kubota<br>et al <sup>5</sup> |
|          |                         |  |   |  | Colestimide                       | 11 d  | 11.4                        | 2.4    |   |                       |                              |
|          |                         |  |   |  | Bezafibrate                       | 11 d  | 1.9                         | 1.9    |   |                       |                              |
|          |                         |  |   |  | Amoxicillin                       | NA*   | NT                          | 1.5    |   |                       |                              |

G, Generalized; L, localized; NA, not applicable; NT, not tested.

\*Drugs sensitized after onset of cutaneous lesions.

Our observation that all previously reported MDHS cases with available information on viral and *MP* infection were associated with *MP* infection may give an important clue as to the unique features of *MP*-induced drug rash. Further studies of a large series of cases will determine whether MDHS could be one of unique features of drug eruptions associated with *MP* infection.

There are some possible mechanisms acting independently or together that may commit an effector T cell population to respond to multiple medications. One mechanism is the defect of Tregs induced by *MP* infection. MDHS, however, cannot be solely explained by such a functional defect of Tregs, because, in the LTT reaction, depletion of Tregs from peripheral blood mononuclear cells is found to enhance the reaction but not induce MDH.<sup>13</sup>

Another possibility is that MDH could result from activation of cross-reactive effector T cells that can respond to multiple medications. *MP*-specific T cells could cross-react with multiple medications presented by the peptide-HLA complex on the surface of an antigen-presenting cell, as demonstrated in Epstein-Barr virus infection<sup>9</sup>: nevertheless, the intensity of positive LTT reactions became decreased with time in case 1, suggesting that this type of sensitization may not be necessarily lifelong.

In all cases, the introduction of culprit drugs preceded the development of rashes by 4 to 20 days, making it more likely that these drugs played a central role. However, clarithromycin and sitafloxacin were introduced 2 to 3 days after the development of maculopapular rashes in case 1, which casts doubt on their contribution to the development of these rashes. Our observation that positive LTT reactions to all of the drugs used were not necessarily detected greater than 100 days after clinical resolution in case 1 suggested that MDH could be transiently observed immediately after and during the development of immune responses associated with *MP* infection. *MP* infection could serve to enhance the activation of drug-specific T cells by abrogating Treg function or cause de novo sensitization to the drugs used for treatment for *MP* infection, like clarithromycin, in case 1. Another possible explanation for MDH is that *MP* infection could result in a decrease in the threshold for activation of drug-specific effector T cells with a low affinity to the drug that are otherwise unresponsive to the drugs in the setting of no antecedent infection. Because any treatment including antibiotics cannot eliminate the organism from respiratory secretions<sup>7</sup> and severe skin symptoms do not respond well to the treatment,

antibiotic therapy that may cause MDHS in some patients is not recommended for *MP* patients with eruptions. Thus, patients presenting with a history of cough, dyspnea, and fever together with MDH should be screened for *MP* infection.

This report raises awareness that ADRs associated with *MP* infection can present with MDHS and suggests that this phenotype may often progress to severe forms of ADRs if the withdrawal of the culprit drugs is delayed. We recommend that any patient with drug eruptions exhibiting MDHS, regardless of the presence of respiratory symptoms, be suspected of underlying or preceding *MP* infection even if asymptomatic. To minimize the risk of unnecessary immunologic sensitization to multiple medications in the setting of *MP* infection, LTT should be used to predict potential reactivity to multiple medications in *MP* patients.

#### REFERENCES

1. Chiriac AM, Demoly P. Multiple drug hypersensitivity syndrome. *Curr Opin Allergy Clin Immunol*. 2013;13:323-329.
2. Sullivan TJ, Remedios C, Ong MD, Gilliam LK. Studies of the multiple drug allergy syndrome. *J Allergy Clin Immunol*. 1989; 83:270.
3. Gex-Collet C, Helbling A, Pichler WJ. Multiple drug hypersensitivity—proof of multiple drug hypersensitivity by patch and lymphocyte transformation tests. *J Invest Allergol Clin Immunol*. 2005;15:293-296.
4. Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. *Allergy*. 2004;59:809-820.
5. Kubota Y, Nakamura J, Nakayama J. Stevens-Johnson syndrome due to allopurinol with positive DLST to several other drugs. *Jpn J Dermatol*. 2006;116:927-934. (in Japanese).
6. Kurata M, Kano Y, Sato Y, Hirahara K, Shiohara T. Synergistic effects of mycoplasma pneumoniae infection and drug reaction on the development of atypical Stevens-Johnson in adults. *Acta Derm Venereol*. 2016;96:111-113.
7. Schalock PCDJ. Mycoplasma pneumoniae-induced cutaneous disease. *Int J Dermatol*. 2009;48:673-681.
8. Takahashi R, Kano Y, Yamazaki Y, Kimishima M, Mizukawa Y, Shiohara T. Defective regulatory T cells in patients with severe drug eruptions: timing of the dysfunction is associated with the pathological phenotype and outcome. *J Immunol*. 2009; 182:8071-8079.
9. White KD, Chung W-H, Hung S-I, Mallal S, Phillips EJ. Evolving models of the immunopathogenesis of T cell-mediated drug allergy: the role of host, pathogens, and drug response. *J Allergy Clin Immunol*. 2015;136:219-234.
10. Takeo N, Hatano Y, Yamamoto K, Shiota S, Fujiwara S. Case of mycoplasma pneumoniae infection with maculopapular-type eruptions due to acetaminophen. *J Dermatol*. 2013;40: 304-306. (in Japanese).
11. Gomi M, Shiraishi Y, Mitsuyama Y, et al. A case of toxic epidermal necrolysis during the course of a mycoplasma pneumoniae. *Clin Dermatol*. 2008;62:120-123. (in Japanese).
12. Shiohara T, Takahashi R, Ushigome Y, Kano Y. Regulatory T cells in severe drug eruptions. *Curr Immunol Rev*. 2014;10: 41-50.
13. Srinoulprasert Y, Pichler WJ. Enhancement of drug-specific lymphocyte proliferation using CD25(hi)-depleted CD3(+) effector cells. *Int Arch Allergy Immunol*. 2014;163:198-205.