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

Yumi Aoyama, MD, PhD,[a,b] Fumihisa Sawada, MD,[a,b]
Eiichi Makino, MD, PhD,[a,b] and Tetsuo Shiohara, MD, PhD[c]
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.[1] 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MDHS, these cases pose the fear of progressing to more severe and widespread forms of ADRs unless the culprit drugs are withdrawn.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,[2] a recent study clearly shows that MDHS can be most efficiently proven by an in vitro lymphocyte transformation test (LTT).[3,4] Interestingly, sporadic case reports described that MDH or drug reactions were observed associated with *Mycoplasma pneumoniae* (*MP*) infection.[5-7] 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.[8,9]

Abbreviations used:

ADRs:	adverse drug reactions
LTT:	lymphocyte transformation test
MDH:	multiple drug hypersensitivity
MDHS:	multiple drug hypersensitivity syndrome
MP:	*Mycoplasma pneumoniae*
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[a]; Department of Dermatology, Kawasaki Medical School, Kurashiki[b]; and Department of Dermatology, Kyorin University School of Medicine.[c]

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.

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

http://dx.doi.org/10.1016/j.jdcr.2017.03.005

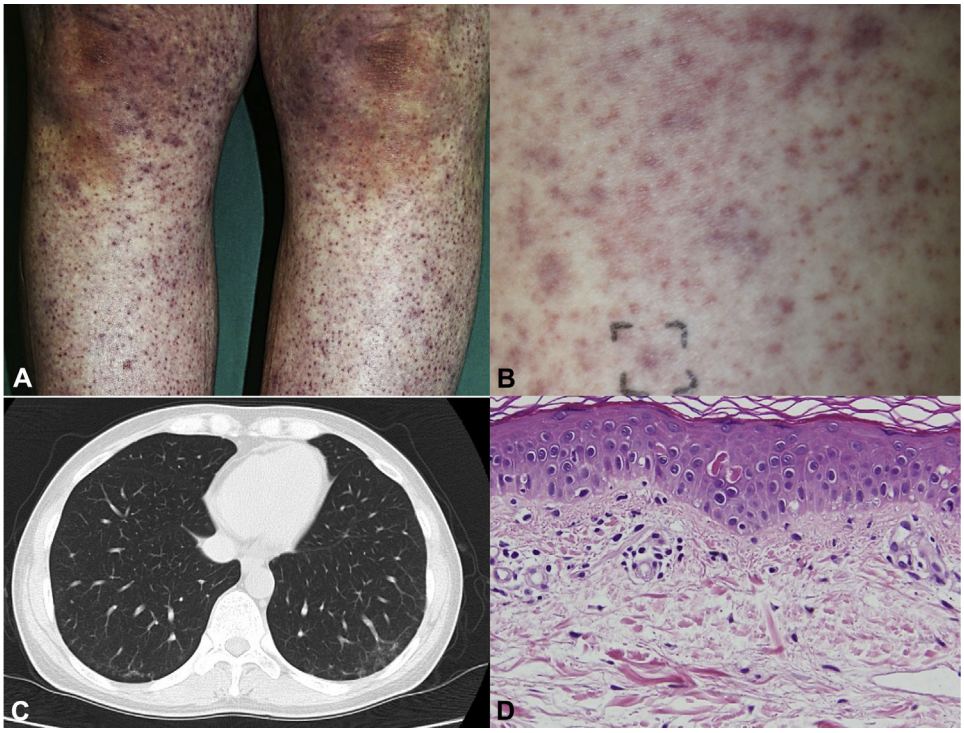

Fig 1. Clinical and histopathologic findings. **A**, Purplish erythema diffusely distributed to the lower extremities. **B**, Closer view of the purplish erythema. **C**, Computed tomography scan of the chest shows bilateral pulmonary homogeneous ground-glass opacity. **D**, Scant basal vacuolar change 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/μL with 39% of neutrophils and 50% of lymphocytes; platelet, 11.1 $\times$ 10^4/μL; 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[5,10,11]: 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.