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High occurrence of simultaneous multiple-drug hypersensitivity syndrome induced by first-line anti-tuberculosis drugs

Da Woon Sim, Hye Su You, Ji Eun Yu and Young-Il Koh*

ABSTRACT

Background: Multiple drug hypersensitivity syndrome (MDHS) results in treatment delay or failure and often results in severe drug hypersensitivity reactions. There are few reports of MDHS in response to anti-tuberculosis drugs; however, clinical information is scarce. Understanding the frequency and clinical characteristics of simultaneous MDHS against first-line anti-tuberculosis drugs in patients with non-severe drug hypersensitivity reactions is necessary.

Methods: We reviewed 27 patients with drug fever or maculopapular exanthem in response to first-line anti-tuberculosis drugs between January 2010 and June 2019. Drug fever or maculopapular exanthem occurred when isoniazid, rifampin, ethambutol, and pyrazinamide were administered simultaneously. Drug provocation tests for the 4 drugs were performed to identify the culprit drugs.

Results: All patients showed positive reactions to 1 or more drugs. MDHS was diagnosed in 13 (48%) patients, of whom 11 and 2 patients reacted to 2 and 3 drugs, respectively. In comparison to the patients with single-drug hypersensitivity, the patients with MDHS did not exhibit any differences in characteristics. Ethambutol and rifampin were the common drugs that induced a reaction, and the combination of these 2 drugs induced MDHS most frequently. Among the patients with MDHS, there were no differences between the drugs that caused drug fever and maculopapular exanthem. All patients with MDHS were successfully treated with alternative drugs.

Conclusions: Simultaneous MDHS may occur frequently in patients with drug fever or maculopapular exanthem caused by first-line anti-tuberculosis drugs, indicating the need to evaluate the allergy responses for all 4 drugs, even in patients without severe drug hypersensitivity. The combination of ethambutol and rifampin was the most common trigger that induced MDHS.

Keywords: Anti-tuberculosis drug, Delayed hypersensitivity reaction, Drug hypersensitivity, Drug provocation test, Multiple drug hypersensitivity

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INTRODUCTION

Drug hypersensitivity reaction (DHR) poses a significant public health problem.[1] In particular, multiple drug hypersensitivity syndrome (MDHS) influences the choice of drugs, resulting in a negative impact on the quality of medical care;[2] however, the occurrence is rare.[3] MDHS is defined as DHR to at least 2 chemically and pharmacologically distinct drugs.[3] MDHS differs from cross-reactivity, flare-up reactions of the drug reaction with eosinophilia and systemic symptoms syndrome, or multiple drug intolerance syndrome.[1,3,4] MDHS can be divided into simultaneous, sequential, and distant subtypes.[4] Human immunodeficiency virus infection[1,5] or systemic lupus erythematous[1] are risk factors for the development of MDHS, indicating that a disease or condition associated with immune dysregulation might contribute to the development of MDHS.

Tuberculosis is a major infectious disease caused by *Mycobacterium tuberculosis*, which is not only 1 of the top 10 diseases causing death worldwide but also the most common cause of death from a single infectious organism. The disease burden is quite substantial. According to a recent World Health Organization (WHO) report, tuberculosis occurred in 10 million patients and caused 1.2 million deaths in 2019 globally.[6] In Korea, tuberculosis remains a serious health problem with a high incidence rate, compared with that in other developed countries.[7,8] Tuberculosis may be associated with alterations in the cellular and humoral immune responses,[9,10] intensifying the development of DHR or MDHS. Tuberculosis treatment is initiated with first-line anti-tuberculosis drugs, such as isoniazid, rifampin, ethambutol, and pyrazinamide, for 2 months and then continued with isoniazid and rifampin for 4 months. Adverse drug reaction induced by any of the 4 drugs is common and results in various clinical manifestations.[11,12] Patients with tuberculosis may prematurely discontinue their medication owing to adverse drug reaction.[11,13] Approximately 60% of tuberculosis patients experience adverse drug reaction.[14] Roughly one-third of adverse drug reactions are DHR.[14] The 4 drugs are administered concomitantly in a combination treatment, which promotes the possibility of developing simultaneous MDHS. Several cases of MDHS associated with anti-tuberculosis drugs have been reported.[11,15,16] Additionally, in a few studies of DHR, such as drug fever,[17] maculopapular exanthem,[18] and drug reaction with eosinophilia and systemic symptoms syndrome[18,19] caused by anti-tuberculosis drugs, some patients with MDHS have been included.

MDHS may result in a treatment failure in tuberculosis, because the first-line anti-tuberculosis drugs cannot be used. However, if the culprit drugs are identified accurately, tuberculosis could be managed with alternative safe anti-tuberculosis drugs or through desensitization. One problem is that anti-tuberculosis drugs are administered simultaneously; therefore, it is difficult to identify the causative drugs based on a patient's medical history.[12,20] Tuberculosis occurs in the lungs and also in some extra-pulmonary sites; therefore, adverse drug reactions associated with anti-tuberculosis drugs are witnessed by doctors from various medical fields. We have frequently experienced MDHS cases associated with first-line anti-tuberculosis drugs in practice. Indeed, it has been reported that MDHS could develop more frequently in severe DHR.[21]

Here, we analyzed the frequency of simultaneous MDHS to first-line anti-tuberculosis drugs and the clinical characteristics of the patients. Only patients with drug fever or maculopapular exanthem were included because drug provocation tests can be safely performed and the investigation of MDHS in patients with non-severe DHR was the focus of this study.

METHODS

Patients

We performed a retrospective study to investigate MDHS caused by anti-tuberculosis drugs at a single tertiary care center. The data were obtained from electronic medical records. Patients admitted at our allergy division between January 2010 and June 2019 were included. We selected patients who developed drug fever or maculopapular exanthem following the administration of the

No.	Diagnosis	Fever	Exanthem	Blood eosinophils (/μL)	Culprit drug on provocation test				MDHS	Alternative treatment	Outcome
					INH	RFP	EMB	PZA			
1	Drug fever	Yes	No	630	Yes	No	Yes	Yes	Yes	Prothionamide, moxifloxacin, cycloserine	Success
2	Drug fever	Yes	No	80	No	Yes	No	No	No	INH, cycloserine, moxifloxacin	Success
3	Drug fever	Yes	Yes	400	No	No	Yes	No	No	INH, RFP	Success
4	Drug fever	Yes	Yes	0	No	Yes	No	Yes	Yes	INH, EMB, cycloserine	Success
5	Drug fever	Yes	Yes	2,610	No	Yes	Yes	No	Yes	INH, PZA, prothionamide, para-aminosalicylic acid	Success
6	Drug fever	Yes	Yes	90	Yes	Yes	Yes	No	Yes	Cycloserine, prothionamide, moxifloxacin	Success
7	Drug fever	Yes	No	10	No	No	Yes	Yes	Yes	INH, RFP	Success
8	Drug fever	Yes	Yes	1,100	No	Yes	Yes	No	Yes	INH, moxifloxacin, cycloserine prothionamide	Success
9	MPE	No	Yes	840	No	No	Yes	No	No	INH, RFP	Success
10	MPE	No	Yes	400	No	No	Yes	Yes	Yes	INH, RFP	Success
11	MPE	No	Yes	400	Yes	No	Yes	No	Yes	RFP, PZA, moxifloxacin, cycloserine	Success
12	MPE	No	Yes	300	No	No	No	Yes	No	INH, RFP	Success
13	MPE	No	Yes	100	No	No	No	Yes	No	INH, RFP	Success
14	MPE	No	Yes	200	No	Yes	Yes	No	Yes	INH, PZA, moxifloxacin	Success
15	MPE	No	Yes	230	No	No	Yes	No	No	INH, RFP	Success
16	MPE	No	Yes	400	Yes	No	Yes	No	Yes	RFP, PZA, levofloxacin	Success
17	MPE	No	Yes	130	No	Yes	No	No	No	INH, cycloserine, moxifloxacin	Success

(continued)

No.	Diagnosis	Fever	Exanthem	Blood eosinophils (/μL)	Culprit drug on provocation test				MDHS	Alternative treatment	Outcome
					INH	RFP	EMB	PZA			
18	MPE	No	Yes	2,470	No	Yes	Yes	No	Yes	INH, PZA, levofloxacin	Success
19	MPE	No	Yes	370	No	Yes	Yes	No	Yes	INH, PZA, moxifloxacin, cycloserine	Success
20	MPE	No	Yes	800	No	Yes	No	No	No	INH, EMB, PZA, moxifloxacin	Success
21	MPE	No	Yes	80	No	Yes	No	No	No	EMB, levofloxacin, cycloserine	Success
22	MPE	No	Yes	410	Yes	Yes	No	No	Yes	Cycloserine, prothionamide, levofloxacin	Success
23	MPE	No	Yes	1,800	No	Yes	No	No	No	INH, EMB, moxifloxacin	Success
24	MPE	No	Yes	300	No	No	Yes	No	No	Unknown	Follow-up loss
25	MPE	No	Yes	900	No	No	Yes	No	No	INH, RFP	Success
26	MPE	No	Yes	1,040	No	No	Yes	No	No	INH, RFP	Success
27	MPE	No	Yes	590	Yes	No	No	No	No	EMB, PZA, Levofloxacin, Cycloserine	Success

Table 1. (Continued) Important individual data of patients. *EMB: ethambutol, INH: isoniazid, MDHS: multiple drug hypersensitivity syndrome, MPE: maculopapular exanthem, PZA: pyrazinamide, RFP: rifampin*

standard regimen of first-line anti-tuberculosis drugs (isoniazid, rifampin, ethambutol, and pyrazinamide). The culprit drugs were identified based on the drug provocation test.

Ethics approval

The present study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki. This study was approved by the Institutional Review Board. The need for informed consent was waived.

Diagnosis of drug fever, maculopapular exanthem, and MDHS

Drug fever is defined as a febrile response to the administration of anti-tuberculosis drugs, in the absence of other conditions that can be a reliable cause of the fever, which disappears within 72 h after ceasing drug administration. Skin rash or blood eosinophilia may accompany drug fever. Persistent systemic organ involvement is absent;[17,22,23] however, transient hepatic or renal abnormality could be present. Maculopapular exanthem is defined as erythematous macules and papules over the trunk and extremities without fever; it may be accompanied by blood eosinophilia. Persistent systemic organ involvement does not occur;[24] however, there can be a transient hepatic or renal abnormality. Patients with severe cutaneous adverse reactions, such as drug reaction with eosinophilia and systemic symptoms syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis, were excluded based on clinical and laboratory

Characteristics	Drug fever (n = 8)	Maculopapular exanthem (n = 19)
Age (median, range) (years)	66 (28–85)	63 (23–81)
Female (n, %)	5 (62)	11 (58)
Site of mycobacterium tuberculosis infection (n, %)		
Pulmonary tuberculosis	7 (88)	5 (26)
Extra-pulmonary tuberculosis	1 (12)	14 (74)
Allergic diseases (n, %)[a]	1 (13)	3 (16)
Previous drug allergy (n, %)	0 (0)	0 (0)
Current drug allergy		
Latency period (median, range) (days)	17 (10–62)	17 (3–94)
Fever (n, %)	8 (100)	0 (0%)
Exanthem (n, %)	5 (62)	19 (100)
Blood eosinophils (median, range) (/μL)	245 (0–2,610)	400 (80–2,470)
Aspartate aminotransferase (median, range) (U/L)	24 (15–194)	26 (15–128)
Alanine aminotransferase (median, range) (U/L)	19 (7–86)	22 (10–103)
Creatinine (median, range) (mg/dL)	0.7 (0.5–1.0)	0.7 (0.4–8.8)
Positive human immunodeficiency virus (n, %)[b]	0/7 (0)	0/15 (0)
Positive anti-nuclear antibody (n, %)[b]	2/4 (50)	3/10 (30)
Comorbidity (n, %)		
Hypertension	4 (50)	9 (47)
Chronic kidney disease	0 (0)	1 (5)
Diabetes Mellitus	2 (25)	3 (16)

Table 2. Characteristics of patients. a. Allergic diseases include one or more of asthma, rhinitis, atopic dermatitis, and food allergy b. The tests were performed in some patients
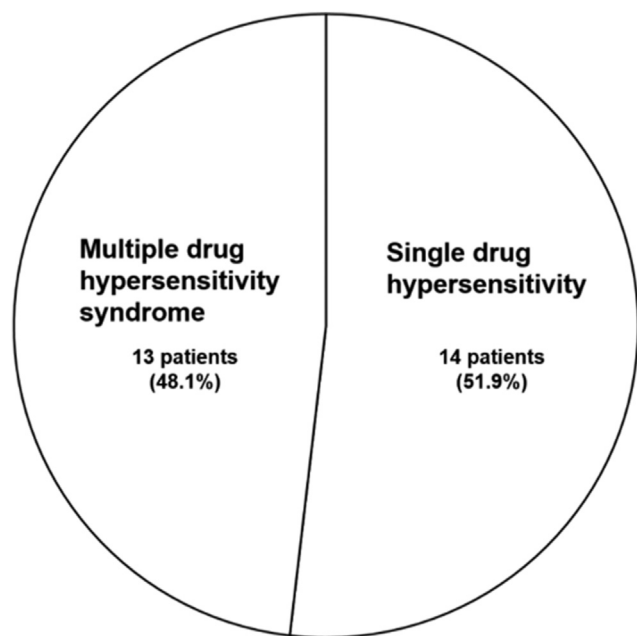
Fig. 1 Proportion of patients with multiple drug hypersensitivity syndrome

examination. MDHS was defined as having 2 or more culprit drugs that induce drug fever or maculopapular exanthem.[4]

Drug provocation test

Drug provocation test for the individual anti-tuberculosis drugs was performed with 1/10, 3/10, and full doses at 12 h intervals. The drugs were administered in the order of pyrazinamide, isoniazid, ethambutol, and rifampin, based on our personal experiences. The full dose was the therapeutic dose that the patient took during the tuberculosis treatment. Responses were monitored for 12 h following the administration of 1/10 or 3/10 dose and for 24 h following the full dose. If there were no reactions, we proceeded with a drug provocation test for the next drug. If a reaction occurred, the drug provocation test was discontinued, and the administration of the next drug was postponed until the symptoms disappeared.

Characteristics	Single (n = 14)	MDHS (n = 13)	p-value
Age (median, range) (years)	63 (33–79)	63 (23–85)	0.807
Female (n, %)	8 (57)	8 (62)	0.816
Site of mycobacterium tuberculosis infection (n, %)			0.085
Pulmonary tuberculosis	4 (29)	8 (62)	
Extra-pulmonary tuberculosis	10 (71)	5 (38)	
Allergic diseases (n, %)[a]	2 (14)	6 (46)	0.936
Previous drug allergy (n, %)	0 (0)	0 (0)	N.A.
Current drug allergy			
Latency period (median, range) (days)	16 (3- 94)	21 (10–66)	0.953
Fever (n, %)	2 (14)	6 (46)	0.070
Exanthem (n, %)	13 (93)	11 (85)	0.496
Blood eosinophils (median, range) (/μL)	350 (80–1,800)	400 (0–2,610)	0.564
Aspartate aminotransferase (median, range) (U/L)	25 (15-94)	26 (15-194)	0.211
Alanine aminotransferase (median, range) (U/L)	23 (12-39)	18 (7-103)	0.469
Creatinine (median, range) (mg/dL)	0.8 (0.5-8.8)	0.6 (0.4-0.9)	0.234
Positive human immunodeficiency virus (n, %)[b]	0/14 (0)	0/13 (0)	N.A.
Positive anti-nuclear antibody (n, %)[b]	2/8 (25)	3/6 (50)	0.334
Comorbidity (n, %)			
Hypertension	8 (57)	5 (39)	0.322
Chronic kidney disease	1 (7)	0 (0)	0.326
Diabetes Mellitus	4 (29)	1 (8)	0.163

Table 3. Comparisons of characteristics between single drug hypersensitivity and MDHS in all patients. *MDHS: multiple drug hypersensitivity syndrome. a. Allergic diseases include one or more of asthma, rhinitis, atopic dermatitis, and food allergy b. The tests were performed in some patients*
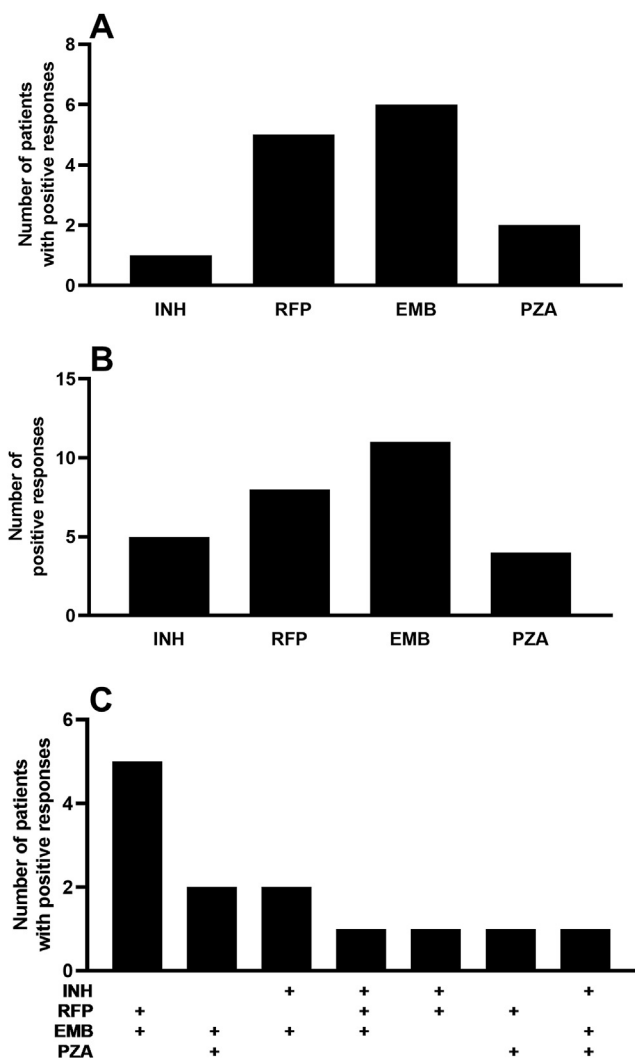
Fig. 2 Frequency of culprit drugs in patients with single-drug hypersensitivity (A) and multiple drug hypersensitivity syndrome (B and C). The frequency was expressed as the number of patients with positive responses in A and C and as the number of positive responses in B on drug provocation tests. EMB: Ethambutol; INH: Isoniazid; PZA: Pyrazinamide; RFP: Rifampin

Drug provocation test was considered positive if clinical manifestations of drug fever or maculopapular exanthem were present.

Statistical analysis

Data were presented as medians and ranges for continuous variables and as numbers and percentages for categorical variables. Means were subjected to the Mann–Whitney U test or to the chi-square test using SPSS software, version 20.0 (SPSS, Inc., Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

RESULTS

Characteristics of the patients

Eight patients with drug fever and 19 patients with maculopapular exanthem were included in the study (Table 1). In the group of patients with drug fever, the median age was 66 years old, and the proportion of females was 62%. Tuberculosis sites were the lungs in 7 patients and extra-pulmonary organs (small intestine) in 1 patient. None of the patients had allergic diseases, such as asthma, rhinitis, atopic dermatitis, or food allergy, or any prior drug allergies. Median latent time between the administration of the drug and the appearance of DHR was 17 days. Fever ranged from 37.9 to 40 °C. Cutaneous exanthem and blood eosinophilia ($>500/\mu L$) each occurred in 5 of the patients. Transient hepatitis (alanine aminotransferase $>$ upper limit of normal range) was observed in 3 patients, and there was no renal involvement. Human immunodeficiency virus infection and systemic lupus erythematous are risk factors for the development of MDHS;[1,5] therefore, human immunodeficiency virus and antinuclear antibody tests were performed in most of the patients. The results were negative in 7 patients who were tested for human immunodeficiency virus and presented no clinical evidence of human immunodeficiency virus infection. Antinuclear antibody was positive in 2 of 4 patients who were tested, but there was no clinical evidence of systemic lupus erythematous (Table 2).

In the group of patients with maculopapular exanthem, the median age was 63 years old, and the proportion of female patients was 58%. Tuberculosis sites were the lung in 5 patients and extra-pulmonary organs (small intestine, 5 patients; lymph nodes, 3 patients; meninges, 3 patients; urinary tract, 2 patients; and colon, 1 patient), in 14 patients. None of the patients had allergic diseases or prior drug allergies. Median latent time to the development of maculopapular exanthem was 17 days. No fever was noted. Blood eosinophilia occurred in 15 patients. Transient hepatitis was observed in 4 patients, and no renal involvement was found; however, 1 patient had an underlying chronic kidney disease. No positive results for human immunodeficiency virus were found in 15 patients who were tested. Antinuclear antibody

Characteristics	Drug fever (n = 6)	Maculopapular exanthem (n = 7)	p-value
Age (median, range) (years)	67 (28–85)	63 (23–81)	0.879
Female (n, %)	4 (67)	4 (57)	0.725
Site of mycobacterium tuberculosis infection (n, %)			0.135
Pulmonary tuberculosis	5 (83)	3 (43)	
Extra-pulmonary tuberculosis	1 (17)	4 (57)	
Allergic diseases (n, %)[a]	1 (17)	1 (14)	0.906
Previous drug allergy (n, %)	0 (0)	0 (0)	N.A.
Current drug allergy			
Latency period (median, range) (days)	21 (10–62)	21 (12–66)	0.836
Blood eosinophils (median, range) (/μL)	360 (0–2,610)	400 (200–2,470)	0.836
Aspartate aminotransferase (median, range) (U/L)	22 (15–194)	33 (21–128)	0.366
Alanine aminotransferase (median, range) (U/L)	11 (7–86)	20 (10–103)	0.295
Creatinine (median, range) (mg/dL)	0.7 (0.5–0.7)	0.6 (0.4–0.9)	0.534
Positive human immunodeficiency virus (n, %)[b]	0/6 (0)	0/6 (0)	N.A.
Positive anti-nuclear antibody (n, %)[b]	2/4 (50)	1/2 (50)	1.000
Comorbidity (n, %)			
Hypertension	3 (50)	2 (29)	0.725
Chronic kidney disease	0 (0)	0 (0)	N.A.
Diabetes Mellitus	1 (17)	0 (0)	0.335

Table 4. Comparisons of characteristics between drug fever and maculopapular exanthem in patients with multiple drug hypersensitivity syndrome. *a. Allergic diseases include one or more of asthma, rhinitis, atopic dermatitis, and food allergy b. The tests were performed in some patients*

was positive in 3 of 10 patients who were tested. There was no clinical evidence of human immunodeficiency virus infection or systemic lupus erythematous (Table 2).

Comparison between single-drug hypersensitivity and MDHS in all patients

Among the 27 patients with drug fever or maculopapular exanthem, MDHS was diagnosed in 13 (48%) patients (Fig. 1); 11 MDHS patients reacted to 2 drugs, and 2 patients had MDHS to 3 drugs (Table 1). There were 6 patients with drug fever and 7 with maculopapular exanthem.

MDHS patients did not exhibit any differences in age, sex, tuberculosis infection site, accompanying allergic disease, or prior drug allergy, compared with that in the 14 patients with single-drug hypersensitivity. No differences in the rate of occurrence of human immunodeficiency virus infection or systemic lupus erythematous were noted; however, the tests for human immunodeficiency virus and antinuclear antibody were not performed in all patients. In terms of current drug allergies, there were no differences in latency, fever, skin exanthem, blood eosinophilia, or transient hepatitis between the 2 groups (Table 3).

We aimed to compare the culprit drugs between the single-drug hypersensitivity and MDHS groups. In patients with single-drug hypersensitivity, the culprit drugs were ethambutol in 6 patients, rifampin in 5 patients, pyrazinamide in 2 patients, and isoniazid in 1 patient (Fig. 2A). In MDHS patients, 28 positive responses were observed, in which the culprit drugs were ethambutol in 11 responses, rifampin in 8 responses, isoniazid in 5 responses, and pyrazinamide in 4 responses (Fig. 2B). In particular, a combination of
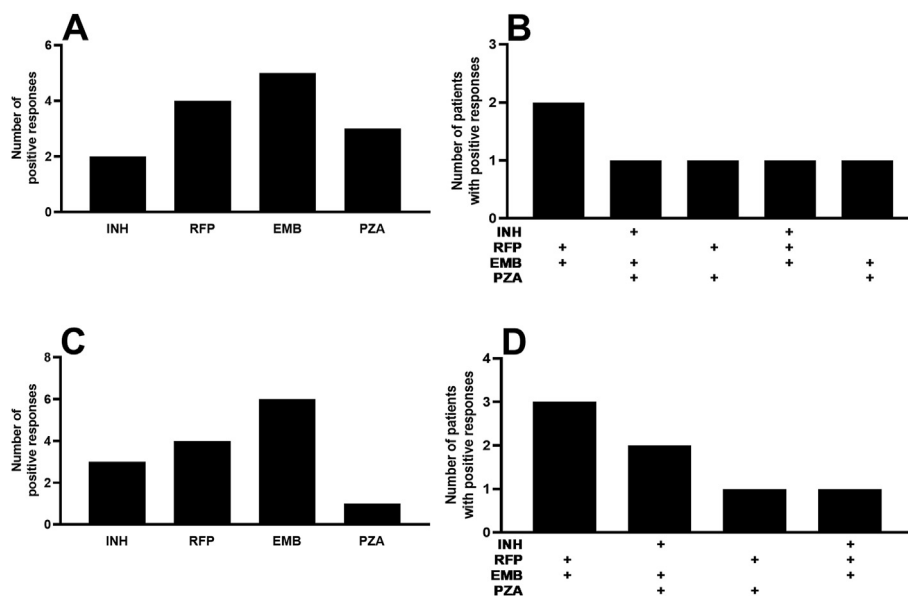
Fig. 3 Frequency of culprit drugs that induce drug fever (A and B) and maculopapular exanthem (C and D) in patients with multiple drug hypersensitivity syndrome. The frequency was expressed as the number of positive responses in A and C and as the number of patients with positive responses in B and D on drug provocation tests. EMB: Ethambutol; INH: Isoniazid; PZA: Pyrazinamide; RFP: Rifampin

ethambutol and rifampin was the most common culprit that induced MDHS (Fig. 2C).

Comparisons between drug fever and maculopapular exanthem in patients with MDHS

When the analysis was limited to MDHS patients, there were no differences in age, sex, tuberculosis infection site, accompanying allergic disease, prior drug allergy, human immunodeficiency virus infection, or systemic lupus erythematous between patients with drug fever and those with maculopapular exanthem. Clinical features of the current drug allergies did not differ between the 2 groups (Table 4).

In terms of culprit drugs, in patients with drug fever, the culprit drugs were ethambutol in 5 responses, rifampin in 4 responses, pyrazinamide in 3 responses, and isoniazid in 2 responses (Fig. 3A). The combination of ethambutol and rifampin was the most common culprit that induced MDHS (Fig. 3B). In patients with maculopapular exanthem, the culprit drugs were ethambutol in 6 responses, rifampin in 4 responses, isoniazid in 3 responses, and pyrazinamide in 1 response (Fig. 3C). The combination of ethambutol and rifampin was the most common culprit that induced MDHS (Fig. 3D).

Outcomes of the tuberculosis treatment

All patients were treated successfully with alternative anti-tuberculosis drugs, except 1 patient in the single-drug hypersensitivity group, who was lost during the follow-up. The medications were adjusted to be exclusively second-line drugs in 3 patients, a combination of first-line and second-line drugs in 13 patients, and a continuation of first-line drugs other than the culprit drugs in 9 patients. When the analysis was limited to MDHS patients, 3, 8, and 2 patients were treated with second-line drugs, the combination of first-line and second-line drugs, and first-line drugs, respectively (Table 1). There was no DHR to the second-line anti-tuberculosis drugs in any of the patients.

DISCUSSION

In this study, nearly half of the patients with drug fever or maculopapular exanthem in response to first-line anti-tuberculosis drugs were having simultaneous MDHS to isoniazid, rifampin, ethambutol, and/or pyrazinamide. Patients with MDHS did not exhibit any unique clinical characteristics compared with those of patients with single-drug hypersensitivity. The combination of ethambutol and rifampin was the most common culprit that induced MDHS. Clinical characteristics and

common culprit drugs did not differ between drug fever and maculopapular exanthem. Patients with MDHS were successfully treated with alternative anti-tuberculosis drugs for tuberculosis, and their outcomes did not vary compared with those in patients with single-drug hypersensitivity.

It has been reported that the prevalence of MDHS is very low. According to the literature about MDHS from a large database, MDHS was found in only 2.5% of patients with confirmed DHR.[3] In contrast, our current study showed that 48% of patients with DHR induced by first-line anti-tuberculosis drugs had MDHS. These findings suggest that the occurrence of MDHS in response to first-line anti-tuberculosis drugs may be much higher when compared with that in response to other drugs. However, the prevalence of MDHS is increased to 18% in patients with drug reaction with eosinophilia and systemic symptoms syndrome when compared with that in other patients,[21] suggesting that MDHS could occur more frequently in patients with severe DHR, compared with those with a milder form. This study did not include severe DHR; only drug fever or maculopapular exanthem patients were included. Collectively, even in non-severe DHR, the prevalence of MDHS to first-line anti-tuberculosis drugs may be substantially high. A recent study showed that 42.9% (6/14) of the patients with severe DHR, such as drug reaction with eosinophilia and systemic symptoms syndrome, were diagnosed with MDHS caused by anti-tuberculosis drugs.[19]

However, at this time, we do not know the reasons for the high occurrence of MDHS in response to anti-tuberculosis drugs. First, we considered the known risk factors, such as human immunodeficiency virus infection[1,5] and systemic lupus erythematous,[1] which did not differ between the single-drug hypersensitivity and MDHS groups; however, not all patients were tested. Additionally, the various clinical features did not differ between the 2 groups, which are indicative of no specific risk factors for the development of MDHS in this study. Therefore, it could be hypothesized that the *M. tuberculosis* infection in itself might be a possible risk factor for the development of MDHS. Tuberculosis infection is associated with some alterations in the cellular and humoral immune responses. HLA-DR + effector CD4$^+$ T cells, which are resistant to the suppression of regulatory T cells, may be expanded in patients with tuberculosis.[9] It is possible that DHR may develop more easily under the activated T cell microenvironment. Additionally, the level of regulatory T cells is reduced in patients undergoing tuberculosis treatment,[25,26] which may enhance the development of DHR in these patients. In terms of humoral immunity, IgG and IgM antibodies against the tuberculosis antigen are produced,[10] and immune complexes are elevated in patients with tuberculosis.[27] Therefore, tuberculosis infection might contribute in part to the development of MDHS via the enhancement of T cell or immune complex-mediated hypersensitivity reactions. Additional explanations for the higher occurrence of MDHS could be possible, as it is proposed that the fixed combination treatment, high drug dose, and long treatment period could be risk factors for the occurrence of MDHS.[4] The 4 anti-tuberculosis drugs are simultaneously administered once in a combination form,[12] and the possibility of sensitization to each drug could be the same. Doses of first-line anti-tuberculosis drugs are considered to be quite high.[12] Recently, high dose beta-lactam antibiotics were reported to increase the development of MDHS.[28] Tuberculosis treatment is continued for longer durations, compared with the treatment duration in other infectious diseases.[12] The prolonged treatment could increase the possibility of developing immune reactions to the drugs.

We wanted to evaluate which anti-tuberculosis drugs were the most frequent culprit in inducing MDHS. Ethambutol and rifampin were the most common causative drugs that induced MDHS in all patients; however, the same pattern was observed in patients with single-drug hypersensitivity. In addition, the combination of these 2 drugs most frequently induced MDHS. There are few studies on the frequency of anti-tuberculosis drugs inducing MDHS. Fang et al.[17] reported 11 cases of MDHS among 78 patients with drug fever caused by first- or second-line anti-tuberculosis drugs, and the combination of rifampin and rifapentine was the most common culprit. However, unlike the result from this study, ethambutol was not the common culprit drug in cases of single-drug hypersensitivity or MDHS in the previous study.[17] The reasons for the difference are not clear. There are
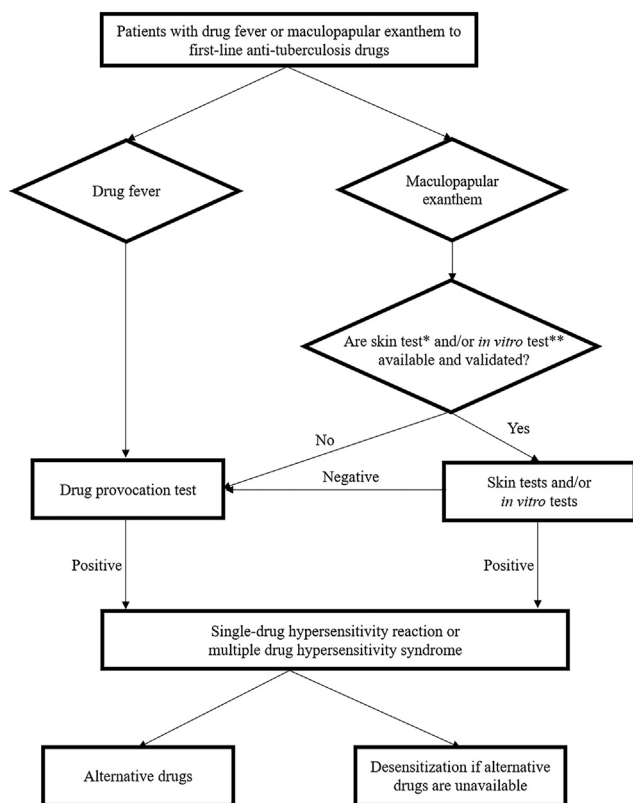
Fig. 4 A proposed algorithm for the evaluation and management of patients with drug fever or maculopapular exanthem in response to first-line anti-tuberculosis drugs. *Skin tests include patch test and delayed intradermal test. **In vitro* test means lymphocyte transformation test

few studies on the frequency of culprit anti-tuberculosis drugs in single-drug hypersensitivity. Based on the results from this study, we could recommend the order of drug administration for the drug provocation test with the 4 first-line anti-tuberculosis drugs. If there is an allergic reaction to 1 test drug, it is necessary to wait for several days until the symptoms are resolved before proceeding to test the other drugs. If a drug with low probability of positive reaction is tested early, the time required for completing the drug provocation test can be reduced. Ethambutol and rifampin are better options for later administration, compared with pyrazinamide and isoniazid. In addition, the occurrence of MDHS in response to anti-tuberculosis drugs could be higher than expected; therefore, doctors should consider performing drug provocation test for all the anti-tuberculosis drugs that are considered for simultaneous administration in patients with suspected DHR. One may wonder how frequently second-line drugs could induce hypersensitivity reactions. We tried to find confirmed cases of hypersensitivity

reactions to second-line drugs following drug provocation tests over the same study period between January 2010 and June 2019. Only 2 patients were found to have drug fever or maculopapular exanthema in response to second-line drugs. The hypersensitivity reaction occurred to moxifloxacin in 1 patient and cycloserine in another. There were no MDHS cases to second-line drugs. Additionally, no cases of hypersensitivity reactions to second-line drugs occurred, even in patients with single-drug hypersensitivity or MDHS to first-line drugs who had taken second-line drugs as safe alternatives. Therefore, in our experience, the frequency of hypersensitivity reactions to second-line drugs might be lower than that to first-line drugs, although further studies are needed.

We found favorable outcomes for the treatment of tuberculosis in all patients with MDHS in this study. In all patients, alternative anti-tuberculosis drugs were used to treat tuberculosis, based on the drug provocation test results. Therefore, we strongly recommend that doctors actively test for culprit drugs using allergy tests in patients suspected with DHR to anti-tuberculosis drugs. If alternative anti-tuberculosis drugs are not available, drug desensitization could be another option to treat tuberculosis;[18] however, this was not used in the patients included in this study.

Next, we wanted to assess whether clinical characteristics, including risk factors or culprit drugs, differed according to the type of Gell–Coombs hypersensitivity reaction in patients with MDHS. This study included patients with drug fever or maculopapular exanthem, which are established to be mediated through the type III immune complex[23,31] or type IV T cell hypersensitivity reaction,[22,31] respectively. There were no differences in the frequency of culprit drugs, risk factors, or other clinical features, between the patients with type III and IV hypersensitivity reaction, suggesting that the clinical pattern of MDHS may be similar between the humoral and cellular immunity.

Immunologic tests, such as skin tests or *in vitro* tests, are required to be performed for diagnosing MDHS;[32] however, this requirement is still under discussion. We agree with the need for these tests. However, in this study, the immunologic tests were not included because the drug fever is

type III hypersensitivity reaction,[23,31] and the skin and *in vitro* tests are not yet available for this. Only drug provocation test was used to identify the culprit drugs in patients with drug fever in the earlier study by Fang et al.[17] In patients with maculopapular exanthem, which is known to be type IV hypersensitivity reaction,[22,31] a patch test, delayed intradermal test, or lymphocyte transformation test could be used to determine the culprit drugs. However, even for the patch test, which has been employed for a long time, positive rates are only 10–40% for maculopapular exanthem; however, it is a little higher (32–64%) in patients with drug reaction with eosinophilia and systemic symptoms syndrome.[33] In addition, based on our experiences in clinical practice, the sensitivity of a patch test to anti-tuberculosis drugs appears to be much lower than the described rates. Therefore, we believe that the skin tests may not provide any information on the culprit drugs. The immunological tests effective for identifying anti-tuberculosis drugs are not established; however, they have been reported in 1 case report[15] and study.[18] Therefore, the immunological tests may not be useful in identifying the culprit drugs for anti-tuberculosis drugs induced maculopapular exanthem; however, further studies are needed. Alternatively, it could be reasonable to rely on only drug provocation test in patients with anti-tuberculosis drug induced maculopapular exanthem, as in this study. Some earlier studies have also established the usefulness of drug provocation test without skin tests in non-immediate mild cutaneous reactions.[34-36] We assume that a positive drug provocation test response is mediated by an immunologic mechanism in patients with drug fever or maculopapular exanthem; however, an immunological test was not performed. There is a latency period before the development of immunologic reactions, and the median latency period was 17 days in our patients with drug fever and maculopapular exanthem.

Based on our findings, we might propose an algorithm for the evaluation and management of patients with drug fever or maculopapular exanthem to first-line anti-tuberculosis drugs (Fig. 4). In patients with drug fever, it is reasonable to perform drug provocation tests without skin or *in vitro* tests to determine the culprit drugs. In patients with

maculopapular exanthem, the patch test, delayed intradermal test, lymphocyte transformation test, or a combination may be considered initially if the tests are available and validated. If not, or if the tests are negative, the drug provocation test should be performed. In any case, if culprit drugs are determined, alternative safe drugs or desensitization may be considered to treat tuberculosis. However, it may be conceivable to try second-line drugs as alternative drugs without identifying culprit drugs via drug provocation test if it is true that hypersensitivity reactions to second-line drugs occur less frequently. It is well known that second-line drugs have less anti-tuberculosis effects and many side effects.[29] The minimum treatment period can be increased up to 18 months when using only second-line drugs without first-line drugs.[30] Therefore, the proposed algorithm using drug provocation test would be more cost effective, in terms of therapeutic effect and treatment duration.

The present study has the obvious limitations of being a single center study with a small number of patients, potential genetic predisposition of the population, and selection bias, which might not allow for generalization of our findings and might also partly explain the higher occurrence of MDHS.

CONCLUSION

In cases of DHR caused by first-line anti-tuberculosis drugs, the occurrence of MDHS may be substantially high, even in the non-severe forms. Physicians should consider the possibility of MDHS in patients with suspected anti-tuberculosis drugs induced DHR. We recommend performing allergy tests, including drug provocation test, for the 4 first-line drugs. Among the 4 drugs, ethambutol and rifampin could be the common culprit drugs, and the combination of these 1 may be the most frequent culprit in inducing MDHS. Further investigations including higher numbers of patients will be needed to elucidate the mechanism why the occurrence of MDHS to first-line anti-tuberculosis drugs may be higher in tuberculosis patients.

Abbreviations
DHR: Drug hypersensitivity reaction; MDHS: Multiple drug hypersensitivity syndrome.

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