



# Anti-Mi-2 antibody titers and cutaneous manifestations in dermatomyositis

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## Abstract

The anti-Mi-2 antibody is a dermatomyositis (DM)-specific autoantibody. It is thought to be associated with photosensitivity in patients with DM because higher expression levels of Mi-2 antigens have been found in UV-irradiated cultured cells and because epidemiological studies have supported this association. This study aims to identify the relations between anti-Mi-2 antibody titers measured by ELISA and clinical characteristics in patients with DM. We focused on analyzing associations between anti-Mi-2 antibody titers and cutaneous manifestations. This retrospective analysis covered 160 adult DM patients. Anti-Mi-2 antibodies were detected by an in-house ELISA, and anti-Mi-2 titers were measured by a manufactured ELISA. Twelve of the 160 (7.5%) patients were anti-Mi-2 positive. The anti-Mi-2-positive patients showed extremely elevated muscle enzyme levels ( $P < 0.0001$ ), less frequent interstitial lung disease complication ( $P = 0.031$ ), and favorable survival rate (100%) ( $P = 0.07$ ). No correlations were found between anti-Mi-2 antibody titers and clinical characteristics or skin manifestations, including photosensitive rashes. Further investigation is necessary to elucidate the pathological significance of the anti-Mi-2 antibody in DM.

## KEYWORDS

anti-Mi2 antibody, dermatomyositis, ELISA, photosensitivity, titer

## 1 | INTRODUCTION

Dermatomyositis (DM) is a systemic autoimmune disorder characterized by symmetrical proximal muscle weakness and muscle inflammation with specific skin symptoms. Recent studies have demonstrated that dermatomyositis (DM)-specific autoantibodies correlate with clinical manifestations and complications.<sup>1,2</sup> The anti-Mi-2 antibody is a DM-specific autoantibody that is positive in 4%–30% of DM patients, and is associated with classic DM skin rash, favorable response to steroids, and favorable prognosis.<sup>1</sup> The target protein is known to be a component of the nucleosome remodeling deacetylase complex.<sup>3</sup> Several reports suggest that anti-Mi-2 is

associated with ultraviolet (UV) exposure. Adult DM and juvenile female DM patients living in US geoclimatic regions with higher UV exposure are frequently anti-Mi-2 positive.<sup>4,5</sup> Laboratory investigations have shown that Mi-2 antigen expression is elevated in cells cultured with UV exposure and that this elevated expression persists for 16 hours after exposure.<sup>6</sup> Since a recent paper showed the relationship between anti-Mi-2 antibody titers and DM disease severity and activity,<sup>7</sup> we wanted to know whether each DM clinical symptom or feature relates to the anti-Mi-2 antibody titer. We investigated the correlation between anti-Mi-2 antibody titers and skin manifestations, especially those that seem to be associated with UV exposure.

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## 2 | METHODS

### 2.1 | Patients

Serum samples and clinical information were collected as described in our previous study.<sup>8</sup> The samples were obtained from adult Japanese patients with DM who were followed from 2003 to 2016. A detailed medical history was gathered from each patient by unified questionnaire. Of the 160 DM patients, 88 patients fulfilled the “definite to probable” criterion of Bohan and Peter,<sup>9</sup> and the remaining 72 patients were diagnosed with clinically amyopathic DM according to the criteria proposed by Sontheimer.<sup>10</sup> Ethical approval for the study was obtained from Nagoya University and individual institutional review boards, and all sera were collected after the subjects gave written informed consent.

### 2.2 | ELISA

Autoantibodies against Mi-2 antibody in 160 DM patients were tested by antigen-capture ELISA according to our published protocols.<sup>11,12</sup> Twelve anti-Mi-2-positive sera were detected. These 12 sera were measured for titers of anti-Mi-2 by using an ELISA kit developed and manufactured by Medical and Biological Laboratories (MBL; Nagoya, Japan), a kit that is now covered by medical insurance and is widely used in Japan.<sup>13</sup>

### 2.3 | Statistical analyses

Fisher exact probability tests were used to compare frequencies of the clinical features between the two groups. Mann-Whitney *U* tests were used to compare titers of anti-Mi-2 antibody and clinical items including ages, maximum levels of creatine kinase (CK), and disease durations (month). *P* values of less than 0.05 were considered significant.

## 3 | RESULTS

### 3.1 | Demographic data of anti-Mi-2-positive DM patients

One hundred sixty patients (110 females, 50 males) diagnosed with DM were studied.

Of these 160 dermatomyositis patients, 12 patients were anti-Mi-2-antibody-positive (7.5%). The ages were  $57.1 \pm 16.7$  (mean  $\pm$  standard deviation) years for the anti-Mi-2-positive patients and  $58.7 \pm 14.1$  for the anti-Mi-2-negative patients ( $P = 0.93$ ). Ten of the 12 (87%) anti-Mi-2-positive patients and 100 of the 148 (67%) anti-Mi-2-negative patients were female ( $P = 0.21$ ). Hereinafter, we refer to the respective groups as “the positive group” and “the negative group.”

Interstitial lung disease (ILD) is a less frequent complication in the positive group (16.7%) than in the negative group (56.8%) ( $P = 0.031$ ). Six patients in the negative group were excluded for insufficient data. Cancers were found in two (16.7%) patients in

**TABLE 1** Clinical and laboratory characteristics of the anti-Mi-2-positive and anti-Mi-2-negative groups

	anti-Mi-2 (+) n = 12	anti-Mi-2 (-) n = 148	<i>P</i> value
Age	57.1 $\pm$ 16.7	58.7 $\pm$ 14.1	0.93
Female patients	10 (83.3%)	100 (67.6%)	0.21
Interstitial lung disease	2 (16.7%)	75 <sup>b</sup> (56.8%)	0.031
Cancer	2 (16.7%)	39 (26.3%)	0.73
Creatine kinase <sup>a</sup>	3697	1004.7 <sup>c</sup>	<0.0001
Survival	12 (100%)	110 <sup>d</sup> (76.9%)	0.07
Interval between onset and hospital visit (months)	4.1 $\pm$ 6.2	5.3 $\pm$ 10.7 <sup>e</sup>	0.84

<sup>a</sup>Maximum level.

<sup>b</sup>Six patients were excluded for insufficient data.

<sup>c</sup>Three patients were excluded for insufficient data.

<sup>d</sup>Five patients were excluded for insufficient data.

<sup>e</sup>15 patients were excluded for insufficient data.

positive group (colon cancer and thyroid cancer) and in 39 (26.3%) patients in the negative group ( $P = 0.73$ ). CK max was significantly higher for the positive group (3697 U/L [mean]) than for the negative group (1004.7 U/L [mean]) ( $P < 0.0001$ ). Three patients in the negative group were excluded for insufficient data. The survival rate was 100% in the positive group and 77% in the negative group ( $P = 0.07$ ). Five patients in the negative group were excluded for insufficient data. There was no difference in the interval between DM onset and hospital visit between the positive group (4.1  $\pm$  6.2 months) and the negative group (5.3  $\pm$  10.7 months) ( $P = 0.84$ ). Fifteen patients in the negative group were excluded for insufficient data (Table 1).

### 3.2 | Correlations between clinical and laboratory features and anti-Mi-2 antibody titers

Next, we analyzed the correlations between anti-Mi-2 titers obtained by MBL ELISA kits and the clinical/laboratory findings in 12 patients determined to be anti-Mi-2-positive as measured by the in-house ELISA. Age ( $P = 0.33$ ), CK max ( $P = 0.99$ ), and interval (months) between DM onset and hospital visit ( $P = 0.08$ ), and number of skin rash types (heliotrope, Gottron sign/papule, facial erythema, periungual erythema, V-neck sign, shawl sign, skin ulcer) ( $P = 0.7$ ) were investigated for an association with anti-Mi-2 titers by Spearman's rank correlation coefficient (Table 2). We also analyzed differences in titers with vs. without various skin symptoms (facial erythema [ $P = 0.42$ ], heliotrope rash [ $P = 0.58$ ], Gottron's sign/papule [ $P = 0.6$ ], periungual erythema [ $P = 0.53$ ], V-neck or shawl sign [ $P = 0.56$ ], and skin ulcer [ $P = 0.14$ ]). In addition, we analyzed differences in titers with versus without malignancy ( $P = 0.3$ ), ILD ( $P = 0.62$ ), and muscle weakness ( $P = 0.18$ ). Muscle weakness was judged as positive in cases with a Manual Muscle Test score, and five patients were excluded for insufficient data (Table 3).

**TABLE 2** Correlations between clinical and laboratory features and anti-Mi-2 antibody titers

Clinical and laboratory features	Anti-Mi-2 titers (mean ± standard deviation)	Correlation coefficient	P value
Age	57.1 ± 16.7	0.4	0.27
Creatine kinase <sup>a</sup>	3697 ± 3227	0.04	0.99
Interval between DM onset and hospital visit (months) <sup>b</sup>	4.17 ± 6.2	-0.5	0.08
Number of skin rash types	3.5 ± 1.32	0.96	0.7

DM, dermatomyositis.

<sup>a</sup>Maximum level.<sup>b</sup>Months between dermatomyositis onset and first hospital visit.**TABLE 3** Correlations between presence/absence of complications/symptoms and anti-Mi-2 titers in 12 patients

Clinical features	Number (mean Mi-2 titer)		P value
	(+)	(-)	
Sex	10 females (144.9)	2 males (142.9)	0.52
Muscle weakness <sup>a</sup>	6 (148)	1 (163)	0.18
Interstitial lung disease	2 (146.5)	10 (144.1)	0.62
Malignancy	2 (153.5)	10 (142.7)	0.3
Skin symptoms			
Facial erythema	10 (151.7)	2 (142.1)	0.42
Heliotrope rash	4 (141.3)	8 (146.1)	0.58
Gottron's sign/papule	10 (144.7)	2 (143.5)	0.6
Periungual erythema	11 (143.9)	1 (152)	0.53
V-neck or shawl sign	7 (141.4)	5 (146.7)	0.56
Skin ulcer	1 (115)	11 (147.1)	0.14

<sup>a</sup>Five patients were excluded for insufficient data.

## 4 | DISCUSSION

In our study, the anti-Mi-2 positive patients showed extremely elevated muscle enzyme levels, the less ILD complication, and favorable survival rates. All these results were similar to those of previous studies.<sup>1</sup> None of the clinical features nor any of the laboratory findings (age, CK max, number of skin rash types, sex, muscle weakness, ILD, malignancies) had statistically significant correlations with the anti-Mi-2 antibody titers. As UV exposure upregulates Mi-2 antigen expression in cultured keratinocytes,<sup>6</sup> we expected that the total number of skin rash types and several sunburn-like skin rashes, such as facial erythema or V-neck sign, might be associated with the anti-Mi-2 titers. However, neither rash types nor rash numbers were found to be associated with the anti-Mi-2 titers.

In the present study, none of the clinical features or laboratory symptoms were significantly associated with anti-Mi-2 titers.

However, the intervals from DM onset to hospital visit were greater in patients with lower anti-Mi-2 titers. Some reports mentioned that the anti-Mi-2 antibody titers gradually decreased with treatment in line with the patient's recovery, and these reports proposed that anti-Mi-2 antibody titers are useful indicators of DM disease activity during follow-up.<sup>13,14</sup> There is the possibility that the decrease in anti-Mi-2 antibody over time may not be associated with the clinical course.

There are several limitations to the present study. The number of DM patients with anti-Mi-2 antibodies was too small to obtain conclusive results. Since the prevalence of anti-Mi-2 is relatively low (2%; 9/376) in Japanese DM patients,<sup>1</sup> a multicenter study is necessary to enroll a sufficient number of anti-Mi-2 positive DM patients. In addition, we need to perform prospective and longitudinal analyses. Moreover, it may be that the titers measured by ELISA kits (MBL) are unsuitable for the purpose of this study because the ELISA kits use methods in which antibody titers are determined by using a single dilution of sera compared with a single dilution of the positive control.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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