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ORIGINAL ARTICLE

The spectrum and clinical significance of myositis-specific autoantibodies in Chinese patients with idiopathic inflammatory myopathies

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Abstract

Objectives The aim of this study is to analyze the prevalence of myositis-specific autoantibodies (MSAs) and to elucidate their associations with clinical features in Chinese patients with polymyositis (PM) and dermatomyositis (DM).

Methods Twelve subsets of MSAs including anti-Mi-2, anti-TIF1-γ, anti-MDA5, anti-NXP2, anti-SAE1, anti-SRP, anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, and anti-HMGCR antibodies were tested. Four hundred and ninety-seven PM/DM patients were enrolled. Clinical features and laboratory data were collected. The frequency of MSAs and the correlations with clinical phenotypes were calculated by SPSS 21.0.

Results MSAs were present in 65.4% in PM/DM patients. Anti-TIF1-γ (14.3%), anti-MDA5 (12.5%), and anti-Jo-1 (10.1%) were the three commonest MSAs. Anti-SAE1 (OR 14.877, 95% CI 1.427–155.074), anti-SRP (OR 4.339, 95% CI 1.529–12.312) and anti-TIF1-γ (OR 2.790, 95% CI 1.578–4.935) were associated with dysphagia. In contrast, anti-MDA5 (OR 0.356, 95% CI 0.148–0.856) might decrease the frequency of this manifestation. Interstitial lung disease (ILD) was observed more frequently in patients carrying anti-EJ (OR 14.202, 95% CI 1.696–118.902), anti-Jo-1 (OR 11.111, 95% CI 3.306–37.335), and anti-MDA5 (OR 3.109, 95% CI 1.578–6.128). On the contrary, anti-Mi-2 (OR 0.180, 95% CI 0.055–0.589), anti-TIF1-γ (OR 0.163, 95% CI 0.080–0.333), and anti-HMGCR (OR 0.058, 95% CI 0.007–0.451) were protective factors against developing ILD. Anti-TIF1-γ was an independent risk factor for cancer-associated myositis (OR 4.237, 95% CI 1.712–10.487).

Conclusions PM/DM patients had high frequencies of MSAs. Several MSAs were independent factors in determining unique clinical phenotypes.

Keywords Dermatomyositis · Extramuscular feature · Myositis-specific autoantibody · Polymyositis

Introduction

Idiopathic inflammatory myopathies (IIMs) are a group of systemic autoimmune diseases characterized by subacute or insidious proximal limb muscle weakness, elevated serum muscle enzymes, myopathic features on electromyography (EMG), and abnormal muscle histology [1]. The existence of myositis-specific autoantibodies (MSAs) in serum has received much attention because it is a crucial feature that characterizes IIM patients. MSAs are uniquely expressed in IIM patients and often mutually exclusive. Thus, they are proposed as a diagnostic component for IIM [2].

It is clinically useful to detect MSAs in IIM patients. Previous literature indicated that MSAs correlated with distinct clinical phenotypes, treatment outcomes, and prognosis [3, 4]. However, there are conflicting conclusions from previous studies as a result of differences in IIM subtypes and sample sizes. In addition, Hall et al. and Labrador-Horrillo et al. reported that the frequency of anti-MDA5 antibodies in their Caucasian cohorts was lower than that of the Japanese and Chinese cohorts, indicating that the occurrence of MSAs could vary with different ethnicities [5–8].

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There are few studies that examine the prevalence of MSAs and the correlations between different MSAs and clinical phenotypes in Chinese IIM patients [9]. Therefore, in the present study, we examined the MSA profiles in a large cohort of IIM patients in China and analyzed their possible clinical associations, aiming to provide valuable data for clinical work with Chinese IIM patients.

Materials and methods

Patients and sera

This retrospective study enrolled 497 patients with polymyositis (PM) and dermatomyositis (DM), including 30 juvenile patients, who were treated at the Department of Rheumatology, China-Japan Friendship Hospital, China, from April 2002 to December 2015. The patients with PM/DM fulfilled the criteria defined by Bohan and Peter, and clinically amyopathic DM (CADM) fulfilled the Sontheimer's criteria [10, 11]. Serum samples were obtained from all patients in their first visit to our department. These sera were stored at − 80 °C before use. The study was approved by the ethics committee of the China-Japan Friendship Hospital (approval number: 2016-117).

Clinical data

Demographic and clinical features of the IIM patients were available through a systemic record review. Clinical manifestations included myalgia, limb muscle weakness, cutaneous involvement, arthritis, dysphagia, interstitial lung disease (ILD), heart involvement, cancer, and loss of body weight. Cutaneous features of interest were heliotrope rash, V sign, shawl sign, mechanic's hands, Gottron's sign, periungual erythema, cutaneous ulcer, and calcinosis. ILD was diagnosed based on chest computer tomographies, while heart involvement was defined by abnormal electrocardiography or echocardiogram. Cancer related to IIM was defined as 3 years around the diagnosis.

Laboratory data consisted of serum transaminase (ALT and AST), lactate dehydrogenase (LDH), creatine kinase (CK), α-hydroxybutyrate dehydrogenase (HBDH), creatinine (CRE), immunoglobulin (IgG, IgM, and IgA), complement (C3 and C4), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and lymphocyte subsets.

Autoantibody detection

The assay of the 11 MSAs subsets (anti-Mi-2, anti-TIF1-γ, anti-MDA5, anti-NXP2, anti-SAE1, anti-SRP, anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, and anti-OJ) was performed by using EUROLINE autoimmune inflammatory myopathies Ag (IgG) test kit (order No: DL 1530-1601-4G, EUROIMMUN, Germany) according to the manufacturer's protocol. The positive control was provided by the test kit and the sample buffer was provided as a negative control. EUROBlotOne (EUROIMMUN, Germany) was used to detect the signal intensity, and the cutoff threshold was above 25.

The anti-HMGCR autoantibody was detected by using the QUANTA Lite HMGCR assay (catalog number: 704760, Inova Diagnostics, Inc., USA) according to the manufacturer's protocol. The negative control was provided by the test kit. The optical density of the samples was measured by using iMark (Bio-Rad Laboratories, Inc., USA). The level above 20 U was positive.

Statistical analysis

Univariate analysis was used to characterize patients with and without certain clinical subtypes by using the chi-squared test (categorical data), *t* test (continuous data with normal distribution), or the Mann-Whitney *U* test (continuous data with non-normal distribution). Because these MSAs are often mutually exclusive, separate models were required to analyze the effect of each autoantibody on certain clinical subtypes. In these models, associated factors that proved to be statistically significant in univariate analysis together with one particular MSA subtype were selected to establish predictors for multivariate analysis, and odds ratios (ORs) were obtained using logistic regression. Data were expressed as means ± standard deviation (SD) or medians with interquartile range (25% percentile–75% percentile) for continuous variables and as proportions for categorical variables. A p value less than 0.05 was generally considered significant. In certain condition, the corrected p value was used. For a value of p less than 0.001 in analyzing, it was noted as $p < 0.001$. SPSS 21.0 was used for all statistical analyses.

Results

Demographic, clinical, and laboratory features of IIM patients

The study enrolled 497 IIM patients, consisting of 375 DM and 122 PM patients. In order to clarify the effect of MSA in IIM patients, we described the data according to whether the patients had MSA or not. Their demographic, clinical, and laboratory features were recorded in detail in Table 1.

MSA profiles in IIM patients

MSAs occurred in 325 IIM patients. Anti-TIF1-γ, anti-MDA5, and anti-Jo-1 were the three commonest MSAs in IIM patients. The distribution of the MSAs was shown in Table 2.

Table 1 Clinical and laboratory features of patients with MSAs and patients without MSAs

	IIM patients with MSAs ($n = 325$)	IIM patients without MSAs ($n = 172$)	p
Female gender (F/M)	224/101	100/72	0.016*[a]
Age onset (years)	47.23 ± 15.46	41.49 ± 16.31	0.000
Age (years)	49.37 ± 14.85	44.53 + 15.48	0.001
Disease duration (m)	9 (3.24)	12 (4.48)	0.006*
Treatment-naïve, *n* (%)	131(40.3%)	55(32.0%)	0.068
Clinical manifestations			
Myalgia, *n* (%)	175 (53.8%)	92 (53.5%)	0.939
Muscle weakness, *n* (%)	253 (77.8%)	134 (77.9%)	0.988
Cutaneous manifestations, *n* (%)	252 (77.5%)	109 (63.4%)	0.001*
Heliotrope rash, *n* (%)	183 (56.3%)	83 (48.3%)	0.087
V sign, *n* (%)	152 (46.8%)	55 (32.0%)	0.001*
Shawl sign, *n* (%)	106 (32.6%)	47 (27.3%)	0.224
Mechanic's hands, *n* (%)	87 (26.8%)	30 (17.4%)	0.020*
Gottron's sign *n* (%)	145(44.6%)	59(34.3%)	0.026*
Periungual erythema, *n* (%)	16 (4.9%)	12 (7.0%)	0.345
Cutaneous ulcer, *n* (%)	24 (7.4%)	7 (4.1%)	0.146
Calcinosis, *n* (%)	10 (3.1%)	5 (2.9%)	0.916
Arthritis, *n* (%)	114(35.1%)	57 (33.1%)	0.665
Dysphagia, *n* (%)	112 (34.5%)	34 (19.8%)	0.001*
ILD *n* (%)	169 (52.0%)	79 (45.9%)	0.198
Cardiac manifestations, *n* (%)	134 (41.2%)	65 (37.8%)	0.457
Cancer, *n* (%)	28 (8.6%)	8 (4.7%)	0.105
Weight loss, *n* (%)	75 (23.1%)	35 (20.3%)	0.486
Laboratory features			
ALT (IU/L) median (25%, 75%)	43 (24, 90)	38 (22, 86)	0.231
AST (IU/L) median (25%, 75%)	42 (24, 91)	32 (20, 59)	0.003*
LDH (IU/L) median (25%, 75%)	288 (213, 444)	238 (190, 344)	0.001*
CK (IU/L) median (25%, 75%)	217 (67, 1331)	146 (47, 716)	0.039*
HBDH (IU/L) median (25%, 75%)	206 (146, 324)	169 (132, 254)	0.001*
CRE (umol/L) mean ± SD	50.43 ± 14.92	50.14 ± 14.77	0.838
IgG (mg/dL) median (25%, 75%)	1220 (973, 1590)	1140 (858, 1550)	0.080
IgA (mg/dL) median (25%, 75%)	211(144, 293)	204 (142, 299)	0.791
IgM (mg/dL) median (25%, 75%)	116 (79, 169)	110 (75, 155)	0.385
C3 (mg/dL) mean ± SD	85.89 ± 21.32	89.21 ± 23.94	0.128
C4 (mg/dL) median (25%, 75%)	19.3 (15.8, 23.5)	19.1 (14.9, 23.9)	0.661
CRP (mg/dL) median (25%, 75%)	0.47 (0.21, 1.24)	0.36 (0.17, 0.82)	0.052
ESR (mm/h) median (25%, 75%)	16 (7, 38)	12 (7, 32)	0.078
Lymphocyte (cell/μL) median (25%, 75%)	1200 (770, 1750)	1460 (1000, 2030)	0.003*
T (CD3+) (cell/μL) median (25%, 75%)	805 (502, 1259)	958 (642, 1417)	0.003*
T (CD3 + CD4+) (cell/μL) median (25%, 75%)	494 (303, 790)	559 (338.5, 825)	0.074
T (CD3 + CD8+) (cell/μL) median (25%, 75%)	272 (163, 443)	373 (221, 554)	0.000*

*p value was less than 0.05

A significantly higher frequency of MSAs was observed in the DM patients than that in the PM patients. Anti-TIF1-γ with a frequency of 18.9% was the most frequently detected MSA in DM patients, followed by anti-MDA5 and anti-Jo-1. For PM patients, the frequency of anti-SRP was the highest with a frequency of 16.4%, followed by anti-Jo-1 and anti-

Table 2 Frequency of MSAs in patients with DM and PM

	All ($n = 497$), n (%)	DM ($n = 375$), n (%)	PM ($n = 122$), n (%)	p (DM vs PM)
MSA positivity	325 (65.4)	262 (69.9)	63 (51.6)	0.000*[a]
Anti-Mi2	31 (6.2)	27 (7.2)	4 (3.3)	0.120
Anti-TIF1-γ	71 (14.3)	71 (18.9)	0 (0)	0.000*
Anti-MDA5	62 (12.5)	61 (16.3)	1 (0.8)	0.000*
Anti-NXP2	26 (5.2)	22 (5.9)	4 (3.3)	0.265
Anti-SAE1	10 (2.0)	9 (2.4)	1 (0.8)	0.479
Anti-SRP	28 (5.6)	8 (2.1)	20(16.4)	0.000*
Anti-HMGCR	23 (4.6)	8 (2.1)	15 (12.3)	0.000*
Anti-ARS	93 (18.7)	70 (18.7)	23 (18.9)	0.964
Anti-Jo-1	50 (10.1)	33 (8.8)	17 (13.9)	0.101
Anti-PL-7	22 (4.4)	18 (4.8)	4 (3.3)	0.478
Anti-PL-12	9 (1.8)	8 (2.1)	1 (0.8)	0.579
Anti-EJ	13 (2.6)	12 (3.2)	1 (0.8)	0.269
Anti-OJ	0	0	0	NS[b]

*p value was less than 0.05

NS not stated

HMGCR. Interestingly, among the PM patients, one carried anti-MDA5 and none carried anti-TIF1-γ.

In the 70 DM and 23 PM patients who carried anti-ARS, anti-Jo-1 occurred most frequently (47.1% and 73.9%, respectively), and anti-OJ was observed in neither subgroups. In addition, 20 patients carried two kinds of MSAs in their sera.

The distribution of MSAs in IIM patients according to age and gender

Because the co-existing MSAs might alter the analysis, 20 patients were removed from the analyses. In order to clarify whether age affects the distribution of MSAs in IIM patients, the 477 patients were divided into three subgroups according to the age of onset (age < 18, between 18 and 65, and ≥ 65). The frequencies differed among patients carrying anti-TIF1-γ, anti-SAE1, anti-SRP, and anti-Jo-1, according to the chi-squared test results. IIM patients between 18 and 65 were more likely to have high frequencies of anti-SRP and anti-Jo-1. On the other hand, elderly IIM patients (age ≥ 65) seemed to carry higher frequencies of anti-TIF1-γ and anti-SAE1. However, in the analysis between two groups, only the older patients of the anti-TIF1-γ autoantibody showed a higher percentage than the other two groups ($p < 0.017$). (Supplement 1).

We also compared the prevalence of MSA subtypes between female and male patients, and no significant difference was observed. Before the serum samples were obtained, 177 patients were untreated and 300 had been treated. These IIM patients were divided into two subgroups. No significant differences existed between them with respect to MSA subtypes.

Correlations between MSAs and clinical features according to univariate analysis

Since certain MSA subtype correlated with distinct clinical features, we focused on the association between MSAs and cutaneous manifestations, muscle weakness, and four different crucial extramuscular complications of IIMs (dysphagia, ILD, cancer, and cardiac manifestations).

Patients with anti-TIF1-γ and anti-MDA5 seemed likely to develop Gottron's sign. In contrast, patients with Gottron's sign carried less frequency of anti-SRP and anti-HMGCR ($p < 0.05$). As for cutaneous ulcers, a serious cutaneous manifestation, anti-MDA5 occurred more frequently in IIM patients than in those without ($p < 0.05$). According to imaging findings performed during the disease course, 15 patients developed calcinosis. The anti-NXP2 autoantibody was more frequently found in patients with calcinosis than in those without (33.3% vs 4.1%, $p < 0.001$). In addition, patients carrying anti-Mi2 (DM), anti-TIF1-γ (DM), anti-MDA5 (DM), and anti-Jo-1 (DM) also developed calcinosis, although the percentage was small. Of all the IIM patients, 370 experienced definitive muscle weakness. Anti-NXP2 and anti-SRP were shown to correlate with this feature. Patients carrying these autoantibodies seemed more likely to develop muscle weakness (Supplement 2).

As for heart involvement, 190 out of 477 patients exhibited cardiac manifestations. Patients with anti-MDA5 seemed likely to develop cardiac manifestations, and patients with anti-Mi2 might reduce the occurrence of this phenomenon.

Dysphagia occurred in 139 out of 477 patients, and the frequency of anti-TIF1-γ was the highest in this subgroup of patients. Univariate analysis showed that anti-TIF1-γ, anti-

NXP2, anti-SAE1, anti-SRP, and anti-HMGCR were associated with dysphagia in IIM patients, while patients with anti-MDA5 might reduce the occurrence of this complication.

About half, or 49.9% (238/477), of IIM patients had ILD. Nine MSA subsets were proved to be associated with ILD in IIM patients, namely anti-Mi2, anti-TIF1-γ, anti-MDA5, anti-NXP2, anti-HMGCR, anti-Jo-1, anti-PL7, anti-PL-12, and anti-EJ, according to univariate analysis. Patients with ILD more frequently carried anti-MDA5, anti-Jo-1, anti-PL7, anti-PL-12, and anti-EJ.

There were 34 patients, 33 DM and 1 PM patients, who had cancer during their IIM disease course. The frequency of anti-TIF1-γ antibody was significantly different between patients with and without cancer (61.8% vs 10.4%, $p < 0.001$). Additionally, patients carrying anti-NXP2 (DM), anti-SAE1 (DM), and anti-ARS (DM) also had cancer during their disease course (Table 3).

Correlations between MSAs and clinical features according to logistic regression analysis

To demonstrate whether the MSAs were independent factors of certain clinical subtypes, separate models were established to include clinical and laboratory variables, which were proved to be statistically significant in the univariate analyses.

Although some MSA subsets seemed to be related to Gottron's sign, cutaneous ulcers and calcinosis according to univariate analysis, only anti-MDA5 (OR 3.831, 95% CI 1.887–7.778, $p < 0.001$) and anti-NXP2(OR 7.974, 95% CI 1.993–31.907, $p = 0.003$) were independent factors for Gottron's sign and calcinosis, respectively, according to logistic regression analysis. As for muscle weakness, no MSA subtype was proved to be an independent factor.

In the separate model for cardiac manifestations, no MSA subtype was an independent factor via logistic regression.

As for dysphagia, logistic regression showed that anti-NXP2 (OR 2.372, 95% CI 0.894–6.290, $p = 0.083$) and anti-HMGCR (OR 1.598, 95% CI 0.498–5.125, $p = 0.431$) were not independent factors of dysphagia, but anti-TIF1-γ, anti-MDA5, anti-SAE1, and anti-SRP were still effective predictors. Patients carrying anti-MDA5 might experience dysphagia less frequently. The other three autoantibodies might increase dysphagia tendencies during the IIM disease course.

Separate models were established to analyze whether the nine MSA subtypes were independent factors of ILD. Anti-MDA5, anti-Jo-1, and anti-EJ were independent risk factors for ILD, while anti-Mi2, anti-TIF1-γ, and anti-HMGCR seemed to be protective. Unlike in univariate analysis, logistic regression analysis showed that anti-NXP2, anti-PL7, and anti-PL-12 were not independent factors for ILD.

In the separate model, anti-TIF1-γ was identified as an independent risk factor for cancer in IIM patients (OR 4.237, 95% CI 1.712–10.487, $p = 0.002$) (Table 4).

Discussion

Our study specifically focused on the spectrum of MSAs in Chinese PM/DM patients, in which 12 subsets of MSAs were investigated. MSA occurrence in the IIM patients was 65.4% in

Table 3 Frequency of MSAs in patients with and without certain clinical features

	Cardiac manifestation			Dysphagia			ILD			Cancer		
	With, $n = 190$	Without, $n = 287$	p	With, $n = 139$	Without, $n = 338$	p	With, $n = 238$	Without, $n = 239$	p	With, $n = 34$	Without, $n = 443$	p
Anti-Mi2	4	18	0.034*[a]	5	17	0.498	4	18	0.002*	0	22	0.365
Anti-TIF1-γ	23	44	0.321	32	35	0.000*	18	49	0.000*	21	46	0.000*
Anti-MDA5	30	28	0.048*	8	50	0.006*	45	13	0.000*	0	58	0.048*
Anti-NXP2	12	12	0.296	13	11	0.006*	6	18	0.012*	1	23	0.864
Anti-SAE1	4	4	0.819	6	2	0.013*	4	4	1.000	1	7	1.000
Anti-SRP	6	16	0.218	13	9	0.002*	8	14	0.194	0	22	0.365
Anti-HMGCR	8	14	0.734	11	11	0.027*	1	21	0.000*	0	22	0.365
Anti-Jo-1	19	24	0.541	7	36	0.052	40	3	0.000*	2	41	0.726
Anti-PL-7	8	9	0.535	6	11	0.767	13	4	0.026*	0	17	0.494
Anti-PL-12	4	5	1.000	1	8	0.406	8	1	0.043*	1	8	1.000
Anti-EJ	7	6	0.295	3	10	0.858	12	1	0.002*	0	13	0.641
Anti-OJ	0	0	NS	0	0	NS	0	0	NS	0	0	NS

*p value was less than 0.05

NS not stated

Table 4 MSA subtypes with predictive value for certain clinical feature in IIM patients

	OR	95% CI	*p*
Cardiac			
Anti-Mi2	0.447	0.133–1.504	0.193
Anti-MDA5	1.700	0.858–3.368	0.129
Dysphagia			
Anti- TIF1-γ	2.790	1.578–4.935	0.000*[a]
Anti-MDA5	0.356	0.148–0.856	0.021*
Anti-NXP2	2.372	0.894–6.290	0.083
Anti-SAE1	14.877	1.427–155.074	0.024*
Anti-SRP	4.339	1.529–12.312	0.006*
Anti-HMGCR	1.598	0.498–5.125	0.431
ILD			
Anti-Mi2	0.180	0.055–0.589	0.005*
Anti-TIF1-γ	0.163	0.080–0.333	0.000*
Anti-MDA5	3.109	1.578–6.128	0.001*
Anti-NXP2	0.625	0.199–1.962	0.420
Anti-HMGCR	0.058	0.007–0.451	0.007*
Anti-Jo-1	11.111	3.306–37.335	0.000*
Anti-PL12	4.909	0.452–53.317	0.191
Anti-PL7	3.044	0.607–15.257	0.176
Anti-EJ	14.202	1.696–118.902	0.014*
Cancer			
Anti-TIF1-γ	4.237	1.712–10.487	0.002*
Anti-MDA5	0.000	NS	NS

*p value was less than 0.05

NS not stated

our study, which was different from previous studies [3, 12]. This may be related to the cohort size and different ethnicities. Our finding indicates that IIM is an autoimmune disease with a high prevalence of MSA. There were 20 patients who concurrently carried two MSA subsets even though the coexistence of two MSA subsets in the same patient is rare [3, 4, 13].

The profile of MSAs in DM patients was significantly different profile from that in PM patients. In DM patients, anti-TIF1-γ was the most frequent, followed by anti-MDA5 and anti-Jo-1. This finding differed from the other study on MSA profile in Chinese and other DM patients due to different sample sizes and ethnicity [9, 14]. Besides, there were differences in the frequency of each autoantibody between other reports and ours [15, 16]. In PM patients, the most frequent MSA was anti-SRP, which occurred significantly more frequently than in DM patients. The occurrence of anti-HMGCR, which was associated with severe myopathy, was obviously higher in PM patients [3, 17]. The other MSAs occurred at rates between 1.8 and 6.2%, except for anti-OJ which could not be detected in our patients.

MSAs are useful in predicting certain clinical features in PM and DM patients [18]. In this study, we focused on the correlations between MSAs and some crucial cutaneous manifestations, muscle weakness, and extramuscular phenotypes that affect prognosis during the IIM disease course. We found that some phenotypes were closely linked with these autoantibodies.

Four kinds of MSAs correlated with Gottron's sign, which is a characteristic and diagnostic rash in IIM patients [19]. Although anti-TIF1-γ was not an independent risk factor for Gottron's sign, it occurred more frequently in these patients, a finding that was in agreement with the previous study from a UK cohort of juvenile DM patients [20]. In contrast, anti-MDA5 was a risk factor for Gottron's sign. Previous studies found that this manifestation was associated with anti-MDA5, especially when accompanied by ulcers [21]. However, we did not study patients with Gottron's sign according to the presence or absence of ulcers. This was a limitation of our study. Because anti-SRP and anti-HMGCR autoantibodies were likely to be biomarkers for necrotizing autoimmune myopathy (NAM) patients with less or no rash, IIM patients with these antibodies including majority of DM experienced less occurrence of Gottron's sign [22]. Recently, the association between skin ulcers and anti-MDA5 has attracted more attention as a predictive and prognostic factor of rapidly progressing ILD, which is consistent with our conclusion [23, 24]. Calcinosis causes recurrent inflammation or infection locally and leads to considerable disability. A recent study mentioned that anti-TIF1-γ (negative) and anti-NXP2 (positive) were independent predictors of calcinosis in DM patients [25]. In our study, although patients with anti-TIF1-γ did not frequently develop calcinosis, there was no difference between the occurrence of calcinosis in patients with or without this MSA via univariate analysis. Anti-NXP2 was a definitive predictor of calcinosis according to univariate analysis and logistic regression, which echoed the findings in juvenile DM patients [26]. We also found one patient with calcinosis who carried anti-MDA5, a phenomenon that has been reported by Hall JC et al. [5]. However, no correlation between anti-MDA5 and calcinosis was found in our or any other studies [25].

Although the frequency of anti-TIF1-γ was the highest in patients with muscle weakness, there was no statistical relation between this autoantibody and muscle weakness. However, anti-NXP2 and anti-SRP were associated with muscle weakness according to univariate analysis. In recent studies, almost all patients who carried the anti-NXP2 antibody experienced severe muscle weakness [27, 28]. Anti-SRP, which occurred with high frequency in NAM patients, was also associated with muscle weakness [22].

Heart involvement varies from 6 to 75% in IIM patients and is a prognostic factor of the disease [29]. According to the current literature, patients who carry anti-SRP have a high frequency of cardiac manifestations in juvenile DM patients [30]. In our study, anti-Mi2 and anti-MDA5 antibodies were

related to this phenomenon, but they were not independent factors for cardiac manifestation.

Dysphagia is a common clinical manifestation, and previous studies found that the prevalence ranged from 32 to 84% in IIM patients [28, 31, 32]. Among juvenile IIM patients, dysphagia occurred most frequently in patients carrying anti-SRP and anti-NXP2 [30]. Notably, several autoantibodies (anti-TIF1-γ, anti-MDA5, anti-SAE1, and anti-SRP) were associated with dysphagia in IIM patients, according to our findings. However, the pathogenesis was not clear. In univariate and logistic regression analysis, muscle weakness was found to associate with dysphagia. Thus, we speculate that dysphagia, secondary to pharyngeal muscle weakness, correlates with the autoantibodies that have been proven to associate with severe myositis. For example, in our study, patients carrying anti-MDA5 seemed less likely to develop dysphagia, and anti-MDA5 mainly occurred in CADM patients who had slight or no myositis [33, 34].

ILD is a severe complication of IIM with an occurrence ranging from 5 to 80% and associated with increased morbidity and mortality [35]. Recent studies demonstrated that anti-MDA5 was strongly associated with rapidly progressive ILD and poor prognosis, not only in Asian populations, but also in American populations [3, 33, 36]. In our study, we identified that anti-MDA5 was an independent risk predictor of ILD. In the univariate analysis of possible associations between anti-ARSs and ILD, it was found that anti-Jo-1, anti-PL7, anti-PL-12, and anti-EJ were correlated with ILD in IIM patients. However, in the logistic regression analysis, both anti-Jo-1 and anti-EJ seemed to be potential independent risk predictors for ILD but not anti-PL7 and anti-PL-12, a finding that contradicts those from previous literatures [37]. The reason might be associated with sample size and selection bias. Interestingly, patients carrying anti-Mi2 and anti-TIF1-γ seemed to have a lower risk for developing ILD, and previous literature supports our findings [33, 38]. Furthermore, patients carrying anti-HMGCR seemed less likely to develop ILD, suggesting that anti-HMGCR might play a protective role against ILD in IIM patients.

We found obvious differences between the subgroups of patients carrying anti-TIF1-γ with and without cancer. Logistic regression analysis found that anti-TIF1-γ was an independent risk factor for cancer in IIM patients. The striking association between anti-TIF1-γ and cancer-associated DM has largely been confirmed in many reports [39–41]. The presence of anti-NXP2 was generally thought to be associated with cancer, especially in males [40]. However, in recent research, Wang L also reported that malignancy was rare in Chinese adult patients with NXP2 [42]. In our study, we did not reach the same conclusion. In the 34 cancer-associated patients, only one carried anti-NXP2. The percentage of patients who carried anti-NXP2 with cancer seemed lower in comparison to those without cancer although the difference was not significant.

Our study has a few limitations. Not all of the sera from the enrolled IIM patients were obtained at the time of disease onset. MSA levels decreased when the disease was effectively controlled and increased when the disease relapsed [43, 44]. Besides, some data were excluded from consideration because of the co-existing MSAs in our cohort. These conditions mean that our study does not reflect the initial state of the MSA profile in IIM patients. Moreover, the method of detecting autoantibodies in IIM patients was the Euroimmun blotting instead of immunoprecipitation, which may also impact the results. A previous research which compared these two methods thought the former had high prevalence of multiple positivity and the high discordant rate of certain autoantibody. [45]. More detailed data and multicenter studies are still needed to accurately assess the profile of MSAs in IIM patients.

Conclusion

In summary, majority of IIM patients carried MSAs in their sera, and the prevalence and profile of MSAs were dependent on the disease subtype. Our findings suggested that MSAs were associated with certain clinical features. For future studies, it might be helpful to define and monitor the cutaneous manifestations and extramuscular features that occur during the IIM disease course.

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Compliance with ethical standards

Disclosures None.

References

1. Dimachkie MM, Barohn RJ, Amato AA (2014) Idiopathic inflammatory myopathies. Neurol Clin 32:595–628
2. Hoogendijk JE, Amato AA, Lecky BR, Choy EH, Lundberg IE, Rose MR, Vencovsky J, de Visser M, Hughes RA (2004) 119th ENMC International Workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10-12 October 2003, Naarden, The Nertherlands. Neuromuscul Disord 14:337–345
3. Ghirardello A, Bassi N, Palma L, Borella E, Domeneghetti M, Punzi L, Doria A (2013) Autoantibodies in polymyositis and dermatomyositis. Curr Rheumatol Rep 15(335):335
4. Tansley SL, Betteridge ZE, McHugh NJ (2013) The diagnostic utility of autoantibodies in adult and juvenile myositis. Curr Opin Rheumatol 25:772–777

5. Hall JC, Casciola-Rosen L, Samedy LA, Werner J, Owoyemi K, Danoff SK, Christopher-Stine L (2013) Anti-melanoma differentiation-associated protein 5-associated dermatomyositis: expanding the clinical spectrum. Arthritis Care Res (Hoboken) 65:1307–1315
6. Koga T, Fujikawa K, Horai Y, Okada A, Kawashiri SY, Iwamoto N, Suzuki T, Nakashima Y, Tamai M, Arima K, Yamasaki S, Nakamura H, Origuchi T, Hamaguchi Y, Fujimoto M, Ishimatsu Y, Mukae H, Kuwana M, Kohno S, Eguchi K, Aoyagi K, Kawakami A (2012) The diagnostic utility of anti-melanoma differentiation-associated gene 5 antibody testing for predicting the prognosis of Japanese patients with DM. Rheumatology (Oxford) 51:1278–1284
7. Cao H, Pan M, Kang Y, Xia Q, Li X, Zhao X, Shi R, Lou J, Zhou M, Kuwana M, Ding X, Zheng J (2012) Clinical manifestations of dermatomyositis and clinically amyopathic dermatomyositis patients with positive expression of anti-melanoma differentiation-associated gene 5 antibody. Arthritis Care Res (Hoboken). 64:1602–1610
8. Labrador-Horrillo M, Martinez MA, Selva-O'Callaghan A, Trallero-Araguas E, Balada E, Vilardell-Tarres M et al (2014) Anti-MDA5 antibodies in a large Mediterranean population of adults with dermatomyositis. J Immunol Res 2014:290797
9. Chen Z, Hu W, Wang Y, Guo Z, Sun L, Kuwana M (2015) Distinct profiles of myositis-specific autoantibodies in Chinese and Japanese patients with polymyositis/dermatomyositis. Clin Rheumatol 34:1627–1631
10. Bohan A, Peter JB (1975) Polymyositis and dermatomyositis (first of two parts). N Engl J Med 292:344–347
11. Sontheimer RD (2002) Dermatomyositis: an overview of recent progress with emphasis on dermatologic aspects. Dermatol Clin 20:387–408
12. Cruellas MG, Viana Vdos S, Levy-Neto M, Souza FH, Shinjo SK (2013) Myositis-specific and myositis-associated autoantibody profiles and their clinical associations in a large series of patients with polymyositis and dermatomyositis. Clinics (Sao Paulo) 68:909–914
13. Nakajima A, Yoshino K, Soejima M, Kawaguchi Y, Satoh T, Kuwana M, Yamanaka H (2012) High frequencies and coexisting of myositis-specific autoantibodies in patients with idiopathic inflammatory myopathies overlapped to rheumatoid arthritis. Rheumatol Int 32:2057–2061
14. Zampeli E, Venetsanopoulou A, Argyropoulou OD, Mavragani CP, Tektonidou MG, Vlachoyiannopoulos PG, Tzioufas AG, Skopouli FN, Moutsopoulos HM (2018) Myositis autoantibody profiles and their clinical associations in Greek patients with inflammatory myopathies. Clin Rheumatol 38:125–132. https://doi.org/10.1007/s10067-018-4267-z
15. So H, Ip RW, Wong VT, Yip RM (2018) Analysis of anti-melanoma differentiation-associated gene 5 antibody in Hong Kong Chinese patients with idiopathic inflammatory myopathies: diagnostic utility and clinical correlations. Int J Rheum Dis 21:1076–1081
16. Fujimoto M, Murakami A, Kurei S, Okiyama N, Kawakami A, Mishima M, Sato S, Seishima M, Suda T, Mimori T, Takehara K, Kuwana M (2016) Enzyme-linked immunosorbent assays for detection of anti-transcriptional intermediary factor-1 gamma and anti-Mi-2 autoantibodies in dermatomyositis. J Dermatol Sci 84:272–281
17. Ge Y, Lu X, Peng Q, Shu X, Wang G (2015) Clinical characteristics of anti-3-hydroxy-3-methylglutaryl coenzyme A reductase antibodies in Chinese patients with idiopathic inflammatory myopathies. PLoS One 10:e0141616
18. Ghirardello A, Borella E, Beggio M, Franceschini F, Fredi M, Doria A (2014) Myositis autoantibodies and clinical phenotypes. Auto Immun Highlights 5:69–75
19. Muro Y, Sugiura K, Akiyama M (2016) Cutaneous manifestations in dermatomyositis: key clinical and serological features-a comprehensive review. Clin Rev Allergy Immunol 51:293–302
20. Gunawardena H, Wedderburn LR, North J, Betteridge Z, Dunphy J, Chinoy H, Davidson JE, Cooper RG, McHugh N, Juvenile Dermatomyositis Research Group UK (2008) Clinical associations of autoantibodies to a p155/140 kDa doublet protein in juvenile dermatomyositis. Rheumatology (Oxford) 47:324–328
21. Cao H, Xia Q, Pan M, Zhao X, Li X, Shi R, Zhou M, Ding X, Kuwana M, Zheng J (2016) Gottron papules and Gottron sign with ulceration: a distinctive cutaneous feature in a subset of patients with classic dermatomyositis and clinically amyopathic dermatomyositis. J Rheumatol 43:1735–1742
22. Basharat P, Christopher-Stine L (2015) Immune-mediated necrotizing myopathy: update on diagnosis and management. Curr Rheumatol Rep 17:72
23. Ishigaki K, Maruyama J, Hagino N, Murota A, Takizawa Y, Nakashima R, Mimori T, Setoguchi K (2013) Skin ulcer is a predictive and prognostic factor of acute or subacute interstitial lung disease in dermatomyositis. Rheumatol Int 33:2381–2389
24. Fiorentino D, Chung L, Zwerner J, Rosen A, Casciola-Rosen L (2011) The mucocutaneous and systemic phenotype of dermatomyositis patients with antibodies to MDA5 (CADM-140): a retrospective study. J Am Acad Dermatol 65:25–34
25. Ichimura Y, Matsushita T, Hamaguchi Y, Kaji K, Hasegawa M, Tanino Y, Inokoshi Y, Kawai K, Kanekura T, Habuchi M, Igarashi A, Sogame R, Hashimoto T, Koga T, Nishino A, Ishiguro N, Sugimoto N, Aoki R, Ando N, Abe T, Kanda T, Kuwana M, Takehara K, Fujimoto M (2012) Anti-NXP2 autoantibodies in adult patients with idiopathic inflammatory myopathies: possible association with malignancy. Ann Rheum Dis 71:710–713
26. Bodoki L, Nagy-Vincze M, Griger Z, Betteridge Z, Szöllősi L, Dankó K (2014) Four dermatomyositis-specific autoantibodies-anti-TIF1-γ, anti-NXP2, anti-SAE and anti-MDA5-in adult and juvenile patients with idiopathic inflammatory myopathies in a Hungarian cohort. Autoimmun Rev 13:1211–1219
27. Valenzuela A, Chung L, Casciola-Rosen L, Fiorentino D (2014) Identification of clinical features and autoantibodies associated with calcinosis in dermatomyositis. JAMA Dermatol 150:724–729
28. Gunawardena H, Betteridge ZE, McHugh NJ (2009) Myositis-specific autoantibodies: their clinical and pathogenic significance in disease expression. Rheumatology (Oxford) 48:607–612
29. Dobloug C, Garen T, Bitter H, Stjärne J, Stenseth G, Grøvle L, Sem M, Gran JT, Molberg Ø (2015) Prevalence and clinical characteristics of adult polymyositis and dermatomyositis; data from a large and unselected Norwegian cohort. Ann Rheum Dis 74:1551–1556
30. Cavazzana I, Fredi M, Selmi C, Tincani A, Franceschini F (2017) The clinical and histological Spectrum of idiopathic inflammatory myopathies. Clin Rev Allergy Immunol 52:88–98
31. Rider LG, Shah M, Mamyrova G, Huber AM, Rice MM, Targoff IN, Miller FW, Childhood Myositis Heterogeneity Collaborative Study Group (2013) The myositis autoantibody phenotypes of the juvenile idiopathic inflammatory myopathies. Medicine (Baltimore) 92:223–243
32. Satoh M, Tanaka S, Ceribelli A, Calise SJ, Chan EK (2017) A comprehensive overview on myositis-specific antibodies: new and old biomarkers in idiopathic inflammatory myopathy. Clin Rev Allergy Immunol 52:1–19
33. Hallowell RW, Danoff SK (2014) Interstitial lung disease associated with the idiopathic inflammatory myopathies and the antisynthetase syndrome: recent advances. Curr Opin Rheumatol 26:684–689
34. Kiely PD, Chua F (2013) Interstitial lung disease in inflammatory myopathies: clinical phenotypes and prognosis. Curr Rheumatol Rep 15:359
35. Moghadam-Kia S, Oddis CV, Sato S, Kuwana M, Aggarwal R (2016) Anti-MDA5 is associated with rapidly progressive lung disease and poor survival in U.S. patients with amyopathic and myopathic dermatomyositis. Arthritis Care Res (Hoboken). 68:689–694

36. Kalluri M, Sahn SA, Oddis CV, Gharib SL, Christopher-Stine L, Danoff SK, Casciola-Rosen L, Hong G, Dellaripa PF, Highland KB (2009) Clinical profile of anti-PL-12 autoantibody. Cohort study and review of the literature. Chest. 135:1550–1556
37. García-De La Torre I (2015) Clinical usefulness of autoantibodies in idiopathic inflammatory myositis. Front Immunol 6:331
38. Trallero-Araguás E, Rodrigo-Pendás JA, Selva-O'Callaghan A, Martínez-Gómez X, Bosch X, Labrador-Horrillo M et al (2012) Usefulness of anti-p155 autoantibody for diagnosing cancer-associated dermatomyositis: a systematic review and meta-analysis. Arthritis Rheum 64:523–532
39. Fiorentino DF, Chung LS, Christopher-Stine L, Zaba L, Li S, Mammen AL, Rosen A, Casciola-Rosen L (2013) Most patients with cancer-associated dermatomyositis have antibodies to nuclear matrix protein NXP-2 or transcription intermediary factor 1 γ. Arthritis Rheum 65:2954–2962
40. Lu X, Yang H, Shu X, Chen F, Zhang Y, Zhang S, Peng Q, Tian X, Wang G (2014) Factors predicting malignancy in patients with polymyositis and dermatomyositis: a systematic review and meta-analysis. PLoS One 9:e94128
41. Danieli MG, Gelardi C, Guerra F, Cardinaletti P, Pedini V, Gabrielli A (2016) Cardiac involvement in polymyositis and dermatomyositis. Autoimmun Rev 15:462–465
42. Wang L, Huang L, Yang Y, Chen H, Liu Y, Liu K, Liu M, Xiao Y, Luo H, Zuo X, Li Y, Xiao X, Zhang H (2018) Calcinosis and malignancy are rare in Chinese adult patients with myositis and nuclear matrix protein 2 antibodies identified by an unlabeled immunoprecipitation assay. Clin Rheumatol 37:2731–2739
43. Muro Y, Sugiura K, Hoshino K, Akiyama M (2012) Disappearance of anti-MDA-5 autoantibodies in clinically amyopathic DM/interstitial lung disease during disease remission. Rheumatology (Oxford) 51:800–804
44. Marie I, Hatron PY, Cherin P, Hachulla E, Diot E, Vittecoq O, Menard JF, Jouen F, Dominique S (2013) Functional outcome and prognostic factors in anti-Jo-1 patients with antisynthetase syndrome. Arthritis Res Ther 15:R149
45. Cavazzana I, Fredi M, Ceribelli A, Mordenti C, Ferrari F, Carabellese N, Tincani A, Satoh M, Franceschini F (2016) Testing for myositis specific autoantibodies: comparison between line blot and immunoprecipitation assays in 57 myositis sera. J Immunol Methods 433:1–5