Modern Rheumatology, **35**, 2025, 118–125
DOI: https://doi.org/10.1093/mr/roae052
Advance Access Publication Date: 28 May 2024
Original Article

Clinical importance of anti-Ro52 antibody in polymyositis and dermatomyositis

Toshiki Sugita, Hiroto Tsuboi*, Naoki Sugita, Rai Akiyoshi, Yuki Kuroda, Akira Kawashima, Fumina Kawashima, Daiki Tabuchi, Fumika Honda, Ayako Ohyama, Saori Abe, Ayako Kitada, Hiromitsu Asashima, Haruka Miki, Shinya Hagiwara, Yuya Kondo and Isao Matsumoto

Department of Rheumatology, Institute of Medicine, University of Tsukuba, Ibaraki, Japan

*Correspondence: Hiroto Tsuboi; Hiroto-Tsuboi@md.tsukuba.ac.jp; Department of Rheumatology, Institute of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan.

ABSTRACT

Objectives: To clarify the clinical features of anti-Ro52 antibody (Ab)-positive polymyositis (PM)/dermatomyositis (DM).

Methods: We retrospectively examined the clinical features and status of anti-Ro52 Abs in patients with PM/DM admitted to the University of Tsukuba Hospital between January 2019 and February 2023. We compared the anti-Ro52 Ab-positive and anti-Ro52 Ab-negative groups.

Results: A total of 40 patients were selected and analysed. Twenty-three cases were PM, and 17 cases were DM (including six clinically amyopathic DM). Twenty-two cases were positive for anti-Ro52 Ab, 14 for anti-ARS Ab, and 6 for anti-MDA5 Ab. Interstitial lung disease was detected in 29 cases, nine of which were rapidly progressive. Glucocorticoid-resistant cardiomyopathy was detected in six cases. Of the 22 anti-Ro52 Ab-positive cases, only 3 were single-positive and the remaining 19 cases simultaneously had other autoantibodies. Comparing the anti-Ro52 Ab-positive and anti-Ro52 Ab-negative groups, the frequencies of anti-ARS Ab positivity (63.6% vs. 0%), interstitial lung disease (95.5% vs. 44.4%), glucocorticoid-resistant cardiomyopathy (27.3% vs. 0%), concomitant use of immunosuppressants (95.5% vs. 55.6%), and levels of C-reactive protein were significantly higher in the anti-Ro52 Ab-positive group ($P < .05$).

Conclusions: Anti-Ro52 Abs were frequently positive in PM/DM, and may be useful as a severity marker.

KEYWORDS: Polymyositis; dermatomyositis; anti-Ro52 antibody

Introduction

Polymyositis (PM) and dermatomyositis (DM) are connective tissue diseases (CTDs) that cause symmetric proximal muscle weakness due to inflammation of skeletal muscle and are classified as forms of idiopathic inflammatory myopathy (IIM). These diseases are clinically characterised by Raynaud's phenomenon, joint symptoms, interstitial lung disease (ILD), cardiac involvement, and malignancy, in addition to muscle and skin symptoms [1, 2]. In particular, ILD and cardiac involvement are poor prognostic factors in PM/DM [3, 4].

Autoantibodies in IIM are classified into myositis-specific autoantibodies (MSAs), which are highly specific for diagnosis, and myositis-associated autoantibodies (MAAs) found in other autoimmune diseases, including IIM [5, 6]. Anti-ARS and anti-MDA5 antibodies (Abs) are two representative MSAs. Patients with anti-ARS Abs are frequently associated with ILD and are reported to respond well to glucocorticoid (GC) therapy while having a high relapse rate [7]. Anti-MDA5 Abs are found in clinically amyopathic DM (CADM), which is frequently complicated by ILD (especially rapidly progressive ILD) and is considered a poor prognostic factor [8, 9].

On the other hand, MAAs are less specific for IIM and may be present in patients with other CTDs [10]. Anti-Ro52 Abs, the most common MAAs, are a subtype of anti-Ro/SS-A Abs and are detected in various CTDs, including IIM, systemic lupus erythematosus (SLE), and systemic sclerosis, as well as Sjögren's syndrome (SS). Anti-Ro52 Abs are involved in the regulation of Type I interferon (IFN) and have recently been reported to correlate with disease severity in CTDs [11]. Particularly in patients with IIM, anti-Ro52 Abs are positive in ∼30%, often coexist with anti-ARS and anti-MDA5 Abs, and have been reported to correlate with the prevalence and severity of ILD [11]. This study aims to analyse the clinical characteristics of anti-Ro52 Ab-positive PM/DM and to evaluate the usefulness of anti-Ro52 Ab as a severity marker.

Materials and methods

Patients

Patients with PM/DM admitted to the University of Tsukuba Hospital (Ibaraki, Japan) between January 2019 and February 2023, who were examined for status of anti-Ro52 Ab, were included in this study. All patients were above 18 years.

Received 12 January 2024; Accepted 23 May 2024
© Japan College of Rheumatology 2024. Published by Oxford University Press.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site–for further information please contact journals.permissions@oup.com.

Downloaded from https://academic.oup.com/mr/article/35/1/118/7683746 by University of Library and Information Science user on 10 January 2025

PM/DM was diagnosed based on the 2015 revised Japanese Ministry of Health, Labour and Welfare criteria for the diagnosis of PM/DM, including nine clinicopathologic findings: (1) rashes—Heliotrope rash, Gottron's papules, or Gottron's sign; (2) proximal weakness, upper or lower extremity and trunk; (3) muscle pain on grasping or spontaneous muscle pain; (4) elevation of creatine kinase (CK) or aldolase; (5) electromyographic findings of myositis; (6) nondestructive arthritis or arthralgias; (7) systemic inflammatory signs; (8) anti-aminoacyl-tRNA synthetase autoantibody; and (9) muscle biopsy evidence of myositis. Definite PM was defined as any four of nine of these findings without rash, while definite DM was defined as rashes +4 other findings [12]. CADM was diagnosed according to the criteria suggested by Gerami [13]. Patients were divided into anti-Ro52 Ab-positive and anti-Ro52 Ab-negative groups to compare their clinical presentations.

Approval for this study was obtained from the Clinical Research Ethics Review Committee, University of Tsukuba Hospital (approval number: H29-154). All methods were performed in accordance with the relevant guidelines and regulations. With the approval of the Clinical Research Ethics Review Committee, University of Tsukuba Hospital, the need for written informed consent was waived by the opt-out method on the website of University of Tsukuba Hospital (https://tsukuba-rheumatology.jp/) because of the retrospective and observational design that used only clinical data obtained through daily clinical practice.

Data collection

This study was designed as a single-centre retrospective observational study. We retrospectively investigated patient characteristics and laboratory findings, including CK, lactate dehydrogenase (LDH), C-reactive protein (CRP), Krebs von den Lungen-6, ferritin, and immunoglobulin G (IgG). ILD was defined as the presence of abnormal chest computed tomography (CT) findings (consolidations, reticulation, grand glass opacity, etc.), with the exclusion of infection. Serum cardiac muscle troponin T, electrocardiogram, echocardiogram, and cardiac magnetic resonance imaging (MRI) were used to evaluate cardiomyopathy.

Anti-SS-A/Ro was measured using the Chemiluminescent Enzyme Immunoassay kit (STACIA MEBLux, Medical and Biological Laboratories, MBL) (only anti-Ro60) or the Ouchterlony method (ENA-2, MBL) (both anti-Ro52 and Ro60). Anti-ARS, anti-MDA5, anti-Mi-2, and anti-TIF1γ were measured using the Enzyme-linked Immunosorbent Assay kit (MESACUP, BML). Anti-Ku, anti-PM-Scl75, anti-PM-Scl100, anti-SRP, anti-Jo-1, anti-PL-7, anti-PL-12, anti-OJ, anti-EJ, and anti-Ro52 were measured by immunoblot assay (EUROLINE Myositis profile 3, EUROIMMUN Japan).

Statistical analysis

Descriptive statistics for clinical characteristics are expressed as percentages and medians. Continuous variables were compared using the Mann–Whitney *U* test. Categorical data were compared using Fisher's exact test. The survival rates were analysed using the Kaplan–Meier method, and differences between groups were assessed by the log-rank test. Probability values of less than .05 in a two-tailed test were considered significant.

Results

Characteristics and clinical presentations

A total of 40 patients were analysed in this study. Characteristics and clinical features of all patients are detailed in Table 1. The median age at diagnosis was 61.5 [interquartile range 48.8–69.3] years, and 34 patients were female. Twenty-three cases were PM, and 17 cases were DM (including six CADM). Anti-Ro52 Ab was positive in 22 cases (55.0%), anti-ARS Ab in 14 cases (35.0%), and anti-MDA5 Ab in 6 cases (15.0%). Anti-SS-A/Ro Ab was positive in eight cases (20.0%). ILD was detected in 29 cases, nine of which were rapidly progressive. GC-resistant cardiomyopathy was detected in six cases, malignancy in three cases, and SS in four cases. GC was used in almost all patients, and steroid pulse therapy was used in nine patients. Concomitant use of immunosuppressive drugs was found in 31 patients, with tacrolimus in 24 cases and intravenous cyclophosphamide (IVCY) in 12 cases.

Comparison of anti-Ro52 Ab-positive and anti-Ro52 Ab-negative groups

Comparing the anti-Ro52 Ab-positive and anti-Ro52 Ab-negative groups, the frequencies of anti-ARS Ab positivity (63.6% vs. 0%), ILD (95.5% vs. 44.4%), GC-resistant cardiomyopathy (27.3% vs. 0%), concomitant use of immunosuppressants (95.5% vs. 55.6%), and levels of CRP [0.66 (0.16–1.46) vs. 0.09 (0.04–0.35)] were significantly higher in the anti-Ro52 Ab-positive group ($P < .05$) (Table 2). Serum IgG levels also tended to be higher in the positive group ($P = .051$). The frequencies of PM/DM, positivity of anti-MDA5 Abs, malignancies, and SS were comparable between groups.

Ab profiles

Of the 22 cases positive for anti-Ro52 Abs, only three were single-positive, while the remaining 19 cases simultaneously had other autoantibodies; 14 cases with anti-ARS Abs, 2 cases with anti-SRP Abs, 2 cases with anti-MDA5 Abs, 1 case with anti-PM-Scl75 Abs, and 1 case with anti-Ku Abs (Figure 1). One case was triple-positive for anti-Ro52, anti-ARS, and anti-SRP Abs. All 14 anti-ARS Ab-positive cases were positive for anti-Ro52 Abs. Of all anti-Ro52 Ab-positive patients, 14 were anti-ARS Ab-positive and 8 were anti-ARS Ab-negative. There were no significant differences in patient backgrounds, clinical data, complications, or medications between the anti-ARS Ab-positive and anti-ARS Ab-negative groups (Table 3). Anti-ARS Abs included four cases with anti-Jo-1 Abs, six cases with anti-EJ Abs, one case with anti-OJ Abs, three cases with anti-PL-7 Abs, and two cases with anti-PL-12 Abs. In one case, anti-EJ and anti-PL-7 Abs coexisted, and in another case, anti-EJ and anti-PL-12 Abs coexisted. There were no significant differences in clinical features among ARS subtypes. Among the anti-ARS Ab-negative cases, one case was anticytoplasmic Ab-positive and was single-positive for anti-Ro52 Abs. There was a possibility that this patient might be positive for anti-OJ Abs, since anti-OJ Abs cannot be detected by commercial kits [14].

Clinical courses

CK levels improved significantly in both the anti-Ro52 Ab-positive and anti-Ro52 Ab-negative groups at 4 weeks after the start of treatment (Figure 2(a)). Among the 29 patients

Downloaded from https://academic.oup.com/mr/article/35/1/118/7683746 by University of Library and Information Science user on 10 January 2025

Table 1. Baseline clinical features of the 40 enrolled patients.

Clinical characteristics	Median (interquartile range) or number (%)
Age, years	61.5 (48.8–69.3)
Sex, M/F	6/34
PM/DM/CADM	23/17/6
CK, mg/dl	431 (221–1286)
LDH, mg/dl	357 (285–478)
IgG, mg/dl ($n = 67$)	1652 (1327–2200)
Ferritin, ng/ml	134 (50–472)
CRP, mg/dl	0.30 (0.09–1.32)
Antinuclear Ab	
Homogeneous	7 (17.5%)
Speckled	16 (40.0%)
Centromere	4 (10.0%)
Nucleolar	4 (10.0%)
Cytoplasmic	13 (32.5%)
Anti-Ro52 Ab-positive	22 (55.0%)
Anti-SS-A Ab-positive	8 (20.0%)
Anti-ARS Ab-positive	14 (35.0%)
Anti-MDA5 Ab-positive	6 (15.0%)
Organ involvement	
ILD	29 (72.5%)
Rapidly progressive ILD	9 (22.5%)
GC-resistant cardiomyopathy	6 (15.0%)
Sjögren's syndrome	4 (10.0%)
Malignancy	3 (7.5%)
GC	39 (97.5%)
GC pulse therapy	9 (22.5%)
Initial dose of equivalent PSL (mg/day)	50.0 (40.0–60.0)
IVIG	2 (5.0%)
Concomitant use of immunosuppressants	31 (77.5%)
TAC	24 (60.0%)
IVCY	12 (30.0%)
AZP	4 (10.0%)
MMF	3 (7.5%)
TOF	3 (7.5%)
MTX	2 (5.0%)
CyA	1 (2.5%)

Abbreviations: AZP, azathioprine; CyA, cyclosporin A; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; MTX, methotrexate; PSL, prednisolone; TAC, tacrolimus hydrate; TOF, tofacitinib citrate.

Table 2. Clinical characteristics of patients with or without anti-Ro52 Ab.

Clinical characteristics	Anti-Ro52 Ab-negative ($n = 18$)	Anti-Ro52 Ab-positive ($n = 22$)	*P*-value
Age, years	65.5 (50.0–70.0)	58.5 (48.3–65.0)	.355
Sex, M/F	2/16	4/18	.673
PM/DM	11/7	12/10	.755
CADM	4	2	.381
CK, mg/dl	395 (188–787)	486 (260–1424)	.308
LDH, mg/dl	336 (282–466)	372 (295–518)	.591
IgG, mg/dl ($n = 67$)	1480 (1258–1652)	1889 (1426–2290)	.051
Ferritin, ng/ml	66 (45–309)	159 (89–540)	.212
CRP, mg/dl	0.09 (0.04–0.35)	0.66 (0.16–1.46)	.017
Antinuclear Ab			
Homogeneous	6 (33.3%)	1 (4.5%)	.033
Speckled	7 (38.9%)	9 (40.1%)	1.000
Centromere	1 (5.6%)	3 (13.6%)	.613
Nucleolar	3 (16.7%)	1 (4.5%)	.310
Cytoplasmic	2 (11.1%)	11 (50.0%)	.016
Anti-SS-A Ab-positive	2 (11.1%)	6 (27.2%)	.258
Anti-ARS Ab-positive	0 (0%)	14 (63.6%)	.001
Anti-MDA5 Ab-positive	4 (22.2%)	2 (9.1%)	.381
Organ involvement			
ILD	8 (44.4%)	21 (95.5%)	<.001
Rapidly progressive ILD	3 (16.7%)	6 (27.3%)	.476
GC-resistant cardiomyopathy	0 (0%)	6 (27.3%)	.024
Sjögren's syndrome	0 (0%)	4 (18.2%)	.114
Malignancy	3 (16.7%)	0 (0%)	.083
GC	17 (94.4%)	22 (100%)	1.000
GC pulse therapy	3 (16.7%)	6 (27.3%)	.476
Initial dose of equivalent PSL (mg/day)	50.0 (40.0–50.0)	50.0 (45.0–60.0)	.200
IVIG	1 (5.6%)	1 (4.5%)	1.000
Concomitant use of immunosuppressants	10 (55.6%)	21 (95.5%)	.013
TAC	8 (44.4%)	16 (72.7%)	.106
IVCY	4 (22.2%)	8 (36.4%)	.491
AZP	3 (16.7%)	1 (4.5%)	.310
MMF	1 (5.6%)	2 (9.1%)	1.000
TOF	3 (16.7%)	1 (4.5%)	.310
MTX	1 (5.6%)	1 (4.5%)	1.000
CyA	0 (0%)	1 (4.5%)	1.000

Abbreviations are the same as in Table 1.

with ILD complication (21 in the anti-Ro52 Ab-positive group and 8 in anti-Ro52 Ab-negative group), 25 patients (19 in the anti-Ro52 Ab-positive group and 6 in the anti-Ro52 Ab-negative group) were evaluated for efficacy of treatment by CT within the first 3 months of treatment. ILD improved in 15 patients (78.9%) in the positive group and in 6 patients (100%) in the negative group, including four CADM, as assessed by CT within 3 months. Four of 19 patients in the positive group with ILD showed deterioration or remained unchanged although there was no significant difference in the response to treatment of ILD between the anti-Ro52 Ab-positive and anti-Ro52 Ab-negative groups ($P = .540$) (Figure 2(b)). Comparison of anti-Ro52 Ab-positive ($n = 21$) and anti-Ro52 Ab-negative ($n = 8$) groups among 29 patients with ILD complication showed no significant differences in clinical course, imaging, treatment response, or outcome other than patient background such as anti-ARS Abs or anti-MDA5 Abs (Table 4).

GC-resistant cardiomyopathy was observed in six patients, all of whom were positive for anti-Ro52 Abs (Table 5). We defined cardiomyopathy as a newly diagnosed conduction block on electrocardiogram or late gadolinium enhancement (LGE) findings on MRI or newly diagnosed reduced ejection fraction on echocardiography, which was not due to myocardial ischaemia. We also defined GC resistance as the appearance of new myocardial involvement, despite therapeutic intervention with GC or the absence of cardiomyopathy improvement after initiation of treatment. Anti-ARS Abs were positive in five of the six patients. Five patients had abnormal electrocardiogram findings, and all had abnormal findings on echocardiography, including high tricuspid regurgitation

Downloaded from https://academic.oup.com/mr/article/35/1/118/7683746 by University of Library and Information Science user on 10 January 2025

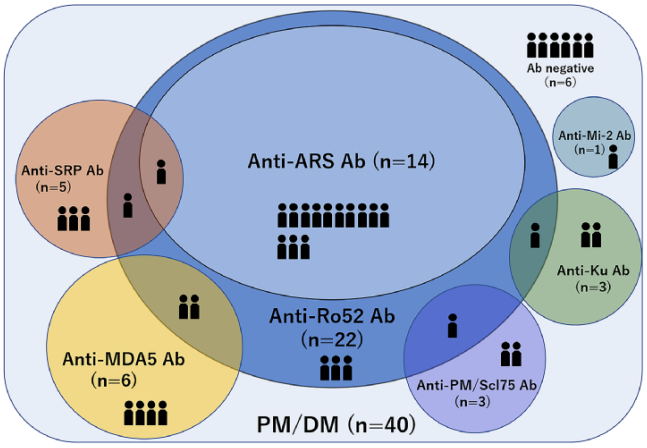

Figure 1. Autoantibody profiles for all patients.

Venn diagram representing the profile of autoantibodies in 40 PM and DM patients.

pressure gradient, pericardial effusion, systolic dysfunction, and myocardial oedema. Although three patients had tricuspid regurgitation pressure gradient levels above 30 mmHg, all were mild or moderate elevations, so cardiac catheterisation was not performed and treatment for pulmonary hypertension was not required. Regarding the pericardial effusion, all cases were accompanied by new conduction block or LGE findings on MRI or reduced ejection fraction other than effusion, which were considered to be pericarditis associated with cardiomyopathy. Immunosuppressive drugs, including IVCY, were effective in five of the six patients, while the remaining single patient developed complete atrioventricular block even after the addition of immunosuppressive drugs, leading to pacemaker implantation.

Discussion

In this study, 40 patients were included and divided into anti-Ro52 Ab-positive (22 patients) and anti-Ro52 Ab-negative groups (18 patients). In the positive group, only three cases were single-positive for anti-Ro52 Abs, while the other 19 cases were associated with other autoantibodies. Anti-ARS Abs were positive in 14 patients, all of whom were also positive for anti-Ro52 Abs, while there was no clinically significant difference between the anti-ARS Ab-positive and anti-Ro52 Ab-negative groups in the anti-Ro52 Ab-positive patients. Comparing the anti-Ro52 Ab-positive and anti-Ro52 Ab-negative groups, the positive group had significantly higher rates of ILD, GC-resistant cardiomyopathy, concomitant use of immunosuppressive drugs, and higher levels of CRP. Although there was no significant difference in mortality between the two groups, all six patients in the anti-Ro52 Ab-negative group with ILD, including four with CADM, showed improvement on CT after treatment. We focused on three important findings as follows.

First, in our study, the positive rate of anti-Ro52 Abs was the highest at 55.0% among all MSAs and MAAs, while the single-positive rate was low at 7.5%. The prevalence of anti-Ro52 Abs in IIM is reported to be 30–35% [15, 16], and many of these cases show overlap with other autoantibodies. In another report, anti-Ro52 Abs were found in 52.9% (81 of 153 cases) of DM patients, of which 9.2% (14 cases) were single-positive and 43.8% (67 cases) had overlap with other autoantibodies [17]. Thus, although the positive rate of anti-Ro52 Abs in IIMs is high, many of these cases coexist with other Abs. In CTDs other than PM/DM, positive rates of anti-Ro52 Abs are also high, reported to be 37–75% in primary SS and 42–50% in SLE [11]. In primary SS, anti-Ro52 Abs are associated with the presence of ILD, severe salivary dysfunction, and hypergammaglobulinemia [18, 19]. In SLE, anti-Ro52 Abs are associated with high immunoglobulin levels and decreased leukocyte and lymphocyte counts, plus a higher activity score [20]. Anti-Ro52 Abs are frequently detected in CTDs, including PM/DM, and present unique clinical features for each disease.

Second, we noted that ILD and GC-resistant myocarditis were significantly more frequent in the anti-Ro52 Ab-positive group than the anti-Ro52 Ab-negative group. Anti-Ro52 Ab

Table 3. Clinical characteristics in Ro52 Ab-positive patients with or without anti-ARS Ab.

Clinical characteristics	Anti-ARS Ab-negative ($n = 8$)	Anti-ARS Ab-positive ($n = 14$)	*P*-value
Age, years	54.5 (43.5–66.5)	60.0 (50.0–64.5)	.562
Sex, M/F	2/6	2/12	.602
PM/DM	5/3	7/7	.675
CADM	2 (25.0%)	0 (0.0%)	.121
CK, mg/dl	663 (252–1330)	435 (279–1424)	1.000
LDH, mg/dl	414 (347–519)	359 (268–517)	.453
IgG, mg/dl ($n = 67$)	1798 (1478–2274)	1894 (1480–2290)	.198
Ferritin, ng/ml	412 (165–794)	132 (61–199)	.117
CRP, mg/dl	0.54 (0.16–1.52)	0.66 (0.24–1.26)	.973
Antinuclear Ab			
Homogeneous	1(12.5%)	0 (0%)	.364
Speckled	4(50.0%)	5(35.7%)	.662
Centromere	1(12.5%)	2(14.3%)	1.000
Nucleolar	0(0%)	1(7.1%)	1.000
Cytoplasmic	1(12.5%)	10(71.4%)	.024
Anti-SS-A Ab-positive	3 (37.5%)	3 (21.4%)	.624
Anti-MDA5 Ab-positive	2 (25.0%)	0 (0%)	.121
Organ involvement			
ILD	7 (87.5%)	14 (100%)	.367
Rapidly progressive ILD	2 (25.0%)	4 (28.6%)	1.000
GC-resistant cardiomyopathy	1 (12.5%)	5 (35.7%)	.613
Sjögren's syndrome	1 (12.5%)	3 (21.4%)	1.000
Malignancy	0 (0%)	0 (0%)	1.000
GC	8 (100%)	14 (100%)	1.000
GC pulse therapy	3 (37.5%)	3 (21.4%)	.624
Initial dose of equivalent PSL (mg/day)	50.0 (50.0–51.3)	50.0 (40.0–60.0)	.804
IVIG	1 (12.5%)	0 (0%)	1.000
Concomitant use of immunosuppressants	7 (87.5%)	14 (100%)	.367
TAC	6 (75.0%)	10 (71.4%)	1.000
IVCY	3 (37.5%)	5 (35.7%)	1.000
AZP	1 (12.5%)	0 (0%)	.364
MMF	1 (12.5%)	1 (7.1%)	1.000
TOF	1 (12.5%)	0 (0%)	.364
MTX	0 (0%)	1 (7.1%)	1.000
CyA	0 (0%)	1 (7.1%)	1.000

Abbreviations are the same as in Table 1.

Downloaded from https://academic.oup.com/mr/article/35/1/118/7683746 by University of Library and Information Science user on 10 January 2025

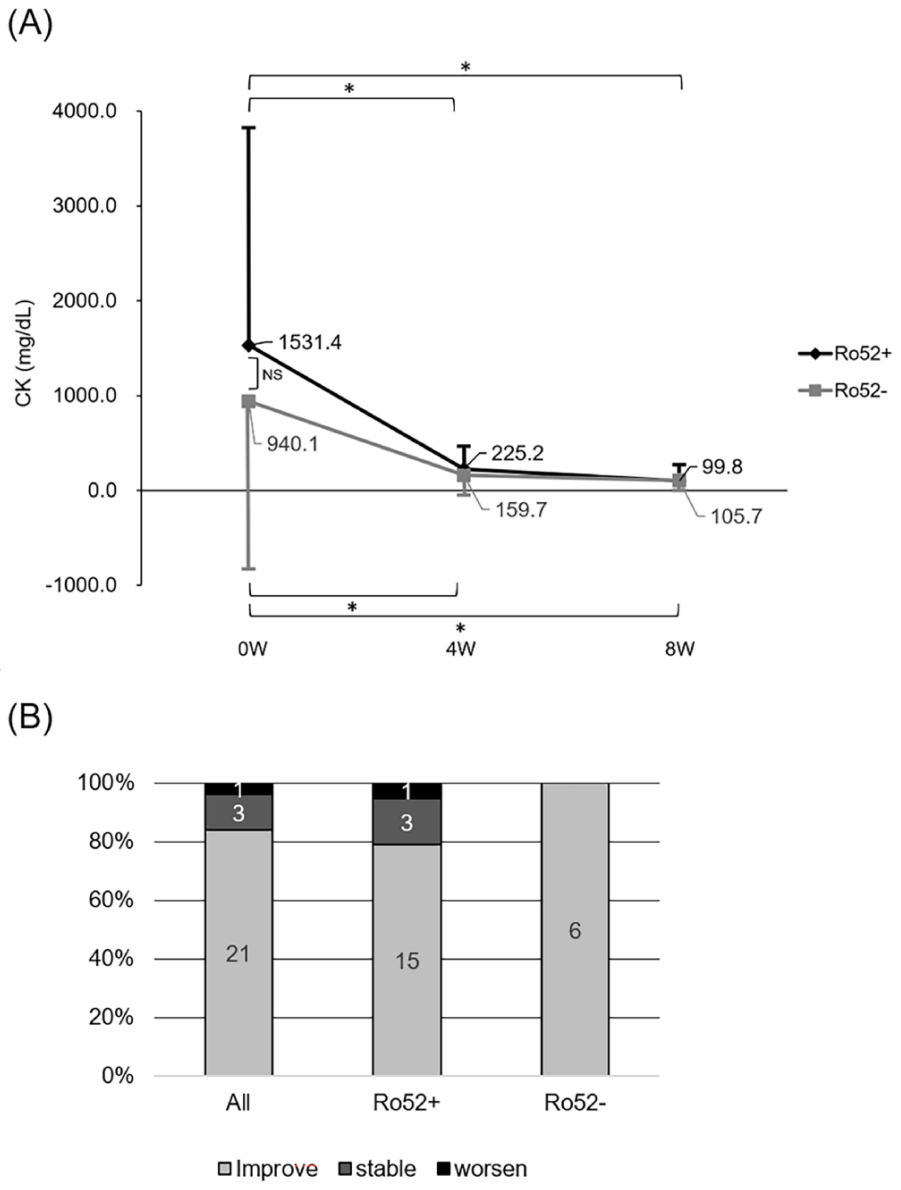

Figure 2. Clinical courses after treatment.

(a) Changes in CK values after treatment. *$P < .05$ vs. 0 weeks (baseline), Wilcoxon signed rank test. NS = not significant. (b) Efficacy of treatment on ILD as assessed using CT within 3 months. The numbers represent the cases in each category. There were no significant differences in the response to treatment of ILD between the anti-Ro52 Ab-positive and anti-Ro52 Ab-negative groups ($P = .540$).

has been reported to be an independent risk factor for ILD in DM [17], and the anti-Ro52 Ab-positive rate in IIM with ILD has been reported to be 40–60% in anti-ARS Ab-positive patients [21, 22] and 60–70% in anti-MDA5 Ab-positive patients [23, 24], which is higher than those in all IIMs. Although anti-MDA5 Abs are independently associated with rapidly progressive ILD and mortality [25], more severe ILD and higher mortality have been reported in coexisting cases with anti-Ro52 Abs [24]. Therefore, the presence of both anti-MDA5 Abs and anti-Ro52 Abs should be considered a risk factor for developing severe ILD and anti-Ro52 Ab may be useful as a severity marker in practice for CADM. Cardiomyopathy in IIM was previously considered a rare complication, but recent cohorts have shown that its frequency is increasing, with reported incidence rates ranging from 9 to 72% [26]. A relatively large longitudinal study of 162 patients with IIM reported that myocardial involvement was the major poor prognostic factor for death [3]. However, there is only one report of association between anti-Ro52 Abs and myocardial involvement. A report from China showed that positive rates of anti-Ro52 and anti-Jo-1 Abs were significantly higher in DM patients with cardiomyopathy complications than in cases without [27]. Additionally, another paper from the same university reported that, among anti-ARS Ab-positive IIM patients, those with myocardial involvement had significantly higher positivity for anti-Ro52 Abs [28]. Although the causal relationship between anti-Ro52 Abs and myocardial damage has not been clarified, in

Downloaded from https://academic.oup.com/mr/article/35/1/118/7683746 by University of Library and Information Science user on 10 January 2025

Table 4. Clinical characteristics in patients with ILD complication with or without anti-Ro52 Ab.

Clinical characteristics	Anti-Ro52 Ab-negative ($n = 8$)	Anti-Ro52 Ab-positive ($n = 21$)	*P*-value
Age, years	66.0 (51.5–74.3)	59.0 (49.0–65.0)	0.330
Sex, M/F	2/6	4/17	1.000
PM/DM	2/6	11/10	0.238
CADM	4	2	0.034
CK, mg/dl	347 (182–451)	438 (254–1317)	0.131
LDH, mg/dl	377 (340–448)	368 (287–479)	0.770
IgG, mg/dl ($n = 67$)	1465 (1105–1791)	1911 (1397–2309)	0.193
Ferritin, ng/ml	302 (83–862)	159 (76–459)	0.605
CRP, mg/dl	0.35 (0.03–1.62)	0.71 (0.17–1.51)	0.524
Anti-SS-A Ab-positive	1 (12.5%)	5 (23.8%)	0.647
Anti-ARS antibody-positive	0 (0%)	14 (66.6%)	0.002
Anti-MDA5 Ab-positive	4 (50.0%)	2 (9.5%)	0.034
Rapidly progressive ILD	3 (37.5%)	6 (28.6%)	0.675
Imaging patterns			
UIP	2 (25.0%)	0 (0%)	0.069
NSIP	3 (37.5%)	11 (52.4%)	0.682
OP	3 (37.5%)	8 (38.1%)	1.000
DAD	0 (0%)	2 (9.5%)	1.000
GC	7 (87.5%)	21 (100.0%)	0.276
GC pulse therapy	3 (37.5%)	5 (23.8%)	0.646
Initial dose of equivalent PSL (mg/day)	50.0 (47.5–55.0)	50.0 (45.0–60.0)	0.912
IVIG	0 (0%)	1 (4.8%)	1.000
Concomitant use of immunosuppressants	7 (87.5%)	20 (95.2%)	0.483
TAC	5 (62.5%)	16 (76.2%)	0.646
IVCY	4 (50.0%)	8 (38.1%)	0.683
AZP	1 (12.5%)	1 (4.8%)	0.483
MMF	1 (12.5%)	1 (4.8%)	0.483
TOF	3 (37.5%)	1 (4.8%)	0.053
MTX	0 (0%)	1 (4.8%)	1.000
CyA	0 (0%)	1 (4.8%)	1.000
Treatment response			
Improve	6 (75.0%)[a]	17 (81.0%)	1.000
Stable	0 (0%)	3 (14.3%)	0.540
Worsen	0 (0%)	1 (4.8%)	1.000
Outcome			
Death	0 (0%)	2 (9.5%)	1.000
Relapse	0 (0%)	3 (14.3%)	0.540

Abbreviations: DAD, diffuse alveolar damage; NSIP, nonspecific interstitial pneumonia; OP, organising pneumonia; UIP, usual interstitial pneumonia. The other abbreviations are the same as in Table 1.
[a]$N = 2$, unknown because of loss of follow-up.

the present study, GC-resistant myocardial involvement was also significantly more frequent in the anti-Ro52 Ab-positive group. Therefore, when we treat anti-Ro52 Ab-positive IIM cases, it is recommended to evaluate cardiac enzymes, plus electrocardiography and echocardiography. If cardiomyopathy is present, the use of immunosuppressive agents (such as IVCY) should be considered instead of GC monotherapy. Moreover, we believe that it highlights the importance of careful follow-up not only at the time of diagnosis but also after therapeutic intervention by monitoring cardiac enzymes and echocardiography.

Third, although there were no differences in mortality in this study, the use of immunosuppressive drugs was significantly more frequent in the anti-Ro52 Ab-positive group, which may be related to disease severity through associations with Ro52. Ro52 protein, also known as TRIM21, is a cytoplastic protein with a crucial role in the regulation of inflammation in innate immunity. It consists of four domains: an N-terminal RING domain, a B-box domain, a coiled-coil domain, and a PRY-SPRY domain [29]. TRIM21 induces the proteasomal degradation of pathogens and activates innate immune signals through transcription factors such as NFκB and IRF. On the other hand, TRIM21 is induced by Type I IFN and negatively regulates overproduction of Type I IFN through autophagy [30]. Thus, TRIM21 has both activating and inhibitory effects on innate immunity and anti-Ro52 Abs may amplify Type I IFN by suppressing the inhibitory effect of TRIM21. Additionally, TRIM21 regulates IRF5 expression through ubiquitination [31], thereby playing an inhibitory role in human B-cell proliferation. SLE patients positive for anti-Ro52 Abs exhibit significantly enhanced differentiation of quiescent B cells into plasmablasts and increased Ab production [32]. This observation suggests that anti-Ro52 Abs may contribute to B-cell differentiation by suppressing TRIM21 function. In our study, serum IgG levels tended to be higher in the anti-Ro52 Ab-positive group. This suggests that anti-Ro52 Abs might be involved in B-cell activation in PM/DM. While anti-Ro52 Abs are not highly specific for certain autoimmune diseases, they have recently attracted attention as markers of disease severity. The multifaceted impact of anti-Ro52 Abs on immune regulatory machinery, such as IFN signalling and B-cell differentiation, highlights a potential significance in understanding and assessing the severity of autoimmune diseases.

Our study has several limitations. First, multivariate analysis could not be performed owing to the insufficient number of patients. Moreover, all anti-ARS Ab-positive cases were anti-Ro52 Ab-positive; the influence of anti-ARS Abs could thus not be ignored with regard to our results. Second, anti-OJ Abs are difficult to measure with commercial kits [14], and one case of single-positive for anti-Ro52 Abs was positive for anticytoplasmic Abs and may have been positive for anti-OJ Abs. Third, we could not confirm whether the IFN signature was actually increased in the anti-Ro52 Ab-positive group as serum IFN signatures were not measured. Further research is needed with large numbers of cases and their IFN signature values. Finally, as our design was a monocentred, retrospective observational study; multicentre prospective studies with matching treatment between anti-Ro52 Ab-positive or anti-Ro52 Ab-negative cases are a natural evolution for verifying the conclusions of this study.

In conclusion, our study suggests that anti-Ro52 Abs are frequently positive in PM/DM and positive cases have significantly higher rates of anti-ARS Ab positivity, ILD, GC-resistant cardiomyopathy, concomitant use of immunosuppressants, and higher levels of CRP. Anti-Ro52 Ab might therefore be useful as a severity marker in PM/DM because of its tight association with prognosis.

Downloaded from https://academic.oup.com/mr/article/35/1/118/7683746 by University of Library and Information Science user on 10 January 2025

Table 5. Clinical characteristics of patients with GC-resistant cardiomyopathy.

		1	2	3	4	5	6
Age, years		48	72	53	58	62	57
Sex, M/F		M	F	F	F	F	F
PM/DM		DM	PM	PM	PM	PM	PM
L/D baseline	CK, mg/dl	1979	1460	1317	8285	6771	792
	CK-MB, mg/dl	ND	20	29	159	395	17
	cTnT, ng/ml	ND	0.24	0.31	0.36	1.34	0.13
	CRP, mg/dl	4.01	0.81	1.32	0.09	3.20	9.64
Anti-Ro52 Ab		+	+	+	+	+	+
Anti-ARS Ab		+	+	+	+	+	–
Anti-MDA5 Ab		–	–	–	–	–	–
Other Abs		Jo-1	EJ	PL-7	EJ	PL-7, SRP	–
Symptoms		–	Leg oedema	Pulsation	–	–	–
Newly diagnosed ECG		WNL	Negative T wave	NSVT Complete AV block	Negative T wave ST depression	Bifascicular block	Bifascicular block
UCG	EF	50%	40%	75%	60%	60%	70%
	TRPG (mmHg)	27	20	42	22	33	37
	Pericardial effusion	–	+	+	+	+	+
	Myocardial oedema	–	–	–	+	–	–
MRI (LGE)		+	–	+	+	–	ND
Immunosuppressive treatment		PSL, CyA, MMF, IVCY	PSL, TAC, IVCY	PSL, IVCY	PSL, TAC, IVCY	PSL, IVCY	PSL, TAC, IVCY
Other treatment		BBL ACEI	BBL diuretics	BBL diuretics	ARB diuretics	–	Diuretics
Outcome	Overall	Improve	Improve	Worsen	Improve	Improve	Improve
	Details of findings	Improvement of EF	Negative cTnT, improvement of leg oedema	Pacemaker implantation	Negative cTnT, improvement of myocardial oedema	Negative cTnT, decrease of pericardial effusion	Negative cTnT, decrease of pericardial effusion

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AV, atrioventricular; BBL, beta-blocker; cTnT, cardiac muscle troponin T; CyA, cyclosporin A; ECG, electrocardiogram; EF, ejection fraction; F, female; M, male; L/D, laboratory data; MMF, mycophenolate mofetil; ND, not determined; NSVT, nonsustained ventricular tachycardia; ST, the part from the end of the S wave to the beginning of the T wave; PSL, prednisolone; TAC, tacrolimus hydrate; TRPG, tricuspid regurgitation pressure gradient; UCG, ultrasonic echocardiography; WNL, within normal limits.

Acknowledgements

The authors would like to thank Dr Bryan J. Mathis of the University of Tsukuba Hospital International Medical Center for language revision.

Conflict of interest

None declared.

Funding

None declared.

References

[1] Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975;**292**:344–7.
[2] Lundberg IE, de Visser M, Werth VP. Classification of myositis. *Nat Rev Rheumatol* 2018;**14**:269–78.
[3] Danko K, Ponyi A, Constantin T *et al*. Long-term survival of patients with idiopathic inflammatory myopathies according to clinical features: a longitudinal study of 162 cases. *Medicine* 2004;**83**:35–42.
[4] Fathi M, Lundberg IE. Interstitial lung disease in polymyositis and dermatomyositis. *Curr Opin Rheumatol* 2005;**17**:701–6.
[5] Betteridge Z, Tansley S, Shaddick G *et al*. Frequency, mutual exclusivity and clinical associations of myositis autoantibodies in a combined European cohort of idiopathic inflammatory myopathy patients. *J Autoimmun* 2019;**101**:48–55.
[6] Satoh M, Tanaka S, Ceribelli A *et al*. A comprehensive overview on myositis-specific antibodies: new and old biomarkers in idiopathic inflammatory myopathy. *Clin Rev Allergy Immunol* 2017;**52**:1–19.
[7] Yoshifuji H, Fujii T, Kobayashi S *et al*. Anti-aminoacyl-tRNA synthetase antibodies in clinical course prediction of interstitial lung disease complicated with idiopathic inflammatory myopathies. *Autoimmunity* 2006;**39**:233–41.
[8] Yoshida N, Okamoto M, Kaieda S *et al*. Association of anti-aminoacyl-transfer RNA synthetase antibody and anti-melanoma differentiation-associated gene 5 antibody with the therapeutic response of polymyositis/dermatomyositis-associated interstitial lung disease. *Respir Investig* 2017;**55**:24–32.
[9] Li L, Wang Q, Yang F *et al*. Anti-MDA5 antibody as a potential diagnostic and prognostic biomarker in patients with dermatomyositis. *Oncotarget* 2017;**8**:26552–64.
[10] Betteridge Z, McHugh N *et al*. Myositis-specific autoantibodies: an important tool to support diagnosis of myositis. *J Intern Med* 2016;**280**:8–23.
[11] Decker P, Moulinet T, Pontille F *et al*. An updated review of anti-Ro52(TRIM21) antibodies impact in connective tissue diseases clinical management. *Autoimmun Rev* 2022;**21**:103013.
[12] Jinnin M, Ohta A, Ishihara S *et al*. First external validation of sensitivity and specificity of European League Against Rheumatism (EULAR)/ American College of Rheumatology (ACR) classification criteria for idiopathic inflammatory myopathies with a Japanese cohort. *Ann Rheum Dis* 2020;**79**:387–92.

Downloaded from https://academic.oup.com/mr/article/35/1/118/7683746 by University of Library and Information Science user on 10 January 2025

[13] Gerami P, Schope JM, McDonald L *et al*. A systemic review of adult-onset clinically amyopathic dermatomyositis (dermatomyositis siné myositis): a missing link within the spectrum of the idiopathic inflammatory myopathies. *J Am Acad Dermatol* 2006;**54**:597–613.
[14] Hamaguchi Y, Kuwana M, Takehara K. Comparison of anti-OJ antibody detection assays between an immunoprecipitation assay and line blot assay. *Mod Rheumatol* 2017;**27**:551–2.
[15] Koenig M, Fritzler MJ, Targoff IN *et al*. Heterogeneity of autoantibodies in 100 patients with autoimmune myositis: insights into clinical features and outcomes. *Arthritis Res Ther* 2007;**9**:R78.
[16] Schulte-Pelkum J, Fritzler M, Mahler M. Latest update on the Ro/SS-A autoantibody system. *Autoimmun Rev* 2009;**8**:632–7.
[17] Xing X, Li A, Li C. Anti-Ro52 antibody is an independent risk factor for interstitial lung disease in dermatomyositis. *Respir Med* 2020;**172**:106134.
[18] Retamozo S, Akasbi M, Brito-Zerón P *et al*. Anti-Ro52 antibody testing influences the classification and clinical characterisation of primary Sjögren's syndrome. *Clin Exp Rheumatol* 2012;**30**:686–92.
[19] Dong X, Zhou J, Guo X *et al*. A retrospective analysis of distinguishing features of chest HRCT and clinical manifestation in primary Sjögren's syndrome-related interstitial lung disease in a Chinese population. *Clin Rheumatol* 2018;**37**:2981–8.
[20] Kvarnström M, Dzikaite-Ottosson V, Ottosson L *et al*. Autoantibodies to the functionally active RING-domain of Ro52/SSA are associated with disease activity in patients with lupus. *Lupus* 2013;**22**:477–85.
[21] Rutjes SA, Vree Egberts WT, Jongen P *et al*. Anti-Ro52 antibodies frequently co-occur with anti-Jo-1 antibodies in sera from patients with idiopathic inflammatory myopathy. *Clin Exp Immunol* 1997;**109**:32–40.
[22] Marie I, Hatron PY, Dominique S *et al*. Short-term and long-term outcome of anti-Jo1-positive patients with anti-Ro52 antibody. *Semin Arthritis Rheum* 2012;**41**:890–9.
[23] Xu A, Ye Y, Fu Q *et al*. Prognostic values of anti-Ro52 antibodies in anti-MDA5-positive clinically amyopathic dermatomyositis associated with interstitial lung disease. *Rheumatology (Oxford)* 2021;**60**:3343–51.
[24] Gui X, Shenyun S, Ding H *et al*. Anti-Ro52 antibodies are associated with the prognosis of adult idiopathic inflammatory myopathy-associated interstitial lung disease. *Rheumatology* 2022;**61**:4570–8.
[25] Wu X, Guo L, Fu Y *et al*. Interstitial lung disease in anti-MDA5 positive dermatomyositis. *Clin Rev Allergy Immunol* 2021;**60**:293–304.
[26] Chen F, Peng Y, Chen M. Diagnostic approach to cardiac involvement in idiopathic inflammatory myopathies. *Int Heart J* 2018;**59**:256–62.
[27] Li YH, Du Y, Liu ML *et al*. Analysis of immunological characteristic of dermatomyositis patients with myocardial involvement. *Zhonghua Yi Xue Zhi* 2020;**100**:753–6.
[28] Luo L, Xing XY, Xiao YS *et al*. Clinical and immunological characteristics of patients with anti-synthetase syndrome complicated with cardiac involvement. *Beijing Da Xue Bao Yi Xue Ban* 2021;**53**:1078–82.
[29] Jones EL, Laidlaw SM, Dustin LB *et al*. TRIM21/Ro52-roles in innate immunity and auto immune disease. *Front Immunol* 2021;**12**:738473.
[30] Rhodes DA, Isenberg DA. TRIM21 and the function of antibodies inside cells. *Trends Immunol* 2017;**38**:916–26.
[31] Lazzari E, Korczeniewska J, Gabhann JN *et al*. TRIpartite Motif 21 (TRIM21) differentially regulates the stability of interferon regulatory factor 5 (IRF5) isoforms. *PLoS One* 2014;**9**:e103609.
[32] Kunishita Y, Yoshimi R, Kamiyama R *et al*. TRIM21 dysfunction enhances aberrant B-cell differentiation in autoimmune pathogenesis. *Front Immunol* 2020;**11**:98.

Downloaded from https://academic.oup.com/mr/article/35/1/118/7683746 by University of Library and Information Science user on 10 January 2025