Original Article

Anti-SS-A/Ro antibody positivity as a risk factor for relapse in patients with polymyositis/dermatomyositis

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Text pages:10, tables:2, figures:2

Key words: anti-SS-A/Ro antibodies, dermatomyositis, polymyositis, ,

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ABSTRACT

Objective: To elucidate predictors of relapse in patients with polymyositis and dermatomyositis (PM/DM).

Methods: Fifty PM/DM patients who achieved disease stabilization at Okayama University Hospital in 2004-2014 were enrolled retrospectively. Candidate predictors such as demographic factors, clinical symptoms, laboratory data, and treatment status were compared.

Results: The mean age of enrolled patients was 58 years; 34 were female. The patient groupings were as follows: 21 with PM, 27 with DM, and 2 with clinically amyopathic DM. During a mean observation period of 685 days, 5 patients (10%) died and 20 (40%) relapsed. The relapsed patients displayed baseline muscle weakness less frequently (85% vs. 100%, $p = 0.03$) and anti-SS-A/Ro antibody more frequently (65% vs. 27%, $p = 0.007$). Anti-SS-A/Ro-positive patients exhibited a higher relapse rate than anti-SS-A/Ro-negative patients (log-rank test, $p = 0.03$). Anti-SS-A/Ro-positive patients also exhibited higher anti-Jo-1 antibody positivity and lower levels of serum complement. After adjusting anti-Jo-1 antibody positivity, age, sex, CK < 500 IU/L, and lung involvement, anti-SS-A/Ro positivity was still an independent risk factor for higher relapse-rate (odds ratio, 5.5; 95% confidence interval, 1.4-25.1).

Conclusion: Anti-SS-A/Ro antibody positivity may be a useful biomarker for prediction of relapse.

INTRODUCTION

Polymyositis (PM) and dermatomyositis (DM) are idiopathic inflammatory diseases characterized by proximal skeletal muscle weakness and/or distinctive skin manifestations. Various vital organs such as the lung and heart are involved; malignancies may develop. Clinical symptoms are temporarily improved in many patients on treatments, but most experience relapse and/or chronic progression [1-3].

Several reports have investigated risk factors for mortality in patients with PM/DM, such as malignancy, male sex, advanced age, and lung involvement, but the risk factors for relapse remain unexplored [1-6]. Recently, clinically amyopathic DM (CADM), which exhibits the characteristic skin lesions of DM but lacks muscle weakness, was also reported as a mortality risk, but the correlation between CADM and relapse is still unknown [5, 6].

Anti-SS-A/Ro is one of the autoantibodies associated with inflammatory myopathies. Previous reports have shown that patients with inflammatory myopathies are sometimes positive for anti-SS-A/Ro-52 antibody [7-10] and other reports have shown that anti-SS-A/Ro positivity is a poor prognostic factor in patients with PM/DM [4, 11]. Anti-SS-A/Ro-52 antibody is also associated with complication and progression of interstitial lung disease (ILD) in PM/DM [12]; therefore, anti-SS-A/Ro may be associated with not only mortality, but also with relapse in patients with PM/DM.

In the present study, we evaluated relapse in patients with PM/DM and explored the risk factors for lower relapse after disease stabilization. We also investigated the clinical characteristics of patients with PM/DM displaying anti-SS-A/Ro antibody positivity.

MATERIALS AND METHODS

Patient selection

We conducted a retrospective study of patients with PM/DM who achieved disease stabilization during treatment at Okayama University Hospital from 2004 to 2014. Initially, 144 patients were identified according to the International Classification of Diseases, 9th Revision (ICD-9) codes for DM (710.3) and PM (710.4). Of these 144 patients, 33 were excluded because they were first diagnosed before 2004. Of 111 newly diagnosed patients, we enrolled 49 patients as DM / PM using the Bohan and Peter criteria (probable or definite) [13]. Subsequently, 2 of remaining 62 patients were enrolled as CADM using criteria for CADM (i.e., showed typical cutaneous symptom of DM without clinical muscle symptoms [14]). Disease activity was assessed based on the definition options of the myositis intention to treat activity index (MITAX) scoring

system [15]). Disease stabilization was defined as option ≤ 2 in all MITAX items: no exacerbation of clinical symptoms and muscle enzyme laboratory data for at least 4 weeks after initiation of treatment. In the end, one patient who did not achieve disease stabilization was also excluded. Finally, 50 patients were included in the present study (Figure 1).

This study was conducted according to the Declaration of Helsinki and the ethical guidelines for epidemiological research in Japan. Informed consent to participate in the study was obtained from all participants.

Data collection

The following data were collected at baseline: age, sex, time to diagnosis, underlying comorbidities, clinical symptoms, laboratory data, histological data, and treatment status. Laboratory data before the initial treatments included creatine kinase (CK), C-reactive protein (CRP), ferritin, sialylated carbohydrate antigen (KL-6), anti-SS-A/Ro antibody (UniCAP EliA/Phadia or MESACUP-2/MBL), and anti-Jo-1 antibody UniCAP EliA/Phadia or MESACUP-2/MBL). In 29 patients, we also measured the levels of anti-PL-7 antibody, anti-PL-12 antibody, anti-EJ antibody, anti-SRP antibody, anti-Ku antibody, anti-OJ antibody, anti-Mi-2 antibody, anti-PM-Scl75 antibody, and anti-PM-Scl100 antibody using the line blot test kit (Myositis Profile Euro line Blot test kit, Euro Immune, Lubeck, Germany). Electromyography, muscle biopsy, and skin biopsy results were also collected. ILD was diagnosed using thoracic computed tomography. Treatment status included an initial daily dose of glucocorticoid, and concomitant use of glucocorticoid pulse therapy, immunosuppressants, and intravenous immunoglobulin (IVIG).

Relapse rate was the primary outcome of the present study. Relapse was defined as option ≥ 3 in at least one MITAX item, e.g., exacerbation of muscle weakness, ILD, skin rash, arthritis, and/or elevation of myogenic enzymes, that required additional treatment or change of treatment.

Statistical analysis

Clinical characteristics were presented as the mean ± standard deviation (SD) of the number of patients. Continuous variables were compared using Student's *t*-test or the Mann-Whitney U test depending on data distribution, and categorical variables were compared using Fisher's direct probability test. The association of candidate predictors with relapse was modeled with multivariate logistic regression analysis. Selection of candidate predictors was based on the result of univariate analysis and previous reports. Cumulative relapse rate was analyzed using the Kaplan-Meier method and the log-rank test. A p-value of < 0.05 was considered significant. All statistical analyses were performed using the JMP 8.0.2 software package (SAS Institute Inc.,

Cary, NC, USA).

RESULTS

Baseline characteristics and treatment status

The mean age of enrolled patients was 58 years; 34 (68%) were female. The patients were classified as 21 (42%) with PM (12 probable and 9 definite), 27 (54%) with DM (15 probable and 12 definite), and 2 (4%) with CADM. Malignancy was present in 6 patients and Sjögren's syndrome was present in 3. ILD was diagnosed in 30 (60%) patients. Proximal muscle weakness evaluated by the attending physician was found in 47 (94%) patients and myogenic enzymes were elevated in 49 patients (98%). Antibody positivity in the enrolled patients was as follows: anti-Jo-1 antibody, 8 of 50 (16%); anti-SS-A/Ro antibody, 21 of 50 (42%); anti-PL-7 antibody, 4 of 28 (14%); anti-PL-12 antibody, 2 of 28 (7%); anti-EJ antibody, 2 of 28 (7%); anti-SRP antibody, 2 of 28 (7%); and anti-Ku antibody, 2 of 28 (7%). Electromyography was obtained for 34 patients and 21 (62%) showed myogenic abnormalities. Muscle biopsy was performed in 38 patients and skin biopsy was performed in 27. Histological findings were consistent with myositis in 23 (61%) of 38 patients who underwent muscle biopsy, and were compatible with DM in 23 (85%) of 27 patients who underwent skin biopsy.

All patients were treated with glucocorticoids as induction therapy. The mean initial prednisolone (PSL) dose was 46 mg and concomitant glucocorticoid pulse therapy was used in 13 (26%) patients. Immunosuppressants were used in 24 (48%) patients (tacrolimus in 12, azathioprine in 4, cyclosporine in 4, cyclophosphamide in 3, and methotrexate in 1). IVIG was administered in 4 patients.

Clinical course and risk factors for relapse

Disease stabilization in the 50 enrolled patients was achieved at a mean of 33 days after the initiation of treatment. After disease stabilization, 5 patients died during the mean observation period of 680 ± 697 days. The cause of death in these 5 patients was as follows: 2 due to malignancy (one with Stage IIIA ovarian cancer and the other with Stage IV lung cancer), 1 due to *Pneumocystis jiroveci* pneumonia (PCP), and 2 due to unknown causes.

Twenty (40%) patients experienced relapse at least once and required additional treatments or change of treatment. The mean period to first relapse after disease stabilization was 342 ± 317 days. **All patients experienced relapse after more than 30 days after disease stabilization.** Among 20 relapsed patients, 12 showed exacerbation of myositis, 7 showed exacerbation of ILD, 4 showed exacerbation of skin lesions, and

2 showed exacerbation of arthritis. One patients relapsed at day 166 and died of lung cancer at day 757. The mean daily dose of PSL was 11 ± 10 mg in 19 of 20 patients and 9 of these 20 were administered the following immunosuppressants concomitantly: cyclosporine in 4 patients, tacrolimus in 2, azathioprine in 1, and methotrexate in 2.

By univariate analysis, patients with relapse manifested baseline muscle weakness less frequently and anti-SS-A/Ro antibody more frequently than did those without relapse (85% vs. 100%, $p = 0.03$ and 65% vs. 27%, $p = 0.007$, respectively). No significant difference was observed for any other factors such as demographic factors, complications, positivity of autoantibodies other than anti-SS-A/Ro antibody, and treatment status (Table 1). Of 29 patients evaluated by the line blot test, patients with anti-ARS antibody exhibited higher relapse rate than in those without anti-ARS antibody (71% vs. 25%, $p = 0.01$). The time from onset of symptoms to diagnosis tended to be longer in relapsed patients than in non-relapsed patients, but the difference was not significant. (176 ± 182 days vs. 128 ± 135, $p = 0.30$). On using the log-rank test, patients with anti-SS-A/Ro antibody also exhibited a **higher** relapse rate than those without anti-SS-A/Ro antibody ($p = 0.03$) (Fig.2).

Differences in clinical features between anti-SS-A/Ro antibody-positive and -negative patients with PM/DM

The characteristics of anti-SS-A/Ro antibody-positive and -negative patients with PM/DM are shown in Table 2. Age, sex, and clinical symptoms related to PM/DM, such as muscle weakness and interstitial lung disease, were comparable in both groups. Anti-Jo-1 antibody positivity was significantly more common in anti-SS-A/Ro antibody-positive patients than in -negative patients (29% vs. 7%, $p = 0.04$). As a whole anti-ARS antibody, positivity was higher in anti-SS-A/Ro antibody-positive patients than in -negative patients (79% vs. 21%, $p = 0.001$). As for serum complement levels were also significantly lower in anti-SS-A/Ro antibody-positive patients than in -negative patients (C3: 94 ± 21 vs. 108 ± 23, $p = 0.03$; C4: 20 ± 8 vs. 28 ± 9, $p = 0.0017$; and CH50: 42 ± 11 vs. 49 ± 10, $p = 0.015$).

After adjusting anti-Jo-1 antibody positivity in addition to age, sex, CK < 500 IU/L, and lung involvement, anti-SS-A/Ro antibody was still an independent risk factor for higer relapse rate (odds ratio, 5.5; 95% CI, 1.4 - 25.1).

DISCUSSION

This is the first report to demonstrate anti-SS-A/Ro antibody positivity as a risk factor for relapse in patients

with PM/DM. All but 1 patient achieved disease stabilization in our selected population. Of these, 5 of 50 with PM/DM died and 40% experienced relapse within the observation period.

Of 5 patients who died in the present study, 2 died due to malignancy and 1 died due to PCP, but none died of PM/DM. Previous studies with longer observation periods (ranging from 3 to 12 years) showed that malignancy, male sex, advanced age, and lung involvement including ILD were possible risk factors for mortality in patients with PM/DM [1, 3-5]. The most common cause of death in the previous studies was malignancy, and 2 patients died of malignancies shortly after diagnosis in our case series [1, 2, 4]. Therefore, malignancy would be an adverse prognostic factor regardless of observation period. Advanced age, male sex, and lung involvement are also well-known risk factors for infection in patients with connective tissue disease. [16-18]. Since a recent report showed that infection is the leading cause of mortality among hospitalized patients with PM/DM [19] and 1 patient also died of PCP in our study, these factors were surrogates for the risk of infectious complications.

Twenty (40%) patients experienced relapse within the observational period. Relapse rates were lower than in previous studies (58%-65%) because of the short observation period [2]. Even though only one report showed that advanced age, longer time to diagnosis, and ILD were possible risk factors for relapse in PM/DM without statistical significance, these factors were not different between patients with or without relapse in the present study [2]. Although the definition of activity of PM/DM in clinical studies was not established until recently, 65-98% of patients with PM/DM achieved improvement of clinical symptoms or laboratory findings [1-3]. These results including our present study demonstrated that the current standard remission induction treatment achieved substantive clinical improvement in patients with PM/DM. Considering that the initial treatment response in PM/DM was fair, disease-related mortality risk factors may also be considered possible factors for relapse. A previous report described ILD with mild elevation of serum CK levels in patients with DM, indicating that CADM is a mortality risk factor [5]. As all patients without muscle weakness, including 2 patients with CADM, experienced relapse in the present study, CADM may be a risk factor for relapse.

Anti-SS-A/Ro is an autoantibody known to be related to inflammatory myopathies; a previous report showed that about 20-40% of patients with inflammatory myopathies were positive for anti-SS-A/Ro-52 antibody [7-10]. Anti-SS-A/Ro-52 antibody was associated with complication and progression of ILD in PM/DM and other connective tissue diseases [12]. Over 70% of Jo-1-positive patients with myositis exhibited anti-SS-A/Ro-52 antibody positivity related to symptomatic ILD, malignant complication, and poor survival

[11]. A recent report showed that anti-SS-A/Ro antibody positivity was a poor prognostic factor not only in Jo-1-positive populations but also in all myositis populations [4]. Even in our study, anti-Jo-1 antibody positivity and the complication of ILD were more common in patients with anti-SS-A/Ro antibody than in those without anti-SS-A/Ro antibody. In the present study, anti-SS-A/Ro antibody positivity was identified as a risk factor for relapse after adjusting for the complication of ILD and anti-Jo-1 antibody positivity. Therefore, anti-SS-A/Ro antibody may also emerge as a poor prognostic factor if this study is performed with a longer observation period. In addition, lower levels of serum complement were found in anti-SS-A/Ro antibody-positive patients, suggesting that anti-SS-A/Ro antibody may affect the pathology caused by immune complexes in patients with PM/DM.

Several limitations warrant attention in the present study. First, we excluded a patient who did not achieve disease stabilization and therefore our treatment may be inadequate for prevention of relapse. As only one patient did not achieve disease stabilization, the influence of selection bias was minimal. Second, our results may be affected by indication bias because the treatments were determined at the discretion of the attending physicians. Third, we could not assess disease activity using a validated tool such as the Disease Activity Core Set Measures recommended by the International Myositis Assessment & Clinical Studies Group because of the lack of Visual Analog Scale and Health Assessment Questionnaire data. Fourth, we could not adjusted whole anti-ARS antibody positivity by multivariate analysis because anti-ARS antibody except for anti-Jo-1 antibody was checked in only a half of enrolled patients. A prospective study with strict treatment and assessment protocols should be performed to overcome these biases.

In conclusion, anti-SS-A/Ro antibody positivity was a risk factor for relapse in patients with PM/DM who achieved disease stabilization. Anti-SS-A/Ro antibody positivity might thus be a useful biomarker for prediction of relapse after disease stabilization in patients with PM/DM.

ACKNOWLEDGEMENTS

The authors thank all medical staff members in our department.

CONFLICT OF INTEREST

Jun Wada receives speaker honoraria from Astellas, Boehringer Ingelheim, Novartis, and Tanabe Mitsubishi, and receives grant support from Astellas, Bayer, Chugai, Daiichi Sankyo, Kissei, Kyowa Hakko Kirin, MSD,

Otsuka, Teijin, Torii, Pfizer, Takeda, and Taisho Toyama. None of the other authors have any conflicts of interest.

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Table 1. Baseline characteristics of patients with or without relapse

	With relapse (n=20)	Without relapse (n=30)	*p*
Age (years), mean (SD)	54 (14)	61 (12)	0.08
Time to diagnosis (day), mean (SD)	176 (182)	128 (135)	0.30
Female sex, n (%)	14 (70)	20 (67)	0.80
Classification of myositis			
PM, n (%)	6 (30)	15 (50)	0.11
DM, n (%)	12 (60)	15 (50)	
CADM, n (%)	2 (10)	0 (0)	
Malignancy, n (%)	1 (5)	5(16)	0.21
Muscle weakness, n (%)	17 (85)	30 (100)	0.03*
Interstitial lung disease, n (%)	12 (60)	18 (60)	1.00
CK (IU/l), mean (SD)	1636 (1881)	3506 (4791)	0.10
CRP (mg/dl), mean (SD)	1.8 (3.1)	1.2 (2.3)	0.42
Ferritin (ng/ml), mean (SD)	701 (1097)	353 (322)	0.12
KL-6 (U/ml), mean (SD)	461 (246)	481 (379)	0.84
Anti-Jo-1 antibody, n (%)	5 (25)	3 (10)	0.16
Anti-SS-A/Ro antibody, n (%)	13 (65)	8 (27)	0.007*
Initial daily dose of PSL (mg/day), mean (SD)	45 (12)	47 (14)	0.71
mPSL pulse use, n (%)	5 (25)	8 (27)	0.90
Concomitant immunosuppressant, n (%)	10 (50)	14 (47)	0.82
Tacrolimus, n	3	9	
Azathioprine, n	3	1	
Cyclosporine, n	1	3	
Cyclophosphamide , n	3	0	
Methotrexate, n	0	1	
IVIG, n (%)	1 (5)	3 (10)	0.52

PM: polymyositis, DM: dermatomyositis, CADM: clinically amyopathic dermatomyositis, CK: creatine kinase, CRP: C-reactive protein, KL-6: sialylated carbohydrate antigen, PSL: prednisolone, mPSL: methylprednisolone, IVIG: intravenous immunoglobulin

Table 2. Comparison of anti-SS-A/Ro antibody-positive and -negative patients

		SS-A/Ro (+) (n=21)	**SS-A/Ro (-) (n=29)**	***p***
Age (year), mean (SD)		56 (15)	60 (12)	0.32
Time to diagnosis (day), mean (SD)		172 (182)	129 (134)	0.33
Female sex, n (%)		17 (81)	17 (59)	0.95
Classification of myositis, n (%)				
	PM	7 (33)	14 (48)	0.57
	DM	13 (62)	14 (48)	
	CADM	1 (5)	1(4)	
Malignancy, n(%)		2 (10)	4 (14)	0.65
Muscle weakness		19 (91)	28 (97)	0.37
Interstitial lung disease, n (%)		15 (71)	15 (52)	0.16
CK (IU/l), mean (SD)		2057 (1985)	3266 (4922)	0.29
CRP (mg/dl), mean (SD)		1.6 (3.0)	1.3 (2.3)	0.70
Ferritin (ng/ml), mean (SD)		464 (628)	490 (778)	0.91
KL-6 (U/ml), mean (SD)		504 (284)	448 (361)	0.58
Anti-Jo-1 antibody, n (%)		6 (29)	2 (7)	0.039*
IgG (mg/dl), mean (SD)		1814 (609)	1530 (670)	0.15
CH50 (U/ml), mean (SD)		42 (11)	49 (10)	0.015*
C3 (mg/dl), mean (SD)		94 (21)	108 (23)	0.031*
C4 (mg/dl), mean (SD)		20 (8)	28 (9)	0.0017*

PM: polymyositis, DM: dermatomyositis, CADM: clinically amyopathic dermatomyositis, CK: creatine kinase, CRP: C-reactive protein, KL-6: sialylated carbohydrate antigen

FIGURE LEGENDS

Figure 1. Patient selection

PM: polymyositis, DM: dermatomyositis, CADM: clinically amyopathic dermatomyositis

Figure 2. Time to relapse in anti-SS-A/Ro antibody-positive and -negative patients with PM/DM

Relapse rates in anti-SS-A/Ro antibody-positive and -negative patients with PM/DM.

PM: polymyositis, DM: dermatomyositis