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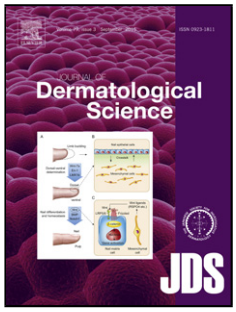

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Letter to the Editor

CLINICAL CHARACTERISTICS OF ANTI-RO52α AND ANTI-RO52β ANTIBODIES IN DERMATOMYOSITIS/POLYMYOSITIS

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The anti-Ro52 antibody is found in a number of autoimmune diseases, including

Sjögren's syndrome (SS), systemic lupus erythematosus, systemic sclerosis and dermatomyositis (DM)/polymyositis (PM). It is most frequently found in SS (37.4-66.7%) and second-most frequently in DM/PM (26.3-31.2%) [1]. It is also one of the most common autoantibodies in inflammatory myopathies and is classified as a myositis-associated antibody (MAA), which is frequently found in PM/DM but not specific for this diagnosis [2, 3]. There are two spliced forms of the Ro52 antigen: Ro52α and Ro52β. Ro52β was reported in 1995 as a splice variant of Ro52, in which exon4 of Ro52α is deleted. Ro52β was found to be expressed in the human heart [4]. We investigated the clinical and laboratory characteristics of DM/PM patients with anti-Ro52α/β antibodies in this study.

Two hundred twenty-eight Japanese patients were enrolled. Demographic and medical information was retrospectively collected from chart reviews or unified questionnaires. One hundred forty-nine patients fulfilled the criteria of Bohan and Peter for DM/PM [5], and the remaining 79 met the criteria for clinically amyopathic DM (CADM) [6]. Of the 228 patients, 82 patients had classical DM, 79 had CADM, 48 had cancer-associated DM, 8 had juvenile DM, 10 had PM and 1 had myositis overlap syndrome. Interstitial lung disease (ILD) was diagnosed by chest X-ray and/or high-resolution computed

tomography of the lungs. Ethical approval for the study was obtained from the individual institutional review boards.

All sera were tested by anti-Ro52 (Ro52α) enzyme-linked immunosorbent assay (ELISA) kits (Orgentec®, Mainz, Germany). To measure antibodies to Ro52β, an in-house ELISA (iELISA) using biotinylated recombinant Ro52β protein, which was produced from the full-length cDNA clone of human Ro52β in pBluescript cDNA using the T7 Quick Coupled Transcription/Translation System (Promega®, Madison, WI, USA), was applied, and we followed the procedures in previously published protocols [7, 8] except for using a serum dilution buffer containing 0.05% sodium dodecyl sulfate and 10% fetal bovine serum.

Myositis-specific autoantibodies (MSA), including anti-Mi-2, anti-TIF1γ, anti-MDA-5, anti-NXP-2, anti-TIF1β, anti-HMG-CoA, anti-SRP54, and anti-SAE1/2; and MAA, including anti-Ku70/80 and anti-PM/Scl-75/100, were tested by iELISA with biotinylated recombinant proteins [8]. When the results obtained by anti-aminoacyl-transfer RNA synthetase (anti-ARS) ELISA kits (MBL®, Nagoya, Japan) were positive, autoantibodies against the individual ARS, e.g., EJ, Jo-1, KS, PL-7 and PL-12, were tested by iELISA

[8]. The results were analyzed by Fisher's exact test, Mann-Whitney U test, or log rank test, as appropriate, using SPSS version 22 (IBM, Armonk, NY, USA). P values less than 0.05 were considered significant.

Forty-five of the 228 patients were anti-Ro52α-positive (19.7%) (Table 1). Although 4 anti-Ro52α-positive and 23 anti-Ro52α-negative patients were excluded for insufficient data, 31 patients out of the 41 anti-Ro52α-positive patients (76%) had ILD (P=0.0024). ILD was a significantly frequent complication in the anti-Ro52α-positive patients. In the 228 patients, anti-MDA5 was most frequently found, in 48 patients (20.9%), followed by anti-TIF1γ, anti-ARS, anti-Mi-2, anti-NXP2 and other antibodies. Nineteen patients out of the 33 anti-Ro52α-positive patients (58%) had anti-ARS antibodies. Anti-ARS antibodies were more frequently found in anti-Ro52α-positive patients than in anti-Ro52α-negative patients (P<0.0001). The frequencies of anti-Ro52α-positive patients among patients with each subtype of anti-ARS autoantibody were as follows: 57% (8 patients out of 14 anti-Jo-1-positive patients) of the anti-Jo-1-positive patients, 66% (6/9) of the anti-EJ-positive patients, 60% (3/5) of the anti-PL-7-positive patients, 67% (2/3) of the anti-KS-positive patients, and 50% (1/2) of the anti-PL-12-positive patients.

Next, we tried to find the clinical features of the anti-Ro52α-positive patients in the three major MSAs (anti-ARS, anti-MDA5 and anti-TIF1γ)-positive groups (Supplementary Table S1). We analyzed age, sex, type of myositis, presence of ILD/cancer, peaks of serum creatine kinase (CK), and characteristic skin manifestations. No clinical features were associated with the presence/absence of anti-Ro52α, except for the significantly lower peak of serum CK in the anti-Ro52α-positive patients among the anti-MDA5-positive patients (122.8±121.0 IU/ml in anti-Ro52α-positive patients vs. 268.7±387.5 IU/ml in anti-Ro52α-negative patients, P=0.02).

Autoantibodies to Ro52β were screened in sera from the 228 patients. Twenty-six patients (11.4%) were anti-Ro52β-positive, and all 26 of these patients were also anti-Ro52α-positive. The demographic and clinical features of the 19 anti-Ro52α single-positive patients and of the 26 both anti-Ro52α- and anti-Ro52β-positive patients are shown in Table 2. The average age of DM onset is significantly higher for the both anti-Ro52α- and anti-Ro52β-positive group (P=0.005). The peak of serum CK is higher in the both anti-Ro52α- and anti-Ro52β-positive patients, but not significantly (P=0.069). Interestingly, all 6 patients in whom no MSA/MAA was found other than anti-Ro52 were both anti-Ro52α- and anti-Ro52β-positive (P=0.03).

Anti-Ro52 has been known to be associated with ILD and Raynaud's phenomenon, but some reports were controversial [1]. A juvenile myositis study showed that anti-Ro52 in DM/PM was frequently detected with anti-ARS and strongly associated with ILD in each MSA subgroup [9]. In our study, we found no greater prevalence of ILD complication with anti-Ro52-positive patients in each MSA subgroup (Supplementary Table S1). This was partly because the total frequency of ILD in our study is very high: 93% (27/29) in anti-ARS, and 95% (45/47) in anti-MDA5. Interestingly, 6 anti-Ro52-positive patients with no other MSA/MAA (Supplementary Table S2) were complicated with ILD (4/6 patients, 67%) more frequently than were patients with no MSA/MAA (12/43, 27%) (P=0.07).

In the study of 89 anti-Jo-1-positive patients, 36 of these patients were anti-Ro52 positive and the presence of anti-Ro52 was associated with more severe myositis [10]. Our present study, which is the first report on anti-Ro52β in a myositis cohort, shows that the both anti-Ro52α- and anti-Ro52β-positive sera had a higher peak of serum CK than those of anti-Ro52α single-positive sera. The anti-Ro52 antibody, which is also reported to be associated with severe disease activity [9.10], may have the effect of strengthening the

myositis symptoms, and broad reactivity to both Ro52α and Ro52β may be more critical to this effect.

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Table 1. Clinical and laboratory features of patients with anti-Ro52α

	anti-Ro52α (+) N=45	anti-Ro52α (-) N=183	P value
age	54.4±14.5	53.1±19.0	0.22
female	34 (76%)	126 (69%)	0.47
No. of patients with cancer	6 (13%)	43 (23%)	0.16
No. of patients with ILD	31 (76%)*	78 (49%)**	0.0024
mean peak serum creatine kinase (IU/ml)	990.6±1835.6***	1274.0±2260.8****	0.40
No. of patients with each MSA			
MDA5	12 (26.6%)	36 (19.6%)	0.31
ARS	19 (42%)	14 (7.1%)	<0.000001
TIF1γ	4 (8.9%)	37 (20%)	0.086
Mi-2	1 (2.2%)	12 (6.5%)	0.47
MJ	1 (2.2%)	11 (6%)	0.47
SAE	1 (2.2%)	5 (2.1%)	1
SRP	0 (0%)	4 (2.1%)	1
No. of patients with other MAA			
PM/Scl	1 (2.2%)	5 (2.7%)	1
Ku	0 (0%)	2 (1%)	1

*,**,***,****; 4, 23, 2, and 16 cases were excluded, respectively, for insufficient data.

ARS: aminoacyl tRNA synthetases

ILD: interstitial lung disease.

MAA: myositis-associated autoantibodies

MSA: myositis-specific autoantibodies

None: No MSA or MAA other than anti-Ro52 was detected

Table 2 Clinical and laboratory features of patients with anti-Ro52α and anti-Ro52β

	anti-Ro52α with anti-Ro52β (N=26)	anti-Ro52α without anti-Ro52β (N=19)	P value
age	59.8±12.8	46.9±13.6	0.005
female	21 (81%)	13 (68.4%)	0.49
No. of patients with cancer	4 (15%)	2 (11%)	1
No. of patients with ILD	17 (71%)*	15 (79%)**	0.50
mean peak serum creatine kinase (IU/ml)	1267.5±2164.4	606.1±1200.7	0.069
No. of patients with each MSA			
MDA5	5 (19%)	7 (37%)	0.31
ARS	9 (35%)	10 (52%)	0.35
TIF1γ	3 (12%)	1 (5.2%)	0.62
SAE	1 (3.8%)	0 (0%)	1
Mi-2	1 (3.8%)	0 (0%)	1
MJ	1 (3.8%)	0 (0%)	1
No. of patients with other MAA			
PM/Scl	0 (0%)	1 (5.2%)	0.42
No. of patients without any MSA	6 (23%)	0 (0%)	0.03
heliotrope	13*(59%)	7*(47%)	0.54
Gottron	19*(86%)	11*(73%)	0.34
mechanic's hand	3*(14%)	3*(20%)	0.69

*, **; 4 and 2 cases were excluded, respectively, for insufficient data.

ARS: aminoacyl tRNA synthetases

Gottron: Gottron's sign/papule

ILD: interstitial lung disease

MAA: myositis-associated autoantibodies

MSA: myositis-specific autoantibodies

None: No MSA or MAA other than anti-Ro52 was detected