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Association between clinical phenotypes of dermatomyositis and polymyositis with myositis-specific antibodies and overlap systemic autoimmune diseases

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Abstract

The aim of this study was to evaluate the association between clinical phenotypes of dermatomyositis (DM) and polymyositis (PM) with myositis-specific antibodies (MSAs), and overlap diagnosis of systemic autoimmune diseases.

This cross-sectional study was conducted on 67 patients with DM and 27 patients with PM recruited from a regional hospital in southern Taiwan. Clinical phenotypes of DM and PM were assessed and MSAs were measured using a commercial line blot assay. The association of clinical phenotypes of DM and PM with MSAs and overlap diagnosis of systemic autoimmune diseases was performed using univariate and multiple logistic regression analyses.

Clinically, patients with DM and PM and overlap diagnosis of systemic sclerosis were associated with a higher risk of interstitial lung diseases (ILDs) (odds ratio [OR] = 6.73; $P = .048$), Raynaud phenomenon (OR = 7.30; $P = .034$), and malignancy (OR = 350.77; $P = .013$). The risk of malignancy was also associated with older age (OR 1.31; $P = .012$), and male patients were associated with a higher risk of fever. For MSAs, anti-aminoacyl-tRNA synthetase antibodies were associated with ILD, antinuclear antibody were associated with a lower risk of arthritis, anti-transcription intermediary factor 1-gamma antibodies were associated with milder symptoms of muscle weakness, anti-Ku antibodies were associated with overlap diagnosis of systemic lupus erythematosus, and anti-Ro52 antibodies were associated with the development of Raynaud phenomenon and Sjögren syndrome.

MSAs and overlap diagnosis of systemic sclerosis were significantly associated with clinical phenotypes of DM and PM. Physicians should be vigilant for malignancy in older DM and PM patients with overlap diagnosis of systeic sclerosis. The possibility of developing ILD in patients with overlap diagnosis of systemic sclerosis or serum positivity of anti-aminoacyl-tRNA synthetase antibodies should be considered.

Abbreviations: ANA = antinuclear antibody, anti-ARS = anti-aminoacyl-tRNA synthetase, CI = confidence interval, DM = dermatomyositis, ILD = interstitial lung disease, MDA = melanoma differentiation-associated protein, MSAs = myositis-specific antibodies, NXP-2 = nuclear matrix protein 2, OR = odds ratio, PM = polymyositis, SAE1 = small ubiquitin-like modifier activating enzyme 1, TIF1-γ = transcription intermediary factor 1-gamma.

Keywords: dermatomyositis, interstitial lung disease, malignancy, overlap syndrome, polymyositis, systemic sclerosis

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1. Introduction

Dermatomyositis (DM) and polymyositis (PM) are rare systemic autoimmune diseases, and the prevalence is 2.9 per 100,000 persons in Taiwan.[1] DM and PM are characterized by immune-mediated destruction of muscle tissue leading to varying degree of muscle weakness. DM is further associated with a characteristic rash, including heliotrope rash, Gottron purple, "V" sign or "shawl" sign. In addition, patients with DM and PM may develop particular clinical phenotypes, including interstitial lung disease (ILD), Raynaud phenomenon, arthritis, fever, calcinosis, or even malignancy leading to increased mortality.[2–4] These specific phenotypes of patients with DM or PM are well-known to be associated with the presence of myositis-specific autoantibodies (MSAs).[5,6] However, patients with DM or PM frequently develop other systemic autoimmune diseases, so call "overlap syndrome", including systemic sclerosis, Sjögren syndrome, systemic lupus erythematosus, and rheumatoid arthritis.[7–9] These diseases are themselves often associated with ILD, arthritis, Raynaud phenomenon, fever, calcinosis, or increased risk of malignancy. Nevertheless, few studies have addressed the impact of the association of these systemic autoimmune diseases on the clinical manifestation of patients with DM and PM,[10–14] and analyses of the effect of individual systemic autoimmune diseases were even more scarce.[15,16] Therefore, the aim of this cross-sectional study was to identify the association between the overlap systemic autoimmune diseases and MSAs with different clinical phenotypes of DM and PM. In addition, this study also explored the association between overlap systemic autoimmune diseases and MSAs in these patients.

2. Methods

2.1. Ethical issues

This study was approved by the institutional review board of Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (No. B10703022) and written informed consents were obtained from all participants. The study was carried out in accordance with the Declaration of Helsinki.

2.2. Study design and study population

This was a cross-sectional study conducted at the rheumatology department of Dalin Tzu Chi Hospital, which is a referral center for rheumatic diseases in southern Taiwan, from February of 2019 to January of 2020. Patients, aged 20 years and above, were enrolled from the outpatient or inpatient department.

After evaluating by serum muscle enzymes, electromyography, magnetic resonance imaging, or muscle biopsy, the diagnosis of DM or PM was made based on Bohan and Peter[17,18] criteria. Clinical phenotypes of DM or PM, including classic DM rash, prominent proximal lower limb weakness, associated fever symptom, Raynaud phenomenon, arthritis, ILD, malignancy, and calcinosis were evaluated during the enrollment. These phenotypes were comprehensively evaluated in the inpatient department with physical examination and imaging studies, including X-ray, sonography and computed tomography, tissue biopsy (if needed) by rheumatologists who had practiced for more than 10 years. Blood sample was drawn to measure MSAs using commercial Euroline Autoimmune Inflammatory Myopathies 16 Ag IgG platform tests (EUROIMMUN, Lübeck, Germany), which is a immunoblot strip coating for antigen, including Mi-2α, Mi-2β, polymyositis/systemic scleroderma-75, polymyositis/systemic scleroderma-100, Ku, Jo-1 (histidyl-tRNA synthetase), signal recognition particle, PL-7 (anti-threonyl-tRNA synthetase), PL-12 (anti-alanyl-tRNA synthetase), EJ (anti-glycyl tRNA synthetase), OJ (anti-isoleucyl-tRNAsynthetase), transcription intermediary factor 1-gamma (TIF1-γ), melanoma differentiation-associated protein (MDA) 5, nuclear matrix protein 2 (NXP-2), anti-small ubiquitin-like modifier activating enzyme 1 (SAE1), and Ro52. The analysis was performed according to the manufacturer's recommendation, and therefore borderline Euroline results were classified as negative. Positive anti-Mi2 antibodies were defined as either positive for anti-Mi-2α and Mi-2β antibodies. Positive anti-aminoacyl-tRNA synthetase (anti-ARS) antibodies were defined as either positive of anti-Jo-1, PL-7, PL-12, EJ, or OJ antibodies. The overlap diagnosis of systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, or systemic sclerosis was based on the corresponding classification criteria.[19–22]

2.3. Statistical analysis

Results are represented as mean and standard deviation or n (%), as appropriate. Mann–Whitney *U* test, Fisher exact test or Pearson chi-squared test was used, as appropriate, to compare continuous or categorical variables between patients with PM and DM. Univariate logistic regression analyses were performed to obtain odds ratios (OR) and 95% confidence intervals (CI) for clinical phenotypes of DM and PM (classic DM rash, proximal lower limb weakness, fever, and Raynaud phenomenon) with positivity of MSAs, demographic data, and overlap systemic autoimmune diseases. Variables with P value $< .20$ were further entered into separate multiple logistic regression models to assess the corresponding independent variables associated with classic DM rash, proximal lower limb weakness, fever, and Raynaud phenomenon. A P value $< .05$ was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp, Armonk, NY).

3. Results

3.1. Demographic data of patients with DM and PM

A total of 67 patients with DM and 27 patients with PM were included in our study and their demographic data were shown in Table 1. The classic DM rash (77.6%) was only noted in patients with DM, and a high proportion (40.3% vs 18.5%; $P = .035$) of patients with DM developed ILD. Among the MSAs, anti-SAE1 was not detected in our study.

3.2. Association of clinical phenotypes of DM and PM with myositis specific autoantibodies and overlap systemic autoimmune diseases

Results of univariate logistic regression analyses of the clinical phenotypes of DM and PM, including classic DM rash, proximal lower limb weakness, fever, and Raynaud phenomenon with demographic data, overlap systemic autoimmune diseases, and MSAs are shown in Table 2. As expected, the classic DM skin was only noted in patients with DM. In addition, those who were anti-TIF1-γ-positive were less likely to develop prominent proximal lower limb weakness (OR = 0.08, 95% CI: 0.01–0.72, $P < .05$). Male patients with DM and PM were associated with fever

Table 1

Demographic data of patients with dermatomyositis and polymyositis.

Variable	Dermatomyositis n = 67		Polymyositis n = 27		*P* value
	n	(%)	n	(%)	
Female	50	(74.6)	19	(70.4)	.673
Age, yr, mean (standard deviation)	55.2	(12.7)	51.0	(16.9)	.254
Clinical symptoms					
Proximal lower limb weakness	42	(62.7)	17	(63.0)	.980
Fever	3	(4.5)	2	(7.4)	.447
Malignancy	5	(7.5)	2	(7.4)	.679
Classic dermatomyositis rash	52	(77.6)	0	(0.0)	<.001
Calcinosis	4	(6.0)	0	(0.0)	.251
Arthritis	27	(40.3)	7	(25.9)	.189
Interstitial lung diseases	27	(40.3)	5	(18.5)	.044
Raynaud phenomenon	8	(11.9)	6	(22.2)	.205
Comorbidity					
Rheumatoid arthritis	4	(6.0)	1	(3.7)	.553
Systemic lupus erythematosus	9	(13.4)	5	(18.5)	.531
Sjögren syndrome	8	(11.9)	5	(18.5)	.403
Systemic sclerosis	4	(6.0)	3	(11.1)	.321
ANA, nuclear	36	(53.7)	15	(55.6)	.872
ANA, cytoplasmic	18	(26.9)	7	(25.9)	.926
Myositis-specific antibodies					
Anti-Ro52	25	(37.3)	8	(29.6)	.480
Anti-ARS	16	(23.9)	2	(7.4)	.055
Anti-OJ	0	(0)	0	(0)	n.c.
Anti-EJ	2	(3.0)	0	(0)	.506
Anti-PL-12	2	(3.0)	1	(3.7)	.643
Anti-PL-7	2	(3.0)	0	(0)	.506
Anti-Jo-1	10	(14.9)	1	(3.7)	.116
Anti-SRP	3	(4.5)	3	(11.1)	.227
Anti-PM/Scl	2	(3.0)	3	(11.1)	.141
Anti-Ku	2	(3.0)	2	(7.4)	.325
Anti-SAE1	0	(0.0)	0	(0.0)	n.c.
Anti-NXP-2	2	(3.0)	0	(0.0)	.506
Anti-MDA-5	1	(1.5)	0	(0.0)	.713
Anti-TIF1-γ	7	(10.4)	0	(0.0)	.085
Anti-Mi2	2	(3.0)	0	(0.0)	.506

ANA = antinuclear antibody, MDA-5 = melanoma differentiation-associated protein 5, n.c. = not calculable, NXP-2 = nuclear matrix protein 2, PM/Scl = polymyositis/systemic scleroderma, SAE1 = small ubiquitin-like modifier activating enzyme 1, SRP = signal recognition particle, TIF1-γ = transcription intermediary factor 1-gamma.

Table 2

Univariate logistic regression analyses of demographic data, overlap systemic autoimmune diseases, and myositis-specific antibodies with classic dermatomyositis rash, proximal lower limb weakness, fever, or Raynaud phenomenon among patients with dermatomyositis and polymyositis.

Variable	Classic dermatomyositis rash	Proximal lower limb weakness	Fever	Raynaud phenomenon
Male (reference: female)	1.30 (0.51–3.29)	1.37 (0.52–3.60)	**12.95*** (1.37–122.31) *P* = .025	0.41 (0.09–1.99)
Age (per yr)	1.02 (0.99–1.06)	0.99 (0.96–1.02)	1.06 (0.98–1.15)	1.01 (0.97–1.05)
Dermatomyositis (reference: polymyositis)	n.c.	0.99 (0.39–2.49)	0.59 (0.09–3.72)	0.48 (0.15–1.53)
Overlap disease				
Rheumatoid arthritis	0.52 (0.08–3.27)	0.88 (0.14–5.57)	n.c.	n.c.
Systemic lupus erythematosus	0.78 (0.25–2.42)	0.54 (0.17–1.69)	n.c.	0.94 (0.19–4.76)
Sjögren syndrome	0.65 (0.20–2.11)	0.94 (0.28–3.14)	n.c.	1.91 (0.45–8.04)
Systemic sclerosis	0.30 (0.05–1.61)	1.53 (0.28–8.33)	n.c.	**5.18*** (1.02–26.32) (*P* = .047)
ANA, nuclear	1.62 (0.72–3.69)	0.57 (0.24–1.34)	1.28 (0.20–8.04)	2.38 (0.69–8.22)
ANA, cytoplasmic	1.04 (0.41–2.61)	2.30 (0.82–6.46)	1.91 (0.30–12.18)	1.12 (0.32–3.97)
Myositis-specific antibodies				
Anti-Ro52	1.69 (0.71–4.04)	0.71 (0.30–1.70)	1.25 (0.20–7.87)	2.93 (0.92–9.35)
Anti-ARS	1.80 (0.61–5.29)	1.70 (0.55–5.25)	3.04 (0.47–19.72)	0.285 (0.04–2.34)
Anti-SRP	0.80 (0.15–4.16)	n.c.	4.20 (0.39–44.92)	3.17 (0.52–19.22)
Anti-PM/Scl	0.52 (0.08–3.27)	0.13 (0.01–1.25)	n.c.	n.c.
Anti-Ku	0.26 (0.03–2.55)	1.82 (0.18–18.22)	n.c.	1.97 (0.19–20.46)
Anti-NXP-2	0.80 (0.05–13.25)	0.59 (0.04–9.68)	n.c	n.c.
Anti-MDA-5	n.c.	n.c.	n.c.	n.c.
Anti-TIF1-γ	5.35 (0.62–46.30)	**0.08*** (0.01–0.72) *P* = .024	n.c.	n.c.
Anti-Mi2	n.c.	n.c.	n.c.	n.c.

Values are odds ratio (95% confidence interval).

ANA = antinuclear antibody, anti-ARS = anti-aminoacyl-tRNA synthetase, MDA-5 = melanoma differentiation-associated protein 5, n.c. = not calculable, NXP-2 = nuclear matrix protein 2, PM/Scl = polymyositis/systemic scleroderma, SRP = signal recognition particle, TIF1-γ = transcription intermediary factor 1-gamma.

* $P < 0.05$.

Table 3

Multiple logistic regression analysis of demographic data, overlap systemic autoimmune diseases, and myositis-specific antibodies with classic dermatomyositis rash, proximal lower extremities muscle, fever, or Raynaud phenomenon among patients with dermatomyositis and polymyositis.

Variable	Classic dermatomyositis rash	Proximal lower limb weakness	Fever	Raynaud phenomenon
Male (reference: female)			**13.05*** (1.35–126.33) (*P* = .030)	
Age (per yr)	1.02 (0.99–1.06)		1.06 (0.97–1.15)	
Overlap disease				
Systemic sclerosis	0.34 (0.06–1.90)			**7.30*** (1.16–45.90) (*P* = .034)
ANA, nuclear		0.88 (0.33–2.30)		1.54 (0.41–5.79)
ANA, cytoplasmic		1.87 (0.62–5.63)		
Myositis-specific antibodies				
Anti-Ro52				**3.74*** (1.01–13.85) (*P* = .049)
Anti-PM/Scl		0.12 (0.01–1.21)		
Anti-TIF1-γ	4.77 (0.54–41.88)	**0.09*** (0.01–0.88) (*P* = .039)		

Values are odds ratio (95% confidence interval).

ANA = antinuclear antibody, PM/Scl = polymyositis/systemic scleroderma, TIF1-γ = transcription intermediary factor 1-gamma.

* $P < .05$.

(OR = 12.95, 95% CI: 1.37–122.31, $P < .05$). Those with an overlap diagnosis of systemic sclerosis were associated with a higher risk of developing Raynaud phenomenon (OR = 5.18, 95% CI: 1.02–26.32, $P < .05$).

Results of multiple logistic regression analyses are shown in Table 3. Patients with positive anti-TIF1-γ were less likely to develop prominent proximal lower limb weakness (OR = 0.09, 95% CI: 0.01–0.88, $P < .05$). Male patients with DM and PM were also significantly associated with fever (OR = 13.05, 95% CI: 1.35–126.33, $P < .01$). Those with overlap diagnosis of systemic sclerosis (OR = 7.30, 95% CI: 1.16–45.90, $P < .05$) or anti-Ro52-positive (OR = 3.74, 95% CI: 1.01–13.85, $P < .05$) were associated with a higher risk of Raynaud phenomenon.

In Table 4, univariate logistic regression analyses of the clinical phenotypes of DM and PM, including arthritis, ILD, malignancy, or calcinosis with demographic data, overlap systemic autoimmune diseases, and MSAs were performed. We found that patients with an overlap diagnosis of Sjögren syndrome were associated with a higher risk of arthritis (OR = 3.39, 95% CI: 1.01–11.36, $P < .05$). Those with ILD were associated with DM (OR = 2.97, 95% CI: 1.00–8.81, $P < .05$), positive cytoplasmic pattern in antinuclear antibody (ANA) (OR = 2.85, 95% CI: 1.11–7.34, $P < .05$), anti-Ro52-positive (OR = 3.26, 95% CI: 1.33–8.00,

Table 4

Univariate logistic regression analyses of demographic data, overlap systemic autoimmune diseases, and myositis-specific antibodies with arthritis, interstitial lung disease, malignancy, or calcinosis among patients with dermatomyositis and polymyositis.

Variable	Arthritis	Interstitial lung disease	Malignancy	Calcinosis
Male (reference: female)	0.60 (0.22–1.64)	0.39 (0.13–1.16)	1.11 (0.20–6.14)	0.92 (0.09–9.24)
Age (per yr)	1.02 (0.99–1.06)	1.03 (0.99–1.06)	**1.22**** (1.06–1.40) (*P* = .007)	0.98 (0.91–1.05)
Dermatomyositis (reference: polymyositis)	1.93 (0.72–5.19)	**2.97*** (1.00–8.81) (*P* = .036)	1.01 (0.19–5.54)	n.c.
Overlap disease				
Rheumatoid arthritis	7.87 (0.84–73.52)	3.10 (0.49–19.60)	3.46 (0.33–36.00)	n.c.
Systemic lupus erythematosus	0.98 (0.30–3.19)	0.48 (0.12–1.86)	0.95 (0.10–8.54)	6.50 (0.84–50.59)
Sjögren syndrome	**3.39*** (1.01–11.36) (*P* = .048)	2.61 (0.80–8.57)	1.04 (0.12–9.43)	n.c.
Systemic sclerosis	1.36 (0.28–6.45)	2.81 (0.59–13.41)	**15.56**** (2.57–94.34) (*P* = .003)	n.c.
ANA, nuclear	0.44 (0.18–1.03)	1.37 (0.58–3.25)	2.23 (0.41–12.11)	0.84 (0.11–6.20)
ANA, cytoplasmic	0.60 (0.22–1.64)	**2.85*** (1.11–7.34) (*P* = .030)	0.44 (0.05–3.83)	0.92 (0.09–9.24)
Myositis-specific antibodies				
Anti-Ro52	0.83 (0.34–2.01)	**3.26*** (1.33–8.00) (*P* = .010)	1.42 (0.30–6.79)	n.c.
Anti-ARS	0.86 (0.29–2.54)	**11.28***** (3.29–38.61) (*P* < .001)	0.67 (0.08–6.08)	1.43 (0.14–14.62)
Anti-SRP	0.88 (0.15–5.05)	0.37 (0.04–3.29)	n.c.	5.67 (0.50–64.77)
Anti-PM/Scl	n.c.	3.10 (0.49–19.60)	3.46 (0.33–36.00)	n.c.
Anti-Ku	1.81 (0.24–13.49)	n.c.	n.c.	9.67 (0.76–122.45)
Anti-NXP-2	1.79 (0.11–29.53)	1.97 (0.12–32.53)	n.c.	n.c.
Anti-MDA-5	n.c.	n.c.	n.c.	n.c.
Anti-TIF1-γ	0.69 (0.13–3.75)	0.30 (0.04–2.62)	n.c.	n.c.
Anti-Mi2	1.79 (0.11–29.53)	n.c.	n.c.	n.c.

Values are odds ratio (95% confidence interval).

ANA = antinuclear antibody, anti-ARS = anti-aminoacyl-tRNA synthetase, MDA-5 = melanoma differentiation-associated protein 5, n.c. = not calculable, NXP-2 = nuclear matrix protein 2, PM/Scl = polymyositis/systemic scleroderma, SRP = signal recognition particle, TIF1-γ = transcription intermediary factor 1-gamma.

* $P < .05$.

** $P < 0.01$.

*** $P < 0.001$.

Table 5

Multiple logistic regression analyses of demographic data, overlap systemic autoimmune diseases, and myositis-specific antibodies with arthritis, interstitial lung disease, malignancy, or calcinosis among patients with dermatomyositis and polymyositis.

Variable	Arthritis	Interstitial lung disease	Malignancy	Calcinosis
Male (reference: female)		2.98 (0.76–11.60)		
Age (per yr)	1.01 (0.98–1.05)	1.02 (0.98–1.07)	**1.31*** (1.06–1.61) (P=.012)	
Dermatomyositis (reference: polymyositis)	2.09 (0.72–6.60)	2.83 (0.74–10.85)		
Overlap disease				
Rheumatoid arthritis	4.81 (0.36–65.88)			
Systemic lupus erythematosus				5.08 (0.44–58.51)
Sjögren syndrome	3.34 (0.82–13.52)	2.06 (0.36–11.74)		
Systemic sclerosis		**6.73*** (1.02–44.38) (P=.048)	**350.77*** (3.42–35983.20) (P=.013)	
ANA, nuclear	**0.40*** (0.16–0.99) (P=.045)			
ANA, cytoplasmic		2.52 (0.76–8.42)		
Myositis-specific antibodies				
Anti-Ro52		0.81 (0.19–3.45)		
Anti-ARS		**9.90**** (2.20–44.22)		
Anti-SRP				4.80 (0.28–81.68)
Anti-Ku				2.41 (0.09–62.96)

Values are odds ratio (95% confidence interval).

ANA = antinuclear antibody, anti-ARS = anti-aminoacyl-tRNA synthetase, SRP = signal recognition particle.

* $P < .05$.

** $P < .01$.

$P < .05$) or anti-ARS-positive (OR = 11.28, 95% CI: 3.29–38.61, $P < .001$). In addition, those with malignancy were associated with age (OR = 1.22, 95% CI: 1.06–1.40, $P < .01$) and an overlap diagnosis of systemic sclerosis (OR = 15.56, 95% CI: 2.57–94.34, $P < .01$). No significant risk factors were associated with calcinosis.

In Table 5, results from multiple logistic regression analyses showed that positive ANA was associated with a lower risk of arthritis (OR = 0.40, 95% CI: 0.16–0.99, $P < .05$). The overlap diagnosis of systemic sclerosis (OR = 6.73, 95% CI: 1.02–44.38, $P < .05$) and positivity of anti-ARS antibodies (OR = 9.90, 95% CI: 2.21–44.22, $P < .01$) were associated with ILD. Age (OR = 1.31, 95% CI: 1.06–1.61, $P < .05$) and an overlap diagnosis of systemic sclerosis (OR = 350.77, 95% CI: 3.42–35983.20, $P < .05$) were associated with a high risk of malignancy. No significant risk factors were associated with calcinosis.

3.3. Association of myositis specific autoantibodies with overlap diagnosis of systemic autoimmune diseases

In Table 6, we analyzed association with myositis specific autoantibodies with overlap diagnosis of systemic autoimmune diseases. We excluded anti-NXP-2, anti-MDA-5 and anti-Mi2 antibodies from analysis because they were rarely detected (n < 4) in our study. We found that that the presence of anti-Ku antibody was associated with an overlap diagnosis with systemic lupus erythematosus (OR = 21.54, 95% CI: 2.06–225.79, $P < .05$). The presence of anti-Ro52 was associated with an overlapping diagnosis of Sjögren syndrome (OR = 34.29, 95% CI: 4.20–279.88, $P < .001$).

3.4. The effect of sex on clinical phenotypes of dermatomyositis and polymyositis with myositis-specific antibodies and overlap systemic autoimmune diseases

The effect of sex on clinical phenotypes of DM and PM with MSAs and overlap systemic autoimmune diseases was shown in Table 7. In the univariate analysis, only male patients were associated with a higher risk of fever (OR = 12.95, 95% CI: 1.37–122.30, $P < .05$) and the association remained statistically significantly after multiple logistic regression analyses (OR = 14.88, 95% CI: 1.38–160.38, $P < .05$).

4. Discussion

In this study, we found that patients with DM and PM with overlap systemic autoimmune diseases, especially systemic

Table 6

The association of overlap autoimmune diseases with MSAs in patients with dermatomyositis and polymyositis.

Variable	Rheumatoid arthritis (n = 5)	Systemic lupus erythematosus (n = 14)	Sjögren syndrome (n = 13)	Systemic sclerosis (n = 7)
Anti-Ro52	2.95 (0.467–18.62)	0.70 (0.20–2.45)	**34.29**** (4.20–279.88) ($P < .001$)	0.29 (0.03–2.49)
Anti-ARS	1.06 (0.11–10.09)	0.28 (0.04–2.34)	3.27 (0.92–11.58)	n.c.
Anti-SRP	n.c.	1.15 (0.12–10.69)	n.c.	n.c.
Anti-PM/Scl	n.c.	4.28 (0.65–28.31)	n.c.	3.46 (0.33–36.00)
Anti-Ku	n.c.	**21.54*** (2.06–225.79) (P=.010)	n.c.	4.67 (0.42–51.96)
Anti-TIF1-γ	n.c.	n.c.	1.04 (0.12–9.43)	n.c.

Values are odds ratio (95% confidence interval).

ARS = anti-aminoacyl-tRNA synthetase, n.c. = not calculable, PM/Scl = polymyositis/systemic scleroderma, SRP = signal recognition particle, TIF1-γ = transcription intermediary factor 1-gamma.

* $P < .05$.

** $P < .001$.

Table 7

The effect of sex on clinical phenotypes of dermatomyositis and polymyositis with myositis-specific antibodies and overlap systemic autoimmune diseases.

Variable	Sex, n (%)				Odds ratio (95% confidence interval)	
	Female n = 69 (73.4)		Male n = 25 (26.6)		Univariate logistic regression analysis	Multiple logistic regression analysis
Dermatomyositis	50	(75.8)	16	(24.2)	0.68 (0.26–1.79)	
Polymyositis	19	(67.9)	9	(32.1)	1.48 (0.56–3.92)	
Age, yr, mean (standard deviation)	53.7	(14.2)	54.9	(13.9)	1.01 (0.97–1.04)	
Clinical symptoms						
Proximal lower-limb weakness	42	(71.2)	17	(28.8)	1.37 (0.52–3.60)	
Fever	1	(20.0)	4	(80.0)	12.95* (1.37–122.30)	14.88* (1.38–160.38)
Malignancy	5	(71.4)	2	(28.6)	1.11 (0.20–6.14)	
Classic dermatomyositis rash	37	(71.2)	15	(28.8)	1.30 (0.51–3.29)	
Amyopathic dermatomyositis	3	(60.0)	2	(40.0)	1.91 (0.30–12.18)	
Calcinosis	3	(75.0)	1	(25.0)	0.92 (0.09–9.24)	
Arthritis	27	(79.4)	7	(20.6)	0.60 (0.22–1.64)	
Interstitial lung diseases	27	(84.4)	5	(15.6)	0.39 (0.13–1.16)	0.34 (0.10–1.18)
Raynaud phenomenon	12	(85.7)	2	(14.3)	0.41 (0.09–1.99)	
Comorbidity						
Rheumatoid arthritis	4	(80.0)	1	(20.0)	0.68 (0.07–6.36)	
Systemic lupus erythematosus	13	(92.9)	1	(7.1)	0.18 (0.02–1.45)	0.17 (0.02–1.44)
Sjögren syndrome	10	(76.9)	3	(23.1)	0.80 (0.20–3.20)	
Systemic sclerosis	7	(100.0)	0	(0.0)	n.c.	
ANA, nuclear	39	(76.5)	12	(23.5)	0.71 (0.28–1.78)	
ANA, cytoplasmic	17	(68.0)	8	(32.0)	1.44 (0.53–3.92)	
Myositis-specific antibodies						
AntiRo52	27	(81.8)	6	(18.2)	0.49 (0.17–1.39)	0.53 (0.16–1.70)
Anti-ARS	14	(77.8)	4	(22.2)	0.75 (0.22–2.54)	
Anti-OJ	0	(0.0)	0	(0.0)	n.c.	
Anti-EJ	2	(100.0)	0	(0.0)	n.c.	
Anti-PL-12	3	(100.0)	0	(0.0)	n.c.	
Anti-PL-7	1	(50.0)	1	(50.0)	2.83 (0.17–47.09)	
Anti-Jo-1	8	(72.7)	3	(27.3)	1.04 (0.25–4.27)	
Anti-SRP	4	(66.7)	2	(33.3)	1.41 (0.24–8.24)	
Anti-PM/Scl	4	(80.0)	1	(20.0)	0.68 (0.07–6.36)	
Anti-Ku	4	(100.0)	0	(0.0)	n.c.	
Anti-SAE1	0	(0.0)	0	(0.0)	n.c.	
Anti-NXP-2	1	(100.0)	0	(0.0)	n.c.	
Anti-MDA-5	1	(100.0)	0	(0.0)	n.c.	
Anti-TIF1-γ	7	(100.0)	0	(0.0)	n.c.	
Anti-Mi2	2	(100.0)	0	(0.0)	n.c.	

ANA = antinuclear antibody, anti-ARS = anti-aminoacyl-tRNA synthetase, MDA-5 = melanoma differentiation-associated protein 5, n.c. = not calculable, NXP-2 = nuclear matrix protein 2, PM/Scl = polymyositis/systemic scleroderma, SRP = signal recognition particle, TIF1-γ = transcription intermediary factor 1-gamma.
* $P < .05$.

sclerosis was associated with a higher risk of Raynaud phenomenon and ILD, which is consistent with results from previous studies.[12,15] These clinical phenotypes are well-documented in patients with systemic sclerosis.[23] Thus, we proposed that an overlap diagnosis of systemic sclerosis would contribute to the development of ILD and Raynaud phenomenon in patients with DM and PM. It is of interest to know whether the risk of Raynaud phenomenon and ILD would change in patients with systemic sclerosis combined with an overlap diagnosis of DM and PM. We noted that 7.4% (n = 7) patients in our study were diagnosed with cancer in our study. The cancer types were bladder cancer (n = 2), thyroid cancer (n = 2), lymphoma (n = 1), breast cancer (n = 1), and lung cancer (n = 1). In addition, the risk of cancer was very high in older patients with DM and PM combined with an overlap diagnosis of systemic sclerosis. Patients with DM and PM or systemic sclerosis are well known to have an elevated risk of developing cancer, and it is suspected that the cancer itself can play a critical role in the immunopathogenesis of both systemic autoimmune diseases.[24] Therefore, clinicians should remain vigilant for signs and symptoms of cancer in older patients with DM and PM combined with overlap diagnosis of systemic sclerosis.

In this study, positive anti-MDA-2 antibodies were noted in just 2.1% (n = 2) and no anti-SAE1 was found, which had made it unable to show any associations with clinical phenotypes. We believed that this is due to the different environment or genotype,[25] but we did observe a strong association between ILD and anti-ARS antibodies,[26] an association between the presence of anti-TIF1-γ antibodies and milder symptoms of muscle weakness,[27] and an association between the presence of anti-Ku antibodies and systemic lupus erythematosus,[28,29] as reported in previous studies. On the other hand, the association of fever and male patients with DM and PM, the presence of anti-Ro52 with the development of Raynaud phenomenon, and positivity of ANA with a lower risk of developing arthritis were unique findings of our study. There were inconsistent reports

regarding the association of anti-Ku antibodies in systemic lupus erythematosus patients with DM and PM.[30,31] However, due to the rare occurrence of DM and PM patients and even rarer positivity of specific MSA and overlap diagnosis of systemic autoimmune diseases, further studies using registry samples[10] might be needed to elucidate their relationships.

We noted 2 limitations in this study. First, our patients were recruited from the southern part of Taiwan, which might limit the generalization of our conclusion. Second, the study sample was small and only a few or even no patients were positive to several MSAs, including antisignal recognition particle, anti-Ku, anti-NXP-2, anti-MDA-5, anti-SAE1, and anti-Mi2 antibodies. Therefore, their possible associations will need further validation. Patients with DM and PM are a group of rare diseases with diverse clinical manifestations, and we believe that these data are useful for future meta-analyses.

In conclusion, we found that DM and PM patients with overlap diagnosis of systemic sclerosis were associated with a higher risk of ILD, Raynaud phenomenon, and malignancy, particularly among older patients. Physician should be vigilant for malignancy in older DM and PM patients with overlap diagnosis of systemic sclerosis. The possibility of developing ILD in patients with overlap diagnosis of systemic sclerosis or serum positivity of anti-ARS should be considered. We also found the followings: anti-ARS antibodies were associated with ILD, ANA were associated with a lower risk of arthritis, anti-TIF1-γ antibodies were associated with milder symptoms of muscle weakness, anti-Ku antibodies were associated with overlap diagnosis of systemic lupus erythematosus, and anti-Ro52 antibodies were associated with the development of Raynaud phenomenon and Sjögren syndrome. The recognition of specific MSAs patterns and overlap diagnosis of systemic autoimmune diseases is important in the caring of patients with DM and PM.

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