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ORIGINAL RESEARCH

Clinical Characteristics of Dermatomyositis with Interstitial Lung Disease: A Retrospective Case–Control Study

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ABSTRACT

Introduction: Interstitial lung disease (ILD) is a common complication of dermatomyositis (DM) and one of the main risk factors for poor prognosis in DM patients. The aim of this study was to reveal the clinical characteristics of DM patients with ILD.

Methods: Clinical data from the Second Affiliated Hospital of Soochow University were used to conduct a retrospective case–control study. Univariate and multivariate logistic regression analysis were performed to identify risk factors for ILD in DM.

Results: A total of 78 DM patients were included in this study, including 38 DM patients with ILD and 40 DM patients without ILD. Compared with patients without ILD, patients with ILD were older (59.6 vs. 51.2 years, $P = 0.004$), and had higher rates of clinically amyopathic DM (CADM) (45 vs. 20%, $P = 0.019$), Gottron's papules (76 vs. 53%, $P = 0.028$), mechanic's hands (13 vs. 0%, $P = 0.018$), myocardial involvement (29 vs. 8%, $P = 0.014$), and higher positive rates of anti-SSA/Ro52 (74 vs. 20%, $P < 0.001$) and anti-melanoma differentiation-associated gene-5 (MDA5) (24 vs. 8%, $P = 0.048$) antibodies, while albumin (ALB) (34.5 vs. 38.0 g/l, $P = 0.006$), prognostic nutritional index (PNI) (40.3 vs. 44.7, $P = 0.013$), the rates of muscle weakness (45 vs. 73%, $P = 0.013$) and heliotrope rash (50 vs. 80%, $P = 0.005$) were lower. In addition, the five patients who died were all DM patients with ILD (13 vs. 0%, $P = 0.018$). Multivariate logistic regression showed that old age (odds ratio [OR] = 1.119, 95% confidence interval [CI] = 1.028–1.217, $P = 0.009$), Gottron's papules (OR = 8.302, 95% CI = 1.275–54.064, $P = 0.027$) and anti-SSA/Ro52 (OR = 24.320, 95% CI = 4.102–144.204, $P < 0.001$) were independent risk factors for ILD in DM.

Conclusions: DM patients with ILD usually present with older age, higher rates of CADM, Gottron's papules, mechanic's hands, myocardial involvement, higher positive rates of anti-MDA5 and anti-SSA/Ro52 antibodies, lower ALB, PNI, and lower rates of muscle weakness and heliotrope rash. Old age, Gottron's papules, and anti-SSA/Ro52 were independent risk factors for ILD in DM.

Keywords: Dermatomyositis; Interstitial lung disease; Clinically amyopathic dermatomyositis; Anti-MDA5 antibody; Anti-SSA/Ro52 antibody

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Key Summary Points

Why carry out this study?

Interstitial lung disease (ILD) is a common complication of dermatomyositis (DM) and one of the main risk factors for poor prognosis in DM patients.

However, the clinical characteristics of DM patients with ILD are not clear.

The aim of this study was to reveal the clinical characteristics of DM patients with ILD.

What was learned from the study?

DM patients with ILD usually present with older age, higher rates of clinically amyopathic DM, Gottron's papules, mechanic's hands, myocardial involvement, higher positive rates of anti-MDA5 and anti-SSA/Ro52 antibodies, lower albumin, prognostic nutritional index (PNI), and lower rates of muscle weakness and heliotrope rash.

Old age, Gottron's papules, and anti-SSA/Ro52 were independent risk factors for ILD in DM.

Understanding the clinical characteristics of DM patients with ILD is helpful for clinicians to develop individualized treatment plans for each patient.

INTRODUCTION

Dermatomyositis (DM) is a kind of idiopathic inflammatory myopathy that is characterized by characteristic skin lesions and clinical heterogeneous systemic manifestations. DM typically involves skin lesions such as heliotrope rash and Gottron's papules, while muscular lesions are usually characterized by symmetrical proximal extremities muscle weakness [1]. Some patients have characteristic skin involvement without significant muscle lesions, which is called clinically amyopathic DM (CADM) [2].

In addition to skin and muscle manifestations, DM can also involve other organs. Common extramuscular manifestations include interstitial lung disease (ILD), myocardial involvement, and malignancy. Among them, ILD is a common complication of DM and one of the main risk factors for a poor prognosis of patients with DM [3]. Recent studies have found that some of the DM patients with ILD can develop into rapidly progressive ILD (RP-ILD). These patients typically present with CADM and are positive for anti-melanoma differentiation-associated gene-5 (MDA5) antibodies, with a mortality rate of nearly 50% at 6 months [4, 5]. However, studies have shown that early use of tofacitinib can effectively improve the prognosis of DM patients with positive anti-MDA5 antibody and ILD [5]. Therefore, early diagnosis and treatment is the key to improving the prognosis of DM patients with ILD.

Due to a lack of relevant clinical studies, the clinical characteristics of DM patients with ILD are not clear at present. Therefore, we collected the clinical data of DM patients in our department in recent years and conducted this single-center case–control study. Through this study, we hope that clinicians can better understand the potential risk factors of DM patients with ILD and improve their prognosis.

METHOD

Subjects

The study subjects were all in patients diagnosed with DM in the Rheumatology Department of the Second Affiliated Hospital of Soochow University from January 2010 to November 2022. Since this study focused on the clinical features of DM patients with ILD, patients with a history of respiratory diseases such as emphysema were excluded. All design and reporting methods of the study were in accordance with the STROBE statement for observational studies [6]. This study was conducted in accordance with the World Medical

Association Declaration of Helsinki and was approved by the Human Ethics Review Committee of the Second Affiliated Hospital of Soochow University (JD-HG-2023-09). All patients signed informed consent to participate in the study.

Diagnostic Criteria

DM is diagnosed according to the 2017 ACR/EULAR classification criteria [7]. The diagnosis of CADM refers to the standard proposed by Sontheimer [2], that is, the patient has skin damage without muscle disease symptoms and lasts for more than 6 months. ILD was diagnosed based on respiratory symptoms and high-resolution computed tomography (HRCT) findings of the chest [8]. RP-ILD was defined as ILD with rapid progression within 3 months after symptom onset, and slowly progressive ILD was defined as ILD with asymptomatic or slow progression for more than 3 months [9].

Data Collection

In this study, relevant clinical data were collected by retrospectively reviewing the medical records of patients who were hospitalized for the first time, and the prognosis was understood through follow-up.

The clinical characteristics recorded mainly include age, gender, course of disease, rash, arthritis, cutaneous ulceration, malignancy, treatment, prognosis, and other basic information. In addition, this study also focused on the autoantibodies of patients, including antinuclear antibodies (ANAs) and myositis-specific autoantibodies. ANAs were detected by the ANA kit according to the manufacturer's instructions (Euroimmun, Germany), and myositis-specific autoantibodies were detected by a third-party testing company (EUROIMMUN Medical Laboratory Diagnostics Stock Company, China) using immunoblotting.

The serological indexes of patients were also included in the analysis, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), α-hydroxybutyrate dehydrogenase (α-HBDH), creatine kinase (CK), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum ferritin, albumin (ALB), neutrophil (NEUT) count, lymphocyte (LYM) count, and platelet (PLT) count.

In addition, we also calculated CRP-to-ALB ratio (CAR), NEUT-to-LYM ratio (NLR), PLT-to-LYM ratio (PLR), prognostic nutritional index (PNI) (PNI = ALB + 5 × LYM), and systemic immune-inflammation index (SII) (SII = PLT × NEUT/LYM).

Statistical Analysis

Demographic and disease characteristics were assessed using standard descriptive statistics. Continuous variables are expressed as mean ± standard deviation (SD), while categorical variables are expressed as quantity and percentage. For continuous variables, the two-tailed Student's t test or Mann–Whitney U test was used for analysis. For categorical variables, the χ^2 or Fisher's exact test was used for analysis. Univariate and multivariate logistic regression analyses were performed to identify risk factors for ILD in DM. P values < 0.05 were considered statistically significant. All statistics were carried out using SPSS 24 software.

RESULTS

Clinical Characteristics of All Patients

A total of 78 patients with DM were included in this study, including 38 (49%) DM patients with ILD, and the remaining 40 (51%) DM patients without ILD. The clinical characteristics of all patients are shown in Table 1. The average age of patients with DM was 55.9 years old. There were 29 (37%) male patients, with an average course of 25.1 months. Among them, 25 (32%) patients were diagnosed with CADM, five (6%) developed RP-ILD, 22 (28%) received previous treatment, and 46 (59%) had muscle weakness. Gottron's papules (64%) and heliotrope rash (65%) were the most common skin lesions, and four (5%) patients were complicated with malignancy. Most patients (94%) received

Table 1 Clinical characteristics of all patients with DM

Clinical characteristics	All patients (n = 78)	DM patients with ILD (n = 38)	DM patients without ILD (n = 40)	P value
Age (years)	55.9 ± 12.2	59.6 ± 8.6	51.2 ± 13.9	0.004
Male	29 (37%)	14 (37%)	15 (38%)	0.952
Course of disease (months)	25.1 ± 50.3	26.3 ± 39.4	24.0 ± 59.3	0.836
CADM	25 (32%)	17 (45%)	8 (20%)	0.019
RP-ILD	5 (6%)	5 (13%)	0	0.018
Previous treatment	22 (28%)	12 (32%)	10 (25%)	0.519
Muscle weakness	46 (59%)	17 (45%)	29 (73%)	0.013
Gottron's papules	50 (64%)	29 (76%)	21 (53%)	0.028
Heliotrope rash	51 (65%)	19 (50%)	32 (80%)	0.005
V-sign erythema	25 (32%)	10 (26%)	15 (38%)	0.290
Shawl sign	14 (18%)	6 (16%)	8 (20%)	0.628
Skin erythema	17 (22%)	7 (18%)	10 (25%)	0.482
Raynaud's phenomenon	1 (1%)	1 (3%)	0	0.487
Periungual erythema	9 (12%)	5 (13%)	4 (10%)	0.734
Arthritis	24 (31%)	11 (29%)	13 (33%)	0.734
Mechanic's hands	5 (6%)	5 (13%)	0	0.018
Cutaneous ulceration	5 (6%)	3 (8%)	2 (5%)	0.671
Malignancy	4 (5%)	0	4 (10%)	0.116
Myocardial involvement	14 (18%)	11 (29%)	3 (8%)	0.014
Glucocorticoids	73 (94%)	37(97%)	36 (90%)	0.359
Low-dose glucocorticoids (< 30 mg/day)	20 (26%)	9 (24%)	11 (28%)	0.700
Medium-dose glucocorticoids (30-80 mg/day)	51 (65%)	27 (71%)	24 (60%)	0.305
High-dose glucocorticoids (> 80 mg/day)	1 (1%)	1 (3%)	0	0.487
Immunosuppressants	53 (68%)	29 (76%)	24 (60%)	0.123
Dead	5 (6%)	5 (13%)	0	0.018

Data are reported as mean ± SD or population (%)
CADM clinically amyopathic dermatomyositis, *DM* dermatomyositis, *ILD* interstitial lung disease, *RP-ILD* rapidly progressive interstitial lung disease, *SD* standard deviation

glucocorticoid treatment, including 20, 51 and one patients with low, medium, and high doses, respectively. Fifty-three (68%) were treated with immunosuppressants, including methotrexate, mycophenolate mofetil (MMF), tacrolimus, leflunomide, cyclosporine, azathioprine, etc. A total of five (6%) patients died.

Comparison of Clinical Characteristics Between DM with ILD and DM Without ILD

The comparison of clinical characteristics between the two groups is shown in Table 1. Compared with DM patients without ILD, DM patients with ILD were older (59.6 vs. 51.2 years, $P = 0.004$), and had higher rates of CADM (45 vs. 20%, $P = 0.019$), Gottron's papules (76 vs. 53%, $P = 0.028$), mechanic's hands (13 vs. 0%, $P = 0.018$) and myocardial involvement (29 vs. 8%, $P = 0.014$). However, the rates of muscle weakness (45 vs. 73%, $P = 0.013$) and heliotrope rash (50 vs. 80%, $P = 0.005$) was lower in DM patients with ILD. All five patients who died were DM patients with ILD (13 vs. 0%, $P = 0.018$). The male ratio (37 vs. 38%, $P = 0.952$), course of disease (26.3 vs. 24.0 months, $P = 0.836$) and previous treatment ratio (32 vs. 25%, $P = 0.519$) were similar between the two groups. Although there was no statistical difference, DM patients with ILD had a lower prevalence of malignancy (0 vs. 10%, $P = 0.116$), which may be related to the small sample size. In terms of clinical symptoms such as V-sign erythema, shawl sign, skin erythema, Raynaud's phenomenon, periungual erythema, arthritis and cutaneous ulceration, the rates of the two groups were similar. In terms of treatment, the use rates of glucocorticoids (97 vs. 90%, $P = 0.359$) and immunosuppressants (76 vs. 60%, $P = 0.123$) in patients with ILD were higher than those in patients without ILD, but there was no significant difference.

Comparison of Serum Antibodies Between DM with ILD and DM Without ILD

The comparison of serum antibodies between the two groups is shown in Table 2. ANA was the most common antibody in both groups, with a positive rate of 68 and 50%, respectively ($P = 0.098$). Compared with patients without ILD, patients with ILD had higher positive rates of anti-SSA/Ro52 (74 vs. 20%, $P < 0.001$) and anti-MDA5 antibodies (24 vs. 8%, $P = 0.048$). There was no significant difference between the

Table 2 Comparison of serum antibodies between DM with ILD and DM without ILD

Antibodies	DM patients with ILD ($n = 38$)	DM patients without ILD ($n = 40$)	*P* value
ANA	26 (68%)	20 (50%)	0.098
Anti-SSA/Ro52	28 (74%)	8 (20%)	< 0.001
Anti-SSA/Ro60	10 (26%)	6 (15%)	0.216
Anti-MDA5	9 (24%)	3 (8%)	0.048
Anticentromere	1 (3%)	1(3%)	1.000
Anti-U1RNP	2 (5%)	3 (8%)	1.000
RF	3 (8%)	2 (5%)	0.671
Anti-Jo-1	8 (21%)	4 (10%)	0.176
Anti-Mi-2	2 (5%)	2 (5%)	1.000
Anti-EJ	4 (11%)	0	0.052
Anti-PL-7	2 (5%)	3 (8%)	1.000
Anti-PL-12	2 (5%)	0	0.234
Anti-OJ	1 (3%)	1 (3%)	1.000
Anti-SAE1	0	1 (3%)	1.000
Anti-TIF1	2 (5%)	1 (3%)	0.610
Anti-Ku	1 (3%)	1 (3%)	1.000
Anti-PM-Scl75	2 (5%)	2 (5%)	1.000
Anti-HMGCR	1 (3%)	0	0.487
Anti-ds-DNA	1 (3%)	0	0.487
Anti-SSB	1 (3%)	2 (5%)	1.000

Data are reported as population (%)
ANA antinuclear antibody, *DM* dermatomyositis, *ILD* interstitial lung disease, *RF* rheumatoid factor

Table 3 Comparison of serological indexes between DM with ILD and DM without ILD

Serological indexes	DM patients with ILD (n = 38)	DM patients without ILD (n = 40)	P value
ALT (U/l)	51.1 ± 54.2	65.1 ± 74.1	0.346
AST (U/l)	61.2 ± 79.7	75.9 ± 95.6	0.464
LDH (U/l)	433.5 ± 378.3	309.9 ± 170.1	0.064
α-HBDH (U/l)	274.7 ± 140.3	231.6 ± 142.4	0.183
CK (U/l)	542.7 ± 1033.6	634.7 ± 1269.8	0.728
ESR (mm/h)	54.7 ± 122.3	30.3 ± 27.4	0.223
CRP (mg/l)	16.6 ± 22.0	20.8 ± 36.1	0.533
Serum ferritin (μg/l)	707.7 ± 636.7	560.9 ± 627.9	0.309
ALB (g/l)	34.5 ± 6.1	38.0 ± 5.1	0.006
NEUT (10^9/l)	6.6 ± 4.0	5.6 ± 5.6	0.389
LYM (10^9/l)	1.2 ± 0.6	1.3 ± 0.7	0.302
PLT (10^9/l)	231.4 ± 90.2	233.3 ± 92.9	0.926
CAR	530.0 ± 742.4	617.9 ± 1187.6	0.698
NLR	7.8 ± 10.6	6.2 ± 10.0	0.481
PLR	245.5 ± 159.6	237.3 ± 211.8	0.848
PNI	40.3 ± 7.9	44.7 ± 7.1	0.013
SII (10^9/l)	1775.7 ± 2179.4	1994.8 ± 5214.7	0.811

Data are reported as mean ± SD

α-HBDH α-hydroxybutyrate dehydrogenase, *ALB* albumin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CADM* clinically amyopathic dermatomyositis, *CAR* CRP-to-ALB ratio, *CK* creatine kinase, *CRP* C-reactive protein, *DM* dermatomyositis, *ESR* erythrocyte sedimentation rate, *ILD* interstitial lung disease, *LDH* lactate dehydrogenase, *LYM* lymphocyte count, *NEUT* neutrophil count, *NLR* NEUT-to-LYM ratio, *PLR* PLT-to-LYM ratio, *PLT* platelet count, *PNI* prognostic nutritional index, *RP-ILD* rapidly progressive interstitial lung disease, *SD* standard deviation, *SII* systemic immune-inflammation index

two groups in anti-SSA/Ro60, anticentromere, anti-U1RNP, and other antibodies. However, we still observed that patients with ILD had higher positive rates of anti-SSA/Ro60 (26 vs. 15%, P = 0.216), anti-Jo-1 (21 vs. 10%, P = 0.176) and anti-EJ antibodies (11 vs. 0%, P = 0.052).

Comparison of Serological Indexes Between DM with ILD and DM Without ILD

The comparison of serological indexes between the two groups is shown in Table 3. ALB (34.5 vs. 38.0 g/l, P = 0.006) and PNI (40.3 vs. 44.7, P = 0.013) in patients with ILD were significantly lower than those without ILD. Patients with ILD had higher LDH (433.5 vs. 309.9 U/l, P = 0.064), α-HBDH (274.7 vs. 231.6 U/l, P = 0.183), ESR (54.7 vs. 30.3 mm/h, P = 0.223), serum ferritin (707.7 vs. 560.9 μg/l, P = 0.309) and NEUT (6.6×10^9/l vs. 5.6×10^9/l, P = 0.389), but lower ALT (51.1 vs. 65.1 U/l, P = 0.346), AST (61.2 vs. 79.9 U/l, P = 0.464), CK (542.7 vs. 634.7 U/l, P = 0.728), CRP (16.6 vs. 20.8 mg/l, P = 0.533), LYM (1.2×10^9/l vs. 1.3×10^9/l, P = 0.302) and PLT (231.4×10^9/l

Table 4 Risk factors for ILD in DM by logistic models

Variables	Univariate analysis			Multivariate analysis		
	B	OR (95% CI)	*P*	*B*	OR (95% CI)	*P*
Age	0.059	1.061 (1.016, 1.108)	0.008	0.112	1.119 (1.028, 1.217)	0.009
CADM	1.175	3.238 (1.186, 8.842)	0.022	2.051	7.775 (0.389, 155.567)	0.180
Muscle weakness	− 1.181	0.307 (0.120, 0.789)	0.014	− 0.457	0.633 (0.029, 13.819)	0.771
Gottron's papules	1.070	2.915 (1.103, 7.704)	0.031	2.117	8.302 (1.275, 54.064)	0.027
Heliotrope rash	− 1.386	0.250 (0.092, 0.681)	0.007	− 0.911	0.402 (0.055, 2.929)	0.368
Mechanic's hands	21.395	1958151353 (0, ∞)	0.999			
Malignancy	− 21.257	5.8643E−10 (0, ∞)	0.999			
Myocardial involvement	1.614	5.025 (1.277, 19.766)	0.021	0.103	1.108 (0.084, 14.662)	0.938
ANA	0.773	2.167 (0.861, 5.453)	0.101			
Anti-SSA/Ro52	2.416	11.200 (3.884, 32.296)	< 0.001	3.191	24.320 (4.102, 144.204)	< 0.001
Anti-MDA5	1.342	3.828 (0.949, 15.431)	0.059	1.332	3.790 (0.387, 37.116)	0.252
Anti-Jo-1	0.875	2.400 (0.658, 8.757)	0.185			
Anti-EJ	21.365	1900558664.000 (0, ∞)	0.999			
LDH	0.002	1.002 (1.000, 1.005)	0.091	0.001	1.001 (0.995, 1.008)	0.674
ALB	− 0.114	0.893 (0.819, 0.972)	0.009	− 0.274	0.760 (0.542, 1.066)	0.112
PNI	− 0.078	0.925 (0.867, 0.986)	0.017	0.135	1.145 (0.894, 1.466)	0.283

ALB albumin, *ANA* antinuclear antibody, *CADM* clinically amyopathic dermatomyositis, *CI* confidence interval, *LDH* lactate dehydrogenase, *OR* odds ratio, *PNI* prognostic nutritional index

vs. 233.3 × 10^9/l, $P = 0.926$). However, the results were not statistically different. In addition, there were no significant differences in CAR, NLR, PLR, and SII between the two groups.

Risk Factors for ILD in DM

We conducted univariate and multivariate logistic regression analysis to identify risk factors for ILD in DM (Table 4). Multivariate logistic regression showed that old age (odds ratio [OR] = 1.119, 95% confidence interval [CI] = 1.028–1.217, $P = 0.009$), Gottron's papules (OR = 8.302, 95% CI = 1.275–54.064, $P = 0.027$) and anti-SSA/Ro52 (OR = 24.320, 95% CI = 4.102–144.204, $P < 0.001$) were independent risk factors for ILD in DM.

Clinical Characteristics and Serological Antibody Analysis of CADM

In order to further explore the characteristics of CADM, clinical characteristics and serological antibodies of CADM and classical DM were compared and summarized in Table 5. In terms of clinical characteristics, compared with classical DM patients, the use rate of low-dose glucocorticoids (48 vs. 15%, $P = 0.002$) in patients with CADM was higher, while the use rate of medium-dose glucocorticoids (44 vs. 76%, $P = 0.006$) was lower. Interestingly, patients with CADM had lower rates of ILD (32 vs. 60%, $P = 0.019$), but higher rates of RP-ILD (16 vs. 2%, $P = 0.034$) compared to those with classical DM. In terms of serum antibodies, patients with CADM had a higher positive rate of anti-MDA5

Table 5 Clinical characteristics and serum antibodies of CADM

Clinical characteristics and antibodies	CADM (n = 25)	Classical DM (n = 53)	P value
Age (years)	56.8 ± 11.8	55.0 ± 12.5	0.551
Male	8 (32%)	21 (39.6%)	0.516
Course of disease (months)	11.3 ± 25.7	31.7 ± 57.5	0.033
ILD	8 (32%)	32 (60%)	0.019
RP-ILD	4 (16%)	1 (2%)	0.034
Muscle weakness	0	46 (87%)	< 0.001
Previous treatment	4 (16%)	18 (34%)	0.100
Gottron's papules	17 (68%)	17 (62%)	0.622
Heliotrope rash	15 (60%)	36 (68%)	0.492
V-sign erythema	7 (28%)	18 (34%)	0.598
Shawl sign	3 (12%)	11 (21%)	0.529
Skin erythema	5 (20%)	12 (23%)	0.792
Raynaud's phenomenon	1 (4%)	0	0.321
Periungual erythema	4 (16%)	5 (9%)	0.457
Arthritis	8 (32%)	16 (30%)	0.872
Mechanic's hands	1 (4%)	4 (8%)	1.000
Cutaneous ulceration	3 (12%)	2 (4%)	0.320
Malignancy	1 (4%)	3 (6%)	1.000
Myocardial involvement	5 (20%)	9 (17%)	0.759
Glucocorticoids	23 (92%)	50 (94%)	0.653
Low-dose glucocorticoids (< 30 mg/day)	12 (48%)	8 (15%)	0.002
Medium-dose glucocorticoids (30-80 mg/day)	11 (44%)	40 (76%)	0.006
High-dose glucocorticoids (> 80 mg/day)	0	1 (2%)	1.000
Immunosuppressants	16 (64%)	37 (70%)	0.608
Dead	4 (16%)	1 (2%)	0.034
ANA	14 (56%)	32 (60%)	0.714
Anti-SSA/Ro52	11 (44%)	25 (47%)	0.793
Anti-SSA/Ro60	5 (20%)	11 (21%)	0.939
Anti-MDA5	9 (36%)	3 (6%)	0.001
Anticentromere	1 (4%)	1 (2%)	0.541
Anti-U1RNP	1 (4%)	4 (8%)	1.000
RF	2 (8%)	3 (6%)	0.653

Table 5 continued

Clinical characteristics and antibodies CADM(n = 25)	Classical	DM(n = 53)	P value
Anti-Jo-1	4 (16%)	8 (15%)	1.000
Anti-Mi-2	0	4 (8%)	0.300
Anti-EJ	1 (4%)	3 (6%)	1.000
Anti-PL-7	2 (8%)	3 (6%)	0.653
Anti-PL-12	2 (8%)	0	0.100
Anti-OJ	1 (4%)	1 (2%)	0.541
Anti-SAE1	0	1 (2%)	1.000
Anti-TIF1	0	3 (6%)	0.547
Anti-Ku	0	2 (4%)	1.000
Anti-PM-Scl75	1 (4%)	3 (6%)	1.000
Anti-HMGCR	1 (4%)	0	0.321
Anti-ds-DNA	0	1 (2%)	1.000
Anti-SSB	0	3 (6%)	0.547

Data are reported as mean ± SD or population (%)
ANA antinuclear antibody, *CADM* clinically amyopathic dermatomyositis, *DM* dermatomyositis, *ILD* interstitial lung disease, *RF* rheumatoid factor, *RP-ILD* rapidly progressive interstitial lung disease, *SD* standard deviation

antibody than patients with classical DM (36 vs. 6%, P = 0.001).

Clinical Characteristics of Dead Patients

In order to explore the clinical characteristics of the dead patients, we further summarized the data of the five dead patients. All the five dead patients were complicated with ILD, with an average age of 62 years. In terms of autoantibodies, four patients were positive for anti-MDA5 antibody, while all five patients were positive for anti-SSA/Ro52 antibody. In the aspect of serological indexes, the increase of serum ferritin was the most significant feature. Four patients had serum ferritin > 2000 ng/ml, while the remaining one had serum ferritin of 752 ng/ml. In addition, we found that four patients were positive for Epstein–Barr virus.

DISCUSSION

In this single-center case–control study, we collected clinical data from 78 patients with DM in our department. We compared the DM patients with ILD with those without ILD to find the similarities and differences in clinical characteristics between the two groups.

Our study showed that the mean age of the overall patients with DM was 55.9 years. Among them, male patients accounted for 37%, while patients with CADM accounted for 32%. These data are similar to those reported by Bendewald et al. [10]. Gottron's papules and heliotrope rash were the most common skin lesions, affecting 64% and 65% of patients, respectively. In the comparison of the two groups of patients, we found that DM patients with ILD were older, with higher rates of Gottron's papules, mechanic's hands, CADM, myocardial involvement and death, and lower rates of muscle

weakness and heliotrope rash. These characteristics may indicate potential risk factors for such patients. Cao et al. found that DM patients with ulcerative Gottron's papules have an increased risk of ILD [9], which is similar to our findings.

A large number of previous studies have shown that DM is associated with a higher risk of malignancy [11–17]. Population-based retrospective studies have shown that the prevalence of DM with malignancy is about 20% [18–21]. Interestingly, DM patients associated with ILD have a significantly reduced risk of malignancy [22, 23]. In this study, we also observed that all four patients with malignancy were DM patients without ILD. However, the protective mechanism of ILD against malignancy remains unclear. Future research is expected to reveal its mechanism.

According to the current evidence, systemic glucocorticoids are still the basis for initial treatment of dermatomyositis related muscle diseases [24]. The initial dose of prednisone is usually 0.5 mg/kg/day. For patients with severe muscle involvement or progressive ILD, 500-1000 mg/day × 3 days of methylprednisolone pulse therapy can be considered [25, 26]. In addition, antimalarial drugs, MMF, methotrexate and other immunosuppressive drugs can be considered according to the different conditions of patients [27], while immunoglobulin can be used to treat refractory DM after the failure of other drugs [28]. Notably, MMF is currently considered the preferred first-line agent for DM with ILD [27]. In this study, most patients used glucocorticoids and immunosuppressants, which is consistent with the current recommendation. In the comparison between the two groups of patients, the five patients who died were all DM patients with ILD. This suggests that DM patients with ILD may have more serious disease and need more active immunosuppressive therapy.

In terms of autoantibodies, we found that the positive rate of ANA was the highest in both groups. In addition, the positive rates of anti-SSA/Ro52 and anti-MDA5 antibodies increased significantly in patients with ILD. Many studies have shown that anti-MDA5 DM usually present with CADM, which is significantly associated with ILD and RP-ILD [4, 29, 30]. In this study, we also found that the positive rate of anti-MDA5 antibody and the rate of CADM were higher in DM patients with ILD, which was consistent with previous study. Recently, Xu et al. found that anti-SSA/Ro52 antibody is prevalent in anti-MDA5 DM, and is associated with poor prognosis [31], which is consistent with our results. Therefore, CADM patients with positive anti-SSA/Ro52 and anti-MDA5 antibodies are associated with more aggressive clinical manifestations [31].

In addition, we also found that DM patients with ILD had higher positive rates of anti-SSA/Ro60, anti-JO-1, and anti-EJ antibodies. Anti-aminoacyl-transfer RNA synthetase (ARS) antibodies includes anti-Jo-1, anti-PL7, anti-PL12, anti-EJ, anti-OJ, anti-KS, anti-Zo, and anti-Ha/YRS antibodies. Patients with positive antibodies of these antibodies are called anti-synthase antibody syndrome, which is a special phenotype of DM [32]. Patients with anti-synthetase syndrome are usually associated with symptoms such as fever, ILD, arthritis, Raynaud's phenomenon, Gottron's papules, and mechanic's hands. In our study, the positive rates of anti-JO-1 and anti-EJ antibodies were higher in patients with ILD, which is consistent with the clinical features of anti-synthetase syndrome.

In terms of serological indexes of the two groups, we found that ALB and PNI were significantly reduced in patients with ILD, which may be related to the severity of the disease and long-term malnutrition. In addition, we also found that the increase of serum ferritin was a valuable feature of patients with ILD, while the two groups were similar in ALT, AST, LDH, α-HBDH, CK, ESR, CRP, NEUT, LYM and PLT. In recent years, elevated serum ferritin has been considered as one of the risk factors for poor prognosis in anti-MDA5 DM [33, 34]. High levels of serum ferritin are associated with macrophage activation syndrome, which is commonly used to refer to a secondary hemophagocytosis observed in rheumatic diseases [35, 36]. The mechanism mainly includes lack of regulation of T lymphocytes and excessive cytokine (such as TNF-α, IL-β, IL-6, IL-18, etc.), leading to the activation of macrophages [11, 36]. However, the role of serum ferritin in the pathogenesis of DM remains unclear.

Recently, a study developed and validated a scoring model called FLAIR to predict mortality in CADM-ILD patients [37], in which serum ferritin ≥ 636 ng/ml was a risk factor. In our study, four of the five patients who died with ILD had serum ferritin > 2000 ng/ml, and one patient had serum ferritin of 752 ng/ml. This further supports the importance of serum ferritin in predicting poor outcomes. However, serum ferritin lacks specificity in diagnosis.

Our multivariate logistic regression showed that old age, Gottron's papules and anti-SSA/Ro52 were independent risk factors for ILD in DM. This result was consistent with previous studies [9, 31]. Some variables that may have clinical significance, such as malignancy, myocardial involvement, ALB, have no statistical significance in multivariate logistic regression. This may be related to the small sample size.

We also focused on the data of five patients who died and found that they had some common clinical features. All the five patients had ILD and old age, with high positive rates of anti-MDA5 and anti-SSA/Ro52 antibodies, and significantly increased serum ferritin. This is basically consistent with previous studies [31, 37]. In addition, we also found that these five patients had a high positive rate of Epstein–Barr virus infection. Viruses may play a role in triggering immune activation in DM [38]. However, some scholars tried to isolate the specific virus from DM muscle tissue without success [39]. Future research may further reveal the relationship between viruses and DM.

Those patients with DM specific skin lesions but without myopathy are called CADM, which is currently considered as a subtype of DM [2]. CADM is usually diagnosed after 6 months of absence of myopathy [40]. In this study, we found that the percentage of muscle weakness in patients with CADM was significantly lower, which was consistent with the characteristics of the disease itself. In addition, we also found that patients with CADM had a lower rate of previous treatment, a shorter course of disease, a higher rate of RP-ILD, and a higher positive rate of anti-MDA5 antibody. The characteristics of low rate of previous treatment and short course of disease suggest that patients with CADM are more acute and severe than those with classical DM. This verified that anti-MDA5 DM usually presented with CADM and had a higher rate of RP-ILD [4, 29]. These findings suggest that clinicians should pay more attention to patients with CADM.

There are some limitations to our study. First, the total number of patients included in this study is small. Secondly, the generality of the results may be limited by the fact that this was a single-center study conducted in our hospital. Finally, some patients with ILD were severely ill and unable to perform lung function test, and most of our patients were not tested for lung function due to their poor compliance or physician omissions in ordering test. Therefore, the results of lung function test are not presented in our article. Despite these limitations, our study still revealed some distinct clinical features of DM patients with ILD, which has important guiding significance in clinical practice.

CONCLUSIONS

Our study shows that DM patients with ILD have some distinct clinical characteristics compared with those without ILD, such as older age, higher rates of CADM, Gottron's papules, mechanic's hands, myocardial involvement, higher positive rates of anti-MDA5 and anti-SSA /Ro52 antibodies, lower ALB, PNI, and lower rates of muscle weakness and heliotrope rash. Old age, Gottron's papules, and anti-SSA/Ro52 were independent risk factors for ILD in DM. When treating patients with DM, clinicians should pay attention to these clinical characteristics and formulate the best treatment plan for each patient.

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Compliance with Ethics Guidelines. This study was conducted in accordance with the World Medical Association Declaration of Helsinki and was approved by the Human Ethics Review Committee of the Second Affiliated Hospital of Soochow University (JD-HG-2023–09). All patients signed informed consent to participate in the study.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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