Original Article

Clinical impact of antineutrophil cytoplasmic antibody positivity on the occurrence of interstitial lung disease in patients with polymyositis/dermatomyositis

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Background: This study investigated the clinical impact of antineutrophil cytoplasmic antibody (ANCA) positivity on the occurrence of interstitial lung disease (ILD) in patients with probable and definite polymyositis (PM)/dermatomyositis (DM) who met both the Bohan and Peter and the 2017 European League Against Rheumatism/American College of Rheumatology criteria.

Methods: The medical records of 75 PM/DM patients were retrospectively reviewed. ANCA and anti-Jo 1 positivity at diagnosis were obtained, and pulmonary function test and chest high-resolution computed tomography results at ILD occurrence were collected. The follow-up duration based on ILD was defined as the period from the time of PM/DM diagnosis to the occurrence of ILD in PM/DM patients with ILD and to the last visit for those without ILD.

Results: The median age was 50.0 years and 21.3% were male. ANCA and anti-Jo 1 were detected in 12 (16.0%) and 26 patients (34.7%), respectively. ILD occurred in 32 patients, 24 of whom had ILD at the time of PM/DM diagnosis. Anti-Jo 1 was detected more often in PM/DM patients without ANCA than those with (39.7% *vs.* 8.3%). ILD occurred more frequently in PM/DM patients with ANCA than those without ANCA (75.0% *vs.* 36.5%). However, the occurrence of ILD was not affected by anti-Jo 1 positivity. Furthermore, ANCA-positive PM/DM patients exhibited a significantly lower cumulative ILD-free survival rate than ANCA-negative PM/DM patients (P=0.009).

Conclusions: ANCA positivity at the time of PM/DM diagnosis might be an important risk factor for ILD in PM/DM patients.

Keywords: Antineutrophil cytoplasmic antibody (ANCA); polymyositis; dermatomyositis; interstitial lung disease (ILD)

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Introduction

Idiopathic inflammatory myopathy (IIM) is a cluster of chronic autoimmune diseases that are characterized by typical inflammation of the muscle fibres.

IIM includes five types of myopathies; namely, polymyositis (PM), dermatomyositis (DM), overlap myositis, sporadic inclusion body myositis, and necrotising autoimmune myopathy (1). Among these IIMs, both PM and DM mainly present symmetrical proximal muscle weakness (2). Compared to PM, DM has two distinct features: typical cutaneous changes and two peak ages, as DM occurs in both young patients in their teens and adults in their 40s and 50s, whereas PM mainly occurs in older patients (3).

In 1975, Bohan and Peter proposed the classification criteria for PM/DM (the Bohan and Peter criteria). The typical cutaneous changes such as heliotrope rash with periorbital oedema and violaceous erythema and Gottron's sign enabled the distinction of DM from PM. Conversely, in the absence of typical cutaneous changes, histological confirmation of muscle inflammation by muscle biopsy was considered essential for the classification as definite PM or DM (4,5). However, the Bohan and Peter criteria include no specific descriptions of histological findings, and they do not mention autoantibodies. Accordingly, there has been a demand for new classification criteria to overcome these limitations.

In 2017, the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) proposed the new classification criteria for adult and juvenile idiopathic inflammatory myopathies, which are based on the scoring system (the 2017 EULAR/ACR criteria) (6). Although the use of the 2017 EULAR/ACR criteria in classifying PM/DM are currently encouraged, the Bohan and Peter criteria remain widely used because of their convenience and significant concordance rate with the 2017 EULAR/ACR criteria (7).

Interstitial lung disease (ILD) is a relatively common systemic complication of PM/DM. ILD occurs in 19–40% of PM/DM patients, and non-specific interstitial pneumonia (NSIP) on high-resolution computed tomography (HRCT) is more common than usual interstitial pneumonia (UIP) (8,9). In addition, a meta-analysis reported a global prevalence rate of ILD in patients with PM/DM of 41.0% with higher rates in Asian patients compared to those in American and European patients (42.0%, 35.0%, and 26.0%, respectively) (10). Anti-Jo 1 is associated with ILD in PM/DM, and a previous study reported that 72.5% of anti-Jo 1-positive patients with antisynthetase syndrome exhibited ILD (11).

Anti-Jo 1 is a representative aminoacyl transfer RNA (tRNA) synthetase and is strongly associated with antisynthetase syndrome characterised by ILD, myositis, Raynaud's' phenomenon, and arthritis (12). A study reported that anti-Jo 1 antibodies were found in 15–25% of PM/DM patients (13). Anti-Jo 1 status reportedly predicted the clinical course of ILD in PM/DM patients; moreover, anti-Jo 1-positive ILD patients showed a different prognosis from that of anti-Jo 1-negative ILD patients (11,14,15). Therefore, we expected anti-Jo 1 status to be significantly associated with an increase in the occurrence of ILD.

Antineutrophil cytoplasmic antibody (ANCA) is a group of autoantibodies targeting neutrophil-specific proteins including myeloperoxidase (MPO) and proteinase 3 (PR3), that plays an important role in the classification ANCA-associated vasculitis (AAV) (16,17). Despite the lack of knowledge of the shared pathophysiological mechanism between PM/DM and AAV, there have been several reports regarding overlap syndrome between these conditions (18,19). In contrast, ILD is an established manifestation of AAV in addition to PM/DM (20,21). The reported prevalence rate of ILD in AAV ranges from 7% to 47%, and UIP confirmed on HRCT was more common than other ILD patterns (21-23). Until now, the ANCA positivity rate and the association between ANCA positivity and ILD occurrence in PM/DM patients without overlapping syndromes of AAV and PM/DM have not been reported. Hence, this study investigated the clinical impact of ANCA positivity on the occurrence of ILD in patients with probable and definite PM/DM who met both the Bohan and Peter and 2017 EULAR/ACR criteria. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-604/rc).

Methods

Patients

The electronic medical records of 79 patients with PM/DM were retrospectively reviewed. The inclusion criteria were (I) patients who were initially classified as having PM/DM at the Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, between January 2005 and June 2021; (II) patients who fulfilled the Bohan and Peter criteria for probable and definite PM/DM (4,5); (III) patients who met the 2017

EULAR/ACR criteria for probable and definite PM/DM or who were reclassified according to those criteria (6); (IV) patients whose medical records were sufficiently completed to allow the collection of clinical and laboratory data at the time of PM/DM diagnosis; (V) patients with available results of both ANCA tests such as an indirect immunofluorescence assay (IIFA) for perinuclear (P)-ANCA and cytoplasmic (C)-ANCA and an antigen-specific immunoassay for MPO-ANCA and PR3-ANCA (24).

The exclusion criteria were (I) patients with concomitant serious medical conditions such as malignancies, infectious diseases requiring hospitalisation, and other autoimmune diseases related to ANCA positivity, including AAV or primary sclerosing cholangitis (16,17,25); (II) patients who had not been followed up for 3 months or more; (III) patients who had ever received immunosuppressive drugs for the treatment of PM/DM or ILD before PM/DM diagnosis; (IV) patients to whom drugs that cause ANCA positivity such as propylthiouracil or hydralazine were administered (26,27).

Of the 79 patients, three patients were excluded because they had only IIFA results for ANCA. Of the remaining 76 patients, one patient was excluded because the PM was accompanied by concomitant primary sclerosing cholangitis. Finally, this study included and analysed 75 PM/DM patients.

Clinical and laboratory data

Regarding variables at the time of PM/DM diagnosis, age and sex were collected as demographic data, and ANCA types and their positivity were also confirmed. The results of ANCA tests were accepted when tests were performed within 7 days of PM/DM diagnosis. The numbers of patients satisfying components constituting the Bohan and Peter criteria and the 2017 EULAR/ACR criteria, and the laboratory results including creatine phosphokinase (CPK) (IU/L), lactate dehydrogenase (LDH) (IU/L), and aldolase

Table 1 Characteristics of patients with PM/DM at diagnosis and during follow-up (N=75)

Variables	Values
At the time of diagnosis	
Demographic data	
Age (years)	50.0 (20.0)
Male gender	16 (21.3)
ANCA positive	
ANCA positivity	12 (16.0)
MPO-ANCA (or P-ANCA) positive	11 (14.7)
PR3-ANCA (or C-ANCA) positive	1 (1.3)
Subtype	
PM	29 (38.7)
DM	46 (61.3)
Bohan and Peter criteria components	
Symmetrical proximal muscle weakness	71 (94.7)
Muscle biopsy consistent with PM/DM [62]*	51 (82.3)
Elevated muscle enzyme	74 (98.7)
Abnormal EMG [73]**	65 (89.0)
Dermatologic feature	44 (58.7)
Definite PM according to the Bohan and Peter criteria (of 29 PM patients)	22 (75.9)
Definite DM according to the Bohan and Peter criteria (of 46 DM patients)	37 (80.4)

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Values
2017 EULAR/ACR criteria components	
Age of onset of first symptom18–40 years	20 (26.7)
Age of onset of first symptom ≥40 years	55 (73.3)
Objective symmetric weakness, usually progressive, of the proximal upper extremities	52 (69.3)
Objective symmetric weakness, usually progressive, of the proximal lower extremities	67 (89.3)
Neck flexors are relatively weaker than neck extensors	8 (10.7)
In the legs, proximal muscle are relatively weaker than distal muscles	41 (54.7)
Heliotrope rash	14 (18.7)
Gottron's papules	16 (21.3)
Gottron's sign	10 (13.3)
Dysphagia or esophageal dysmotility	7 (9.3)
Anti-Jo 1 antibody positive	26 (34.7)
Elevated serum levels of CPK or LDH or AST or ALT	74 (98.7)
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers [62]*	16/62 (25.8)
Perimysial and/or perivascular infiltration of mononuclear cells [62]*	16/62 (25.8)
Perifascicular atrophy [62]*	11/62 (17.7)
Rimmed vacuoles [62]*	2/62 (3.2)
Total score	
Definite PM according to the 2017 EULAR/ACR criteria (of 29 PM patients)	9 (31.0)
Definite DM according to the 2017 EULAR/ACR criteria (of 46 DM patients)	29 (63.0)
PM/DM-related laboratory results	
CPK (IU/L)	543.0 (3,193.0)
LDH (IU/L)	472.0 (455.0)
Aldolase (sigma U/mL)	21.8 (38.1)
During follow-up	
ILD	32 (42.7)
Follow-up duration based on ILD (months)	19.0 (71.0)

Values are expressed as a median (interquartile range) or n (%). *, muscle biopsy was performed in 62 patients; **, EMG was performed in 73 patients. PM/DM, polymyositis/dermatomyositis; ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; EMG, electromyography; CPK, creatine phosphokinase; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; EULAR, the European League Against Rheumatism; ACR, American College of Rheumatology; ILD, interstitial lung disease.

(sigma U/mL) are shown in *Table 1*.

Regarding variables during follow-up, all-cause mortality and ILD were investigated as poor outcomes. The follow-up duration based on all-cause mortality was defined as the period from the time of PM/DM diagnosis to death for the deceased patients and from diagnosis to the last visit for the surviving patients. The follow-up duration based on ILD was defined as the period from the time of PM/DM diagnosis to the occurrence of ILD in PM/DM patients with ILD and to the last visit for those without ILD.

ANCA measurement

Myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA were measured using the novel anchor-coated highly sensitive (hs) Phadia ELiA (Thermo Fisher Scientific/Phadia, Freiburg, Germany) and human native antigens, on the Phadia250 analyser. We used immunoassays as the primary screening method for ANCA; however, when patients were found to be negative for ANCA by an antigen-specific assay but positive for perinuclear (P)-ANCA or cytoplasmic (C)-ANCA by an indirect immunofluorescence assay, they were considered to have MPO-ANCA or PR3-ANCA when AAV was strongly suspected based on the clinical and laboratory features (28).

Definitions of probable and definite PM and DM

In terms of the Bohan and Peter criteria, patients satisfying three out of the five components were classified as having probable PM/DM, and while those satisfying 4 or more components were classified as having definite PM/DM. In terms of the 2017 EULAR/ACR criteria, patients with a total aggregated score of ≥5.5 without biopsy or ≥6.7 with biopsy were defined as probable PM/DM. Patients with a total aggregated score of ≥7.5 without biopsy or ≥8.7 with biopsy were categorised as definite PM/DM (4-6).

Evaluation of ILD

Chest HRCT was performed to determine ILD occurrence when ILD was suspected on chest radiography. Since lung biopsy was not performed in all patients, the HRCT findings were roughly divided into UIP and non-UIP (8,29). HRCT features frequently seen in UIP include honeycombing, traction bronchiectasis, and traction bronchiolectasis, which may be seen with the concurrent presence of ground-glass opacification and fine reticulation (29). Among the results of pulmonary function tests (PFT), both the forced volume capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO), which reflect the severity of ILD, were collected (9).

Definition of AAV

We used the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides and the 2007 algorithm for classifying AAV proposed by the European Medicine Agency to diagnose AAV (16,17).

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as medians with interquartile ranges, whereas categorical variables are expressed as numbers (percentages). Significant differences between the two categorical variables were analysed using the Chi-square and Fisher's exact tests. Significant differences between two continuous variables were compared using the Mann-Whitney U test. Comparison of the cumulative survivals rates between the two groups was analysed by the Kaplan-Meier survival analysis with the log-rank test. P values less than 0.05 were considered statistically significant.

Ethical statement

The present study was approved by the Institutional Review Board (IRB) of Severance Hospital (Seoul, Korea; No. 4-2021-1057) and conducted in accordance with the Declaration of Helsinki (as revised in 2013). Given the retrospective study design and the use of anonymized patient data, the requirement for written informed consent was waived.

Results

Characteristics

Among the variables collected at the time of PM/DM diagnosis, the median age was 50.0 years and 21.3% of patients were male. ANCA was detected in 12 patients (16.0%), 11 of whom had MPO-ANCA (or P-ANCA). Meanwhile, anti-Jo 1 was positive in 26 patients (34.7%). The numbers of patients satisfying each component of the two classification criteria are summarised in *Table 1*. In particular, in terms of the 2017 EULAR/ACR criteria, the median total score was 8.6. Of the 75 patients, 29 (38.7%) and 46 (61.3%) were classified as having PM and DM, respectively. Of the 29 PM patients, 22 (75.9%) were classified as having definite PM and seven (24.1%) as probable PM based on the Bohan and Peter criteria, while 9 patients (31.0%) were classified as having definite PM and 20 (69.0%) as probable PM based on the 2017 EULAR/ACR criteria. In contrast, of the 46 DM patients, 37 (80.4%) were classified as having definite DM and nine (19.6%) as probable DM based on the Bohan and Peter criteria, and 29 (63.0%) were categorised as having definite DM and 17

(37.0%) as probable DM based on the 2017 EULAR/ACR criteria. The median CPK, LDH and aldolase values were 543.0 IU/L, 472.0 IU/L and 21.8 sigma U/mL, respectively.

Among the variables collected during the median follow-up duration of 19.0 months, ILD occurred in 32 patients, 24 of whom had ILD at the time of PM/DM diagnosis (*Table 1*).

Comparison analyses according to ANCA positivity

All patients with PM/DM were divided into two groups according to ANCA positivity: patients with ANCA and those without ANCA. Among the variables collected at diagnosis, PM/DM patients with ANCA less frequently exhibited abnormal electromyography (EMG) findings compared to patients without ANCA (66.7% *vs.* 93.4%, P=0.021). In contrast, PM/DM patients with ANCA more frequently presented with Gottron's sign compared to patients without ANCA (41.7% *vs.* 7.9%, P=0.007), despite the lack of significant difference in the proportions of DM patients. Anti-Jo 1 was detected more often in PM/DM patients without ANCA than those with (39.7% *vs.* 8.3%, P=0.048). The levels of CPK, LDH, and aldolase did not differ significantly between the groups. Among the variables collected during follow-up, ILD occurred more frequently in PM/DM patients with ANCA than those without ANCA (75.0% *vs.* 36.5%, P=0.023). Conversely, the follow-up duration based on ILD was also significantly shorter in PM/DM patients with ANCA (P=0.033) (*Table 2*).

Comparisons of ILD occurrence according to the presence of ANCA and anti-Jo 1

Contrary to the finding of the significantly higher occurrence of ILD in ANCA-positive patients, we observed no significant difference in the occurrence of ILD between 26 PM/DM patients with anti-Jo 1 and 49 patients without (50.0% *vs.* 38.8%, P=0.350) (*Table 3*).

Among 75 PM/DM patients, one patient (1.3%) had both ANCA and anti-Jo 1, 11 patients (14.7%) had only ANCA without anti-Jo 1, only anti-Jo 1 without ANCA was detected in 25 patients (33.3%), and neither ANCA nor anti-Jo 1 was detected in 38 patients (50.7%). We observed significant difference in the occurrence of ILD

Table 2 Comparison of the characteristics of patients with PM/DM based on ANCA positivity

Variables	PM/DM patients without ANCA (N=63)	PM/DM patients with ANCA (N=12)	P value
At the time of diagnosis			
Demographic data			
Age (years)	48.5 (22.0)	54 (9.0)	0.140
Male gender	15 (23.8)	1 (8.3)	0.442
Subtype			
PM	24 (38.1)	5 (41.7)	1.000
DM	39 (61.9)	7 (58.3)	1.000
PM/DM-related manifestations based on Bohan and Peter criteria			
Symmetrical proximal muscle weakness	61 (96.8)	10 (83.3)	0.118
Muscle biopsy consistent with PM/DM*	42/51 (82.4)	9/11 (81.8)	1.000
Elevated muscle enzyme	63 (100.0)	11 (91.7)	0.160
Abnormal EMG**	57/61 (93.4)	8/12 (66.7)	0.021
Dermatologic feature	37 (58.7)	7 (58.3)	1.000
Parameters based on 2017 EULAR classification criteria for idiopathic inflammatory myositis			
Age of onset of first symptom 18–40 years	19 (30.2)	1 (8.3)	0.164
Age of onset of first symptom ≥40 years	44 (69.8)	11 (91.7)	0.164
Objective symmetric weakness, usually progressive, of the proximal upper extremities	46 (73.0)	6 (50.0)	0.170

Table 2 (*continued*)

Table 2 (*continued*)

Variables	PM/DM patients without ANCA (N=63)	PM/DM patients with ANCA (N=12)	P value
Objective symmetric weakness, usually progressive, of the proximal lower extremities	56 (88.9)	11 (91.7)	1.000
Neck flexors are relatively weaker than neck extensors	6 (9.5)	2 (16.7)	0.606
In the legs, proximal muscle are relatively weaker than distal muscles	32 (50.8)	9 (75.0)	0.205
Heliotrope rash	13 (20.6)	1 (8.3)	0.444
Gottron's papules	13 (20.6)	3 (25.0)	0.711
Gottron's sign	5 (7.9)	5 (41.7)	0.007
Dysphagia or esophageal dysmotility	7 (11.1)	0 (0)	0.589
Anti-Jo 1 antibody positive	25 (39.7)	1 (8.3)	0.048
Elevated serum levels of CPK or LDH or AST or ALT	63 (100.0)	11 (91.7)	0.160
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers*	13/51 (25.5)	3/11 (27.3)	1.000
Perimysial and/or perivascular infiltration of mononuclear cells*	11/51 (21.6)	5/11 (45.5)	0.132
Perifascicular atrophy*	10/51 (19.6)	1/11 (9.1)	0.671
Rimmed vacuoles*	2/51 (3.9)	0/11 (0)	1.000
Total score	8.9 (3.1)	7.9 (4.7)	0.767
PM/DM-related laboratory results			
CPK (IU/L)	638.5 (3,106.3)	380.0 (3,226.0)	0.826
LDH (IU/L)	495.5 (429.0)	434.0 (587.0)	0.301
Aldolase (sigma U/mL)	22.3 (35.9)	12.3 (55.9)	0.179
During follow-up			
ILD	23 (36.5)	9 (75.0)	0.023
Follow-up duration based on ILD (months)	34.0 (85.0)	2.5 (26.0)	0.033

Values are expressed as a median (interquartile range) or N (%). *, muscle biopsy was performed in 62 patients; **, EMG was performed in 73 patients. PM/DM, polymyositis/dermatomyositis; ANCA, antineutrophil cytoplasmic antibody; EMG, electromyography; CPK, creatine phosphokinase; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; EULAR, the European League Against Rheumatism; ILD, interstitial lung disease.

Table 3 Comparison of the ILD prevalence of patients with PM/DM based on ANCA and anti-Jo 1 positivity

Variables	ILD	P value
ANCA		0.023
Without (N=63)	23 (36.5)	
With (N=12)	9 (75.0)	
Anti-Jo 1		0.350
Without (N=49)	19 (38.8)	
With (N=26)	13 (50.0)	

Values are expressed as N (%). ILD, interstitial lung disease; PM/DM, polymyositis/dermatomyositis; ANCA, antineutrophil cytoplasmic antibody.

Table 4 Comparison of the ILD prevalence of patients with PM/DM between 4 subgroups based on ANCA and anti-Jo 1 positivity

	Anti-Jo 1 (–)	Anti-Jo 1 (+)	P value
ANCA (–)	11/38 (28.9%)	12/25 (48.0%)	0.124
ANCA (+)	8/11 (72.7%)	1/1 (100.0%)	>0.999
P value	0.014	>0.999	

ILD, interstitial lung disease; PM/DM, polymyositis/dermatomyositis; ANCA, antineutrophil cytoplasmic antibody.

Table 5 Comparison of the pulmonary function tests and chest HRCT pattern of patients with PM/DM-ILD based on either ANCA positive or anti-Jo 1 antibody positive

Variables	ANCA			Anti-Jo 1		
	Without (N=23)	With ANCA (N=9)	P value	Without (N=19)	With ANCA (N=13)	P value
FVC, %	55.5 (17.0)	76.0 (26.0)	0.002	64.5 (32.0)	61.0 (14.0)	0.226
DLCO, %	56.5 (31.0)	67.0 (21.0)	0.173	60.0 (22.0)	64.0 (32.0)	0.824
UIP	6 (26.1)	5 (55.6)	0.213	7 (36.8)	4 (30.8)	1.000

Values are expressed as a median (interquartile range) or n (%). HRCT, high-resolution computed tomography; PM/DM, polymyositis/dermatomyositis; ILD, interstitial lung disease; ANCA, antineutrophil cytoplasmic antibody; FVC, forced volume capacity; DLCO, diffusing capacity of the lung for carbon monoxide; UIP, usual interstitial pneumonia.

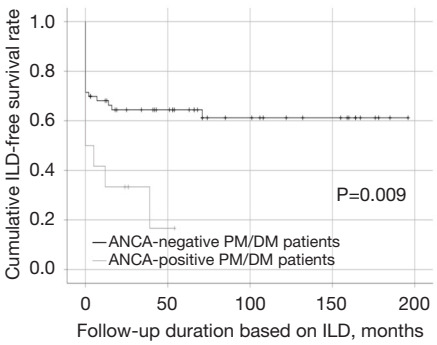

Figure 1 Cumulative ILD-free survival rates. ANCA-positive PM/DM patients showed a significantly lower occurrence rate of ILD compared to ANCA-negative patients. ILD, interstitial pneumonia; ANCA, antineutrophil cytoplasmic antibody; PM, polymyositis; DM, dermatomyositis.

between 38 ANCA-negative, anti-Jo 1-negative PM/DM patients and 11 ANCA-positive, anti-Jo 1-negative patients (28.9% versus 72.7%, P=0.014) (*Table 4*). Other than that, no statistical significance was observed for ILD occurrence among the 4 groups.

Comparisons of FVC, DLCO, and UIP according to the presence of ANCA and anti-Jo 1

To assess the results of ILD-related variables according to the presence of ANCA and anti-Jo 1, 32 PM/DM patients were further analysed. PM/DM-ILD patients with ANCA showed a higher FVC than those without ANCA (55.5% *vs.* 76.0%, P=0.002), but we observed no significant differences in DLCO and UIP between the two groups. None of the three variables differed significantly between PM/DM-ILD patients with anti-Jo 1 and those without (*Table 5*).

Comparisons of cumulative ILD-free survival rates

ANCA-positive PM/DM patients exhibited a significantly lower cumulative ILD-free survival rate than ANCA-negative PM/DM patients (P=0.009) (*Figure 1*). PM/DM patients with anti-Jo 1 tended to exhibit a lower cumulative ILD-free survival rate than those without, but the difference was not statistically significant (P=0.392) (Figure S1).

When classified into four groups according to the presence and absence of ANCA and anti-Jo 1, ANCA-positive and anti-Jo 1-positive patients had the highest cumulative occurrence rate of ILD, followed by ANCA-positive anti-Jo 1-negative patients (Figure S2). We divided the 75 patients into two groups, PM and DM, and investigated the cumulative ILD-free survival rates between them. In both groups, patients with ANCA tended to exhibit a lower cumulative ILD-free survival rate compared to that in patients without ANCA, and PM patients showed a result closer to statistical significance than DM patients (P=0.059 *vs.* P=0.082); however, the differences were not statistically significant (Figure S3).

Comparisons of cumulative survival rates

When we investigated the clinical effect of the presence or absence of ILD on all-cause mortality, PM/DM patients with ILD showed a tendency to exhibit a lower patients' survival rate than those without ILD; however, it was not statistically significant (P=0.062) (Figure S4A). In addition, when only PM/DM-ILD patients were included in the analysis of the effects of UIP and non-UIP on all-cause mortality, the cumulative patients' survival rates between PM/DM-ILD patients with UIP and those with non-UIP did not differ significantly (Figure S4B). Furthermore, examination of the differences in the prognosis of death

between patients with ILD at the time of and after PM/DM diagnosis in 32 PM-DM-ILD patients showed no significant difference in the cumulative patients' survival rates (Figure S4C).

Application of the AAV criteria to ANCA-positive patients

We applied two criteria, the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides and the 2007 algorithm for classifying AAV proposed by the European Medicine Agency, to ANCA-positive PM/DM patients (16,17). However, none of them was classified as having AAV. As the inclusion criteria included only patients without overlap syndrome of AAV and PM/DM.

Discussion

We thought that anti-Jo 1 might be involved in the induction of ILD in PM/DM patients. However, the results in our analysis of 75 PM/DM patients showed that ANCA positivity was associated with an increased occurrence rate of ILD (*Figure 1*), while anti-Jo 1 positivity was not.

We propose several hypotheses to explain this discrepancy. First, the presence of ANCA may have diminished the strength of the association between anti-Jo 1 positivity and the occurrence of ILD in terms of pathological mechanism. In *Table 4*, when ANCA negative, anti Jo-1 positive patients tend to have more ILD than anti Jo-1 negative patients, although not statistically significant. Among the possible pathological mechanisms by which anti-Jo 1 could affect the occurrence of ILD, immune complexes including anti-Jo 1 and RNA have been reported as possible endogenous inducers that could promote IFN-alpha production in plasmacytoid dendritic cells; thus, increased IFN-alpha might play an important role in the occurrence and progression of ILD (30,31). In terms of the pathophysiology of ILD in AAV, three hypotheses have been proposed. First, ILD might occur because of repeated episodes of diffuse alveolar haemorrhage resulting from pulmonary capillaritis. Second, ILD might be a consequence of direct damage to vascular inflammation by MPO-ANCA. Finally, intrinsic factors such as existing lung diseases or environmental factors such as cigarette smoking might activate the endothelial cells of the lung capillaries and accelerate MPO expression, leading to an increase in circulating MPO-ANCA (32-35). Therefore, it may be impossible to explain the results of this study through the pathological mechanism because of the lack of known common features between anti-Jo 1 and ANCA in participating in the occurrence of ILD occurrence.

Second, ANCA production may play an antagonistic role with anti-Jo 1 production. In *Table 4*, when ANCA positive, Anti-Jo-1 positive rate is less than that when ANCA negative. These results suggest that it may be difficult for ANCA and anti-Jo 1 to exist simultaneously in PM/DM patients.

Third, the anti-Jo 1 positive rate may have been lower than that of the general cohort of PM/DM patients. The reported occurrence rate of ILD in anti-Jo 1-positive PM/DM patients was approximately 55% (36). In this study, the occurrence rate of ILD in PM/DM patients with anti-Jo 1 was 50.0%. Therefore, anti-Jo 1 played a role in the development of ILD properly as usual. A previous study reported the anti-Jo 1 positivity rates ranging from 15% to 30% of PM/DM patients (37). In this study, the anti-Jo 1 positivity rate was 34.6%. Therefore, the anti-Jo 1 positivity rate and the occurrence rate of ILD in anti-Jo 1-positive PM/DM patients were consistent with those of previous studies. As the evidence refutes the three hypotheses presented above, further studies are needed on the role of ANCA in the pathogenesis and the association between ANCA and anti-Jo 1 positivity in PM/DM patients.

We also evaluated which subtype of IIM was more susceptible to the effect of ANCA positivity on the occurrence of ILD. No IIM subtypes was more strongly associated with ANCA positivity and the occurrence of ILD (Figure S3).

ILD is a major risk factor for mortality in PM/DM patients. The three most common causes of mortality in PM/DM patients were pulmonary infection (35%), ILD (21%), and both infection and ILD (25%) (38). When we investigated the clinical effect of the presence or absence of ILD on all-cause mortality, PM/DM patients with ILD have a lower survival rate than those without ILD, but there is no statistical significance (Figure S4A).

In this study, the degree of restrictive pulmonary insufficiency based on FVC in PM/DM patients with ANCA was better than those without ANCA. However, we observed no significant differences in the degree of DLCO and the frequency of UIP between the two groups. We assumed two reasons for this discrepancy: first, only ILD occurrence and UIP patterns were investigated on HRCT, and the analysis of the three-dimensional invasion area of the actual ILD was not performed using the automated reconstruction of HRCT findings; and second, ANCA was tested within 7 days of PM/DM diagnosis, while PFT were performed when the occurrence of ILD was confirmed on

HRCT. Therefore, the discrepancy might be due to a time gap between the time of ANCA tests and that of PFT and HRCT performance.

Another interesting finding was that PM/DM patients with ANCA more frequently showed Gottron's sign at diagnosis compared to patients without ANCA. Since Gottron's sign is a typical cutaneous change in DM patients, only DM patients were selected and the frequency of Gottron's sign according to the presence or absence of ANCA was investigated again. Of the 46 DM patients, 5 of 7 DM patients with ANCA and 5 of 39 without ANCA exhibited Gottron's sign (71.4% *vs.* 12.8%, P=0.003). Although Gottron's sign has been previously reported in patients with overlap syndrome of AAV and IIM, patients with overlap SD were not included in this study, so the possibility that Gottron's sign was confused with the cutaneous manifestation of AAV could be excluded (18).

This study is the first demonstrate the clinical impact of ANCA positivity on the occurrence of ILD in patients with PM/DM based on both the Bohan and Peter and the 2017 EULAR/ACR criteria. However, this study has several limitations. The number patients included in this study was not large enough to generalise the results owing to the limitations of the single-centre study and the exclusion of patients lacking ANCA test results at diagnosis. Moreover, as a limitation inherent to its retrospective study design, this study could not perform serial and regular ANCA testing, PFT, and HRCT; thus, it was impossible to determine the direct association between ANCA positivity and the occurrence of ILD. Anti-MDA5 antibody was known to be associated with the development of ILD in PM/DM patient, but this test was not performed in this study.

In conclusion, the results of our study demonstrated that ANCA positivity at the time of PM/DM diagnosis might be an important risk factor for ILD in PM/DM patients. Therefore, we suggest that physicians perform ANCA tests at the time of PM/DM diagnosis, and pay close attention to regular monitoring of the occurrence of ILD in patients with ANCA during follow-up.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-604/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-604/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-604/coif). The authors report that this work was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare (No. HI14C1324); the Handok Inc., Seoul, Republic of Korea (No. HANDOK 2021-006); and Celltrion Pharm, Inc. Chungcheongbuk-do, Republic of Korea (No. NCR 2019-6). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The present study was approved by the Institutional Review Board (IRB) of Severance Hospital (Seoul, Korea; No. 4-2021-1057) and conducted in accordance with the Declaration of Helsinki (as revised in 2013). Given the retrospective study design and the use of anonymized patient data, the requirement for written informed consent was waived.

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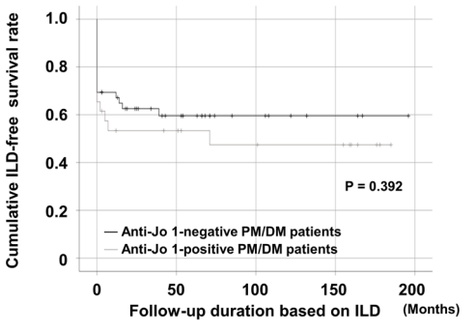

Figure S1 Comparison of cumulative ILD-free survival rates between PM/DM patients with anti-Jo 1 and those without anti-Jo 1.

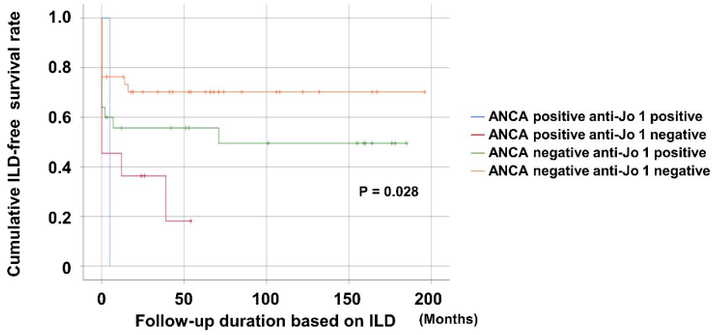

Figure S2 Comparison of cumulative ILD-free survival rates among PM/DM patients with ANCA and anti-Jo 1, those with ANCA and without anti-Jo 1, those without ANCA and with anti-Jo 1, and those without ANCA and anti-Jo 1. ILD, interstitial pneumonia; ANCA, antineutrophil cytoplasmic antibody; PM, polymyositis; DM, dermatomyositis.

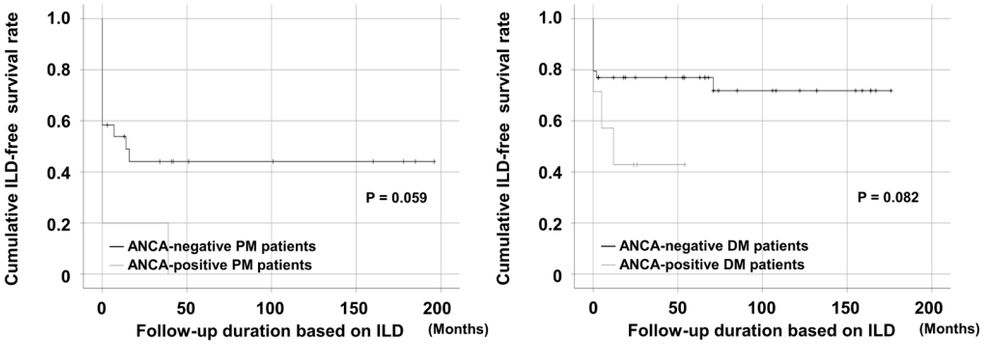

Figure S3 Comparison of cumulative ILD-free survival rates between PM patients with ANCA and those without ANCA and between DM patients with ANCA and those without ANCA. ILD, interstitial pneumonia; ANCA, antineutrophil cytoplasmic antibody; PM, polymyositis; DM, dermatomyositis.

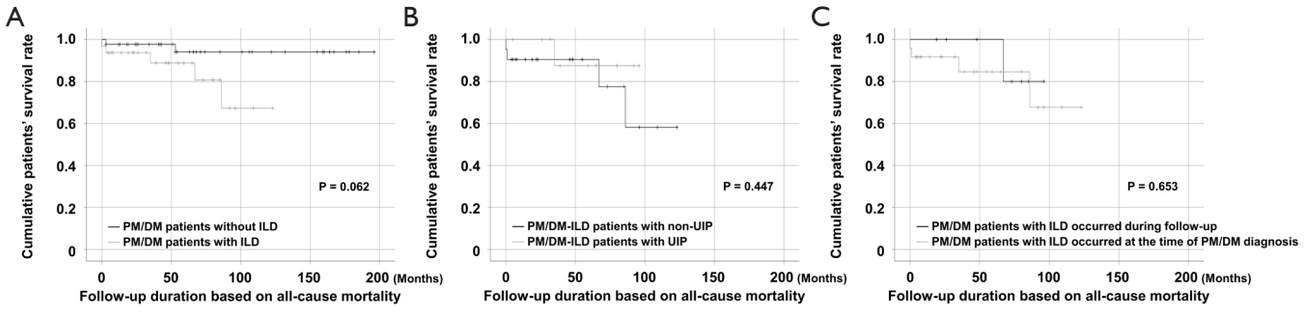

Figure S4 Comparison of cumulative survival rates between PM/DM patients with ILD and those without ILD, between PM/DM-ILD patients with UIP and those with non-UIP, and between PM/DM-ILD patients who had ILD during follow-up and those who had ILD at the time of PM/DM diagnosis. ILD, interstitial pneumonia; ANCA, antineutrophil cytoplasmic antibody; PM, polymyositis; DM, dermatomyositis.

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