ARTICLE

# Muscular and extramuscular clinical features of patients with anti-PM/Scl autoantibodies

Rebecca De Lorenzo, MD,* Iago Pinal-Fernandez, MD, PhD,* Wilson Huang, BS, Jemima Albayda, MD, Eleni Tiniakou, MD, Cheilonda Johnson, MD, MHS, Jose C. Milisenda, MD, Maria Casal-Dominguez, MD, Andrea M. Corse, MD, Sonye K. Danoff, MD, PhD, Lisa Christopher-Stine, MD, MPH, Julie J. Paik, MD, MHS,† and Andrew L. Mammen, MD, PhD†

**Correspondence**
Dr. Mammen
andrew.mammen@nih.gov or Dr. Paik
jpaik1@jhmi.edu

*Neurology*® 2018;90:e2068-e2076. doi:10.1212/WNL.0000000000005638

**CME Course**
NPub.org/cmelist

## Abstract

### Objective
To define the clinical features of myositis patients with anti-PM/Scl-75 and/or anti-PM/Scl-100 autoantibodies at disease onset and during the course of disease and compare them to patients with other forms of myositis.

### Methods
In this longitudinal cohort study, the prevalence and severity of clinical features at disease onset and during follow-up were compared between anti-PM/Scl-positive patients and those with the antisynthetase syndrome (AS), dermatomyositis (DM), and immune-mediated necrotizing myopathy (IMNM).

### Results
Forty-one anti-PM/Scl-positive, 132 AS, 178 DM, and 135 IMNM patients were included. Although muscle weakness was a presenting feature in just 37% of anti-PM/Scl-positive patients, 93% eventually developed weakness. Unlike the other groups, anti-PM-Scl-positive patients had more severe weakness in arm abductors than hip flexors. Interstitial lung disease was a presenting feature in just 10% of anti-PM/Scl-positive patients, but occurred in 61% during follow-up; fewer patients with DM (13%, $p < 0.001$) and IMNM (6%, $p < 0.001$) and more patients with AS (80%, $p < 0.05$) developed interstitial lung disease during the course of disease. Mechanic's hands (80%), Raynaud syndrome (78%), sclerodactyly (66%), telangiectasias (66%), esophageal reflux disease (61%), subcutaneous edema (46%), puffy hands (39%), and calcinosis (39%) occurred more frequently in anti-PM/Scl-positive patients than in the other groups. Although 30% of anti-PM/Scl-positive patients met criteria for systemic sclerosis, less than 5% had renal crisis or finger ulcerations. No differences were found between patients with only anti-PM/Scl-100 or only anti-PM/Scl-75 autoantibodies.

### Conclusions
Unlike patients with DM, AS, or IMNM, anti-PM/Scl-positive patients have weaker arm abductors than hip flexors. Anti-PM/Scl-positive patients also have the most extensive extramuscular features.

*These authors contributed equally to this work as first authors.

†These authors contributed equally to this work as last authors.

From the National Institute of Arthritis and Musculoskeletal and Skin Diseases (R.D.L., I.P.-F., W.H., J.C.M., M.C.-D., A.L.M.), NIH, Bethesda; and Johns Hopkins University School of Medicine (I.P.-F., J.A., E.T., C.J., M.C.-D., A.M.C., S.K.D., L.C.-S., J.J.P., A.L.M.), Baltimore, MD.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

## Glossary

**AS** = antisynthetase syndrome; **CK** = creatine kinase; **DLCO** = diffusing capacity of the lungs for carbon monoxide; **DM** = dermatomyositis; **FVC** = forced vital capacity; **ILD** = interstitial lung disease; **IMNM** = immune-mediated necrotizing myopathy; **SSc** = systemic sclerosis.

The autoimmune myopathies are a heterogeneous group of diseases that affect skeletal muscle as well as other organ systems.[1] Dermatomyositis (DM), the antisynthetase syndrome (AS), and immune-mediated necrotizing myopathy (IMNM) are 3 of the most common and well-defined subtypes of autoimmune myopathy. In addition, myositis frequently overlaps with other connective tissue diseases.[2] Specifically, systemic sclerosis (SSc) is the most common syndrome overlapping with myositis, accounting for approximately 40% of all cases of myositis overlap.[2–4]

Many patients with myositis and myositis overlap syndromes have autoantibodies that are associated with distinctive clinical features.[5–9] Among the autoantibodies found in those with both myositis and SSc, those directed against the 75-kDa and/or 100-kDa subunits of the human exosome complex (i.e., the PM/Scl complex) are especially common.[10,11] Previous studies described the association of anti-PM/Scl antibodies with a constellation of clinical manifestations including myositis, interstitial lung disease (ILD), arthritis, Raynaud syndrome, dysphagia, and mechanic's hands.[10,12–16] However, no prior study has described the presenting clinical features of anti-PM/Scl-positive patients or their emergence during the course of disease. Moreover, it remains unknown whether patients with autoantibodies against only the 75-kDa (anti-PM/Scl-75) or 100-kDa (anti-PM/Scl-100) subunits of PM/Scl have distinct clinical features.

In the present study, we performed a longitudinal cohort study of anti-PM/Scl-positive patients and analyzed their demographic, clinical, and laboratory features in comparison to patients with DM, AS, and IMNM. Furthermore, we investigated phenotypic differences between patients positive only for either anti-PM/Scl-75 or anti-PM/Scl-100 autoantibodies.

## Methods

### Study population and autoantibody testing

All patients enrolled in the Johns Hopkins Myositis Center Longitudinal Cohort between 2002 and 2016 were included in the study.

Serum samples were tested for anti-PM/Scl autoantibodies by line blot (EUROLine Myositis Profile 4; EUROIMMUN, Luebeck, Germany) as well as by either immunoprecipitation at the Oklahoma Medical Research Foundation and/or by a Quest Diagnostics Myositis Panel. Patients positive for other myositis-specific autoantibodies by 2 different validated techniques[17,18] were used as comparator groups; patients were classified as having AS if they had autoantibodies against Jo-1, PL-7, or PL-12, were included in the DM group if they had autoantibodies recognizing Mi2, NXP2, TIF1g, or MDA5, and were considered to have IMNM if they tested positive for anti-SRP or anti-HMGCR autoantibodies. Other factors, including the degree or pattern of muscle weakness, muscle biopsy findings, or extramuscular features (i.e., DM rash or AS-associated manifestations), were not used for categorization of the controls into AS, DM, or IMNM groups.

Strength was evaluated by the examining physician using the Medical Research Council scale. This scale was transformed to the Kendall 0–10 scale for analysis purposes as previously described.[19] Serial strength measurements for each patient were made by the same physician. For the purposes of analyses, right- and left-side measurements for arm abduction and hip flexion strength were combined and the average was used for calculations (possible range 0–10). Skin manifestations specific for DM (i.e., heliotrope rash or Gottron sign) and sclerodactyly (with or without skin thickening proximal to fingers with no other scleroderma-like disorder explaining the findings), symptoms of esophageal involvement, and AS-associated clinical features (e.g., mechanic's hands, Raynaud phenomenon, arthritis, fever) were documented both retrospectively at the onset of the disease and prospectively at each visit. ILD was defined through a multidisciplinary approach as recommended by the American Thoracic Society.[20] Pulmonary function testing included spirometry, lung volumes measured by helium dilution, and diffusing capacity by single-breath carbon monoxide based on American Thoracic Society criteria.[21] Pulmonary hypertension was defined as definite if the patient had a mean pulmonary arterial pressure of ≥25 mm Hg at rest by right heart catheterization or as probable if an echocardiogram showed a right systolic ventricular pressure >40 mm Hg.[22]

Muscle enzyme levels and pulmonary function tests were included for analysis if obtained within a period of 6 weeks before or after strength testing (except for peak, minimum, and mean values, of which all available data were included).

All available muscle biopsies from anti-PM/Scl-positive patients were evaluated for the presence of perivascular inflammation, perifascicular atrophy, primary inflammation (focal invasion of nonnecrotic muscle fibers by inflammatory cells), and necrotizing features (muscle fiber necrosis without primary inflammation or perifascicular atrophy).

Thigh MRI was performed as explained elsewhere.[23] In short, we evaluated 15 muscles bilaterally in each patient, recording the presence of muscle edema, fascial edema, atrophy, or fatty replacement. The percentage of patients showing each one of the features in one or more muscles was used to compare anti-PM/Scl-positive patients to the remainder of the groups.

### Standard protocol approvals and patient consents

This study was approved by the Johns Hopkins institutional review board. Written informed consent was obtained from each participant.

### Statistical analysis

Dichotomous variables were expressed as percentages and absolute frequencies, and continuous features were reported as means and SDs. Pairwise comparisons for categorical variables between groups were made using $\chi^2$ test or Fisher exact test, as appropriate. Student *t* test was used to compare continuous variables among groups, and paired *t* test was used to compare the level of weakness of different muscle groups. Creatine kinase (CK), a highly positively skewed variable, was expressed as median, first, and third quartile for descriptive purposes and was transformed through a base-10 logarithm for regression analysis.

To account for differing numbers of visits per patient, the evolution of the pulmonary function tests, CK levels, and muscle strength were studied using multilevel linear regression models with random slopes and random intercepts. The mean of hip flexor and arm abductor strength (range 0–10) was used as the strength outcome for regression analysis.

Locally weighted regression was applied to graphically analyze the evolution of the strength, CK levels, and pulmonary function tests. Kaplan-Meier curves were used to study the evolution of each of the clinical features over time.

The influence of nonmodifiable risk factors (sex, race, duration of disease, and age at onset of the first symptom), the corticosteroid dose, and the administration of IV immunoglobulins, rituximab, methotrexate, azathioprine, and mycophenolate were used as adjusting covariates. Other treatments administered to less than 10% of the cohort were not included in the analysis.

As previously described, indirect standardization was used to compare the mortality and cancer risk that we observed in our sample with the number of cases that one would expect in the general population with the same age and sex distribution.[18]

All statistical analyses were performed using Stata/MP 14.1. A 2-sided $p$ value ≤0.05 was considered statistically significant with no adjustment for multiple comparisons.

### Data availability

No unpublished data related to this study are publicly available.

## Results

### Patients

Of the 2,175 patients enrolled in the Myositis Center Longitudinal Cohort Study, which includes patients with both immune and nonimmune disorders, 949 patients had known or suspected myositis and were tested for myositis autoantibodies. Among these, 41 (4%) were positive for anti-PM/Scl autoantibodies, 26 (63%) were positive for both anti-PM/Scl-75 and anti-PM/Scl-100, 8 (20%) were positive only for anti-PM/Scl-100, and 7 (17%) were positive only for anti-PM/Scl-75. The control groups, which were defined based on the presence of myositis-specific autoantibodies, were also identified from among Myositis Center patients with known or suspected myositis and included 178 patients with DM, 132 with AS, and 135 with IMNM. The general features of anti-PM/Scl and the control groups are detailed in table 1. Among the anti-PM/Scl-positive group, 30% met the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc.[24]

No anti-PM/Scl-positive patient was also positive for another myositis-specific autoantibody. Among anti-PM/Scl-positive patients, the myositis-associated autoantibodies anti-Ro52 and anti-NT5C1a were found in 32% and 5%, respectively. No anti-PM/Scl patient died during the period of this study or developed cancer within 3 years of the onset of the autoimmune disease. Thus, compared with the normal population of the same age and sex, there was no increase in mortality rate (95% confidence interval 0–2.95) or cancer rate (95% confidence interval 0–3.4).

### Muscle involvement

#### Patients with anti-PM/Scl have deltoid weakness greater than hip flexor weakness and muscle biopsies revealing intense perivascular inflammation

At disease onset, weakness was present in a minority (37%) of anti-PM/Scl-positive patients but in a majority of patients with AS (55%, $p < 0.05$) and IMNM (81%, $p < 0.001$) (tables e-1 and e-2, links.lww.com/WNL/A506). However, during the follow-up period, most anti-PM/Scl, DM, AS, and IMNM patients developed weakness (93%, 85%, 90%, and 96%, respectively) with no differences between groups (table 2). Similar to patients with DM and AS, patients with anti-PM/Scl had modest proximal muscle weakness with mean hip flexor and mean arm abduction strength of 9.2 and 8.6 strength units, respectively. Patients in the anti-PM/Scl group had substantially stronger hip flexors than those in the IMNM group (6.7, $p < 0.001$). However, the mean arm abduction strength of the anti-PM/Scl patients was remarkably similar to those with IMNM (8.6 vs 8.5).

Of note, in patients with anti-PM/Scl, arm abductor strength was decreased compared to hip flexors (8.6 vs 9.2, $p = 0.03$). The opposite pattern of arm abduction vs hip flexor strength was observed in patients with AS (9.3 vs 9.0, $p < 0.001$), DM (9.1 vs 8.8, $p = 0.001$), and IMNM (8.5 vs 6.7, $p < 0.001$)

**Table 1** General features of patients positive for anti-PM/Scl autoantibodies and patients in control groups

| | Anti-PM/Scl (n = 41) | DM (n = 178) | AS (n = 132) | IMNM (n = 135) |
|---|---|---|---|---|
| **Sex, female, % (n)** | 73 (30) | 75 (134) | 73 (97) | 63 (85) |
| **Race, % (n)** | | | | |
| **White** | 88 (36) | 77 (137) | 61 (81)[b] | 67 (91)[a] |
| **Black** | 7 (3) | 12 (22) | 30 (39)[b] | 24 (32)[a] |
| **Other races** | 5 (2) | 11 (19) | 9 (12) | 9 (12) |
| **Age of onset, y, mean (SD)** | 42.2 (15.0) | 47.1 (15.6) | 45.0 (13.3) | 51.5 (14.9)[c] |
| **Time of follow-up, y, mean (SD)** | 6.5 (4.7) | 4.3 (3.5)[c] | 4.7 (3.9)[a] | 4.0 (3.9)[c] |
| **No. of visits per participant, mean (SD)** | 12.2 (8.3) | 9.9 (7.4) | 9.6 (7.2) | 9.1 (9.2) |
| **Cancer associated myositis, % (n)** | 0 (0) | 8 (15) | 3 (4) | 5 (7) |
| **Death during follow-up, % (n)** | 0 (0) | 4 (7) | 10 (13)[a] | 4 (5) |
| **Nucleolar ANA pattern, % (n)** | 94 (30) | 5 (5)[c] | 11 (6)[c] | 15 (6)[c] |
| **Anti-Ro52, % (n)** | 32 (13) | 22 (39) | 80 (106)[c] | 8 (11)[c] |
| **Treatments, % (n)** | | | | |
| **Corticosteroids** | 88 (36) | 83 (147) | 96 (127) | 75 (101) |
| **Azathioprine** | 41 (17) | 26 (47) | 58 (76) | 27 (36) |
| **Methotrexate** | 37 (15) | 51 (90) | 47 (62) | 50 (67) |
| **Mycophenolate** | 56 (23) | 35 (63)[a] | 38 (50)[a] | 20 (27)[c] |
| **IV immunoglobulin** | 27 (11) | 48 (86)[a] | 37 (49) | 37 (50) |
| **Rituximab** | 7 (3) | 16 (28) | 20 (27) | 24 (32)[a] |

Abbreviations: ANA = antinuclear antibody; AS = antisynthetase syndrome; DM = dermatomyositis; IMNM = immune-mediated necrotizing myopathy. Dichotomous variables are expressed as % (count) and continuous variables as mean (SD). Bivariate comparisons of continuous variables were made using Student *t* test, while bivariate comparisons of dichotomous variables were made using either $\chi^2$ test or Fisher exact test, as appropriate. Each one of the clinical groups was compared to the sample of anti-PM/Scl patients.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.

(table 3). In anti-PM/Scl-positive patients, the degree of arm abductor weakness was associated with age at onset; specifically, younger patients had decreased strength in this muscle group compared with older participants ($p < 0.001$). Of note, 9 (23%) anti-PM/Scl-positive patients also had distal weakness. Among these, 7 (88%) did not have significant sclerodactyly or arthritis to suggest that the distal weakness was independent of the muscle disease.

Multilevel regression analysis confirmed that anti-PM/Scl patients were stronger than patients with IMNM (1.4 strength points difference, $p < 0.001$) but were not weaker than patients with AS and DM, independent of the time from onset, age, sex, race, or treatments at any given time during follow-up. Anti-PM/Scl patients who were positive for anti-Ro52 showed more severe muscle involvement in the univariate analysis (mean hip flexor strength 8.3 vs 9.6, $p = 0.01$; mean arm abductor strength 7.5 vs 9.1, $p = 0.03$), but this result was not confirmed in the multilevel study.

Patients with significant weakness at the first visit tended to regain full strength within the first year of treatment (figure e-1, links.lww.com/WNL/A505) using a combination therapy of corticosteroids plus mycophenolate, methotrexate, or azathioprine. Significant flares of weakness (defined either as increasing CK levels or worsening weakness) after treatment introduction were exceptional in our cohort.

Perivascular inflammation, found in 17 of 21 (81%) available muscle biopsies, was the most common histopathologic feature in patients with anti-PM/Scl antibodies; these perivascular collections were often quite extensive (figure 1). Perifascicular atrophy was noted in just 24% of anti-PM/Scl biopsies; this was decreased compared to biopsies from DM (56%, $p = 0.02$) and AS (52%, $p = 0.05$). Predominant perifascicular necrosis was not observed. Necrosis without primary inflammation (i.e., lymphocytic invasion of healthy myofibers) or perifascicular atrophy was less common in the anti-PM/Scl group than in IMNM

**Table 2** Cumulative clinical features of patients positive for anti-PM/Scl autoantibodies and patients in control groups

| | Anti-PM/Scl (n = 41) | DM (n = 178) | AS (n = 132) | IMNM (n = 135) |
|---|---|---|---|---|
| **Muscle involvement** | | | | |
| **Muscle weakness** | 93 (38) | 85 (152) | 90 (119) | 96 (130) |
| **Myalgia** | 68 (28) | 56 (100) | 65 (86) | 52 (70) |
| **Skin involvement** | | | | |
| **DM-specific skin involvement** | 85 (35) | 96 (170)[a] | 62 (82)[b] | 4 (6)[c] |
| **SSc-specific skin involvement** | 66 (27) | 2 (3)[c] | 13 (17)[c] | 0 (0)[c] |
| **Raynaud syndrome** | 78 (32) | 22 (40)[c] | 39 (52)[c] | 15 (20)[c] |
| **Telangectasias** | 66 (27) | 21 (37)[c] | 20 (26)[c] | 8 (11)[c] |
| **Ulcers** | 5 (2) | 14 (25) | 7 (9) | 0 (0) |
| **Carpal tunnel** | 15 (6) | 8 (15) | 20 (27) | 10 (13) |
| **Livedo reticularis** | 12 (5) | 12 (22) | 10 (13) | 4 (5) |
| **Mechanic's hands** | 80 (33) | 28 (49)[c] | 58 (77)[a] | 5 (7)[c] |
| **Calcinosis** | 39 (16) | 21 (38)[a] | 9 (12)[c] | 1 (1)[c] |
| **Subcutaneous edema** | 46 (19) | 18 (32)[c] | 27 (35)[a] | 4 (6)[c] |
| **Puffy hands** | 39 (16) | 8 (15)[c] | 10 (13)[c] | 0 (0)[c] |
| **Lung involvement** | | | | |
| **Interstitial lung disease** | 61 (25) | 13 (24)[c] | 80 (106)[a] | 6 (8)[c] |
| **Pulmonary hypertension** | 12 (5) | 3 (5)[a] | 20 (27) | 1 (2)[b] |
| **Esophageal involvement** | | | | |
| **Gastroesophageal reflux disease** | 61 (25) | 29 (52)[c] | 29 (38)[c] | 25 (34)[c] |
| **Dysphagia** | 56 (23) | 53 (95) | 18 (24)[c] | 39 (53) |
| **Joint involvement** | | | | |
| **Arthritis** | 46 (19) | 18 (32)[c] | 55 (72) | 6 (8)[c] |
| **Arthralgia** | 78 (32) | 51 (90)[b] | 62 (82) | 36 (49)[c] |
| **Systemic involvement** | | | | |
| **Fever** | 7 (3) | 18 (32) | 24 (32)[a] | 7 (10) |
| **Sicca syndrome** | 59 (24) | 31 (55)[c] | 48 (63) | 19 (26)[c] |
| **Pericarditis** | 0 (0) | 0 (0) | 1 (1) | 0 (0) |
| **Glomerulonephritis** | 0 (0) | 0 (0) | 1 (1) | 0 (0) |

Abbreviations: AS = antisynthetase syndrome; DM = dermatomyositis; IMNM = immune-mediated necrotizing myopathy; SSc = systemic sclerosis.
Data represent % (n). Chi-square or Fisher exact tests were used to compare each one of the clinical groups with the anti-PM/Scl patients.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.

(24% vs 80%, $p < 0.001$) but had a similar frequency in DM (13%) and AS (22%). Primary inflammation was more common in anti-PM/Scl (33%) patients than in DM (9%, $p = 0.03$) but occurred at a similar frequency in IMNM (16%) and AS (30%).

Immunostaining for MHC-I was performed in 5 anti-PM/Scl-positive cases; 3 cases had diffuse MHC-I upregulation and a fourth case had predominant perifascicular MHC-I staining. Only 3 cases were stained for membrane attack complex and this was negative in each case. Five cases were stained for

**Table 3** Muscle strength, muscle enzyme levels, and ancillary testing in patients with anti-PM/Scl autoantibodies and in control groups

| | Anti-PM/Scl (n = 41) | DM (n = 178) | AS (n = 132) | IMNM (n = 135) |
|---|---|---|---|---|
| **Mean hip flexor strength** | 9.2 (1.5) | 8.8 (1.8) | 9.0 (1.5) | 6.7 (2.7)[c] |
| **Hip flexors strength at last visit** | 9.1 (1.8) | 9.1 (1.9) | 9.1 (1.6) | 6.9 (3.5)[c] |
| **Mean arm abductor strength** | 8.6 (2.3) | 9.1 (1.6) | 9.4 (1.1)[b] | 8.5 (1.9) |
| **Arm abductors strength at last visit** | 8.7 (2.4) | 9.3 (1.9) | 9.4 (1.3)[a] | 8.8 (2.3) |
| **Muscle MRI, % (n)** | | | | |
| **Muscle edema** | 39 (7) | 71 (60)[b] | 76 (45)[b] | 90 (74)[c] |
| **Atrophy** | 22 (4) | 23 (19) | 29 (17) | 66 (54)[c] |
| **Fatty replacement** | 50 (9) | 49 (41) | 59 (35) | 88 (72)[c] |
| **Fascial edema** | 56 (10) | 51 (43) | 69 (41) | 35 (29) |
| **Irritable EMG, % (n)** | 40 (14) | 45 (73) | 39 (46) | 77 (98)[c] |
| **Median CK** | 138 (80–472) | 117 (68–290) | 282 (114–963)[a] | 1401 (502–2,969)[c] |
| **Maximum CK** | 1,200 (247–3,000) | 719 (139–3,508) | 1,352 (396–5,850) | 4,706 (2,000–8,990)[c] |
| **Mean aldolase** | 13.9 (12.7) | 9.4 (7.5)[b] | 24.4 (43.8) | 29.3 (29.7)[b] |
| **Maximum aldolase** | 24.1 (23.6) | 13.4 (16.3)[b] | 54.4 (184.0) | 49.9 (60.3)[a] |
| **Mean FVC** | 85.0 (22.7) | 89.2 (21.0) | 72.5 (19.5)[b] | 87.8 (20.0) |
| **Minimum %FVC** | 77.0 (22.5) | 86.2 (23.3)[a] | 65.4 (22.6)[b] | 86.6 (20.6) |

Abbreviations: AS = antisynthetase syndrome; CK = creatine kinase; DM = dermatomyositis; FVC = forced vital capacity; IMNM = immune-mediated necrotizing myopathy.
Strength and FVC values are expressed as means (SD) and CK as medians (quartile 1–quartile 3). Bivariate comparisons were made using Student *t* test for the strength and Wilcoxon rank sum test for CK. Mean strength was defined as the mean strength of all the visits, excluding the first one. Each one of the clinical groups was compared to the sample of anti-PM/Scl patients.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.

alkaline phosphatase and none of these had increased staining of the perimysium as reported in some types of myositis (e.g., AS).

Of note, thigh MRI revealed muscle edema less frequently in anti-PM/Scl-positive patients (39%) compared to all the other myositis control groups (71% in DM, 76% in AS, and 90% in IMNM, all $p < 0.008$). In anti-PM/Scl-positive patients, the prevalence of atrophy (22%) and fatty replacement (50%) was lower than in IMNM (each $p < 0.001$) (table 3).

EMG revealed an irritable myopathy in 40% of anti-PM/Scl patients, which was observed in a similar proportion of patients with DM (45%) and AS (39%) and in a higher proportion of patients with IMNM (77%, $p < 0.001$) (table 3).

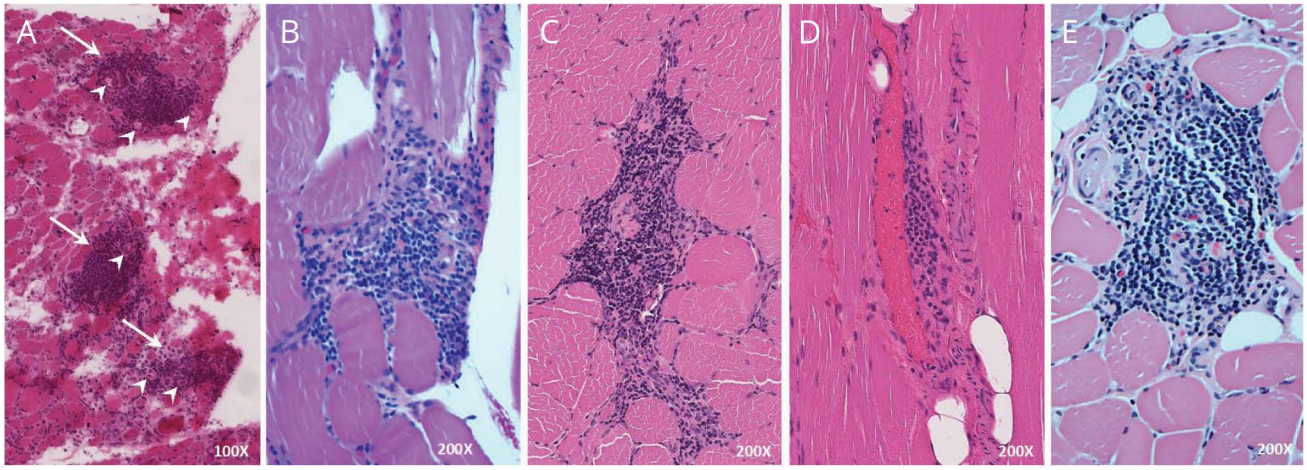
## Interstitial lung disease

### Anti-PM/Scl patients have mild ILD

At disease onset, ILD was present in just 10% of anti-PM/Scl patients, which was similar to the prevalence of ILD in those with DM (6%) and increased compared to those with IMNM (1%, $p < 0.05$). Compared to those with anti-PM/Scl, early ILD was more common in those with AS (52%, $p < 0.001$). Despite the infrequency of ILD at onset, during the course of disease, 61% of anti-PM/Scl patients eventually developed this lung manifestation. Although patients with AS were even more likely to develop ILD over time (80%, $p < 0.05$), patients with DM were less likely to develop ILD (13%, $p < 0.001$) than those with anti-PM/Scl autoantibodies (table 2).

When present, lung involvement in anti-PM/Scl patients appeared to be milder than in patients with AS (table 3). Overall, percentage-predicted forced vital capacity (%FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO) in the anti-PM/Scl patients tended to be stable over time (data not shown). Nevertheless, during the first 6 months after the first visit, percentage-predicted FVC tended to increase with no change in the DLCO, suggesting that the cause of functional lung improvement during this period was due to recovery of muscle function (data not shown). Multilevel regression analysis confirmed that, at any given point

**Figure 1** Muscle biopsies from patients positive for anti-PM/Scl autoantibodies show intense perivascular inflammation




(A) The arrows indicate perivascular collections of inflammatory cells, and vessels are marked by the arrowheads. (A–E) Each panel shows an example of perivascular inflammation from a different patient. Hematoxylin & eosin staining.

during follow-up and independently of the age at onset, race, sex, or treatment regimen, anti-PM/Scl patients had higher % FVC than patients with AS (13% difference, $p = 0.003$) and were not different compared to patients with DM or IMNM (both $p > 0.05$).

Pulmonary hypertension was virtually unheard of in patients with anti-PM/Scl (0%), DM (0%), AS (1%), or IMNM (0%) at disease onset (table 2). However, over time, 12% of anti-PM/Scl patients developed definite or probable pulmonary hypertension. In contrast, only 3% ($p < 0.05$) of patients with DM and 1% ($p < 0.05$) of patients with IMNM were ever diagnosed with pulmonary hypertension. When present, pulmonary hypertension in anti-PM/Scl patients was mild, usually secondary to ILD, and did not require any specific management.

## Extramuscular clinical features

### Anti-PM/Scl patients have highly prevalent extramuscular clinical features

Compared to the other groups, the onset of disease in anti-PM/Scl patients was more frequently associated with sclerodactyly (table e-1, links.lww.com/WNL/A506). Similar to patients with early AS, patients with early anti-PM/Scl were more likely to have Raynaud syndrome and mechanic's hands than those with DM or IMNM (all $p < 0.001$). During the course of the disease, many skin features were more prevalent in anti-PM/Scl patients compared to the other groups (table 2). Most developed heliotrope or Gottron rashes (85%), mechanic's hands (80%), sclerodactyly (66%), Raynaud phenomenon (78%), and/or telangiectasias (66%). Other cutaneous findings such as calcinosis (39%), subcutaneous edema (46%), and/or puffy hands (39%) were more common and appeared at a faster rate in anti-PM/Scl-positive patients than in patients from the other groups (table 2; figure e-2, links.lww.com/WNL/A505). Gastroesophageal reflux eventually occurred in 61% of anti-PM-Scl patients, which was increased compared to the other groups. Arthritis documented on clinic examination (46%) and sicca syndrome (59%) were more common in anti-PM/Scl patients than in patients with DM or IMNM (table 2, figure e-2). It is of interest that mechanic's hands were present in even more anti-PM/Scl-positive patients than in patients with AS (80% vs 58%, $p < 0.05$). Of note, clinical features associated with severe SSc, such as the presence of renal crisis (3%) or hand ulceration (5%), were uncommon in anti-PM/Scl patients. We did not find other differences in clinical features or disease activity between anti-PM/Scl patients with heliotrope rash, Gottron sign, or perifascicular atrophy and those without these characteristics.

Both at onset and during the course of the disease, patients positive for both anti-PM/Scl-75 and anti-PM/Scl-100 showed very similar phenotypes and severity of disease compared to those positive for just one of these autoantibodies (tables e-3 to e-5).

# Discussion

In this study, we have defined the unique clinical phenotype of patients with anti-PM/Scl autoantibodies. First, patients with anti-PM/Scl autoantibodies have a distinctive pattern of muscle weakness in which arm abductors are weaker than hip flexors. In contrast, hip flexors are weaker than arm abductors in those with DM, AS, or IMNM. Of note, clinicians at the Johns Hopkins Myositis Center have anecdotally noted marked deltoid atrophy (in the absence of diffuse scleroderma causing skin tightening) in several anti-PM/Scl patients. Although data regarding this clinical feature were not systematically collected in all patients, we suspect deltoid atrophy

may be a distinguishing feature of patients with anti-PM/Scl myositis and that this explains the unique pattern of weakness in these patients. Future prospective studies using ultrasound or imaging to quantify deltoid atrophy will be important to confirm this observation.

Second, compared to the other groups, anti-PM/Scl-positive patients are more likely to have extramuscular manifestations including mechanic's hands, Raynaud syndrome, sclerodactyly, telangiectasias, esophageal reflux disease, subcutaneous edema, puffy hands, and calcinosis. Of note, anti-PM/Scl-positive patients were even more likely than patients with AS to have 2 of the classic features of AS: mechanic's hands and Raynaud syndrome. Similarly, although calcinosis is known to be a concern in patients with DM, this feature occurred even more frequently in those with anti-PM/Scl autoantibodies. These observations highlight the utility of testing for myositis autoantibodies, which correlate with unique clinical phenotypes.

Additional insight into the anti-PM/Scl phenotype can be gleaned by comparing this group to each of the other groups individually. Compared to the DM group, anti-PM/Scl-positive patients were just as likely to initially present with muscle, lung, and joint involvement but less likely to have Gottron sign or a heliotrope rash. However, during the course of disease, anti-PM/Scl-positive patients were more likely to develop lung and joint involvement than patients with DM. It is of interest that while 85% to 96% of both anti-PM/Scl-positive and DM patients eventually developed muscle weakness and the classic skin manifestations of DM, muscle biopsies from only one-quarter of the former patients had perifascicular atrophy (the pathognomonic muscle biopsy feature of DM) compared with more than half of the latter. Anti-PM/Scl patients were also more likely to have primary inflammation than patients with DM. These histopathologic findings suggest that the mechanisms underlying myositis in anti-PM/Scl patients may be different than those in patients with DM.

Anti-PM/Scl-positive and AS patients also presented differently. For example, patients with AS were more likely to have muscle weakness, ILD, and joint involvement and less likely to have Gottron sign or heliotrope rash. However, as the disease progressed, anti-PM/Scl-positive and AS patients experienced similar rates of muscle weakness and joint involvement. During disease evolution, patients with AS continued to have higher rates of ILD and more severe ILD. The observation that patients with AS had lower FVCs despite a tendency to be stronger than anti-PM/Scl patients suggests that the difference in FVC was not attributable to a difference in diaphragmatic strength. Muscle biopsies were similar when comparing anti-PM/Scl to AS patients.

Patients with IMNM were phenotypically most distinct from those with anti-PM/Scl autoantibodies. Patients with IMNM were more likely to have weakness at disease onset and during the course of follow-up. Patients with IMNM also had higher peak CK levels and more severe weakness of the hip flexors, knee flexors, and knee extensors than anti-PM/Scl patients. Of note, patients with IMNM were not weaker than anti-PM/Scl patients in the upper extremities; this reflects the distinct pattern of muscle weakness already described in the latter group. Finally, muscle biopsies from anti-PM/Scl-positive patients were more likely to have primary inflammation and less likely to have a necrotizing muscle biopsy compared to patients with IMNM.

It has been reported[25] that antibodies against PM/Scl-75 and PM/Scl-100 identify different subsets of patients with SSc. However, in the current study, we detected no clinical differences between patients with only anti-PM/Scl-75 or only anti-PM/Scl-100 autoantibodies.

In accordance with other studies describing muscle biopsies from patients with anti-PM/Scl autoantibodies,[12,26] we found that the muscle biopsy features in these patients included a predominance of perivascular inflammation but scarce perifascicular atrophy compared to patients with DM or AS.

In this longitudinal cohort study, we show that in patients positive for anti-PM/Scl autoantibodies, muscle involvement is responsive to immunosuppressant treatment and patients tend to recover well during the first year of treatment. In addition, ILD seems to be stable over time in these patients, and recovery during the first months of follow-up appears to be associated with an increase in the strength of respiratory muscles. The fact that lung functional impairment is stable during follow-up suggests that the inflammatory phase of the ILD occurs soon after the onset of the syndrome, with subsequent residual irreversible damage.

In this study, we have shown that patients with anti-PM/Scl autoantibodies have a distinct clinical phenotype characterized by extensive extramuscular manifestations and a unique pattern of weakness in which arm abductors are weaker than hip flexors. We also found that anti-PM/Scl-positive patients have little in common with IMNM patients but do share certain features with AS patients (e.g., frequent ILD, arthritis, and mechanic's hands) and DM patients (frequent heliotrope rash and Gottron papules). Since patients with anti-PM/Scl autoantibodies have a unique phenotype, we propose that future classification schemes should recognize "the anti-PM/Scl syndrome" as a distinct subtype of myositis. Future studies will be required to determine whether anti-PM/Scl autoantibodies are pathogenic or epiphenomena of some other process.

## Author contributions

Rebecca De Lorenzo: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, statistical analysis. Iago Pinal-Fernandez: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, statistical analysis, study supervision. Wilson Huang: drafting/revising the

manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Jemima Albayda: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. Eleni Tiniakou: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, contribution of vital reagents/tools/patients. Cheilonda Johnson: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. Jose C. Milisenda: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval. Maria Casal-Dominguez: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Andrea M. Corse: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Sonye K. Danoff: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval. Lisa Christopher-Stine: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and will give final approval, contribution of vital reagents/tools/patients, acquisition of data, obtaining funding. Julie J. Paik: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, statistical analysis, study supervision. Andrew L. Mammen: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision, obtaining funding.

## Study funding

This research was supported in part by the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the NIH. S.K.D., L.C.-S., and the Myositis Research Database are supported by the Huayi and Siuling Zhang Discovery Fund. I.P.-F.'s research is supported by a Fellowship from the Myositis Association. J.J. P. is supported by the Doris Duke Early Investigator Award. E. T. is supported by grants from the Rheumatology Research Foundation and the Jerome L. Greene Foundation.

## Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Received October 9, 2017. Accepted in final form March 21, 2018.

## References

1. Dalakas MC. Inflammatory muscle diseases. N Engl J Med 2015;373:393–394.
2. Troyanov Y, Targoff IN, Tremblay JL, Goulet JR, Raymond Y, Senecal JL. Novel classification of idiopathic inflammatory myopathies based on overlap syndrome features and autoantibodies: analysis of 100 French Canadian patients. Medicine 2005;84:231–249.
3. Pakozdi A, Nihtyanova S, Moinzadeh P, Ong VH, Black CM, Denton CP. Clinical and serological hallmarks of systemic sclerosis overlap syndromes. J Rheumatol 2011;38: 2406–2409.
4. Aguila LA, Lopes MR, Pretti FZ, et al. Clinical and laboratory features of overlap syndromes of idiopathic inflammatory myopathies associated with systemic lupus erythematosus, systemic sclerosis, or rheumatoid arthritis. Clin Rheumatol 2014;33: 1093–1098.
5. Mammen AL. Autoimmune myopathies: autoantibodies, phenotypes and pathogenesis. Nat Rev Neurol 2011;7:343–354.
6. Vincze M, Molnar PA, Tumpek J, et al. An unusual association: anti-Jo1 and anti-SRP antibodies in the serum of a patient with polymyositis. Clin Rheumatol 2010;29: 811–814.
7. Sugie K, Tonomura Y, Ueno S. Characterization of dermatomyositis with coexistence of anti-Jo-1 and anti-SRP antibodies. Intern Med 2012;51:799–802.
8. Nakajima A, Yoshino K, Soejima M, et al. High frequencies and co-existing of myositis-specific autoantibodies in patients with idiopathic inflammatory myopathies overlapped to rheumatoid arthritis. Rheumatol Int 2012;32:2057–2061.
9. Love LA, Leff RL, Fraser DD, et al. A new approach to the classification of idiopathic inflammatory myopathy: myositis-specific autoantibodies define useful homogeneous patient groups. Medicine 1991;70:360–374.
10. Oddis CV, Okano Y, Rudert WA, Trucco M, Duquesnoy RJ, Medsger TA Jr. Serum autoantibody to the nucleolar antigen PM-Scl: clinical and immunogenetic associations. Arthritis Rheum 1992;35:1211–1217.
11. Brouwer R, Pruijn GJ, van Venrooij WJ. The human exosome: an autoantigenic complex of exoribonucleases in myositis and scleroderma. Arthritis Res 2001;3:102–106.
12. Marguerie C, Bunn CC, Copier J, et al. The clinical and immunogenetic features of patients with autoantibodies to the nucleolar antigen PM-Scl. Medicine 1992;71: 327–336.
13. Vandergheynst F, Ocmant A, Sordet C, et al. Anti-PM/Scl antibodies in connective tissue disease: clinical and biological assessment of 14 patients. Clin Exp Rheumatol 2006;24:129–133.
14. D'Aoust J, Hudson M, Tatibouet S, et al. Clinical and serologic correlates of anti-PM/Scl antibodies in systemic sclerosis: a multicenter study of 763 patients. Arthritis Rheumatol 2014;66:1608–1615.
15. Hausmanowa-Petrusewicz I, Kowalska-Oledzka E, Miller FW, et al. Clinical, serologic, and immunogenetic features in Polish patients with idiopathic inflammatory myopathies. Arthritis Rheum 1997;40:1257–1266.
16. Selva-O'Callaghan A, Labrador-Horrillo M, Solans-Laque R, Simeon-Aznar CP, Martinez-Gomez X, Vilardell-Tarres M. Myositis-specific and myositis-associated antibodies in a series of eighty-eight Mediterranean patients with idiopathic inflammatory myopathy. Arthritis Rheum 2006;55:791–798.
17. Mammen AL, Chung T, Christopher-Stine L, et al. Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. Arthritis Rheum 2011;63:713–721.
18. Pinal-Fernandez I, Casal-Dominguez M, Huapaya JA, et al. A longitudinal cohort study of the anti-synthetase syndrome: increased severity of interstitial lung disease in black patients and patients with anti-PL7 and anti-PL12 autoantibodies. Rheumatology 2017;56:999–1007.
19. Rider LG, Werth VP, Huber AM, et al. Measures of adult and juvenile dermatomyositis, polymyositis, and inclusion body myositis: Physician and Patient/Parent Global Activity, Manual Muscle Testing (MMT), Health Assessment Questionnaire (HAQ)/Childhood Health Assessment Questionnaire (C-HAQ), Childhood Myositis Assessment Scale (CMAS), Myositis Disease Activity Assessment Tool (MDAAT), Disease Activity Score (DAS), Short Form 36 (SF-36), Child Health Questionnaire (CHQ), Physician Global Damage, Myositis Damage Index (MDI), Quantitative Muscle Testing (QMT), Myositis Functional Index-2 (FI-2), Myositis Activities Profile (MAP), Inclusion Body Myositis Functional Rating Scale (IBMFRS), Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), Cutaneous Assessment Tool (CAT), Dermatomyositis Skin Severity Index (DSSI), Skindex, and Dermatology Life Quality Index (DLQI). Arthritis Care Res 2011;63 (suppl 11):S118–S157.
20. Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2013;188:733–748.
21. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005;26:720–735.
22. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67–119.
23. Pinal-Fernandez I, Casal-Dominguez M, Carrino JA, et al. Thigh muscle MRI in immune-mediated necrotising myopathy: extensive oedema, early muscle damage and role of anti-SRP autoantibodies as a marker of severity. Ann Rheum Dis 2017;76:681–687.
24. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737–2747.
25. Hanke K, Bruckner CS, Dahnrich C, et al. Antibodies against PM/Scl-75 and PM/Scl-100 are independent markers for different subsets of systemic sclerosis patients. Arthritis Res Ther 2009;11:R22.
26. Pinal-Fernandez I, Casciola-Rosen LA, Christopher-Stine L, Corse AM, Mammen AL. The prevalence of individual histopathologic features varies according to autoantibody status in muscle biopsies from patients with dermatomyositis. J Rheumatol 2015;42:1448–1454.