Interstitial Lung Disease Associated with Anti-PM/Scl or Anti-Aminoacyl-tRNA Synthetase Autoantibodies: A Similar Condition?

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ABSTRACT. ***Objective.*** To compare anti-PM/Scl autoantibody-associated interstitial lung disease (ILD) with anti-aminoacyl-tRNA synthetases (anti-ARS) autoantibody-associated ILD.

Methods. We retrospectively studied 21 patients with ILD from a department of respiratory medicine, including 9 with anti-PM/Scl autoantibodies (6 women, median age 55 yrs, followup 5.5 yrs) and 12 with anti-ARS autoantibodies (6 women, median age 59 yrs, followup 2.3 yrs).

Results. Pulmonary manifestations in patients with anti-PM/Scl autoantibody-associated ILD usually followed the extrapulmonary manifestations of the connective tissue disease (CTD) (7/9 cases). The predominant imaging features on initial high resolution computed tomography were ground-glass attenuation and reticular opacities, and mainly suggested nonspecific interstitial pneumonia in both groups. CTD was classified as dermatomyositis (DM; 2), undifferentiated CTD (2), cutaneous limited systemic sclerosis (2), rheumatoid arthritis (RA; 1), and overlap syndrome (1) in the anti-PM/Scl group; and polymyositis (4), undifferentiated CTD (5), DM (1), amyopathic DM (1), and RA (1) in the anti-ARS group. Frequencies of arthralgia, Raynaud phenomenon, cutaneous rash, and mechanic's hands were comparable in both groups. Myalgia or muscle weakness was present in 0/9 PM/Scl and 5/12 ARS patients ($p < 0.05$). More than 1 autoantibody was present in 11 patients. ILD worsened despite treatment in 4 patients with anti-PM/Scl autoantibodies and 2 with anti-ARS autoantibodies, and included 1 death.

Conclusion. Anti-PM/Scl and anti-ARS antibodies are associated with similar clinical manifestations, with the exception only of more overt myositis in the latter, therefore challenging the clinical specificity of the antisynthetase syndrome. (First Release March 15 2010; J Rheumatol 2010; 37:1000–9; doi:10.3899/ jrheum.090652)

Key Indexing Terms:
INTERSTITIAL LUNG DISEASE MYOSITIS SYSTEMIC SCLERODERMA
ANTI-AMINOACYL-tRNA SYNTHETASE ANTIBODIES ANTI-PM/Scl ANTIBODIES

The anti-aminoacyl-tRNA synthetase antibodies (anti-ARS) include anti-Jo1, the most common, and anti-PL7, anti-PL12, anti-OJ, anti-EJ, anti-KS, anti-YRS, and anti-Zo antibodies. Several studies have shown an increased risk of interstitial lung disease (ILD) in patients with myositis and anti-ARS antibodies, an association often referred to as the so-called antisynthetase syndrome, encompassing arthritis, mechanic's hand, fever, and Raynaud phenomenon in addition to myositis and ILD[1-3].

Anti-PM/Scl antibodies have been described in a subgroup of patients diagnosed with myositis and/or systemic sclerosis (SSc)[4,5]. Interestingly, the clinical features associated with anti-PM/Scl antibodies overlap with those of the antisynthetase syndrome[1,6]. Further, anti-PM/Scl and anti-ARS antibodies are both associated with a conserved, Caucasian haplotype known as the HLA 8.1 ancestral haplotype, containing HLA-DRB1 *03/DQA1 *05/DQB1 *02 haplotypes[3,4,7-9]. Despite the high frequency of ILD in patients with anti-PM/Scl antibodies, little is known about its imaging pattern, chronology relative to extrapulmonary manifestations, and outcome. Anti-ARS-related ILD has been studied more extensively and has prognostic implications[10]. The aims of our study were to describe the clinical, imaging, and functional characteristics and outcome of

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patients with ILD associated with anti-PM/Scl antibodies, and to compare them to ILD associated with anti-ARS antibodies.

MATERIALS AND METHODS

Patient selection. We retrospectively selected patients evaluated between January 1995 and September 2008 in a department of respiratory medicine specialized in rare pulmonary disease, especially ILD, on the basis of the detection of anti-PM/Scl or anti-ARS autoantibodies, and the presence of ILD as defined by diffuse infiltrative opacities on high resolution computed tomography (HRCT) of the chest. Anti-PM/Scl and anti-ARS antibodies were systematically assessed in all patients routinely evaluated for ILD, and results were prospectively registered in a dedicated database in the department of immunology that performs autoimmunity analysis for the whole institution. One author (JCL) reviewed the medical records, pulmonary function tests, and laboratory tests of all patients at diagnosis, at 1-year followup, and at last followup.

Diagnostic criteria for CTD. Criteria for the diagnosis of possible, probable, or definite polymyositis (PM) and dermatomyositis (DM) were those described by Bohan and Peter[11]. Criteria for other CTD included the 1987 revised American College of Rheumatology criteria for rheumatoid arthritis (RA)[12], the preliminary criteria for SSc[13], the 1997 revised criteria for systemic lupus erythematosus[14], and the European/American consensus criteria for Sjögren's syndrome[15]. Amyopathic DM was diagnosed when a patient had heliotrope rash and/or Gottron sign, and no muscle weakness or abnormalities (normal muscle enzyme levels, electromyography, muscle biopsy, and muscle magnetic resonance imaging)[16]. Early SSc was diagnosed according to the 2001 criteria proposed by Leroy and collaborators[17]. Patients with CTD-associated antibodies and symptoms suggestive of a CTD but not fulfilling the above criteria were classified as having undifferentiated CTD (UCTD).

Laboratory test results. Biochemical assessment was performed as part of routine evaluation of the diagnosis of ILD and included C-reactive protein (CRP; normal < 5 mg × l^{-1}), creatine phosphokinase (normal < 175 U × l^{-1}), aldolase (normal < 8.5 U × l^{-1}), lactic dehydrogenase (LDH; normal < 248 U × l^{-1}), and gammaglobulins (normal < 12.5 g × l^{-1}). All patients with ILD underwent systematic immunologic investigation including antinuclear antibodies (ANA), anti-PM/Scl, anti-Mi2, autoantibodies against the major anti-extractable nuclear antigens [SSA/Ro, SSB/La, Sm, U1-ribonucleoprotein, topoisomerase-1 (Scl70), Jo1], anti-double stranded DNA (anti-dsDNA) antibodies, anti-cyclic citrullinated peptide antibodies, rheumatoid factor, and antineutrophil cytoplasmic antibodies (ANCA). Anti-ARS antibodies other than anti-Jo1 (anti-PL7, PL12, OJ, and EJ) were assessed in case of positive cytoplasmic staining of HEp-2 cells and/or suggestive clinical features. Anti-fibrillarin, anti-RNA polymerase-I, and anti-Th/To antibodies were assessed in case of a nucleolar pattern of ANA. Anti-RNA polymerase III antibodies were detected in case of granular or nucleolar pattern of ANA. Techniques of antibody detection are described in Table 1. All sera were stored at –80°C in a sera collection that was approved by the Institutional Review Board of the Hospices Civils de Lyon.

Characteristics of ILD. Lower limits of diffusing capacity of the lung for carbon monoxide (DLCO), vital capacity, and total lung capacity were defined as < 80% of the predicted values. Hypoxemia was defined by room-air arterial oxygen tension (PaO_2) < 10 kPa (75 mm Hg). Normal reference values for bronchoalveolar lavage (BAL) differential cell count were < 15% lymphocytes, < 5% neutrophils, and < 1% eosinophils[18]. Lung HRCT scans at diagnosis were read by 2 chest physicians expert in ILD (VC, JFC) without knowledge of serological or histopathological information. The categories assessed were ground-glass attenuation, consolidation, parenchymal micronodules, reticulation, honeycombing, and traction bronchiectasis. Imaging patterns were classified as usual interstitial pneumonia (UIP) pattern (combination of reticular opacities, traction bronchiectasis, and honeycombing with basal and subpleural predominance, and minimal ground-glass opacities); nonspecific interstitial pneumonia (NSIP) pattern (combination of ground-glass attenuation and reticulation, with little if any honeycombing); organizing pneumonia (OP) pattern (patchy consolidation); or unclassifiable pattern[19]. All lung biopsy specimens were evaluated by consensus by 3 of the authors experienced in ILD, and were classified using published guidelines[19]. All patients underwent routine echocardiographic assessment at the diagnosis of ILD and during followup. Right-side heart catheterization was performed in patients with elevated systolic right ventricular pressure (> 45 mm Hg) or right ventricular dysfunction. Pulmonary arterial hypertension was defined according to guidelines[20].

Treatment and outcome. ILD response to therapy was classified into 3 categories (improvement, stable, and failure) according to the American-European International Consensus Statement[19]. The response of myositis to therapy was evaluated according to the objective improvement of muscle strength and change in muscle enzyme levels.

Data analysis. Two-by-two tables were constructed based on dichotomous data, including clinical, radiological, and biological variables with thresholds provided by manufacturers. Statistical analysis of dichotomous variables was performed using 2-sided Fisher's exact test. Mann-Whitney test was used for continuous variables. Analyses were performed with SPSS 16.0 for Windows with significance established at $p < 0.05$.

RESULTS

Patients. Nine patients with anti-PM/Scl and 12 with anti-ARS antibodies and ILD were studied. Anti-ARS antibodies consisted of 7 anti-Jo1, 3 anti-PL7, 1 anti-EJ, and 1 double-positive for anti-EJ and anti-OJ antibodies. One patient diagnosed with undifferentiated CTD and both anti-PM/Scl and anti-Jo1 antibodies developed chronic respiratory failure despite immunosuppressive therapy; manifestations of the CTD were limited to mildly elevated serum muscle enzyme at diagnosis; lung transplant was performed, and the patient remained asymptomatic until last followup; this patient was excluded from the comparison between the anti-ARS and anti-PM/Scl groups. Paraneoplasic CTD was diagnosed in none of the patients. Silicosis and hypersensitivity pneumonitis were ruled out in all cases.

Respiratory involvement and manifestations. The general characteristics and respiratory manifestations of patients with anti-PM/Scl and anti-ARS antibodies were compared (Table 2, Table 3). The prevalence of dyspnea, cough, and crackles did not significantly differ between the 2 groups. Pulmonary function test results were available in all patients.

Eleven of 12 patients with anti-ARS antibodies and 7 of 9 patients with anti-PM/Scl antibodies had reduced vital capacity, total lung capacity, or DLCO (nonsignificant; NS). The mean vital capacity was 71.6% ± 16.2% and 71.5% ± 18.5%, mean total lung capacity 67.9% ± 14.9% and 65.7% ± 14.8%, and mean DLCO 62.6% ± 19.9% and 65.1% ± 16.1% in the anti-PM/Scl and anti-ARS groups, respectively (NS). Two of 9 patients with anti-PM/Scl antibodies and 4 of 12 patients with anti-ARS antibodies were hypoxemic at rest at diagnosis (NS). Differential cell counts of BAL performed in 5 patients with anti-PM/Scl and 11 patients with anti-ARS showed no significant difference between the groups (Figure 1).

Table 1. Techniques of detection of autoantibodies.

Autoantibody	Detection Method
Antinuclear antibody (ANA)	Indirect immunofluorescence technique with HEp2 cells (Biorad, Marnes la Coquette, France)
Anti-extractable nuclear antigen antibody	ELISA (Biorad)
Anti-PM/Scl	2 ELISA techniques using either the PM-1α peptide or a human recombinant PM/Scl-100 antigen according to the manufacturer's instructions (Euroimmun, Lubeck, Germany; Phadia, Saint-Quentin en Yvelines, France). Considered positive when titer was ≥ 20 and 15 AU × ml^{-1}, respectively
Anti-Jo1	ELISA according to manufacturer's instructions (Biorad), with titer considered positive when ≥ 40 AU × ml^{-1}
Anti-PL7 and anti-PL12	Dot technique according to manufacturer's instructions (D-TEK, Diasorin, Antony, France)
Anti-OJ, anti-EJ, anti-RNA polymerase-I, III, and anti-Th/To	Immunoprecipitation test using radiolabeled *in vitro* synthesized antigens (laboratory of Prof. H.P. Seelig, Institute of Immunology, Karlsruhe University, Karlsruhe, Germany)
Anti-fibrillarin	Western blot (Prof. Seelig, Karlsruhe University, Karlsruhe, Germany)
Anti-Mi2	Dot blot technique according to manufacturer's instructions (D-TEK, Antony, France)
Anti-dsDNA	Radioimmunoassay (Farr analysis; Siemens, Paris, France)
Anti-CCP	Quanta Lite™ ELISA (Menarini, Inova Diagnostics, Antony, France)
Rheumatoid factor	In-house ELISA

Table 2. Characteristics of patients at diagnosis of interstitial lung disease (ILD).

Characteristic	Anti-PM/Scl, n (%)	Anti-ARS, n (%)
Age at first symptom, yrs, median (range)	55 (35–75)	59 (15–75)
F/M	6/3	6/6
Smokers	3/9	5/12
Current	0	1
Former	3	4
Fatigue	4/9 (44)	7/12 (58)
Weight loss	0/9 (0)	5/12 (42)*
Dyspnea	9/9 (100)	11/12 (92)
Cough	6/9 (67)	5/12 (42)
Crackles	9/9 (100)	12/12 (100)
Hemoptysis	0/9 (0)	0/12 (0)
Finger clubbing	3/9 (33)	2/12 (17)
Right ventricular failure	0/9 (0)	1/12 (8)

* p = 0.045, Fisher's exact test.

Chest computed tomography. The predominant features on the initial HRCT were ground-glass attenuation and reticulation in both groups, with frequent association of some areas of consolidation (Table 4, Figure 1). Traction bronchiectases, micronodules, and honeycombing were uncommon. In the anti-PM/Scl patients, the HRCT pattern was mostly suggestive of NSIP in 8 cases and OP in 1 case. In anti-ARS patients, HRCT was suggestive of NSIP pattern in 9 cases and of UIP and OP patterns in 1 case each, and were unclassifiable in 1 case (Table 3, Figure 2). One current smoker patient with anti-ARS antibodies had typical imaging features of combined pulmonary fibrosis and emphysema. Imaging findings and HRCT patterns were not statistically different between the groups.

Characteristics of the CTD. Extrapulmonary manifestations of CTD among anti-PM/Scl and anti-ARS patients were present in all patients, except one with anti-PM/Scl antibodies (Table 5, Table 6). Remarkably, no patient with anti-PM/Scl antibodies had muscle weakness or pain throughout followup, compared to 5 of 12 patients with anti-ARS antibodies (p = 0.045). All patients with electromyographic evidence of myositis had elevated muscle enzyme levels. Arthralgia principally involved the small joints of the hands (6/6 anti-PM/Scl patients, 7/9 anti-ARS patients; NS), as well as wrists, elbows, shoulders, knees, and feet. No patient had articular deformities. One patient with anti-ARS antibodies had typical features of Sjögren syndrome with sicca syndrome, positive Schirmer test, confirmatory salivary gland biopsy, and splenomegaly. Another patient with anti-ARS antibodies had nephrotic syndrome and microscopic hematuria without renal insufficiency; renal biopsy revealed minimal change of glomerulopathy. The CTD in patients with anti-PM/Scl were DM (n = 2), limited cutaneous SSc (2), RA (1), UCTD (2), and overlap syndrome with coexistence of amyopathic DM, limited cutaneous SSc and Sjögren syndrome (1). Among the anti-ARS group, CTD were classified as PM (n = 4), UCTD (5), amyopathic DM (1), DM (1), and RA (1). Confidence for the diagnosis of DM/PM was definite in 4 cases, probable in 2 cases, and possible in 3 cases.

Chronology of pulmonary and CTD manifestations. Pulmonary symptoms preceded CTD manifestations by 4

Table 3. Clinical respiratory manifestations, lung function variables at diagnosis of ILD, and outcome. Negative values for time interval indicate that pulmonary symptoms preceded the onset of CTD manifestations.

Case	Time Interval from CTD to Pulmonary Symptoms, yrs	Respiratory Symptoms	VC	TLC	DLCO	Duration of ILD FU, yrs	HRCT Pattern/ Lung Pathology	PHT	Treatment	Outcome of ILD 1 Year	Outcome of ILD Last FU
Anti-ARS											
1	0	D	53	56	31	1.8	OP/OP	–	CS, IVIG, PE, CYC, MMF	I	I
2	–4	D	63	48	66	2.5	NSIP/NSIP	–	CS, AZA	W	I
3	–1	D	43	43	72	1.5	NSIP/NA	+	CS	I	I
4	1	D	42	42	65	1.8	UIP/NA	–	CS, MTX, LEF	W	I
5	0	D, C	51	58	54	2.5	NSIP/NA	–	CS	I	I
6	0	D, C	66	65	65	0.5	Unclass/NA	–	CS	Death	—
7	228	—	83	73	102	2.8	NSIP/NA	–	CS, MTX	S	S
8	–12	D, C	111	96	NA	2.3	NSIP/DAD	–	CS, AZA, MMF, IVIG	S	W
9	0	D	85	75	38	2.3	NSIP/UIP	–	CS	I	W
10	0	D, C	101	78	78	4.7	NSIP/Unclass	–	CS, AZA	W	I
11	72	D, FC	85	74	70	4.5	NSIP/NA	–	CS, MTX, INF, LEF	I	I
12	–192	D, C, FC	75	80	75	21.4	NSIP/Unclass	–	CS, AZA	I	I
Anti-PM/Scl											
13	–4	D, C	85	80	80	4.7	NSIP/UIP	–	CS	I	I
14	72	D	49	43	30	8.0	NSIP/NA	+	CS, GT, DP, MTX	S	S
15	48	D, C	107	96	73	11.0	NSIP/NA	+	CS, CYC	S	W
16	324	D, C, FC	80	76	73	5.5	NSIP/NA	–	CS	I	W
17	84	D, C	66	57	55	7.2	NSIP/NSIP	–	CS, AZA	I	I
18	84	D	59	65	77	45	NSIP/NA	–	CS, CYC	I	W
19	NA	D, FC	57	47	23	5.0	NSIP/NAP	+	CS	S	S
20	—	D, C, FC	87	80	90	3.8	OP/NA	–	CS	I	I
21	0	D, C	54	68	65	1.0	NSIP/NSIP	–	CS	W	W
Anti-PM/Scl and anti-ARS											
22	0	D, C	87	79	90	2.4	UIP/UIP	+	CS, CYC	W	LT

AZA: azathioprine; C: cough; CS: corticosteroid; CYC: cyclophosphamide; D: dyspnea; DLCO: carbon monoxide transfer factor; DP: D-penicillamine; FC: finger clubbing; FU: followup; GT: gold therapy; INF: infliximab; IVIG: intravenous immunoglobulin; I: improvement; LEF: leflunomide; LT: lung transplant; MMF: mycophenolate mofetil; MTX: methotrexate; NA: not assessed; NSIP: nonspecific interstitial pneumonia; OP: organizing pneumonia; PE: plasma exchanges; PHT: pulmonary hypertension; S: stable; TLC: total lung capacity; UIP: usual interstitial pneumonia; Unclass: unclassifiable; VC: vital capacity; W: worsening.

months in 1 patient with anti-PM/Scl, and by a median interval of 8 months in 4 patients with anti-ARS (NS). Pulmonary symptoms were concomitant with the CTD manifestations in 1 anti-PM/Scl case and 5 anti-ARS cases (NS). Pulmonary manifestations occurred after CTD features in 5 anti-PM/Scl patients (median interval 84 mo) and in 3 anti-ARS patients (median interval 72 mo) (NS). The information was not available for one anti-PM/Scl patient.

Echocardiographic findings. Two patients had asymptomatic pericardial effusion (1 with anti-Jo1 antibodies, 1 with anti-PL7 antibodies), which regressed with immunosuppressive therapy. Pulmonary hypertension was present at echocardiography in 3 patients with anti-PM/Scl and 1 patient with anti-ARS antibodies, and was confirmed by right-side heart catheterization in all cases. One further patient with anti-PM/Scl antibodies had right ventricular dilatation without pulmonary hypertension at right-side heart catheterization. No patient had left ventricular failure.

Lung pathology. Video-assisted thoracoscopic lung biopsy was performed in 8 cases. The pathological patterns were 1 UIP and 2 NSIP in the anti-PM/Scl group, and 1 UIP, 1 NSIP, and 1 diffuse alveolar damage in the anti-ARS group. In addition, 2 anti-ARS patients had unclassifiable interstitial pneumonia. Transbronchial biopsy specimens showed typical features of OP in 1 patient with anti-ARS antibodies.

Laboratory results. Serum CRP, serum LDH, and hypergammaglobulinemia were not significantly different between the 2 groups (Table 7). ANA were present in all 12 patients with anti-ARS antibodies, with a characteristic cytoplasmic pattern in 10 patients (7 also had a homogeneous, speckled, or nucleolar pattern). Seven of 9 patients with anti-PM/Scl antibodies had ANA, 6 with a homogeneous nucleolar pattern (Table 6, Table 7). Rheumatoid factor was found in 4 patients with anti-ARS antibodies and 3 patients with anti-PM/Scl antibodies. Three patients with anti-ARS antibodies and 1 with anti-PM/Scl antibodies had

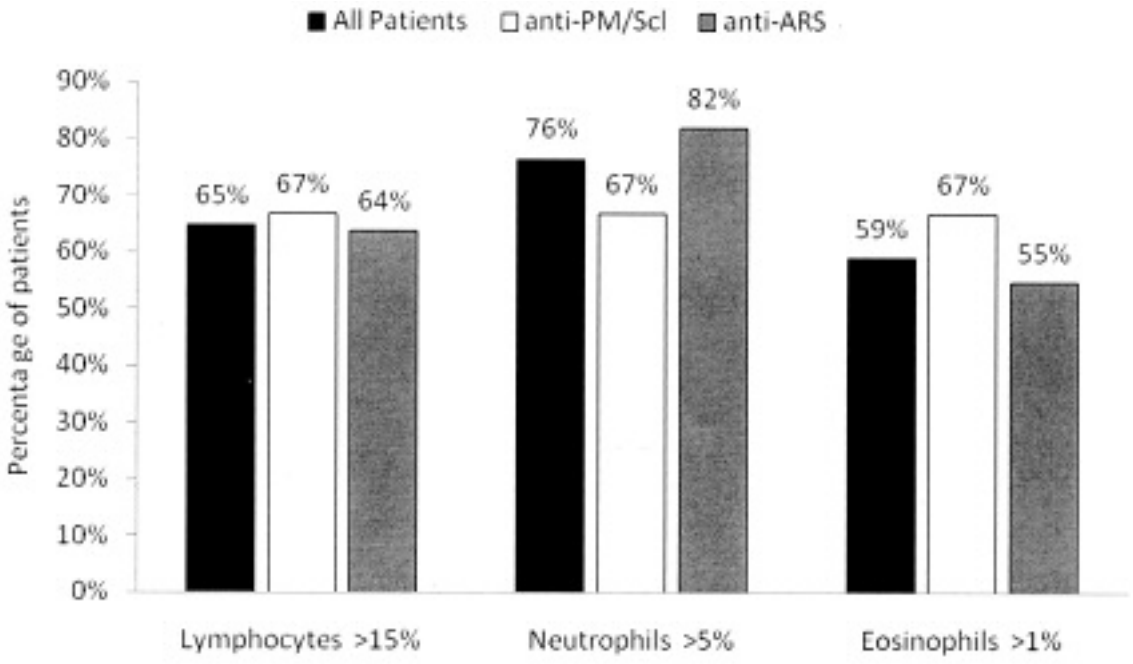

Figure 1. Differential cell counts in bronchoalveolar lavage fluid at presentation.

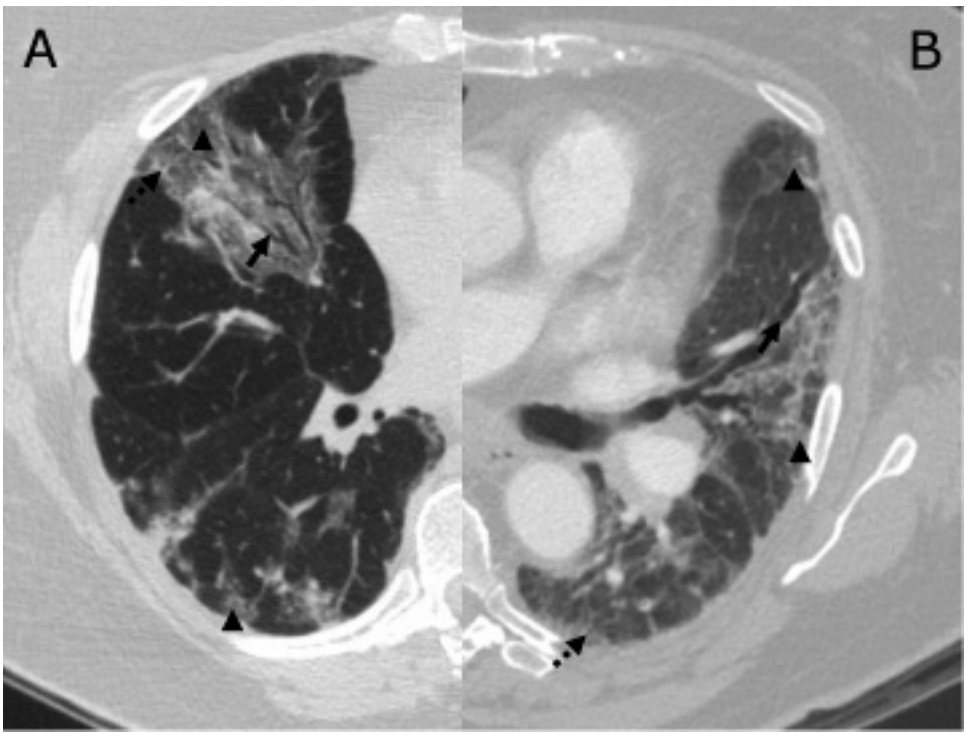

Figure 2. High-resolution computed tomography of patients with anti-ARS (A) and antiPM/Scl antibodies (B) showing traction bronchiectasis (arrow), reticulation (broken arrow), ground-glass attenuations (arrowheads), and absence of honeycombing. The imaging pattern is suggestive of nonspecific interstitial pneumonia.

anti-cyclic citrullinated peptide antibodies; all of them had arthralgia and 1 patient fulfilled the diagnostic criteria for RA. One patient within each group had mixed cryoglobulinemia. Among patients with anti-PM/Scl antibodies, associated autoantibodies included anti-topoisomerase-1 (n = 1 patient), anti-fibrillarin (1), anti-Ro (1), anti-dsDNA (2), and

Table 4. Imaging findings.

Feature	Anti-PM/Scl, n (%)	Anti-ARS, n (%)
Location		
Predominantly subpleural	3/9 (33)	4/12 (33)
Predominantly basal	8/9 (89)	12/12 (100)
Ground-glass attenuation	8/9 (89)	11/12 (92)
Consolidation	8/9 (89)	6/12 (50)
Traction bronchiectasis	2/9 (22)	3/12 (25)
Honeycombing	0/9 (0)	1/12 (8)
Reticular opacity	6/9 (67)	10/12 (83)
Micronodules	2/9 (22)	0/12 (0)
Predominant feature		
Reticulation	6/9 (67)	9/12 (75)
Ground-glass attenuation	2/9 (22)	2/12 (17)
Consolidation	1/9 (11)	1/12 (8)

Table 5. Comparison of muscle assessment and symptoms at followup.

Feature	Anti-PM/Scl, n (%)	Anti-ARS, n (%)
Muscle involvement	0/9 (0)	5/12 (42)*
Proximal muscle weakness	0/9 (0)	4/12 (33)
Muscle pain	0/9 (0)	5/12 (42)*
Elevated muscle enzyme level	2/6 (33)	5/9 (56)
Elevated CK level	2/6 (33)	4/9 (44)
Electromyographic signs	1/4 (25)	4/5 (80)
Positive muscle biopsy	0/1 (0)	2/3 (67)
Arthralgia	6/9 (67)	9/12 (75)
Arthritis	3/9 (33)	2/12 (17)
Raynaud phenomenon	3/9 (33)	4/12 (33)
Gottron sign or papules	2/9 (22)	2/12 (17)
Heliotrope erythema	2/9 (22)	0/12 (0)
Mechanic's hands	2/9 (22)	3/12 (25)
Fever	2/9 (22)	4/12 (33)
Sicca symptoms	4/9 (44)	1/12 (8)
Sclerodactyly/puffy fingers	3/9 (33)	1/12 (8)
Trunk scleroderma	0/9 (0)	0/12 (0)
Capillaroscopy abnormalities	4/5 (80)	3/5 (60)

CK: creatine kinase. * $p < 0.045$, Fisher's exact test.

anticentromere antibodies (1). Anti-dsDNA, ANCA with proteinase-3 specificity, anti-La, and anti-Mi2 antibodies were detected in anti-ARS-positive patients (1 each). Eight patients had 2 autoantibodies, including 5 with anti-PM/Scl and 3 with anti-ARS, and 3 patients had at least 3 autoantibodies (1 with anti-PM/Scl, 2 with anti-ARS).

Treatment and outcomes. All patients received oral corticosteroids, starting with prednisone 0.5–1 mg × kg^{-1} × day^{-1} equivalent dose. The proportions of patients with improvement or stable or worsening disease did not differ (Table 3, Table 8). The proportion of patients requiring immunosuppressive therapy was higher in the anti-ARS group ($p = 0.02$), because of severe myositis (in 2 patients also treated with intravenous immunoglobulin, alone or associated with plasma exchanges and rituximab) or arthritis (in 2 anti-ARS-positive patients also treated with methotrexate followed by leflunomide). Methotrexate was required in only 1 anti-PM/Scl-positive patient for extrapulmonary involvement, i.e., corticosteroid-resistant arthritis.

The median duration of followup was 5.5 years (range 3.8–15.3) for the anti-PM/Scl group and 2.4 years (range 0.5–21.4) for the anti-ARS group. The mean interval from onset of pulmonary symptoms to the last followup (or death) was 5.0 years (range 1.0–11.0) for the anti-PM/Scl group and 2.3 years (range 0.5–21.4) for the anti-ARS group. One patient with anti-ARS antibodies died from subacute respiratory failure 4 months after the onset of ILD. Treatment and outcome did not significantly differ between the 2 groups at last visit (Table 8). Two patients in each group needed longterm oxygen therapy. Muscle manifestations improved with immunosuppressive treatment in all patients. Severe drug-related side effects occurred in 3 patients (hematologic toxicity with cyclophosphamide in 2, methotrexate-induced pneumonitis in 1 patient).

DISCUSSION

A similar proportion of patients with either anti-ARS or anti-PM/Scl antibodies was found in our cohort evaluated for ILD in a tertiary care center. All anti-PM/Scl patients had symptomatic pulmonary involvement with a globally favorable prognosis comparable to that of patients with anti-ARS antibodies. In contrast to anti-ARS-related ILD, anti-PM/Scl-related ILD usually developed after extrapulmonary manifestations of CTD, and rarely preceded them or remained isolated. The extrapulmonary manifestations were characterized by a similar prevalence of Raynaud phenomenon, arthralgia, and mechanic's hands. Manifestations associated with anti-PM/Scl and anti-ARS antibodies differed only by a significantly lower prevalence of clinical myositis.

Features of ILD associated with anti-PM/Scl antibodies have not previously been reported in detail[5,21]. The most common HRCT findings of anti-PM/Scl-related ILD were basilar irregular opacities with areas of ground-glass attenuation, reticulation, and little architectural distortion, a pattern suggestive of NSIP, and were consistent with previous series of DM/PM-associated ILD[10,22-24]. The prevalence of traction bronchiectases, which are common in idiopathic NSIP, varies across the series in DM/PM[10,22,23,25]. Honeycombing, which is considered a hallmark of UIP, was absent in patients with anti-PM/Scl antibodies, consistent with a NSIP pattern on HRCT and a favorable outcome[22,23,26].

Interestingly, anti-PM/Scl-associated ILD in the absence of overt CTD manifestations and similar to conditions reported in patients with anti-ARS antibodies[27,28] has not been reported previously. This condition has likely been underrecognized, because the anti-PM/Scl autoantibodies are often not measured in the absence of clinical myositis or SSc manifestations[29]. In addition, our series was character-

Table 6. CTD manifestations and biological data of patients.

Case	Age, yrs Sex	Autoantibodies	Muscle Involvement				CTD Features	CTD Classification
			Bohan and Peter Criteria	Proximal Weakness	CK	Aldolase		
Anti-ARS								
1	51 M	ANA, Jo 1, Cryo	4	+	15598	249	RP, GN, A, P, Fe	PM
2	67 M	ANA, Jo 1, CCP	0	–	—*	—	A	UCTD
3	72 F	ANA, Jo 1	2	+	—	11	RP, CA	PM
4	55 F	ANA, Jo 1	0	–	NA	NA	A, S	UCTD
5	62 F	ANA, Jo 1, RF	3	–	477	28	CA, A, Fe	PM
6	75 M	ANA, Jo 1, PR3	4	+	1569	42	RP	PM
7	50 F	ANA, Jo 1	1	–	—	—	GS, MH, A	ADM
8	69 F	ANA, EJ	3	+	2044	45	A, GS, purpura, MH, Fe	DM
9	75 M	ANA, OJ, EJ, RF	0	–	NA	NA	A, rash, Fe	UCTD
10	38 M	ANA, PL7	1	–	262	—	MH, RP, P, CA	UCTD
11	48 M	ANA, PL7, Mi2, CCP, RF	0	–	NA	NA	A	RA
12	15 F	ANA, PL7, Mi2, dsDNA, La, CCP, RF	0	–	—	NA	A, SS	UCTD
Anti-Pm/Scl								
13	50 F	ANA, PM/Scl, RF	3	–	439	32	A, PE, MH	DM
14	75 M	PM/Scl, RF	0	–	—	—	A, RN, Fe, SS	RA
15	58 M	ANA, PM/Scl, Scl70	0	–	NA	NA	RP, A, S, CA, D, SS, DU, CC	lcSSc
16	73 M	ANA, PM/Scl, Fibrillarin	1	–	—	—	GP, HE, PE, DU, S, D, SS, RP, A, N, CC, MH, CA	SSS+lcSSc+ ADM
17	37 F	ANA, PM/Scl,dsDNA	2	–	330	20	GP, HE, PE, A, CA, Fe	DM
18	50 F	ANA, PM/Scl, Ro, dsDNA	0	–	NA	NA	S, CA	lcSSc
19	74 F	ANA, PM/Scl, CCP, RF, Cryo	0	–	—	NA	SS, A, RP, LC	UCTD
20	54 F	PM/Scl	0	–	NA	NA	—	—
21	55 F	ANA, PM/Scl, ACA	0	–	—	—	RP	UCTD
Anti-ARS and anti-PM/Scl								
22	42 M	ANA, PM/Scl, Jo 1	1	–	320	20	—	UCTD

* Indicates normal enzyme level. A: arthritis; ACA: anticentromere antibodies; ADM: amyopathic dermatomyositis; ANA: antinuclear antibodies; CA: capillaroscopy abnormalities; CC: cutaneous calcinosis; CCP: anticyclic citrullinated peptide antibodies; CK: creatine kinase; Cryo: mixed cryoglobulinemia; D: subjective dysphagia; DM: dermatomyositis; dsDNA: double-stranded DNA; DU: digital ulcers; Fe: fever; GN: glomerulonephritis; GP: Gottron papules; GS: Gottron sign; HE: heliotrope erythema; LC: liver cirrhosis; lcSSc: limited cutaneous; MH: mechanic's hands; NA: not assessed; N: neuropathy; P: pericarditis; PE: periungual erythema; PM: polymyositis; RA: rheumatoid arthritis; RF: rheumatoid factor; RN: rheumatoid nodules; RP: Raynaud phenomenon; S: sclerodactyly; SS: sicca syndrome; SSS: secondary Sjögren syndrome; UCTD: undifferentiated connective tissue disease.

Table 7. Main biology findings.

Feature	Anti-PM/Scl, n (%)	Anti-ARS, n (%)
Antinuclear antibodies	7/9 (78)	12/12 (100)
Homogeneous pattern	2/9 (22)	5/12 (42)
Speckled pattern	1/9 (11)	1/12 (8)
Nucleolar pattern	6/9 (67)	1/12 (8)*
Cytoplasmic pattern	0/9 (0)	10/12 (83)**
Cryoglobulinemia	1/4 (25)	1/2 (50)
Elevated lactate dehydrogenase	3/9 (33)	6/12 (50)
Hypergammaglobulinemia	3/9 (33)	3/11 (27)
Elevated C-reactive protein	4/9 (44)	7/11 (64)

* $p < 0.007$; ** $p < 0.0002$, Fisher's exact test.

ized by the low prevalence of definite CTD, highlighting the need for careful assessment of patients presenting with ILD in search of manifestations of formes frustes of CTD, notably amyopathic DM (DM rash without myositis) and SSc *sine* scleroderma characterized by visceral organ involvement (lungs, kidneys, gastrointestinal tract) with abnormal nailfold capillaries and ANA[30]. Thus, recognition of the underlying CTD requires careful examination of patients, including Raynaud phenomenon, cutaneous changes suggestive of SSc or DM, arthralgia of hands, muscle symptoms, sicca symptoms, nailfold capillaroscopy, and measurement of muscle enzyme levels. Autoantibodies could be evaluated comprehensively, based on ANA pattern on immunofluorescence, especially in cases of the cytoplasmic pattern (suggestive of anti-ARS antibodies or anti-signal recognition particle antibodies) or nucleolar pattern (suggestive of anti-PM/Scl, anti-Th/To, anti-fibrillarin, or anti-RNA polymerase I antibodies). However, as some patients have no ANA and often no typical cytoplasmic or nucleolar pattern, specific antibodies should be analyzed in all suspected cases, independently of the detection of ANA[31]. Early diagnosis of an underlying CTD may lead to prompt identification of life-threatening manifestations that may follow diagnosis of ILD, such as scleroderma renal cri-

Table 8. Treatment and outcome of ILD at 1 year and at the end of followup.

Time	Group	Improvement, n (%)	Stable, n (%)	Worsening/Death, n (%)
1 year	Anti-PM/Scl, n = 9	5 (56) (CS 5 + IS 1)	3 (33) (CS 3)	1 (11) (CS 1)
	Anti-ARS, n = 12	6 (50) (CS 6 + IS 4)	2 (17) (CS 2 + IS 2)	4 (33) (CS 4 + IS 2)
End of followup	Anti-PM/Scl, n = 9	3 (33) (CS 3 + IS 1)	2 (22) (CS 2 + IS 1)	4 (44) (CS 4 + IS 2)
	Anti-ARS, n = 11	8 (72) (CS 8 + IS 5)	1 (9) (CS 1 + IS 1)	2 (18) (CS 2 + IS 1)

CS: corticosteroids; IS: immunosuppressive drugs.

sis or severe involvement of pharyngeal function in PM/DM. Further, diagnosing the CTD may contribute to adapting therapy and evaluating the prognosis of disease[32]. There are no evidence-based treatment recommendations for patients with ILD and anti-ARS or anti-PM/Scl antibodies, and management should be adapted individually, based on the severity and outcome of ILD regardless of the immunology profile. It is our practice to use oral corticosteroids as first-line treatment, with additional immunosuppressive therapy in patients with progressive disease despite corticosteroids or in whom disease control requires daily prednisone doses of 20 mg or higher.

Surprisingly, 11 of 21 patients had a combination of autoantibodies reported as specific for CTD subsets (e.g., anti-dsDNA and lupus, anti-cyclic citrullinated peptide antibody and RA, anti-Mi2 and DM, or anti-Scl70/anti-fibrillarin and diffuse cutaneous SSc) or mutually exclusive (e.g., double anti-ARS positivity, anti-Mi2 and anti-ARS, or presence of 2 antinucleolar autoantibodies)[33]. Extensive immunological assays have shown that patients with DM/PM are characterized by frequent association of autoantibodies with marked serological heterogeneity rather than single specificity[34]. Interpretation of immunological test results and the inference between the presence of autoantibodies and clinical symptoms may be hazardous in the absence of a study specifically dedicated to this complex condition[35]. To confirm the presence of true-positive anti-PM/Scl and exclude false-positives, we performed 2 ELISA using different antigens, i.e., a human recombinant PM/Scl-100 protein and the PM1-α antigen. All 9 patients with anti-PM/Scl autoantibodies were positive in both assays, including the 3 patients without nucleolar fluorescence on ANA. The specificity of the ELISA for anti-PM/Scl autoantibodies using the PM1-α antigen was reported to be 93% for the diagnosis of myositis/SSc overlap[36]. As the majority of our patients with anti-ARS still have limited followup experience, it cannot be excluded that some may eventually develop a more overt form of CTD.

The peculiar clinical pattern of patients with anti-ARS antibodies, i.e. myositis, ILD, arthritis, sclerodactyly, sicca syndrome, Raynaud phenomenon, and mechanic's hands, was shared by patients with anti-PM/Scl antibodies. Our findings are supported by a previous study showing similar clinical features associated with anti-PM/Scl and anti-ARS antibodies except for sclerodactyly that was not assessed[6]. Reciprocally, patients with anti-ARS antibodies commonly have manifestations belonging to both the SSc and the PM/DM spectra that are usually described as related to anti-PM/Scl antibodies, including slight SSc-like cutaneous changes or involvement of the gastrointestinal tract[2,8,27,37-41]. We therefore consider that patients with anti-PM/Scl and anti-ARS antibodies belong to the same clinical diagnostic group. Of note, alleles of the 8.1 Caucasian ancestral haplotype including HLA-DRB1*03, DQA1*05, and DQB1*02 correlate closely with both autoantibodies[3,4,8,42]. HLA-DRB1*03 is implicated in the development of ILD among patients with CTD and predicted the occurrence of ILD in mixed CTD[43], SSc[44], and DM/PM, irrespective of myositis subtype or presence of autoantibodies in the latter[42]. HLA-DRB1*03 may represent a determinant factor in the development of systemic manifestations in patients with anti-ARS and anti-PM/Scl antibodies[6]. Other HLA markers also differentiate anti-PM/Scl from anti-ARS patients. Hence, HLA-DPB1*0101 allele, a gene separated from the 8.1 Caucasian ancestral haplotype, was shown to be associated only with anti-Jo1-positive PM/DM compared to those positive for anti-PM/Scl[9]. It is conceivable that the HLA haplotype correlates better than the subtype of autoantibody with the clinical phenotype.

There are several limitations to our study. First, not all patients had a lung and muscle biopsy, due to the retrospective study design. However, in the absence of muscle weakness or muscle enzyme elevation, systematic invasive testing would be difficult to warrant. Second, the small numbers of subjects in each group limited the statistical power of the comparison and did not allow testing for non-identity. A larger multicenter prospective study is needed to confirm our analysis. Third, multiple comparisons may statistically yield spurious false-positive results, and our study was exploratory and hypothesis-generating. Fourth, systematic screening for non-Jo1 ARS antibodies was not performed in our population of ILD patients, and it is conceivable that the

frequency of anti-PL-7 and PL-12 antibodies may have been underestimated[31]. Fifth, this series represents recruitment from a tertiary department of respiratory medicine, and results may not be applicable in another setting.

Our hypothesis-generating study supports the notion that anti-PM/Scl and anti-ARS antibodies are associated with similar ILD.

We report an original series of patients with ILD associated with anti-PM/Scl antibodies, including a subset of patients who did not share the classical myositis-scleroderma syndrome, but presented with no or minimal manifestations of myositis. Our study showed that the populations delineated by anti-PM/Scl and anti-ARS antibodies are not as homogeneous as previously thought, and largely overlap, with the exception of more frequent overt myositis in patients with anti-ARS antibodies. Similar clinical and especially pulmonary manifestations are observed in patients with anti-PM/Scl or anti-ARS antibodies, challenging the clinical specificity of the antisynthetase syndrome.

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REFERENCES

1. Venables PJ. Polymyositis-associated overlap syndromes. Br J Rheumatol 1996;35:305-6.
2. Marguerie C, Bunn CC, Beynon HL, Bernstein RM, Hughes JM, So AK, et al. Polymyositis, pulmonary fibrosis and autoantibodies to aminoacyl-tRNA synthetase enzymes. Q J Med 1990;77:1019-38.
3. Love LA, Leff RL, Fraser DD, Targoff IN, Dalakas M, Plotz PH, et al. A new approach to the classification of idiopathic inflammatory myopathy: myositis-specific autoantibodies define useful homogeneous patient groups. Medicine (Baltimore) 1991;70:360-74.
4. 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;35:1211-7.
5. Marguerie C, Bunn CC, Copier J, Bernstein RM, Gilroy JM, Black CM, et al. The clinical and immunogenetic features of patients with autoantibodies to the nucleolar antigen PM-Scl. Medicine (Baltimore) 1992;71:327-36.
6. 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;55:791-8.
7. Genth E, Mierau R, Genetzky P, von Muhlen CA, Kaufmann S, von Wilmowsky H, et al. Immunogenetic associations of scleroderma-related antinuclear antibodies. Arthritis Rheum 1990;33:657-65.
8. Hausmanowa-Petrusewicz I, Kowalska-Oledzka E, Miller FW, Jarzabek-Chorzelska M, Targoff IN, Blaszczyk-Kostanecka M, et al. Clinical, serologic, and immunogenetic features in Polish patients with idiopathic inflammatory myopathies. Arthritis Rheum 1997;40:1257-66.
9. Chinoy H, Payne D, Poulton KV, Fertig N, Betteridge Z, Gunawardena H, et al. HLA-DPB1 associations differ between DRB1*03 positive anti-Jo-1 and anti-PM-Scl antibody positive idiopathic inflammatory myopathy. Rheumatology 2009;48:1213-7.
10. Marie I, Hachulla E, Cherin P, Dominique S, Hatron PY, Hellot MF, et al. Interstitial lung disease in polymyositis and dermatomyositis. Arthritis Rheum 2002;47:614-22.
11. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975;292:344-7.
12. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
13. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980;23:581-90.
14. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.
15. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554-8.
16. Gerami P, Schope JM, McDonald L, Walling HW, Sontheimer RD. A systematic review of adult-onset clinically amyopathic dermatomyositis (dermatomyositis sine myositis): a missing link within the spectrum of the idiopathic inflammatory myopathies. J Am Acad Dermatol 2006;54:597-613.
17. LeRoy EC, Medsger TA Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol 2001;28:1573-6.
18. Bronchoalveolar lavage constituents in healthy individuals, idiopathic pulmonary fibrosis, and selected comparison groups. The BAL Cooperative Group Steering Committee. Am Rev Respir Dis 1990;141:S169-202.
19. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002;165:277-304.
20. Galie N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. Eur Heart J 2004;25:2243-78.
21. Gaudin C, Fortenfant F, Adoue D, Beyne-Rauzy O. Anti PM-Scl antibodies. Study of prevalence and of meaning. Rev Med Interne 2006;27:665-70.
22. Mino M, Noma S, Taguchi Y, Tomii K, Kohri Y, Oida K. Pulmonary involvement in polymyositis and dermatomyositis: sequential evaluation with CT. AJR Am J Roentgenol 1997;169:83-7.
23. Douglas WW, Tazelaar HD, Hartman TE, Hartman RP, Decker PA, Schroeder DR, et al. Polymyositis-dermatomyositis-associated interstitial lung disease. Am J Respir Crit Care Med 2001;164:1182-5.
24. Cottin V, Thivolet-Bejui F, Reynaud-Gaubert M, Cadranel J, Delaval P, Ternamian PJ, et al. Interstitial lung disease in amyopathic dermatomyositis, dermatomyositis and polymyositis. Eur Respir J 2003;22:245-50.
25. Travis WD, Hunninghake G, King TE Jr, Lynch DA, Colby TV, Galvin JR, et al. Idiopathic nonspecific interstitial pneumonia: report of an American Thoracic Society project. Am J Respir Crit Care Med 2008;177:1338-47.
26. Bonnefoy O, Ferretti G, Calaque O, Coulomb M, Begueret H, Beylot-Barry M, et al. Serial chest CT findings in interstitial lung

disease associated with polymyositis-dermatomyositis. Eur J Radiol 2004;49:235-44.
27. Friedman AW, Targoff IN, Arnett FC. Interstitial lung disease with autoantibodies against aminoacyl-tRNA synthetases in the absence of clinically apparent myositis. Semin Arthritis Rheum 1996;26:459-67.
28. Fujita J, Ohtsuki Y, Yoshinouchi T, Yamadori I, Bandoh S, Tokuda M, et al. Idiopathic non-specific interstitial pneumonia: as an "autoimmune interstitial pneumonia". Respir Med 2005;99:234-40.
29. Vano Sanchis D, Arranz Garcia G, Yglesias PJ. Systemic sclerosis sine scleroderma presenting as pulmonary interstitial fibrosis. Clin Rheumatol 2006;25:382-3.
30. Cottin V. Interstitial lung disease: are we missing formes frustes of connective tissue disease? Eur Respir J 2006;28:893-6.
31. Fischer A, Swigris JJ, du Bois RM, Lynch DA, Downey GP, Cosgrove GP, et al. Anti-synthetase syndrome in ANA and anti-Jo-1 negative patients presenting with idiopathic interstitial pneumonia. Respir Med 2009;103:1719-24.
32. Park JH, Kim DS, Park IN, Jang SJ, Kitaichi M, Nicholson AG, et al. Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease-related subtypes. Am J Respir Crit Care Med 2007;175:705-11.
33. Ho KT, Reveille JD. The clinical relevance of autoantibodies in scleroderma. Arthritis Res Ther 2003;5:80-93.
34. Koenig M, Fritzler MJ, Targoff IN, Troyanov Y, Senecal JL. Heterogeneity of autoantibodies in 100 patients with autoimmune myositis: insights into clinical features and outcomes. Arthritis Res Ther 2007;9:R78.
35. Warner NZ, Greidinger EL. Patients with antibodies to both PmScl and dsDNA. J Rheumatol 2004;31:2169-74.
36. Mahler M, Raijmakers R, Dahnrich C, Bluthner M, Fritzler MJ. Clinical evaluation of autoantibodies to a novel PM/Scl peptide antigen. Arthritis Res Ther 2005;7:R704-13.
37. Vazquez-Abad D, Rothfield NF. Sensitivity and specificity of anti-Jo-1 antibodies in autoimmune diseases with myositis. Arthritis Rheum 1996;39:292-6.
38. Schmidt WA, Wetzel W, Friedlander R, Lange R, Sorensen HF, Lichey HJ, et al. Clinical and serological aspects of patients with anti-Jo-1 antibodies — an evolving spectrum of disease manifestations. Clin Rheumatol 2000;19:371-7.
39. Targoff IN, Arnett FC, Berman L, O'Brien C, Reichlin M. Anti-KJ: a new antibody associated with the syndrome of polymyositis and interstitial lung disease. J Clin Invest 1989;84:162-72.
40. Jablonska S, Chorzelski TP, Blaszczyk M, Jarzabek-Chorzelska M, Kumar V, Beutner EH. Scleroderma/polymyositis overlap syndromes and their immunologic markers. Clin Dermatol 1992;10:457-72.
41. 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 (Baltimore) 2005;84:231-49.
42. Chinoy H, Salway F, Fertig N, Shephard N, Tait BD, Thomson W, et al. In adult onset myositis, the presence of interstitial lung disease and myositis specific/associated antibodies are governed by HLA class II haplotype, rather than by myositis subtype. Arthritis Res Ther 2006;8:R13.
43. Gendi NS, Welsh KI, Van Venrooij WJ, Vancheeswaran R, Gilroy J, Black CM. HLA type as a predictor of mixed connective tissue disease differentiation. Ten-year clinical and immunogenetic followup of 46 patients. Arthritis Rheum 1995;38:259-66.
44. Briggs DC, Vaughan RW, Welsh KI, Myers A, duBois RM, Black CM. Immunogenetic prediction of pulmonary fibrosis in systemic sclerosis. Lancet 1991;338:661-2.