Antisynthetase Syndrome with Anti-Jo1 Antibodies in 48 Patients: Pulmonary Involvement Predicts Disease-modifying Antirheumatic Drug Use

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ABSTRACT. ***Objective.*** To analyze the characteristics, outcomes, and predictive factors of disease-modifying antirheumatic drug (DMARD) use in 48 patients with antisynthetase syndrome [characterized by myositis, interstitial lung disease (ILD), arthritis, Raynaud's phenomenon (RP), and/or mechanic's hands] and the presence of anti-histidyl-transfer RNA synthetase (anti-Jo1) autoantibodies.

Methods. Forty-eight patients (33 women, 15 men) who were anti-Jo1-positive referred to one center between 1998 and 2008 were analyzed retrospectively.

Results. The median age of disease onset was 43 years [interquartile range (IQR) 33–53 yrs]. The median followup was 5 years (IQR 2–8 yrs). At diagnosis, 81% of patients presented with myositis, 80% ILD, 77% arthralgia, 48% RP, and 21% mechanic's hands. During the followup, 14 patients (29%) had no need for DMARD, while 34 (71%) required DMARD. Patients with mechanic's hands ($p = 0.02$) and higher creatine phosphokinase at diagnosis (median 6070 IU/l vs 1121 IU/l; $p = 0.002$) were more likely to need DMARD. ILD, noted on computed tomography scan by a nonspecific interstitial pneumonia score, was lower in the group of patients with no DMARD need (4 vs 7; $p = 0.04$). Twenty patients (44%) presented with a pulmonary aggravation (worsening of radiologic score of ILD and/or pulmonary function test results) leading to DMARD use. Nonspecific interstitial pneumonia score (7 vs 5; $p = 0.05$) and total lung volume (57.5% vs 70%; $p = 0.02$) values predicted pulmonary aggravation.

Conclusion. Our study outlines the burden of chest involvement for the prognosis of antisynthetase syndrome in terms of patients' requirement for DMARD therapy. (First Release Aug 1 2012; J Rheumatol 2012;39:1835–9; doi:10.3899/jrheum.111604)

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Anti-histidyl-tRNA synthetase (anti-Jo1) antibodies are found in 25%–30% of patients with idiopathic inflammatory myopathies[1], frequently in the context of an antisynthetase syndrome (anti-SS) characterized (with the addition of myositis) by the association of interstitial lung disease (ILD), arthritis, Raynaud's phenomenon (RP), and mechanic's hands[2].

The aim of our retrospective study was to analyze the characteristics and outcome of 48 patients with anti-Jo1 antibodies, according to their clinical presentation and treatments, to assess predictive factors that could be associated with need (or not) for disease-modifying antirheumatic drugs (DMARD).

MATERIALS AND METHODS

Patients. We retrospectively identified all patients with positive anti-Jo1 autoantibodies, diagnosed at the Pitié-Salpêtrière Hospital laboratory over a 10-year period (1998-2008), with a minimal followup of 1 year. Patients were divided into 2 groups. The first, referred to as DMARD need, was defined by ineffectiveness of initial treatment necessitating increase of prednisone doses (> 0.5 mg/kg/day) and/or addition of and/or change in the associated immuno-

suppressive or modulator drugs (including methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, cyclophosphamide, polyvalent immunoglobulins, rituximab, plasmapheresis, and etanercept). The remaining patients were classified in the second group, referred to as those with no DMARD need.

Computed tomography (CT) evaluations. CT scans of the chest with multidetector (16–64) CT examinations were performed in 37 patients. CT scans of patients presenting with nonspecific interstitial pneumonia (NSIP) pattern were assessed by 2 radiologists (CB, DT) who attributed an extent score of lung infiltration based on 5 selected axial images. Scoring was based on the CT scoring system of Kazerooni, *et al*[3] at each level: from 0, if there was no infiltration, to 5, if the extent was greater than 75%.

Statistical analysis. Quantitative data are presented using median and interquartile range (IQR). Comparisons were performed using Fisher's exact test or Wilcoxon rank test, as appropriate.

RESULTS

Anti-Jo1 antibodies were found in 166 sera samples representing 65 patients. Complete medical records were available for 48 patients (Table 1). Median age at disease onset was 43 years (IQR 33–53). Their median followup was 5 years (IQR 2–8).

The median creatine phosphokinase (CK) level was 4975 IU/l (IQR 1865 to 9915.5 IU/l). Antinuclear antibody titers were low positive (from 1/80 to 1/160) in 29 patients (60%) and elevated (≥ 1/320) in 14 patients (29%). Among the myositis-associated autoantibodies, the most frequently found was anti-SSA, in 31 patients (65%; Table 1).

ILD was detected in 34 of 37 patients who had a reviewed CT scan. The radiological pattern was suggestive of NSIP in 27 patients; 14 presented a pattern of NSIP without CT findings of fibrosis (Figure 1A) and 13 with CT findings of fibrosis (Figure 1B). The median score of the extent of lung infiltration in patients presenting an NISP pattern was 5 (IQR 4–8). The radiological pattern was suggestive of organizing pneumonia (Figure 1C, 1D) in 5 patients and usual interstitial pneumonia (Figure 1E) in 2 patients. Presence of anti-SSA autoantibodies was associated with a decrease of most of the pulmonary test results: total lung volume (TLV; p = 0.009), respiratory volume (RV; p = 0.003), DLCO (p = 0.01), alveolar volume (VA; p = 0.07), and DLCO/VA ratio (p = 0.007), while the ratio of forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC ratio) increased (p = 0.007).

Predictive factors of DMARD need. All treated patients (47/48) received prednisone (initial dose 1 mg/kg/day) during a median of 4.5 years (IQR 1.8–7.0), 6 of them as a single therapy. During the followup, 14 patients (29%) presented an improvement or a stabilization with no DMARD need, while 34 (71%) patients required DMARD therapy (Table 2). There were no differences of sex, ethnic origin, or age at onset in the 2 groups of patients. Among clinical signs observed at diagnosis, patients with mechanic's hands (p = 0.02) and higher CK values at diagnosis [median 6070 IU/l (IQR 3000 to 11,600) vs 1121 IU/l (IQR 478 to 5000); p = 0.002] were more likely to need DMARD (Table 2). Prevalence of autoantibodies was similar within the 2 groups of patients. Median NSIP

Table 1. Clinical characteristics and prevalence of autoantibodies at diagnosis in 48 patients with anti-Jo1 antibodies.

Characteristic	Patients, n (%)
At onset	
Myositis preceding ILD	15 (31.2)
ILD preceding myositis	8 (16.6)
Simultaneous myositis ILD	20 (41.7)
Myositis without ILD	4 (8.3)
ILD without myositis	1 (2.1)
Myositis	
Proximal muscle weakness	39 (81.2)
Severe weakness (MRC ≤ 3/5)	24 (50)
Muscle pain	34 (70.8)
Dysphagia	13 (27)
ILD	
Effort dyspnea	38 (79.2)
Severe dyspnea (NYHA ≥ 3)	19 (39.6)
Articular involvement	
Arthralgia	37 (77.1)
Severe arthritis	3 (6.2)
Raynaud's phenomenon	23 (47.9)
Severe Raynaud's	4 (8.3)
Mechanic's hands	10 (20.8)
General signs	
Fever	15 (31.2)
Fever > 38.5°	3 (6.2)
Weight loss	6 (12.5)
Associated signs	
Sicca symptoms	18 (37.5)
Focal lymphocytic sialadenitis on labial salivary gland biopsy	7 (14.6)
Scleroderma signs	15 (31.2)
Palpebral edema	8 (16.7)
Periungual erythema	10 (20.8)
Cutaneous rash	13 (27)
Antinuclear antibody	
Nuclear fluorescence	19 (39.6)
Cytoplasmic fluorescence	35 (72.9)
Myositis-specific antibodies (anti-SRP and/or anti-Mi-2)	0 (0.0)
Myositis-associated antibodies	
Anti-SSA	31 (64.6)
SSA-Ro52	29 (60.4)
SSA-Ro60	11 (22.9)
Anti-RNP	2 (4.2)
Anti-Ku	0 (0.0)
Anti-PM-Scl	0 (0.0)
Other antibodies	
Anti-SSB	4 (8.3)
Anti-Scl-70	1 (2.1)
Anticentromere	4 (8.3)
Anti-Sm	0 (0.0)
Anti-DNA, n = 39	3 (7.7)
Antihistone, n = 46	1 (2.2)
Rheumatoid factor, n = 36	9 (25.0)
Anticardiolipin antibody, n = 25	5 (20.0)
ANCA, n = 24	1 (4.2)

ILD: interstitial lung disease; MRC: Medical Research Council; NYHA: New York Heart Association; ANCA: antineutrophil cytoplasmic antibodies; SRP: signal recognition particles.

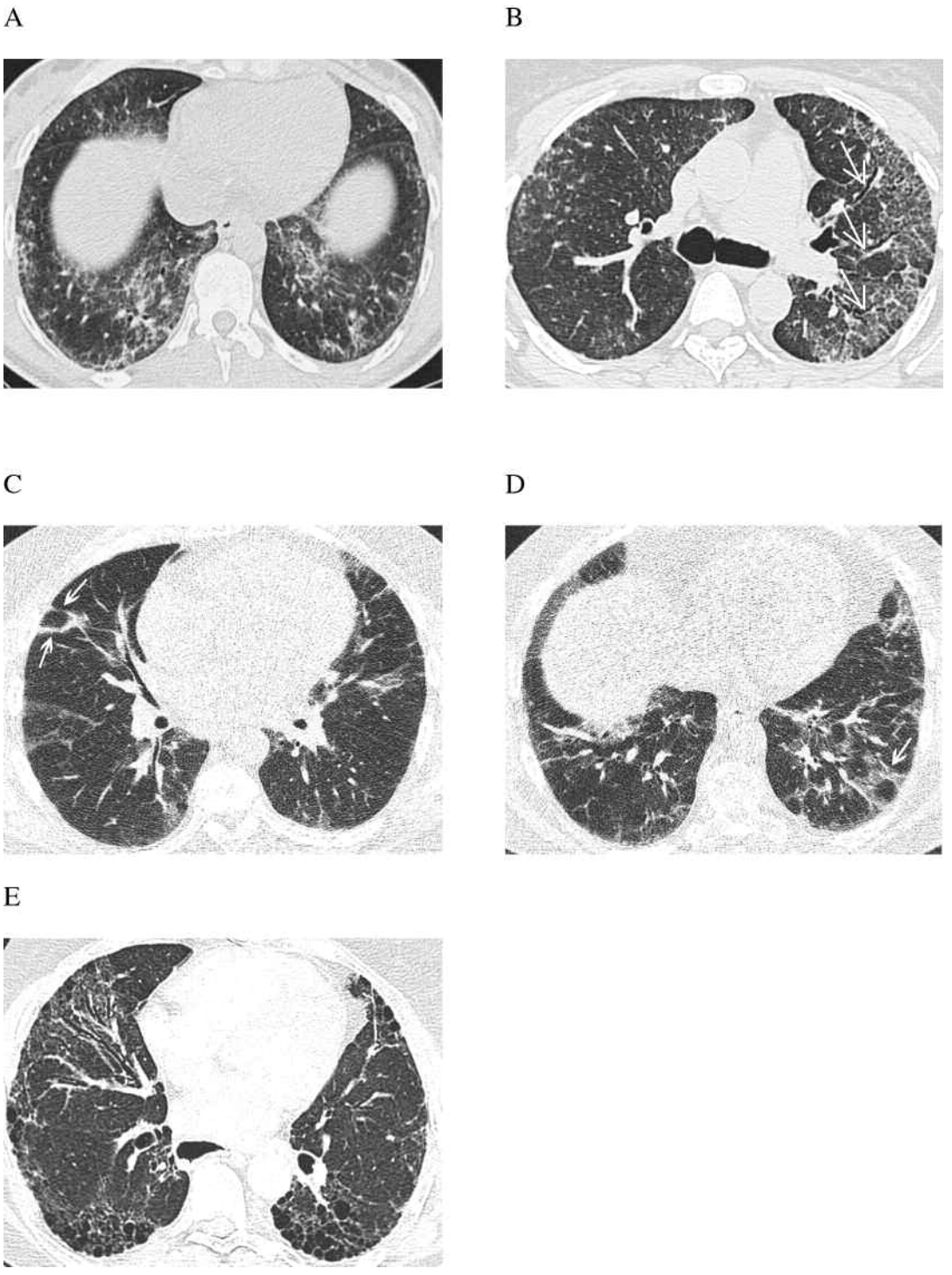

Figure 1. A. Axial computed tomography (CT) scan at the level of the lower lobes. Pattern suggestive of nonspecific interstitial pneumonia (NSIP): bilateral patchy areas of ground-glass opacities containing intralobular reticular opacities without bronchiectasis or honeycombing. There is sparing of the subpleural areas in the posterior parts of the lower lobes. B. Axial thin collimation CT scan at the level of the carina. Bilateral patchy areas of ground-glass opacities predominant in the left lower lobe containing intralobular reticular lines and distortion and dilatation of bronchial lumens in the left lung (traction bronchiectasis; arrows) suggestive of NSIP with fibrosis. C. Axial images at the level of the left pulmonary vein; and D. at the level of basilar segments of the lower lobes. Bilateral patchy areas of intense ground-glass and consolidation with subpleural and perilobular distribution with reversed halo sign (arrows) suggestive of organizing pneumonia. E. Axial image at the level of the mid-part of the lungs. Ground-glass opacity in the right middle lobe and typical honeycombing in the posterior subpleural areas of lower lobes suggestive of usual interstitial pneumonia. Note dilatation of the esophagus.

Table 2. Clinical features and pulmonary measures at diagnosis and DMARD need in 48 patients with anti-Jo1 antibodies.

Feature	Without DMARD, n (%)	With DMARD, n (%)	p
Overall	14 (100.0)	34 (100.0)	
Myositis			
Proximal muscle weakness	9 (64.3)	30 (88.2)	0.10
Severe weakness (MRC ≤ 3/5)	4 (28.6)	20 (58.8)	0.11
Muscle pain	8 (57.1)	26 (76.5)	0.29
Dysphagia	1 (7.1)	12 (35.3)	0.07
Interstitial lung disease			
Effort dyspnea	9 (64.3)	29 (85.3)	0.13
Severe dyspnea (NYHA ≥ 3)	3 (21.4)	16 (47.1)	0.12
Articular involvement			
Proximal arthralgia	9 (64.3)	26 (76.5)	0.48
Distal arthralgia	9 (64.3)	23 (67.7)	1.0
Severe arthritis	1 (7.1)	2 (5.9)	1.0
Raynaud's phenomenon	4 (28.6)	19 (55.9)	0.12
Severe Raynaud's	1 (7.1)	3 (8.8)	1.0
Mechanic's hands	0 (0.0)	10 (29.4)	0.02
General signs			
Fever	3 (21.4)	12 (35.3)	0.50
Fever > 38.5°C	1 (7.1)	2 (5.9)	1.0
Weight loss	0 (0.0)	6 (17.7)	0.16
Associated signs			
Sicca symptoms	7 (50.0)	11 (32.3)	0.33
Sicca syndrome (LSGB ≥ 3)	4 (28.6)	3 (10.0)	0.18
Scleroderma signs	3 (21.4)	12 (35.3)	0.50
Skin changes			
Palpebral edema	2 (12.3)	6 (17.7)	1.0
Periungual erythema	1 (7.1)	9 (26.5)	0.24
Cutaneous rash	3 (21.4)	10 (29.4)	0.73
Comorbidity			
Thyroid pathology	0 (0.0)	4 (11.8)	0.31
Associated autoimmune disease	6 (46.1)	8 (25.0)	0.29
Pulmonary measures			
HRCT scan, n = 38			
Cellular NSIP pattern	10 (35.7)	4 (40.0)	1.0
Fibrotic NSIP pattern	10 (35.7)	4 (40.0)	1.0
NSIP score*, n = 27	7 [5 to 9.5]	4 [3 to 5]	0.04
OP pattern	4 (14.3)	1 (10.0)	1.0
UIP pattern	1 (3.6)	0 (0.0)	1.0
Pulmonary function tests			
TLV, n = 41	83.5 (61–88)	60 (52–78)	0.08
RV, n = 40	78 (63–79)	62 (48–79)	0.11
FEV1, n = 39	83 (68.5–95.5)	62 (52–84)	0.17
FVC, n = 39	84.5 (67–91.5)	62 (55–78)	0.15
FEV1/FVC ratio, n = 40	103 (93–106)	100 (95–107)	0.95
DLCO, n = 38	64 (43–84)	47.5 (38–55)	0.09
VA, n = 37	71 (53.5–76.5)	56 (52–64)	0.18
DLCO/VA ratio, n = 38	92.5 (69.5–112.5)	78 (65–93)	0.25
PaO_2, n = 38	78.9 (73.2–84.5)	82.6 (72.0–89.5)	0.55

* NSIP score was evaluated on lung HRCT scan. OP: organizing pneumonia; UIP: usual interstitial pneumonia; LSGB: labial salivary gland biopsy; DMARD: disease-modifying antirheumatic drug; PFT: pulmonary function tests; TLV: total lung volume; RV: respiratory volume; VA: alveolar volume; FEV1/FVC: ratio of forced expiratory volume in 1 s to forced vital capacity; NSIP: nonspecific interstitial pneumonia; HRCT: high-resolution computed tomography; MRC: Medical Research Council; NYHA: New York Heart Association.

score was lower in the group of patients with no DMARD need [4 (IQR 3 to 5) vs 7 (IQR 5 to 9.5); p = 0.04], while a trend to decreased results of some pulmonary tests (TLV, RV, DLCO) in the group of patients with DMARD need was observed (Table 2). Further, during followup, 10 patients (21%) presented with muscle aggravation (worsening of mus-

cle weakness or myalgia with serum CK elevation) and 20 (44%) presented with pulmonary aggravation (worsening of radiologic score of ILD and/or of pulmonary function test results) requiring DMARD. Higher CK levels were predictive of muscle flair [median 7935 IU/l (IQR 5000 to 13,100) vs 3900 IU/l (IQR 1474 to 8900); p = 0.01]. Moreover, RP [13 (65%) vs 7 (28%); p = 0.02], NSIP score [7 (IQR 5 to 12) vs 5 (IQR 4 to 6); p = 0.05], and TLV values [57.5% (IQR 51 to 66) vs 70% (IQR 60 to 84); p = 0.02] were predictive of pulmonary aggravation.

DISCUSSION

This cohort of 48 patients who were anti-Jo1-positive and underwent longterm followup is one of the largest described to date[4,5,6,7,8,9,10], permitting us to outline predictive factors of prognosis (i.e., DMARD use). The incidence of other autoantibodies shows that anti-SSA, and notably Ro-52, are mostly found in association with anti-Jo1. The NSIP pattern was the most frequently observed in our cohort of patients, in accord with previous studies[10,11,12,13]. Nevertheless, Yousem, *et al*[14] reported a predominant frequency of the usual interstitial pneumonia pattern (on CT scan and pulmonary pathology) among 20 anti-Jo1-positive patients. Among our 48 patients, 29 had a second CT scan, with a mean followup period of 29 (range 4–79) months. A change in the initial pattern was observed in 12 patients, with notable progression to fibrotic disease in 4 (2 fibrotic NSIP, 2 usual interstitial pneumonia). Patients who had a pulmonary biopsy in the study from Yousem, *et al*[14] may be evaluated at a later stage of their disease.

Mechanic's hands, higher CK level, and NSIP score values are predictive of disease progression requiring DMARD. RP, lower TLV, and again, higher NSIP score values are also predictive of pulmonary progression requiring DMARD. It appears then that lung involvement is one of the most important predictive factors for chronic disease progression necessitating DMARD use. Presence of anti-SSA autoantibodies was associated with a significant decrease of TLV, RV, or DLCO, all measures that were also associated in our study with a need for DMARD when decreasing. In the literature, an association with anti-SSA antibodies predicts more severe ILD[6] and ILD progression is associated with acute onset[10].

Finally, corticosteroids, generally associated with other immunosuppressants, were used in the vast majority of our patients. No particular association can be recommended, since none appears to prevent use of DMARD. Because of the lack of evidence-based results in the literature, no further recommendations are available, notably for the treatment of ILD in anti-SS. Because of this very particular clinical presentation and prognosis, anti-SS should not be categorized as ordinary polymyositis or dermatomyositis in the design of future trials.

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