Clinical Spectrum Time Course in Anti Jo-1 Positive Antisynthetase Syndrome

Results From an International Retrospective Multicenter Study

Lorenzo Cavagna, MD, Longa Nuño, MD, Carlo Alberto Scirè, MD, Marcello Govoni, MD, Francisco Javier Lopez Longa, MD, Franco Franceschini, MD, Rossella Neri, MD, Santos Castañeda, MD, Walter Alberto Sifuentes Giraldo, MD, Roberto Caporalí, MD, Florenzo Iannone, MD, Enrico Fisaro, MD, Giuseppe Paolazzi, MD, Raffaele Pellerito, MD, Andreas Schwarting, MD, Lesyay Ann Saketkoo, MD, Norberto Ortego-Centeno, MD, Luca Quartiuccio, MD, Elena Bartoloni, MD, Christof Specker, MD, Trinitario Pina Murcia, MD, Renato La Corte, MD, Federica Furini, MD, Valentina Foschi, MD, Javier Bachiller Corral, MD, Paolo Aiò, MD, Ilaria Cavazzana, MD, Julia Martínez-Barro, MD, Michelle Hinojosa, MD, Margherita Giannini, MD, Simone Barsotti, MD, Julia Menke, MD, Kostantinos Triantafyllias, MD, Rosetta Vitetta, MD, Alessandra Russo, MD, Gianluigi Bajocchi, MD, Elena Bravi, MD, Giovanni Barausse, MD, Roberto Bortolotti, MD, Carlo Selmi, MD, Simone Parisi, MD, Carlmaurizio Montecucco, MD, and Miguel Angel González-Gay, MD, on Behalf of AENEAS (American-European NEtwork of Antisynthetase Syndrome) collaborative group.

Abstract: Anti Jo-1 antibodies are the main markers of the antisynthetase syndrome (ASSD), an autoimmune disease clinically characterized by the occurrence of arthritis, myositis, and interstitial lung disease (ILD). These manifestations usually co-occur (for practical purpose complete forms) in the same patient, but cases with only 1 of 2 of these findings (for practical purpose incomplete forms) have been described. In incomplete forms, the ex novo occurrence of further manifestations is possible, although with frequencies and timing not still defined. The aim of this international, multicenter, retrospective study was to characterize the clinical time course of anti Jo-1 positive ASSD in a large cohort of patients. Included patients should be anti Jo-1 positive and with at least 1 feature between arthritis, myositis, and ILD. We evaluated the differences between complete and incomplete forms, timing of clinical picture appearance and analyzed factors predicting the

Copyright 2015 Wolters Kluwer Health, Inc. All rights reserved.

DOI: 10.1097/MD.000000000001144

www.md-journal.com
appearance of further manifestations in incomplete ASSD. Finally, we collected 225 patients (58 males and 167 females) with a median follow-up of 80 months. At the onset, complete ASSD were 44 and incomplete 181. Patients with incomplete ASSD had frequently only 1 of the classic triad findings (110 cases), in particular, isolated arthritis in 54 cases, isolated myositis in 28 cases, and isolated ILD in 28 cases. At the end of follow-up, complete ASSD were 113, incomplete 112. Only 5 patients had an isolated arthritis, only 5 an isolated myositis, and 15 an isolated ILD. During the follow-up, 108 patients with incomplete forms developed further manifestations. Single main feature onset was the main risk factor for the ex novo appearance of further manifestation. ILD was the prevalent ex novo manifestation (74 cases). In conclusion, ASSD is a condition that should be carefully considered in all patients presenting with arthritis, myositis, and ILD, even when isolated. The ex novo appearance of further manifestations in patients with incomplete forms is common, thus indicating the need for an adequate clinical and instrumental follow-up. Furthermore, the study clearly suggested that in ASSD multidisciplinary approach involving Rheumatology, Neurology, Pneumology, and Internal Medicine specialists is mandatory.

(Medicine 94(32):e1144)

INTRODUCTION

Antisynthetase syndrome (ASSD) is a connective tissue disease characterized by the classic triad arthritis, myositis, and interstitial lung disease (ILD).1–3 Raynaud’s phenomenon, mechanic’s hands, and fever are other relevant but less prevalent clinical findings.1,4 The most frequent antisynthetase antibody is anti Jo-1, directed against the histidyl-tRNA synthetase, whereas other antisynthetase specificities (eg, anti-PL-7, PL-12, EJ, KS, OJ, YRS, Zo) are less frequently identified.2,5 The literature data have shown that the clinical phenotype of ASSD is generally associated with the underlying specificity of antisynthetase antibody: patients with anti Jo-1 antibodies had higher frequencies of myositis, polyarthritis, and ILD, whereas “isolated ILD” is typical of anti-PL7 and anti-PL12 antibodies.

However, the clinical presentation of anti Jo-1 ASSD varies greatly, with cases presenting without the classic triad.2,5–10 In these patients, the clinical picture may evolve during follow-up.6 Furthermore, ASSD is characterized by a large heterogeneity in the severity of clinical findings,5,11,12 in particular, for joint involvement, ranging from simple polyarthralgia,7 to a symmetrical polyarthritis,6 and that may be also particular, for joint involvement, ranging from simple polyarthritis,6 and that signed the informed consent as approved by the local Institutional Ethics Board. Type and characteristics of clinical features, outcomes, laboratory and instrumental investigations, at the onset and during follow-up, were retrospectively collected.

As previously described,7 ILD was defined instrumentally by a restrictive pulmonary function test pattern (Forced Vital Capacity (FVC) ≤ 80%, Forced Expiratory Volume in the first second (FEV1)/FVC ≥ 70%, decreased or normal FEV1, and/or <20% reduction in diffusion capacity of the lung for carbon monoxide), after excluding other causes different from ILD, and/or by signs of alveolitis/fibrosis on high-resolution computed tomography (HRCT).7 ILD presentation was defined as acute/subacute when dyspnoea began acutely and progressed rapidly (within 4–6 weeks from symptom onset), chronic when dyspnoea began insidiously and progressed slowly, and asymptomatic when lung involvement was only instrumental. Screening for ILD occurrence was regularly performed during follow-up.

Patients with muscle enzyme elevation (creatine phosphokinase and/or aldolase) and the presence of typical electrocardiography alterations and/or compatible muscle biopsy findings were considered as having muscle involvement. Myositis onset was defined as classic (muscle strength deficit) or hypomyopathic (instrumental/laboratory evidence of muscle impairment without strength deficit). Muscle enzymes were regularly assessed during follow-up.

Arthritis occurrence (joints swelling and tenderness required) and its presentation pattern (eg, symmetrical polyarthritis, oligoarticular/asymmetrical arthritis), fever, mechanic’s hands, and Raynaud’s phenomenon were assessed clinically.

Plain X-rays were performed to identify joint erosions.

The onset of ASSD was considered from the first pulmonary, muscular or joint symptom. Clinical features onset was considered concurrent in cases of <3 months of delay between manifestations’ presentation. For practical purposes, patients with arthritis, ILD, and myositis were defined as having a complete ASSD, whereas patients lacking at least one of these features were defined as having an incomplete form.

Autoantibody Profiling

Autoantibodies were considered positive after 2 tests confirmations and with at least 1 positivity obtained in the leading reference/tertiary center. In leading centers, anti Jo-1 positivity, other additional anti-extractable nuclear antigen specificities, IgM-RF and ACPA were tested by well-validated methods (Appendix 1).

Statistical Analysis

Descriptive data were reported as absolute and relative frequencies, mean and standard deviation, median, and interquartile range (IQR) based on the type of the variable distribution. Comparison between groups was firstly tested by the chi-squared test, t test, or Mann–Whitney test. The association between clinical and laboratory variables with disease progression were modeled using logistic regression models, both univariate and multivariate. Given the lack of knowledge on prespecified confounders, all the candidate variables tested in the univariate models were retained in the construction of the full, adjusted model. Standard diagnostic tests and goodness of fit were systematically assessed. The results are presented as odds ratios (OR) and 95% confidence intervals (95% CIs).

Analyses were performed using STATA software package (2009, release 11; StataCorp, College Station, TX).
We included in the study 225 patients (58 males and 167 females). Clinical characteristics, according to clinical phenotype presentation, have been summarized in Table 1 (at disease onset) and Table 2 (at the last follow-up).

### TABLE 1. Main Characteristics of Anti Jo-1 Patients at Disease Onset According to Presentation Pattern

| Patient Characteristics at the Onset | Complete Form Subset | Incomplete Form Subset | P       |
|-------------------------------------|----------------------|------------------------|---------|
| Number of patients, % of total      | 44 (19.5)            | 181 (80.5)             | –       |
| Age, yr (median, IQR)               | 53.5 (46.5–62.0)     | 53 (42–63)             | 0.41\(^*\) |
| Diagnostic delay, mo (median, IQR)  | 2.5 (2.0–10.5)       | 10 (2.0–28.5)          | 0.191\(^*\) |
| Males/females                       | 10/34                | 48/133                 | 0.75    |
| Arthritis, n (% of subset)          | 44 (100)             | 100 (55)               | –       |
| RA-like, n (% of arthritis)         | 32 (72)              | 65 (65)                | 0.47    |
| Arthritis IgM-RF positive/patients checked, % | 8/42 (19) | 36/97 (37)            | 0.057   |
| Arthritis ACPA positive/patients checked, % | 3/36 (8.5) | 12/73 (16.5)          | 0.39    |
| Myositis, n (% of subset)           | 44 (100)             | 81 (45)                | –       |
| Classic onset, n (% of myositis)    | 32 (73)              | 61 (75)                | 0.92    |
| Hypomyopathic onset, n (% myositis) | 12 (27)              | 20 (25)                | –       |
| Interstitial lung disease, n (% of subset) | 44 (100)      | 70 (38.5)              | –       |
| Acute/subacute onset, n (% of ILD)  | 17 (38.5)            | 29 (4.5)               | 0.90    |
| Chronic onset, n (% of ILD)         | 16 (36.5)            | 26 (37)                | –       |
| Asymptomatic onset, n (% of ILD)    | 11 (25)              | 15 (21.5)              | –       |
| Anti-Ro positive/patients checked, %| 29/41 (71)           | 89/178 (50)            | 0.026   |
| Fever/patients checked, %           | 14/43 (32.5)         | 43/179 (24)            | 0.34    |
| Raynaud’s phenomenon/patients checked, % | 9/42 (21.5)          | 33/175 (19)            | 0.87    |
|                                       | 12/42 (28.5)         | 40/179 (22.5)          | 0.51    |

ACPA = anti-cyclic citrullinate peptide antibodies; IgM-RF = IgM rheumatoid factor; ILD = interstitial lung disease; IQR = interquartile range; RA = rheumatoid arthritis.

\(^*\) Independent sample T test (if equal variances) or Welch test (if unequal variances). Others: Chi-squared test.

### RESULTS

We included in the study 225 patients (58 males and 167 females). Clinical characteristics, according to clinical phenotype presentation, have been summarized in Table 1 (at disease onset) and Table 2 (at the last follow-up).

### TABLE 2. Main Features of Anti Jo-1 Patients at Last Follow-Up Available According to the Presentation Pattern

| Patient Characteristics at Last Follow-Up | Complete Form Subset | Incomplete Form Subset | P       |
|------------------------------------------|----------------------|------------------------|---------|
| Number of patients, % of total           | 113 (50)             | 112 (50)               | –       |
| Age, yr (median, IQR)                    | 61 (53–72)           | 61 (50–72)             | 0.99\(^*\) |
| Disease follow-up, mo (median, IQR)      | 87 (50.3–167.5)      | 70.5 (36.0–134.5)      | 0.21\(^*\) |
| Males/females                            | 27/86                | 31/81                  | 0.62    |
| Arthritis, n (% of subset)               | 113 (100)            | 59 (52.5)              | –       |
| RA-like, n (% of arthritis)              | 79 (70)              | 34 (57.5)              | 0.149   |
| Arthritis IgM-RF positive/patients checked, % | 32/109 (29)          | 16/58 (27.5)           | 0.95    |
| Arthritis ACPA positive/patients checked, % | 11/82 (13.5)         | 5/45 (11)              | 0.92    |
| Myositis, n (% of subset)                | 113 (100)            | 64 (57)                | –       |
| Classic onset, n (% of myositis)         | 80 (71)              | 45 (70)                | 0.92    |
| Hypomyopathic onset, n (% myositis)      | 33 (29)              | 19 (30)                | –       |
| Interstitial lung disease, n (% of subset) | 113 (100)         | 76 (68)                | –       |
| Acute/subacute onset, n (% of ILD)       | 37 (33)              | 28 (37)                | 0.49    |
| Chronic onset, n (% of ILD)              | 45 (40)              | 30 (39.5)              | –       |
| Asymptomatic onset, n (% of ILD)         | 31 (27)              | 18 (22.5)              | –       |
| Fever/patients checked, %                | 43/112 (38)          | 35/110 (32)            | 0.38    |
| Raynaud’s phenomenon/patients checked, % | 36/111 (32.5)        | 31/109 (28.5)          | 0.62    |
|                                       | 50/112 (44.5)        | 32/110 (29)            | 0.024   |

ACPA = anti-cyclic citrullinate peptide antibodies; IgM-RF = IgM rheumatoid factor; ILD = interstitial lung disease; IQR = interquartile range; RA = rheumatoid arthritis.

\(^*\) Independent sample T test (if equal variances) or Welch test (if unequal variances) or Wilcoxon rank-sum test (if not normally distributed). Others: Chi-squared test.
Patients' Characteristics at the End of Follow-Up

Arthritis was observed in 172 patients (76.5%). It was polyarticular and symmetrical in the majority of cases (113, 66% of arthritis). The remaining patients (59, 34% of arthritis) had an oligoarticular/asymmetrical arthritis. IgM-RF was positive in 48/167 arthritis patients (29%), while ACPA in 16/127 (12.5%). Four of the 6 no-arthritis patients (67%) IgM-RF positive at baseline developed arthritis (1 oligoarticular/asymmetrical, 3 polyarticular symmetrical). The only nonarthritis ACPA positive patient at baseline, developed an oligoarticular/asymmetrical arthritis. We observed radiographic erosions in 36/167 patients (21.5%) with available plain radiographs; 27 patients (75%) had a symmetrical polyarthritis and 9 (25%) had an oligoarticular/asymmetrical arthritis (P = 0.085). IgM-RF was positive in 19 patients (53%) with erosive disease, and ACPA in 8/29 patients (27.5%). Both were statistically significantly associated with the occurrence of erosions (P < 0.001 and P = 0.009, respectively). Myositis was disclosed in 177 cases (79%). The presentation pattern was mainly classic (125 patients, 71% of myositis). ILD was observed in 189 patients (84%). The pattern of presentation was acute/subacute in 65 cases (34% of ILD), chronic in 75 (40%), and asymptomatic in 49 (26%).

The prevalence of patients presenting with arthritis, myositis, and ILD according to follow-up duration is shown in Figure 1. Fever was observed in 78/222 cases (35%), mechanic’s hands in 67/220 (30%), and Raynaud’s phenomenon in 82/222 (37%).

With respect to disease onset, 107 of 181 (59%) patients with incomplete forms developed further manifestations within a median time of 12 months (IQR 6–40.8). Feature progression was observed in 85 patients with 1 manifestation onset (77% of this subset) and in 22 patients with 2 manifestations onset (31% of this subset). In 19 patients with 1 feature onset, clinical progression occurred in 2 different stages, the first in median at 12 months after disease onset (IQR 4.5–23.5 months) and the second at 24 months (IQR 11.25–67.5) after the first progression. Complete and incomplete forms were equally distributed (113 and 112 cases, respectively). The subsequent progression from incomplete to complete form was observed in 69 cases and the prevalence of complete forms regularly and steadily increased with the length of follow-up (Figure 2): 47 patients (43%) had 1 manifestation onset and 22 patients (31%) 2 manifestations onset (P = 0.150). Patients with persistent incomplete form had only arthritis (5 cases, 4.5% of subset), only ILD (15, 13%), only myositis (5, 4.5%), arthritis and myositis (28, 23%), arthritis and ILD (28, 25%), and ILD and myositis (33, 30%). An ex novo ILD was observed in 74 cases, representing 67% of the patients without ILD at baseline. Forty-three of 54 patients (80% of subset) with isolated arthritis at the onset developed ILD, thus representing more than 50% of ex novo ILD.

The median disease duration was 82 months (IQR 40–147), which was not statistically different between complete and incomplete forms (P = 0.21). In the 41 patients (18%) lost to
follow-up, the median follow-up duration was 51 months (IQR 24–95); 88.5 months (IQR 43–153) in the 148 patients still on follow-up; and 96 months (IQR 59–179) in the 36 patients who lost to follow-up; and 96 months (IQR, 43–153) in the 148 patients still on follow-up, the median follow-up duration was 51 months (IQR 51–167) in the 148 patients still on follow-up; and 96 months (IQR 59–179) in the 36 patients who lost to follow-up, the length of follow-up can be different).

**TABLE 3.** Analysis of Disease Characteristics Associated With Manifestation Progression in Patients With Incomplete ASSD

| Incomplete ASSD |  |
|-----------------|--|
| **Progression (N = 107)** | **No Progression (N = 74)** | **Univariate Analysis, OR (95% CI)** | **Multivariate Analysis, OR (95% CI)** |
| Age at onset (median in yr; IQR) | 53 (42–63) | 52.5 (42–64) | 0.99 (0.97, 1.01) | 1.00 (0.97, 1.03) |
| Disease duration (median in mo; IQR) | 89 (56–167) | 65 (30–122) | 1.00 (1.00, 1.01) | 1.00 (0.99, 1.01) |
| Male gender, % | 26 (54) | 22 (45) | 0.75 (0.38, 1.47) | 1.06 (0.46, 2.40) |
| Anti-Ro+/patients checked, % | 55/106 (52) | 34/72 (47) | 1.20 (0.66, 2.19) | 1.32 (0.65, 2.71) |
| Patients with 1 manifestation onset, % | 85/107 (79.5) | 25/74 (34) | 7.57 (3.86, 14.83) | 7.81 (3.74, 16.30) |
| Patients with 2 manifestations onset, % | 22/107 (20.5) | 49/74 (66) | Reference | Reference |
| Patients with fever at onset, % | 21/107 (20) | 22/72 (30.5) | 0.55 (0.27, 1.10) | 0.71 (0.30, 1.67) |
| Patients with Raynaud’s phenomenon at onset, % | 24/107 (22.5) | 16/72 (22) | 1.01 (0.49, 2.07) | 1.00 (0.42, 2.36) |
| Patients with mechanic’s hands at onset, % | 22/104 (21) | 11/71 (15.5) | 1.46 (0.66, 3.24) | 1.92 (0.74, 4.95) |

ASSD = antisynthetase syndrome; CI = confidence interval; IQR = interquartile range; OR = odds ratio.

We confirmed\(^5\) that anti-Jo-1 ASSD is more common in women, with a female-to-male ratio of 2:3. Unlike Hervier et al.,\(^2\) who reported polyarthritis as the main form of joint manifestation, in our series, peripheral polyarthritis was the most common type of joint involvement. Besides having an RA-like pattern in the majority of cases, IgM-RF and ACPA were frequently positive. The positivity of IgM-RF and ACPA was associated with the occurrence of typical RA erosions, confirming previous observations from other series of anti-Jo-1 ASSD patients\(^13,14,123\) and in other connective tissue diseases.\(^16,17\) This finding is of great relevance because arthritis is frequently the only classic triad finding at disease onset,\(^6\) and, because of that, some patients may be misclassified as having RA. Furthermore, we observed that the rate of clinical picture progression in patients presenting only with arthritis is as high as 90% of cases. According to our results, we could speculate that some cases of anti-TNF-alpha-induced anti-Jo-1 positive polymyositis reported in the setting of RA, may be more related to the natural history of the disease rather than to anti-TNF-
alpha agents. This statement is strengthened by the ab initio presence of anti Jo-1 antibodies in some of these cases.24–26

Muscle involvement was mainly symptomatic, as well as ILD, but asymptomatic cases are not uncommon. Strengthening previous suggestions,27 our data indicate that anti Jo-1 antibody search should not be restricted to patients with myositis but also performed in cases of isolated ILD or isolated peripheral arthritis, even though RA is more likely than any other potential entity. In fact, the identification of anti Jo-1 is relevant because of its diagnostic and clinical value. This strategy is mandatory because the risk of clinical picture progression is high in incomplete forms, in particular in patients presenting with 1 manifestation. The delay between the appearances of different manifestations is very long, ranging from a few months to a several years and this is also possible in 2 different stages. ILD was the most frequent new finding observed, and 68% of incomplete forms without ILD at baseline developed ILD during follow-up. Interestingly, 50% of patients who developed ILD during follow-up had only arthritis at disease onset, thus re-strengthening the need for an adequate differential diagnosis and subsequent ILD screening in arthritis patients. We confirmed that anti-Ro positivity is frequent in anti Jo positive patients,28 showing that it was mainly associated with a complete onset.

The overall survival was good, thus indicating a substantial good prognosis, independently to the occurrence of established negative risk factors such as ILD.2,29,30 However, the 18% of patients were lost to follow-up and we cannot be certain of their final outcome. Pulmonary hypertension prevalence was not substantially different from that previously reported in another large series,31 and it was equally observed in both complete and incomplete forms.

We are aware of the potential limitations of this study. The main criticism is that we included patients diagnosed in rheumatology units, with a subsequent risk of selection bias, as the high percentage of onset manifestations of this syndrome suggested. Nevertheless, we also observed a high number of patients presenting with only ILD or only myositis. These findings seem to refute a potential selection bias. Another potential limitation is the retrospective nature of our study, thus with an increased risk of incompleteness.32,33 Furthermore, we cannot exclude a possible delay in the diagnosis of asymptomatic ILD and the temporal timing of 3 months to define contemporary the onset of different manifestations is arbitrary. Finally, although proposed,30 so far there are no approved classification criteria for ASSD, although this point should be considered as a commonly shared selection bias in all studies up to now published.

In order to reduce the risk of false positive tests and the subsequent selection bias, we required double test positivity not only for anti Jo-1 but also for Ig-M RF, ACPA, and anti-Ro.

Even though experimental models are available,34,35 incomplete anti Jo-1 positive ASSD are a perfect model for pathogenic studies in humans, in particular for ILD. In fact, no other autoimmune diseases have such a high trend toward the occurrence of established negative risk factors such as ILD.29,30 However, the 18% of patients were lost to follow-up and we cannot be certain of their final outcome. Pulmonary hypertension prevalence was not substantially different from that previously reported in another large series,31 and it was equally observed in both complete and incomplete forms.

In conclusion, our study suggests that anti Jo-1 antibodies positivity in these patients is relevant because it may be a predictor of the ex novo occurrence of further manifestations during follow-up.

REFERENCES

1. Imbert-Masseau A, Hamidou M, Agard C, et al. Antisynthetase syndrome. Joint Bone Spine. 2003;70:161–168.
2. Chatterjee S, Prayson R, Farver C. Antisynthetase syndrome: not just an inflammatory myopathy. Cleve Clin J Med. 2013;80:655–666.
3. Dugar M, Cox S, Limaye V, et al. Clinical heterogeneity and prognostic features of South Australian patients with anti-synthetase autoantibodies. Intern Med J. 2011;41:674–679.
4. Lega JC, Fabien N, Reynaud Q, et al. The clinical phenotype associated with myositis-specific and associated autoantibodies: a meta-analysis revisiting the so-called antisynthetase syndrome. Autoimmun Rev. 2014;13:883–891[PMID: 24704867].
5. Hervier B, Devilliers H, Stanciu R, et al. Hierarchical cluster and survival analyses of antisynthetase syndrome: phenotype and outcome are correlated with anti-tRNA synthetase antibody specificity. Autoimmun Rev. 2012;11:210–217.
6. Lefevre G, Meyer A, Lanay D, et al. Seronegative polymyositis revealing antisynthetase syndrome: a multicentre study of 40 patients. Rheumatology (Oxf). 2015;54:927–932.
7. Cavagna L, Caporalì R, Abdir-Ali L, et al. Cyclosporine in anti-Jo1-positive patients with corticosteroid-refractory interstitial lung disease. J Rheumatol. 2013;40:484–492.
8. Yang CJ, Sheu CC, Ou TT, et al. Combined lung fibrosis and ‘mechanic’s hand’: a clinical diagnostic clue to amyopathic antisynthetase syndrome. Respiratory. 2008;13:611–614.
9. Plastiras SC, Soliotis FC, Vlahoyiannopoulos P, et al. Interstitial lung disease in a patient with antisynthetase syndrome and no myositis. Clin Rheumatol. 2007;26:108–111.
10. Watanabe K, Handa T, Tanizawa K, et al. Detection of antisynthetase syndrome in patients with idiopathic interstitial pneumonias. Respir Med. 2011;105:1238–1247.
11. Yoshifuji H, Fujii T, Kobayashi S, et al. Anti-aminocyl-tRNA synthetase antibodies in clinical course prediction of interstitial lung disease complicated with idiopathic inflammatory myopathies. Autoimmunity. 2006;39:233–241.
12. Hamaguchi Y, Fujimoto M, Matsushita T, et al. Common and distinct clinical features in adult patients with anti-aminocyl-tRNA synthetase antibodies: heterogeneity within the syndrome. PLoS ONE. 2013;8:e60442.
13. Cavagna L, Fusetti C, Montecucco C, et al. Anticyclic citrullinated peptide antibodies as markers of erosive arthritis in antisynthetase syndrome. J Rheumatol. 2010;37:1967author reply 1968.
14. Kaneko Y, Hanakoa H, Hirakata M, et al. Distinct arthropathies of the hands in patients with anti-aminocyl tRNA synthetase antibodies: usefulness of autoantibody profiles in classifying patients. Rheumatology (Oxf). 2014;53:1120–1124.
15. Cavagna L, Monti S, Grosso V, et al. The multifaceted aspects of interstitial lung disease in rheumatoid arthritis. Biomed Res Int. 2013;2013:759–760.
16. Chan MT, Owen P, Dunphy J, et al. Associations of erosive arthritis with anti-cyclic citrullinated peptide antibodies and MHC class II alleles in systemic lupus erythematosus. J Rheumatol. 2008;35:77–83.
17. Ingegnoli F, Galbiati V, Zeni S, et al. Use of antibodies recognizing cyclic citrullinated peptide in the differential diagnosis of joint involvement in systemic sclerosis. Clin Rheumatol. 2007;26:510–514.
18. Wasicek CA, Reichlin M, Montes M, et al. Polymyositis and interstitial lung disease in a patient with anti-Jo1 prototype. Am J Med. 1984;76:538–544.
19. Hervier B, Benveniste O. Clinical heterogeneity and outcomes of antisynthetase syndrome. *Curr Rheumatol Rep.* 2013;15:349.

20. Cavagna L, Prisco E, Montecucco C, et al. Pulmonary arterial hypertension in antisynthetase syndrome: comment on the article by Chatterjee and Farver. *Arthritis Care Res (Hoboken).* 2011;63:633–664 author reply 634.

21. Chatterjee S, Farver C. Severe pulmonary hypertension in anti-Jo-1 syndrome. *Arthritis Care Res (Hoboken).* 2010;62:425–429.

22. Marie I, Josse S, Hatron PY, et al. Interstitial lung disease in anti-Jo-1 patients with antisynthetase syndrome. *Arthritis Care Res (Hoboken).* 2013;65:800–808.

23. Meyer A, Lefevre G, Bierry G, et al. In antisynthetase syndrome, ACPA are associated with severe and erosive arthritis: an overlapping rheumatoid arthritis and antisynthetase syndrome. *Medicine (Baltimore).* 2015;94:e523.

24. Ishikawa Y, Yukawa N, Ohmura K, et al. Etanercept-induced anti-Jo-1-antibody-positive polymyositis in a patient with rheumatoid arthritis: a case report and review of the literature. *Clin Rheumatol.* 2010;29:563–566.

25. Musial J, Undas A, Celinska-Lowenhoff M. Polymyositis associated with infliximab treatment for rheumatoid arthritis. *Rheumatology (Oxf).* 2003;42:1566–1568 [PMID: 14645861].

26. Urata Y, Wakai Y, Kowatari K, et al. Polymyositis associated with infliximab treatment for rheumatoid arthritis. *Mod Rheumatol.* 2006;16:410–411.

27. Ghirardello A, Zampieri S, Tarricone E, et al. Clinical implications of autoantibody screening in patients with autoimmune myositis. *Autoimmunity.* 2006;39:217–221.

28. Marie I, Hatron PY, Dominique S, et al. Short-term and long-term outcome of anti-Jo1-positive patients with anti-Ro52 antibody. *Semin Arthritis Rheum.* 2012;41:890–899.

29. Marie I, Josse S, Decaux O, et al. Comparison of long-term outcome between anti-Jo1- and anti-PL7/PL12 positive patients with antisynthetase syndrome. *Autoimmun Rev.* 2012;11:739–745.

30. Johnson C, Connors GR, Oaks J, et al. Clinical and pathologic differences in interstitial lung disease based on antisynthetase antibody type. *Respir Med.* 2014;108:1542–1548.

31. Hervier B, Meyer A, Dieval C, et al. Pulmonary hypertension in antisynthetase syndrome: prevalence, aetiology and survival. *Eur Respir J.* 2013;42:1271–1282.

32. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emerg Med J.* 2003;20:54–60.

33. Song JWCK. Observational studies: cohort and case-control studies. *Plast Reconstr Surg.* 2010;126:2234–2242.

34. Ascherman D. Animal models of inflammatory myopathy. *Curr Rheumatol Rep.* 2012;14:257–263.

35. Sciorati C, Esposito A, Campana L, et al. 7-Tesla magnetic resonance imaging precisely and noninvasively reflects inflammation and remodeling of the skeletal muscle in a mouse model of antisynthetase syndrome. *Biomed Res Int.* 2014;2014:879703.