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

Results From an International Retrospective Multicenter Study

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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 or 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

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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.

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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[5]: 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 polyarthralgias,[5] to a symmetrical polyarthritis,[6] and that may be also seropositive,[13,14] for both Ig-M rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA).

Despite these sparse data, no previous studies have specifically analyzed the presentation pattern of the disease and its variations over time, leaving the disease course of ASSD poorly understood. For this reason, we set up this multicenter international retrospective study including anti Jo-1 positive ASSD to assess the disease course and outcomes of these patients. Our hypothesis is that anti Jo 1 positive patients frequently presented with an incomplete ASSD and that the ex novo occurrence of further manifestations in this setting is really common.

METHODS

Patients

Twenty-four rheumatology centers from Italy, Spain, Germany, and the USA were involved in the study. We included patients with at least 2 anti Jo-1 positive tests, with 1 or more findings between arthritis, myositis, and ILD, 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) $\leq$ 80%, Forced Expiratory Volume in the first second (FEV1)/FVC $\geq$ 70%, decreased or normal FEV1, and/or $<$20% reduction in diffusing 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 (creatinine phosphokinase and/or aldolase) and the presence of typical electromyography 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).

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 (41.5)	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
Mechanic's hands/patients checked, %	9/42 (21.5)	33/175 (19)	0.87
Raynaud's phenomenon/patients checked, %	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).

Patients' Characteristics at Disease Onset

Arthritis was observed in 144 patients (64.5%). It was polyarticular and symmetrical in the majority of cases (97, 67% of arthritis). The remaining patients (47, 33%) had an oligoarticular/asymmetrical arthritis. RF-IgM was positive in 44/139

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 (23.5)	
Anti-Ro positive/patients checked, %	62/109 (57)	56/110 (51)	0.45
Fever/patients checked, %	43/112 (38)	35/110 (32)	0.38
Mechanic's hands/patients checked, %	36/111 (32.5)	31/109 (28.5)	0.62
Raynaud's phenomenon/patients checked, %	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.

arthritis patients (31.5%), while ACPA in 15/109 (13.5%). RF-Ig M was tested in 74 patients without arthritis (91% of subset) and was positive in 6 cases (8% of assessed patients), ACPA in 60 patients (74% of subset) and were positive in 1 case (1.5% of assessed patients).

Myositis was evidenced in 125 (55.5%) cases and its presentation was mainly classic (93 patients, 74.5% of cases). One hundred fourteen patients (51%) had ILD. Presentation was acute/subacute in 46 cases (40% of ILD), chronic in 42 (37% of ILD), and asymptomatic in 26 (23%). Anti-Ro antibodies were positive in 118/219 patients (54%). Fever was observed in 57/222 cases (25.5%), mechanic's hands in 42/217 (19.5%), and Raynaud's phenomenon in 52/221 (23.5%). Raynaud's phenomenon preceded other manifestations in 9 cases (17%, median 13 months, IQR 12–48).

Only 44 patients (19.5%) had a complete ASSD. One hundred ten patients (49%) had only 1 onset finding: arthritis in 54 cases (49% of subset), ILD and myositis in 28, respectively, (25.5%). The remaining 71 patients (31.5% of total) with incomplete forms had: arthritis and myositis (28 cases, 39.5% of this subset); arthritis and ILD (18, 25%); ILD and myositis (25, 35.5%). The median diagnostic delay of anti Jo-1 positive ASSD was 6 months (IQR 2–21), without statistically significant differences between complete and incomplete forms ($P = 0.191$). The median age at disease onset was 53 years (IQR 43–63). We did not observe statistically significant differences in age at disease onset between complete and incomplete forms ($P = 0.41$). By comparing remaining characteristics, the only statistically significant difference we observed was that anti-Ro positivity was more frequent in complete than in incomplete forms ($P = 0.026$). See text in Supplementary File for first line treatments.

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%) Ig-M 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

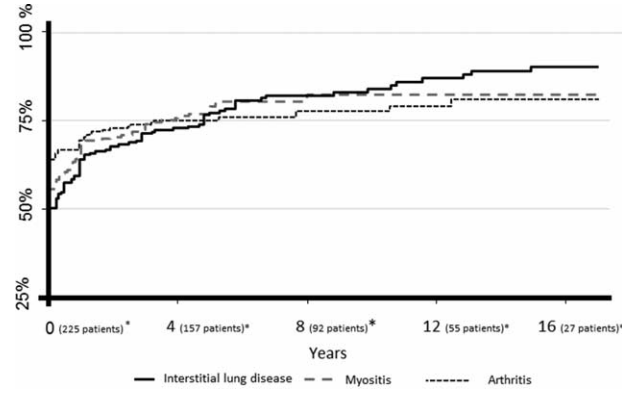

FIGURE 1. Over time prevalence of patients with arthritis, myositis, and Interstitial lung disease. ∗Patients on follow-up.

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 (26, 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

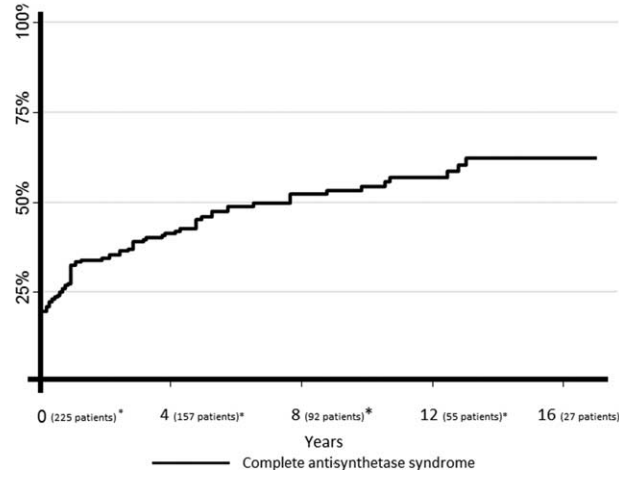

FIGURE 2. Over time prevalence of patients with a complete antisynthetase syndrome (arthritis, myositis, and interstitial lung disease). ∗Patients on follow-up.

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.
* 174/181 patients with complete data.

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 had died. None of the patients lost to follow-up had a complete form at disease onset. Subsequently, 9 of these patients (22%) developed a complete ASSD and other 6 (15%) progressed but not to a complete form. In patients lost to follow-up, the length of follow-up and the rate of ex novo manifestations appearance were statistically reduced with respect to other patients ($P = 0.002$ in both cases).

Death was disease related in 9 cases (25 % of subset), not disease related in 17 (49%), and not specified in 10 (26%). After Doppler echocardiography screening, pulmonary hypertension was diagnosed by Right Heart Catheterization in 20 patients (9% of total); in 10 with complete and 10 with incomplete form and it was the cause of death in 4 cases.

At the end of follow-up, Raynaud's phenomenon was more commonly observed in incomplete than in complete ASSD ($P = 0.024$). For overall prescribed treatments and risk of withdrawal for side effects/progression on therapy see Figure S1.

Factors Associated With Pattern Disease Progression

The clustering of factors potentially associated with a pattern progression and the results of univariate and multivariate analyses are shown in Table 3. In both cases, the onset as 1 manifestation was the main risk factor for the subsequent progression of the clinical pattern.

CONCLUSIONS

To the best of our knowledge, here we described the largest cohort of anti Jo-1 positive ASSD ever collected. This cohort also has one of the largest follow-ups ever reported. This is the first study specifically focused on the course of ASSD clinical pattern. According to our findings, the course of anti Jo-1 positive ASSD is very variable, in most cases presenting as an incomplete form, and in particular with a single feature including arthritis, myositis, or ILD. Patients with incomplete forms often develop subsequent manifestations, particularly ILD, all along the follow-up period (Figure 1) and the frequency of complete forms increases from 19.5% to 50% of cases. Progression seems particularly relevant in patients presenting with a single feature and it may occur even in 2 different stages. The delay between the development of different manifestations ranges from a few months to a several years. Differential diagnosis may be challenging,[15] in particular in patients with arthritis, because presentation pattern is often like rheumatoid arthritis (RA), with the possible positivity of IgM-RF and ACPA. Furthermore, IgM-RF and ACPA are associated with the occurrence of joint erosions, as previously described in other connective tissue diseases.[16,17] According to our results, we think that the anti Jo-1 should be tested not only in patients with myositis and ILD but also in subjects with peripheral arthritis, even though a diagnosis of RA is more likely. Furthermore, periodic screening for the occurrence of further manifestations and for ILD in particular is mandatory in incomplete forms.

From the first description in 1976,[18] the complexity and extension of the clinical phenotype in anti Jo-1 positive ASSD has increased gradually.[2,5,19–21] Although included in the family of myositis, the prevalence of ILD and arthritis is not particularly different from that of myositis, and ILD is the main prognostic factor in this setting.[19,22] On this basis, in keeping with Chatterjee et al,[2] we think that ASSD is a really complex entity within the context of different rheumatic conditions.

We confirmed[19] that anti Jo-1 ASSD is more common in women, with a female-to-male ratio of 2:3. Unlike Hervier et al,[5] who reported polyarthralgia 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[13,14,23] 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.[5,29,30] 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 progression of clinical spectrum. However, taking into account the frequency of this syndrome, the variability of clinical presentation and timing of evolution, the networking of a large number of centers and of different specialists such as Rheumatology, Pneumology, Neurology, and Internal Medicine seems to be the only way available to us to fully understand the mechanisms underlying ASSD.

In conclusion, our study suggests that anti Jo-1 antibodies positivity should be ruled out in all patients presenting with isolated myositis, ILD, and arthritis, even though other diagnoses are possible. The clinical implication of anti Jo-1 positivity in these patients is relevant because it may be a predictor of the ex novo occurrence of further manifestations during follow-up.

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