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ORIGINAL ARTICLES

Clinical characterisation of a multicentre nationwide cohort of patients with antisynthetase syndrome

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ABSTRACT

Background: Antisynthetase syndrome (ASyS) is characterised by the association of inflammatory myopathy, interstitial lung disease (ILD), arthritis, Raynaud's phenomenon (RP) or mechanic's hands (MH), with the presence of anti-aminoacyl-tRNA-synthetase antibodies (anti-ARS). It has been suggested that different anti-ARS may be associated with distinct clinical pictures.

Objective: To characterise the clinical and immunological features of a multicentric nationwide cohort of ASyS patients.

Methods: This is a multicentre retrospective cohort study including patients with ASyS from nine Portuguese rheumatology centres. Data on patients' demographics, signs and symptoms, laboratory results, pulmonary imaging findings and treatment with immunomodulators were collected. Comparison between patients with different anti-ARS antibodies was made using the Chi-square test for categorical variables and Student's t-test or Man-Whitney test for continuous variables, considering anti-Jo1 positive patients as the reference group.

Results: Seventy patients were included (70% female) with a median age in years at disease onset of 52 (15-75) years and median follow-up time of 3 years (range 0-32). The three most common clinical manifestations were ILD (n=53, 75.7%), followed by arthritis (n=43, 61.4%) and myositis (n=37, 52.9%). Forty-three patients were positive for anti-Jo1 (61.4%), 11 for anti-PL12 (15.7%), 10 for anti-PL7 (14.3%), 4 for anti-EJ (5.7%), and 2 for anti-OJ (2.9%) antibodies. Antibody co-positivity with anti-Ro52 antibodies was found in 15 patients (21.4%) and was more prevalent in anti-Jo1 patients. ILD prevalence was similar in the different anti-ARS subgroups, without statistically significant differences. Patients positive for anti-PL7 antibodies had significantly lower risk of presenting arthritis (p=<0.05) and those positive for anti-PL-12 antibodies had a significantly lower risk of presenting myositis than the reference group of anti-Jo1 positive patients (p=<0.05). RP was more frequently found in patients positive for anti-PL-12 than in anti-Jo1-positive patients (p=<0.05). Malignancies were reported in four (5.7%) patients, none of whom were anti-Ro52-positive, and one of such patients had a double malignancy. Only three deaths were reported. Corticosteroids were the most frequently prescribed therapy and the use of immunosuppressive drugs was decided according to the type of predominant clinical manifestation.

Conclusion: The three most common clinical manifestations were ILD, followed by arthritis and myositis. Patients positive for anti-PL7 antibodies had significantly lower risk of presenting arthritis and those positive for anti-PL-12 antibodies had a significantly lower risk of presenting myositis than the reference group of anti-Jo1 positive patients. RP was more frequently found in patients positive for anti-PL-12 than in anti-Jo1-positive patients. Corticosteroids were the most frequently prescribed therapy. These results are generally concordant with data retrieved from international cohorts.

Keywords: Antisynthetase syndrome; Anti-aminoacyl RNA-synthetase antibodies; Inflammatory myopathy; Interstitial lung disease; Arthritis; Mechanic's hands; Raynaud phenomenon.

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INTRODUCTION

Antisynthetase syndrome (ASyS) is characterised by the association of inflammatory myopathy, interstitial lung disease (ILD), arthritis, Raynaud's phenomenon (RP) or mechanic's hands (MH) with the presence of anti-aminoacyl-tRNA-synthetase antibodies (anti-ARS)[1-3]. Additionally, the manifestation of other symptoms frequently associated with rheumatoid arthritis, Sjögren's syndrome and systemic sclerosis are also common[2,3]. This clinical heterogeneity can make ASyS hard to diagnose if not readily considered.

Several anti-ARS have been described, with anti-histidyl tRNA synthetase antibody (anti-Jo1) being the most common. However, other anti-ARS including anti-alanyl (PL12), anti-threonyl (PL7), anti-isoleucyl (OJ), and anti-glycyl (EJ) tRNA-synthetase antibodies are now also routinely identified[4,5]. Of note, the specific anti-ARS and the co-positivity with anti-Ro52 have been proposed as major prognostic indicators, predicting the manifestations and the severity of ASyS. It has been suggested that patients expressing anti-Jo1 antibodies are more likely to have inflammatory muscle involvement, whereas patients positive for anti-PL7 and anti-PL12 antibodies are more likely to have ILD and gastrointestinal complications. In addition, anti-Ro52 has been associated with higher cancer risk and more severe muscle and joint involvement[6-7].

Previous studies have been developed to evaluate ASyS characteristics according to specific immunological profiles, including the clinical features associated with each anti-ARS, the evolution of disease manifestations over time and the survival rates. Two large cohort studies[8,9] compared the clinical features of patients positive for anti-Jo1 antibodies with patients expressing other anti-ARS, finding evidence that non-anti-Jo1 patients, particularly anti-PL7 and anti-PL12, were more likely to have isolated lung involvement and increased mortality. Moreover, two large multicentric cohort studies described the natural history of anti-Jo1-positive ASyS[10,11], clarifying the dynamic nature of ASyS manifestations over time, its clinical heterogeneity and the tendency of ASyS-associated ILD to the chronicity.

This paper aims to characterise the clinical and immunological features of a multicentric cohort of Portuguese patients positive for different ASyS autoantibodies. As primary objective, this work aims to describe the clinical and immunologic features of Portuguese patients diagnosed with ASyS. Additionally, we aimed to explore if different anti-ARS were associated with particular disease features.

METHODS

Study design

A retrospective multicenter cohort study was performed, including patients diagnosed with ASyS, followed in nine Portuguese rheumatology departments across the country, up to September 2020. Patients were classified as ASyS if they met Solomon or Connors criteria[12,13]. Clinical information was collected retrospectively for all patients with anti-ARS antibodies by reviewing their clinical charts, with the information subsequently exported in an anonymised form to be evaluated. To exclude false-positive patients, we only included patients who met the following inclusion criteria: 1) at least two consecutive positive tests for anti-ARS using the same method; 2) clinical presentation compatible with ASyS, including ILD, muscle or joint involvements. There were no exclusion criteria. This study was conducted according to the principles of the Declaration of Helsinki (revised in Fortaleza – 2013) and after approval from the Ethics Committee of Centro Académico de Medicina de Lisboa.

Variables collected

Data on demographic characteristics (gender, age), disease duration, follow-up time, patients' signs and symptoms, laboratory results, radiological findings (chest computed tomography), pulmonary function tests and treatment with immunomodulators were collected.

Disease Manifestation's

ILD was assumed in patients with a restrictive pattern in pulmonary function tests (PFTs), [i.e., forced vital capacity (FVC) ≤ 80% with forced expiratory volume in the first second/forced vital capacity (FEV1/FVC) ≥ 70%], a reduction in the diffusing capacity of the lungs for carbon monoxide (DLCO) < 80%, or the identification of consolidation, ground glass or reticular pattern on chest high-resolution computed tomography (HRCT). PFTs were routinely performed at baseline as a quick and non-invasive screening method of lung involvement in patients with early connective tissue disease. Chest HRCT was performed at ASyS diagnosis and in the case of respiratory symptoms (cough or dyspnea) or) abnormal PFTsincluding DLCO impairment. ILD presentation was defined as acute/subacute when dyspnea began acutely and progressed rapidly (four to six weeks from symptom onset), chronic when dyspnea began insidiously and progressed slowly, and asymptomatic when lung involvement was not clinically evident.

Muscle involvement was defined by a decreased score on Manual Muscle Testing (MMT), high serum muscle enzymes (serum creatinine phosphokinase or aldolase level), typical myopathic electromyographic changes, muscle biopsy and/ or muscle magnetic resonance with myopathic pattern. Myositis was defined as classic (with a proximal muscle strength deficit) or

hypomyopathic (normal muscle strength). Arthritis was defined by clinically evident joint(s) swelling and tenderness. Accompanying clinical findings like fever, mechanic hands and RP were also collected.

Statistical Analysis

Continuous variables with normal distributions were reported as means and standard deviations. If continuous variables had skewed distributions, the medians and interquartile ranges were reported. Categorical variables were presented as frequencies and percentages. Data referring to baseline clinical and immunologic features, comorbidities and treatments used are presented both for the whole cohort and according to the immunological profile. Comparison between patients with different anti-ARS antibodies was made using the Chi-square test for categorical variables and Student's t-test or Man-Whitney test for continuous variables, considering anti-Jo1 positive patients as the reference group, since they are the group with the best defined clinical course. Statistical analysis was performed using SPSS software (IBM, version 24, Armonk, NY, USA). All calculations were made based on observed data. The threshold for statistical significance was a p-value inferior to 0.05.

RESULTS

In total, we included 70 patients from nine Portuguese centres. The median age in years at disease onset was 52 (15-75) years. The female gender was predominant, accounting for 70% of patients (n=49). Overall, there was a median delay in diagnosis of 6.0 (interquartile range, (IQR 1-23) years and a median follow-up time of 3.0 (IQR 0-32) years. The clinical and immunological features of these patients are shown in Table 1. In brief, the three more common clinical manifestations were ILD (n=53, 75.7%), with the nonspecific interstitial pneumonia (NSIP) pattern counting for approximately half of the cases (56.6%), followed by arthritis (n=43, 61.4%) and myositis (n=37, 52.9%). Forty-three patients were positive for anti-Jo1 (61.4%), 11 for anti-PL12 (15.7%), 10 for anti-PL7 (14.3%), 4 for anti-EJ (5.7%), and 2 for anti-OJ (2.9%) antibodies.

Disease manifestations according to different anti-ARS positivities

Anti-Jo1 antibodies (n=43)

From the 43 patients positive for anti-Jo1 antibodies the most frequent clinical finding was ILD (N=34/43, 79.1%), with the NSIP pattern accounting for the majority of the cases (N=19/34, 55.9%). Arthritis was the second most common triad finding (N=33/43, 76.7%), being mainly polyarticular and symmetrical (N=24/33, 72.7%), followed by myositis (N=26/43, 60.5%). Anti-Ro52 co-positivity was detected in 13 patients. Two patients (4.7%) died: in one patient, death was caused by a respiratory infection in the context of ILD. (Table 1). The cause of death of the other patient is unknown. Malignancy was noted in three patients (7.0%): two cases of colon cancer and one case of lung cancer.

Anti-PL12 antibodies (n=11)

ILD was the most common triad finding (N=8/11, 72.7%), followed by arthritis (N=5/11, 45.4%) and myositis (N=3/11, 27.3%), which occurred with significantly less frequency as compared to anti-Jo1 positive patients (p=0.02). Accompanying findings included RP (N=7/11, 63.6%), which was significantly more common than in the Jo1 group (p=0.04), and also MHs (N=3/11, 27.3%), and fever (N=2/11, 20.2%). (Table 1) One death was reported in this group in a patient diagnosed with malignancy of the gastrointestinal tract (colon and oesophagus).

Anti-PL7 antibodies (n=10)

ILD was the most common triad finding (6/10, 60.0%), with the NSIP pattern accounting for half of the cases (N=3/6, 50.0%), followed by myositis (4/10, 40.0%) and arthritis (N=2/10, 20.0%), which occurred less frequently than in anti-Jo1 positive patients (p=0.02). (Table 1) Accompanying findings included MH (N=4/10, 40.0%). No deaths or malignancies were reported in this group.

Anti-EJ antibodies (n=4)

ILD was identified in all patients (N=4/4, 100.0%), with an equitable distribution between the four patterns of lung involvement (table 1). Myositis was the second most common triad finding (N=3/4, 75.0%), followed by arthritis (N=2/4, 50.0%).

Anti-OJ antibodies (n=2)

Triad findings included ILD (N=1/2, 50.0%) with non-specific-pattern identified, myositis (N=1/2, 50.0%) and arthritis (N=1/2, 50.0%) in similar frequencies. Accompanying findings included MH (N=1/2, 50%). One patient died.

Malignancies and causes of death

Malignancies were reported in four (5.7%) of the 70 patients with ASyS, and one patient had a double malignancy. The cancer diagnosis was made within five years of the onset of the disease. Three patients were anti-Jo1 positive, and one was positive for the PL-12 antibody (Supplement – Table I). Three patients had colon cancer, one of them with concomitant oesophageal cancer, and there was one case of lung cancer. The patient with lung cancer had concomitant ILD (non-specific pat-

Table I. Patient characteristics according to the anti-ARS.

Variables	Overall, n=70	Jo-1, n=43 (61.4%)	PL12, n=11 (15.7%)	PL7, n=10 (14.3%)	EJ, n=4 (5.7%)	OJ, n=2 (2.9%)
Female, n (%)	49 (70)	29 (67.4)	9 (81.8)	7 (70)	2 (50)	2 (100)
Median age in years at disease onset (IQR)	52 (15-75)	48 (15-70)	59 (20-70)	62 (39-73)	60 (40-65)	73.5 (72-75)
Median follow-up time in yrs (IQR)	3 (0-32)	5.2 (0-32)	3 (0-13)	1 (1-4)	4 (2-21)	1 (0-2)
Median diagnostic delay in yrs (IQR)	6 (1-33)	7 (1-33)	7 (2-19)	4 (1-23)	12.5 (2-21)	1.5 (1-2)
Myositis, n (%)	**37 (52.9)**	**26 (60.5)**	**3 (27.3)****	**4 (40)**	**3 (75)**	**1 (50)**
ILD, n (%)	53 (75.7)	34 (79.1)	8 (72.7)	6 (60)	4 (100)	1 (50)
ILD pattern - NSIP, n (%)	30 (56.6)	19 (55.9)	6 (75)	3 (50)	1 (25)	0
ILD pattern - UIP, n (%)	6 (11.3)	3 (8.8)	1 (12.5)	1 (16.7)	1 (25)	0
ILD pattern - other specific pattern, n (%)	6 (11.3)	4 (11.8)	0	2 (33.3)	1 (25)	0
ILD pattern - non-specific pattern, n (%)	11 (15.7)	8 (23.5)	1 (12.5)	0	1 (25)	1 (100)
Arthritis, n (%)	**43 (61.4)**	**33 (76.7)**	**5 (45.4)**	**2 (20)***	**2 (50)**	**1 (50)**
Mechanic's hands (%), n (%)a	23 (32.9)	15 (34.9)	3 (27.3)	4 (40)	0	1 (50)
Fever, n (%)a	7 (10)	4 (9.3)	2 (20.2)	0	1 (25)	0
Raynaud phenomenon, n (%)	22 (31.4)	11 (25.6)	7 (63.6)*	2 (20)	2 (50)	0
Anti-Ro52, n (%)	15 (21.4)	13 (30.2)	1 (12.5)*	1 (10)*	-	-
Malignancy, n (%)	4 (5.7)	3 (7.0)	1 (9.1)	0	0	0
Deaths, n (%)	4 (5.7)	2 (4.7)	1 (12.5)	0	0	1 (50)

Statistical analysis between anti-Jo-1 group and the other anti-ARS groups are represented below the variable analysed. ARS - anti-aminoacyl-tRNA-synthetase antibodies; ILD - interstitial lung disease; IQR- interquartile range; NSIP - Nonspecific interstitial pneumonia; UIP - Usual interstitial pneumonia; yrs – years. Statistically significant differences in bold. *p<0.05 in comparison to anti-Jo1 group **p<0.01 in comparison to anti-Jo1 group a – non-significatif when comparing anti-Jo1 with other anti-ARS subgroups.

Table II. Treatment carried out in the initial phase and in the maintenance phase, according to anti-ARS

Treatment, n(%)	Initial treatment, n	Maintenance treatment, n	Overall, n (%)	Jo1, n=43	PL12, n=11	PL7, n=10	EJ, n=4	OJ, n=2
Oral CTs	56	45	56 (80)	39 (90.7)	8 (72.7)	3 (30)	4 (100)	2 (100)
CT pulse	8	0	8 (11.4)	3 (69.8)	3 (27.3)	1 (10)	0	0
AZA	18	13	19 (27.1)	14 (32.6)	3 (27.3)	0	2 (50)	0
HCQ	12	12	12 (17.1)	8 (18.6)	1 (9.1)	2 (20)	0	1 (50)
MTX	16	15	16 (22.9)	12 (27.9)	2 (18.2)	1 (10)	1 (25)	0
MMF	10	18	18 (25.7)	9 (20.9)	3 (27.3)	3 (30)	2 (50)	1 (50)
CYC	7	0	7 (10)	4 (9.3)	0	3 (30)	0	0
IVIG	6	0	6 (8.6)	6 (14)	0	0	0	0
RTX	0	5	5 (7.1)	5 (11.6)	0	0	0	0
Tacrolimus	0	1	1 (1.4)	1 (2.3)	0	0	0	0

AZA – azathioprine; CTs – corticosteroids; CYC – cyclophosphamide; HCQ – hydroxychloroquine; IVIG - Intravenous immunoglobulin; MTX – methotrexate; MMF - mycophenolate mofetil; RTX - rituximab

tern).

Four (5.7%) of the 70 anti-ARS-positive patients died during the follow-up period. Deaths occurred in two patients positive for anti-Jo1, one positive for PL-12 and one positive for OJ. Causes of death included malignancy progression in one patient and infection in the other. Unfortunately, it was not possible to find the cause of death for the remaining two patients.

TREATMENT

As for treatment (Table 3), the most frequently prescribed drug in the initial phase of the disease were corticosteroids (n=56, 80%), with an average initial dose of 28 ± 26 mg/day. In eight patients, induction with methylprednisolone pulses was performed, and in six patients, intravenous immunoglobulin (IVIG) cycles were used as initial treatment. Seven patients with severe ILD did induction therapy with cyclophosphamide (CYC).

Regarding maintenance treatment, 45 patients were maintained on low dose corticosteroids (mean dose of 5.8 ± 6.6 mg/day). Currently, 36 patients are on azathioprine (AZT), mycophenolate mofetil (MMF) or rituximab (RTX) as maintenance therapy due to pulmonary involvement requiring imunossupression.

Hydroxychloroquine (HCQ) and methotrexate (MTX) were prescribed mostly in anti-Jo1 positive patients (N=8/12, 66.7%, and N=12/16, 75%, respectively). All patients under these therapies had joint involvement requiring specific treatment for arthritis control (Tables II).

There were also six anti-Jo1 positive patients with significant muscle involvement requiring IVIG therapy as induction therapy. One anti-Jo1 positive patient with ILD (NSIP pattern) and myositis was treated with a calcineurin inhibitor (tacrolimus) (Tables II).

DISCUSSION

This comprehensive report aimed to describe and compare the clinical features of Portuguese ASyS patients, both generally and according to the different anti-ARS positivities. Most patients on our cohort reported a disease onset between the fourth and sixth decades of age, except for the anti-OJ-positive patients, for whom the median age of diagnosis occurred later than 70 years of age. Attention should be noted to the small number of patients in the OJ group and the fact that this antibody is of more recent availability in the blots used in hospitals. According to the literature, AsyS occurs mainly in adults with average age 50 years, with is in accordance with our cohort[16]. Gender frequency was not significantly different between the different anti-ARS groups.

Although the frequency of different clinical manifestations varied slightly according to the different anti-ARS positivities, we confirmed that most patients in our ASyS cohort share a number of characteristic clinical features. Of note, typical triad manifestations were present in all anti-ARS groups. Besides, RP and MH were also commonly reported, in accordance with previous reports[14].

It has been suggested that each of the anti-ARS may define a clinically distinct phenotype and serve as a predictor for clinical complications [8]. The prevalence of ILD, the most common disease manifestation in our cohort, did not differ among patients with different immunophenotypes. This contrasts with the literature, in which anti-PL7/PL12 positive patients were reported to have ILD more commonly than those positive for anti-Jo1 antibodies[14,15]. Most patients in our cohort had arthritis, with greater prevalence in anti-Jo1-positive patients. Although anti-PL7-positive patients had significantly lower rates of arthritis when compared to the reference group, all other anti-ARS antibodies conferred a risk of arthritis similar to that of anti-Jo1-positive patients. Cavagna *et al.* showed that, even if arthritis was substantially more frequent in anti-Jo1 positive patients (about 75%), the characteristics were similar independently of the underlying anti-ARS specificity. Furthermore, 40%–50% of the non-anti-Jo1 ARS patients had arthritis[16].

Muscle involvement is one of the most characteristic features of the ASyS. Nonetheless, its severity is milder compared with other types of myositis[16]. Most patients who were positive for anti-Jo1, anti-EJ, and anti-PL7 antibodies had myositis. Of note, only patients positive for anti-PL-12 antibodies had a significantly lower risk of presenting myositis than the reference group of anti-Jo1 positive patients. These results are concordant with a longitudinal cohort reported by Pinal-Fernandez *et al.*[17] and Cavagna *et al.*[16]. One of the two patients positive for anti-OJ in our cohort had myositis. There is still some controversy in the literature regarding the association of anti-OJ antibodies with myositis[18], probably due to its low prevalence.

RP is a nonspecific manifestation present in several rheumatic diseases, including ASyS[12]. In our cohort, it was more frequently found in patients positive for anti-PL-12 than in anti-Jo1-positive patients. Hamaguchi *et al.* also found a higher prevalence of RP in anti-PL12-positive patients[14]. Instead, MH and fever were similar across different anti-ARS groups.

Although some reports have associated ASyS with cancer[15, 19], those studies were not adjusted for age and sex. Further studies have refuted this observation, suggesting that ASyS is not associated with cancer[20]. Only four cases of neoplasia were registered, which translates into a very low relative frequency (5.7%). The size of our sample limits possible associations between cancer and ASyS. The mortality incidence in our cohort was

5.7% (n=4).

Anti-Ro52 can be associated with many autoimmune rheumatic diseases, but it is especially prevalent in anti-Jo1 patients[19,21]. In our cohort, we also found greater co-positivity with anti-Ro52 for anti-Jo1 when compared with anti-PL12 or anti-PL7 patients (p=0.03). In this patients group, they were found to have a higher percentage of arthritis (86.7%), ILD (60%) and myositis (40%).

Treatment for ASyS can be challenging given that there are no specifically approved medications, and there are very few comparative studies for various proposed therapies. Studies have not demonstrated a role for specific therapies based on autoantibody profiles[22]. Careful diagnostic testing is needed to determine the extent and profile of disease in ASyS. Patients with this diagnosis should undergo HRCT and PFTs to assess for ILD, CK, and a careful strength examination to assess for myositis, and rheumatoid factor (RF) or anti-citrullinated peptide antibody (ACPA) and joint examination to assess for arthritis. Once the patient's clinical phenotype is clear, treatment should be targeted at the most severe and life- or organthreatening clinical manifestations (typically ILD and myositis). Corticosteroids have long been first-line treatment, although when corticosteroids are used as monotherapy to treat ASyS-associated lung disease, there is frequent recurrence with tapering. Additional immunosuppressive agents (HCQ, MTX, AZT, MMF, cyclosporine, tacrolimus, IVIG, CYC and RTX) are added for arthritis, refractory muscle or lung disease, and as a corticosteroid-sparing[22-24]. However, there is little consensus about which option is preferred, and their use to treat ASyS-related ILD is off-label. In our cohort, corticosteroids were used in many patients as induction therapy (n=56, 80%) and is kept in a significant percentage of patients as maintenance treatment (n=45, 64.3%). CYC and IVIG were used as induction therapy in patients with severe lung and muscle involvement, respectively. As described in the literature, due to toxicity, CYC is often reserved for severe or refractory ASyS-ILD[23]. For acute, severe, or recalcitrant myositis, more aggressive agents can be used, and these may include IVIg, CYC or RTX[24]. As maintenance therapy, prescriptions were made according to recommendations in the literature. MMF, AZT, and RTX were mainly used when lung involvement was predominant[22,25,26], HCQ and MTX to control joint manifestations[27], and the calcineurin inhibitor (tacrolimus) was used in a patient with refractory ILD and myositis[28].

ASyS patients share clinical characteristics, including the ASyS triad and accompanying findings. Therefore, it is crucial to raise awareness that these antibodies are associated with a clinical phenotype known as ASyS since several anti-ARS-positive patients are not correctly recognised as having ASyS[29]. The importance of keeping this in mind is that the heterogeneity in disease expression can lead to a delay in the diagnosis and morbidity.

The main limitation of this study is its retrospective design and sample size. However, when studying rare diseases, such as ASyS, many relevant contributions come indeed from retrospective analysis. Additionally, the EJ and OJ groups are particularly small (n = 4 and n=2, respectivelly) not really allowing reliable comparisons.

CONCLUSION

This is the first study investigating the clinical and immunological profiles of Portuguese patients with ASyS. The three most common clinical manifestations were ILD, followed by arthritis and myositis. Patients positive for anti-PL7 antibodies had significantly lower risk of presenting arthritis and those positive for anti-PL-12 antibodies had a significantly lower risk of presenting myositis than the reference group of anti-Jo1 positive patients. RP was more frequently found in patients positive for anti-PL-12 than in anti-Jo1-positive patients. Corticosteroids were the most frequently prescribed therapy. The use of immunosuppressive drugs was decided according to the type of predominant clinical manifestation. Our data suggest that the course of anti-Jo1, anti-PL7, anti-PL12, anti-EJ and anti-OJ-positive ASyS is broadly similar, regardless of the specific antibody associated with the disease.

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SUPPLEMENTARY MATERIAL

Table I. Cases of malignancy in patients with anti-aminoacyl-tRNA synthetase antibodies (Anti-ARS)

Anti-ARS	Age	Sex	Type of malignancy
Anti-Jo1	68	F	Colon cancer
Anti-PL-12	69	F	Colon and oesophagus cancer
Anti-Jo1	56	M	Colon cancer
Anti-Jo1	73	M	Lung cancer

Anti-Jo1 - anti histidyl-tRNA synthetase antibodies; Anti-PL-12: anti-alanyl-tRNA synthetase antibodies; F – female; M – male.