Timing of onset affects arthritis presentation pattern in antisynthetase syndrome

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Abstract

Objective

To evaluate if the timing of appearance with respect to disease onset may influence the arthritis presentation pattern in antisynthetase syndrome (ASSD).

Methods

The patients were selected from a retrospective large international cohort of ASSD patients regularly followed-up in centres referring to AENEAS collaborative group. Patients were eligible if they had an antisynthetase antibody testing positive in at least two determinations along with arthritis occurring either at ASSD onset (Group 1) or during the course of the disease (Group 2).

Results

445 (70%; 334 females, 110 males, 1 transsexual) out of the 636 ASSD we collected had arthritis, in the majority of cases (367, 83%) from disease onset (Group 1). Patients belonging to Group 1 with respect to Group 2 had an arthritis more commonly polyarticular and symmetrical (p=0.015), IgM-Rheumatoid factor positive (p=0.035), erosions at hands and feet plain x-rays (p=0.036) and more commonly satisfying the 1987 revised classification criteria for rheumatoid arthritis (RA) (p=0.004). Features such as Raynaud's phenomenon, mechanic's hands and fever (e.g. accompanying findings) were more frequently reported in Group 2 (p=0.005).

Conclusion

In ASSD, the timing of appearance with respect to disease onset influences arthritis characteristics. In particular, RA features are more common when arthritis occurs from ASSD onset, suggesting an overlap between RA and ASSD in these patients. When arthritis appears during the follow-up, it is very close to a connective tissue disease-related arthritis. Also, the different prevalence of accompanying features between these two groups is in line with this possibility.

Key words

antisynthetase syndrome, arthritis pattern, timing of onset

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Introduction

Arthritis is a well-established feature of antisynthetase syndrome (ASSD), reported in up to 80% of cases and representing, together with myositis and interstitial lung disease (ILD), the classic clinical triad of the disease (1-4). In ASSD, arthritis may appear either at disease onset (5, 6) or during the follow-up (4), with heterogeneous characteristics from both the clinical, laboratory and radiology point of view (4, 6-8). The differential diagnosis of rheumatoid arthritis (RA) is frequently challenging, especially at disease onset (4) and in patients presenting with an isolated arthritis (5), who are at increased risk for the subsequent occurrence of lacking triad features (5, 9).

Despite better awareness, several questions on arthritis still remain unanswered in this setting. The aim of this study is to evaluate in a large cohort of patients if characteristics of arthritis occurring after ASSD onset (*e.g.* in the follow-up of these patients) are different from those of arthritis occurring at disease onset.

Methods

Patients

Patients were selected from a retrospective large cohort of ASSD patients regularly followed-up at 48 Rheumatology, Pneumology and Neurology centres from Italy (n=28), Spain (n=9), Germany (n=6), Portugal (n=1), Norway (n=1), Sweden (1), USA (n=1) and Mexico (n=1). Patients were eligible if they had an antisynthetase antibody testing positive in at least two determinations along with arthritis (observed by an experienced rheumatologist in all cases) at the onset or during the disease course and if they signed the informed consent as approved by the local Institutional Ethics Board. Type and characteristics of arthritis and other clinical features, laboratory and instrumental investigations, at onset and during follow-up, were then evaluated. As previously described (4, 5), arthritis occurrence (joint swelling and tenderness required) and its presentation pattern (*e.g.* symmetrical polyarthritis, oligoarticular/asymmetrical arthritis) were clinically assessed. The majority of patients had hand and feet plain x-rays. ILD was defined instrumentally by a restrictive pulmonary function test (PFT) pattern (FVC ≤80%, FEV1/FVC ≥70%, decreased or normal FEV1, and/or <20% reduction in DLCO), and/or by signs of alveolitis/fibrosis on high-resolution computed tomography (HRCT). PFTs were performed at baseline as part of the assessment of lung involvement in an early arthritis/connective tissue disease and then regularly during the follow-up. Lung HRCT was performed in the case of respiratory symptoms, altered PFTs and when antisynthetase antibodies were found positive. Patients with muscle enzyme elevation (creatinine phosphokinase and/or aldolase) and the presence of typical electromyography alterations and/or compatible muscle biopsy findings and/or compatible muscle magnetic resonance, were considered as having muscle involvement. Muscle enzymes were routinely performed at baseline and during the follow-up in all patients, regardless of the occurrence of muscle symptoms.

The onset of ASSD was considered as the time of the first pulmonary, muscular or joint symptom or sign. The onset of clinical features was considered concurrent in cases of less than 3 months of delay after the presentation of manifestations. Patients included in this study were divided into 2 clinical groups: Group 1 – arthritis at disease onset; Group 2 – arthritis after disease onset (*ex-novo arthritis, i.e.* more than 3 months after the onset of the first non-arthritis triad finding).

Patients were also assessed for the occurrence of accompanying features and related time of appearance. Fever was considered related to ASSD in case of a body temperature ≥38°C for more than 10 days without evidence of other possible causes. Mechanic's hands were defined as the occurrence of a thickened, hyperkeratotic, and fissured aspect of the radial sides of the fingers of the hands, in absence of any other possible explanations. Raynaud's phenomenon was defined as the occurrence of a transient finger ischaemia after cold exposure, confirmed by a clinician.

Autoantibody profile

Autoantibodies were considered posi-

Table I. Main demographics and clinical characteristics of patients according to cluster and timing of arthritis appearance with respect to other classic triad findings. If not otherwise stated, percentage are calculated according to the number of patients with available information within the group.

	Group 1: arthritis at disease onset	Group 2: arthritis after disease onset (*ex novo* arthritis)	*p*-value
Number of patients (% of total)	367 (83)	78 (17)	–
Median age in years at disease onset (IQR)	51 (41-60)	53 (39-61)	0.940^
Median diagnostic delay in months (IQR)	6 (2-27)	9 (3-18)	0.107**
Median follow-up in months (IQR)	74 (32-143)	95 (48-178)	0.038**
Females (%)	272 (74)	62 (79)	0.337
Males (%)	94 (26)*	16 (21)	
Anti Jo-1 positive (%)	304 (83)	62 (79)	0.483
Non-anti JO-1 positive (%)	63 (17)	16 (21)	
Anti-Ro antibodies positive (%)	200 (56)	41 (53)	0.544
Anti-RO antibodies negative (%)	155 (44)	37 (47)	
Symmetrical polyarthritis (%)	**258 (71)**	**43 (57)**	**0.015**
Oligoarticular/asymmetrical arthritis (%)	**106 (29)**	**33 (43)**	
IgM-RF positive (%)	**94 (27)**	**11 (15**	**0.035**
IgM-RF) negative (%)	**257 (73)**	**62 (85)**	
ACPA positive (%)	33 (11)	5 (8)	0.575
ACPA negative (%)	274 (89)	55 (92)	
Patients with x-rays joint erosions (%)	**51 (16)**	**4 (6)**	**0.036**
Patients without x-rays joint erosions (%)	**273 (84)**	**63 (94)**	
Patients satisfying the 1987 revised ACR classification criteria for RA (%)	**241 (69)**	**37 (51)**	**0.004**
Patients NOT satisfying the 1987 revised ACR classification criteria for RA (%)	**109 (31)**	**35 (49)**	
Fever (%)§	91 (26)	25 (33)	0.211
No fever (%)§	261 (74)	51 (67)	
Raynaud's phenomenon (%)§	**95 (27)**	**33 (43)**	**0.007**
No Raynaud's phenomenon (%)§	**254 (73)**	**44 (57)**	
Mechanic's hands (%)§	91 (26)	27 (36)	0.082
No Mechanic's hands (%)§	258 (74)	48 (64)	
Accompanying features (%)§	**183 (56)**	**56 (74)**	**0.005**
No accompanying findings (%)§	**144 (44)**	**20 (26)**	

RF: Rheumatoid factor; ACPA: anticyclic citrulinated peptide antibodies; ILD: interstitial lung disease. *plus one transexual. §number of accompanying findings ever presented, concomitantly or before arthritis occurrence. Median time from disease to arthritis onset in group 2 (interquartile range): 20 months (10-46 months).
Statistical analysis: ^Independent sample *t*-test, **Welch-test. Other: Chi square test.

tive after two testing confirmations along with at least one positivity obtained in the leading reference/tertiary centre. In leading centres, besides antisynthetase antibodies, other additional anti-extractable nuclear antigen specificities and IgM-RF and ACPA were tested by well-validated methods (Appendix).

Statistical analysis

Descriptive data were reported or considered 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 chi-square test, *t*-test or Mann-Whitney test, based on the variable type and distribution. Analyses were performed using STATA software package (2009, release 11; StataCorp, TX, USA).

Results

In our cohort of 636 ASSD, 445 patients (70%; 334 females, 110 males, 1 transsexual) had arthritis. In these patients, the median (IQR) age at disease onset was 51 (41–60) years, the diagnostic delay was 7 (2–23) months and the duration of follow-up 79 (36–149) months.

Anti-Jo-1 antibodies were positive in 366 (82%) patients, non-anti Jo-1 antibodies in 79 (18%). Within non-anti-Jo-1 positive patients, 33 (42%) were anti-PL-7 positive, 29 (37%) anti-PL-12, 9 (11%) anti-EJ and 4 (5%) anti-OJ. Also, 4 patients (5%) had a double positivity (1 OJ/EJ and 3 PL-7/PL-12). Anti-Jo-1 and non-anti-Jo-1 positive patients were equally distributed between the two clinical groups (p=0.489). In particular, Group 1 included 303 (83%) anti-Jo-1 and 63 (17%) non-anti-Jo-1 positive patients, Group 2, 62 (79%) anti-Jo-1 and 16 (21%) non-anti-Jo-1 positive patients.

Clinical, laboratory and radiologic findings of all patients are shown in table 1. Whereas the 1987 revised ACR classification criteria for RA (10) were tested in the majority of patients, we could test only 78 (18%) for the new 2010 ACR/EULAR classification criteria for RA (11), reason that lead us to not include the obtained result in the study. Even if this study was not aimed at comparing the inter-centre variability, arthritis characteristics were equally distributed between the different centres involved and between different referral areas (data not shown). Regarding treatments, the majority of group 2 patients were on immunosuppressants when arthritis appeared. All 78 patients (100%) were on low dose prednisone (< 5mg/day), 35 (45%) on azathioprine, 12 (15%) on mycophenolate mofetil, 8 (10%) on cyclosporine, 4 (5%) on cyclophosphamide and 1 (1%) on hydroxychloroquine.

Figure 1 shows the cluster of triad findings presented at disease onset in the 2 Groups.

Discussion

To date, this is the largest study ever to address arthritis assessment in ASSD, and the first to include a large number of non-anti-Jo-1 positive patients. Our findings indicate that arthritis in ASSD occurs mainly at disease onset and to a lesser extent during the follow-up. Furthermore, we found that arthritis characteristics are heterogeneous within the syndrome and influenced by its timing of onset. In particular, RA-like clinical, laboratory and radiologic features are

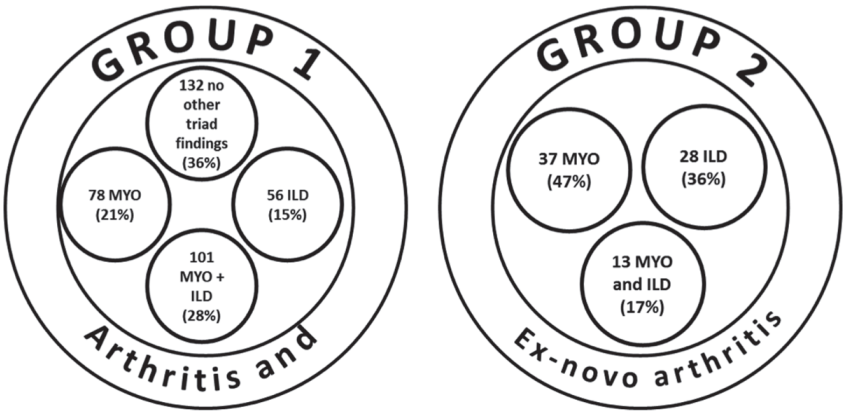

Fig. 1. Cluster of triad findings in different groups. Inner circles: Group 1, triad findings occurring concomitantly to arthritis at disease onset. Group 2, triad findings presented before the appearance of arthritis. MYO: myositis; ILD: interstitial lung disease.

Appendix

List of kits/methodologies used

Anti synthetase antibodies
- INNO-LIA, Immunogenetics Ghent, Belgium
- EliA Jo-1, Phadia, Freiburg, Germany
- ELiA CTD screen, Phadia, Freiburg, Germany
- Zenit RA Jo-1, Menarini Diagnostic, Firenze, Italy
- QUANTA Flash Jo-1, Inova Diagnostics, Werfen Groupe San Diego, USA
- ENA-abs, Euroimmun, Lübeck, Germany
- Counterimmunoelectrophoresis, Bunn CC, Gharavi AE, Hughes GRV. *J Clin Lab Immunol* 1982; 8: 13-17.
- Dot Blot Miositis/Esclero Palex Medical, Barcelona, Spain
- ELISA ORG 514, ORGENTEC, Mainz, Germany
- Myositis Profile Euroline Blot test kit, Euroimmun, Lübeck, Germany
- DotDiver ANAcyto 10, GA Generic Assays GmbH, Berlin, Germany
- MYOSITIS PROFILE - 12 Ag, AL AD-MYOS12D ALIFAX Srl, Padua, Italy BD

Anticyclic citrullinated peptide antibodies
- Aeskulisa 3166 CCP, Aesku.system GmbH & Co, Wendelsheim, Germany
- Anti-CCP EDIA, Eurodiagnostica, Malmoe, Sweden
- Quanta Flash (CIA) CCP3, INOVA Diagnostics a Werfen Company, San Diego
- Home-made ELISA, Anzilotti C *et al*. Antibodies to viral citrullinated peptide in rheumatoid arthritis. *J Rheumatol* 2006; 33: 647-51.
- Zenit RA CCP, Menarini Diagnostic, Firenze, Italy
- EliA CCP, Phadia, Freiburg, Germany (Torino)
- Anti-CCP Ab's, Roche Diagnostics, Mannheim, Germany
- anti-CCP2 ELISA, Immunoscan RA, Euro-Diagnostica, Malmoe, Sweden

Rheumatoid factor IgM antibodies
- Nephelometry
- Reuma Latex test, Sclavo diagnostics International, Sovicille, Italy
- Elia RF IgM, Phadia, Freiburg, Germany
- RF Ab's: Roche Diagnostics, Mannheim, Germany
- RF IgM, (K6078) Vista 1500, Siemens Healthcare Diagnostics

more likely observed in patients presenting arthritis from disease onset and to a lesser extent in those presenting with an *ex-novo* arthritis during the follow-up. Conversely, we first observed that ASSD accompanying findings (*e.g.* fever, Raynaud's phenomenon and mechanic's hands) are significantly less frequent in the clinical Group 1 (arthritis at disease onset) when compared to Group 2 (arthritis after disease onset *-ex-novo arthritis*).

We have recently published a study focused on the evolution of the concept of articular involvement in ASSD (5). In this paper, we have shown how this concept steadily changed over time, from the simple term of polyarthralgia reported in the first studies, to that of symmetrical polyarthritis described in the last ones. Furthermore, we showed that the overlapping aspects between ASSD and RA are common in anti-Jo-1 positive patients presenting with arthritis from disease onset in general and with an isolated arthritis in particular (4, 5).

At that time, due to the limited number of patients developing an *ex-novo* arthritis during the follow-up, we left a relevant question unanswered: is arthritis phenotype different in patients in whom joint involvement appears *ex-novo* during the follow-up? With the increased number of centres participating in the AENEAS collaborative group, in the present study we have reached a number of patients that may be large enough to answer this question. Furthermore, we enlarged the spectrum of analysis by including also a relevant number of patients with other antisyntethase antibodies specificities. First of all, in this study we confirmed that it is often difficult to perform a differential diagnosis between ASSD and RA at disease onset because of several clinical, laboratory and radiology similarities. However, the most interesting results we disclosed was that *ex-novo* arthritis is more frequently oligoarticular and asymmetrical with respect to that appearing at disease onset. Conversely, IgM RF positivity and the radiographic evidence of joint erosions were more commonly observed in Group 1 with respect to Group 2. Furthermore, the 1987 ACR revised classification criteria for RA were less frequently satisfied in patients from Group 2 when compared to Group 1. Unfortunately, we were able to test only a limited number of patients with the 2010 new classification criteria for RA, without the possibility of drawing conclusions. From the serological point of view, anti-Ro antibodies were equally distributed among groups, thus without other implications to that of potential ASSD markers, at least for arthritis aspects.

If we consider the treatments ongoing when arthritis appeared, in the majority of cases, the drugs used are not considered effective from the articular point of view along the entire spectrum of rheumatic conditions. We may suppose that the influence of these treatments

on arthritis presentation pattern (and on joint erosions) was minimal.

Our results indicate that arthritis in ASSD is a heterogeneous condition, with different characteristics that are linked to the timing of the appearance of arthritis. In particular, patients presenting *ex-novo* arthritis during the follow-up less frequently have laboratory, clinical and radiology features typical of RA, suggesting that different mechanisms may drive arthritis occurrence in the different phases of ASSD. Another factor supporting this hypothesis is that the typical accompanying findings of ASSD were rare in Group 1 and more common in Group 2. As recently suggested by the members of the French "Club Rhumatisme and inflammation" (8), we think that an overlap between RA and ASSD may occur in the first phases of the disease, whilst a "true" ASSD-related arthritis during the follow-up.

Another interesting observation derived from the evaluation of Group 1 was that the association between arthritis and ILD was observed in 157 patients (44% of the group), 56 of them (15% of the group) without concomitant myositis. Since ILD frequently occurs at RA onset (12), arthritis in ASSD is frequently "RA-like" (4, 5, 8), and ILD is a common manifestation of ASSD (2, 3, 13-18), we think that some patients diagnosed with RA with lung involvement could be in fact not diagnosed ASSD.

The study has some limits. In particular, the main criticism is related to its retrospective design. It is well known that these studies are intrinsically associated with an increased risk of incompleteness (19, 20). In fact, arthritis serological, radiology and clinical data were available in the majority of cases but not in all cases. Another potential limitation is that anti-synthetase antibodies were assessed using different commercially available kits in different centres. Nevertheless, when considering these limitations, we have to take into account that so far no prospective studies that address ASSD are available, and that other multicentre studies previously performed had the same problems that we have discussed (2, 9, 21, 22). Another bias is that we checked only few patients for the newly available RA classification criteria (11) and not for the new 2010 ACR/EULAR classification criteria for RA. This bias could be overcome in the incoming prospective part of the AENEAS project. Finally, we cannot exclude that some of the patients included in Group 1, who had an isolated arthritis at disease onset, could have presented an asymptomatic ILD or myositis. We think that this limitation could be resolved only in the case of a very early identification of antisyntethetase antibodies and of a very early diagnosis of ASSD. However, we think that thanks to the results obtained by the AENEAS collaborative group (4, 5) and by the French "Club Rhumatisme et inflammation" (2, 8, 21) the sensibility of clinicians in the early diagnosis of ASSD in arthritis patients could steadily increase in the next years.

In conclusion, we have shown that heterogeneity is a typical hallmark of arthritis in ASSD, that differences found in our series may indicate different phenotypes of the disease and that arthritis pathogenesis in ASSD is complex and potentially different in various disease phases.

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References

1. IMBERT-MASSEAU A, HAMIDOU M, AGARD C, GROLLEAU JY, CHERIN P: Antisynthetase syndrome. *Joint Bone Spine* 2003; 70: 161-8.
2. 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; 12: 210-7.
3. HERVIER B, BENVENISTE O: Clinical heterogeneity and outcomes of antisynthetase syndrome. *Curr Rheumatol Rep* 2013; 15: 349.
4. CAVAGNA L, NUNO L, SCIRE CA *et al*.: Clinical spectrum time course in Anti Jo-1 positive antisynthetase syndrome: results from an international retrospective multicenter study. *Medicine* (Baltimore) 2015; 94: e1144.
5. CAVAGNA L, NUNO L, SCIRE CA *et al*.: Serum Jo-autoantibody and isolated arthritis in the antisynthetase syndrome: review of the literature and report of the experience of AENEAS Collaborative Group. *Clin Rev Allergy Immunol* 2017; 52: 71-80.
6. LEFEVRE G, MEYER A, LAUNAY D *et al*.: Seronegative polyarthritis revealing antisynthetase syndrome: a multicentre study of 40 patients. *Rheumatology* (Oxford) 2015; 54: 927-32.
7. CAVAGNA L, FUSETTI C, MONTECUCCO C, CAPORALI R: Anticyclic citrullinated peptide antibodies as markers of erosive arthritis in antisynthetase syndrome. *J Rheumatol* 2010; 37: 1967; author reply 1968.
8. 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.
9. TRALLERO-ARAGUAS E, GRAU-JUNYENT JM, LABIRUA-ITURBURU A *et al*.: Clinical manifestations and long-term outcome of anti-Jo1 antisynthetase patients in a large cohort of Spanish patients from the GEAS-IIM group. *Semin Arthritis Rheum* 2016; 46: 225-31.
10. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
11. ALETAHA D, NEOGI T, SILMAN AJ *et al*.: 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010; 69: 1580-8.
12. CAVAGNA L, MONTI S, GROSSO V *et al*.: The multifaceted aspects of interstitial lung disease in rheumatoid arthritis. *Biomed Res Int* 2013; 2013: 759760.
13. STANCIU R, GUIGUET M, MUSSET L *et al*.: Antisynthetase syndrome with anti-Jo1 antibodies in 48 patients: pulmonary involvement predicts disease-modifying antirheumatic drug use. *J Rheumatol* 2012; 39: 1835-9.
14. LABIRUA-ITURBURU A, SELVA-O'CALLAGHAN A, MARTINEZ-GOMEZ X, TRALLERO-ARAGUAS E, LABRADOR-HORRILLO M, VILARDELL-TARRES M: Calcineurin inhibitors in a cohort of patients with antisynthetase-associated interstitial lung disease. *Clin Exp Rheumatol* 2013; 31: 436-9.
15. DUGAR M, COX S, LIMAYE V, BLUMBERGS P, ROBERTS-THOMSON PJ: Clinical heterogeneity and prognostic features of South Australian patients with anti-synthetase autoantibodies. *Intern Med J* 2011; 41: 674-9.
16. ROJAS-SERRANO J, HERRERA-BRINGAS D, MEJIA M, RIVERO H, MATEOS-TOLEDO H, FIGUEROA JE: Prognostic factors in a cohort of antisynthetase syndrome (ASS): serologic profile is associated with mortality in patients with interstitial lung disease (ILD). *Clin Rheumatol* 2015; 34: 1563-9.
17. LABIRUA-ITURBURU A, SELVA-O'CALLAGHAN A, VINCZE M *et al*.: Anti-PL-7 (anti-threonyl-tRNA synthetase) antisynthetase syndrome: clinical manifestations in a series of patients from a European multicenter study (EUMYONET) and review of the literature. *Medicine* (Baltimore) 2012; 91: 206-11.
18. CAVAGNA L, CAPORALI R, ABDI-ALI L, DORE R, MELONI F, MONTECUCCO C: Cyclosporine in anti-Jo1-positive patients with cortico-steroid-refractory interstitial lung disease. *J Rheumatol* 2013; 40: 484-92.
19. MANN CJ: Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emerg Med J* 2003; 20: 54-60.
20) SONG JW CK: Observational studies: cohort and case-control studies. *Plast Reconstr Surg* 2010; 126: 2234-42.
21. LEFEVRE G, MEYER A, LAUNAY D *et al*.: Seronegative polyarthritis revealing antisynthetase syndrome: a multicentre study of 40 patients. *Rheumatology* (Oxford) 2015; 54: 927-32.
22. CONNORS GR, CHRISTOPHER-STINE L, ODDIS CV, DANOFF SK: Interstitial lung disease associated with the idiopathic inflammatory myopathies: what progress has been made in the past 35 years? *Chest* 2010; 138: 1464-74.