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Scleroderma specific autoantibodies in rheumatoid arthritis and Sjögren's syndrome patients with interstitial lung disease: Prevalence and associations

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ABSTRACT

Systemic sclerosis (SSc) has been classically linked to interstitial lung disease (ILD) development, often in association with specific SSc autoantibodies. In the present report, we aimed to estimate the prevalence of SSc autoantibodies in 60 seropositive RA and 41 primary SS patients complicated or not by ILD. SSc autoantibodies were determined in patients' sera by a commercial immunoblot assay. RA ILD patients displayed higher frequency of SSc-specific antibodies at strong titers compared to RA-with no lung involvement (25% vs 3.1%, p = 0.01)[OR 95% CI:10.9 (1.2–94.5)], with no differences detected between primary SS groups. These data indicate that many seropositive RA ILD patients probably represent an overlap RA/SSc entity, requiring tailored diagnostic and therapeutic approach.

1. Introduction

Pulmonary involvement is a rather common extra-articular manifestation of both rheumatoid arthritis (RA) and to a lesser extent primary Sjögren's syndrome (SS), manifested as parenchymal, pleural and/or airway pathology [1,2]. The reported prevalence rates of both RA and SS related lung disease vary greatly, depending on the implemented screening methods, the characteristics of the populations selected and the severity of respiratory complaints [1,2]. Most studies report a prevalence rate of 9–21% of pulmonary involvement in primary SS patients, mostly expressed as tracheobronchial disease rather than interstitial lung disease (ILD) [3–5]. ILD is the most prevalent type of lung involvement in RA patients, associated with an unfavorable impact on their quality of life and survival [1]. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide autoantibodies (anti-CCP) confer increased risk of ILD in RA patients [1,6]. ILD is present in patients with many connective tissue diseases (CTDs), especially systemic sclerosis (SSc) and idiopathic inflammatory myopathies (IIM) [7]. Over the last years, an increasing number of autoantibodies targeted against cellular antigens such as SSc-specific and anti-Ro52 autoantibodies have been associated with ILD in SSc and overlapping clinical entities [7–9] and several of these have been included in the serologic classification criteria of interstitial pneumonia with autoimmune features (IPAF) [10]. In the present report, the prevalence of SSc-specific and anti-Ro52 autoantibodies in seropositive RA patients and primary SS patients with and without ILD was determined and potential clinical and serological associations were explored.

2. Patients and methods

2.1. Patients

The initial study population included 165 unselected primary SS and seropositive RA patients with available high resolution computed

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tomography scans (HRCTs), performed because of the presence of respiratory complaints, abnormal lung sounds or suspicious findings on chest radiography. Among this group, 26 RA patients and 38 primary SS patients were excluded from the study, as their HRCTs were characterized by either atypical or non-specific for ILD imaging findings/patterns, such as pleural effusion, airway disease (emphysema, bronchiectasis, bronchial wall thickening) and parenchymal/interstitial abnormalities (nodules, consolidation, interstitial thickening, ground glass opacities) not consistent with diffuse parenchymal lung disease in terms of location, distribution, or extent (i.e focal/unilateral lesions, atypical location). Thus, the final study population included 101 patients, 28 RA and 9 primary SS patients with ILD as well as 32 RA and 32 primary SS patients with no evidence of lung involvement on HRCTs. All RA and primary SS patients fulfilled the 2010 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) RA classification criteria [11] and 2016 ACR/EULAR primary SS classification criteria, respectively [41].

Among the RA group, most patients were females (70%) with a mean age of 63.4 ± 11.5 years and mean age at RA diagnosis of 50.2 ± 14.2 years. Among the primary SS group, 87.8% of the patients were females with a mean age of 60.3 ± 12.3 years and mean age at SS diagnosis of 52.7 ± 14.3 years. Clinical and laboratory features, immunological profile and imaging findings were documented, following thorough chart review taken from patients' medical records. These patients were referred to the Molecular Physiology and Clinical Applications Unit, Department of Physiology, National and Kapodistrian University of Athens by MG, CPM and HMM for evaluation of SSc autoantibodies. All patients gave informed consent prior to the inclusion in the study. The study protocol was approved by the Ethics Committee, National and Kapodistrian University of Athens.

2.2. Clinical and laboratory features

For both RA and primary SS patients, demographic data including age and sex, smoking history (pack years), age at diagnosis and at HRCT evaluation as well as clinical features including Raynaud's phenomenon, arthralgias/arthritis, myalgias, oral/ocular dryness, salivary gland enlargement, dysphagia, digital ulcers, and respiratory manifestations (shortness of breath, cough, hemoptysis, rales, wheezing and rhonchi) were recorded. Disease activity score 28 (DAS28) [12] and EULAR SS disease activity index (ESSDAI) [13], as well as laboratory parameters including complete blood count, renal and muscle function tests, gamma globulins and inflammatory markers were documented at the time of RA and primary SS diagnosis. Antinuclear antibody (ANA) titers and antibodies against extractable nuclear antigens were also recorded for all study participants, where available.

2.3. Imaging findings

All HRCTs were reviewed by an expert chest radiologist (KT) unaware of clinical or serological data. The RA ILD group consisted of 28 patients, while the primary SS ILD group consisted of 9 patients. Both the RA and primary SS no-lung groups included 32 patients each. Based on imaging findings, the ILD groups were further classified into usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), organizing pneumonia (OP) or combined pulmonary fibrosis and emphysema (CPFE). In the RA ILD group, one patient had findings consistent with OP, two patients with CPFE, five with NSIP and twenty with UIP (Supplementary Table 1). In the primary SS ILD group, four patients showed evidence of UIP and five of NSIP (Supplementary Table 2).

UIP features include predominantly subpleural bibasilar reticular abnormalities with honeycombing and traction bronchiectasis and little to no ground glass opacities (GGOs). NSIP findings include GGOs as a dominant feature and reticulation without honeycombing and OP is characterized by peripheral and peribronchial patchy consolidations primarily located in the lower lobes. Combined pulmonary fibrosis and emphysema (CPFE), characterized by concurrent airway and interstitial disease, includes co-existing bibasilar reticulation and centrilobular or paraseptal emphysema mainly in the upper lung lobes [1,14]. No primary SS patients displayed imaging findings consistent with lymphocytic interstitial pneumonia (LIP).

2.4. Antibodies against SSc-specific antigens and Ro52

Sera collected from all 101 patients were tested by a Euroline immunoblot assay (EUROLINE Systemic sclerosis Nucleoli profile) for autoantibodies against the following autoantigens: Scl-70 (topoisomerase I), CENP-A (centromere protein A), CENP-B, RP-11, RP-155 (RNA polymerase III targets), fibrillarin (U3 ribonucleoprotein-RNP), Th/To, Pm/Scl-100 (polymyositis/scleroderma), Pm/Scl-75, Ku, NOR90 (nucleolus organizer region 90), PDGFR (platelet derived growth factor receptor). According to the instructions by the manufacturer, positive SSc-specific autoantibody titers were considered those with signal intensity ≥11, as assessed using a flatbed scanner and appropriate software. Samples with positive titers were further divided in those with medium titers (medium signal intensity between 11 and 25, +) and strong titers (strong/very strong signal intensity >25, ++/+++).

2.5. Statistical analysis

Statistical analysis was performed with the SPSS v.21 package. Mann-Whitney and chi-squared tests were used to draw two-group comparisons for continuous and categorical data respectively. Difference was considered statistically significant if $p < 0.05$.

3. Results

3.1. Demographic, clinical, laboratory and imaging features of the study population

In Supplementary Table 1, demographics, clinical, laboratory and imaging findings for the RA patient group are displayed. Approximately half of them had a history of smoking (45.6%) with high disease activity at the time of RA diagnosis, as calculated with DAS28 (5.1 ± 1.6). As previously stated, all patients were seropositive either for RF (91.7%) and/or anti-CCP antibodies (90.6%), while the presence of ANAs (≥1/160) was detected in 52.8% of RA patients.

In Supplementary Table 2, demographics, clinical, laboratory and imaging findings for the primary SS patient group are shown. Like RA patients, almost half of primary SS patients were ever smokers (46.7%). ESSDAI levels at SS diagnosis was 6.5 ± 7.3. Focal sialadenitis with a focus score ≥1 in minor salivary gland tissues was present in 68.6% of SS patients (mean focus score of 1.6 ± 1.5), and 77.4% of the patients had objective findings of ocular dryness by Schirmer's test and ocular staining examination. ANA positivity was found in 85.3% of primary SS patients, whereas 70.7% and 35.9% was the prevalence of anti-Ro and anti-La positivity, respectively in this patient population.

3.2. Associations of demographic, clinical and laboratory features with ILD in RA and primary SS patients

As shown in Table 1, RA patients with ILD were predominantly males (46.4% vs 15.6%, $p = 0.009$) with a heavier smoking history (36 ± 42 vs 8 ± 15 pack-years, $p = 0.04$) compared to those with no ILD involvement. They also displayed more frequently respiratory abnormalities (92.6% vs 14.8%, $p < 0.001$) as well as higher white blood cell (WBC) counts (8746 ± 3064/μL vs 6882 ± 1536/μL, $p = 0.01$). The two groups did not differ significantly in any extra-pulmonary clinical manifestations.

Primary SS patients with ILD were older at the time of CT evaluation than those without (66.9 ± 16.8 years vs 58.5 ± 10.2 years, $p = 0.04$).

Table 1
Demographic, clinical, laboratory features and immunological profile of seropositive RA patients with and without ILD.

	ILD Group (n = 28)	No lung Group (n = 32)	p-value
Demographic Data			
Age of RA diagnosis (years) (mean ± SD)	52.5 ± 13.9	48.2 ± 14.4	0.31
Age at HRCT evaluation (years) (mean ± SD)	66.4 ± 9.8	60.7 ± 12.4	0.08
Disease Duration at time of CT evaluation (years) (mean ± SD)	13.9 ± 12.9	11.9 ± 11.0	0.6
Female Sex (%)	53.6	84.4	**0.009**
Ever smoking (%)	51.9	40	0.37
Smoking (pack-years) (mean ± SD)	36 ± 42	8 ± 15	**0.04**
Clinical Characteristics			
DAS28 at first evaluation (mean ± SD)	5.5 ± 1.8	4.8 ± 1.2	0.07
Respiratory Abnormalities (%)	92.6	14.8	**<0.001**
Raynaud's Phenomenon (%)	32	13.3	0.1
Dysphagia (%)	0	0	NA
Myalgia (%)	24	23.1	0.94
Dry Mouth (%)	34.6	24.1	0.4
Dry Eyes (%)	30.8	24.1	0.58
Photosensitivity (%)	4	10.7	0.36
Digital Ulcers (%)	4	0	0.29
Laboratory Features			
WBC (cells/μL) (mean ± SD)	8746 ± 3064	6882 ± 1536	**0.01**
LDH (IU/L) (mean ± SD)	240 ± 81	239 ± 111	0.83
CRP (mg/dL) (mean ± SD)	1.6 ± 1.5	0.8 ± 0.6	0.06
Hypergammaglobulinemia (%)	39.1	35	0.78
Autoantibody Profile			
RF titers (IU/mL) (mean ± SD)	404 ± 620	280 ± 422	0.55
RF positivity (%)	96.4	87.5	0.21
Anti-CCP titers (U/mL) (mean ± SD)	249 ± 237	263 ± 224	0.76
Anti-CCP positivity (%)	89.3	92	0.74
ANA positivity (%) (≥1/160)	48.1	57.7	0.49

ANA: Antinuclear antibodies, CCP: cyclic citrullinated peptide, CRP: C reactive protein, DAS28: disease activity score 28, HRCT: high resolution computed tomography, LDH: lactate dehydrogenase, RA: Rheumatoid Arthritis, RF: Rheumatoid factor, SD: standard deviation, SSc: Systemic sclerosis, WBC: white blood cells.

They also displayed respiratory abnormalities more frequently (100% vs 22.2%, $p < 0.001$), had higher ESSDAI scores at diagnosis (12.9 ± 9.6 vs 4.3 ± 5.1, $p = 0.001$) as well as higher rates of elevated C-reactive protein levels (44.4% vs 12.9%, $p = 0.04$). No other statistically significant differences were detected between the two groups (Table 2).

3.3. Frequency of SSc-specific and anti-Ro52 antibodies in RA and primary SS groups, according to the presence of ILD

SSc-specific antibodies in all titers tended to be more frequently detected in RA ILD patients compared to those without (42.9% vs 21.9%, $p = 0.08$). This trend was mainly attributed to the statistically significant difference between the two groups at strong titers (25% vs 3.1%, $p = 0.01$), as shown in Fig. 1A, with no significant difference detected at medium titers (21.4% vs 18.8%, $p = 0.8$) (Fig. 1B). Of interest, the presence of strong titer SSc-specific antibodies in RA patients conferred eleven-fold increase of ILD risk [OR 95% CI: 10.9 (1.2–94.5)]. There were no differences in anti-Ro52 positivity between the two groups either in all (7.1% vs 9.4%, $p = 0.76$) (Fig. 1C), strong (3.6% vs 9.4%, $p = 0.37$) or medium titers (3.6% vs 0%, $p = 0.28$) measured (data not shown).

No statistically significant differences were found in the prevalence of SSc-specific or anti-Ro52 autoantibodies (strong or medium titers) between the ILD and no-lung involvement groups of primary SS patients (Fig. 1A–C).

Table 2
Demographic, clinical, laboratory features and immunological profile of primary SS patients with and without ILD.

	ILD Group (n = 9)	No lung Group (n = 32)	p-value
Demographic Data			
Age of primary SS diagnosis (years) (mean ± SD)	58 ± 17.1	50.5 ± 12.8	0.28
Age at HRCT evaluation (years) (mean ± SD)	66.9 ± 16.8	58.5 ± 10.2	**0.04**
Disease Duration (years) (mean ± SD)	6.9 ± 7.8	7.5 ± 8.9	0.79
Female Sex (%)	77.8	90.6	0.3
Ever smoking (%)	25	54.5	0.15
Pack-years (mean ± SD)	1.3 ± 2.3	13.5 ± 17.8	0.1
Histologic Features			
MSGB positivity (FS > 1) (%)	83.3	65.5	0.39
Focus score (mean ± SD)	1.9 ± 1.7	1.6 ± 1.5	0.9
Clinical Features			
ESSDAI at disease diagnosis (mean ± SD)	12.9 ± 9.6	4.3 ± 5.1	**0.001**
Respiratory Abnormalities (%)	100	22.2	**<0.001**
Positive ocular test (%)	77.8	77.3	0.98
Dry Eyes (%)	88.9	86.2	0.84
Dry Mouth (%)	87.5	93.3	0.59
Arthralgias (%)	44.4	66.7	0.23
SGE (%)	11.1	21.4	0.49
Dysphagia (%)	12.5	29.6	0.33
Raynaud's Phenomenon (%)	44.4	36.7	0.67
Chronic Fatigue (%)	22.2	26.7	0.8
Digital Ulcers (%)	11.1	0	0.08
Palpable Purpura (%)	11.1	0	0.07
Lymphadenopathy (%)	22.2	3.6	0.08
Laboratory Values			
Leukopenia (WBC <3000/μL repeatedly) (%)	0	6.5	0.43
WBC (cells/μL) (mean ± SD)	6219 ± 1358	5831 ± 2040	0.25
Neutrophil absolute number (cells/μL) (mean ± SD)	3565 ± 911	3189 ± 1344	0.2
Lymphocyte absolute number (cells/μL) (mean ± SD)	1790 ± 514	2032 ± 731	0.37
Hemoglobin (g/dL) (mean ± SD)	12.4 ± 1.7	13.2 ± 0.9	0.19
LDH (IU/L) (mean ± SD)	270 ± 111	187 ± 47	0.16
Elevated CRP (%) (over 0.5 mg/dL)	44.4	12.9	**0.04**
Autoantibody Profile			
ANA positivity (%) (≥1/160)	88.9	84	0.72
RF positivity (%)	33.3	32.1	0.95
Anti-Ro positivity (%)	55.6	75	0.26
Anti-La positivity (%)	22.2	40	0.33

ANA: Antinuclear antibodies, CRP: C reactive protein, dL: deciliter, ESR: erythrocyte sedimentation rate, ESSDAI: EULAR Sjögren's syndrome disease activity index, HRCT: high resolution computed tomography, LDH: lactate dehydrogenase, mg: milligrams, MSGB: minor salivary gland biopsy, RF: rheumatoid factor, SD: standard deviation, SGE: salivary gland enlargement, SS: Sjogren's Syndrome, SSc: Systemic sclerosis, WBC: white blood cells.

3.4. Distribution of SSc-specific antibody reactivities in RA and primary SS groups

At strong titers, a distinctive non-overlapping pattern of SSc-specific antibodies was detected. Specifically, antibodies against RP155, Th/To, fibrillarin and NOR90 were exclusively detected in the RA ILD group while only anti-Pm/Scl-100 was detected in the no-lung RA group (Fig. 2 A&B). At medium titers, RA ILD patients were predominantly positive for anti-Pm/Scl-75 and anti-RP155 antibodies (25%), with lower prevalence but equal distribution of anti-Pm/Scl-100, anti-RP11, anti-Ku and anti-Th/To antibodies (12.5%). Anti-Th/To were the most frequently detected antibodies, followed by reactivities to RP155 and RP11 antigenic targets in the RA no-lung group (Suppl Table 3).

As shown in Fig. 2C&D, in the setting of primary SS, distinct non overlapping reactivities between ILD and no lung group were also detected. More specifically, the primary SS ILD group displayed only

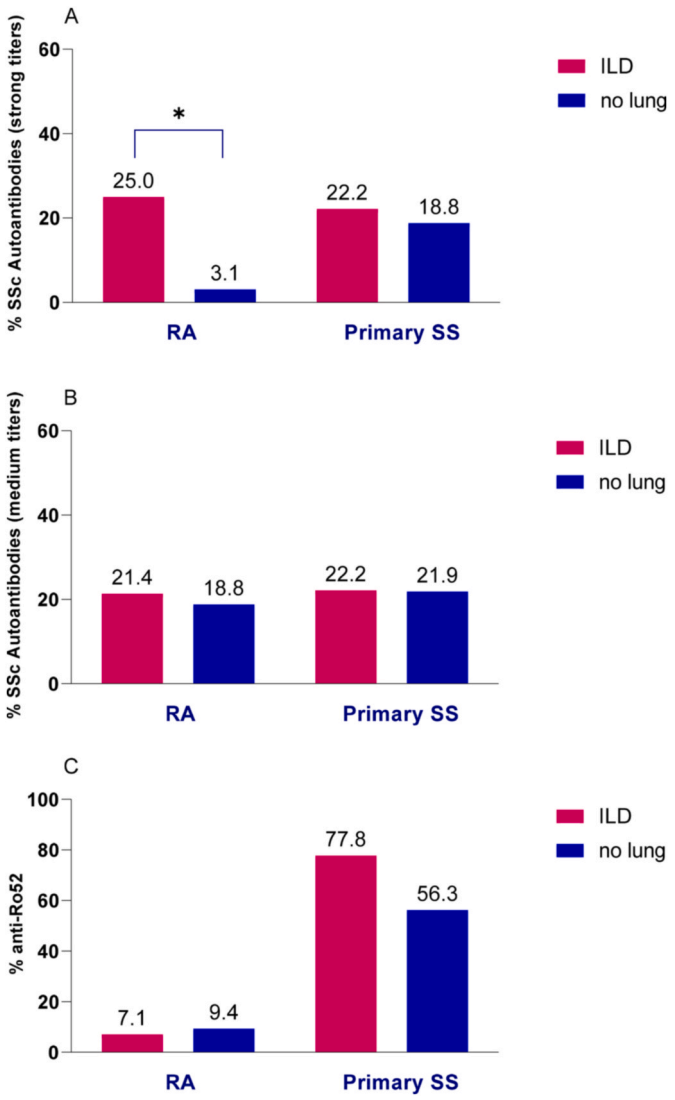

Fig. 1. Prevalence of SSc-specific and anti-Ro52 antibodies in RA ILD and primary SS ILD patients compared to their respective groups with no lung involvement A. strong titers, B. medium titers C. Anti-Ro52 all titers (only statistically significant p values shown).

anti-Scl-70 and anti-RP155 positivity, while sera from the no-lung group showed reactivities primarily for centromere antigens (CENP-A/B) and to a lesser extent anti-Pm/Scl-100, anti-Th/To and anti-NOR-90. At medium titers, the SSc-specific antibodies detected in ILD primary SS patients were anti-Pm/Scl-100, anti-RP155 and anti-Ku while the no-lung group was predominated by anti-Th/To reactivity, followed by antibodies against Pm/Scl-100, CENPA/B, RP11, Ku and fibrillarin at equal values (Suppl Table 4).

3.5. Associations of SSc-specific antibodies with clinical and laboratory features in distinct RA and primary SS groups

There were no demographic, clinical or laboratory associations of SSc-specific antibodies in all titers. In RA patients positive for SSc-specific antibodies at strong titers respiratory abnormalities were more common (87.5% vs 47.2%, $p = 0.04$). No clinical or laboratory associations of medium-titer SSc-specific antibodies were detected.

Primary SS patients positive for SSc-specific antibodies at all titers were more likely to suffer from arthralgias (85.7% vs 48%, $p = 0.02$), yet no other association with clinical or laboratory data was revealed. At strong titers, SSc-specific antibodies were associated with the presence of chronic fatigue (71.4% vs 16%, $p = 0.004$), arthralgias (100% vs 48%, $p = 0.01$), but absence of anti-La antibodies (0% vs 44%, $p = 0.03$). SSc-specific antibodies at medium titers were only associated with higher frequency of smoking (100% vs 38.1%, $p = 0.02$) (data not shown).

4. Discussion

In the present study, we report for the first time that nearly half of seropositive RA patients with ILD display serum SSc-specific autoantibodies at medium and strong titers compared to one fifth of their counterparts with no lung involvement, based on the results of a commercially available immunoblot assay. This difference between the two groups was mainly attributed to statistically significant differences at strong rather than medium titers, with one fourth of RA ILD patients displaying SSc-specific antibodies at strong titers compared to only one patient among those with no evidence of lung involvement. Anti-Ro52 prevalence was similar between the two groups and accounted for 11.4% of the entire RA population, as previously shown [15,16]. While anti-Ro52 antibodies were previously linked with ILD in the context of IIM [17], such association was not observed in our study population.

In agreement with former studies, predictors of lung involvement in the setting of RA included presence of respiratory manifestations, male sex and history of smoking [1,18,19]. However, in contrast to previous reports, disease duration and DAS28 scores were not linked to ILD in the present study, though CRP levels tended to be higher in our RA ILD group [1,18,19]. Higher WBC counts were also associated with the presence of ILD in our RA patients, a finding that remains to be elucidated. The presence of Raynaud's phenomenon and digital ulcers was higher in RA ILD patients, but this difference did not reach statistical significance.

Unlike RA patients, primary SS patients with ILD did not display significant differences in the frequency of SSc-specific autoantibodies compared to primary SS patients without lung disease. This could be attributed to the high prevalence of anticentromere antibodies in the setting of primary SS [20] as well as SSc-specific autoantibodies in sicca patients fulfilling the histopathologic criteria for primary SS [21]. In our study, ILD in primary SS was associated with older age, though not longer disease duration, a known risk factor for primary SS lung disease [2]. All patients in the ILD group displayed respiratory manifestations compared to approximately one fifth of the no-lung group, an association that underlines the importance of further work-up in symptomatic patients. Moreover, primary SS patients with ILD had more frequently positive CRP values, as has been previously described [22], as well as higher ESSDAI scores at disease diagnosis. While ILD in the setting of primary SS has also been associated with the presence of monoclonal gammopathy [4], this finding was not confirmed in our study.

The distinctive non-overlapping patterns of SSc-autoantibodies at strong titers in RA ILD (RP155, Th/To, fibrillarin and NOR90) and no-lung groups (Pm/Scl100) is somewhat intriguing, possibly mirroring distinct pathogenetic pathways between the two groups. A similar pattern at strong titers was also observed in primary SS, with ILD patients displaying antibodies against Scl-70 and RP155, while patients with no lung involvement were positive for anti-Pm/Scl-100, anti-centromere, anti-Th/To and anti-NOR-90. The antigenic targets of these autoantibodies are involved in various vital cellular processes, such as DNA replication (DNA-topoisomerase/Scl-70) and organization (CENPA/B), transcription/housekeeping (NOR90, RP11, RP155) and RNA processing (Pm/Scl, Th/To, U3-RNP) [8,23]. Whether different autoantibody functions are related to generation of distinct clinical phenotypes remains to be further explored. Most of SSc-specific antibodies detected in this cohort have been previously associated with either ILD or pulmonary hypertension, Raynaud's phenomenon, digital ulcers, gastrointestinal involvement, and myositis in patients with SSc and other overlap entities [8,24].

The strong association of SSc-specific autoantibodies with ILD in the setting of well-defined seropositive RA, could imply that RA patients

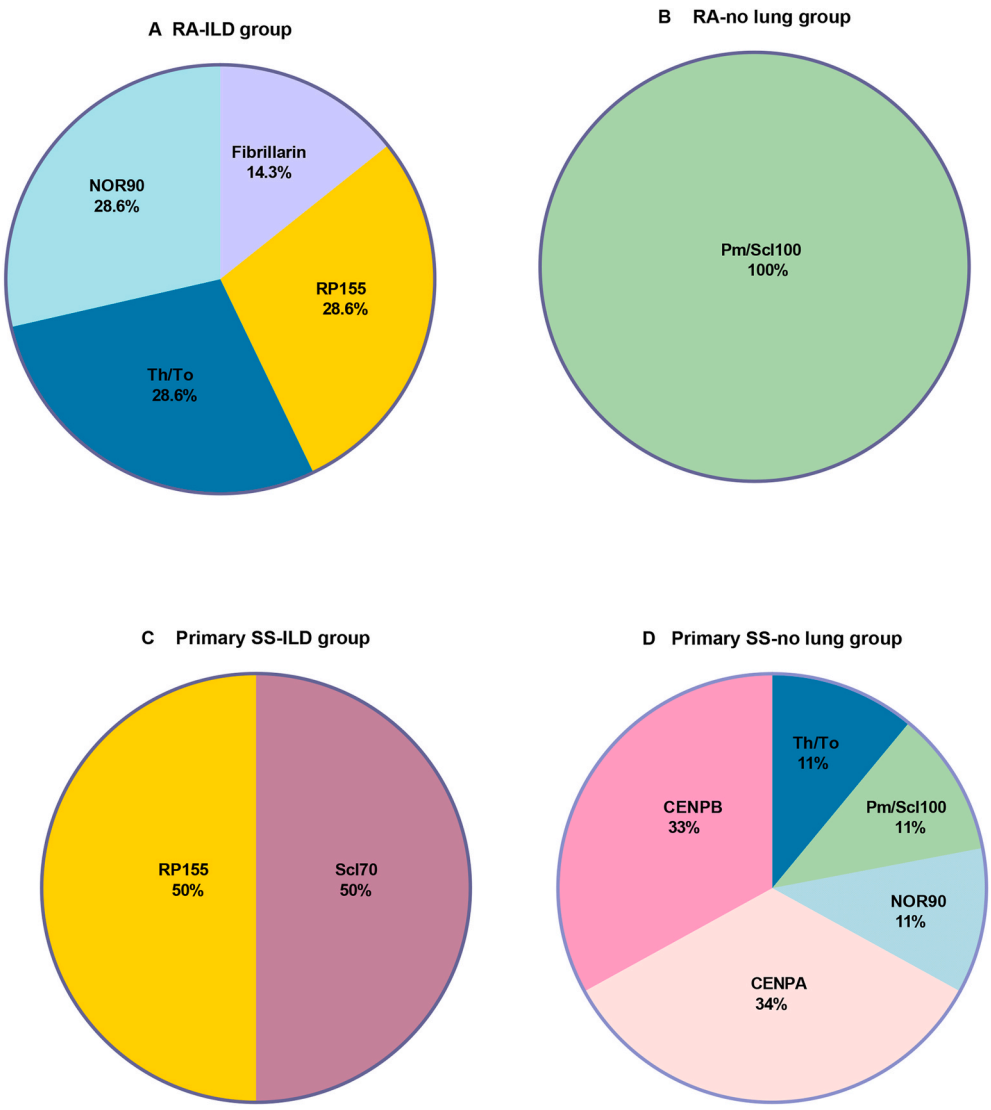

Fig. 2. Distribution of SSc-specific antibodies at strong titers in RA and primary SS patients at **A.** RA-ILD group**, B.** RA no-lung group, **C.** Primary SS-ILD group, **D.** Primary SS no-lung group (the percentage shown refers to the number of times an antibody has appeared in relation to all other antibodies – a patient could be positive for more than one antibody in either strong or medium titers).

with ILD represent a distinct disease subset with overlapping features between RA and SSc, with lack of florid SSc manifestations such as Raynaud's phenomenon or cutaneous involvement. Early detection of SSc antibodies could be important in clinical practice as it may mandate further diagnostic (eg screening for pulmonary hypertension) and therapeutic approaches of these patients. Thus, therapeutic options that are currently used in SSc-ILD and are also appropriate for management of arthritis, such as abatacept, rituximab and tocilizumab [25] could be considered to be initiated early in the disease course. The latter has also been used effectively in SARS-CoV-2 pneumonia, which shares similarities in both pathological and radiological findings with ILDs [26]. Another intriguing prospect in the management of ILDs is the use of JAK inhibitors, as JAK/STAT signaling has been implicated in both animal and human models of interstitial pneumonia [26] and contributes to type I interferon (IFN) signal transduction, a cytokine previously associated with ILD pathogenesis [27]. Towards the same lines, ILD is a common clinical manifestation of type I interferonopathies, a group of genetic disorders characterized by augmented type I interferon activity [27] and higher levels of type I IFN have also been associated with diffuse SSc, in association with lung involvement [28,29]. Selection of these therapeutic agents in RA-ILD is increasingly supported by accumulating evidence showing their superiority against anti-TNF agents in the presence of pulmonary disease [30–33]. It is tempting to speculate that induction of type I IFN pathway associated with TNF inhibition could be related to anti-TNF ineffectiveness previously observed in an RA-ILD setting [34–36].

Though concomitant presence of RA and scleroderma (fulfilling criteria for both diseases) have been previously described in few studies [37–39], it is the first time that SSc-specific antibodies are detected in an RA cohort with evidence of ILD. Remarkably, shared human leukocyte antigen (HLA) haplotypes associated with both RA and SSc have been previously reported [37].

The main limitation of this study is the small size of patient cohorts. Investigation of SSc-specific antibody associations with distinct clinical, laboratory and imaging features would yield more concrete outcomes with a greater number of patients. Moreover, the clinical significance of medium titers of autoantibodies in commercial immunoblot assays remains to be delineated, given the previously reported false positive results in low values [40]. In this setting, an identification of a reference method for the detection of SSc-specific autoantibodies may be of paramount importance to exclude the possibility of false positive results. Finally, long term follow-up may prove that the patient with those

autoantibodies may evolve to clinically evident overlap of RA and SSc.

5. Conclusion

In conclusion, serological testing for SSc-specific autoantibodies should be offered in the context of seropositive RA with evidence of interstitial lung involvement even in the absence of florid scleroderma features. This could aid at early identification of a distinct overlapping entity characterized by features of typical inflammatory arthritis and lung disease reminiscent of scleroderma, which could benefit from tailored diagnostic and therapeutic approaches. Additional and larger studies exploring the role of SSc-specific autoantibodies in RA patients are warranted to confirm our observations.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtauto.2022.100183.

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