Sjögren's syndrome and other rare and complex connective tissue diseases: an intriguing liaison

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ABSTRACT

Sjögren's syndrome (SS) is a systemic autoimmune disease that frequently occurs concomitantly with other systemic connective tissue disorders, including rare and complex diseases such as systemic lupus erythematosus (SLE) and systemic sclerosis (SSc). The presence of SS influences the clinical expression of the other autoimmune diseases, thus offering the unique opportunity to explore the similarities in genetic signatures, as well as common environmental and biologic factors modulating the expression of disease phenotypes. In this review, we will specifically discuss the possibility of defining "SS/SLE" and "SS/SSc" as distinct subsets within the context of connective tissue diseases with different clinical expression and outcomes, thus deserving an individualised assessment and personalised medical interventions.

Introduction

Sjögren's syndrome (SS) is a complex autoimmune disorder that may co-occur with other major rheumatic diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory myopathies (IIM) and systemic sclerosis (SSc) (1-3). The coexistence of SS with neuromyelitis optica spectrum disorder (NMOSD) (4), primary biliary cholangitis (5) and coeliac disease (6) is also well-known, thus offering a unique opportunity to explore genetic, environmental and biologic factors that may contribute to phenotypic heterogeneity in autoimmunity (7).

Historically, the diagnosis of 'secondary' SS (sSS) has been made in patients presenting symptoms of dryness in the presence of other rare or complex rheumatic connective tissue disease (rCTDs), in contrast to the term 'primary' SS (pSS) that it is used to identify patients with SS in the absence of another underlying rheumatic disorder (8). However, nowadays it has been questioned whether the concept of 'primary' and 'secondary' may still have "une raison d'être" (8, 9). Indeed, sSS has been scarcely investigated leaving several research questions that need to be answered regarding its clinical expression, long-term outcome and targeted therapies. In this review we will summarise the most relevant literature contributions on the topic, particularly focusing on the association between SS and two other rare and complex diseases: SLE and SSc. We will specifically discuss the possibility of defining "SS/SLE" and "SS/SSc" as distinct phenotypes of autoimmunity that combine both SS features and the clinical and serological manifestations of other CTDs, thus deserving a personalised assessment and targeted medical interventions.

SS/SLE subset: distinctive clinical, serological features and long-term prognosis

SS and SLE are known to share multiple genetic, epigenetic, and immunological features, however, they remain different conditions with distinctive features (10, 11). The possible association between SS and SLE has been largely recognised in the literature (12-19). According to a recent meta-analysis, the frequency of SS/SLE ranges from 14 to 17.8% of SLE patients (7).

However, the true prevalence of this subset might remain underestimated. This is due to two main reasons: on one hand, oral and ocular tests are not routinely performed in SLE patients in the absence of sicca symptoms (20); on the other hand, sicca symptoms often lack in younger SS patients or may due to drugs taken by the patients, making it challenging to determine the specific SS/SLE status in SLE patients (21, 22). The latter aspect often results in SLE patients being diagnosed as having "secondary" SS later into their disease. Another layer of complexity is added when considering that patients with SS who have a higher systemic disease activity profile, may have manifestations overlapping those of SLE, such as arthritis, lymphadenopathy, fever, subacute cutaneous lupus erythematosus, cytopenia, myositis, myelitis or peripheral neuropathy. Finally, this raises the question of why is SS commonly regarded as "secondary" to SLE and other rCTDs, rather than the opposite, or simply noting that more than one condition can coexist in the same patient.

In fact, nowadays, several evidences support the hypothesis that SS/SLE may represent a well-defined clinical entity, rather than the mere overlap of independent autoimmune systemic diseases.

Temporal relationship between SS and SLE

The traditional definition of "secondary" SS has generally suggested a sort of sequential order with SS manifestations occurring afterwards in patients with a pre-existing diagnosis of SLE (9). However, the diagnosis of SS may precede or occur concomitantly with the diagnosis of SLE. For instance, in a cohort study by Manoussakis *et al*. (14), in 18 out of 26 SS/SLE patients (69.2%), sicca manifestations preceded the onset of SLE by a median time of 4 years, 4 out of 26 patients developed SS and SLE manifestations at the same time, and finally, in the remaining 4 patients SLE was diagnosed 2-3 years before SS. Szanto *et al*. analysed the disease onset of 53 SS/SLE patients, and found that in 15% of cases, SS preceded SLE (15). In a larger cohort of SS/SLE patients, SS diagnosis preceded SLE onset by more than 1 year in 15% patients (median 3 years). On the contrary, SS was documented within 1 year of the onset of SLE in 47% patients, and after more than 1 year in 42% patients (median 7 years) (23).

Epidemiological, clinical and serological features

Since the first descriptions of SLE and SS, many distinctive clinical-serological features have been identified in SS/SLE patients (Table I) (24-26). From an epidemiological point of view, according to the vast majority of the studies, SS/SLE patients are predominantly females and significantly older than SLE patients (7), but younger than patients with pSS (14). Moreover, from a clinical point of view, SS/SLE patients seem to have a lower prevalence of kidney involvement than SLE patients (14, 27). Noteworthy, Nossent *et al*. (12) showed a statistically significant superior overall 20 years survival rate in SS/SLE patients as compared to isolated SLE patients. Interestingly, some studies showed a lower prevalence of associated SS in SLE black patients, who are known to suffer more frequently of an aggressive disease course, with higher prevalence of renal involvement. Despite experiencing less internal organ involvement, a systemic inflammatory state with higher levels of proinflammatory cytokines (*i.e*. TNF-α, IL-6, MCP-4, MIP-1β, IL12/IL-23p40, and IP-10) has been described in the SS/SLE subgroup compared to SLE, with possible clinical and therapeutic implications (19). Finally, as Gal *et al*. (28) have described differences of anti-Ro52-kD/SSA and the anti-Ro60-kD/SSA distribution were found between the pSS and SS/SLE patients, with anti-Ro60-kD/SSA autoantibodies being significantly more frequent in the latter group than in pSS. By contrast, isolated anti-Ro52 reactivity has been primarily found in pSS patients (29). The most relevant differences in clinical phenotype and autoantibodies profile between isolated SLE and SS/SLE patients are summarised in Table I.

On the opposite side, SS/SLE patients appear to present more frequently with Raynaud's Phenomenon (RP), arthritis, serositis and central nervous system involvement when compared with pSS patients (14). Moreover, in the study from Szanto *et al*. (15) a higher frequency of antiphospholipid syndrome, anaemia, leukopenia, lymphopenia, renal, lung, central nervous system, and skin involvement was reported in SS/SLE patients compared to primary SS patients. On the contrary, pSS patients have been found to display more often sicca symptoms, parotid enlargement and lymphadenopathy (11, 14). Finally, concerning the immunologic profile, a higher prevalence of ANA, anti-dsDNA, anti-cardiolipin antibodies, anti-B2GPI, anti-U1snRNP has been observed in SS/SLE compared to primary SS (14). Szanto *et al*. also found higher frequency of anti-Ro and anti-La autoantibodies and lower frequency of RF in SS/SLE patients (15).

Although the distinctive features of SS/SLE have been clearly defined, the key question as whether considering SS/SLE patients as a distinct subgroup might have clinical, prognostic and therapeutic implications remains unsolved. Interestingly, the recent ACR/EULAR 2019 criteria of SLE and ACR/EULAR 2016 criteria of SS allow to distinguish SLE from primary SS and are both fulfilled by patients with SS/SLE (30).

Regarding the risk for lymphoproliferation, SS/SLE subset has been scarcely investigated. Lofstrom *et al*. noticed a statistically significant association between sicca syndrome, parotid enlargement and non-Hodgkin's lymphoma in SLE patients (31). Furthermore, Bernatsky *et al*. (32) showed that a diagnosis of SS could be made in 20% of SLE patients who developed lymphoma, but indeed, this aspect deserves further investigations.

Treatment options

Regarding the possibility that SS/SLE subset may respond differently to specific therapeutic strategies, interesting data have recently come out (9, 20). Indeed, targeting B cells has been widely seen as a potential therapeutic option for both SLE and pSS (33). A variety of B cell disturbances has been described in both diseases. B cells do not only

Table I. Clinical-serological features identified in SS/SLE patients.

Authors, year		SS/SLE *vs*. SLE patients		
	Prevalence	Clinical phenotype	Autoantibody profile	SS classification criteria
Nossent *et al*. 1998 (12)	19.6%	Older age Less renal involvement More thrombocytopenia Superior survival rate		Preliminary European Criteria 1993 (101)
Gilboe *et al*. 2001 (13)	11.1%	Less renal involvement Lower SF-36 vitality score Higher VAS fatigue score	More anti-Ro and anti-La	Preliminary European Criteria 1993 (101)
Manoussakis *et al*. 2004 (14)	9.2%	Older age More Raynaud ph. Less renal involvement Less lymphadenopathy Less thrombocytopenia	More anti-La and RF	European Classification criteria 1996 (102)
Szanto *et al*. 2006 (15)	15.5%	Older age More thyroid disease	More anti-Ro and anti-La	AECG 2002 (103)
Scofield *et al*. 2007 (17)	14.9%	More thyroid disease		AECG 2002 (103)
Pan *et al*. 2008 (18)	6.5%	Older age Less renal involvement	More anti-Ro and anti-La, anti-dsDNA	AECG 2002 (103)
Baer *et al*. 2010 (23)	14.5%	Older age More white More photosensitivity More oral ulcers More Raynaud ph. Lower renal involvement Higher SLICC/ACR score	More anti-Ro and anti-La, anti-dsDNA, anti RNP	Bloch Criteria 1965 (104)
Ruacho *et al*. 2020 (19)	23%	Older age More leukocytopenia More peripheral neuropathy Lower renal involvement	More anti-La and RF	AECG 2002 (103)

contribute to the production of autoantibodies, they are also involved in abnormal cytokine secretion, presentation of autoantigens, B cell receptor signalling deregulation and increased expression of the co-stimulatory molecules(34). The main alteration of B cell homeostasis in SLE is the expansion of peripheral $CD27^{high}$ plasmablasts. Likewise, increased plasmablasts have been also observed in the blood of patients with primary SS as well as increased plasma cells in the salivary glands of these patients (35). Several abnormalities have also been described regarding transitional B cells in SLE (36). Similarly, increased transitional B cells have been described in serum and glandular infiltrates of patients with SS, where they receive survival signals via BlyS thus contributing to the progression of organ damage (37, 38).

BLyS has also been found in high concentrations in serum of SLE patients (39). The two large phase III trials [BLISS-52 (40) and BLISS-76 (41)] with belimumab, a humanised monoclonal antibody against soluble BLyS, carried out in moderately active non-nephritis SLE patients met their primary efficacy end-point of clinical superiority compared to placebo plus standard of care. BLyS inhibition induces slow, selective B cell depletion particularly affecting transitional, naive B cell lines and the CD27-isotype-switched memory population (42). In parallel, BLyS has also been found elevated in the serum of primary SS patients correlating with the level of RF and anti-SSA antibodies. In the Belimumab in Sjögren's syndrome (BELISS) study, an open-label trial assessing the efficacy and safety of belimumab in primary SS, showed that 60% of patients receiving belimumab achieved a clinical response in dryness score, fatigue score, pain score, and systemic activity score reduction as well as in B cell activation biomarkers improvement (43).

Among B depleting strategy, another interesting option for both SLE and associated SS is represented by rituximab, a chimeric mouse/human monoclonal antibody against CD20 and both mature B cells and B cell precursors from the pre-B cell stage onwards (44). Rituximab treatment led to a long-standing reduction of peripheral memory B cells with a delayed recovery of blood memory B cells compared to memory B cells in tissue (44). A number of open-label prospective and retrospective studies have demonstrated the effectiveness of rituximab in the management of moderately severe to severe SLE (42). Moreover, although the rituximab Phase III randomised controlled trials, the EXPLORER trial (45) (non-renal SLE patients) and the LUNAR trial (46) (lupus nephritis patients), did not reach the endpoints, noteworthy, B cell-

depleting therapy was associated with statistically significant improvement in complement C3 levels and dsDNA antibodies. Analogously, in primary SS, despite encouraging preliminary evidences, two large randomised trials, TRACTISS(47) and TEAR (48) did not demonstrate a clear superiority of rituximab versus placebo (49). On the basis of the new insights acquired, future approaches are currently being investigated in both diseases to induce a more profound B depletion including the combination of rituximab and belimumab (50-52).

Concrete data on the efficacy of B depleting therapy in SS/SLE patients have been recently pointed out in the post hoc analysis of the EMBODY phase III trials with epratuzumab, a humanised anti-CD22 monoclonal antibody(20). CD22 is an adhesion molecule and co-receptor for BCR, and attenuates BCR signalling. The post hoc analysis has shown that epratuzumab improved SLE-specific clinical outcomes at week 48, compared with placebo in patients with a diagnosis of associated SS. Epratuzumab infusion resulted in a reduction of CD27- transitional and naive B cells, B cell reduction was faster in patients with associated SS. The authors concluded that patients with SLE and associated SS treated with epratuzumab showed improvement in SLE disease activity, which was associated with bioactivity, such as decreases in B cell number and IgM level (20).

Recognising patients with SS/SLE as a distinct subset of disease based on immunological and molecular mechanisms may open new avenues for targeting shared common pathogenic cells and pathways. From this perspective, given that the interferon signature is shared by SLE and SS, targeting the interferon pathways may represent a promising strategy for the treatment of SS/SLE subset. The Janus kinase inhibitor tofacitinib that inhibits both type I and type II interferon has been recently shown as well-tolerated in subjects with mild-to-moderately active SLE(53). Similarly, phase III of the studies BRAVE I (NCT03616912) and BRAVE II (NCT03616964) aim to assess the effects of baricitinib in patients with SLE, and are currently recruiting patients. Tofacitinib (NCT04496960) and baricitinib (NCT04916756) will be also assessed in SS in randomised controlled trials that are still recruiting. Noteworthy, several new strategies are in the pipeline and they appear extremely interesting (54). For instance, the possibility of modulating CD40–CD40 ligand interaction or targeting kinases (*i.e.* Bruton's tyrosine kinase (BTK) and phosphatidylinositol 3-kinase (PI3K)) have all appeared particularly promising preclinically and ongoing trials may confirm these preclinical data (50, 55).

In conclusion, there is an increasing awareness that SS/SLE may indeed offer a unique opportunity to understand the expression, long-term evolution and outcome of autoimmune phenotypes among patients affected by CTDs.

SS/SSc subset: distinctive clinical, serological features and long-term prognosis

The interplay between SS and SSc is generally considered as particularly complex encompassing a wide spectrum of clinical intermediate and overlapping phenotypes. Indeed, sicca symptoms are quite common in SSc, but they have been generally attributed to fibrotic changes in the salivary glands (56). Still, the "true" association of SSc and SS has been reported in up to one-third of SSc patients, especially in limited cutaneous SSc subtypes with a prevalence varying from 17%-29% of SSc patients (57-62). Intriguingly, according to the current literature, approximately the 10% of patients with pSS may present a scleroderma-like patternat the nailfold videocapillaroscopic analysis (63). Differential features in patients with positive lip biopsy or in relation to positivity of anti–anti-SSA/Ro or anti-SSB/La antibodies were not detected. The presence of marked capillary dilation in pSS patient with associated RP indicates the need to exclude an overlapping syndrome (63).

Table II summarises the most relevant differences in clinical phenotype and autoantibodies profile among SSc, SS and SS/SSc patients. As shown in the Table, similarly to SLE, there might be evidence that SS/SSc patients actually represent a distinct subset within the autoimmunity rCTDs spectrum.

Serological and clinical features

From a serological point of view, patients with SS and SSc show more frequently anticentromere antibodies (ACA) and a spreading of autoimmunity, with additional autoantibodies and autoimmune diseases, particularly primary biliary cholangitis (PBC) (56, 62, 64, 65).

In fact, ACA might also be detected in approximately 5–10% of SS patients without evidence of full-blown SSc, but in presence of severe glandular and extra-glandular SS-related manifestations (66-72). In patients with SSc, ACA recognise 3 centromeric proteins (CENP) identified as autoantigens localised at the kinetochore plates: CENP-A, CENP-B, and CENP-C(73). In SS/SSc, the specific target of ACA is unknown. Salliot *et al*. showed that all their SS/ACA patients recognised the same target, CENP-B(67). Gelber *et al*. showed that while patients with SS predominantly recognised CENP-C alone, dual recognition of CENP-B and CENP-C was most frequently detected in SSc (74). Recently, Kajio *et al*. (73) carried out a comprehensive detailed analysis of the ACAs specificity in 241 patients with SSc, SS and PBC. The authors found a broad spectrum of serum autoantibodies against the centromere-kinetochore macrocomplex and they found that the prevalence of each antibody specificity was shared across the three diseases SS, SSc and PBC. Moreover, the authors found that immunostaining of SS/ACA salivary glands showed the accumulation of antibody-secreting cells specific for kinetochore, whereas little reactivity against CENP-B was seen. Based on these findings, the authors proposed the term 'ACA-related disease' to embrace the spectrum of phenotypes encompassing SSc and SS features. By contrast, although relatively common in SS/SSc patients, no conclusive data are available regarding the possible role of anti-Ro52 as a putative biomarker of SS in SSc patients (75).

Table II. The most relevant differences in clinical phenotype and autoantibodies profile among SSc, SS and SS/SSc patients.

Authors, year		SS/SSc vs SSc patients		
	Population	SS/SSc vs SSc patients	SS/SSc vs SS patients	SS/SSc classification criteria
Avouac *et al*. 2006 (64)	SS/SSc	Less lung fibrosis		AECG 2002 (103)/ LeRoy 1988 (105)
Salliot *et al*. 2007 (67)	SS/ACA		More Raynaud's phenomenon More peripheral neuropathy, More KCS More PBC Less anti-Ro and anti-La	AECG 2002 (103)/ LeRoy 1988 (105)
Salliot *et al*. 2007 (62)	SS/SSc	Less lung fibrosis	More peripheral neuropathy More arthritis	AECG 2002 (103)/ LeRoy 1988 (105)
Bournia *et al*. 2010 (66)	SS/ACA	Less telangiectasia Less puffy fingers Less sclerodactyly Less Raynaud Phenomenon Less digital ulcers Less gastrointestinal, Less lung fibrosis	Less dry eye Less hypergammaglobulinemia Less anti-Ro and anti-La More Raynaud Phenomenon More dysfagia	AECG 2002 (103)/ Preliminary American criteria (106) and Early SSc criteria (107)
Kobak *et al*. 2012 (65)	SSc/SS	Less PAH Less lung fibrosis Less sclerodactyly Less telangiectasia		Preliminary European Criteria 1993 (101)/ LeRoy 1988 (105)
Baldini *et al*. 2013 (68)	SS/ACA	Less PAH Less sclerodactyly Less telangiectasia Less digital ulcers	Less anti-Ro and anti-La Less hypergammaglobulinemia More SGE More NHL	AECG 2002 (103)/ Preliminary American criteria (106) and Early SSc criteria (107)
Lee *et al*. 2015 (69)	SS/ACA		Less anti-Ro More Raynaud Phenomenon More sclerodactyly	AECG 2002 (103)/ Preliminary American criteria (106) and Early SSc criteria (107)
Baer *et al*. 2016 (72)	SS/ACA		Older age Less anti-Ro and anti-La, RF Less hypergammaglobulinemia Higher FS More glandular dysfunction	ACR criteria 2012 (108)/n.a.
Tsukamoto *et al*. 2018 (70)	SS/ACA		More Raynaud Phen. More sclerodactyly Less hypergamma, Less leukocytopenia	ACR/EULAR SS 2016 (109)/ ACR/EULAR SSc 2013 (110)
Li *et al*. 2020 (71)	SS/ACA		Less anti-Ro and anti-La More glandular dysfunction	AECG 2002 (103)/n.a
Can *et al*. 2020 (56)	SS/SSc	Older age More anti-Ro		AECG 2002 (103)/ Preliminary American criteria [106] and Early SSc criteria (107)

SS: Sjögren's syndrome; SSc: systemic sclerosis; ACA: anticentromere antibodies; PAH: pulmonary artery hypertension; KCS: keratoconjunctivitis sicca; PBC: primary biliary cholangitis; RF: rheumatoid factor; AECG: American European Consensus Group.

Clinically, the so called "ACA-related disease" defines patients with a less serious SSc. Subjects with SS/ACA or SS/SSc have less frequently telangiectasia, sclerodactyly, digital ulcers, pulmonary hypertension or lung fibrosis; although it remains controversial whether the concomitant presence of anti-Ro52 may increase the frequency of interstitial lung involvement in specifically subsets of SS/SSc overlap patients (62, 64, 76).

On the other hand, with respect to patients with pSS, SS/SSc subjects present more commonly, Raynaud's phenomenon, peripheral neuropathy and less frequently hypergammaglobulinaemia, leukocytopenia, rheumatoid factor, anti-La/SSB, and anti-Ro/SSA, thus implying that ACA antibody governs some clinical features and controls the expression of autoimmune phenotype among patients who have another connective tissue disease (66-72, 77). Moreover, regarding SS-related glandular dysfunction, the individuals with overlap SS/SSc present more severe subjective and objective dryness (67, 72). In addition, histology data have concordantly shown that the glandular

dysfunction is apparently associated with more pronounce labial salivary gland inflammation but not fibrosis suggesting that the typical "SS autoimmune epithelitis" can be also detected in overlap patients(71). From this perspective, Baer *et al*. (72) showed that SS/SSc patients presented a higher percentage of MSGB with FS >2 and a higher mean FS than patients with pSS. No difference was detected among the subgroups regarding glandular fibrosis. Notarstefano *et al*. (78) also compared the number of germinal-centre structures in patients with SS and in SS/ACA individuals describing a similar number and frequency of GC-like structures between the two groups. Intriguingly, according to Lee *et al*. (79), salivary gland ultrasonography revealed that the proportion of patients with OMERACT grades ≥2 was significantly higher in SSc and primary SS groups than those in the idiopathic sicca syndrome group whereas no difference in fibrosis was observed between SSc and pSS groups. Finally, several authors have highlighted that SS/SSc patients may have a comparable risk for lymphoproliferative complications when compared to primary SS patients (66). In a single centre study by Baldini *et al*. we have found that the frequency of lymphoma in the overlap patients was even higher than the one detected in the pSS group (68). Scherlinger *et al*. (80) found that the occurrence of SS was significantly associated with mortality in SSc. The main causes of mortality were infections and diffuse B cell lymphoma. The authors found that with respect to treatments, patients with overlap SSc were more likely to receive corticosteroids, immunosuppressive drugs, and biologic DMARDs than non-overlap SSc patients.

Treatment options

Likewise in SS/SLE patients, targeting B cells may be justified also in patients with SS/SSc (81). A dysregulation of B cell homeostasis has been widely recognised in SSc, with a decrease of both regulatory B cells and $CD19^+$ $CD27^+$ memory B cells (82). Moreover, accumulating evidence have highlighted a crosstalk between B cells and fibroblasts, ultimately leading to skin and organ fibrosis. BAFF levels have been correlated with disease activity and increased IL-6 production by B cells. In turn, IL-6 level correlates with the extent of skin fibrosis, linking B cell activity to fibrosis (82). Two recent meta-analyses have shown that rituximab may be a relatively safe and promising therapeutic option for SSc skin and lung involvement in certain patients however, larger studies are still required to determine whether it stabilises disease progression in general (83, 84). Recently, on the basis of the results of Fascinate (85) and FocuSSced (86) studies, the FDA has also approved tocilizumab to block IL-6 signalling and to slow the rate of decline in pulmonary function in patients with SSc-ILD, regardless of the cutaneous subset (87). IL-6 concentrations are increased in the serum and saliva of SS patients; however, the ETAP study - a phase 2/3 RCT performed with tocilizumab in SS patients - did not reach the endpoints suggesting that cell activation was probably not mediated by IL-6 in most patients with pSS (88). Other therapeutic approaches have been recently evaluated in phase II trials or are ongoing for SSc including abatacept and Jak-inhibitors and it is likely that these drugs may have a rationale also for SS/SSc patients (81).

Intriguingly, from this point of view, Petitdemange *et al*. (89) have recently analysed targeted therapies which development was shared between at least two of the most common autoimmune systemic diseases. The authors identified five targeted therapies shared between SSc and SS including: rituximab, the combination rituximab and belimumab, abatacept, tocilizumab and tofacitinib. The most frequently targeted molecules and pathways were: JAK-STAT pathways, IL-6, costimulation molecules, BAFF and CD20. This is actually not surprising since it reflects the overlap of pathogenic pathways of all these diseases: it also highlights the potential of drug repurposing. The "endotypic" characterisation of SS/SSc subset need to be further supported by the identification of novel molecular and cellular markers and will then help in the future to pave the way for novel approaches that move from the actual classification based on clinical signs and symptoms to patients' clustering based on shared common immunological and molecular mechanisms.

SS and other connective tissue disease, a till now unexplored area

To date only few studies reported the overlap between SS and idiopathic inflammatory myopathies (IIM). In particular, Felten *et al*. (90) described a cohort of 395 pSS followed for more than 60 months, and reported that the occurrence of IIMs was about the 1%, mainly in the form of inclusion body myositis (IBM). A similar prevalence was previously described in another multicentre study performed on 1320 Italian SS, although with a low prevalence of IBM (91). However, it is interesting to observe that the frequency of anti-Ro antibodies in general, and of anti-Ro52 antibodies in particular, in IIMs is common. More specifically, anti-Ro52 antibodies have been identified in about the 50% of patients with antisynthetase syndrome (ASSD) (92) and in about the 30% of patients with anti-MDA5 syndrome (93), but clinical information about dryness and the tests necessary to rule-out a SS were lacking, thus suggesting the potential risk of SS missed diagnosis. Recent advances showed also that anti-Ro52 positivity is associated with isolated ILD (94), with these patients being commonly classified under the heterogeneous umbrella of IPAF (95). Furthermore, anti-Ro52 seems to indicate by itself an ILD with a more aggressive course, independently of patient classification (96-99). In a similar setting, the multidisciplinary approach involving both rheumatologists and pulmonologists may have an added values in term of increased diagnostic performance (100).

Conclusions

Literature data intriguingly suggest that identifying as distinct disease subsets those patients with SS and other autoimmune disorders may offer a unique opportunity to rethink and reclassify complex and rare autoimmune

diseases. Indeed, we may now avoid the term of secondary SS and replace it with the term associated SS. Novel approaches based on diseases deconstruction/diseases reconstruction and applying omics techniques may allow to identify more homogeneous target population and pave new avenues for innovative therapeutic approaches based on common "endotype" rather than "phenotype" stratification.

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