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Sjögren's syndrome is associated with and not secondary to systemic sclerosis

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***Objectives*. When Sjögren's syndrome (SS) is secondary to rheumatoid arthritis, the sicca syndrome is less serious and anti-SSA/SSB antibodies are found less frequently than in primary SS (pSS). When SS is associated with systemic lupus erythematosus, clinical and serological patterns are similar to those of pSS. We aimed to determine whether SS, accompanying systemic sclerosis (SSc), could be considered secondary to or associated with SSc and whether the coexistence of both modifies the severity and the outcome of each disease.**

***Patients and methods*. A retrospective multicentric study was conducted to compare (i) characteristics and complications of SS between 27 patients with SS and SSc (SS-SSc) and 202 patients with pSS, and (ii) the characteristics of SSc and complications between the SS-SSc group and 94 patients with SSc alone.**

***Results*. SS features were similar in both SS-SSc and pSS patients, except for peripheral neuropathy and arthritis, which was more common in SS-SSc than in the pSS patients ($P = 0.02$ and 0.05, respectively). SSc appears to be less severe in patients with SS-SSc than SSc alone with a lower frequency of lung fibrosis ($P = 0.05$). Compared with patients with pSS or SSc alone, SS-SSc patients were more likely to have another autoimmune disorder and other autoantibodies (SS-SSc *vs* pSS, $P = 0.02$ and $P = 0.03$, respectively).**

***Conclusion*. SS seems to be associated with and not secondary to SSc. SS associated with SSc has the same features as pSS, but SSc seems to be less serious. Moreover, the association of SS and SSc is frequently accompanied by a spreading of autoimmunity.**

KEY WORDS: Sjögren's syndrome, Systemic sclerosis, Autoimmune disease, Overlap autoimmune disease.

Introduction

Sjögren's syndrome (SS) is an 'autoimmune epithelitis' characterized by sicca syndrome but also extra-glandular manifestations that reveal the severity of this disorder [1, 2]. SS can occur alone as primary SS (pSS) or accompany other autoimmune disorders as secondary SS (sSS) [3, 4].

Typically, 'secondary' SS is distinguished from 'associated' SS (Table 1). SS, secondary to rheumatoid arthritis (RA), seems to be a complication of these disorders: the sicca syndrome is less serious, anti-Ro/SSA and anti-La/SSB antibodies are less frequently present and the evolution of SS is closely linked to that of RA or PBC [3, 5]. For some authors, SS accompanying primary biliary cirrhosis (PBC) seems to be 'secondary'; however, it keeps controversial because PBC can also occur during pSS [6–9]. In contrast, SS accompanying systemic lupus erythematosus (SLE) or autoimmune thyroiditis shows clinical and serological patterns similar to pSS [10–17], with the same occurrence of anti-SSA/SSB antibodies and the same severity as pSS. Thus, SS seems to be associated with these disorders, with an overlap syndrome [14]. Moreover, the association of SS with other autoimmune disorders could modify the severity of the autoimmune disease associated with SS. Manoussakis *et al.* [14] showed that SLE seemed to be less serious when it was associated with SS, featuring a low occurrence of thrombocytopenia and lymphadenopathic and renal involvement. Moreover, Raynaud's phenomenon, arthritis and dyspareunia were more common when SS was associated with SLE than with pSS [14].

Sicca syndrome is common in systemic sclerosis (SSc) (60%), almost always due to salivary fibrosis. But SS is present in only 17 to 29% of the cases [4, 18–20], and a few and controversial data are available about Sjögren's characteristics in patients with SSc. These controversial data on characteristics of SS associated with SSc are probably due to the lack of a consensual definition of sSS until recently. sSS is now clearly defined by criteria from the American–European consensus group (AECG) published in 2002 [21] and thus, the characteristics of patients with SS and SSc can now be studied.

In the present study, we aimed to assess whether SS accompanying SSc is secondary to or associated with this disease and to determine whether the severity of these two diseases is modified when they are associated.

Patients and methods

Study design

Retrospective and comparative study.

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TABLE 1. Sjögren's syndrome (SS) accompanying other autoimmune diseases and comparison of clinical and immunological features with pSS

	Frequency of SS (%)	Comparison of clinical and immunological features with pSS	Reference Numbers
Rheumatoid arthritis	5–31	Sicca syndrome, extra-glandular manifestations and anti-SSA/SSB antibodies are less common than in pSS	[3–5, 29]
Systemic lupus erythematosus	2–30	Sicca syndrome and presence of anti-SSA/SSB antibodies are similar to pSS	[4, 10–14]
Mixed connectivity tissue disease	14.5–56	Sicca syndrome is similar but anti-SSA/SSB antibodies occur less commonly than in pSS. Raynaud's phenomenon and lung fibrosis are more common than in pSS	[30, 31]
Primary biliary cirrhosis	3–25	Sicca syndrome with predominant xerostomia and lower occurrence of anti-SSA/SSB antibodies than in pSS	[4, 6–9]
Autoimmune thyroiditis	2–20	Sicca syndrome and extra-glandular manifestations and presence of anti-SSA/SSB antibodies are similar to that in pSS	[4, 15–17, 32]
Systemic sclerosis	17–29	Controversial	[4, 18–20]

Setting

Multicentre tertiary-referral clinic.

Selection of patients

The present study included three groups of patients: those with SS and SSc (designated as the SS-SSc group), those with pSS (pSS group) and those only with SSc only (SSc group).

Primary or secondary SS was defined according to the American–European consensus group (AECG) criteria [21]. The diagnosis of SSc followed the American Rheumatism Association and LeRoy *et al.* criteria [22, 23]. Limited cutaneous SSc was defined by skin thickening in areas solely distal to the elbows and knees, with or without facial involvement; diffuse SSc was defined by the presence of skin thickening proximal, as well as distal, to the elbows and knees, with or without facial or truncal involvement [23].

There were 27 patients included in the SS-SSc group followed in the three French departments of rheumatology or internal medicine in teaching hospitals, 202 from the cohort of pSS patients followed in the department of rheumatology of Bicêtre Hospital and 94 from the cohort of 262 patients with SSc followed in the department of internal medicine of Cochin Hospital. To be able to compare the severity of SSc associated or not with SS, we chose SSc patients randomly, except when we needed to have the same proportion of limited *vs* diffuse SSc patients as in the SS-SSc group.

The objectives of the study were to compare SS-SSc with the pSS group for patterns of SS and severity of disease and with the SSc group for patterns of SSc and severity of disease.

Data collection

Demographic features were collected for each patient. For SS, data were collected on subjective and objective xerophtalmia and xerostomia, purpura and parotid gland enlargement. Objective confirmation of xerostomia was an unstimulated salivary flow of <0.1 ml/min or abnormal results of parotid sialography or scintigraphy of salivary glands with $^{99\text{-m}}$Tc. Objective xerophtalmia were present when the Schirmer's test result was abnormal (≤ 5 mm in 5 min) or the Van Bijsterveld score was ≥ 4 after Lissamine green coloration. Previous or present extra-glandular complications of SS were defined as arthritis with objective confirmation of synovitis, purpura, renal involvement, pulmonary involvement assessed by tomodensitometric examination, neuropathic features based on the clinical and electrophysiological presence of sensory or motor deficits, or lymphoma revealed on biopsy.

For SSc, data were collected on sclerodactyly, proximal sclerosis, Raynaud's phenomenon, calcinosis, telangiectasia, oesophageal involvement, lung interstitial syndrome, digital ulcerations or pitting scars and vascular abnormalities seen on nailfold capillaroscopy. The following complications of SSc were collected: heart involvement (such as pericarditis, myocarditis or heart failure), pulmonary arterial hypertension (defined as systolic pulmonary arterial pressure >45 mmHg upon echocardiography and/or mean pulmonary arterial pressure >25 mmHg upon right heart catheterization), lung fibrosis assessed by chest high-resolution computed tomodensitometry and abnormal pulmonary function test values (total lung capacity or vital capacity $<80\%$ of predicted values and/or diffusing capacity/alveolar volume $<75\%$ of that predicted), digital necrosis, scleroderma renal crisis (defined by rapidly progressive oligouric renal insufficiency with no other explanation and/or rapidly progressive arterial hypertension occurring during the course of SSc) and bowel involvement (malabsorption, pseudo-obstruction and bacterial overgrowth).

Moreover, for each disease, data were collected in the presence of an additional autoimmune disorder such as SLE, PBC or autoimmune thyroiditis.

The results of the biopsy of the minor salivary gland were classified according to Chisholm and Mason classification [24]. Immunological data collected from medical files included presence of anti-nuclear antibodies (detected by indirect immunofluorescence), anti-SSA/Ro, SSB/La antibodies and anti-topoisomerase 1 (by ELISA), anti-centromere antibodies (by indirect immunofluorescence), rheumatoid factor (by nephelometry); other antibodies such as anti-mitochondrial, anti-thyroglobulin and anti-thyroid peroxidase antibodies and IgG antibodies to double-stranded DNA. Also recorded were data on the level of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and the level of β_2-microglobulin, C4 complement serum and gammaglobulin (with detection of monoclonal component) and cryoglobulin, considered as activity markers and prognosis factors of SS [25–28].

Statistical analysis

Chi-square testing, with Yate's correction when appropriate, was used to compare the difference in prevalence for qualitative variables. To analyse quantitative values, we used ANOVA or Mann–Whitney tests. The level of significance was set at 5%.

Results

Patient characteristics

The demographic characteristics of the three patient groups (SS-SSc, pSS and SSc) are summarized in Table 2. Women represented 90% of the patients in each group. The mean age at the diagnosis of SS or SSc was similar to the several groups of

TABLE 2. Comparison of demographic characteristics of patients with SS-SSc, pSS alone and SSc alone in each group

	SS-SSc ($n=27$)	pSS ($n=202$)	SSc ($n=94$)	P SS-SSc *vs* pSS	SS-SSc *vs* SSc
Female, *n* (%)	25 (92.6)	187 (95.6)	79 (84.0)	1.0000	0.42
Mean ± SD age at the diagnosis of SS, years (range)	54.6 ± 15.3 (25–77)	51.7 ± 14.6 (24–82)	NA	0.34	NA
Mean ± SD age at the diagnosis of SSc, years (range)	55.0 ± 13.6 (33–73)	NA	50.2 ± 17.0 (20-91)	NA	0.18
Mean ± SD duration of SS symptoms[a], yrs (range)	7.4 ± 6.1 (1–25)	12.8 ± 7.6 (0–35)	NA	0.0004	NA
Mean ± SD duration of SSc symptoms[a], yrs (range)	7.3 ± 7.8 (0–31)	NA	8.4 ± 9.1 (0–53.5)	NA	0.50

[a]Interval of time between the first symptom and the date of study.
SS-SSc, patients with SS and systemic sclerosis; pSS, patients with primary Sjögren's syndrome; SSc, patients with systemic sclerosis alone; NA: not applicable.

patients (range 50–55 yrs). The mean durations of symptoms were 7.4, 8.4 and 12.8 yrs for SS-SSc, SSc and pSS groups, respectively. The duration of SS symptoms was significantly higher in the pSS group than in the SS-SSc group ($P=0.0004$). SS and SSc characteristics of the patients in the 3 groups are indicated in Table 3.

Comparison of Sjögren's syndrome characteristics

SS characteristics were compared between the 27 patients of the SS-SSc group and the 202 patients with only pSS (Table 3). The groups did not differ in subjective and objective evidence of sicca syndrome. A total of 84% of the SS-SSc patients and 91% of the pSS patients had a grade 3 or 4 Chisholm and Mason classification on histologic analysis of biopsy of minor salivary glands ($P=0.54$). In one centre, 11 biopsies were revised and, among them, only two biopsies showed fibrosis also. The prevalence of only anti-SSA and anti-SSA + anti-SSB antibodies was 29.6 and 18.5%, respectively, in the SS-SSc group and did not significantly differ from that found in the pSS group (28.2 and 35%, respectively, $P=1.000$ and $P=0.13$, respectively).

Comparison of Sjögren's syndrome severity

To appreciate the severity of SS, we compared the complications, adverse prognosis factors and activity markers of SS with SS-SSc and pSS groups (Table 4). Overall, the SS-SSc group did not show more complications of SS than the pSS group ($P=0.20$). Nevertheless, arthritis and peripheral neuropathic features were more common in these patients than in the pSS group ($P=0.05$ and $P=0.02$, respectively). Concerning the known adverse prognosis factors of SS, the prevalence of monoclonal gammapathic features, parotid gland enlargement and low C4 level were similar in the two groups ($P=1.00$, $P=0.12$ and $P=1.00$, respectively). As activity markers of SS, mean levels of CRP, ESR and levels of β_2-microglobulin and gammaglobulin were comparable ($P=0.85$, $P=0.68$, $P=0.66$, $P=0.81$, respectively). Nevertheless, the presence of monoclonal or polyclonal cryoglobulin was more common in the SS-SSc than in the pSS group ($P=0.003$). This high occurrence of cryoglobulin in SS-SSc patients (20%) was not associated with increased presence of lymphoma in this group. Two of the five patients with peripheral neuropathic features also showed the presence of mixed cryoglobulin level (one monoclonal and one polyclonal). Compared with the patients with pSS, the SS-SSc patients more commonly had a third autoimmune disorder (40.7 *vs* 18.8%, respectively, $P=0.02$), which was PBC in three patients. The other autoimmune diseases were SLE ($n=2$), RA ($n=2$), polymyositis ($n=2$), autoimmune thyroiditis ($n=2$), polychondritis ($n=1$) and mixed connective tissue disease ($n=1$). The prevalence of other antibodies (except anti-SSA, anti-SSB, anti-centromere and anti-SSc-70 antibodies) was significantly higher in the SS-SSc than in the pSS group (33.3 *vs* 16.3%, $P=0.03$). These antibodies were anti-mitochondrial ($n=3$), anti-phospholipid ($n=3$), anti-RNP ($n=3$), anti-thyroglobulin ($n=2$), anti-Sm ($n=2$), IgG to double-stranded DNA, perinuclear anti-neutrophil cytoplasm antibodies, anti-fillagrine and anti-Jo1 antibodies (one patient each).

TABLE 3. Comparison of clinical and immunological characteristics of SS between patients with SS-SSc and pSS alone

	SS-SSc ($n=27$)	pSS ($n=202$)	P
Clinical patterns of SS, *n* (%)			
Subjective xerostomia only	2 (7.4)	5 (2.5)	0.16
Subjective xerophtalmia only	1 (3.7)	6 (2.9)	0.83
Subjective sicca symptoms[a]	24 (89.0)	188 (93.0)	0.43
Objective xerostomia[b]	7/9 (77.7)	39/85 (45.8)	0.07
Objective xerophtalmia[c]	17/21 (81.0)	141 (69.8)	0.28
Histologic patterns of minor salivary gland biopsy			
% with grade 3 or 4[d]	84.2	90.9	0.54
Serological patterns *n* (%)			
Anti-Ro/SSA antibodies only	8 (29.6)	57 (28.2)	1.000
Anti-Ro/SSA and anti-La/SSB antibodies	5 (18.5)	70 (35)	0.13
Positive rheumatoid factor	8/18 (44.4)	116/195 (59.5)	0.32

SS-SSc; patients with Sjögren syndrome and systemic sclerosis; pSS; patients with primary Sjögren's syndrome.
[a]Both subjective xerophtalmia and xerostomia.
[b]Defined as an unstimulated salivary flow less than 0.1 ml/min or an abnormal parotid sialography or an abnormal scintigraphy result of salivary glands with $^{99\text{-m}}$Tc.
[c]Defined as an abnormal Schirmer's test results (≤5 mm in 5 min) or Van Bijsterveld score ≥4 after Lissamine green coloration.
[d]According to Chisholm and Mason classification.

Comparison of systemic sclerosis characteristics and severity

The outcome and complications of SSc were compared between SS-SSc and SSc groups (Table 5). To avoid a bias linked to a differing proportion of patients with limited cutaneous and diffuse SSc, we chose the control group of patients with SSc to have the same proportion of patients with the two forms of SSc as in the group of patients with both SS and SSc. The number of patients still alive at the last recording and with at least one complication of SSc were similar in two groups ($P=0.18$ and $P=0.40$, respectively). Nevertheless, SSc accompanying SS seemed to be less serious than SSc alone: pulmonary arterial hypertension (PAH), heart involvement, lung fibrosis and renal crisis occurred less frequently in the SS-SSc group than in the SSc group but this difference was significant for lung fibrosis ($P=0.05$). Moreover, SS-SSc patients showed more evidence of another autoimmune disorder than patients with SSc alone (40.7 *vs* 12.7%, $P=0.004$).

TABLE 4. Comparison of severity and evolution of Sjögren's syndrome between patients with SS-SSc and pSS alone

	SS-SSc ($n=27$)	pSS ($n=202$)	P
Sjögren's syndrome extra-glandular symptoms, no. of patients (%)			
At least one extra-glandular symptoms	14 (51.8)	74 (36.6)	0.20
Arthritis	9 (33.3)	27 (13.3)	0.05
Lymphoma	0	10 (4.9)	0.55
Peripheral neuropathy	5 (18.5)	8 (3.9)	0.02
Additional autoimmune disease[a]	11 (40.7)	38 (18.8)	0.02
Primary biliary cirrhosis	3 (11.1)	3 (1.5)	0.04
At least one other antibody[b]	9 (33.3)	33 (16.3)	0.03
Adverse prognosis factors, no. of patients (%)			
Monoclonal or polyclonal cryoglobulin	4/20 (20)	3/199 (1.5)	0.003
Monoclonal gammapathy	2/24 (8.3)	14 (6.9)	1.000
Parotid gland enlargement	6 (22.2)	75/201 (37.3)	0.12
Decreased C4 complement level[c]	5/11 (45.4)	101 (50)	1.000
Activity markers of SS			
Mean level of CRP[d] ± S.D.	9.2 ± 17.5	8.59 ± 10.5	0.85
Mean level of ESR[e] ± S.D.	25.8 ± 20.4	28.0 ± 25.8	0.68
β_2-microglobulin serum mean level (mg/l) ± SD	2.15 ± 0.71	2.13 ± 0.1	0.66
Gammaglobulins serum mean level (g/l) ± SD	13.05 ± 4.12	13.7 ± 6.3	0.81

[a]Except SS and SSc.
[b]Except ANA, anti-SSA/SSB, anti-centromere and anti-topoisomerase1 antibodies.
[c]C4 level <0.22 g/l.
[d]CRP, C-reactive protein (mg/l).
[e]ESR, erythrocyte sedimentation rate at 1st hour.
SS-SSc, patients with Sjögren syndrome and systemic sclerosis; pSS, patients with primary Sjögren's syndrome.

TABLE 5. Comparison of severity and evolution of systemic sclerosis between SS-SSc and SSc alone

	SS-SSc ($n=27$)	SSc ($n=94$)	P
Characteristics of systemic sclerosis, *n* (%)			
Limited cutaneous SSc	22 (81.5)	74 (78.7)	1.00
Diffuse SSc	5 (18.5)	20 (21.2)	1.00
Anti-centromere antibody	16/26 (61.5)	38 (40.4)	0.09
Anti-topoisomerase 1	4/26 (15.4)	20/91 (21.9)	0.66
Raynaud's phenomenon	25 (92.6)	89 (94.7)	0.98
Complications of systemic sclerosis, *n* (%)			
Still alive at last recording	27 (100)	84/93 (90.3)	0.18
At least one complication of SSc	12 (44.4)	52/93 (55.9)	0.40
Pulmonary arterial hypertension[a]	2 (7.4)	13/86 (15.1)	0.60
Heart involvement[b]	1 (3.7)	9 (9.5)	0.59
Lung fibrosis[c]	3 (11.1)	27/93 (29.0)	0.05
Serious gastrointestinal tract involvement[d]	2 (7.4)	6 (6.4)	1.000
Scleroderma renal crisis[e]	1 (3.7)	14 (14.9)	0.21
Digital necrosis	6 (22.2)	10 (10.6)	0.22
Additional autoimmune disorder[f]	11 (40.7)	12 (12.7)	0.004
Primary biliary cirrhosis	3 (11.1)	4 (4.2)	0.37
At least one other antibody[g]	9 (33.3)	14 (14.9)	0.07
Monoclonal or polyclonal cryoglobulin	4/20 (20.0)	5 (5.3)	0.09

[a]Defined as mean pulmonary arterial pressure > to 45 mmHg upon echocardiography.
[b]Defined as pericarditis, myocarditis or heart failure.
[c]Defined by chest high-resolution computed tomodensitometry and abnormal pulmonary function test values (total lung capacity or vital capacity <80% of the predicted values and/or diffusing capacity/alveolar volume <75% of that predicted.
[d]Malabsorption, pseudo-obstruction, bacterial overgrowth.
[e]Defined by rapidly progressive oligouric renal insufficiency with no other explanation and/or rapidly progressive arterial hypertension occurring during the course of SSc.
[f]Excepted Sjögren's syndrome and SSc.
[g]Except anti-SSA, anti-SSB, anti-centromere and anti-topoisomerase1 antibodies.

Discussion

In this study, to define the nature of SS that accompanies SSc, clinical, histological and immunological features of SS were compared between 27 patients with both SS and SSc, and 202 patients with pSS according to the revised diagnosis criteria of SS (AECG criteria). SS accompanying SSc shows the same clinical and immunological characteristics of pSS-like SS associated with SLE. We found that SS is associated with and not secondary to SSc, particularly its limited cutaneous form (81%). The presence of anti-SSB antibodies was higher in the pSS group than in the SS-SSc group (35 *vs* 18.5%, $P=0.13$), although not significantly and the low presence of anti-SSB antibodies in the SS-SSc group was not associated with a low occurrence of extra-glandular symptoms. Thus, the association does not modify the severity of SS (extra-glandular manifestations and the presence of activity markers and adverse prognosis factors) despite SS symptoms being lower in duration in the SS-SSc than in the pSS group. Moreover, peripheral neuropathies were significantly more common in patients with the two disorders than in the pSS alone group. Conversely, SSc associated with SS seems to be less serious than SSc alone, particularly, less frequency of pulmonary fibrosis. Lastly, the association of SS with SSc reflects a spreading of autoimmunity since a third autoimmune disorder (particularly PBC) was present in 40% of the cases, as were the autoantibodies other than those observed in SS or SSc in 33.3% of the cases.

In four previous studies, patients with SSc were prospectively evaluated for evidence of SS [18–20, 33]. These studies included only 6–18 patients with both diseases and were not based on the diagnosis of pSS or sSS according to the new AECG criteria. When associated with SS, the limited cutaneous form represents 60–66% of SSc in the literature (*vs* 81% in the present study). The SS patterns were very heterogeneous in these four small studies (Table 6). In another study, 14 patients with SS and CREST syndrome were compared with 29 patients with pSS [34]; the prevalence of anti-SSA and anti-SSB antibodies was significantly lower in the SS-CREST syndrome group than in the pSS group (7 *vs* 79% for anti-SSA antibodies and 0 *vs* 61% for anti-SSB antibodies, respectively).

TABLE 6. Comparison of patients with SS and SSc in the literature and in the present study

	Present study $n=27$	Cipoletti *et al.* [18] $n=6$	Osial *et al.* [19] $n=17$	Drosos *et al.* [20] $n=9$	Alarcon-Segovia *et al.* [33] $n=18$
Limited cutaneous SSc (%)	81.5	66.6	59	NA	NA
Objective xerostomia (%)[a]	77.7	83.3[d]	71	NA	94.4
Objective xerophtalmia (%)[b]	81	100	60	55.5	83.3
Histologic patterns of minor salivary gland biopsy with grade 3 or 4[c]	84.2	NA	100	100	11.1
Anti-Ro/SSA antibodies only (%)	29.6	NA	29	30	NA
anti-Ro/SSA anti-La/SSB (%)	18.5		18	0	NA

NA, not applicable.
[a]Defined as an unstimulated salivary flow less than 0.1 ml/min or an abnormal parotid sialography or an abnormal scintigraphy of salivary glands with $^{99\text{-m}}$Tc.
[b]Defined as an abnormal Schirmer's test ($\leq$5 mm in 5 min) or Van Bijsterveld score $\geq$4 after Lissamine green colouration.
[c]According to Chisholm and Mason classification.
[d] Two or more of the five clinical features of SS included xerostomia, xerophtalmia, salivary gland enlargement, Schirmer's test and rose Bengal dry test.

Our study, with a much higher number of patients, does not confirm these data, but is in accordance with that from Andonopoulos *et al.* [35] who compared SS features in 34 patients with SS and RA and 9 patients with SS and SSc. The authors concluded that SS accompanying SSc is different from SS secondary to RA with higher prevalence of subjective xerostomia, xerophtalmia, parotid glands enlargement and presence of anti-SSA antibodies in the SS-SSc group; the authors proposed the term 'SS accompanying SSc' to describe this association. With our 3-fold higher number of patients, we clearly demonstrate that SS associated with SSc appears as pSS and not like SS secondary to RA. Some extra-glandular complications of SS, such as peripheral neuropathy, could be even more common.

The most interesting finding of our study is the demonstration that SSc seems to be less serious when it is associated with SS. Lung fibrosis, one of the most severe complications of limited SSc, occurred in 29% of the patients with SSc alone and in only 11% of the patients with SS-SSc ($P=0.05$). Also, we found a trend in favour of a reduced prevalence of PAH and of scleroderma renal crisis in the SS-SSc patients (7 *vs* 15%) and (4 *vs* 15%), respectively. Very interestingly, similar features were observed in SLE associated with SS: Manoussakis *et al.* [14] showed that SLE was less serious with a significantly lower prevalence of thrombopenia, lymphadenopathic abnormalities and renal failure in patients with SS and SLE than in patients with SLE alone. This autoimmune diversification seems to be associated with a lower severity of disease.

Last, we found that another autoimmune disease, in particular PBC, accompanied SS and SSc in 40% of the cases. The association of SSc with PBC was described in 1971 by Reynolds *et al.* [36] in six cases. In the literature, some authors considered SS as a complication of PBC [6, 7]. However, according to Skopouli *et al.* [9], PBC can also occur during pSS. The three patients with the triple association SS + PBC + SSc were similar to patients with pSS (all had anti-SSA antibodies). Thus, the triple association SS + PBC + SSc appears to be an overlap syndrome. Later, other reports were added to complete this initial description, and Reynolds' syndrome was found to be associated with SS in 66% of cases [37, 38]. Beyond the association, the presence of auto-antibodies other than anti-SSA, anti-SSB, anti-centromere or anti-topoisomerase 1 was found in 33.3% of our patients with SS and SSc. Thus, this association of SS and SSc is an example of the spreading of autoimmunity; which could be related to a peculiar genetic predisposition that would be interesting to assess.

In conclusion, SS accompanying SSc should be termed as SS associated with, and not secondary to SSc, particularly with the limited cutaneous form. This association does not modify the severity of SS. However, SSc seems to be less serious when it is associated with SS. Moreover, the two diseases are often accompanied by other autoimmune diseases or the presence of other auto-antibodies, which suggests a spreading of auto-immunity that could be associated with a peculiar genetic profile.

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