Sjögren's disease and systemic lupus erythematosus overlap syndrome as distinct entity at the crossroads of two autoimmune disorders: clinical characterisation from two Italian reference centres for both diseases

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Abstract

Objective

To characterise the overlap syndrome between Sjögren's disease (SjD) and systemic lupus erythematosus (SLE).

Methods

Consecutive patients clinically defined as affected by SjD and SLE overlap syndrome (SjD-SLE), belonging to two Italian rheumatology centres were classified following the application of both the SjD and SLE classification criteria. Clinical, functional, ultrasound and histological data were compared with patients suffering from only SjD or SLE.

Results

Compared to SjD controls, SjD-SLE patients were younger at onset ($p<0.0001$). Schirmer's test and parotid swelling were comparable between the two groups, while unstimulated sialometry was more impaired in the SjD controls ($p=0.0001$). SjD-SLE cases showed increased joint ($p=0.009$), mucocutaneous ($p<0.0001$), renal ($p=0.001$) involvement, and serositis ($p<0.0001$). Ultrasound changes in the major salivary glands were prevalent in SjD controls, while the histological findings of the minor salivary glands were similar. Furthermore, SjD-SLE cases presented a higher prevalence of anti-SSA ($p<0.0001$) and lower presence of rheumatoid factor ($p=0.008$) and serum cryoglobulins ($p=0.035$). Compared to SLE controls, SjD-SLE were older ($p=0.044$). The frequency of extra-glandular manifestations of SjD-SLE was similar compared to SLE, including renal involvement. SjD-SLE patients showed higher prevalence of anti-SSA and anti-SSB ($p<0.0001$), C4 reduction ($p=0.011$), and leukopenia ($p=0.025$).

Conclusion

Our data further highlight the limitations of the application of the current classification criteria in overlap syndrome, since they are primarily based on clinical manifestations and common autoantibodies. Molecular signatures may explain clinical similarities and differences among systemic autoimmune diseases, and they may be particularly helpful in overlap syndromes.

Key words

Sjögren's disease, systemic lupus erythematosus, autoimmune diseases, overlap syndrome, salivary glands, anti-SSA antibodies

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Introduction

Sjögren's disease (SjD) is a slowly progressive systemic autoimmune disorder characterised by chronic inflammatory infiltration of the salivary and lacrimal glands, which is clinically expressed with sicca syndrome (1). This disease can occur alone, or in overlap with other autoimmune pathologies such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) or systemic sclerosis (SSc) (2).

Although relevant due to their not rare incidence in daily clinical practice, overlap syndromes are pathologies still poorly characterised in the literature, with consequent uncertainty about prognosis and therapeutic strategy (3, 4).

The coexistence of SLE and SjD was first recognised more than sixty years ago by Heaton, who described SjD as a mild form within the spectrum of SLE manifestations (5). When coexisting, SjD was thought to be a secondary manifestation of SLE, with autoimmune exocrinopathy representing one of multiple organ manifestations of SLE; subjective xerostomia and xerophthalmia are actually common manifestations in patients with SLE (6). Other authors argued that SLE and SjD may be separate autoimmune conditions that occasionally overlap as a result of shared organ manifestations and laboratory features (6). The link between the two pathologies was biologically strengthened by the recognition that anti-Ro/SSA and anti-La/SSB antibodies are common in both diseases (7), and both autoantibodies are strictly related to the interferon type I hyperexpression, that may play a role in the pathogenesis of both diseases. Examples of this are subacute cutaneous lupus erythematosus (SCLE) and anti-dsDNA antibodies, both presumably SLE-specific phenomena, which have been found in patient with established SjD. Similarly, the sharing of less specific organ manifestations, such as photosensitivity, rash, arthritis, demyelinating lesions of the nervous system or leukopenia, makes it difficult to mark a precise boundary between the two entities (8).

In light of developing pathogenetic knowledge translatable into the research of diagnostic and prognostic tests and new targeted treatments, the need for precisely classifying patients affected by overlap syndromes appears increasingly relevant, as well as their characterisation from a clinical, serological, imaging, histological point of view, and the optimisation of their management and treatment.

Methods

All consecutive patients with clinical suspicion of SjD-SLE overlap syndrome were selected by two Italian rheumatology centres. As control groups, consecutive patients classified as SjD or SLE were selected, according to the recent classification criteria (8, 9). Clinical and clinimetric data were collected, including questionnaires for oro-ocular symptoms, visual analogue scale (VAS) for oral and ocular sicca, Schirmer I test, unstimulated sialometry, ultrasound of the major salivary glands (SGUS) and minor (labial) salivary biopsy. The SGUS was performed with a SAMSUNG RS85 ultrasound system with high frequency linear probe (LM4-15B) and two grading systems were evaluated: the original score proposed by De Vita *et al*. in 1992 (SGUS score) (10) and the OMERACT score (11). For both scores, we applied a dichotomous result: negative ultrasound if score <2; positive ultrasound if score ≥2. The biopsy of the minor salivary glands was considered positive for Chisholm and Mason (C-M) scores ≥3 (12). All patients were tested for antinuclear antibodies, anti-SSA/SSB antibodies, rheumatoid factor (RF), cryoglobulins, C3, C4, serum beta2-microglobulin, lymphocyte count, leukocyte count, serum gammaglobulins, κ/λ ratio and LDH. In SjD-SLE and SjD patients ESSDAI and ESSPRI were calculated; in SjD-SLE and SLE patients SLEDAI-2k score was applied. Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data or as median and range for non-normally distributed data. Comparisons were performed using the Student's t-test for independent samples when the data followed a normal distribution; otherwise, the non-parametric Mann-Whitney U-test was applied. Categorical variables

were expressed as frequencies and percentages. All statistical tests were two-tailed, with a significance threshold set at $p<0.05$. Adjustments for multiple comparisons were not applied due to the exploratory nature of the study.

Results

Demographic data

Sixty-three patients with clinical suspicion of SjD-SLE overlap syndrome were identified. After the application of classification criteria for SLE and SjD we finally identified 45 patients (F:M 44:1) which satisfied both the sets and were then defined SjD-SLE patients. They were separately compared with 79 consecutive unselected SjD patients (72 females, 7 males) and 83 SLE patients (70 females and 13 males).

The SjD-SLE group was 35.18±10.77 years old at diagnosis, compared to a mean age of 53.68±11.41 years for SjD ($p<0.0001$) and 32.33±16.07 years for SLE ($p=0.044$) (Table I).

Clinical comparison

Compared to SjD, the overlap group showed a slightly lower incidence of subjective dry eye and dry mouth (respectively 93.3% *vs*. 100%; $p=0.046$ and 84.4% *vs*. 96.2%; $p=0.035$) and a lower incidence of abnormal unstimulated sialometry (82.3% *vs*. 35.6%; $p=0.0001$), but no differences were observed in Schirmer test or in the presence of parotid swelling, neither considering transient (40.0% *vs*. 41.8%; $p=0.847$) nor persistent glandular swelling (13.3% *vs*. 21.5%; $p=0.259$).

The SjD-SLE subgroup showed a higher involvement of joints (77.8% *vs*. 53.9%; $p=0.009$), skin/mucous membranes (60.0% *vs*. 13.2%; $p<0.0001$), kidney (27.3% *vs*. 5.3%; $p=0.001$), and serositis (31.1% *vs*. 3.9%; $p<0.0001$) compared to SjD controls. Compared with SLE controls, the overlap syndrome group showed more subjective and objective sicca symptoms, while extra-glandular manifestations showed a similar frequency, except for serositis, which appeared slightly less frequent in SjD-SLE group (15.7% *vs*. 31.1% $p=0.041$) (Table I). The ESSDAIscore, both at baseline and cumulative, was higher in SjD-SLE than in SjD patients. The ESSDAI domains which greatly contributed to the difference between the two groups are: systemic ($p<0.0001$), articular ($p<0.0001$), renal ($p=0.030$) and haematological ($p=0.001$) domain, in favour of the cases (SjD-SLE), and the glandular domain ($p=0.013$), in favour of the controls (SjD). The ESSPRI score was similar between the two groups. SLEDAI-2K was higher in patients with overlap syndrome than in SLE ($p=0.009$) (Table I).

Immunological profile

SjD-SLE patients showed anti-SSA antibody positive in 100% compared to 78.5% e 38.3% respectively in SjD or SLE (both $p<0.0001$) and anti-SSB antibody positive in 57.8%, similar to SjD patients but higher than SLE patients ($p<0.0001$). No differences were noted concerning anti-dsDNA antibody, anticardiolipin antibodies or lupus anticoagulant (LAC) between SjD-SLE and SLE, while antibeta2glycoprotein1 antibodies were more prevalent in SLE (24% *vs*. 8.9%, $p=0.035$). In the overlap group RF and cryoglobulins were found less frequently than in SjD group (19.5% *vs*. 50.6%; $p=0.008$ and 4.8% *vs*. 25.3%; $p=0.035$, respectively), low C3 was found more frequently than in

Table I. Clinical comparisons between subgroups.

Age at onset					
	SjD-SLE (n=45)	SjD (n=79)	SLE (n=83)	*p*-value SjD-SLE *vs*. SjD	*p*-value SjD-SLE *vs*. SLE
Years	35.18 ± 10.77	53.68 ± 11.41	32.33 ± 16.07	<0.0001	0.044
Glandular manifestations					
	SjD-SLE (n=45)	SjD (n=79)	SLE (n=83)	*p*-value SjD-SLE *vs*. SjD	*p*-value SjD-SLE *vs*. SLE
Subjective oral dryness	42 (93.3%)	79 (100%)	19 (22.9%)	0.046	<0.0001
Subjective ocular dryness	38 (84.4%)	76 (96.2%)	17 (20.5%)	0.035	<0.0001
Schirmer test	30 (66.7%)	63 (79.9%)	=	0.106	=
Unstimulated salivary flow	16 (35.6%)	65 (82.3%)	19 (22.9%)	<0.0001	<0.0001
Parotid swelling (transient)	18 (40.0%)	33 (41.8%)	17 (20.5%)	0.847	<0.0001
Parotid swelling (persistent)	6 (13.3%)	17 (21.5%)	=	0.259	=
Extraglandular manifestations					
	SjD-SLE (n=45)	SjD (n=79)	SLE (n=83)	*p*-value SjD-SLE *vs*. SjD	*p*-value SjD-SLE *vs*. SLE
Joint involvement	35 (77.8%)	41 (53.9%)	58 (69.9%)	0.009	0.338
Mucocutaneous involvement	27 (60.0%)	10 (13.2%)	54 (65.1%)	<0.0001	0.571
Renal involvement	12 (27.3%)	4 (5.3%)	25 (30.1%)	0.001	0.681
Haematologic involvement	25 (56.8%)	(42.1%)	43 (51.8%)	0.120	0.685
Serositis	14 (31.1%)	3 (3.9%)	13 (15.7%)	<0.0001	0.041
Thyroid disease	10 (22.2%)	31 (39.2%)	20 (24.1%)	0.053	0.811
Disease activity index					
	SjD-SLE (n=45)		SjD (n=79)	SLE (n=83)	*p*-value SjD-SLE *vs*. SjD	*p*-value SjD-SLE *vs*. SLE
	median	range	median range	median range		
ESSDAI	10	[5; 12]	3 [0; 8]	NA NA	<0.0001	NA
ESSPRI	6.33	[4.8; 7,16]	5.33 [3.33; 7.66]	NA NA	0.188	NA
SLEDAI-2K	6	[3; 11]	NA NA	4 [0; 7]	NA	0.009

SjD: Sjögren's disease; SLE: systemic lupus erythematosus; SjD-SLE: overlap syndrome SjD and SLE; NA: not applicable; =: absent.

SjD group (55.6% *vs*. 25.6%, *p*=0.001) and low C4 was found more frequently than in SLE group (40% *vs*. 19.3%, *p*=0.011). The presence of leukopenia was similar to SjD group but greater than SLE group (*p*=0.025) (Table II).

Ultrasound and histological comparison

Ultrasound alterations of the major salivary glands were more frequent in SjD patients than in those with SjD-SLE patients according to all the scores, but especially to De Vita *et al*. 1992 score of the submandibular glands (*p*<0.0001). Minor salivary gland biopsy was available for 30 out of 45 SjD-SLE patients and for 62 out of 79 SjD patients. No difference in the histological classification was observed (83.3% *vs*. 85.2%; *p*=0.518) (Table III).

Table II. Laboratory comparisons between subgroups.

Laboratory findings					
	SjD-SLE (n=45)	SjD (n=79)	SLE (n=83)	*p*-value SjD-SLE *vs*. SjD	*p*-value SjD-SLE *vs*. SLE
Anti-Ro/SSA	45 (100.0%)	62 (78.5%)	26 (31.3%)	<0.0001	<0.0001
Anti-La/SSB	26 (57.8%)	40 (50.6%)	6 (7.2%)	0.443	<0.0001
Anti-dsDNA Ab	28 (62.2%)	=	40 (48.2%)	=	0.129
Anticardiolipin Ab	9 (20.0%)	=	28 (33.7)	=	0.102
Antibeta2glycoprotein1 Ab	4 (8.9%)	=	20 (24.1%)	=	0.035
Lupus anticoagulant	6 (13.3%)	=	23 (27.7%)	=	0.064
Rheumatoid factor	8 (19.5%)	40 (50.6%)	=	0.001	=
Serum cryoglobulins	2 (4.8%)	20 (25.3%)	=	0.005	=
C3 reduction	25 (55.6%)	20 (25.6%)	41 (49.4%)	0.001	0.506
C4 reduction	18 (40.0%)	19 (24.4%)	16 (19.3%)	0.068	0.011
Leukopenia	16 (39.0%)	20 (29.9%)	24 (28.9%)	0.326	0.025

SjD: Sjögren's disease; SLE: systemic lupus erythematosus; SjD-SLE: overlap syndrome SjD and SLE; = absent .

Table III. Ultrasound and histological comparisons between subgroups.

Ultrasound features					
	SjD-SLE		SjD		*p*-value
	median	range	median	range	
RPG De Vita *et al*. 1992*	1	[0; 3]	2	[0; 3]	0.014
LPG De Vita *et al*. 1992*	1	[0; 3]	2	[0; 3]	0.019
RSMG De Vita *et al*. 1992*	1	[0; 3]	2	[0; 3]	< 0.0001
LSMG De Vita *et al*. 1992*	1	[0; 3]	2	[0; 3]	< 0.0001
RPG OMERACT*	1	[0; 3]	2	[0; 3]	0.017
LPG OMERACT*	1	[0; 3]	2	[0; 3]	0.016
RSMG OMERACT*	1	[0; 3]	2	[0; 3]	0.002
LSMG OMERACT*	1	[0; 3]	2	[0; 3]	0.008

Histological findings					
	SjD-SLE (n=30)		SjD (n=61)		*p*-value SjD-SLE *vs*. SjD
Positive lip biopsy*	25 (83.3%)		52 (85.2%)		0.518
Chisholm and Mason score*	median	range	median	range	
	3.50	[3; 4]	4.00	[3; 4]	0.496

SjD: Sjögren's disease; SLE: systemic lupus erythematosus; SjD-SLE: overlap syndrome SjD and SLE; * missing data.

Discussion

This retrospective study aimed at characterising the SjD-SLE subset, a distinct clinical entity that has been relatively overlooked in the literature and often excluded from clinical trials, despite its not so uncommon diagnosis in clinical practice. The true prevalence of this subset remains uncertain and may be underestimated. Application of the classification criteria could help to intercept this overlap syndrome early. According to Gianordoli *et al*., the prevalence of SjD in SLE patients is around 23%, if 2002 AECG classification criteria are applied, while it rises to 35% by applying the 2016 ACR-EULAR (13).

In our study, patients with SjD-SLE subset are younger than SLE but older than SjD patients at onset, as reported by the first reports (6, 14-16), and as highlighted in the recent review by Baldini *et al*. (4). Extra-glandular manifestations, such as mucocutaneous, joint, renal and serositis showed similar rate between SJD-SLE and SLE controls, while they more prevalent in SjD-SLE subset in comparison with SjD controls, as expected, contributing to the higher scores of the specific ESSDAI domains. Interestingly, renal involvement was reported at the same rate, around 30%, in both SjD-SLE patients and SLE patients. These data disagree with literature data where renal involvement appeared to be less frequent in SjD-SLE compared to SLE controls (6, 14-16). The anti-SSA antibody prevalence resulted higher in the overlap syndrome than in both SjD or SLE controls, and anti-SSB antibody was also highly represented, with a prevalence at least equal to that reported in SjD. This biologic profile is consistent to what has been reported in previous descriptions (6, 14-16), and to the recently proposed clinical decision model for the prediction of SLE-SjD overlap syndrome (17). In light of these observations, anti-SSA antibodies could be used as a biomarker of the overlap syndrome (18). Both anti-SSA and anti-SSB antibodies have been clearly associated with the type I interferon signature. Indeed, anti-Ro52/SSA antibodies are associated with higher levels of interferon alpha in different diseases (19). Cui Y. demonstrated that

SjD and SLE share common genes involved in the response to interferon, specifically IFI442, ISG15 and ITGB2, and this further strengthens the hypothesis that SLE and SjD present a common pathogenesis and that the overlap of these two pathologies may be more frequent than estimated (20, 21). IFN-1 gene signatures in SLE may be read as an important susceptibility factor for SjD, and the NOD-like receptor signalling pathway was identified as a common pathway (22). Therefore, by better dissecting the characteristics of this subgroup, this study highlighted the clinical features which could be type I interferon-mediated in each disease, and potentially targeted by specific treatments. Interestingly, monogenic type I interferonopathies frequently involve skin, joints and the serosal and pleural surfaces of the abdominal and thoracic viscera. Some authors stated that SLE-SjD subset is characterised by a higher inflammatory state associated with a greater production of pro-inflammatory cytokines (23). Therefore, it is not surprising that anifrolumab, a fully human monoclonal antibody against subunit 1 of the interferon type I receptor, showed greater activity on mucocutaneous and joint involvement, as well as on the haematological manifestations (24), and it is even under study in lupus proliferative nephritis in a phase III trial (clinicaltrials.gov: NCT05138133). Furthermore, several case reports reported the efficacy of JAK inhibitors, which exert a reversible blockade of type I and II interferons, particularly on skin involvement in SLE (25), while JAK inhibitors are currently under investigation for SjD in several clinical trials (clinicaltrials.gov: NCT03100942; NCT04496960; NCT04916756), their efficacy in this setting remaining to be established (26).

Consistently, SjD-SLE patients showed a higher frequency of low C4 and leukopenia compared to SLE and a lower rate of RF or cryoglobulin positivity compared to SjD, supporting the nature of the overlap syndrome as a distinct pathological entity rather than a coexistence of two diseases.

The SGUS and histopathological comparisons between SjD-SLE and SjD patients highlighted the presence of parenchymal alterations in a much lower percentage of subjects with overlap syndrome compared to SjD, mostly at the submandibular level. No differences, however, were observed regarding minor salivary glands histology. These findings are consistent with those of Manoussakis *et al*. (14) and Yang *et al*. (16), who reported no significant differences in the positivity rates of minor salivary gland biopsies. However, Manoussakis *et al*. (14) found that in minor salivary gland biopsies of patients with overlap syndrome perivascular infiltrates can be detected, differently from the classic periductal lymphoepithelial infiltrates typically seen in SjD, thus suggesting the classification of the glandular involvement in SLE as another one among the multiple organ manifestations of SLE. More recently, perivascular infiltrates have been described also in SjD (27).

This study has some limitations. It is a retrospective observational study, and there are missing data, in particular for the histopathological analysis. This could lie on physician's and patient's hesitance to perform lip biopsy in the presence of anti-SSA antibody, which carries similar diagnostic weight as biopsy for SjD classification (8). An additional limitation of this study is the lack of characterisation of anti-SSA in Ro60 and Ro52. However, this is the largest study that reported a fully comprehensive analysis of this subset of patients, including US and histological comparisons with both the single distinct entities, *i.e*. SjD and SLE, from two reference centres for both the diseases.

To conclude, our data further highlight the limitations of the application of the current classification criteria in SjD-SLE overlap syndrome, since they are mostly based on clinical manifestations and common autoantibodies. Molecular dissection of the systemic autoimmune diseases may be helpful in this setting, since it appears as a distinct pathological entity (28). The role of new drugs, aiming at targeting the interferon pathway, may be then further supported in this clinical context.

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