



Clinical and Serological Features of Sjogren Syndrome in Patients with Rheumatoid Arthritis

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Authors' contributions

This work was carried out in collaboration between all authors. Authors GJE and JS designed the study, author BAK wrote the protocol, and wrote the first draft of the manuscript. MI managed the literature searches and analyses of the study. Authors SC and CE managed the experimental process. All authors read and approved the final manuscript.

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ABSTRACT

Background: It is uncertain whether the Sjogren Syndrome (SS) associated with Rheumatoid Arthritis (RA) represents a clinical entity similar to primary SS (pSS) or merely a manifestation in the clinical spectrum of RA. In the present study, we sought to determine the clinic and serologic features of SS associated with RA in comparison to the RA features using well defined SS classification criteria.

Methods: RA patients successively referred for a biologic infusion were questioned on oral and ocular dryness. Schirmer's test and unstimulated salivary flow were performed in each patient. Patients with subjective oral or ocular dryness and/or 1 abnormal objective test underwent a minor salivary gland biopsy. The diagnosis of secondary SS was based on the criteria of European-American consensus group criteria for SS. Clinical and biological parameters of SS and RA (with measure of disease activity and health status of RA, search for Raynaud's phenomenon, anti-CCP, RF anti-SSA-positivity and beta2-microglobulin level) were then compared between patients with/without sSS.

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Results: Among the 76 patients prospectively assessed, 11(14.1%) fulfilled the European-American consensus group criteria for secondary SS. Median age and RA disease duration were similar in patients with sSS as in patients with RA only (63.0 v 59.2, p=0.33; 18.2 vs 13.9, p= 0.12). Median DAS28-ESR and HAQ were not significantly different between patients with sSS and patient with RA only (4.0 vs 4.1, p= 0.8; 0.84 vs 0.81, p=0.7). Patients with sSS had more frequently a Raynaud's phenomenon (27.2 vs 1.5%, p=0.01). RF and anti-CCP-positivity were similar in the 2 groups. The prevalence of anti-SSA antibodies was comparable in the 2 groups (p=1). Median beta2-microglobulin levels were higher in sSS than RA only (2.4 vs 1.9 mg/l, p= 0.02).

Conclusion: 14% of patients with RA had secondary SS in the present study. Conversely to previous reports, secondary SS did not modify the clinical and biologic pattern of RA.

Keywords: Sjogren's syndrome; Rheumatoid arthritis; auto-immunity; sicca syndrome.

1. INTRODUCTION

Sjogren's syndrome (SS) is a chronic autoimmune disorder of the exocrine glands with associated lymphocytic infiltration of the affected glands. Dryness of the mouth and/or the eyes, resulting from involvement of the salivary and lachrymal glands, is most often present.

Sjogren's Syndrome (SS) may be either primary or associated with various auto-immune diseases, including Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), Systemic Sclerosis (SSc). Recently, studies of patients with SS and SLE and patients with SS and SSc demonstrated that clinical features of SLE/SSc on the one hand and SS on the other hand were similar as in patients affected with only SLE, or SSc, or primary SS (pSS). And so, when the SS is associated with these conditions, each of the two associated diseases evolves independently of the other. Few recent studies investigated clinical features of RA and SS in patients with RA associated SS (RA-SS) [1-3]. We therefore conduct a cross-sectional study to investigate clinical and serological features of patients with RA-SS compared with those with RA only in a cohort of French patients.

2. PATIENTS AND METHODS

Between December 2008 and May 2009, 76 French RA patients were included. All patients fulfilled 1987 American College of Rheumatology Criteria (ACR) of RA [4] and were referred to the Rheumatology department of Strasbourg University Hospital for biologic infusion. All patients were questioned by two clinicians (BA.K and M.I) about the presence of subjective symptoms of oral and/or ocular dryness. Then, all patients underwent objective assessment of lachrymal and salivary gland involvement, which

included Shirmer's test (abnormal if ≤ 5 mm in 5 min) and measurement of unstimulated salivary flow (USF, abnormal if $\leq 1,5$ ml in 15 min). Only patients with subjective oral or ocular dryness and/or one abnormal objective test (abnormal Shirmer's test and/or USF) underwent a minor salivary gland biopsy. The diagnosis of secondary SS was based on the criteria of European-American consensus group criteria for SS [5]. Features of RA were compared between patients with/without sSS.

An approval of Institutional Ethics Committee was obtained.

3. DATA COLLECTION

- Clinical examination: with tender joint count (0-28), swelling joint count (0-28), Disease activity score (DAS28) of RA patients was assessed by two rheumatologists as well as mini-HAQ (Health Assessment Questionnaire), usual analogue scales on pain (VAS) (0-100) and patient's global assessment of disease activity and corticosteroid taken.
- Extra-glandular features of SS were determined by clinical examination: Raynaud's phenomenon and Peripheral neuropathy.
- Laboratory features: Laboratory abnormalities were also recorded mainly including whole blood count, auto-antibodies (antinuclear antibody, Rheumatoid factor, Cyclic Citrullinated Peptide Antibody), Lactate dehydrogenase (LDH), C reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Gammaglobulins and beta2-microglobulins ($\beta 2$ -m) were also assessed in all patients.
- Statistical analysis: Fisher's exact tests were used to assess differences for qualitative

variables in clinical and laboratory data between RA and RA with SS groups. To analyse quantitative values, Mann-Whitney tests were used. P value ≤ 0.05 were considered as significant.

4. RESULTS

Among the 76 patients prospectively assessed, 22 patients had sicca syndrome and only 11 (14.1%) fulfilled the European-American consensus group criteria for secondary SS [5]. Six of the 11 RA-sSS had subjective complaints of both ocular and oral dryness, whereas the five remaining patients reported only ocular (3 patients) or only oral dryness (2 patients). Objective features of both ocular and oral dryness were observed in 6 of the 11 patients, ocular dryness only in 4 and oral dryness in one patient. Histological criteria according to focus score ≥ 1 in minor salivary gland biopsy was found in 80% of patients with secondary SS and in only one patient of the group RA (Table 1).

The clinical and biological features were then compared between the 11 patients with RA and

sSS and the 65 patients with only RA. Median age and RA disease duration were similar in patients with sSS and in patients with RA only (63.0 versus 59.2 years, $p=0,33$ and 18.2 versus 13.9 years, $p=0.12$). Number of previous biologics biotherapies, disease activity (DAS28), HAQ and CRP levels were similar irrelevant of the presence of associated SS (Table 2).

The prevalence of distinct disease manifestations of the SS and examination of blood in the two groups are presented in Table 3 and Fig. 1. With regard to peripheral neuropathy and lung involvement, there were no significant differences among the two groups. Nevertheless, Raynaud's phenomenon was more frequent in RA-sSS group than in the RA group ($p=0.01$). The prevalence of RF and anti-CCP anti-bodies was similar in the two groups. The prevalence of anti-SSA antibodies was also comparable in the 2 groups ($p=1$). Mean level of gamma globulin was similar in the 2 groups ($p=0.4$). However, the mean level of $\beta 2$ -microglobulin was significantly higher in RA-sSS group than in RA group ($p=0.02$).

Table 1. Comparison of dryness symptoms between RA and RA-sSS groups

	RA-sSS	RA	p
Subjective xerostomia, n (%)	8 (72,7)	8 (12,3)	0,0002
Subjective xerophthalmia, n (%)	9 (81,8)	12 (18,4)	0,0002
Objective xerostomia, n (%)	7 (63,6)	6 (9,6)	0,0005
Objective xerophthalmia, n (%)	10 (90,9)	10 (15,3)	<0,0001
Histological patterns of minor salivary gland biopsy, n (%)	8 (80)	1 (1,5)	<0,0001

Table 2. Comparison of clinical and biological parameters of RA between RA and RA-sSS groups

Parameter	RA-sSS	RA	p
Mean number of anterior biotherapies	0,8 [0,2-1,5]	1 [0,7-1,3]	0,7
Corticosteroid (%)	67,7	72,7	1
Tender joint count (0-28)	5,6 [0,5-10,7]	6,2 [4,4-7,9]	0,4
Swelling joint count (0-28)	3,2 [0,5-5,8]	3,7 [2,8-4,7]	0,4
VAS pain mean level (100mm)	35,9 [13,1-58,7]	42,4 [36,7-48,2]	0,3
DAS 28 mean level	4,05 [3,1-5,1]	4,13 [3,8-4,5]	0,8
M-HAQ mean level	0,84 [0,4-1,3]	0,81 [0,6-1]	0,7
Mean level of ESR (mm)	24,8 [14-35,6]	20,9 [17,2-24,6]	0,4
Mean level of CRP (mg/l)	12,6 [6,6-18,6]	14 [9,6-18,5]	0,7

VAS: visual analogical scale; M-HAQ: Mini-health assessment questionnaire; ESR: Erythrocyte sedimentation rate; DAS: disease activity sc

Table 3. Comparison of biologic parameters of SS between RA and RA-sSS groups

Parameter	RA-sSS	RA	p
Mean level of LDH	372,2 [307-437]	409,8 [367-451]	0,8
β2-m serum mean level (mg/l)	2,4 [2-2,9]	1,9 [1,8-2,1]	0,02
γ-globulins serum mean level (g/l)	11,6 [9,5-13,8]	11 [10,2-11,8]	0,4

SS: Sjögren syndrome; RA: rheumatoid arthritis; LDH: Lacticodeshydrogenase ; β2-m: beta2-microglobulin; γ-globulins: gammaglobulin

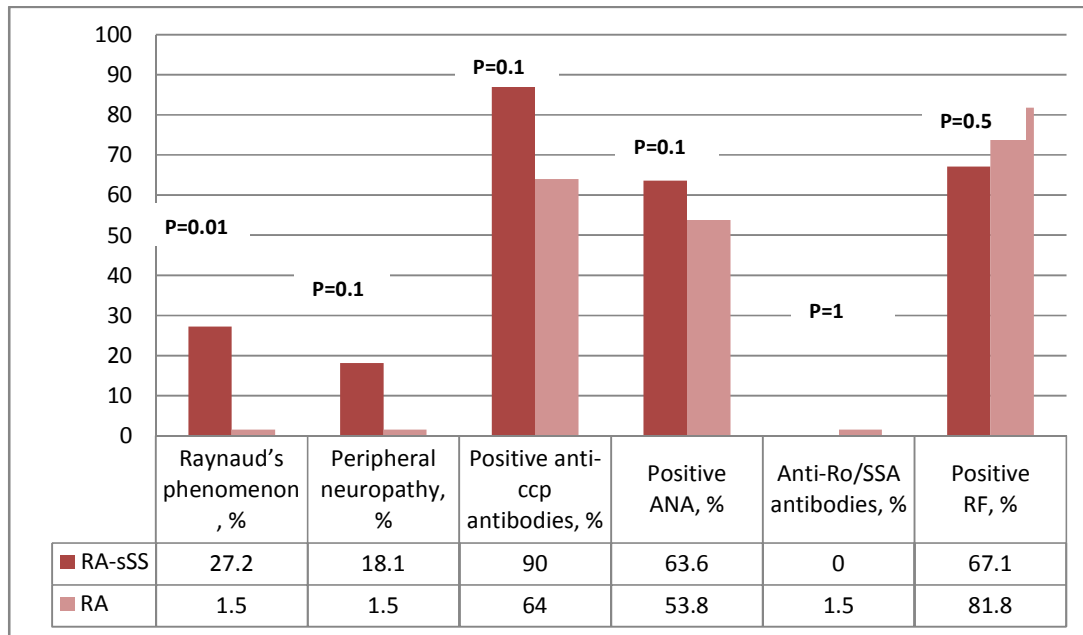


Fig. 1. Comparison of clinical and immunological parameters of SS between RA and RA-sSS groups

SS: Sjögren syndrome; RA: rheumatoid arthritis; ANA: antinuclear antibodies; RF: Rheumatoid Factor;

5. DISCUSSION

In the present study, 76 French patients with severe RA, needing biological therapy, were prospectively evaluated for evidence of sSS according to the revised diagnosis criteria of SS (AECG criteria) [5]. The prevalence of RA-related SS varies largely in literature. In fact, the prevalence ranges from 3.6% to 31% (Table 4) [1-3,6-11]. Some of this variability can be explained by the genetic differences between the population studied, the definition of SS used and the mean duration of the RA.

The analysis of our results revealed the occurrence of sSS in 11 patients (14,5 %) which was not lower than previous studies and which led us conclude that patients with severe RA treated with biologics did not have higher prevalence of sSS.

AECG criteria were used, conversely to the majority of all of post studies [1,2,6-10]. For ethical reasons, no systematic salivary gland biopsies were performed. Histological assessment of salivary glands was only performed in patients with symptoms and/or objective features of dryness (abnormal Shimer's test and/or unstimulated salivary flow) and this could underestimate the prevalence of SS in the present study. In our study, we had not applied the newly proposed American College of Rheumatology (ACR) classification criteria for SS since our inclusion date was previous to the establishment of these criteria [12]. However, there is no clear evidence for increased value of the new ACR criteria over the old AECG criteria from the clinical or biological perspective [13].

Our results show that secondary SS occurrence had no relation to disease duration. This relation was not confirmed by Uhlig et al. [7]. However, a

study conducted in Spain found that patients with RA duration up to 10 years had a prevalence of secondary SS of 17% and after 30 years it was as high as 25% [10].

The second interesting finding of this study lies in the fact that clinical features of RA-sSS were similar to those with only RA. Moreover, the disease activity measured by DAS28 was unaffected by the occurrence of SS. This result was in agreement with that found by Antero et al. [11]. Since patients with SS often complain from pain (joint, but also muscles, and sometimes diffuse pain), it could have been hypothesized that pain VAS, DAS28 or HAQ would be more increased in the group RA-sSS, however, they were actually similar in the two groups. Conversely, He j et al. [3] found that patients with secondary SS had more severe arthritis, fever and rash, than patients with RA only. The number of previous biologic drugs was also similar, suggesting that SS and SS-related

dryness, fatigue or pain had not influence the therapeutic strategy in patients with RA and SS.

Both diseases, RA and SS, are individually risk factors for development lymphoma. Serum β 2-m level, which is a marker of B cell activation, was shown to be up regulated in RA since 1975 [14] and was also increased in patients with RA in the French multicenter prospective cohort ESPOIR and was correlated to disease activity [15]. On the other hand, compared to healthy individuals, patients with SS have a 10 to 50 times higher risk of lymphoma and, according to a large case series, 2% to 9% of patients with SS develops lymphoma [16]. Interestingly, in the present study, serum β 2-m was significantly increased in patient with RA and SS compared to patients with RA alone, suggesting an increased risk of lymphoma. In Finland, a doubled standardized incidence ratio for lymphoma in RA patients with sSS when compared with RA patients without SS was described [17].

Table 4. Prevalence of SS in RA in literature

Authors (year)	Number of patients	RA disease duration	Definition of SS	Prevalence
Adanopoulos et al.1987 [6]	111	3.3 to 9.1 years	SGB and keratoconjunctivitis sicca and/or xerostomia	31%
Uhlig et al. 1999 [7]	636	12,2 years	At least one subjective symptom, positive shirmer test and positive unstimulated whole saliva Without performed SGB	7%
Cimmino et al. 2000 [8]	587	115 months	1 subjective + 1objective sign or SGB or scintigraphy	17.5%
Mattey et al. 2000 [9]	179	NA	Xerostomia and keratoconjunctivitis sicca supported by ophthalmologic examination	12.3%
Carmona et al. 2003 [10]	788	NA	xerophthalmia and/or xerostomia, both objective and subjective	17%
Antero CD et al. 2011 [11]	82	10.2+/-7 years	AECG	24.3%
Kosrirukvongs et al. 2012 [1]	61	NA	Schirmer I test without anesthesia, tear break-up time, rose bengal staining score, severity of keratitis and salivary scintigraphy	22.2%
Haga HJ et al. 2012 [2]	307	10.63 years	Shirmer and unstimulated whole saliva	3.6%
He J et al. 2013 [3]	509	15.5 months	AECG	14%
Present study	76	15,6 years	AECG No systematic SGB	14%

RA: Rheumatoid Arthritis; NA: No assessed, SGB: Salivary Gland Biopsy; AECG: American-European-consensus group criteria.

The last results of the present study concern the immunological pattern of RA related SS with regards to RA. It appears as unusual that antiSSA/antiSSB in sSS was absent. Our results are in contrast with results found in Greek patients, where high titres of RF were associated with the occurrence of SS, while anti-ccp antibodies were not [18].

6. CONCLUSION

In the present study, 14% of patients with RA had secondary SS, in which no systematic salivary gland biopsy was done. Secondary SS did not modify the clinical and immunological pattern of RA. Our important finding was the significantly increased mean level of $\beta 2$ -m in RA-sSS group compared to RA group which may suggest a superimposed lymphoma risk.

CONSENT

Not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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