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Primary Sjögren syndrome and development of another autoimmune rheumatic disease during the follow-up

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Abstract

Background: Primary Sjögren syndrome (pSS) is a chronic autoimmune disease with its main target being exocrine glands, and is the connective tissue disease more frequently associated with other autoimmune diseases. The aim of this study was to assess the frequency of another autoimmune rheumatic disease (ARD) developed in primary Sjögren syndrome (pSS) patients and to describe it's clinical, serological and histologic characteristics.

Materials and methods: This is a retrospective cohort study. Data of patients with pSS diagnosis (American-European criteria 2002), included in the GESSAR database (Grupo de Estudio Síndrome de Sjögren, Sociedad Argentina de Reumatología) were analyzed. The development of a second ARD was registered during the follow up.

Results: 681 patients were included, 94.8% female. The mean age was 54 (SD 14) years and mean age at diagnosis of 50 (SD 13) years. The mean follow-up was 4.7 (SD 4.9) years; 30 patients (4.41%, CI 95%: 3.1–5.7) developed a second ARD during the follow up, incidence rate was 9.1/1000 patients-year (IR 95%: 5.8–12.4/1000 patients-year), the most frequent being rheumatoid arthritis (RA). 96% out of these 30 patients had xerophthalmia, 86.2% xerostomia, 92% positive Schirmer test, 88.24% positive Rosa Bengala test, lisamine green or Ocular Staining Score, 81.2% positive unstimulated salivary flow, 82.1% Ro(+) and 33.33% La(+). Minor salivary gland biopsy had been performed in 14 of the 30 patients, 12 with positive results. There were no statistically significant differences respect baseline characteristics when comparing the patients who developed another ARD to the ones that did not.

Conclusions: Of all the patients analyzed, 4.4% presented another ARD during their follow-up. It is important to be aware of this, to make an early and proper diagnosis and treatment of our patients.

Keywords: Primary Sjögren syndrome, Autoimmune rheumatic disease, Prevalence, Incidence

Key points

- Patients with primary Sjögren's Syndrome may develop another connective tissue disease during follow-up.
- The most frequently connective tissue disease developed during follow-up in the population of patients

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with primary Sjogren's Syndrome studied was rheumatoid arthritis.
- It is important to be aware of this to make an early and proper diagnosis.

Background

Primary Sjögren Syndrome (pSS) is a connective tissue disease with its main target being exocrine glands, mainly lacrimal and salivary. As a consequence, xerophthalmia and xerostomia are the most frequent symptoms [1].

Extra-glandular manifestations are also present in pSS, in some cases these are the first manifestation of the disease and makes the diagnosis difficult.

When Sjögren syndrome (SS) is present with other systemic autoimmune diseases [rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma, dermatopolymyositis (DM)], it is named secondary SS. This is the connective tissue disease more frequently associated with other autoimmune diseases and approximately 30% of the patients with SS present another associated autoimmune condition.

The scenario we are focusing our interest in this paper is related to know more about evolution of the pSS into other defined connective tissue disease. Literature is scarce in this aspect of the disease [2].

We aim to determine through this study the frequency of patients with pSS who developed a second autoimmune rheumatic disease (ARD) after their diagnosis, to find out the connective tissue diseases that these patients developed during the follow up, and to describe the baseline clinical, serological and histological characteristics of the salivary gland of the mentioned patients compared to the ones of patients that have not developed another ARD during the follow-up.

Materials and methods

We collected data from the GESSAR (Grupo de Estudio de Síndrome de Sjögren, Sociedad Argentina de Reumatología) multicentric database, created with the collaboration of national and international experts in SS. Data was registered in electronic database by treating rheumatologist from private and public hospitals, all across the country.

Patients who met the American-European 2002 criteria for pSS and were under current active follow-up by treating physician were enrolled. Informed consent was obtained from all patients in this database. This database was registered to the National Personal Data Protection Registry. Data since diagnosis until the inclusion in the database are collected retrospectively and then updated annually.

An observational, analytical and retrospective cohort study was carried out. It was considered a new autoimmune disease when its development occurred during follow up. The American-European 2002 classification criteria consider for the diagnosis the presence of: ocular symptoms associated to dryness, oral symptoms due to mouth dryness, ocular signs evidenced by tests by Schirmer test or corneal staining, histopathological characteristics in salivary gland biopsy, salivary gland functional tests (salivary scintigraphy, unstimulated salivary flow) and the presence of autoantibodies in serum; antibodies against Ro/SS-A or La/SS-B or both [3]. Patient classifies for pSS by meeting 4 out of 6 of these items. Antibodies and/ or positive biopsy must be presents to classify for pSS. This classification has 97.3–97.5% sensitivity and 91.8–94.2% specificity. These are the only criteria that differentiate pSS from secondary SS, using the last term for patients who have another concomitant connective tissue disease, even in the cases in which the SS had been present years before the other disease. Modified 1997 ACR criteria for SLE, 2010 ACR/EULAR criteria for RA, 2013 ACR/EULAR criteria for Systemic Scleroderma, Rhupus criteria (RA ACR 1987 in addition to SLE ACR 1982 with erosive arthropaty) and Bohan & Peter for DM, and the opinion of the treating rheumatologist were used to the diagnosis of others ARD [4–7]. These diagnoses were entered in specifically predetermined fields of the database and the rheumatologists were specifically asked to evaluate about another ARD development.

Statistical analysis

For the descriptive statistics, the continuous variables were expressed as mean and standard deviation or median and interquartile range according to the distribution and sample size. The categoric variables were expressed in percentages. The continuous variables were compared with t-test or Wilcoxon rank-sum test, and categoric variables comparisons were made with chi square or exact Fisher test, as appropriate.

Results

Six hundred eighty one patients were included in this study from the GESSAR database, 94% women with an average age of 54 (SD 14) years old and an average age of 50 (SD 13) years old when pSS was diagnosed. The mean follow-up was 4.7 (SD 4.9) years. The general features of patients are detailed in Table 1. The clinical manifestations reported correspond to those present at the baseline visit and those developed during the follow-up period or until the development of another ARD.

Thirty patients (4.41%. CI 95%: 3.1–5.7%) developed a second ARD during follow up, the median time until the

Table 1 General features of patients

	N = 681(100%)
Female gender n (%)	511 (94.8)
Age, mean (± SD)	54 (± 14)
Age at diagnosis, mean (± SD)	50 (± 13)
Follow up (years), mean (± SD)	4.7 (± 4.9)
Xeroftalmia n (%)	618/659 (93.78)
Xerostomia n (%)	581/672 (86.46)
Schirmer's positive test n (%)	454/499 (90.98)
Decreased Unstimulated oral salivary flow n (%)	213/258 (82.56)
Rheumatoid Factor (RF) (+) n (%)	303/589 (51.34)
Anti Ro/SS-A (+) n (%)	467/627 (74.48)
Anti La/SS-B (+) n (%)	262/608 (43.09)
Positive biopsy n (%)	345/400 (86.25)
Salivary Gland Enlargement n (%)	186 (27.31)
Neuropathy n (%)	67 (9.84)
Arthralgia n (%)	436 (64.02)
Arthritis n (%)	191 (28.05)
Raynaud's phenomenon n (%)	101 (14.83)

diagnosis of the second connective tissue disease was 4 years (IQR: 2–9); 670 patients were included for survival analysis, 11 patients lack time of follow up and were excluded. The incidence rate of development of another ARD during the follow up was 9.1/1000 patients-year (CI 95%: 5.8–12.4/1000 patients-year). No statistically significant differences were found between both groups in baseline characteristics (Table 2).

Patients that developed another ARD presented: RA 14 patients, scleroderma 9 patients, SLE 5 patients, DM 1 patient, and Rhupus 1 patient (Fig. 1).

The mean age of this subgroup was 53 (± 14) years old, with a mean age at diagnosis of pSS of 48 (± 13), 91% were women. Regarding the dryness symptoms, 96% of the patients had xeropthalmia and 86.2% had xerostomia at diagnosis of pSS. As for objective tests: 92% had positive Schirmer's test, 88.24% positive Rosa

Table 2 Baseline general characteristics of patients who developed another connective tissue disease

	pSS (n = 651)	pSS + another ARD (n = 30)	*p*
Female gender (%)	93.33	96.10	0.34
Mean age (± SD)	54 (± 14)	53 (± 14)	0.83
Age at diagnosis, mean (± SD)	50 (± 13)	48 (± 13)	0.63
Anti Ro/SS-A + (%)	74.12	82.14	0.50
Anti La/SS-B + (%)	43.55	33.33	0.29
RF + (%)	50.80	62.96	0.21
Positive salivary gland biopsy (%)	86.53	78.57	0.42

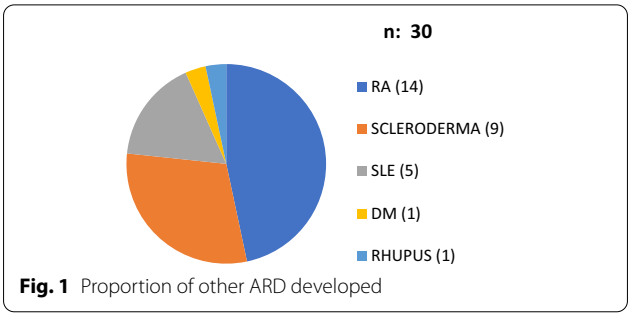

Fig. 1 Proportion of other ARD developed

de Bengala, lisamine green, and/or Ocular Staining Score and 81.2% presented positive unstimulated salivary flow. Fourteen out of these 30 patients underwent salivary gland biopsy, 12 had positive Chilsom's score. Regarding the presence of antibodies, the anti Ro/SS-A was positive in the 82.1% of the patients and the anti La/SS-B in the 33.33%. Of the 14 patients that presented diagnosis of RA during the follow up, 78% had arthralgias, mostly oligoarticular without overt arthritis at the moment of the diagnosis of pSS. RF was performed in 13 patients with positive result. During the follow up these patients developed arthritis, anti citrullinated antibodies (anti-CCP) was tested in 7, results were positive in all of them. While all patients who developed RA presented arthralgias and arthritis, 55% and 21%, respectively ($p < 0.01$ for both comparisons), of patients who persisted whit only pSS diagnosis during the follow up, presented these manifestations.

At diagnosis of pSS, 44% of the patients who developed scleroderma already presented Raynaud's phenomenon and 22.22% presented antinuclear antibody (ANA) with a centromeric pattern. During follow up, 100% of patients who develop scleroderma presented Raynaud versus 13% ($p < 0.01$) of the patients who didn´t develop other ARD. Regarding skin involvement, 2 patients had limited scleroderma, in one patient the presence of acro osteolysis and sclerodermic kidney crisis were recorded. One patient presented pulmonary hypertension and 3 patients presented reflux esophagitis.

Before diagnosis of SLE, 100% referred arthralgias and 80% presented arthritis, while 55% and 21%, respectively ($p < 0.01$ in both comparisons), of patients who persisted whit pSS diagnosis during the follow up, presented these manifestations. 20% presented Raynaud's phenomenon. One patient presented purpura and petechiae with positive anticardiolipin antibodies and leukocytoclastic vasculitis in skin biopsy; later, she was diagnosed with neurolupus. All of them presented positive anti Ro/SSA-A.

The patient who developed Rhupus presented positive ANA, positive anti Ro/SS-A and arthritis.

The patient who was diagnosed DM during follow up, presented myalgias and myositis and also presented a compatible skin biopsy.

Discussion

PSS is an ARD that presents with dryness symptoms in the main mucosas and can also have systemic involvement with extraglandular manifestations. To date, there is scarce data evaluating the prevalence of overlap with another autoimmune disease of connective tissue in patients under follow-up for SS. Fauchais et al. published in 2010 a cohort study with a mean follow-up of 76.1 (±51) months. Fourteen out of 445 patients (3.15%) developed ANA-associated auto-immune disease during the follow-up, being that frequency lower than in our study. Six of the patients development systemic lupus erythematosus, 2 systemic sclerosis and, unlike our study, polymyositis was one of the most frequently observed (5 patients) [8].

Previous studies have classified SS as primary or secondary, according to its association to ARD. Secondary SS includes many ARD such as RA and SLE. This definition has been used for many years, even today. However, the continuous advances in the knowledge of epidemiology and etiopathogenesis suggest that this classification should be reevaluated [9].

The expression of autoimmune diseases usually causes problems in classification, with difficulties in distinguishing one from the other. Like others, patients with pSS often have clinical manifestations and antibodies which are included in the classification criteria of other ARD [9].

Many classification criteria for SS have been established since 1965. The latest one has been recognized by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) [10]. Like the previous criteria, the ACR criteria / EULAR 2016 also classify a patient with pSS using autoantibody testing, dryness measurement, and histopathology [10]. However, the difference is that the 2016 ACR / EULAR criteria add a weighted score for each item, further refining the particular threshold for the eye staining score [10]. Anti-SSB(La) was excluded as an item based on experts opinion and observational data that showed that the presence of anti-SSB(La) without anti-SSA(Ro) antibodies, had no significant association with SS phenotypic features, relative to seronegative participants [10]. Furthermore, the presence of an extra glandular manifestation received credit in the 2016 ACR / EULAR criteria, allowing patients with this characteristic and absence of glandular manifestations to participate in clinical trials and observational studies [10].

The new criteria do not mention secondary SS as a clinical entity or provide a tool for its diagnosis or differentiation [7].

The greater degree of superposition of pSS with other autoimmune diseases occurs with SLE, RA, systemic sclerosis and mixed connective tissue disease (MCTD).

Regarding SLE, there are two main problems of diagnosis: the differentiation between the older SLE onset and the pSS, and the importance of subacute cutaneous lupus in patients with pSS [11].

The Anti Ro/SS-A antibodies play a pathogenic role in erythematous subacute cutaneous lupus (SCLE) and it is based to great extent on observations of skin diseases in neonatal erythematous lupus (NLE) [12]. These antibodies are related to the development of cutaneous lesions in patients with SLE as well as patients with pSS. Polycyclic, photosensitive, erythematous, maculopapular (clinically known as erythema annular) lesions in Asian patients with SS and SCLE in caucasic patients with SLE, are the most characteristic [11]. Anti-52-kda and anti-60-kda antibodies have been studied in serum of patients with SS and it was discovered that none of Ro antibodies could differentiate between annular erythema and SCLE, which suggested that both diseases could have the same pathogenic origin [13]. Some patients diagnosed with isolated SCLE, could have subjacent pSS [11]. In our study, although in the patients who developed SLE the most frequent manifestation was articular involvement, all of them presented positive anti Ro/SSA-A.

Muscle-skeletal manifestations are present in up to a 90% of patients with pSS. In a follow-up of approximately 4 years, 18% of the patients developed polyarthritis, that clinically resembles RA [14].

It is known that anti-CCP are highly specific of RA although it has also been detected in 3% to 9.9% of pSS [15]. In a systematic review with meta-analysis published in 2018, the association between the presence of arthritis and positive anti-CCP in patients with pSS was evaluated. Ten studies were included (1332 patients). Patients with pSS who present anti-CCP show higher risk to develop arthritis as part of the clinical spectrum of the disease, as well as a significant higher risk to develop RA [15]. In our study, in patients who developed RA and the presence of anti CCP was evaluated, they were positive in all of them.

During the last decade, there has been an increasing interest for implementation of ultrasound in rheumatology (US), which is more sensitive to identify bone erosions [14].

A study carried out in Mexico with 17 female patients with pSS, 18 patients with secondary SS and 17 control subjects, evaluated the articular involvement through the use of US. A total of 28 erosions in patients with secondary SS were found, only 3 were found in those who

had pSS, at the wrist level, and there were no erosions observed in the control group [14]. Due to the characteristics of our study, we did not have joint ultrasound results in patients who developed RA.

Regarding scleroderma, recent studies have found a prevalence of sicca symptoms in approximately 67%, whilst secondary SS was found in 14 to 20% of patients with the mentioned disease [16–18].

The pSS is one of the diseases more frequently identified in studies that analyze the clinical characteristics of patients with positive anticentromeric (ACA) antibodies [19–21]. In a study, 28 patients with SS and ACA were evaluated. The predominant clinical features among ACA positive patients were Raynaud's phenomenon. During the follow-up, the development of limited scleroderma was described in 7 (25%) patients and was characterized by incipient cutaneous changes which suggested sclerodactyly. Considering these results, this study concludes to recommend the test ACA in patients with pSS and Raynaud's phenomenon since the fourth part of these patients can have a coexistent limited systemic sclerosis [20]. Regarding the anti-topoisomerase I antibodies, in contrast to ACA, they were found in only 2 out of 402 patients with pSS; and no one of them had clinical characteristics of scleroderma, which suggests that these antibodies have little implication in the pSS [22]. In agreement, in our study we observed that about half of the patients who developed scleroderma had a history of Raynaud's phenomenon, while approximately 25% had a history of positive ACA antibodies.

Finally, patients with pSS may have clinical manifestations included in the classification criteria of MCTD, like swollen hands, synovitis, Raynaud's phenomenon which makes differentiation between pSS and MCTD more difficult. Other superposed diseases happen less frequently and include sarcoidosis (sarcoidosis of type SS presentation versus coexistence of the two diseases), systemic vasculitis and antiphospholipid syndrome (APS). The association between pSS and the other ARD such as inflammatory myopathies, adult 's Still disease, recurrent polychondritis or Behcet 's disease are little frequent which may suggest in these cases a casual association of two autoimmune independent diseases [6, 21–23]. The antiphospholipid antibodies, ANCA antibodies and cryoglobulins are frequently found in patients with pSS with a prevalence that varies between 10 and 20%. The coexistent APS or systemic vasculitis are only detected in around 10% of the cases [23–25]. In the follow-up period of the patients included in our study, the development of any of these pathologies was not observed.

The wide variety of clinical and immunological manifestations in patients with pSS often cause diagnosis problems, especially considering SLE, RA and limited sclerosis which are the most frequently associated pathologies. The overlapping makes differentiation between pSS and secondary SS more difficult.

As weaknesses of this study, we recognize the retrospective collection of data and the relatively short follow-up period.

We consider strengths of our work, being a multicenter study, with a large number of patients, from different regions of our country. This is the first multicenter study carried out in Argentina that considers SS as a primary entity associated with another connective tissue disease and not secondary to it, and that provides useful information regarding the monitoring and prognosis of patients.

Conclusions

Of all the patients analyzed, 4.4% presented another autoimmune rheumatic disease during their follow-up. The presence of certain clinical and serological manifestations could be considered as suggestive of the subsequent development of another autoimmune rheumatic disease. We consider relevant to recognize the possibility of developing another autoimmune rheumatic disease during pSS patients follow up, in order to provide adequate diagnosis and treatment.

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Author contributions
All authors have contributed to the development of this study and its manuscript, and have read and approved the final manuscript. All authors read and approved the final manuscript.

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None.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The multicentric GESSAR database is approved by an independent Ethics Committee (Hospital Británico Ethics Committee-2010) and is attached to international investigational rules of the World Medical Association in Helsinki. Patients must sign an informed consent form prior to their data being included in the database. Patient´s consent was obtained to access the information in their medical histories and to fill in the mentioned data to the database GESSAR. Personal information confidentiality was respected in the registration form, guaranteeing the no-use of the information obtained in harming the subject in study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests related to the content of this manuscript.

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