Renal Involvement In Primary Sjögren's Syndrome: Data From The Spanish Sjögrenser Cohort.

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Abstract

Objectives To investigate the prevalence, associated factors, and effects of primary renal disease on morbidity in patients with primary Sjögren's syndrome (pSS).

Methods All patients in the SJÖGRENSER (registry of adult SSp patients of the Spanish Society of Rheumatology) cohort were retrospectively investigated for the presence of clinically significant renal involvement directly related to pSS activity.

Results Of the 437 patients investigated, 39 (9%) presented overt renal involvement during follow-up. Severe renal disease necessitating kidney biopsy was relatively rare (23%). Renal involvement may complicate pSS at any time during the disease course and is associated with severe disease (indicated by higher scores of involvement, activity, and damage), systemic multiorgan involvement, and a higher frequency of lymphoma. Multivariate analysis showed that older age (odds ratio [OR] 1.03, 95% confidence interval [CI] 1.00–1.07), higher European League Against Rheumatism Sjogren's Syndrome Disease Activity Index scores (OR 1.1, CI 1.03–1.18), serum anti-La/SSB positivity (OR 6.65, CI 1.41–31.372), and non-vasculitic cutaneous involvement (OR 5.47, 1.03–29.02) were independently associated with this complication. Chronic renal failure developed in 23 of 39 patients (59%); only 1 of them progressed to end-stage renal disease necessitating renal replacement therapy. Patients with renal disease showed higher Sjögren's syndrome disease damage index scores, higher rates of hospitalization due to disease activity and higher rates of clinically relevant comorbidities.

Conclusion Renal involvement is an uncommon complication in pSS that was observed in 9% of patients. Although categorized as a non-negligible comorbidity, this condition shows a favorable prognosis.

1.- Background

Primary Sjögren's syndrome (pSS) is a chronic systemic autoimmune disorder that mainly affects the exocrine glands, causing dryness of the main mucosal surfaces and occasional glandular enlargement. Additionally, a variety of systemic (extraglandular) manifestations may occur, including fatigue, musculoskeletal symptoms, cutaneous lesions and internal organ involvement (e.g., pulmonary, renal, hepatic, and neurological lesions)[1].

Primary renal disease in pSS seems not uncommon, although its exact prevalence is still unknown, since it has been reported to occur in 2% to 42% of the patients[2-11]. Renal involvement includes both tubular and glomerular injury, that can appear as the result of two distinct pathophysiological processes[12,13]: *(a)* tubular epithelial disease with a predominantly mononuclear lymphocytic infiltration (similar to that observed in the exocrine glands) of the kidney interstitium around the renal tubules resulting in tubulointerstitial nephritis (TIN) or renal tubular dysfunction and, *(b)* non-epithelial disease with a secondary immune complex-mediated process resulting in glomerulonephritis (GN).

Although some associations have been described[12,13] the factors predisposing patients to this complication remain unclear. It is likely that there are risk factors associated with the development of renal involvement, some of which may be modifiable.

The appearance of renal complications influences the prognosis (functional and vital) and the accumulated damage caused by the disease, although the extent and grade remain unknown.

The aim of the present study was to investigate the prevalence, associated factors, and effects of primary renal disease on morbidity in patients included in the multicenter Spanish pSS cohort SJÖGRENSER (national registry of the Spanish Society of Rheumatology of patients with pSS).

2.- Methods

2.1.- Patient selection.

This retrospective study investigated primary renal disease in all adults included in the SJÖGRENSER registry. This is a cross-sectional hospital-based registry study designed to gain a better understanding of pSS in clinical settings. It includes data of 437 patients who met the 2002 revised American–European Consensus Group (AECG) classification criteria across 33 hospitals in Spain.

The primary objectives of the SJÖGRENSER study were to investigate patients with pSS included in the registry providing data on: (1) clinical characteristics (focused on disease activity and severity), (2) biological (serological) characteristics, (3) hospital admissions and specific comorbidities (tobacco use, hypertension, diabetes mellitus, dyslipidemia, heart failure, ischemic heart disease, peripheral arterial disease, stroke, multiple sclerosis, celiac disease, fibromyalgia, osteoporosis, osteoporotic fractures, osteonecrosis, and neoplasms) and, (4) disease management (pharmacological and non-pharmacological therapies used for the management of pSS and its complications, categorized on the basis of oral, cutaneous, nasal or vaginal involvement, Raynaud's phenomenon, systemic involvement and eye surgery. Treatment with glucocorticoids (GC), immunosuppressants (IS), or other therapies was recorded as follows: *"never", "any use,*" and "*use at last visit".* The objectives and methodology of the SJOGRENSER Registry have been published previously[15] (Additional file 1).

Of the 437 patients included in the registry, we selected those with clinically significant renal involvement directly caused by pSS. Clinically significant renal disease was defined based on ≥1 of the following criteria: (a) renal insufficiency, defined as elevated serum creatinine levels (>1.6 mg/dL) and an estimated glomerular filtration rate <60 mL/min/1.73 m^2, (b) persistent proteinuria >0.5 g/24 h, (c) active urinary sediment (hematuria, pyuria, red blood cell casts), (d) renal tubular acidosis (RTA) or Fanconi´s syndrome, (e) nephrolithiasis or nephrocalcinosis with or without renal colic and, (f) kidney biopsy showing histopathological features of TIN, GN, or both. Primary renal disease was defined as that directly caused by pSS after excluding other known causes of renal injury per the opinion of the investigator that included the patients in the registry.

Clinical, histological, and immunological features, as well as prognosis were evaluated in these patients. The degree of involvement, activity, and damage were assessed using the Sjögren's Syndrome Disease Activity Index (SSDAI), the European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index (ESSPRI), the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), and the Sjögren's Syndrome Disease Damage Index (SSDDI). Major renal clinical outcomes included chronic renal failure (CRF), the need for renal replacement therapy (dialysis or transplantation), and death.

The study protocol was approved by the Institutional Ethics Committee of the Hospital Universitario Puerta de Hierro and subsequently by the local ethics committee of all centers that participated in this research. Informed consent was obtained from all patients, and their clinical records were anonymized prior to analysis. Patient confidentiality was maintained by protecting all patient data in accordance with national regulations. This study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference for Harmonization.

2.2. - Statistical analysis.

Numerical variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as frequencies and percentages. The Student t or Mann–Whitney U test was used to compare numerical variables according to normality adjustments and the chi-squared or Fisher's exact test was used for categorical variables.

Univariate and multivariate analyses (Cox proportional hazards regression) were used to determine the risk factors associated with renal disease. Statistical significance was defined as $P \leq 0.05$.

3.- Results

3.1. Demographic data. Of the 437 patients included in the study, 39 (9%) showed clinically significant renal involvement. Most patients were women (97%), their mean (± SD) age at entry was 63±13 years, and mean disease duration was 11.8±8.2 years. Baseline demographic and clinical characteristics of the SJÖGRENSER cohort, including the group of patients with renal involvement, are shown in Table 1.

3.2. - Renal manifestations. Of the 39 patients with renal involvement, 9 (23%) presented overt renal involvement that was significant enough to warrant the performance of a kidney biopsy. Of them, 6 patients had only TIN, 2 showed only GN (1 mesangial GN and 1 membranoproliferative GN), and 1 showed both TIN and mesangial GN. The clinical presentation, renal biopsy findings, treatment, and prognosis of these 9 patients with pSS and biopsy-proven renal involvement are summarized in Table 2.

Of the remaining 30 patients in whom a kidney biopsy was not performed, 2 showed renal involvement in the context of cryoglobulinemia suspecting a cryoglobulinemic membranoproliferative GN. The other 28 patients were suspected to have chronic TIN or renal tubular dysfunction. Most of these 28 patients presented with an insidious clinical course, with variable but usually mild renal insufficiency, relatively benign findings on urinalysis, and electrolyte disturbances. Urolithiasis or nephrocalcinosis (presumably associated with distal RTA) occurred in 17 patients.

Renal involvement may complicate pSS at any time during the disease course: in 18% (7/39) of cases, renal disease was the presenting manifestation that led to the diagnosis of pSS; in 26% (10/39) it was present at diagnosis or appeared within the first 2 years of disease, and in 56% (22/39) renal disease was a late manifestation (first 2–5 years: 9 patients; 5–10 years: 7 patients, and after >10 years of follow-up: 6 patients).

3.3. Previous and concomitant extraglandular manifestations of primary Sjögren's syndrome. As shown in Tables 1 and 3, most patients who developed renal disease showed previous or concomitant systemic (extraglandular) manifestations during the course of the disease. The most common clinical features included arthralgia/arthritis (79%/44%), hematological abnormalities (77%), lung involvement (23%), lymphadenopathy (23%), peripheral neuropathy (20.5%), gastrointestinal involvement except hepatitis (20.5%), vasculitis (18%), non vasculitic cutaneous involvement (10%), and lymphomas (5%).

With regard to autoantibody profiles, 97% of patients showed positive antinuclear antibodies (ANA), serum anti-Ro/SSA positivity was observed in 100%, anti-La/SSB positivity in 92%, and rheumatoid factor (RF) in 87% of patients. Low C3 or C4 levels were detected in 24% and 29% of patients, respectively. Serum cryoglobulin positivity was observed in 18% of evaluated patients.

3.4. Factors associated with the development of renal disease. Comparison between patients with and without renal involvement is shown in Table 3. Patients with clinically significant renal involvement were significantly older than patients without this complication (p=0.04) and showed a longer disease duration (11.8 years vs. 7.9 years, p=0.007). Additionally, these patients showed higher prevalence rates of ocular complications including corneal ulceration (p<0.001) and chronic posterior blepharitis (p=0.03), glandular inflammation (salivary gland enlargement; p=0.02), myopathy (p=0.01), Raynaud's phenomenon (p=0.05), non-vasculitic cutaneous involvement (P= 0.005), vasculitis (p=0.04), lung disease (p=0.004), peripheral neuropathy (p=0.008), and lymphoma (p=0.006).

Furthermore, we observed statistically significant differences in the immunological profile of these patients who showed higher prevalence of anti-La/SSB (p<0.001) and RF positivity (p=0.005), C4 hypocomplementemia (p=0.01), hypergammaglobulinemia (p=0.01), and cryoglobulin positivity (p=0.08).

Patients with renal involvement also showed higher ESSDAI scores (9±9 vs. 4±5, p <0.001) and SSDAI scores (4±2 vs. 2±2, p<0.001) at the last visit (at enrollment in the registry). The ESSPRI scores were similar in both groups (5.4±2 vs. 5.2±2.3, p=0.561).

Most of these differences remained statistically significant in the comparative study that only included patients with biopsy-proven renal involvement (Additional file 2).

Multivariate analysis (Table 4) showed that older age (odds ratio [OR] 1.03, 95% confidence interval [CI] 1.002–1.073; p=0.038), high ESSDAI scores (OR 1.10, 95% CI 1.035–1.187; p= 0.003), and serum anti-La/SSB positivity (OR 6.65, 95% CI 1.412–31.325; p=0.017) were independently associated with renal disease. Among the various exocrine gland and extraglandular manifestations that showed significant intergroup differences in the comparative analysis, only non-vasculitic cutaneous involvement (annular erythema and erythema multiforme) showed a significant association (OR 5.47, 95% CI 1.034–29.029; p= 0.046) on multivariate analysis.

3.5. Morbidity and mortality rates associated with primary renal disease. The main objectives of this registry study did not include investigation of the specific effects of therapies on individual manifestations; therefore, we can only present data of the specific treatment used in the 9 patients who underwent a biopsy (collected a posteriori, Table 2).

The therapeutic regimen used in patients with pSS with and without renal involvement differed primarily with regard to the administration of moderate-to-high doses of glucocorticoids (Table 3). Fifty-four of patients with renal involvement received corticosteroid and nearly all (86%) received moderate or high doses (≥ 30 mg/day of prednisone or its equivalent), while those without renal involvement underwent much less prednisone treatment (40.5%), and most of them (64.6%) were taking low dose prednisone (p=0.04).

Twenty three of the 39 patients (59%) developed CRF, but only in 1 of them the disease progressed to end-stage renal disease necessitating renal replacement therapy (dialysis or transplantation). None of the patients died.

As expected, the mean SSDDI scores were significantly higher in patients with renal disease than in those without this complication (5.9±1.85 vs. 5.72±1.5, p=0.04). Interestingly, when renal disease was not included as a domain for SSDDI score calculation, the differences disappeared (5.7±1.8 vs. 5.7±1.5; p= 0.953). Based on these data, it can be inferred that renal complications show important weighting in the accumulated damage of the disease.

With regard to comorbidities (Table 5), patients with renal disease showed higher rates of hospitalization due to disease activity (p=0.004) and higher rates of hypertension (p=0.001), dyslipidemia (p=0.01) and ischemic cardiac disease (p=0.004) that are attributable to corticosteroid therapy and the development of CRF in many patients. Osteoporotic fractures (p=0.08) and heart failure (p=0.07) were also more frequent in this group of patients and had a clear tendency to significance.

4.- Discussion

The heterogeneity of disease course and outcome in pSS, coupled with its relative low prevalence, make it difficult for physicians to acquire sufficient clinical experience in the absence of standardization and collaborative efforts. Therefore, much of the clinical research on pSS has been based primarily on registries and on their derived cohorts, which have been an important source of new knowledge about the disease. Registry-based studies usually include a

large number of patients from non-experimental clinical settings and enable more extensive follow-up than that possible in clinical trials, thereby providing more reliable answers to specific questions. In this study, this principle was applicable to investigate renal involvement in pSS, which is one of the most common extraglandular manifestations of pSS.

Based on the data from this registry-based study, the overall prevalence of clinically significant renal involvement was 9% (2% considering only cases with histopathological confirmation). This prevalence rate is quite similar to that reported previously by large-scale retrospective cohort studies performed in Spain (4.3%–5%)[2,3], Greece (4.9%–11%)[4,5] and the UK (6.5%)[6], that also looked for overt renal disease using a similar criteria and have followed the diagnostic criteria of the AECG. However, prospective studies that specifically investigated tubular defects in randomly selected patients with pSS showed that the prevalence of renal involvement was much higher, reaching 42%[7-10].

This disparity in prevalence rates cannot solely be attributed to the use of different diagnostic criteria in these studies, and indicates that renal involvement in pSS is an underdiagnosed problem. In a non-negligible percentage of pSS patients, tubular involvement and TIN are often occult or clinically silent and needs to be specifically looked for[14].

In the present study, renal involvement in pSS mainly manifested as acute or chronic TIN or tubular dysfunction, being less frequent the presence of different types of GN either concomitantly or alone. In nearly all previous studies that have reported biopsy data, TIN was the predominant lesion, found in 70-75% of patients, with the remaining 25%–30% of patients showing glomerular disease[4,11,16-19]. Considering the broad spectrum of histopathological presentations observed in patients with pSS, kidney biopsy is highly recommended to confirm the type of renal injury and rule out other associated conditions (mainly systemic lupus erythematosus [SLE], vasculitis, and non-autoimmune diseases). However, renal biopsies are not always performed in these patients in real-world clinical practice. In this sense, an important feature of our registry (which is also observed in other major studies)[2-11] is the low percentage of patients who underwent a kidney biopsy for the diagnosis of renal disease, in contrast to the usual trend observed in patients with SLE[20]. To date, few reports in the available literature describe biopsy-proven renal disease in patients with pSS: the largest recent studies that investigated this issue reported 41 patients in China[11], 95 in France[16], 33 in Greece[4], 24 in the USA[17], and 13 in Mexico[18]. In our view, part of patients with clinical evidence of renal involvement do not necessarily undergo biopsy because clinicians assume they have TIN and are empirically treated without obtaining a histopathological diagnostic confirmation. Goules et al.[4] followed-up 471 patients with pSS over a mean period of 10 years and concluded that a renal biopsy was not necessary in patients with clinical and laboratory findings suggesting TIN.

Renal disease may complicate pSS at any time during its course. Most reports suggest that renal symptoms usually present 2–7 years after the initial diagnosis of pSS[4,7,11]. In our study, in 56% of cases it was a late complication occurring between 2 and ≥10 years from the time of diagnosis and in 44% kidney involvement was observed at the time of pSS diagnosis or developed within the first 2 years of disease evolution. It is not uncommon (18% in our registry) that renal disease (usually TIN) may be the presenting manifestation that leads to the diagnosis of pSS. A previous study[4] reported that TIN occurred earlier in the course of pSS (approximately within 2 years) than GN secondary to cryoglobulinaemia (8 years); however, this finding was not confirmed by a separate study in which renal disease was diagnosed 2–3 years after the diagnosis of pSS regardless of the histopathological findings[11].

In most patients, renal involvement occurs in the setting of previous or concomitant extraglandular manifestacions[2-11,16-19]. In our registry, apart from the frequent presence of systemic and musculoskeletal symptoms, these patients show higher rates of myopathy, Raynaud's phenomenon, non-vasculitic cutaneous involvement, vasculitis, lung disease, and peripheral neuropathy. Additionally, they have higher prevalence rates of salivary gland enlargement and ocular complications (including corneal ulceration and chronic posterior blepharitis) suggesting more severe exocrine gland

disease, higher frequency of immunological biomarkers of B-cell activation (RF positivity, hypergammaglobulinemia, and cryoglobulinaemia), and increased frequency of lymphoma. The mean SSDAI and ESSDAI scores were also significantly higher in patients with renal disease. Based on these data, it can be inferred that renal involvement primarily occurs in patients with severe disease (with higher scores of involvement, activity and damage), frequent ocular complications, systemic multiorgan involvement during the course of the disease, and increased frequency of lymphoma.

In this study, we observed that older age, active disease defined by higher ESSDAI scores, and anti-La/SSB positivity are significant predictors of renal involvement in pSS. Non-vasculitic cutaneous involvement (annular erythema and erythema multiforme) is also significantly associated with renal disease. Notably, some of these associated factors are coincident with those reported in other studies.

Older age seems be a predictor for developing other extraglandular manifestations, such as pulmonary or neurologic disease[2,21-24]. In all previous large cohort studies[2-10], renal manifestactions in pSS usually also presented in patients aged ≥ 50 years, with the exception of the Chinese cohort in which patients were aged ≤40 years[11]. Although renal dysfunction is an important domain included in the ESSDAI score (which could partly explain the high ESSDAI scores observed in this study), most patients with renal involvement also present with severe extraglandular manifestations, along with biological (inmunological) and hematological abnormalities associated with a high prevalence of anti-Ro/SSA and anti-La/SSB antibodies[2-11].

These antibodies, (particularly anti-La/SSB) are shown to be associated with renal involvement (particularly with TIN) [4,7,9,10,16,17] and with poorer renal prognosis[16], suggesting that these patients with pSS warrant careful workup for renal function. Notably, anti-Ro/SSA and anti-La/SSB antibodies were identified in 100% and 92%, respectively of our patients, whereas previous large-scale epidemiological studies have reported prevalence rates of approximately 55% and 33% for anti-Ro/SSA and anti-La/SSB antibodies, respectively[1-3,25]. Anti-SSA and/or anti-SSB positivity is often considered a marker of disease activity and extraglandular involvement in pSS, including the development of annular erythema[26-29].

Previous studies have documented an association between between disease duration[7,10], hypergammaglobulinaemia[9,11] and gastrointestinal tract involvement[30] and renal disease; however, we could not confirm these associations. Other biological risk factors for renal involvement in pSS identified include the elevated serum creatinine and alpha-1-microglobulin levels[30], and baseline high levels of serum protein and serum beta-2 microglobulin[10].

In our study, renal involvement (particularly in patients with TIN) did not significantly affect patient survival. In one study, the prognosis appears to be worse in patients with predominantly glomerular involvement, with lower survival rates and higher incidence of lymphoma compared with patients with predominantly tubulo-interstitial involvement[4]. In contrast, in other series renal outcomes seem to be better in patients with GN than in those with TIN, perhaps because diagnosis and treatment are possible at an earlier stage of the disease[7,10,11,16-19,30]. Complete normalization of both proteinuria and renal function does not usually occur in many patients (59% in our series) despite treatment, probably due to chronic interstitial fibrosis[4,7,10,11,16-19,30]. Although renal involvement is benign in most patients, terminal CRF can occur in both TIN and GN (reported in 3%–15% of all patients)[4,11,16-19].

Primary renal disease is an important cause of morbidity. Based on our data, we observed that renal complications show important weighting in the accumulated damage of the disease measured using the SSDDI. Additionally, patients with renal involvement show higher rates of hospitalization due to disease activity and higher rates of clinically relevant

comorbidities, such as hypertension, dyslipidemia, ischemic cardiac disease, and osteoporotic fractures that are attributable to corticosteroid therapy and the development of CRF in many patients.

The results of our study need to be interpreted in light of the fact that this is a retrospective study that included patients from an existing cohort and has several limitations. First, the main limitation is that the baseline variables were collected many years into the course of the disease rather than at onset. Second, owing to the multipurpose nature of the SJOGRENSER-TRANS registry, which was never specifically designed to investigate primary renal disease in patients with pSS, renal manifestations were not systematically evaluated, and only the clinically significant cases cases were collected. This could lead to an underestimation of the prevalence of some of these manifestations (TIN and renal tubular dysfunction). And third, the main objectives of this registry-based study did not include investigation of the specific effects of therapies on individual manifestations. Therefore, we could not evaluate the effects of therapeutic interventions on renal disease.

5.- Conclusions

In conclusion, renal involvement is an uncommon complication that occurs in 9% of patients with pSS and usually shows a favorable prognosis, although it is categorized as a non-negligible comorbidity. Renal disease may complicate pSS at any time over its course and usually occurs in patients with severe disease (with higher scores of involvement, activity and damage), systemic multiorgan involvement, and an increased frequency of lymphoma. We identified several risk factors associated with renal involvement in pSS, none of them modifiable, although this categorization can help to identify patients who require careful workup for renal function (older patients with active disease defined by higher ESSDAI scores, anti-La/SSB positivity, and non-vasculitic cutaneous involvement).

Abbreviations

AECG = American–European Consensus Group; ANA = antinuclear antibodies; CRF= chronic renal failure; ESSDAI = European League Against Rheumatism Sjögren's Syndrome Disease Activity Index; ESSPRI = European League Against Rheumatism Sjögren's Syndrome Patient Reported Index; GN = glomerulonephritis; pSS=primary Sjögren's syndrome; RTA = renal tubular acidosis; SJÖGRENSER = registry of adult SSp patients of the Spanish Society of Rheumatology; SLE = systemic lupus erythematosus; SSDAI = Sjögren's Syndrome Disease Activity Index; TIN = tubulointerstitial nephritis

Declarations

Ethics approval and consent to participate: The study protocol was approved by the Institutional Ethics Committee of the Hospital Universitario Puerta de Hierro and subsequently by the local ethics committee of all centers that participated in this research. Informed consent was obtained from the patients, and their clinical records and information were anonymized prior to analysis. The confidential information of the patients was protected according national normative. This study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference for Harmonization.

Consent for publication: Informed consent was obtained from the patients, and their clinical records and information were anonymized prior to analysis. The confidential information of the patients was protected according national normative.

Availability of data and material: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper.

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- Collected and interpreted the data.

- Have been involved in drafting the manuscript or revising it critically for important intellectual content.

- Given final approval of the version to be published.

- Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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References

1.- *Mariette X, Criswell LA. Primary Sjögren's Syndrome. N Engl J Med 2018;378:931-9.*

2.- *Ramos-Casals M, Solans R, Rosas J, Camps MT, Gil A, Del Pino-Montes J, et al; GEMESS Study Group. Primary Sjögren syndrome in Spain: clinical and immunologic expression in 1010 patients.Medicine (Baltimore) 2008;87:210-9.*

3.- *Ramos-Casals M, Brito-Zerón P, Solans R, Camps MT, Casanovas A, Sopeña B, et al. Systemic involvement in primary Sjogren's syndrome evaluated by the EULAR-SS disease activity index: analysis of 921 Spanish patients (GEAS-SS Registry).*

Rheumatology (Oxford) 2014;53:321-31.

4.- *Goules AV, Tatouli IP, Moutsopoulos HM, Tzioufas AG. Clinically significant renal involvement in primary Sjögren's syndrome: clinical presentation and outcome. Arthritis Rheum 2013;65:2945-53.*

5.- *Skopouli FN, Dafni U, Ioannidis JP, Moutsopoulos,HM. Clinical evolution, and morbidity and mortality of primary Sjögren's syndrome. Semin. Arthritis Rheum 2000; 29: 296-304.*

6.- *Abrol E, González-Pulido C, Praena-Fernández JM, Isenberg DA. A retrospective study of long-term outcomes in 152 patients with primary Sjögren's syndrome: 25-year experience. Clin Med 2014;14:157-64.*

7.- Bossini N, Savoldi S, Franceschini F, Mombelloni S, Baronio M, Cavazzana I, et al. Clinical and morphological features of kidney involvement in primary Sjögren's syndrome. Nephrol Dial Transplant 2001;16:2328-36.

8.- Duffles Amarante GB, Zotin MC, Rocha E, Delgado AG, Leite M Jr, Gomes CP. Renal tubular dysfunction in patients with primary Sjögren syndrome. Clin Nephrol 2014;81:185-91.

9.- Aasarød K, Haga HJ, Berg KJ, Hammerstrøm J, Jørstad S. S. Renal involvement in primary Sjögren's syndrome. QJM 2000;93:297-304.

10.- Pertovaara M, Korpela M, Kouri T, Pasternack A. The occurrence of renal involvement in primary Sjögren's syndrome: a study of 78 patients. Rheumatology 1999;38:1113-20.

11.- Ren H, Wang WM, Chen XN, Zhang W, Pan XX, Wang XL et al. Renal involvement and follow-up of 130 patients with primary Sjögren's syndrome. J. Rheumatol 2008; 35:278–84.

12.- Evans R, Zdebik A, Ciurtin C, Walsh SB. Renal involvement in primary Sjögren's syndrome. Rheumatology (Oxford) 2015;54:1541-8.

13.- François H, Mariette X. Renal involvement in primary Sjögren syndrome. Nat Rev Nephrol 2016;12:82-93.

14.- *Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554-8.*

15.- Fernández Castro M, Andreu JL, Sánchez-Piedra C, Martínez Taboada V, Olivé A, Rosas J, et al en representación del Grupo de trabajo en Enfermedades Autoinmunes Sistémicas de la Sociedad Española de Reumatología (EAS-SER) y de la Unidad de Investigación de la Sociedad Española de Reumatología (UI-SER). Sjögren SER: National registry of the Spanish Society of Rheumatology of patients with primary Sjögren syndrome: Objectives and methodology. Reumatol Clin 2016 ;12:184-9.

16.- Jasiek M, Karras A, Le Guern V, Krastinova E, Mesbah R, Faguer S, et al. A multicentre study of 95 biopsy-proven cases of renal disease in primary Sjögren's syndrome. Rheumatology (Oxford) 2017;56:362-70.

17.- *Maripuri S, Grande JP, Osborn TG, Fervenza FC, Matteson EL, Donadio JV, et al. Renal involvement in primary Sjögren's syndrome: a clinicopathologic study. Clin J Am Soc Nephrol 2009;4:1423-31.*

18.- Carrillo-Pérez DL, Tejeda-Maldonado J, Garza-García C, Soto-Abraham V, Hernández-Molina G, Molina-Paredes GA, et al. Biopsy-proven renal involvement and prognosis in 13 hispanic patients with primary Sjögren syndrome. Med Clin (Barc) 2018;150:43-48.

19.- Kidder D, Rutherford E, Kipgen D, Fleming S, Geddes C, Stewart GA. Kidney biopsy findings in primary Sjögren syndrome. Nephrol Dial Transplant.2015;30:1363–9.

20.- Galindo-Izquierdo M, Rodriguez-Almaraz E, Pego-Reigosa JM, López-Longo FJ, Calvo-Alén J, Olivé A, et al; RELESSER Group, from Spanish Society of Rheumatology Systemic Autoimmune Diseases Study Group (EASSER). Characterization of Patients With Lupus Nephritis Included in a Large Cohort From the Spanish Society of Rheumatology Registry of Patients With Systemic Lupus Erythematosus (RELESSER). Medicine (Baltimore) 2016;95:e2891

21.- *Jin Y, Zhang T, Ye W, Zhu X, Wang L, Wang X. Clinical profile and associated factors of pulmonary involvement in primary Sjögren's syndrome. Med Clin (Barc) 2019;153:305-11.*

22.- *Yazisiz V, Arslan G, Ozbudak IH, Turker S, Erbasan F, Avci AB, et al. Lung involve-ment in patients with primary Sjogren's syndrome: what are the predictors?. Rheumatol Int 2010;30:1317–24.*

23.- *Alunno A, Carubbi F, Bartoloni E, Cipriani P, Giacomelli R, Gerli R. The kaleidoscope of neurological manifestations in primary Sjögren's syndrome. Clin Exp Rheumatol 2019;37 Suppl 118:192-8.*

24.- *Margaretten M. Neurologic Manifestations of Primary Sjögren Syndrome. Rheum Dis Clin North Am 2017;43:519-29.*

25.- *Gottenberg JE, Seror R, Miceli-Richard C, Benessiano J, Devauchelle-Pensec V, Dieude P, et al. Serum levels of beta2-microglobulin and free light chains of immunoglobulins are associated with systemic disease activity in primary Sjögren's syndrome. Data at enrollement in the prospective ASSESS cohort. PLoS One 2013;8:e59868.*

26.- *Candon S, Gottenberg JE, Bengoufa D, Chatenoud L, Mariette X. Quantitative assessment of antibodies to ribonucleoproteins in primary Sjögren syndrome: correlation with B-cell biomarkers and disease activity. Ann Rheum Dis 2009;68:1208–12.*

27.- *Hernández-Molina G, Leal-Alegre G, Michel-Peregrina M. The meaning of anti-Ro and anti-La antibodies in primary Sjögren's syndrome. Autoimmun Rev 2011;10:123–5.19.*

28.- *Gottenberg JE, Busson M, Cohen-Solal J, Lavie F, Abbed K, Kimberly RP, et al. Correlation of serum B lymphocyte stimulator and beta2 microglobulin with autoantibody secretion and systemic involvement in primary Sjogren's syndrome. Ann Rheum Dis 2005;64:1050-5.*

29.- *Ramos-Casals N, Brito-Zerón P, Seror R, Bootsma H, Bowman SJ, Dörner T, et al. Characterization of systemic disease in primary Sjögren's syndrome: EULAR-SS Task Force recommendations for articular, cutaneous, pulmonary and renal involvements. Rheumatology (Oxford) 2015;54:2230-8.*

30.- *Luo J, Huo YW, Wang JW, Guo H. High-Risk Indicators of Renal Involvement in Primary Sjogren's Syndrome: A Clinical Study of 1002 Cases. J Immunol Res 2019;2019:3952392.*

Tables

Table 1. Main baseline demographic and clinical characteristics of the SJÖGRENSER-TRANS cohort, including patients with renal involvement.

	All (N=437)	Patients with renal disease (N=39)
Age, years (mean ± SD)	58.6 ± 13	63 ± 13
Sex, woman/man, n (%)	416 (95%) / 21 (5%)	38 (79%) / 1 (3%)
Disease duration at inclusion, years (mean)	10.4	11.8
Histopathology in minor salivary gland*	133 (30.4%)	15 (38.5%)
Glandular inflammation / Salivary gland enlargement	141 (32.2%)	19 (48.7%)
Otorhinolaryngological involvement	206 (47.1%)	24 (61.5%)
Upper airways involvement	84 (19.2%)	10 (25.6%)
Urogenital manifestations	214 (48.9%)	18 (46.2%)
Constitutional symptoms	77 (17.5%)	11 (28.2%)
Lymphadenopathy	69 (15.7%)	9 (23.1%)
Arthritis / Arthralgia	150 (34.3%) / 352 (80.5%)	17 (43.6%) / 31 (79.5%)
Myopathy	10 (2.2%)	3 (7.7%)
Raynaud´s phenomenon	92 (21%)	13 (33.3%)
Non vasculitic cutaneous involvement	13 (2.9%)	4 (10.2%)
Vasculitis	40 (9.1%)	7 (17.9%)
Lung involvement	43 (9.8%)	9 (23.1%)
Gastrointestinal involvement	58 (13.2%)	8 (20.5%)
Hepatitis	33 (7.5%)	3 (7.7%)
Cardiac disease	13 (2.9%)	2 (5.1%)
Peripheral neuropathy	39 (8.9%)	8 (20.5%)
Central nervous system involvement	34 (7.7%)	3 (7.7%)
Hematologic abnormalities	244 (55.8%)	30 (76.9%)
Lymphoma	7 (1.6%)	2 (5.1%)
Positive antinuclear antibodies (ANA at a titer ≥ 1/320)	423 (96.7%)	33 (86.8%)
Positive test for anti-Ro/SSA	409 (93.5%)	39 (100%)
Positive test for anti-La/SSB	293 (67%)	36 (92.3%)
Positive rheumatoid factor	283 (64.7%)	33 (86.8%)
Low C3 levels	65 (14.8%)	9 (23.7%)
Low C4 levels	62 (14.1%)	11 (28.9%)
Hypergammaglobulinemia	229 (52.4%)	28 (73.7%)
Positive cryoglobulins	14 (3.2%)	3 (17.6%)
Antiphospholipid antibody (aPL) positivity	26 (5.9%)	4 (10.3%)

**Focal lymphocytic sialoadenitis evaluated by an expert histopathologist, with a focus score ≥ 1)

Table 2. Clinical and serological data, biopsy findings, treatment, and outcome of our 9 patients with pSS and biopsy-proven renal involvement.

Age (yrs) / Sex	Disease duration *(months)*	KB findings	Immunology	Extraglandular (systemic) manifestations	SCr (eGFR) at KB	Treatment	Follow-up after KB *(months)*	SCr mg/dl (eGFR) at follow up
42/F	334	Mesangial GN + TIN	Anti-Ro/SSA Anti-La/SSB	No	0,58 (>60)	PDN 30 mg/daily and AZA	18	0,70 (> 60)
60/F	174	Chronic TIN	Anti-Ro/SSA Anti-La/SSB	Arthritis, non vasculitic cutaneous involvement, Raynaud´s phenomenon, primary biliary cirrhosis , thrombocytopenia, thyroiditis	0,9 (NA)	PDN 60mg/daily and MMF	108	1,05 (57)
72/F	4	Chronic TIN	Anti-Ro/SSA Anti-La/SSB	No	2,56 (21)	MTP 1 g daily intravenously followed by PDN 30 mg/daily and CYC (6 pulses)	76	1,39 (39)
40/F	0	Chronic TIN	Anti-Ro/SSA Anti-La/SSB	No	1,57 (30)	PDN 30mg/daily and MMF	63	1,83 (28)
59/M	0	Chronic TIN	Anti-Ro/SSA Hypocomplementemia	Peripheral neuropathy (moneuritis multiplex), primary biliary cirrhosis	2,64 (21,6)	MTP 1 g daily intravenously followed by PDN 60 mg/daily and MMF + RTX	72	Renal transplantation
64/F	45	Mesangial GN	Anti-Ro/SSA Anti-La/SSB	Arthritis	0,9 (>60)	PDN 60mg/daily	29	1,10 (56)
57/F	60	Chronic TIN	Anti-Ro/SSA Anti-La/SSB	Arthritis	1,62 (28)	PDN 60mg/daily and MMF + RTX	108	1,11 (45)
57/F	28	Chronic TIN	Anti-Ro/SSA Anti-La/SSB	Arthritis, lung involvement, Raynaud´s phenomenon	0,93 (54)	PDN 60 mg/daily and MMF	29	0,99 (55)
55/F	6	Membranoproliferative GN	Anti-Ro/SSA Hypocomplementemia Positive cryoglobulins	Arthritis, peripheral neuropathy	1,3 (46)	MTP 1 g daily intravenously followed by PDN 60 mg/daily and CYC (6 pulses) → AZA	32	0,91 (53)

Abbreviations: AZA= azathioprine; CYC= cyclophosphamide; eGFR= estimated glomerular filtration rate (mL/min/1.73 m2) ; GN = glomerulonephritis; KB= kidney biopsy; PDN = prednisone; MMF = Mycophenolate mofetil; MTP= Methylprednisolone; PDN= prednisone; RTX = Rituximab; SCr= serum creatinine (mg/dL) ; TIN = tubulointerstitial nephritis.

Table 3. Comparative study between pSS patients with and without renal involvement

	Patients with renal disease (N=39)	Patients without renal disease (N=398)	p
Age, years (mean ± SD)	63 ± 13	58 ± 13	**0.042**
Sex, woman/man, n (%)	38 (97%) / 1 (3%)	378 (95%) / 20 (5%)	0.527
Disease duration at inclusion, years (mean ± SD)	11.8 ± 8.2	7.9±6.3	**0.007**
Histopathology in minor salivary gland*, n (%)	15 (38.5%)	140 (35.3%)	0.479
Corneal ulceration, n (%)	14 (35.9%	55 (13.9%)	**<0.001**
Corneal perforation, n (%)	0 (0%)	1 (0.3%)	0.754
Chronic posterior blepharitis, n (%)	5 (12.8%)	19 (4.8%)	**0.036**
Tooth damage and loss, n (%)	11 (28.2%)	106 (26.7%)	0.840
Glandular inflammation/Salivary gland enlargement, n (%)	19 (48.7%)	122 (30.6%)	**0.022**
Otorhinolaryngological involvement, n (%)	24 (61.5%)	182 (45.7%)	0.061
Upper airways involvement, n (%)	10 (25.6%)	74 (18.6%)	0.290
Urogenital manifestations, n (%)	18 (46.2%)	196 (49.2%)	0.701
Constitutional symptoms, n (%)	11 (28.2%)	66 (16.5%)	0.070
Lymphadenopathy , n (%)	9 (23.1%)	60 (15%)	0.194
Splenomegaly, n (%)	0 (0%)	4 (1%)	0.529
Arthritis / Arthralgia, n (%)	17 (43.6%) / 31 (79.5%)	133 (33.5%) / 321 (80.6%)	0.206/ 0.836
Myopathy, n (%)	3 (7.7%)	7 (1.7%)	**0.018**
Raynaud´s phenomenon, n (%)	13 (33.3%)	79 (19.8%)	**0.05**
Non vasculitic cutaneous involvement, n (%)	4 (10.2%)	9 (2.2%)	**0.005**
Vasculitis, n (%)	7 (17.9%)	33 (8.3%)	**0.047**
Lung involvement, n (%)	9 (23.1%)	34 (8.5%)	**0.004**
Gastrointestinal involvement, n (%)	8 (20.5%)	50 (12.5%)	0.165
Hepatitis, n (%)	3 (7.7%)	30 (7.5%)	0.976
Cardiac disease, n (%)	2 (5.1%)	11 (2.7%)	0.409
Peripheral neuropathy, n (%)	8 (20.5%)	31 (7.8%)	**0.008**
Central nervous system involvement, n (%)	3 (7.7%)	31 (7.8%)	0.979
Hematologic abnormalities, n (%)	30 (76.9%)	214 (53.7%)	0.993
Lymphoma, n (%)	2 (5.1%)	5 (1.3%)	**0.006**
ESSDAI score (mean ± SD)	9 ± 9	4 ± 5	**<0.001**
SSDAI score (mean ± SD)	4 ± 2	2 ± 2	**<0.001**
ESSPRI score (mean ± SD)	5.45 ± 2.06	5.2 5± 2.36	0.561
SSDDI score (mean ± SD)	5.9 ± 1.85	5.72 ± 1.50	0.95
Positive antinuclear antibodies (ANA), n (%)	33 (86.8%)	385 (97%)	0.872
Positive test for anti-Ro/SSA, n (%)	39 (100%)	369 (92.9%)	0.216
Positive test for anti-La/SSB, n (%)	36 (92.3%)	256 (64.5%)	**<0.001**
Positive rheumatoid factor, n (%)	33 (86.8%)	250 (64.4%)	**0.005**
Low C3 levels, n (%)	9 (23.7%)	56 (15%)	0.163
Low C4 levels, n (%)	11 (28.9%)	15 (13.7%)	**0.012**
Hypergammaglobulinemia, n (%)	28 (73.7%)	201 (52.8%)	**0.013**
Positive cryoglobulins, n (%)	3 (17.6%)	11 (6.2%)	**0.08**
Antiphospholipid antibody (aPL) positivity, n (%)	4 (10.3%)	22 (5.6%)	0.506
Treatments			
Glucocorticoids (GLC)			
Never / Any use or use at last visit. , n (%)	18 (46.2 %) / 21 (53.8%)	237 (59.5%) / 161(40.5%)	0.109.
Doses of GLC			
≤ 10 mg/day of prednisone or its equivalent, n (%)	3 (14.3%)	104 (64.6%)	**0.046**
11 - 29 mg/day of prednisone or its equivalent, n (%)	9 (42.9%)	31 (19.3%)	
≥ 30 mg/day of prednisone or its equivalent, n (%)	9 (42.9%)	26 (16.1%)	
Inmunosuppresants			
Never / Any use or use at last visit, n (%)	15 (38.5%) /24 (61.5%	191 / 193	0.227

* Focal lymphocytic sialoadenitis evaluated by an expert histopathologist, with a focus score ≥ 1).

Table 4. Variables associated with the development of renal disease. Results from the bivariate analysis.

	Odds Ratio	95% Confidence Interval	*P*
Age	1.03	1.002-1.073	*0.038*
Disease duration	1.01	0.955-1.074	*0.675*
ESSDAI score	1.10	1.035-1.187	*0.003*
Constitutional symptoms	0.92	0.353-2.411	*0.869*
Glandular inflammation (salivary gland enlargement)	1.99	0.858-4.643	*0.109*
Otorhinolaryngological involvement	2.07	0.901-4.777	*0.086*
Myopathy	3.28	0.508-21.223	*0.212*
Non vasculitic cutaneous involvement (multiform erythema)	5.47	1.034-29.029	*0.046*
Lung involvement	0.95	0.285-3.167	*0.933*
Vasculitis	1.42	0.435-4.684	*0.557*
Peripheral neuropathy	1.17	0.325-4.216	*0.810*
Lymphoma	6.51	0.674-63.071	*0.106*
Positive rheumatoid factor	1.53	0.480-4.934	*0.468*
Positive anti-La/SSB antibodies	6.65	1.412-31.325	*0.017*
Hypocomplementemia (low C4 levels)	1.97	0.747-5.202	*0.173*
Hypergammaglobulinemia	1.80	0.654-4.955	*0.255*

Table 5. Associated comorbidity evaluated in the SJÖGRENSER registry: comparative study between pSS patients with and without renal involvement.

	Patients with renal disease (N=39)	Patients without renal disease (N=398)	*p*
Hospital admissions*, n (%)	13 (33.3%)	61 (15.4%)	**0.004**
Number of hospitalizations, (mean ± SD)	2 ± 1	2 ± 2	0.680
Cataracts, n (%)	7 (17.9%)	41 (10.3%)	0.147
Active smoker, n (%)	2 (5.1%)	31 (7.8%)	0.560
Hypertension, n (%)	19 (48.7%)	93 (23.4%)	**0.001**
Diabetes mellitus, n (%)	4 (10.3%)	24 (6%)	0.306
Dyslipidemia, n (%)	20 (51.3%)	125 (31.5%)	**0.012**
Heart failure, n (%)	3 (7.7%)	10 (2.5%)	0.070
Ischemic heart disease, n (%)	2 (5.1%)	2 (0.5%)	**0.004**
Peripheral arterial disease, n (%)	1 (2.6%)	13 (3.3%)	0.810
Stroke, n (%)	3 (7.7%)	12 (3%)	0.127
Multiple sclerosis, n (%)	0 (0%)	2 (0.5%)	0.667
Celiac disease, n (%)	0 (0%)	5 (1.3%)	0.481
Fibromyalgia, n (%)	3 (7.7%)	61 (15.4%)	0.196
Osteoporosis, n (%)	10 (25.6%)	69 (17.4%)	0.201
Osteoporotic fractures, n (%)	6 (16.2%)	31 (7.9%)	0.084
Osteonecrosis, n (%)	0 (0%)	7 (1.8%)	0.417
Neoplasms, n (%)	4 (10.3%)	17 (4.3%)	0.240

*Only hospitalizations owing to disease activity were considered.

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