Archives of Immunology and Allergy

ISSN: 2639-1848

Volume 1, Issue 2, 2018, PP: 20-24

Sjogren's Syndrome and the Kidney

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Abstract

Sjogren's syndrome is autoimmune disease affecting all exocrine glands. Its man clinical manifestation is the sicca syndrome. Histopathological investigation reveals lympho-plasmocytic infiltration of glandular structures, including lacrimal and salivary glands, liver, pancreas, etc. Renal involvement is present in less than 10% of the cases - usually tubulo-interstitial lesions with distal tubular acidosis, nephrogenic diabetes insipidus, proximal tubular acidosis to acquired Fanconi syndrome, nephrocalcinosis and nephrolithiasis. Less frequently glomerular lesions are observed, including membranoproliferative, focal and segmental sclerosing, IgA and membranous nephritis. Overlap syndromes with systemic lupus, rheumatoid arthritis and other autoimmune rheumatic diseases have been described. We present a series of 12 patients with Sjogren's syndrome and different types of renal involvement.

Keywords: *Sjogren syndrome, renal involvement, nephrocalcinosis, nephrolithiasis, glomerulonephritis.*

Introduction

Sjogren's syndrome (SS) is chronic autoimmune inflammatory disease of the exocrine glands with decreased glandular secretion and dryness of the mucous linings (sicca syndrome). It was described in 1933 by Henrik Sjogren [1]. The histopathological investigations reveal lympho-plasmocytic infiltration and destruction of the affected glandular structures and therefore SS has been named "autoimmune epithelitis" [1,2,3]. The disease affects all exocrine glands, most frequently (in >90% of the cases) the lacrimal and salivary glands with the development of dry eyes and dry mouth. SS can affect multiple glands, including the liver, pancreas, thyroid gland, lungs, and extraglandular structures – the kidneys, joints, peripheral nerves, muscles, etc. Evolution towards non-Hodgkin's lymphoma has been described in <5% of the cases [5].

SS can develop as primary condition or in combination with other disease – autoimmune rheumatic disease (systemic lupus, rheumatoid arthritis, etc.) or infection (hepatitis C). Primary Sjogren's syndrome is a rare disease (affecting 0.01 – 0.23% of the general population) developing more frequently in women (female : male ratio = 9 : 1) [1,2,3]. Its major clinical manifestations are the sicca syndrome and constitutional symptoms (fever, weight loss, general malaise), less frequently other organ involvements are observed (including kidney stones, nephrocalcinosis, renal failure, liver cirrhosis, pancreatits, arthritis, etc.).

The renal involvement in SS has been described in the 1960s [1]. Three major types of urinary tract involvement have been described: [1,2,3,4,5]:

- Renal tubulo-interstitial changes – autoimmune epithelitis, affecting mainly the distal tubules with distal tubular acidosis and nephrocalcinosis with or without nephrolithiasis, proximal tubular

acidosis to acquired Fanconi's syndrome; renal stones in SS are usually accompanied by urinary tract infections;

- Renal glomerular lesions – membranoproliferative (mainly with positive cryoglobulins and rheumatoid factor), membranous, focal and segmental glomerular sclerosis and IgA nephropathy;
- Interstitial cystitis.

Different combinations of the described lesions may develop. The renal involvement in SS may remain clinically silent with asymptomatic erythrocyturia, proteinuria and/or renal failure, or can be manifested with renal colics, muscle weakness and periodic paralyses due to low potassium levels, alkaline-base disturbances, osteoporosis, secondary hyperparathyroidism [1,2,3,4]. Sometimes the kidney involvement may precede the development of the classical sicca syndrome [4].

Materials and Methods

For the period of 10 years, from January 2008 to July 2018, we observed overall 12 patients with Sjogren's syndrome (2 male and 10 female, mean age 55.5 +/- 13.9 years) with renal involvement. All patients were referred to the Clinic of Nephrology for diagnostic evaluation and/or treatment and therefore, all patients had renal involvement in SS. In 6/12 patients SS was associated systemic lupus erythematosus, in 1/12 – with arthropathic psoriasis and systemic amyloidosis (AA), and in 5/12 primary SS was present. In 2/5 patients with primary SS autoimmune thyroid disease was present (Von Basedow's disease in 1 and Hashimoto's thyroiditis in 1) and one patient had generalized lymphadenopathy. All patients had lacrimal and salivary gland involvement, one had chronic pancreatitis. In 10/12 patients the disease debuted with xerophtalmia and/or xerostomia. In one female patient with primary SS the disease debuted with pancreatitis and in another female patient with primary SS nephrogenic diabetes insipidus and nephrocalcinosis were detected 3 years before the appearance of sicca syndrome. The demographic and clinical data of the patients are presented in table 1.

In all patients routine clinical laboratory investigations were performed – ESR, complete blood count, biochemical evaluation, urinalysis, proteinuria, microbiological investigations of the urine, ANA, Ro and La antibodies, C3 and C4 complement fractions using standardized methods. All patients were performed abdominal ultrasound (Esaote MyLab, using 3.5 MHz probe) and if needed – plain abdominal X-ray. If needed. Renal biopsy was performed and further evaluated by pathologist.

Table 1. *Demographic and clinical data of 12 patients with Sjogren's syndrome.*

N	Age (y)	Gender	Other autoimmune disease	Other diseases	Type of renal involvement	Serum creatinine (mcmol/l)	Proteinuria (g/24 h.)	Nephritic urinary sediment	C3	C4	La
1	85	F			Nephrolithiasis	119	0.33	-	0.85	0.22	+
2	49	F	SLE, Raynaud phenomenon		LN IV class	74	0.55	-	0.76	0.14	+
3	36	F	SLE		LN II class	67	0.11	+	1.07	0.16	+
4*	73	F			Nephrocalcinosis + nephrolithiasis	91	0.04	+	0.94	0.32	-
5	56	M	SLE		LN I class	83	0.16	-	0.75	0.20	-
6#	45	F		Von Basedow's disease	Nephrocalcinosis	145	0.45	+	0.72	0.17	+
7	65	F		Hashimoto's thyroiditis	Nephrocalcinosis + nephrolithiasis	97	0.52	-	0.99	0.27	+
8	42	M	SLE		LN class III + IgA GN + nephrocalcinosis	79	0.20	+	1.1	0.32	-

9	57	F	SLE		LN class III + IgA GN	66	0.05	+	0.66	0.12	-
10	54	F	SLE, APS		LN class IV, APS, cryoglobulinemia	82	0.46	-	0.46	0.18	-
11	43	F			Nephrocalcinosis	94	0.53	-	0.79	0.19	-
12	59	F	Psoriasis, systemic amyloidosis (AA)		Glomerulonephritis (C3 + amyloid deposition)	108	0.89	+	0.97	0.26	-

F = female; M = male; SLE = systemic lupus erythematosus; LN = lupus nephritis; GN = glomerulonephritis; APS = antiphospholipid syndrome.

* Patient 4 had chronic pancreatitis that preceded the development of sicca syndrome; # in patient 6 the renal involvement (nephrogenic diabetes insipidus preceded the development of sicca syndrome by 3 years.

Results

As it was mentioned above, all patients were referred to our clinic for diagnostic evaluation of renal involvement. One patient had renal stones, two patients had nephrolithiasis + nephrocalcinosis, two patients had only nephrocalcinosis (figure 1), one patient had nephrocalcinosis and glomerular involvement (IgA nephropathy – focal and segmental proliferative, and SLE), and 6 patients had glomerular involvement (IgA nephropathy – focal and segmental proliferative in 1 and lupus nephritis in underlying systemic lupus in 4 – one with class 1, one with class 2 and two with class 4 lupus nephritis, 1 had glomerular involvement – C3 deposition + amyloidosis).

All patients had positive ANA and positive Ro antibodies, La were positive in 5/12, hypocomplementemia C3 had 6/12, hypocomplementemia C4 – 5/12 (low C3+C4 – 4/12), one patient had cryoglobulinemia + positive IgG anticardiolipin antibodies and history of recurrent miscarriages (secondary antiphospholipid) syndrome. All patients were HBV and HCV negative.

Overall 6/12 patients had mild renal failure (serum creatinine between 91 and 145 mcmol/l), none of the patients had hypercalciemia, 3 patients had metabolic acidosis with mild hyperkaliemia (renal tubular acidosis).

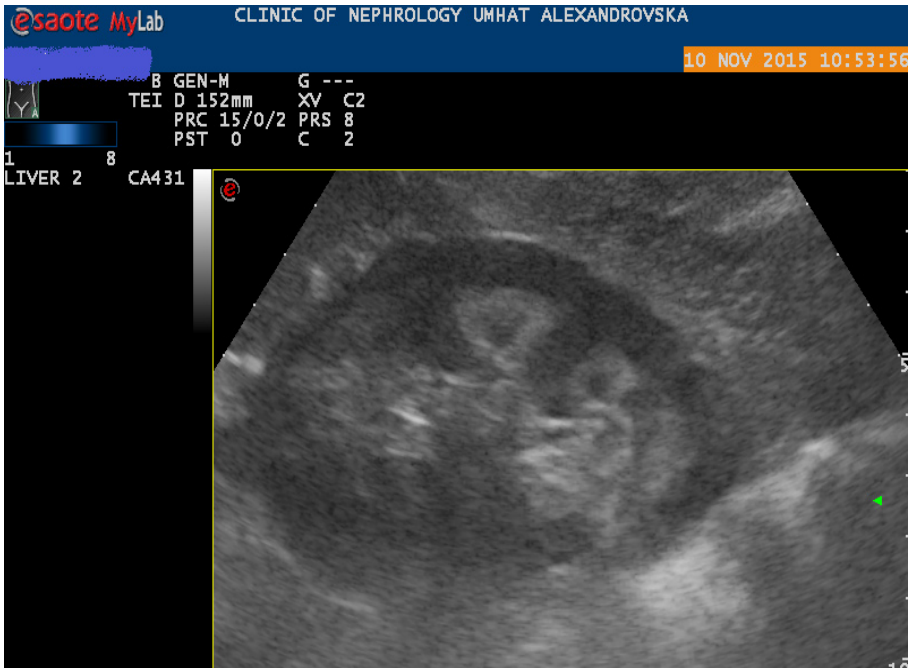

Figure 1. *Renal ultrasound of a female with nephrocalcinosis in primary Sjogren's syndrome.*

Discussion

Sjogren's syndrome is a relatively rare autoimmune disease affecting mainly middle-aged women, associated with lympho-plasmocytic infiltration of glandular and extraglandular structures [1-3]. It can be a primary disease or develop at the background of other autoimmune, neoplastic of infectious disease (mainly hepatitis C). Renal involvement in SS is rare – in less than 10% of the patients. Rarely, kidney involvement may precede the glandular manifestations, such as xerophthalmia and xerostomia [4]. The studies of A.V. Goules et al. [6] have demonstrated clinically significant renal involvement in 34/715 (4.9%) patients with primary SS. In 13 of these 34 patients (38.2%) the authors found tubule-interstitial lesions, in 17 – glomerular, in 5 – combination of both. Overall 11 patients developed renal failure, 9 patients died (4 of them – on dialysis treatment), 9/719 (1.3%) developed non-Hodgkin's lymphoma. It should be noted that 8 of these nine lymphoma patients had renal involvement (glomerulonephritis). The survival analysis in this study showed that the presence of renal involvement is a poor prognostic sign, and the glomerular involvement is associated with increased risk for the development of lymphoma [6].

The studies of S. Maripuri et al. [7] have demonstrated clinically significant renal involvement in 24/7276 (0.33%) patients with primary Sjogren's syndrome observed for a period of 40 years. Seventeen had glomerular involvement, 2 – cryoglobulinemic nephritis (membranoproliferative), 3 had non-specific glomerular lesions. The authors recommend screening for renal involvement in all SS patients – serum creatinine levels, urinalysis, urinary sediment, proteinuria, and renal biopsy if needed, because the affection of the kidney is a poor prognostic sign in these patients and requires active monitoring and more aggressive immunosuppressive treatment.

In our cohort of SS patients with renal involvement 5 had primary SS, 7 had underlying systemic lupus, and 1 had psoriasis and amyloidosis. In primary SS, the main renal involvements were nephrolithiasis and nephrocalcinosis, and in SS with systemic lupus – mainly glomerulonephritis, in 1 patient with psoriasis S3 and amyloid deposition was found in glomeruli. Overall 6/12 patients had mild renal failure (creatinine clearance below 60 ml/min/1,73 m^2 with mild elevation of serum creatinine between 91 and 145 mcmol/l). Two patients with primary SS had concomitant autoimmune thyroid disease – Von Basedow's disease and Hashomoto's thyroidits. In the patient with Von Basedow's disease the renal symptoms (nephritogenic insipid diabetes with renal parenchymal calcifications on ultrasound examination pointing at renal tubule-interstitial affection) appeared three years before the development of xerostomia and later – xerophtalmia. All inveastigated patients were ANA and Ro antibody positive, but La were detected in 5/12 (three with primary SS and 2 with SS plus systemic lupus). One patient with systemic lupus had clinical and laboratory data for secondary antiphospholipid syndrome and cryoglobulinemia.

In conclusion, for the period of 10 years overall 12 patients with SS, both primary and secondary to systemic lupus, were referred to the Clinic of Nephrology for diagnostic evaluation of the renal involvement. The majority of them were middle-aged females, 6 had underlying SLE and 1 had arthropathic psoriasis. In the subgroup with primary SS, the most prevalent type of renal involvement was nephrocalcinosis, with or without nephrolithiasis, and in 1 patient SS even debuted with renal symptoms – nephrogenic diabetes insipidus. One of the patients had pancreatic involvement that appeared to be the first manifestation of SS. In those with SS secondary to systemic lupus, the main type of renal involvement was glomerulonephritis, IgA or attributable to lupus nephritis. In one patient we observed SS secondary to arthropathic psoriasis preceding the development of SS, with positive renal biopsy data for amyloidosis (AA), most probably associated with the chronic arthropathy. Associations of SS with psoriasis have been reported in the literature [8].

One female patient with secondary SS at the background of systemic lupus had positive cryoglobulins and clinical + laboratory data for antiphospholipid syndrome. Both anticardiolipin antibodies with antiphospholipid syndrome and cryoglobulinemia have been described in SS [9,10].

We would like to suggest that all patients with Sjogren's syndrome should be screened for renal involvement – investigation of renal function (serum creatinine and urea levels, total protein, albumin, sodium, potassium, calcium serum levels, alkaline-base balance, urinalysis, urine sediment, proteinuria), abdominal ultrasound,

and if needed they should undergo renal biopsy. In all patients with SS underlying autoimmune rheumatic disease should be sought.

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Citation: **M. Nikolova, G. Ivanov, G. Makova.** *Sjogren's Syndrome and the Kidney. Archives of Immunology and Allergy. 2018; 1(2): 20-24.*