Renal involvement in primary Sjögren's syndrome: natural history and treatment outcome

A.V. Goules[1], D. Geetha[2], L.J. Arend[3], A.N. Baer[1]

[1]Jerome L. Greene Sjögren's Syndrome Center, Division of Rheumatology, Johns Hopkins School of Medicine; [2]Nephrology Division, Johns Hopkins School of Medicine; [3]Pathology Department, Johns Hopkins School of Medicine, Baltimore, MD, USA.

Andreas V. Goules, MD
Duvuru Geetha, MD
Lois J. Arend, MD
Alan N. Baer, MD

Please address correspondence to:
Dr Andreas V. Goules,
Jerome L. Greene Sjögren's Syndrome Center, Division of Rheumatology, Johns Hopkins School of Medicine, Baltimore, MD, USA.

Current address:
Department of Pathophysiology, School of Medicine, National and Kapodistrian University of Athens, Mikras Asias Str 75, 115 27 Athens, Greece.
E-mail: agoules@med.uoa.gr

Received on June 23, 2019; accepted in revised form on July 8, 2019.

Clin Exp Rheumatol 2019; 37 (Suppl. 118): S123-S132.

Key words: Sjögren's syndrome, renal involvement, interstitial nephritis, glomerulonephritis

Funding: this work was supported by NIH grant RO1-DE12354-15A1 (ANB) and the Jerome L. Greene Foundation.

Competing interests: D. Geetha has served as a consultant to ChemoCentryx. A.N. Baer has served as a consultant for Bristol-Myers Squibb, Abbvie and Novartis. The other co-authors have declared no competing interests.

ABSTRACT

Objective. *Overt renal disease in primary Sjögren's syndrome (pSS) manifests as interstitial nephritis and glomerulonephritis. This single centre study aims to describe the natural history and treatment outcome of renal disease in pSS.*

Methods. *pSS patients with renal disease were identified, and clinical features, renal biopsy findings, treatment details and renal outcome were recorded.*

Results. *Of the 20 pSS patients with renal disease, 14 had interstitial nephritis (IN), 3 had glomerulonephritis (GN) and 3 had both entities. In the IN group, 3 patients presented with chronic kidney disease (CKD), 4 with renal tubular acidosis (RTA), 2 with symptomatic hypokalaemia, 4 with renal colic and 1 with haematuria/proteinuria. Eight of 14 patients with IN received systemic immunosuppression (IS) during renal disease course and in 6 patients no beneficial effect was observed on renal function, hypokalaemia and RTA. Six of 14 IN patients developed CKD while 5 of them preserved normal renal function during follow-up. In the GN group, 2 patients presented with CKD, 3 with proteinuria/haematuria and 1 with nephrotic proteinuria. GN renal biopsy findings revealed membranoproliferative (MPGN) (n=3), focal segmental glomerulosclerosis (n=1) and fibrillary glomerulopathy (n=1). All 3 MPGN patients had cryoglobulinaemia and in 1 patient cryoglobulinaemic MPGN was clinically diagnosed. All GN patients were treated with immunosuppressive therapy, with stabilisation or improvement of renal function in the 4 cryoglobulinaemia-associated GN patients only.*

Conclusion. *Interstitial nephritis follows a slow course and does not improve with systemic immunosuppression while GN has a favourable treatment response in those with MPGN pathology.*

Introduction

Renal involvement in pSS is driven by two distinct immunopathologic processes, resulting in either interstitial nephritis (IN) or glomerulonephritis (GN) (1, 2). Depending on the anatomical and functional properties of the affected tubular epithelium by the lymphocytic infiltration of kidney interstitium, a wide clinical spectrum of IN is produced, ranging from benign and subclinical latent distal renal tubular acidosis (dRTA) with impaired urinary acidification to complete dRTA, proximal RTA, nephrogenic diabetes insipidus and in rare cases end-stage kidney disease (1). Interstitial nephritis occurs before or near the onset of sicca symptoms in pSS and evolves slowly, indicative of its usual low-grade inflammatory nature. In some patients though, the chronic and persistent inflammation along with yet unidentified risk factors may lead to end-stage renal disease (3). On the contrary, GN is mainly of the membranoproliferative histologic type and less commonly the mesangial or membranous type, and is attributed to glomerular deposition of immune complexes consisting of type II cryoglobulins, leading to inflammation. GN usually develops as a late complication of pSS with a more abrupt onset compared to IN and is manifested as nephritic syndrome with impaired renal function. Patients with pSS and GN have a less favourable prognosis and may develop severe renal impairment, if left untreated (4).

Although immunosuppressive treatment (IST) is often used for pSS-associated GN, its overall benefit in the management of IN remains unclear. Previous studies with limited numbers of patients have supported a potential benefit of corticosteroids either alone or in combination with another IS agent (ISA) on renal outcome in some pSS patients with IN (5, 6). On the other hand, no benefit was recorded in many

of these patients despite intense (IST). In addition, a few case reports describe improvement of renal function after treatment with rituximab (7, 8). The conflicting results of these studies and the fact that the dose and duration of treatment were quite heterogeneous raise concerns about the use of systemic immunosuppression (IS) in pSS-associated IN. In this retrospective study, we present our experience regarding the clinical picture and management of pSS patients with renal disease, focusing on the effects of systemic (IST) on the course, clinical manifestations and outcome of interstitial nephritis.

Patients and methods

From a longitudinal cohort of pSS patients who were evaluated at the Jerome L. Greene Sjögren's Syndrome Center of the Johns Hopkins Division of Rheumatology, Baltimore, USA, those with either IN or GN were identified. The cohort consisted of patients seen in the Center between July 1, 2009 and September 1, 2016. Clinically significant renal involvement was defined as follows:

1) For IN (one or more of the following items in the context of pSS):
a. Persistently alkaline urinary pH (≥6.5) and/or low specific gravity (≤1.010) for > 3 months in first morning urine sample;
b. Nephrolithiasis or nephrocalcinosis with or without renal colic;
c. Fanconi's syndrome not attributed to any known cause;
d. Hyperchloremic metabolic acidosis with normal anion gap and hypokalaemia or renal colic;
e. Impaired renal function with biopsy-documented IN and no findings suggestive of other aetiology;
f. Tubular proteinuria and/or haematuria with biopsy-documented IN and no findings suggestive of other aetiology.

2) For GN (one or more of the following items in the context of pSS):
a. Proteinuria>500mg/d for >3 months and evidence of cryoglobulinaemia (serum cryoglobulins or RF activity and hypocomplementaemia);
b. Active urine sediment: >5 red blood cells/hpf or red blood casts and evidence of cryoglobulinaemia (cryoglobulins or RF activity and hypocomplementaemia);
c. Impaired renal function with biopsy-documented GN and no findings suggestive of other aetiology;
d. Kidney biopsy demonstrating histologic features of membranoproliferative glomerulopathy and no evidence of other causes.

The 2002 (AECG) criteria were applied for the classification of pSS (9). The clinical, immunologic, laboratory and pathologic data were collected for each patient, along with a detailed history of all systemic immunosuppressive interventions. Renal outcome was evaluated with both creatinine levels and GFR estimated by the modification of diet in renal disease equation (MDRD) (10) and renal response to treatment was defined as a post-treatment increase of eGRF>20ml/min. Confounders of renal function such as family history, drugs, toxins, hypertension, malignancies, diabetes as well as other causes of cryoglobulinaemia including HBV, HCV, HIV infections and active lymphoma were carefully recorded.

Histopathology and immunohistochemical phenotyping of infiltrates

In those SS patients who had both labial minor salivary gland and kidney biopsies, H&E and immunophenotypic studies were performed to reveal similarities and differences of the lymphocytic infiltrates in the two affected tissues. Standard immunohistochemical staining for CD3 (DAKO, Carpinteria CA), CD4 (Ventana, Tucson AZ), CD8 (Cell Marque, Rocklin CA), CD20 (Ventana), CD68 (Ventana), and CD138 (Ventana) was performed on paraffin sections. Quantitative staining of kidney and labial minor salivary gland biopsies was graded using the following criteria based on percentage of interstitium involved: 0-25%, 26-50%, >50%.

Results

Clinical features of SS patients with renal involvement

Twenty patients with a diagnosis of pSS and renal involvement were identified of whom eighteen patients fulfilled the 2002 AECG classification criteria while two met three of six criteria (Tables I and II). The demographic, clinical, laboratory and immunologic features of these patients are being presented in the supplementary Tables S1, S2 and S3. Of the 20 patients, 14 had interstitial nephritis (IN), three had glomerulonephritis (GN) and three had both entities and were classified in the GN group (Tables I and II).

All 14 IN patients were female, their median age of SS onset was 25 years (range: 13–73) and their median SS disease duration until IN onset was 4.5 years (range: 0–9). Clinical features of IN preceded the onset of sicca symptoms in three patients and followed the appearance of glandular manifestations in 11 patients (Table I). Four IN patients presented initially with renal tubular acidosis (RTA), four with renal colic, three with chronic kidney disease, two with symptomatic hypokalaemia and one with proteinuria/haematuria. At the end of follow-up, ten IN patients had developed dRTA features and one proteinuria/haematuria (Table I).

All six GN patients were female, their median age of SS onset was 51.5 years (range: 46–60) and their median SS disease duration until GN onset was nine years (range: 0–14.5) (Table II). Three GN patients presented with proteinuria/haematuria, one with chronic kidney disease (CKD) and proteinuria/haematuria, one with CKD and one with nephrotic-range proteinuria. Among GN patients, RF was present in five, low levels of C4 complement in five and cryoglobulins in three. Interestingly, four of 14 IN patients had palpable purpura of their lower extremities with no other symptom or sign related to systemic vasculitis compared to five of six GN patients of whom only one had also peripheral neuropathy.

Histopathology

Kidney biopsy was performed in seven of 14 IN patients, showing typical lymphocytic infiltration of the interstitium. Of the seven IN patients, three had features of chronic IN with no evidence of fibrosis or tubular atrophy while in the remaining four patients, there was some degree of tubular atrophy and fibrosis. Acute tubulitis was described in one pa-

Table I. Clinical features of pSS patients with IN.

Patient no.	Presentation	Biopsy	pSS duration	RD duration	Lab features	Comments
1	CRF Mild proteinuria	IN	7y	0 CRF	↔C3/C4, RF(-), Cryo(-)	RD onset=CRF
2	CRF	IN	5y	0 CFR	RF (ND), Cryo(-), ↓C4	RD onset=CRF
3	Renal colic renal insufficiency	IN	9y	6 CRF	RF+, Cryo(ND) ↔C4, ↔C3	· 3/4AE: sicca, Ro/La, PGE · IN biopsy
4	Renal colic-hypokalaemia	IN	0y	3 CRF	RF(-), Cryo(-), ↔ C4/C3	· Myasthenia Gravis · Hashimoto-ANA+ · RD before sicca
5	Hypokalemic paralysis	IN	0y	5 NRF	ANA+, RF-, Cryo (ND), C4/C3	· RD before sicca
6	dRTA	ND	4y	5.5NRF	ANA+, RF(+), ↓C3/C4, Cryo(-)	· Coeliac disease · Hashimoto, PBC/AIH · Adrenal insufficiency
7	Symptomatic severe hypokalaemia	ND	3y	17CRF	ANA+,RF(+), ↔C3,/C4, Cryo (ND)	· CD, PG, DH
8	Haematuria, proteinuria	IN	3y	1.5CRF	ANA+, RF(+), ↔C3, ↓C4	· Focal tubulitis
9	CRF	IN	0y	0CRF	ANA+, RF(+), cryo (ND), C3/C4 (ND)	· RD before sicca · RD onset=CRF
10	dRTA	ND	6	15NRF	ANA+, RF(+), cryo(-), ↓C3/C4	
11	Renal colic-hypokalaemia	ND	5y	20NRF	ANA+, RF(+), cryo (ND), ↓C3/C4	
12	Renal colic, haematuria, hypokalaemia	ND	3y	14NRF	ANA+, RF(+), cryo(ND), ↔C3/C4	
13	dRTA-asymptomatic stone disease	ND	5Y	15CRF	ANA+, RF(+), cryo (ND), ↔C3/C4	
14	Hypokalaemia-dRTA	ND	9y	6 CRF	ANA+, RF(+), cryo(-), ↓ C3/C4	

pSS: primary Sjögren's syndrome; IN: interstitial nephritis; CRF: chronic renal failure; dRTA: distal renal tubular acidosis; RD: renal disease; NRF: normal renal function; RF: rheumatoid factor; PGE: parotid gland enlargement; CD: Crohn's disease; PG: pyoderma gangrenosum; ANA: anti-nuclear antibodies; cryo: cryoglobulins; ND: not done; AE: American European Consensus Group Criteria; PBC: primary biliary cirrhosis; AIH: autoimmune hepatitis; DH: dermatitis herpetiformis; ↓: decreased; ↔: normal.

tient (Table I). Three patients (no. 1, 4, 15) had both minor salivary gland and kidney biopsies. The inflammatory infiltrate was similar between the two tissue specimens in all three patients (Fig. 1, 2a, 2b), although in patient no. 15, the periductal infiltrate was much richer in plasmacytes compared to the peritubular infiltrate (Fig. 2c, 2d), and quantitation showed that 72.5% of the interstitium contained CD138+ cells in the salivary gland specimen *versus* only 2.3% in the kidney biopsy (Fig. S1). The kidney showed more CD3 positive cells (23.8% minor salivary gland *vs*. 48% kidney), while both samples had similar staining for CD4, CD8, CD20 and CD68.

Kidney biopsy was performed in five of six GN patients; there was membranoproliferative GN (MPGN) in three, focal segmental glomerulosclerosis (FSGS) in one and fibrillary glomerulopathy (FG) in one (Table II). Patient no. 20 presented with haematuria, proteinuria, renal impairment and a history of palpable purpura. Previous skin biopsy had shown leukocytoclastic vasculitis. Work up for lymphoma was negative and laboratory tests showed low C4 complement levels and positive RF. A kidney biopsy was deferred and the patient was diagnosed as having cryoglobulinaemia-associated GN. All three patients with MPGN by biopsy had cryoglobulinaemia, positive RF and low C4 complement serum levels (Table II).

Renal outcome and treatment

Of the 14 IN patients, three presented with chronic renal failure (CRF) at the time of IN diagnosis while six developed CRF at the end of follow-up after a median renal disease duration of six years (range: 1.5–17) (Table I). The other five IN patients preserved normal renal function after a median renal disease duration of 14 years (range: 5–20) (Table I). Eight IN patients were treated with systemic immunosuppressive agents (ISA) including prednisone>10 mg/d, mycophenolate mofetil (MMF) 1–3 g/d, methotrexate (MTX) >10 mg/weekly and azathioprine (AZA) 200 mg/d (Table III). One patient received one cycle of rituximab and one patient received various anti-TNF agents (infliximab, adalimumab and certolizumab), each one for at least six months in the context of Crohn's disease. No beneficial effect was observed in six of eight IN patients who received (ISA) regarding the parameters of kidney disease including frequency of renal colic,

Table II. Clinical features of pSS patients with GN.

Patient no.	Presentation	Biopsy	pSS duration	RD duration	Lab features	Comments
15	Nephrotic range proteinuria, haematuria, Cr=1.3	IgM/C3 FSGS + Hyalinosis, IN	14.5y	0 CRF	↓C3, ↓C4, RF(-), Cryo(-)	· HTN · IN component (biopsy)
16	CRF=2.0	IgG/IgM MPGN	•3y (pSS started as IN) •7y (GN onset)	•0 CRF (IN+ limited MP) •0 CRF-MP	RF(+), Cryo(+), ↓C4	· Low sg · RF+, ANA+ · IN component (biopsy) · ↓WBC, ↓PLTs, pancreatitis · Scl 70+ · Atypical MS under IFNb
17	CRF=1.6, proteinuria, haematuria	Fibrilary GN	0y	0 CRF	RF(+), Cryo(-), normal C4	· IN component (biopsy) · Already CRF · Also DM, HTN
18	Proteinuria, haematuria	IgM, MPGN	20y	2NRF	RF+, Cryo+, ↓C4	· 3/4AE: sicca, PGE, Ro/La+ · ANA+, RF+ · Vasculitic ulcers
19	Proteinuria, haematuria (2014)/outbreaks of vasculitic purpura	IgG/IgM MPGN	11y	2y NRF	RF(+), Cryo(+), ↓C4, ↓C3	· Cytopenias in the last flare due to CMV, candidal oesophagitis, brain toxoplasmosis
20	Palpable purpura, haematuria, proteinuria, rise in creatinine, pleural effusions	ND	5y	0.5y NFR	RF(+), Cryo(-), ↓C4	· skin biopsy:LCV · negative work up for lymphoma · alopecia, dry mucosa, aCL (+) · PGE

pSS: primary Sjögren's syndrome; GN glomerulonephritis; IN: interstitial nephritis; CRF: chronic renal failure; RD: renal disease; NRF: normal renal function; sg: specific gravity; ANA: anti-nuclear antibodies; RF: rheumatoid factors; cryo: cryoglobulins; ND: not done;AE: American European Consensus Group Criteria; WBC: white blood cells; PLTs: platelets; LCV: leukocytoclastic vasculitis; aCL: anti-cardiolipin; PGE: parotid gland enlargement; MP: membranoproliferative; FSGS: focal segmental glomerulosclerosis; DM: diabetes mellitus; HTN: hypertension; ↓: decreased; ↔: normal.

hypokalaemia, RTA and renal function, either cumulatively or after each course of treatment separately (Table III, Fig. 3a). Patient no. 1 had a significant improvement of renal function after receiving a tapering dose of oral prednisone (initially 60 mg/d) (pre-treatment GFR=21 ml/min, post-treatment GFR=38 ml/min). At the time of IN diagnosis, patient no. 1 was rehydrated, biopsied and started on prednisone with a rapid improvement of renal function. Patient no. 1 had a baseline GFR=38 ml/min, she was receiving an angiotensin converting enzyme inhibitor (ACEi) at the time of IN diagnosis and had a history of a similar episode of deterioration of renal function that improved after intravenous rehydration only. Of the six IN patients who did not receive immunosuppressive treatments, four developed CRF after a median renal disease duration of six years (range: 3–15) while two had normal renal function after 15 and 20 years of renal disease duration respectively (Table III).

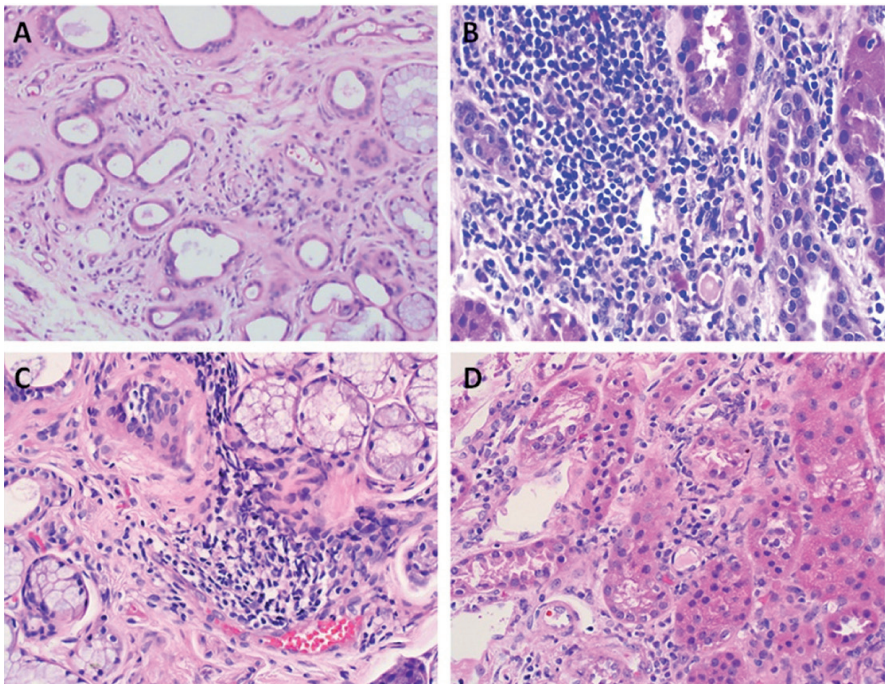

Fig. 1. Haematoxylin and eosin staining of paired minor salivary gland and kidney specimens of 2 patients with primary Sjögren's syndrome and interstitial nephritis: **a**) patient no. 1: minor salivary gland specimen, **b**) patient no. 1: kidney specimen, **c**) patients no. 8: minor salivary gland specimen, **d**) patient no. 8: kidney specimen.

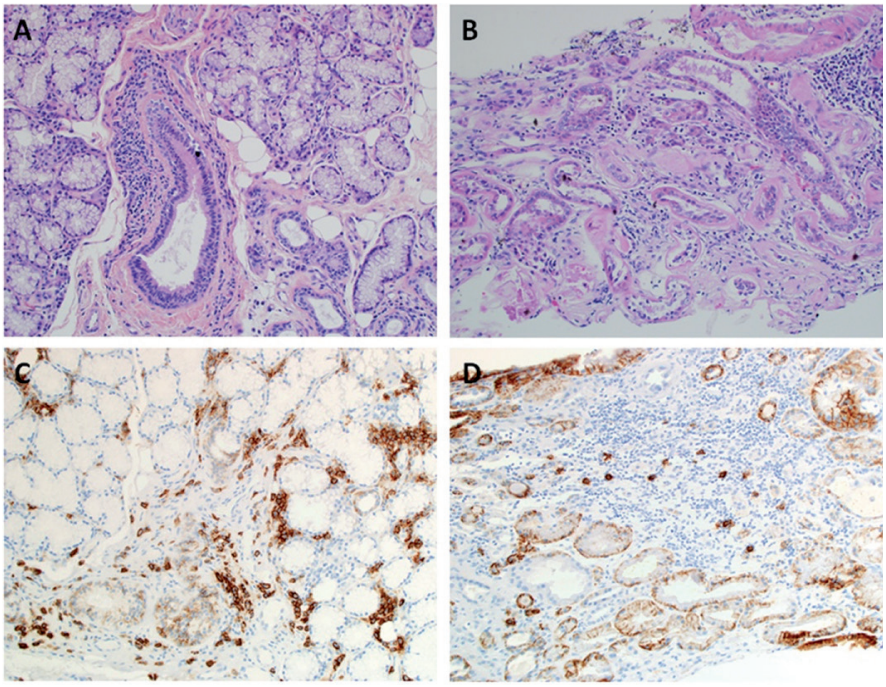

Fig. 2. Haematoxylin and eosin staining and immunophenotypic analysis of paired minor salivary gland and kidney specimen from one patient with primary Sjögren's syndrome and interstitial nephritis (patient no. 15). Haematoxylin and eosin staining: **a**) patient no. 15: minor salivary gland specimen and **b**) patient no. 15: kidney specimen. Immunohistochemical staining for plasma cells (anti-CD138): **c**) Minor salivary gland specimen **d**) Kidney specimen.

Three of six GN patients including those with (FSGS) and (FG), presented with impaired renal function (GFR<60 ml/min) already at the time of GN diagnosis (Table II). All six GN patients were treated with systemic immunosuppressive agents including prednisone 60–10 mg/d, MMF 1–3 g/d, rituximab (one treatment cycle includes two intravenous infusions of 1 gram rituximab each, two weeks apart) and cyclophosphamide 2 mg/kg/d (Table IV). Patient no. 15 had FSGS and received combination treatment with a tapering dose of prednisone 50 mg orally and MMF 2 g/d for five months without preservation or improvement of renal function (pre-treatment GFR=42 ml/min, post-treatment GFR=10 ml/min). Patient no. 17 was diagnosed with (FG) and was treated initially with a tapering dose of prednisone 40 mg/d orally for two months and then with prednisone 10 mg orally along with one cycle of rituximab, without preservation or improvement of renal function (pre-treatment GFR=38 ml/min, post-treatment GFR=18 ml/min). The four remaining patients had cryoglobulinaemia-associated GN: patients no. 16, 18, 19 had biopsy-documented MPGN while patient no. 20 had biopsy-proven leukocytoclastic vasculitis of the skin along with RF and low C4 complement levels. Patient no. 16 was treated with 10 mg prednisone orally and 200 mg hydroxychloroquine for almost four years with slowly progressive deterioration of renal function (pre-treatment GFR=26 ml/min, post-treatment GFR=12 ml/min) and after the second biopsy she received 0.5 mg/kg orally in combination with one cycle of rituximab that led to improvement of renal function after five months (pre-treatment GFR=12 ml/min, post-treatment GFR=21 ml/min). Patient no. 18 received as induction therapy a tapering dose of prednisone 40 mg orally and cyclophosphamide 125 mg/d for three months and subsequently prednisone 25 mg orally along with MMF 3 g/d with preservation of renal function and complete remission of haematuria and proteinuria (pre-treatment GFR = 72 ml/min, urinalysis (UA) = haematuria/proteinuria, post-treatment GFR = 72 ml/min, UA= within normal limits). Patient no. 19 received combination treatment with prednisone (60 mg–6 mg/d) orally and MMF 2 g/d for 10 months resulting in decline of renal function and persistent haematuria/proteinuria (pre-treatment GFR = 64 ml/min, UA = haematuria/proteinuria and post-treatment GFR = 46 ml/min, UA = haematuria/proteinuria) and subsequently she was treated with prednisone 20 mg/d and one cycle of rituximab with improvement of renal function and complete remission of haematuria/proteinuria (pre-treatment GFR = 46 ml/min, UA = haematuria/proteinuria, post-treatment GFR = 60 ml/min, UA = within normal limits). Patient no. 20 was treated with a slowly tapered dose of prednisone 40 mg orally for approximately six months with notable improvement of renal function (unable to calculate GFR, pre-treatment Cr=unknown but raised, post-treatment Cr=1.1) (Table IV, Fig. 3b).

Discussion

In this case series, IN tended to occur near or prior to the onset of sicca symptoms and it was clinically manifested as dRTA with renal colic and/or symptomatic hypokalaemia. Among IN patients with both minor salivary gland and kidney biopsies, the periepithelial inflammatory infiltrate was quite similar, although the infiltrate of the minor salivary glands was richer in plasmacytes compared to kidney tissue specimen from the same patient with IN, as supported also by older studies on kidney biopsies only (11, 12). However, there are studies describing the presence of plasmacytes within the peritubular infiltrate but their role in the pathogenesis of periepithelial manifestations remains unclear (13, 14). The similarity of the periepithelial inflammatory infiltrate between the salivary ductal epithelium and the renal tubules, in combination with findings suggesting that tubular epithelium is activated in a similar way to the salivary epithelium by expressing adhesion and costimulatory molecules (15, 16), further supports the notion that periepithelial manifestations share common immunopathogenic mechanisms-and possibly common epithelial autoantigens driving the local autoimmune responses responsible for the chronic and benign nature of this type of mani-

Table III. Immunosuppressive treatment and renal outcome in pSS patients with IN.

Patient no.	Presentation	Treatment	Before	After	Comments
1	CRF	· Prednisone 60mg (2mo)	· Cr=2.3, GFR=2 1	· Cr=1.4 (2mo), GFR=38	· Cr:1.3-1.5 (at diagnosis) (ACEi, dehydration)
		· Prednisone 40-15mg + MMF 500 x 2 (4mo)	· Cr=1.4, GFR=38	· Cr=1.1, GFR=50 (4mo)	· One dehydration episode: Cr:2.8→1.5
		· Prednisone 3mg + MMF 250x2 (maintenance)-4mo	· Cr=1.3, GFR=41	· Cr=1.3, GFR=41	
2	CRF	· MMF 500mg x 2 (2mo) · MMF 1g x 2 (3mo)	· Cr=1.6, GFR=31 · Cr=1.4, GFR=36	· Cr=1.4, GFR 36 · Cr=1.3, GFR 40 (spike with Cr1.7)	· Cr:1.3-1.5 (at diagnosis)
5	Hypokalaemic paralysis-normal renal function	In 5-year period · Prednisone 50mg · AZA 200mg/d (1y) · MMF 3g/d (6m0) · Rituximab (1cycle)	· Cr=1.0, GFR=64	· Cr=1.0, GFR 64 (after last treatment)	• No effect on controlling hypokalaemia
6	Symptomatic hypokalaemia	· Prednisone up to 20mg, HQ and MMF 3g/d (7years) · MTX (1y)	· Cr=0.7, GFR=108	· Cr=1.1, GFR 61 (last 5years)	• No effect on hypokalaemia
7	Severe hypokalaemia	· Prednisone +MTX (2y) · Infliximab (6mo) · Adalimumab+MTX (5years) · Certolizumab (7mo)	· Cr=1.2, GFR=49	· Cr=2.1, GFR=27 (last 4 years)	· CD (anti-TNF) • No effect on hypokalaemia
8	Cr=1.3, mild proteinuria and haematuria	· Prednisone 40mg/d (2mo) · Prednisone 60mg/d (short course/4ws) · MMF 2g/d(2mo)	· Cr=1.3, GFR=52 · Cr=1.7, GFR=38 · Cr=1.7, GFR=38	• Cr=1.7, GFR 38 · Cr:1.6, GFR=41 · Cr=1.52 , GFR=43	· Focal tubulitis
9	CRF-nephrocalcinosis	· Prednisone 40-15mg/d (2mo) · Prednisone 15mg + MMF 500 x 2 (4mo)	· Cr=2.3, GFR=25 · Cr=2.0, GFR=29	· Cr=2.0, GFR=29 · Cr=2.0, GFR=29	· Cr=1.8 (at diagnosis) · Mild tubulitis
12	Gross haematuria, renal stone disease	MMF 500mgx2→1gx2 (6mo)	· Cr=0.6, GFR=110	· Cr=0.8, GFR=79	· Cr=0.8-1.3, (GFR= 90-70) fluctuations of renal function and deterioration of renal function, pyelonephritis

pSS: primary Sjögren's syndrome; IN: interstitial nephritis; CRF: chronic renal failure; dRTA: distal renal tubular acidosis; RD: renal disease; NRF: normal renal function; RF: rheumatoid factors; CD: Crohn's disease; MMF: mycophenolate mofetil; AZA: azathioprine; MTX: methotrexate.

festations (17). On the contrary, GN presented years after disease onset with haematuria, proteinuria and impaired renal function. The majority of GN patients had type II cryoglobulins with RF activity and low C4 complement levels while the most common histologic type was (MPGN). However, one patient developed (FG); a form of renal disease not previously reported in pSS.

Eight of 14 pSS patients with IN were treated with systemic (ISA), mainly with prednisone and MMF, but no benefit was observed in terms of renal colic frequency, hypokalaemia and dRTA features. In six of eight patents, GFR remained stable or deteriorated while in two of them it was improved >20% compared to baseline/pretreatment GFR (Fig. 3a). However, in one patient, the improvement was at least in part attributed to rehydration while the second patient already had renal failure with low GFR when therapy was initiated. From the six IN patients without (IST), four developed CRF after a few years and two of them maintained normal renal function after many years of follow-up. GN patients with (FSGS) and (FG) developed CRF despite systemic (IST) while the remaining four pSS patients with cryoglobulinaemia-associated GN preserved or improved renal function while renal disease elements such as haematuria or proteinuria were eradicated after treatment (Fig. 3b).

The fact that IN may precede sicca symptoms and present directly as CRF escaping clinical attention, underlines the insidious and slowly progressive nature of IN. Although IN affects at least 40% of pSS patients (18-22), only 5% of them present with clinical manifestations and even fewer develop renal insufficiency (3). In a French study, from the 73 pSS patients with clinically significant and biopsy-proven isolated IN, only four patients developed end-stage renal failure after a median follow-up of five years, confirming the benign nature of IN (23). Considering the pathogenesis of IN, it is reasonable to assume that the disease has a benign course, suggesting that only a small subset of patients requires therapeutic interventions to inhibit the evolution toward CRF. However, no study has ever provided evidence about potential adverse predictors to identify those patients. All previous studies have in-

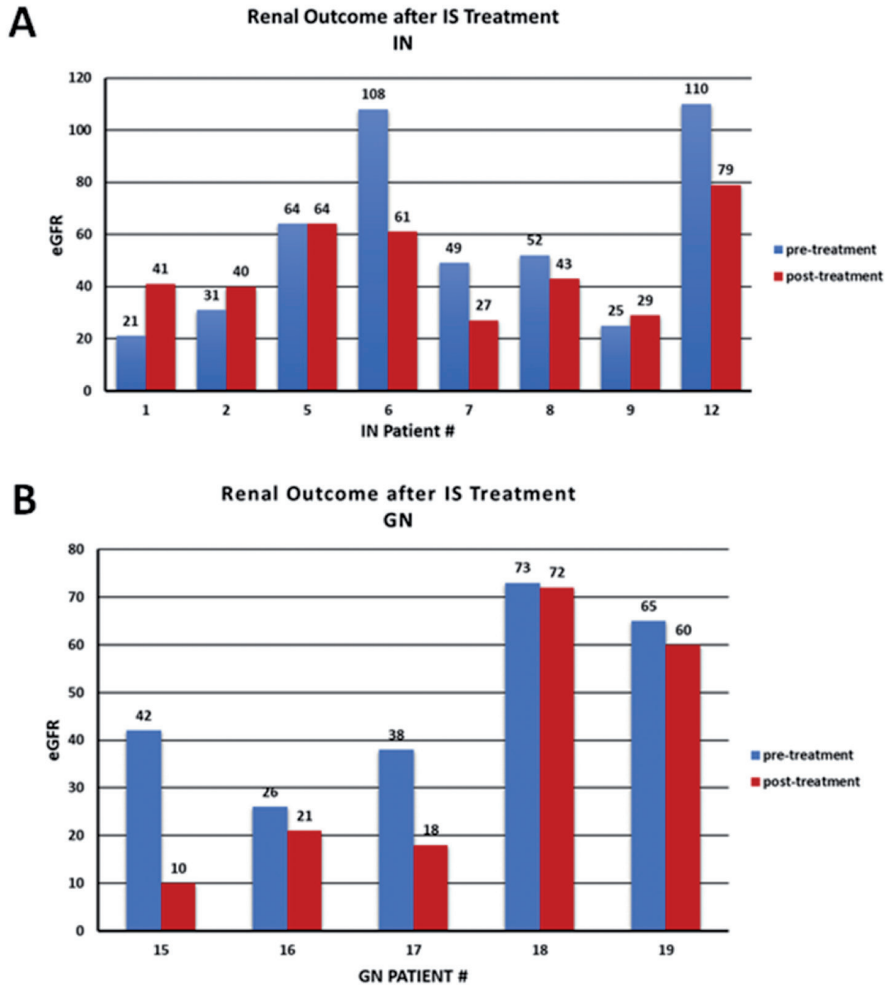

Fig. 3. Immunosuppressive (IS) treatment and renal outcome for pSS patients with: **a**) IN and **b**) GN.

cluded either IN patients based on general histological, clinical and laboratory criteria or pSS patients with kidney disease without distinction between those with GN and IN (24, 25).

A small number of previous studies have included patients with isolated IN who were treated with immunosuppressive agents (5, 6, 23, 24, 26) (Table V). Maripuri *et al*. described 15 pSS patients with biopsy-documented IN who received prednisone, with nine of them having >20% improvement of renal function, as estimated by eGFR. Interestingly, three of nine patients presented with acute renal injury (AKI) in the context of acute tubulitis, one had severe ESRD with very low pre-treatment GFR levels (pre-treatment=5ml/min, post-treatment=9 ml/min) while the remaining five patients had already advanced CKD with pre-treatment GFR<37 ml/min (6). Similarly, Kidder *et al*. published a series of 11 pSS patients with IN of whom seven received prednisone with or without MMF and four remained with no therapy. Only three of seven treated patients had >20% increase of pre-treatment GFR after therapy while three of four untreated patients who presented with (AKI) showed significant spontaneous improvement of GFR during follow-up (5). In another study, 11 patients with IN were treated mainly with prednisone and MMF and the total median GFR increased from 32 ml/min to 42 ml/min while no information was provided for the unique untreated patient (26). In the French study, from the 73 pSS patients with IN patients, 64 were mainly treated with prednisone alone or in combination with another ISA resulting in improvement of mean eGFR from 35 ml/min at baseline to 42.5 ml/min at the 12-month follow-up. Notably, no clinical or therapeutic data were provided regarding the eight untreated patients (23). However, this cohort is characterised by great heterogeneity regarding the dosage, type and duration of treatment that does not necessarily correspond to the follow-up time. Finally, in a recent study by Shen *et al*., pSS patients with IN were assigned to receive either prednisone or prednisone plus cyclophosphamide (27). Fifty-six patients were treated with at least prednisone 15 mg/day, for at least three months and the mean change of eGFR was insignificant as opposed to the 43 patients from the French study who also received only prednisone and gained >20% of mean eGFR compared to baseline. Of note, the 14 patients in the study by Shen *et al*. who received prednisone plus cyclophosphamide displayed >50% increase of mean post-treatment eGFR.

In the studies mentioned previously, although a beneficial effect of (IST) is concluded in some IN patients, the results-especially from the last two studies regarding the administration of prednisone alone- are contradictory. Although, GFR is the best way to evaluate renal function, it is still influenced by many factors including hydration status, age, weight and medications such as diuretics, non-steroid anti-inflammatory drugs (NSAIDs), ACEi, and angiotensin receptor blockers (ARB). It is well recognised that the initiation of treatment with ACEi or ARB may lead to deterioration of renal function up to 20% of GFR. Similarly, the dose and frequency of NSAIDs may affect the perfusion of kidneys, especially in patients who receive diuretics or they have slight volume depletion for any reason. With the exception of the two aforementioned studies, renal outcome in most studies has been expressed by median or mean eGFR change of the total cohort. However, we feel that it is much preferable to describe renal outcome as the percentage of responders with gain of eGFR >20 or 25% for each patient separately, after careful evaluation of patient's status regarding the factors mentioned above and only immediately after the end of administration of immunosuppressive treatment. This approach will allow us to identify more accurately a beneficial effect of IS treat-

Table IV. Immunosuppressive treatment and renal outcome in pSS patients with GN.

Patient no.	Presentation	Biopsy	Treatment	Before	After
15	Nephrotic range proteinuria, haematuria, Cr=1.3	IgM/C3 FSGS + Hyalinosis, IN	· Prednisone 50mg-10mg (2.5mo) · Prednisone 50mg and MMF 1g x 2 (5mo)	· Cr=1.3, GFR 42 · Cr=3.4, GFR=14, Proteinuria, haematuria	· Cr=1.5, GFR 35 · Cr=3.6, GFR=13 (2mo), Cr=4.3, 0GFR=10 (after 5mo therapy)
16	CRF=2.0	IgG/IgM MPGN	· Prednisone 10mg + rebif + HQ (3.5 y, prolonged) · 0.5mg/kg prednisone and rituximab (2 and 5 mo from rituximab)	· Cr=2.0, GFR 26 (first biopsy), · Cr=3.8, GFR=15 proteinuria, haematuria	·Cr=3.8,GFR=15, proteinuria, haematuria (second biopsy) Cr=3.2,GFR=18 (2mo), Cr=2.8, GFR=21 residual proteinuria, mild haematuria (5mo)
17	CRF=1.6, proteinuria, haematuria	Fibrillary GN	· Prednisone 40mg for (2.5mo) · Prednisone 10mg + rituximab (5mo)	· Cr=1.6, proteinuria, haematuria, GFR=38 Cr=3.4, GFR=17, proteinuria	· Cr=1.6-1.7 , GFR 33 Cr=2.8, GRF=18, proteinuria
18	Proteinuria, haematuria, Cr=0.8+ also vasculitic leg ulcers	IgM, MPGN	· (MTX previously) 2-3g MMF plus prednisone 15-5mg/d (leg ulcers 10mo)	· Cr=0.8, no haematuria, no proteinuria, GFR 73	· Cr=0.8, proteinuria, haematuria, GFR 72
			· Cytoxan:125mg and prednisone 40-20mg/d (for almost three months)	· Cr=0.8, proteinuria<1g. microhaematuria, GFR 72	· Cr=0.7-0.8, GFR=72 micro-haematuria, proteinuria
			· Maintenance: prednisone 25mg with MMF 3g (3mo)	· Cr=0.7-0.8, GFR 72 microhaematuria, proteinuria	·Cr=0.8, normal UA, GFR 72
19	Proteinuria, haematuria (2014)/haematuria of renal source since 2008/outbreaks of vasculitic purpura	IgG/IgM MPGN	· Prednisone 4-6mg + HQ + colchicine (for 4Y)	· Cr=0.9-1.0, proteinuria, haematuria, GFR=65	· Cr=0.9-1.0 proteinuria, gross haematuria, GFR=64
			· Prednisone 60-6mg/d+ MMF 2g/d (10mo)	Cr=0.9-1.0 proteinuria, gross haematuria, GFR=64	· Gr=0.9-1.0, improvement of proteinuria, haematuria, GFR 64
			· Prednisone 60-20mg (slow tapering) (5mo) + (MMF for 2.5 mo)	· Cr=1.0-1.3, GFR<60, increased proteinuria, haematuria, GFR=42	· Cr=1.2, GFR=50, RBC=10, P/Cr urine ratio=0.98, GFR=46
			·Prednisone 20-4mg + rituximab (6mo)	· Cr=1.2, GFR=50, RBC=10, Urine p/cr=0.98, GFR=46	Cr=0.9, GFR=60, UA: normal!, GFR 60
20	Palpable purpura, haematuria, proteinuria, rise in creatinine, pleural effusions	ND	· Prednisone 40mg/d +colchicine (slow tapering)	· Raised creatinine, haematuria, proteinuria, leg ulcers/purpura, (No creatinine available)	· Cr=1.17, no episode of vasculitis, residual proteinuria (6mo)

pSS: primary Sjögren's syndrome; GN: glomerulonephritis; CRF: chronic renal failure; MPGN: membranoproliferative; FSGS: focal segmental glomerulosclerosis; MMF: mycophenolate mofetil; AZA: azathioprine; MTX: methotrexate; ND: not done.

ment compared to the mean or median eGFR changes, especially when the number of patients is small or if there is heterogeneity regarding the dose and duration of treatment or inconsistency between the duration of treatment and the follow-up time. Therefore, the mean eGFR post-treatment improvement, may reflect an increase in GFR of only a subset of patients and could be potentially attributed to adjustment of renal function after initiation of treatment with ACEi or ARB, discontinuation of NSAIDs or better hydration status.

In conclusion, (IST) is necessary to retain normal renal function and eradicate residual disease in GN, although the type, dosage and duration of treatment varies among different groups and according to physician's judgment. However, oral prednisone 0.5 mg/kg with or without MMF or rituximab are reasonable treatment options for immune complex-mediated GN while cyclophosphamide should be reserved for severe cases of GN with additional systemic manifestations such as skin vasculitis or peripheral neuropathy. On the contrary, the role of (IST) in the management of IN remains controversial. Further studies with increased number of well-defined patients and after careful evaluation and consideration of various parameters that may potentially affect eGFR, should be conducted for a head-to-head comparison of (IST) *versus* placebo treatment, using the individual change of eGFR as an outcome measure of renal function rather than the mean or median GFR of the total treatment group. To our perception, a pSS patient with IN should be carefully evaluated and closely followed up in order to understand the severity and activity of renal damage. Systemic IST such as prednisone with or without MMF should be reserved either for cases with AKI that cannot be attributed to

Table V. Characteristics of clinical studies with TIN alone pSS patients treated with immunosuppressive agents.

Group (ref)	Treated TIN alone patients	Untreated TIN alone patients	Outcome	Confounders
Maripuri *et al*. (6)	• 15 patients • mainly prednisone, median initial dose 40mg/d (range 30-60mg/d) for median duration of 30w	0 patients	>20% eGFR gain responders: 9	No information
Kidder *et al*. (5)	• 7 patients • mainly prednisone (no information for dose or duration)	4 patients	• Treated patients (>20eGFR gain) ο 4 patients: no ο 3 patients: yes • Untreated patients (>20 eGFR gain) ο 3 patients: yes ο 1 patient: RRT	No information
Evans *et al*. (26)	• 11 patients • mainly prednisone, median initial dose 10mg/d (range 5-20) weaned over 3-6 months + MMF median dose 1000mg/d for median duration 24 months	1 patient	Median eGFR change 10ml/min/1.73m^2 (at follow-up) • Pre=32ml/min/1.73m^2 • Post=42ml/min/1.73m^2	No information
Jasiek *et al*. (23)	• 64 patients • prednizone median initial dose 55mg/d (range 5-80mg/d) for variable duration but at least for 6 months plus rituximab, AZA or MMF	8 patients	• Mean GRF change 7.5ml/min/1.73m^2 • pre=35, post=42.5 (at 12 month follow-up)	No information
Shen *et al*. (27)	• 56 patients • prednisone mean initial dose 25.5mg/d for more than 3 months	0 patients	Mean GFR change: 2.72±19.11 ml/min/1.73m^2 (at 12 month follow-up) Pre=64.86±30.45 ml/min/1.73m^2	ACEi, ARB
Goules *et al*.	• 8 patients • Prednizone initial dose 20-60mg/d for at least 2 months plus MMF, AZA, MTX or anti-TNF (1 case)	6 patients	• Treated patients (>20eGFR gain) ο 6 patients: no ο 2 patients: yes • Untreated patients ο 2 patients: NRF (after years) ο 4 patients: RRT (after years)	ACEi, ARB, NSAIDs, diuretics, HTN, DM

TIN: tubulointerstitial nephritis; pSS: primary Sjögren's syndrome; ACEi: angiotensin converting enzyme inhibitors; ARB: aldosterone receptor blockers; NSAIDs: non-steroidal anti-inflammatory drugs; MMF: mycophenolate mofetil; AZA: azathioprine; MTX: methotrexate; DM: diabetes mellitus; HTN: hypertension.

any other cause and the biopsy reveals severe lymphocytic infiltration with tubulitis or in cases of slow deterioration of renal function due to exclusively biopsy-proven pSS associated lymphocytic infiltration with limited degree of tubular atrophy and fibrosis. The role of rituximab that causes remodelling of B cell compartment (28) or other novel biologic agents in the treatment of renal involvement in pSS, needs further clarification (29).

References

1. GOULES A, MOUTSOPOULOS H: Nephro-Urological Involvement. *In*: RAMOS-CASALS M, JOHN H STONE, MOUTSOPOULOS HM (Eds.): Sjögren's syndrome: Diagnosis and Therpeutics. 1rst Ed, London 2012, 265-80.
2. FRANCOIS H, MARIETTE X: Renal involvement in primary Sjögren syndrome. *Nat Rev Nephrol* 2016; 12: 82-93.
3. GOULES A, MASOURIDI S, TZIOUFAS AG, IOANNIDIS JP, SKOPOULI FN, MOUTSOPOULOS HM: Clinically significant and biopsy-documented renal involvement in primary Sjögren's syndrome. *Medicine* (Baltimore) 2000; 79: 241-9.
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. KIDDER D, RUTHERFORD E, KIPGEN D, FLEMING S, GEDDES C, STEWART GA: Kidney biopsy findings in primary Sjögren's syndrome. *Nephrol Dial Transplant* 2015; 30: 1363-9.
6. MARIPURI S, GRANDE JP, OSBORN TG *et al*.: Renal involvement in primary Sjögren's syndrome: a clinicopathologic study. *Clin J Am Soc Nephrol* 2009; 4: 1423-31.
7. RING T, KALLENBACH M, PRAETORIUS J, NIELSEN S, MELGAARD B: Successful treatment of a patient with primary Sjögren's syndrome with Rituximab. *Clin Rheumatol* 2006; 25: 891-4.
8. SCHILCHER G, SCHWARZ C, HERMANN J: Successful treatment of renal tubular acidosis and recurrent secondary struvite kidney stones with rituximab in a patient with primary Sjögren's syndrome. *Rheumatology* (Oxford) 2017; 56: 498-500.
9. VITALI C, BOMBARDIERI S, JONSSON R *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.
10. LEVEY AS, BOSCH JP, LEWIS JB, GREENE T, ROGERS N, ROTH D: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130: 461-70.
11. MATSUMURA R, KONDO Y, SUGIYAMA T *et al*.: Immunohistochemical identification of infiltrating mononuclear cells in tubulointerstitial nephritis associated with Sjögren's syndrome. *Clin Nephrol* 1988; 30: 335-40.
12. ROSENBERG ME, SCHENDEL PB, MCCURDY FA, PLATT JL: Characterization of immune cells in kidneys from patients with Sjögren's syndrome. *Am J Kidney Dis* 1988; 11: 20-2.
13. SHIOJI R, FURUYAMA T, ONODERA S, SAITO H, ITO H, SASAKI Y: Sjögren's syndrome and renal tubular acidosis. *Am J Med* 1970; 48: 456-63.
14. TALAL N, ZISMAN E, SCHUR PH: Renal tubular acidosis, glomerulonephritis and immunologic factors in Sjögren's syndrome. *Arthritis Rheum* 1968; 11: 774-86.
15. MATSUMURA R, UMEMIYA K, GOTO T *et al*.: Glandular and extraglandular expression of costimulatory molecules in patients with Sjögren's syndrome. *Ann Rheum Dis* 2001; 60: 473-82.
16. MATSUMURA R, UMEMIYA K, NAKAZAWA T *et al*.: Expression of cell adhesion molecules in tubulointerstitial nephritis associated with

Sjögren's syndrome. *Clin Nephrol* 1998; 49: 74-81.
17. MOUTSOPOULOS HM: Sjögren's syndrome: autoimmune epithelitis. *Clin Immunol Immunopathol* 1994; 72: 162-5.
18. AASAROD K, HAGA HJ, BERG KJ, HAMMERSTROM J, JORSTAD S: Renal involvement in primary Sjögren's syndrome. *QJM* 2000; 93: 297-304.
19. BOSSINI N, SAVOLDI S, FRANCESCHINI F *et al*.: Clinical and morphological features of kidney involvement in primary Sjögren's syndrome. *Nephrol Dial Transplant* 2001; 16: 2328-36.
20. PERTOVAARA M, KORPELA M, KOURI T, PASTERNACK A: The occurrence of renal involvement in primary Sjögren's syndrome: a study of 78 patients. *Rheumatology* (Oxford) 1999; 38: 1113-20.
21. POKORNY G, SONKODI S, IVANYI B *et al*.: Renal involvement in patients with primary Sjögren's syndrome. *Scand J Rheumatol* 1989; 18: 231-4.
22. VIERGEVER PP, SWAAK TJ: Renal tubular dysfunction in primary Sjögren's syndrome: clinical studies in 27 patients. *Clin Rheumatol* 1991; 10: 23-7.
23. JASIEK M, KARRAS A, LE GUERN V *et al*.: A multicentre study of 95 biopsy-proven cases of renal disease in primary Sjögren's syndrome. *Rheumatology* (Oxford) 2017; 56: 362-70.
24. REN H, WANG WM, CHEN XN *et al*.: Renal involvement and followup of 130 patients with primary Sjögren's syndrome. *J Rheumatol* 2008; 35: 278-84.
25. YANG HX, WANG J, WEN YB *et al*.: Renal involvement in primary Sjögren's syndrome: A retrospective study of 103 biopsy-proven cases from a single center in China. *Int J Rheum Dis* 2018; 21: 223-9.
26. EVANS RD, LAING CM, CIURTIN C, WALSH SB: Tubulointerstitial nephritis in primary Sjögren's syndrome: clinical manifestations and response to treatment. *BMC Musculoskelet Disord* 2016; 17: 2.
27. SHEN Y, XIE J, LIN L *et al*.: Combination Cyclophosphamide/Glucocorticoids Provide Better Tolerability and Outcomes versus Glucocorticoids Alone in Patients with Sjögren's Associated Chronic Interstitial Nephritis. *Am J Nephrol* 2017; 46: 473-80.
28. LOPEZ J, MERINO L, PIRIS L *et al*.: Rituximab induces a lasting, non-cumulative remodelling of the B-cell compartment. *Clin Exp Rheumatol* 2019; 37: 615-22.
29. FASANO S, ISENBERG DA: Present and novel biologic drugs in primary Sjögren's syndrome. *Clin Exp Rheumatol* 2019; 37 (Suppl. 118): S167-74.