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Review

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Renal involvement in primary Sjögren's syndrome

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Abstract

SS is a prevalent and underdiagnosed systemic disease that primarily affects epithelial tissue. It may affect renal function either as epithelial disease causing tubulointerstitial nephritis or as an immune complex–mediated glomerulopathy. These lesions may cause a variety of clinical features, both overt and occult. The epithelial disease is mediated by B and T cells, notably the Th17 subtype. We review the AQ2 prevalence of renal SS, its presentation, likely pathogenesis and treatment.

Key words: Sjögren's syndrome, tubulointerstitial nephritis, autoimmune epithelialitis, Th17 cells, B cells, distal renal tubular acidosis, Fanconi syndrome, autoantibodies, vasculitis, hypocomplementaemia.

REVIEW

Rheumatology key messages

- Renal disease in primary SS is often occult and needs to be specifically looked for.
- Renal disease in primary SS may be associated with serious morbidity and even mortality.
- Renal primary SS is mainly epithelial and is likely to be driven by the same processes as in other tissues.

Introduction

SS, described by Henrik Sjögren in 1933, is a chronic inflammatory disorder characterized by lymphocytic infiltration of epithelial tissue in exocrine glands and extraglandular sites [1]. Lacrimal and salivary gland infiltration results in the classic sicca syndrome of dry eyes and dry mouth in >90% of patients [2]. However, SS is a heterogeneous disease; extraglandular infiltration can threaten organ function and carries an excess mortality, mainly due to lymphoproliferative disease, which occurs in up to 10% of patients [3]. It may occur alone (primary SS, pSS) or in association with other autoimmune diseases (e.g. SLE).

pSS has been called an autoimmune epithelialitis [4], an apt term since the lymphocytic infiltrate is centred on epithelial cells in each organ that it affects. This includes glandular epithelial cells in the lacrimal and salivary glands, tubular epithelial cells in the kidney, respiratory epithelia and submucosal glands within the lung and biliary epithelia in hepatobiliary disease [5].

It classically occurs in middle-aged women, but can occur in other groups [6]. It has been estimated to affect 0.05–0.23% of the adult population [7]. It may be asymptomatic with the incidental discovery of autoantibodies [8] or it may present with the sicca complex, constitutional symptoms or other organ involvement [9].

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Renal disease in pSS

Renal involvement in pSS was first described in the 1960s with reports of the typical tubular defects [10–12]. These included biopsy series that highlighted tubulointerstitial inflammation as the most common renal lesion [13]. Renal involvement in pSS is the result of two distinct pathophysiological processes: epithelial disease with a predominantly mononuclear lymphocytic infiltration resulting in tubulointerstitial nephritis (TIN) (Fig. 1) and non-epithelial disease with a secondary immune complex–mediated process resulting in glomerulopathy.

Prevalence of renal disease in pSS

Three major series of renal involvement in pSS come from Spain and Greece [2, 7, 14]. These retrospective studies looked for overt disease and identified renal involvement in 5%, 4.9% and 4.3% of patients, respectively.

Ramos-Casals *et al.* [2] defined renal involvement as one of proteinuria >0.5 g/day, active urinary sediment, distal renal tubular acidosis (dRTA), TIN or GN. They retrospectively applied this to a cohort of 1010 patients diagnosed with SS; 5% had evidence of renal involvement. In a cohort of 921 patients with pSS from the same group, 4.3% had renal involvement at some stage [7].

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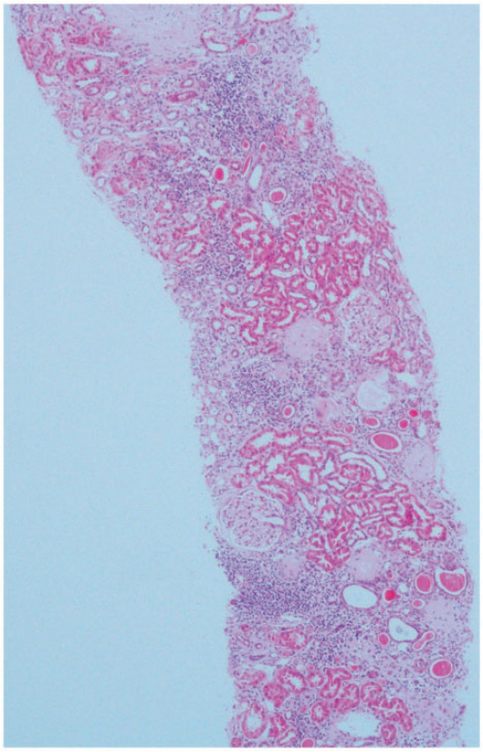
Fig. 1 Slide of a haematoxylin and eosin–stained renal biopsy specimen demonstrating SS-related TIN



Areas with normal tubules are apparent, but localized foci of inflammatory cells have replaced these in other areas.

Goules *et al*. [14] defined renal involvement as one of low specific gravity (<1.010) after water deprivation, urinary pH >7 for >6 months, renal colic with nephrolithiasis or nephrocalcinosis, Fanconi syndrome, impaired excretory function, proteinuria, active urine sediment or histological GN or TIN. When retrospectively applied to a cohort of 715 patients, 35 had evidence of renal disease. A recent UK retrospective study of 152 pSS patients found that 10 (6.5%) had renal involvement, defined by the presence of renal tubular acidosis or GN [15].

However, in prospective studies of randomly selected pSS patients, specifically looking for tubular defects, the prevalence of renal involvement is much higher. The most recent studies estimate proximal injury to be present in 10–42%, dRTA in 5–24% and a concentrating defect in 17–28% [16–19] (Table 1).

Prevalence of different renal lesions

Two large series with biopsy data confirm earlier reports that TIN is the predominant lesion, found in ~75% of patients, with the remaining ~25% of patients having glomerular disease [20, 21].

Maripuri *et al*. [21] reviewed all renal biopsies from a cohort of 7276 patients with pSS between 1967 and 2007. Twenty-four renal biopsies were identified, 17 (71%) of which had primarily TIN, while 7 (29%) had glomerulopathy. Of these, two had co-existent mild TIN.

Ren *et al*. [20] described a cohort of 130 pSS patients. Forty-one of these underwent biopsy, with 80% demonstrating TIN and 20% glomerular disease. However, the Goules *et al*. [14] cohort did not show the same predominance of TIN; of the 33 biopsied patients, 52% had GN, 35% had TIN and 12% had both [14].

Epithelial renal disease in pSS

Histopathology of epithelial pSS

The predominant infiltrating cells are $CD4^+$ T cells in both humans and mouse models, with $CD8^+$ T cells, B cells and macrophages being less numerous [22–24]. $CD8^+$ T cells were the predominant cell that was responsible for tubular invasion in one series [24]. These findings are remarkably similar to those in other affected epithelia.

Much of the data on lymphocytic infiltration of epithelial tissue in pSS has come from labial salivary glands (reviewed by Tzioufas *et al*. [25]). In salivary glands, the type of infiltrate varies [26, 27] and it has been suggested that specific therapies could be employed dependent on the predominant cell subtype found at the presenting biopsy [28]. Whether the histological severity or the predominant cell subtype correlate with patient outcome is unclear. While infiltration at extraglandular sites often coincides with glandular epithelial infiltration, whether one can use salivary gland histology to assess the severity of renal disease is not known.

T cells

$CD4^+$ cells make up the bulk of the T cells present in labial salivary glands and there is evidence for a role of both Th1 and Th2 subtypes. Katsifis *et al*. [29] demonstrated increased levels of the cytokines required for Th17 proliferation (IL-6, IL-23 and TGF-β) and the predominant cytokine produced by Th17 cells (IL-17) in both the serum and salivary glands of pSS patients [29]. Indeed, IL-17 levels seemed to correlate with the severity of the histological lesion. Furthermore, in a mouse model of pSS, knocking out IL-17 prevents development of the disease [30].

IL-22, a cytokine produced by Th17 cells, has increased expression in salivary gland biopsies of pSS, and Th17 cells are the predominant source [31]. It was recently demonstrated that increased IL-17 in the salivary glands of pSS patients was from both $CD4^+$ T cells and mast cells. After treatment with rituximab (RTX), tissue expression of IL-17 decreased, but this was associated with a reduction in mast cell numbers rather than $CD4^+$ T cells [32]. RTX appears to have more than just an anti-B cell effect; similar modulation of the Th17 response by RTX has been shown in the setting of RA [33].

B cells

Evidence for an important role of B cells in pSS includes a high prevalence of autoantibodies, hypergammaglobulinaemia, increased risk of lymphoma, germinal centre

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TABLE 1 Findings from prospective studies of renal pSS

Study	Number of patients	pSS classification used	Autoantibody status, %	SG biopsy findings	Proximal dysfunction or injury (tubular proteinuria), %	dRTA (complete or incomplete), %	Concentrating defect, %	Overall: evidence of any renal dysfunction, %
Amarante *et al.*, 2014 [17]	25	American–European (2002) [68]			16	24	28	Unclear
Bossini *et al.*, 2001 [16]	60	European (1993) [69]	ANA 85 Anti-Ro 80 Anti-La 40	Not reported	10	5 (all complete)	17	27
Aasarød *et al.*, 2000 [18]	62	European (1993) [69]	ANA 81 Anti-Ro or La 32	Performed in 53 patients; focus score $\geqslant$1 in 64%	42	11.3	21	Unclear
Pertovaara *et al.*, 1999 [19]	78	European (1993) [69]	ANA 86 Anti-Ro 74 Anti-La 53	Not reported	14	23 (16 incomplete)	Not assessed	Unclear

Expressed percentages indicate the proportion of the total number of patients, not of the number of patients that underwent testing. dRTA: distal renal tubular acidosis; RTA: renal tubular acidosis; SG: salivary gland.
dRTA: distal renal tubular acidosis; MPGN: mesangioproliferative glomerulonephritis.

formation on histology and response of the disease to anti-B cell therapy.

A range of different autoantibodies are seen in pSS patients. Some are disease markers, some are associated with specific clinical phenotypes and some may have a pathogenic role [34].

Tubular defects

TIN may cause different defects in tubular function (Table 2).

Distal renal tubular acidosis

dRTA is due to inadequate H^+ secretion in the cortical collecting duct by the acid-secreting α-intercalated cells. dRTA may be complete, with systemic metabolic acidosis and inappropriately alkaline urine, or incomplete, where the acidification defect is insufficient to cause overt acidosis; this can be revealed by dynamic testing. Testing can be through administration of either ammonium chloride [35] or furosemide and fludrocortisone [36].

dRTA causes urinary K^+ wasting. Patients may present with hypokalaemic symptoms, including paralysis [37]. Seven per cent of patients in one series presented with hypokalaemic paralysis and one patient had a cardiac arrest [20]. dRTA may also manifest as nephrolithiasis or nephrocalcinosis (Fig. 2), causing renal colic or urosepsis.

In prospective studies designed to look for dRTA in pSS, it is relatively common, in between 5% and 23% of patients [16, 18, 19]; its presence is associated with anti-Ro and La antibodies, longer disease duration, xerostomia, hypertension, higher creatinine and proteinuria. Hypergammaglobulinaemia is also associated with dRTA in pSS [19]. In cohorts of known renal pSS, dRTA is even more common; as high as 70% in one series [20].

We have previously shown that vacuolar H^+-ATPase and anion exchanger 1, transporters crucial to α-intercalated cell function, are undetectable on immunohistochemistry in pSS dRTA [38]. Autoantibodies to these proteins have been demonstrated in patients with pSS dRTA [39], but not consistently [40]. Congenital carbonic anhydrase II (CA II) deficiency also results in dRTA. Autoantibodies to CA II are associated with pSS, especially dRTA. Mice immunized with CA II develop a sialadenitis similar to pSS and a proportion of these mice had TIN [41]. Takemoto *et al.* [42] screened 46 patients with pSS, 13 of whom had dRTA. Compared with controls, autoantibodies to CA II were increased in the pSS cohort and highest in those with dRTA. The same group subsequently immunized mice with CA II. CA II antibodies were associated with the development of a mild TIN in ~50% and dRTA on ammonium chloride testing [43]. Supportive management of dRTA includes supplementation of bicarbonate and potassium (e.g. oral potassium citrate) and close nephro-urological follow-up to prevent complications from nephrolithiasis.

Nephrogenic diabetes insipidus

The initial reports of tubular dysfunction in pSS were of nephrogenic diabetes insipidus (NDI) [10, 11]; it is caused by dysfunction of the principal cells of the collecting duct.

Table 2 A summary of the different clinical features associated with the different lesions of renal pSS

	Mechanism	Presentation
Epithelial disease—secondary to lymphocytic infiltration		
Cortical collecting duct dysfunction (α-intercalated cells)	dRTA: hypokalaemia	Asymptomatic (routine blood tests) Paralysis
	dRTA: nephrolithiasis/nephrocalcinosis, hypercalciuria, hyperphosphaturia, hypocitraturia	Asymptomatic (imaging for other indication) Stones, nephrocalcinosis
Cortical collecting duct dysfunction (principal cells)	Concentrating defect	Polydipsia, polyuria, nocturia
Proximal tubular dysfunction	Phosphaturia Proximal renal tubular acidosis	Asymptomatic (routine blood tests) Osteomalacia Stones, nephrocalcinosis
	Glycosuria Low molecular weight proteinuria	Asymptomatic (routine urinalysis)
Loop of Henle and distal convoluted tubule dysfunction (acquired Gitelman or Bartter syndrome)	Salt loss	Asymptomatic (routine bloods or urinalysis)
	Hypokalaemia alkalosis	Non-specific
	Hypomagnesaemia (more common with Gitelman phenotype) Hypocalciuria (Gitelman phenotype only)	Hypovolaemia and hypotension
Non-epithelial disease—secondary to immune complexes		
Glomerular disease and vasculitis	Glomerular disease	Asymptomatic urinary abnormalities Nephrotic syndrome Hypertension Reduced excretory function
	Systemic vasculitis (cryoglobulinaemia)	Systemic upset Fevers Purpura Neuropathy Glomerular disease (MPGN)
Both epithelial and non-epithelial disease		
Decreased excretory function		Asymptomatic (routine blood tests) Uraemia

dRTA: distal renal tubular acidosis; MPGN: mesangioproliferative glomerulonephritis.

Presentation is with polydipsia, polyuria and nocturia. It may only be apparent on specific testing with the water deprivation test. It is as prevalent in the general pSS population as dRTA, being present in 17–28% of patients (Table 1). In biopsy-proven TIN it is present in ~75% of patients, with only a quarter of these patients being symptomatic [14]. It was even more prevalent in those in which it was tested in Ren *et al.*'s [20] cohort, with 51/60 (85%) patients having evidence of abnormal urinary concentration. NDI in pSS is a disease of adulthood, and the thirst mechanism is almost always robust enough to maintain the serum sodium within the normal range [44], thus specific therapies for NDI (e.g. NSAIDs, diuretics) are not warranted.

Proximal tubular dysfunction

Proximal tubular cells (PTCs) are responsible for the reabsorption of most filtered electrolytes as well as low molecular weight (tubular) proteins, amino acids, glucose and urate. Together, tubular proteinuria, aminoaciduria, glycosuria, phosphaturia, uricosuria and bicarbonaturia comprise the Fanconi syndrome of generalized PTC dysfunction. This may lead to osteomalacia as a consequence of phosphate wasting.

The full Fanconi syndrome is rare in pSS TIN (3% [20]), but evidence of PTC dysfunction is much more common. The most sensitive marker, tubular proteinuria (e.g. retinol binding protein), is present in 10–42% in the general pSS series and up to 87% of those with known renal disease (Table 1).

Other acquired tubular defects

There are case reports of pSS affecting other tubular segments, causing acquired Bartter or Gitelman-like syndromes [45–49]. Intriguingly, one of these cases was reported to have an autoantibody to the NaCl co-transporter (NCC) [48], the transporter affected by Gitelman syndrome.

Non-epithelial renal disease in pSS

Histopathology of pSS GN

The majority of glomerular disease reported in pSS is immune complex-mediated, usually the characteristic

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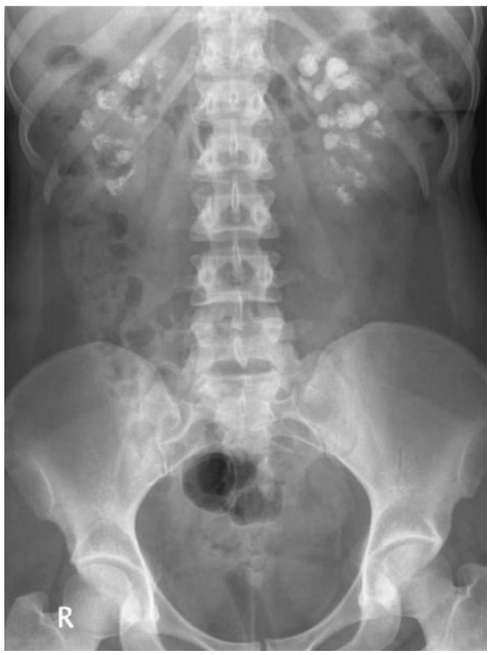
FIG. 2 A plain abdominal X-ray showing bilateral nephrocalcinosis in a patient with SS-related TIN and distal renal tubular acidosis



mesangioproliferative glomerulonephritis (MPGN), which is the most common glomerular lesion in pSS. MPGN is caused by the deposition of immune complexes, which are often cryoglobulins; 64% of all patients with GN were cryoglobulinaemic in the Goules *et al*. series [14].

Cryoglobulins are the result of B cell expansion causing the synthesis of IgM, which binds antigen and IgG. These immune complexes bind to endothelial cells, activate complement and recruit inflammatory cells, causing small vessel vasculitis. In the kidney this manifests as MPGN, either alone or as part of a systemic vasculitis.

GN in pSS occurs later in the disease course than TIN. It is also associated with lymphoma development and thus increased morbidity and mortality [14, 50]. Glomerulopathy presents with typical glomerular features including haematuria, proteinuria, hypertension, reduced glomerular filtration rate and nephrotic syndrome (Table 2). There are various patterns of GN involvement described in SS (supplementary Table S1, available at *Rheumatology* Online).

Decreased excretory function

Decreased excretory function is present in a relatively small proportion of those with renal involvement in pSS, being present in 27–31% in the larger series [14, 20] (supplementary Table S2, available at *Rheumatology* Online). It can occur in those with either interstitial or glomerular disease. In the Goules *et al*. cohort, 54% of those with TIN had reduced excretory function compared with 12% in those with glomerular disease. It was suggested that this may reflect the clinically silent and therefore possibly untreated nature of interstitial disease.

If present, renal impairment in pSS TIN tends to be mild to moderate. However, progressive renal disease can occur, and rates as high as 12% of patients with renal pSS requiring dialysis have been reported [14].

Screening

Given the multiple renal lesions that can occur with pSS and the relative difficulty in recognizing them, we have compiled a guideline for physicians treating pSS patients to help screen for pSS-associated disease and refer the patient to nephrology services if appropriate (supplementary data, guide to screening for renal involvement in pSS, available at *Rheumatology* Online). We have deliberately avoided specialist renal investigations so that screening these patients is feasible in the general clinic setting. These guidelines represent our opinion only and are not based on empirical evidence.

Management

No systemic immunosuppressive treatment is of proven benefit in pSS and treatment is largely based on extrapolations from treatment of other inflammatory conditions (e.g. SLE) and small open-label studies. Some randomized studies have been undertaken, but with negative or conflicting results [51–55].

While HCQ or MTX is the mainstay of uncomplicated pSS, steroids, CYC, anti-proliferative agents, calcineurin inhibitors and biologic agents (e.g. RTX) have been used to manage resistant or extraglandular disease [56, 57]. In addition to a lack of evidence for treatment of extraglandular pSS, there are no randomized studies on the management of pSS TIN, with treatment based on retrospective data of TIN treatment, again with conflicting results [58, 59].

TIN

In Maripuri *et al*.'s cohort [21], 88% were treated with steroids and 53% had additional immunosuppression. The majority had stable renal function; only 18% had progressive renal disease. Ren *et al.* [20] did not distinguish between glomerular and interstitial disease when discussing treatment, but the majority of the cohort had interstitial disease and were treated with immunosuppression (largely steroids alone). The Greek group gave supportive treatment but not immunosuppression to those with interstitial disease [14].

We treat acute TIN with MMF and a weaning course of steroids, reserving B cell depleting therapy for resistant disease. The clinical benefit of this strategy and how long it should be continued is the focus of current study.

GN

Treatment of glomerular disease is based on the histological lesion. Within the renal cohorts described there is no consistent treatment of any of the glomerular disease (supplementary Table S3, available at *Rheumatology*

Online). Most patients were treated with steroids with or without an additional immunosuppressant or plasma exchange. The limited outcome data suggest a reasonable response to any form of immunosuppression. For example, there was no deterioration in function in any of the patients with glomerular involvement treated with immunosuppression in Maripuri *et al.*'s cohort [21].

Studies of non-infectious cryoglobulinaemic vasculitis include large numbers of pSS patients. The CryoVas study included 242 cases of non-infectious vasculitis, 25% of which were due to pSS [60]. In this retrospective cohort, treatment with RTX and corticosteroids was superior to either corticosteroids alone or corticosteroids in combination with an alkylating agent. We therefore favour a steroid and RTX regimen for cryoglobulinaemic vasculitis in the setting of pSS. We reserve plasma exchange for rapidly progressive glomerular or life-threatening disease.

There has been much interest in the use of RTX in pSS in the light of our understanding of the important role B cells play in disease pathogenesis, but also because of the effect RTX has on T cells, in particular modulation of the Th17 response [33]. The majority of recent randomized data in pSS concerns RTX use. Several open-label studies demonstrating a positive effect of using RTX in pSS led to two recent randomized controlled trials (RCTs) [61, 62]. These used improvements in either sicca symptoms or fatigue scores as primary outcomes, with conflicting results [53, 55, 62]. A further RCT of RTX in the UK is under way [63]. We can gain limited information on renal pSS from these trials, but it was interesting to note that five of six patients with renal involvement in recent registry data from France improved with RTX treatment [64]. Other biologic treatments may offer new avenues for the treatment of pSS TIN.

pSS patients may have increased levels of B cell activating factor [65], especially those with lymphoma. Belimumab, an anti-B cell activating factor antibody, has been trialled successfully in phase 2 studies in pSS [66], improving symptom scores.

As Th17 cells appear to have an important role in epithelial inflammation in pSS, secukinumab, an anti-IL17 antibody, may have a role in the treatment of pSS, including renal SS. Furthermore, abatacept is another potential therapy for renal pSS; a recent study showed that it improved salivary histology and saliva production in pSS [67].

Conclusion

Renal pSS is an underdiagnosed problem that can present in a variety of different and covert ways. The pathogenesis of the pSS TIN lesion is likely to be the same as other epithelial lesions in pSS, and T cell responses appear to be important in this. Whether pSS TIN can provide insights into other forms of TIN (e.g. drug-related TIN) or even acute transplant rejection remains to be seen. There is clearly much to be learned from this fascinating interaction of the immune system and the secretory epithelium.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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