Case report on a 32-year-old female with elevated serum creatinine levels and primary Sjögren's syndrome-chronic interstitial nephritis

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Abstract. Primary Sjögren's syndrome (PSS) is a chronic autoimmune disease characterized by lymphoplasmacytic infiltration of the exocrine glands, which results in multiple organs damage. Renal injury affects 0.3-27.0% of PSS patients, and tubulointerstitial nephritis is the most frequent form of nephropathy in PSS. The present study reports on the case of a 32-year-old female with a 1-year history of elevated serum creatinine levels, and a 6-month history of mild pain in the waist and leg. Blood biochemistry tests indicated a creatinine level of 221.3 μmol/l and estimated glomerular filtration rate of 24.6 ml/min/1.73 m^2 [Chronic Kidney Disease Epidemiology (CKD-EPI) formula]. Accordingly, the patient was diagnosed with stage IV chronic kidney disease. To clarify the underlying cause of the disease, a kidney biopsy was performed, which revealed tubular epithelial cells with multiple focal and lamellar atrophy (~60%), as well as extensive renal interstitial fibrosis with scattered inflammatory cell infiltration. Based on these results, the patient was finally diagnosed with severe chronic interstitial nephritis, chronic kidney disease stage IV, PSS and anemia due to chronic kidney disease. The patient was treated with half-dose glucocorticoid (prednisone, 25 mg oral qd maintained up to 12 months). The patient's serum creatinine levels had decreased to 172.4 μmol/l after 1 month and to 178.7 μmol/l after 12 months. The present case concluded that young patients with chronic renal failure should first be assessed for rheumatic immune system diseases. PSS may involve several organs and the clinical manifestations may be varied. Although chronic renal failure is frequently the first manifestation of renal disorder due to PSS, it may be overlooked by clinicians. The present results suggest that further attention should be paid to determine the association between symptoms in the clinical setting.

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Background

PSS is a chronic inflammatory, multi-systemic autoimmune disease (1) that may involve various organs, but commonly results in renal damage (40-50% of cases) (2). Although the condition may be life-threatening in severe cases, the early clinical symptoms of renal lesions in such cases are frequently atypical, and may hence be overlooked by clinicians. The present study reports on the clinical and pathological features, as well as the laboratory and immunofluorescence data of a patient who initially presented with chronic renal insufficiency, but was finally diagnosed with PSS.

Case presentation

A 32-year-old female presented at our hospital The Second Affiliated Hospital of Guangzhou University of Chinese Medicine (Guangzhou, China) in June 2017 with a 1-year history of elevated serum creatinine levels and a 6-month history of mild pain in the waist and leg. For >6 months prior to admission, the patient did not experience any symptoms/complaints including fever, dizziness, headache, cough, expectoration, nausea, vomiting, abdominal pain, diarrhea, hematuria, frothy urine, eyelid, facial or lower extremity edema. The patient had undergone a routine medical examination in June 2018 and ignored the result of blood creatinine levels of 229.0 μmol/l (normal range, 53-98 μmol/l). Thereafter, the patient was admitted to

the First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine (Guangzhou, China) in August 2017 for low back pain, and the laboratory test results indicated a creatinine level of 242.0 μmol/l, urea levels of 11.2 mmol/l (2.86-7.14 mmol/l), parathyroid hormone levels of 73.1 pmol/l (1-10.5 pmol/l), and total cholesterol level of 6.3 mmol/l (3-5.2 mmol/l); the other symptoms/complaints were similar to those observed previously. Furthermore, the presence of kidney stones was noted in a physical examination 1 year previously. The patient had no history of tuberculosis, type 2 diabetes, steroid use, traditional homeopathic remedies or herbal medications.

On admission to our hospital, the patient weighed 47.0 kg, had a body height of 160.0 cm and a body mass index of 18.3 kg/m^2. The patient's blood pressure and pulse were recorded as 123/77 mmHg and 86 beats/min. The patient was mildly anemic, but did not have any goiter or clinically palpable lymph nodes. Furthermore, no gynecomastia, striae or evidence of pruritus was noted. The patient's visual field was normal and no papilledema was detected. The other physical findings were unremarkable.

The laboratory test results on admission and during the follow-up period are presented in Table I. Twenty-four-hour urine output monitoring indicated stable fluctuations from 2,200 to 3,100 ml, and a urine osmolarity of 169.0 mOsm/kg H_2O (normal range, 280.0-310.0 mOsm/kg H_2O) was noted. Based on these results, tests for antinuclear antibodies (ANA; 1:100 granular pattern), along with other tumor, rheumatic disease and immune system markers, were performed, but the results were negative. Thus, the patient was initially diagnosed with severe chronic interstitial nephritis and chronic kidney disease stage IV. As the patient had a long history of xerostomia and dry eye syndrome, the presence of Sjogren's syndrome was suspected. To confirm this hypothesis, a kidney biopsy was performed. Routine clinical examination by specialist including comprehensive light microscopy, immunofluorescence and electron microscopy examination indicated the presence of severe chronic interstitial nephritis (Figs. 1-3), consistent with the biochemical indicators. Furthermore, kidney ultrasonography was performed (Fig. 4), which indicated an abnormal echo of the bilateral kidneys (consistent with sonographic changes in chronic kidney disease), as well as multiple calculi or calcifications in the bilateral kidneys. In addition, salivary gland scintigraphy indicated a decrease in left parotid uptake tracer function, as well as impairment of secretion and excretion. However, no abnormal uptake, secretion or excretion were observed in the right parotid gland and bilateral submandibular glands (Fig. 5).

Based on these results, the patient was diagnosed with severe chronic interstitial nephritis, stage IV chronic kidney disease, PSS and anemia due to chronic kidney disease. To address the PSS-associated chronic interstitial nephritis, the patient was subjected to continuous treatment with half-dose glucocorticoid. Given the presence of PSS, initial treatment involved prednisone (0.5 mg/kg/day), with subsequent slow tapering to 0.5-0.25 mg/kg/day, followed by addition of cyclophosphamide at doses of 800 mg/month over the next 6 months. A 12-month follow-up examination indicated significant improvement (Table I).

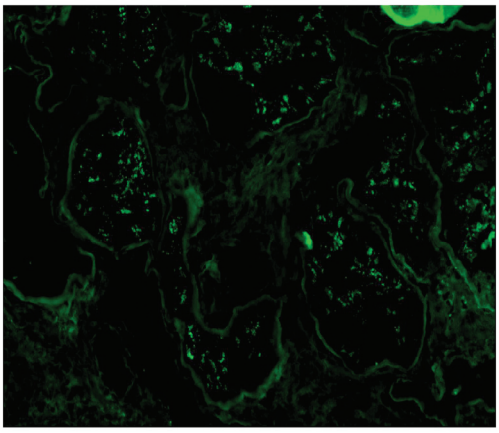

Figure 1. Immunofluorescence to clarify diagnosis. magnification, x400. κ, negative; λ, negative; amyloid A, negative; fibrin, negative; albumin, reabsorbed droplets visible in the renal tubules; IgG1, negative; IgG2, negative; IgG3, negative; IgG4, negative; phospholipase A2 receptor, negative; hepatitis B surface antigen, negative; hepatitis B e antigen, negative; hepatitis B core antigen, negative; C4d, glomeruli in the kidney (-); thrombospondin type 1 domain containing 7A, negative.

Discussion

PSS is a common condition involving various organs. The detection of autoimmune diseases with the exocrine gland as the target organ has improved with the advancements in detection methods and a better understanding of the disease (3). Accordingly, the rate of early detection and diagnosis in cases with PSS has also significantly increased. In particular, kidney damage as a result of PSS has been receiving an increasing amount of attention (4). PSS-associated renal damage may be asymptomatic or may present only as an electrolyte disorder. Furthermore, as the clinical manifestations of the disease in these patients are varied (including proteinuria, simple hematuria, combined hematuria and proteinuria, or nephrotic syndrome and renal insufficiency), and the prognosis is good, only a small number of clinical studies have focused on this condition thus far (5). Although the incidence of renal damage in PSS was previously thought to be low, recent studies indicated a rate of as high as 33.5% (2,6,7). Most cases exhibit renal tubular dysfunction, particularly involving the distal renal tubule. Prominent manifestations include distal renal tubular acidosis, renal diabetes insipidus and urinary concentration dysfunction, followed by glomerulonephritis and partial renal insufficiency (8). As there are no uniform diagnostic criteria for assessing renal damage in PSS patients with mild or no symptoms, the condition is overlooked in most of such cases. Only a small number of such patients exhibit renal failure at the time of visit, and hence, early diagnosis is particularly important.

It is recommended that patients with PSS are screened at least twice a year, including urine protein, urine pH, urine osmotic pressure, serum creatinine, glomerular filtration rate and electrolyte levels (9). The European League Against Rheumatism Sjogren's syndrome disease activity index may be used to assess renal disease activity during follow-up (10). Renal biopsy should be promptly performed, if required, in such cases, and the cause and extent of renal lesions may be determined via renal pathology examinations (11).

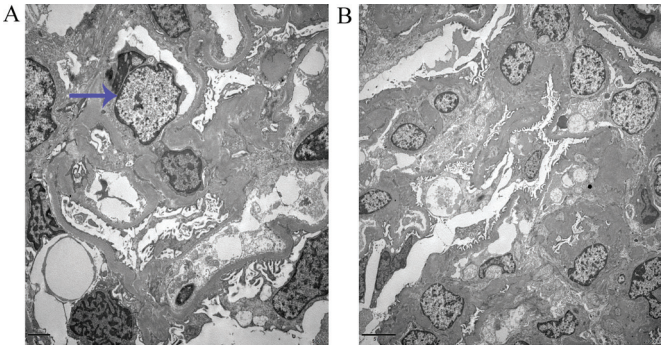

Figure 2. (A) Glomeruli: One glomerulus was detected by electron microscopy. A glomerulus with ischemic shrinkage was detected, and red blood cell aggregation and capillary loop opening were observed. There was no obvious thickening of the renal microcapsule wall layer, vacuolar degeneration of the parietal cells or obvious hyperplasia. There was no obvious basement membrane thickening (thickness, 250-410-nm), although segmental shrinkage was observed. The visceral epithelial cells were swollen and vacuolar degeneration was noted. Partial fusion of the foot processes, and mesangial cell and matrix proliferation were observed. No electron densification was noted. Magnification, x5,000. (B) The renal tubule interstitium exhibited partial tubular atrophy. Renal interstitial collagen proliferation with lymphoid and mononuclear cell infiltration was observed. In the renal interstitial vessels, red blood cell aggregation was noted in individual capillary lumens, and the arteriole walls were thickened. Magnification, x3,000.

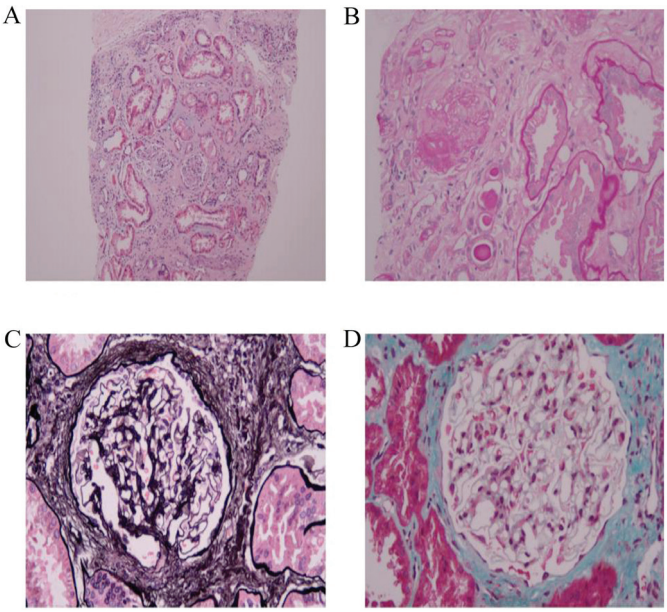

Figure 3. (A) Hematoxylin-eosin staining indicated extensive renal interstitial fibrosis with scattered inflammatory cell infiltration; (B) periodic acid-Schiff staining revealed sclerosis of the glomeruli. magnification, x100. (C) periodic Schiff-methenamine staining indicates that the capillary loops are open and the basement membrane is not thickened; (D) Masson staining reveals no apparent deposition of complexed erythropoietin in the glomeruli. magnification, x400.

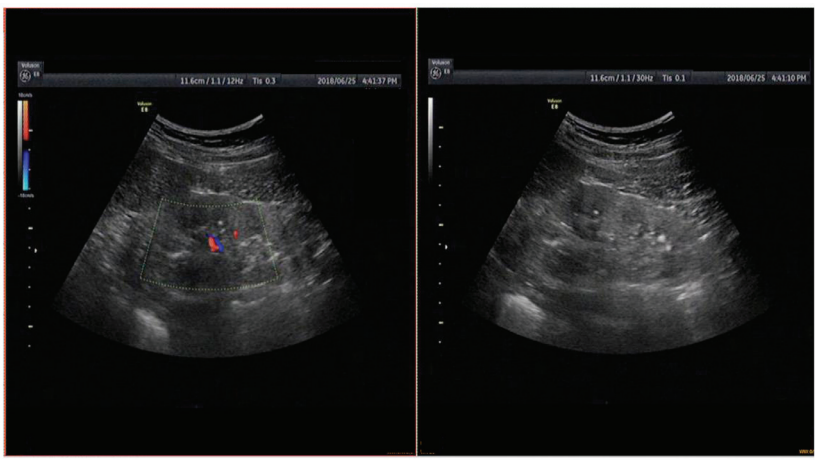

Figure 4. Abnormal echo of the bilateral kidneys (consistent with sonographic changes in chronic kidney disease) indicates multiple calculi or calcifications in the kidneys.

Table I. Laboratory results at presentation and during the follow-up period.

Clinical parameter[a]	First admission	1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
Blood							
Hemoglobin, g/l (115-150)	105	93	110	107	106	107	131
White blood cells, x10^9/l (4-10)	10.2	6.0	13.8	11.4	14.4	15.4	11.0
Platelets, x10^9/l (125-350)	320	204	320	246	283	288	245
Creatinine, μmol/l	221.3	172.4	231.8	180.7	160.0	171.4	178.7
eGFR, ml/min/1.73 m^2 (CKD-EPI)	24.6	33.2	23.2	31.4	36.4	33.4	31.8
K, mmol/l (3.50-5.30)	3.77	3.2	3.3	4.3	3.0	4.0	3.8
Na, mmol/l (137.0-147.0)	135.5	139.9	143.3	141.6	142.0	143.0	142
Cl, mmol/l (96.0-108.0)	106.9	110.9	105.9	102.4	103.4	104.4	103.8
PO_4, mmol/l (0.85-1.51)	1.4	-	-	-	1.2	1.4	1.1
Ca, mmol/l (2.11-2.52)	2.3	2.1	2.1	2.3	2.1	2.4	2.2
MG, mmol/l (0.75-1.02)	0.9	0.8	-	-	0.6	0.8	0.7
PTH, pg/ml (15-65)	475.1	-	-	-	371.5	-	267.4
ANA (Speckled)	+(1:100)				+(1:100)	-	+(1:100)
dsDNA (0.0-20.0)	13.5				21.8	-	14.9
Urine							
Ca, mmol/24 h (0.00-6.20)	1.04						
Protein, mg/24 h (<150)	453.6				383.4		118.4
ALB, mg/24 h (<30)	160.2				119.4		90.7
UPro:UCr mg/g (0.00-100.00)	2,990.3	412.1			385.2	581.0	121.7
ALBU:CrU mg/gCr (0.00-30.00)	1,797.3	109.1			122.9	203.7	82.3
Beta-2 microglobulin, mg/l (<0.4)	4.0	-	-	-	-	-	3.7
PH (4.5-8.0)	6.0		6.0	7.0	6.0	5.5	7.0
SG (1.003-1.030)	1.01	1.00	1.01	1.01	1.00	1.00	1.01

[a]The normal range for each laboratory variable is given in parentheses. K, potassium; Na, sodium; PO4, phosphate radical; Ca, calcium; MG, magnesium; eGFR, Estimation of glomerular filtration rate; Cl, chlorine; PTH, parathormone; ANA, antinuclear antibodies; DsDNA, double-stranded DNA; ALB, albumin; UPro, Urine protein; UCr, urine creatinine; SG, specific gravity.

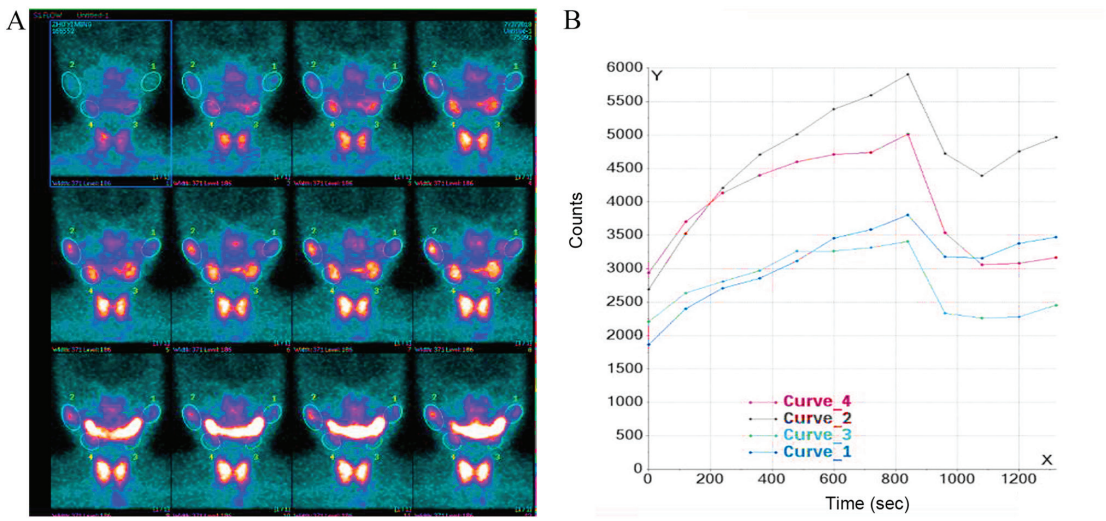

Figure 5. Bilateral parotid gland and submandibular gland. (A) Dynamic imaging of maxillofacial blood flow in the bilateral parotid gland and submandibular gland. (B) Line chart of radioactive distribution. On dynamic imaging of maxillofacial blood flow performed via intravenous injection of the imaging agent, no abnormal radioactivity distribution in the bilateral parotid gland and submandibular gland was observed. In brief, the salivary gland function was dynamically developed for 24 min, vitamin C tablets were ingested after 18 min, and bilateral and anteroposterior plane imaging was performed after gargling, along with delayed flank imaging of the salivary glands. No delay in bilateral parotid and submandibular gland radioactivity uptake was observed, although the right parotid gland and bilateral submandibular gland radioactivity uptake were abnormal but approximately symmetrical. After ingesting vitamin C tablets at 18 min, no obvious radioactivity clearance in the bilateral parotid gland or bilateral submandibular gland, or partial accumulation of radioactivity in the oral cavity was noted. The two sides of the parotid gland and submandibular gland were clearly developed and the distribution of the bilateral parotid gland radioactivity was sparse. Minimal radioactivity distribution was noted in the oral cavity, although this decreased after gargling and delayed imaging.

With regard to treatment, individualized therapy may be suitable, based on the patient's clinical manifestation and the type of renal damage. At present, treatment may be divided into local replacement therapy and systemic treatment (4,12). The present case was managed by low-dose hormone therapy and regular follow-up. The renal function was stable and did not deteriorate during follow-up, which indicated that the treatment was effective. However, it may be necessary to perform further detailed studies in order to better understand the disease mechanism, and large-sample multicenter randomized controlled trials should be performed to assess the efficacy and safety of drugs including hormones and immunosuppressants in these patients with different types of renal damage.

In the clinical setting, patients with kidney stones and renal insufficiency are frequently encountered, and it is likely that kidney dysfunction has led to stone obstruction in these cases. However, it is recommended that clinicians should also consider systemic diseases, including tumors, rheumatism and immune diseases, in such patients. Accordingly, careful assessment of the relevant medical history may help improve the diagnostic accuracy and avoid kidney failure.

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Availability of data and materials

The data used for the preparation of the manuscript, including all relevant raw data, are freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality. Available from the corresponding author upon reasonable request.

Authors' contributions

YY, BZ and JH prepared the manuscript, made substantial contributions to the design of the work and to revise it critically for important intellectual content. XJ and DD critically reviewed the manuscript for important intellectual content and approved the final manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The patient consented to participate and provided written informed consent.

Patient consent for publication

The patient agreed to the publication of their data and images.

Competing interests

The authors declare that they have no competing interests.

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