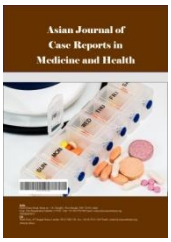

Asian Journal of Case Reports in Medicine and Health

6(2): 1-7, 2021; Article no.AJCRMH.73869

Interstitial Nephritis as the Initial Presentation of Sjogren's Syndrome: A Case Report with Review of Literature

Anirban Sen[1], Atanu Pal[1*], Ankit Ray[1], Koushik Bhattacharjee[1], Dipankar Sircar[1], Arpita Ray Chaudhury[1] and Debabrata Sen[1]

[1]Department of Nephrology, IPGMER & SSKM Hospital, Kolkata, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Hab. Mariusz Cycon, Medical University of Silesia, Poland.
Reviewers:
(1) Brian Mark Churchill, India.
(2) Nneka Chioma Okoronkwo, Abia State University, Nigeria.
(3) Mambap Tatang Alex, University of Bamenda, Cameroon.
Complete Peer review History: https://www.sdiarticle4.com/review-history/73869

Case Report

Received 11 July 2021
Accepted 21 September 2021
Published 25 September 2021

ABSTRACT

Primary Sjögren's syndrome is a rare autoimmune condition affecting the exocrine glands. However, extra-glandular manifestations are not uncommon and may present as the initial symptoms of this disorder. Such cases offer a great challenge to clinicians. Here we present a case of primary Sjögren's syndrome, which presented with incidentally detected renal dysfunction which on investigation revealed distal renal tubular acidosis and tubulointerstitial nephritis. The patient responded to combined therapy of steroid and rituximab and is currently having a stable renal function.

Keywords: Interstitial nephritis, Sjögren Syndrome, extra-glandular features, distal renal tubular acidosis.

ABBREVIATIONS

PSS: Primary Sjögren's Syndrome
TIN: Tubule-Interstitial Nephritis
RTA: Renal Tubular Acidosis
CT: Computed Tomography
PNS: Paranasal Sinus
MRI: Magnetic Resonance Imaging

**Corresponding author: E-mail: dratanupal7@gmail.com;*

IFTA: Interstitial Fibrosis And Tubular Atrophy

1. INTRODUCTION

Primary Sjögren's syndrome (PSS) is an autoimmune condition involving chronic inflammation and lymphocytic infiltration of exocrine glands and extra-glandular tissues [1]. Extra-glandular involvement in PSS falls into two categories: first the periepithelial infiltration in the form of interstitial nephritis, bronchiolitis, and liver involvement, and second the extraepithelial extra-glandular involvement like hypergammaglobulinemia, palpable purpura, glomerulonephritis, and peripheral neuropathy [2]. Tubulointerstitial nephritis (TIN) along with tubular dysfunction is the most common renal involvement associated with PSS but usually occurs late in the disease course [3]. However, predominantly renal symptoms in absence of ocular or oral manifestation have been reported in some cases [4,5,6]. Here we present a case of a 50-year-old female who first presented with incidentally detected renal dysfunction, which on evaluation turned out to be renal tubular acidosis (RTA) and TIN and further workup led to the diagnosis of PSS.

2. CASE PRESENTATION

A 50-year-old, non-diabetic, non-hypertensive, female was referred by the local physician to nephrology outdoor because of incidentally detected rise in serum creatinine. The patient was asymptomatic except for the feeling of fatigue for the last 1 year. She did not have any history of decreased urine output, frothy urine, oedema, joint pain, rash, oral ulcers, alopecia or any over-the-counter medicine use. In her past medical history, she was prescribed potassium citrate supplementation by a local physician 3 years back due to hypokalaemia, which she took for 3 months, but then did not turn up for follow-up. She had no significant family history of any renal or autoimmune disorder.

Her vital signs were normal, and physical examination did not reveal any significant finding. Her routine investigations revealed, sodium 136 mmol/L, potassium 2.2 mmol/L, chloride 104 mmol/L, bicarbonate 19 mmol/L, urea 44 mg/dL, creatinine 2.1 mg/dL, hemoglobin 9.1 mg/dL, total serum protein 6.7 gm/dL and albumin 3.4 gm/dL. Her arterial blood gas revealed pH 7.28, Po2 66 mmHg and Pco2 38 mmHg. These investigations were suggestive of normal anion gap metabolic acidosis with hypokalaemia. Her urine pH was 6.0 and spot urine sodium was 68 mmol/L, urine potassium 42 mmol/L, urine chloride 59 mmol/L, indicating a positive urine anion gap of 51 mmol/L. Normal anion gap Metabolic acidosis in absence of diarrhoea together with defective renal acid secretion and hypokalaemia supported diagnosis of distal RTA.

Routine urine microscopy and urine culture were normal, 24-hour urine protein estimation was 433 mg/24 hours. Ultrasonography revealed bilateral normal-sized kidneys with normal cortical echogenicity and maintained cortico-medullary differentiation. Serum protein electrophoresis and free light chain assay were normal. Her immunological workup is listed in Table 1.

Table 1. Results of immunological workup

Anti-nuclear antibody (ANA)	**Positive, 4+ intensity, coarse speckled pattern**
Anti double-stranded DNA (dsDNA)	Negative
Anti-Smith	Negative
Anti Sjogren's syndrome-related Antigen A (Anti-SS-A)	Positive, 3+ intensity
Anti Sjogren's syndrome-related Antigen B (Anti-SS-B)	Positive, 3+ intensity
Anti-ribonucleoprotein (Anti-RNP)	Negative
Anti-topoisomerase (Anti-SCL)	Negative
Anti-Jo	Negative
Anti-myeloperoxidase antibody (Anti-MPO)	Negative
Anti-proteinase 3 antibody (Anti-PR3)	Negative
Anti-Glomerular basement membrane (Anti-GBM)	Negative
Complement 3 (g/L)	1.10 (0.9-1.80 g/L)
Complement 4 (g/L)	0.23 (0.10-0.40 g/L)
Rheumatoid Factor	Negative
Serum Immunoglobulin A (IgA)	1.68 (0.87-3.94 g/L)
Serum Immunoglobulin G (IgG)	23.7 (5.5-17.2 g/L)
Serum Immunoglobulin M (IgM)	0.98 (0.37-2.86 g/L)

On repeat history taking, she informed having dryness of mouth for the last 6 months and the symptoms relieved by frequently drinking small sips of water along with occasional foreign body sensation in both eyes for the last 3 months. Schirmer's test was performed by an ophthalmologist without topical anaesthesia to measure basal and reflux tear amount and the result was 4mm in the left eye and 7mm in the right eye after 5 minutes. A lip biopsy was done and the report was normal. Based on positive anti-SS-A and anti-SS-B antibodies and positive Schirmer's test in presence of sicca symptoms, diagnosis of PSS was made.

Because of persistent renal dysfunction and proteinuria, a renal biopsy was performed. Light microscopy revealed glomeruli having focal dilatation, congestion of capillary lumina, occasional intra-glomerular lymphocytic infiltration and non-proliferative morphology (Fig. 1 and 2). No evidence of segmental sclerosis, tuft necrosis, congophilic deposition, or crescent formation was seen. Diffuse lymphocytic interstitial infiltration and inflammation are noted. The lymphocytic cells were mainly CD3 positive T cells with sparsely CD20 positive B cells (Fig. 3). Tubules show focally prominent cytoplasmic vacuolar change and scattered hyaline cast in the lumen. Tubular atrophy and interstitial fibrosis (IFTA) involved around 30% of the sampled cortex. Immunofluorescent microscopy was negative for immunoglobulin G, M, A, C3, C1q, Kappa, and Lambda light chains. Electron microscopy revealed normal glomerular architecture, normal glomerular basement membrane and no electron-dense deposits. The biopsy was suggestive of chronic interstitial nephritis.

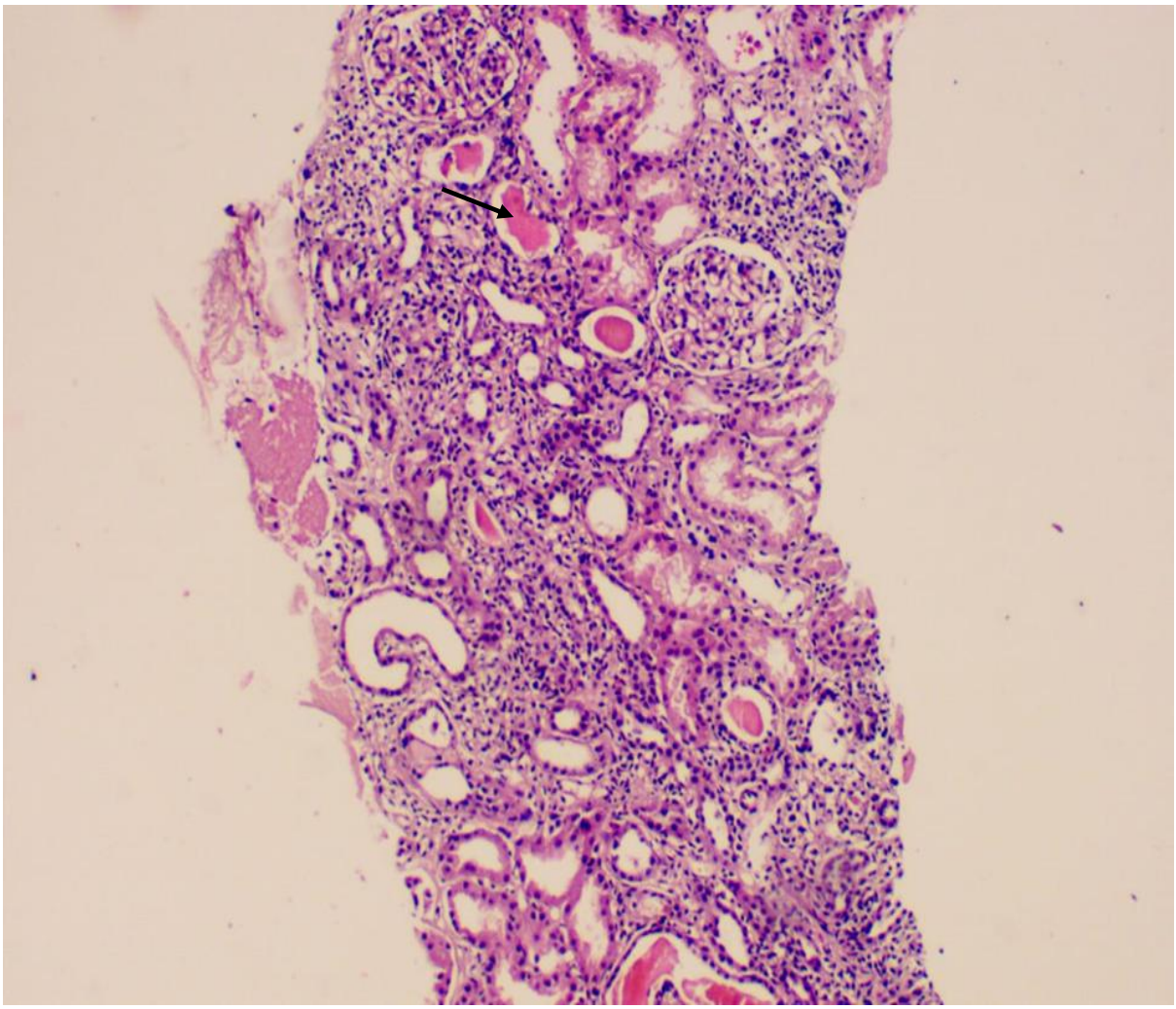

Fig. 1. Light microscopy showing diffuse and intense lymphocytic infiltration of the interstitium along with hyaline cast in the tubular lumen [black arrow]

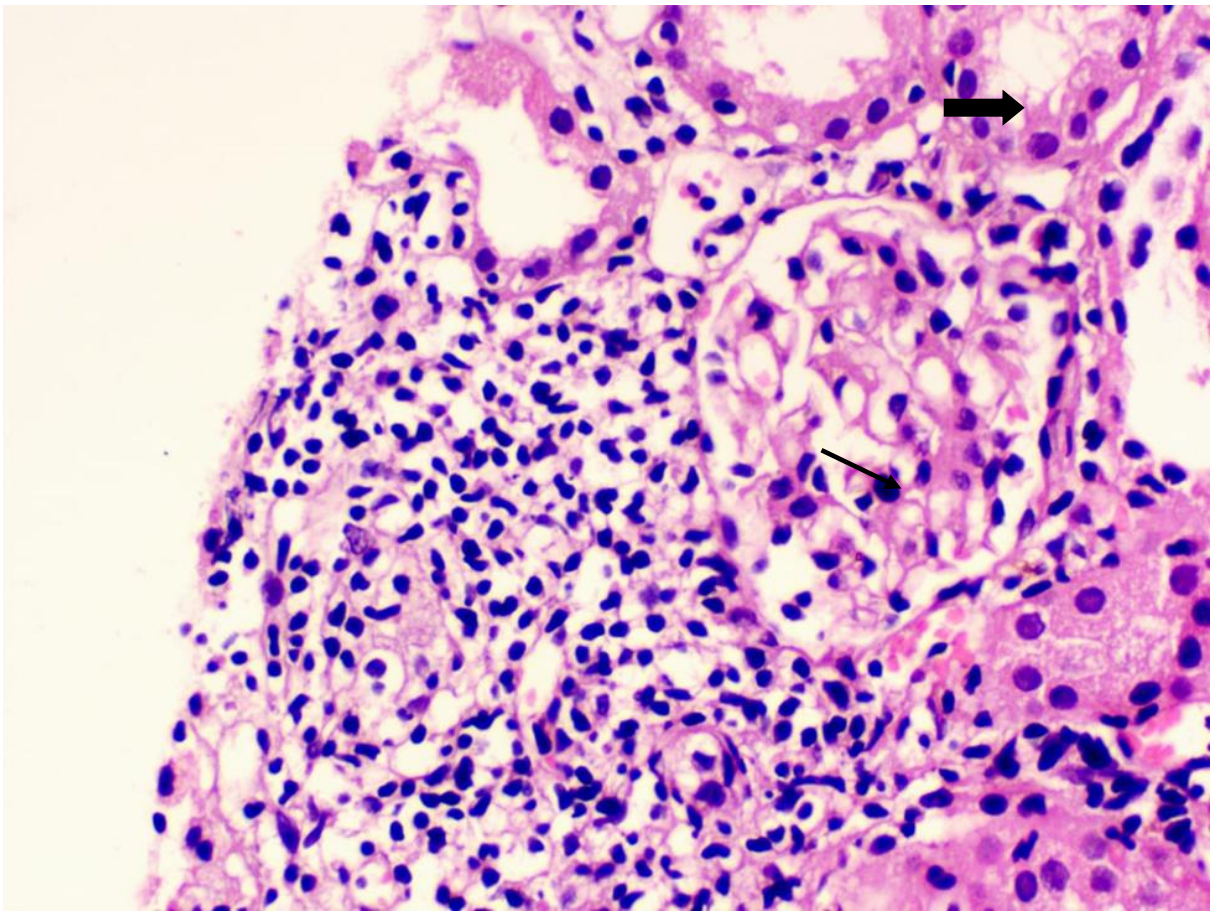

Fig. 2. Light microscopy in high resolution showing intraglomerular lymphocytes [thin arrow] with cytoplasmic vaccuolar changes of the tubular cells [thick arrow]

Computed tomography of chest and PNS, Magnetic Resonance Imaging of brain and nerve conduction study of all four limbs were done to look for other extra-glandular involvement, but were normal.

The patient was initially treated with oral prednisolone at a dose of 1 mg/kg body weight with oral potassium citrate supplementation and artificial tear-drops. When extra-glandular involvement in the form of interstitial nephritis was proven, a second immunosuppressant was added. She was given two doses of intravenous rituximab, 1 gram each, at an interval of 2 weeks apart. Her serum creatinine gradually declined to 1.1 mg/dL and follow-up at six months post-therapy showed stable serum creatinine of 1.2 mg/dL with serum potassium 3.9 on oral supplementation.

3. DISCUSSION

SS is an autoimmune disorder involving both glandular and extra-glandular tissues [1]. Lymphocytic infiltration of salivary and lacrimal glands causes characteristic symptoms of xerosis and xerostomia, whereas infiltration of the kidney, lungs, gastrointestinal tract, and central/peripheral nervous system can cause a variety of atypical manifestations.

Renal manifestation in absence of sicca syndromes is rare in PSS and only few case reports have been published where patients presented with hypokalaemic periodic paralysis, renal tubular acidosis, and renal dysfunction prior to the onset of overt sicca syndromes [4,5,6]. Diagnosis of PSS becomes very challenging in such scenarios and can be delayed for months to years. According to the American-European Consensus Classification Criteria requires the presence of either ocular or oral dryness and a total score of four or more when the weights from the five criteria are summed [7]. Our patient had dry eyes and mouth, positive anti-SS-A, and positive Schirmer test (total score of 4), which led to a diagnosis of PSS. But since sicca syndrome was not the initial presentation in our patient, the diagnosis and initiation of therapy were delayed.

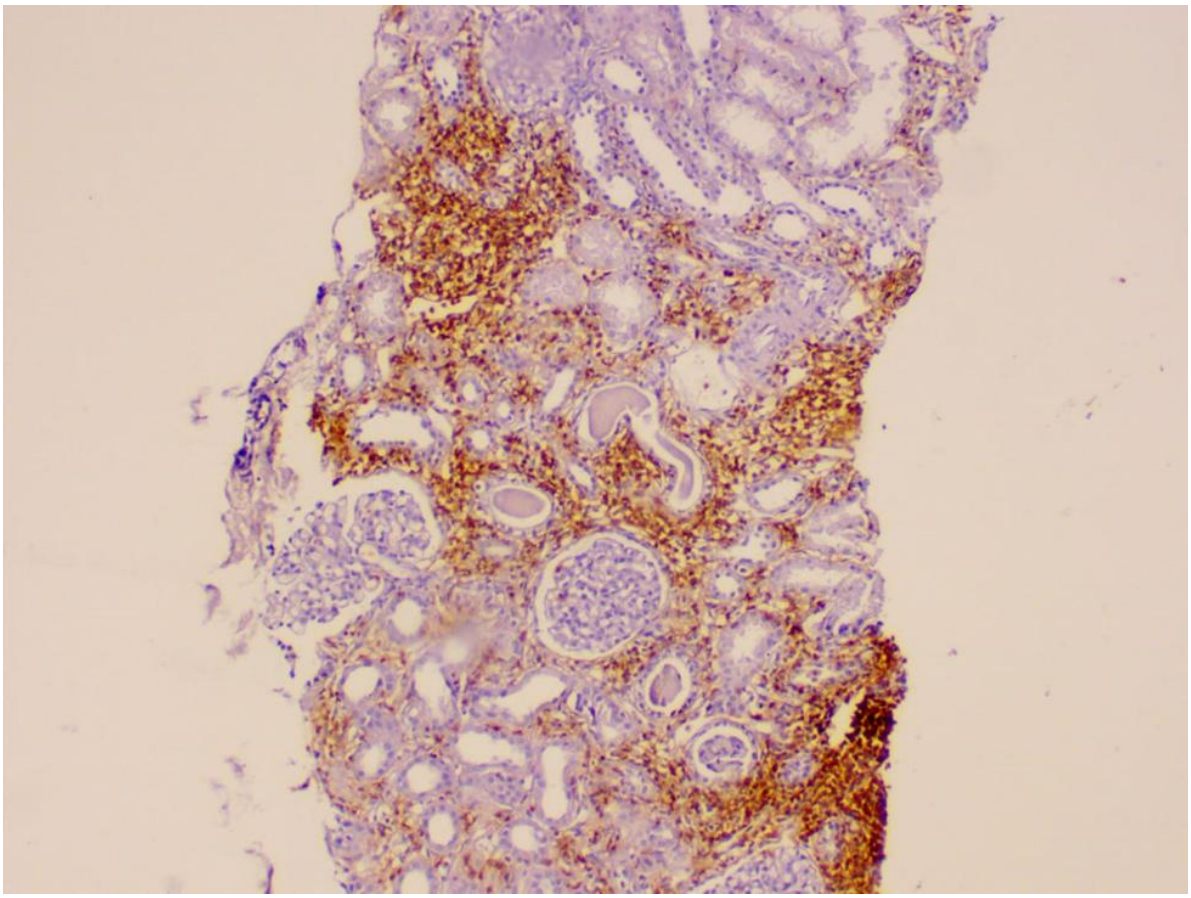

Fig. 3. Immunohistochemistry showing CD3 positive T cells (brown staining areas) infiltrating the interstitium

Extra-glandular manifestations of PSS can occur in up to 25% of patients and can include interstitial lung disease, cutaneous vasculitis, peripheral neuropathy, lymphoma, celiac sprue, and renal involvement. [3].

Clinically significant renal manifestations can be seen in 5% of primary Sjogren's syndrome [8]. TIN is the most common renal manifestation of PSS along with tubular dysfunction which is characterized by distal and less commonly proximal renal tubular acidosis, Gittelman syndrome, hypokalaemia, nephrolithiasis, and nephrocalcinosis [3,9]. In addition, glomerulonephritis and nephrogenic diabetes insipidus can also be seen. Our patient had a history of incidentally detected hypokalaemia 3 years ago which was not evaluated, hence distal Renal Tubular Acidosis could not be picked up early. The exact pathogenic mechanism of renal tubular acidosis is not completely understood but autoantibodies against anion exchanger-1, vacuolar H+-ATPase, and carbonic anhydrase II, have been implicated in the pathogenesis [10,11,12].

Renal biopsy is not indicated for the diagnosis of PSS, but was performed in our case as the patient had renal dysfunction. The most common biopsy finding is TIN with CD4/CD8 T cell predominant infiltration, which is found in almost 80% of the patients [13]. The second most common biopsy findings are various types of glomerular disease like membranous nephropathy, membranoproliferative glomerulonephritis, mesangial proliferative glomerulonephritis, focal crescentic glomerulonephritis, and focal segmental glomerulosclerosis [8,14]. Our patient had TIN, which had progressed to significant chronicity (IFTA 30%), but the glomeruli were spared, hence the patient had minimal non-specific symptoms.

The treatment of PSS mainly aimed at reducing the ocular and oral symptoms. As per guidelines of Sjögren's syndrome Foundation and British Society of Rheumatology, treatment with corticosteroids with or without a second immunosuppressive drug is offered in case of moderate to severe extra-glandular presentation

[15]. In our case since the patient had biopsy-proven TIN with significant renal dysfunction, we decided to start treatment with prednisolone and chose Rituximab as the second immunosuppressive drug in view of lesser nephrotoxicity and better patient compliance. Our patient responded to the therapy and is currently having a stable renal function with minimal sicca symptoms.

4. CONCLUSION

Extra-glandular renal manifestations in absence of ocular or oral symptoms are not uncommon presentations of PSS and clinicians must remain vigilant to diagnose such cases. Patients with idiopathic distal RTA should be thoroughly worked up for Sjögren's syndrome. Early detection and initiation of immunosuppressive therapy can prevent progression to chronic kidney disease in such patients and can improve their quality of life.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

"All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal."

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, *et al*. Classification criteria for Sjögren's syndrome: A revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis. 2002;61:554–8. DOI:10.1136/ard.61.6.554
2. Tzioufas AG, Voulgarelis M. Update on Sjögren's syndrome autoimmune epithelitis: from classification to increased neoplasias. Best Pract Res Clin Rheumatol. 2007;21(6):989-1010.
3. Maripuri S, Grande JP, Osborn TG, Fervenza FC, Matteson EL, Donadio JV, *et al*. Renal involvement in primary Sjögren's syndrome: a clinicopathologic study. Clin J Am Soc Nephrol. 2009;4:1423–31. DOI:10.2215/CJN.00980209
4. Sedhain A, Acharya K, Sharma A, Khan A, Adhikari S. Renal Tubular Acidosis and Hypokalemic Paralysis as a First Presentation of Primary Sjögren's Syndrome. Case Rep Nephrol. 2018; Article ID 9847826. DOI:10.1155/2018/984782
5. Yu Y, Zheng B, Huang J, Deng D, Jing X. Case report on a 32-year-old female with elevated serum creatinine levels and primary Sjögren's syndrome-chronic interstitial nephritis. Exp Ther Med. 2019; 18(6):4363-4367.
6. Garza-Alpirez A, Arana-Guajardo AC, Esquivel-Valerio JA, Villarreal-Alarcón MA, Galarza-Delgado DA. Hypokalemic Paralysis due to Primary Sjögren Syndrome: Case Report and Review of the Literature. Case Rep Rheumatol. 2017; Article ID 7509238. Available:https://doi.org/10.1155/2017/7509238
7. Shiboski SC, Shiboski CH, Criswell LA, Baer A, Challacombe S, Lanfranchi H, et al. American College of Rheumatology classificationcriteria for Sjogren's syndrome: a data-driven, expert consensus approach in the Sjogren's International Collaborative Clinical Alliance Cohort. Arthrit Care Res. 2012;64:475-487.
8. Goules AV, Tatouli IP, Moutsopoulos HM, Tzioufas AG. Clinically significant renal involvement in primary Sjogren's syndrome: clinical presentation and outcome. Arthritis Rheum. 2013;65(11): 2945-53.

9. Shioji R, Furuyama T, Onodera S, Saito H, Ito H, Sasaki Y: Sjogren's syndrome and renal tubular acidosis. Am J Med. 1970; 48:456–63.
10. Bastani L, Haragsim S, Gluck KC. Siamopoulos. Lack of h-atpase in distal nephron causing hypokalaemic distal rta in a patient with sjögren's syndrome. Nephrol Dial Transplant. 1995;10(6):908-9.
11. Takemoto F, Hoshino J, Sawa N, Tamura Y, Tagami T, Yokota M, et al. Autoantibodies against carbonic anhydrase II are increased in renal tubular acidosis associated with Sjögren syndrome. Am J Med. 2005;118(2):181–84.
12. DeFranco PE, Haragsim L, Schmitz PG, Bastani B, Li JP. Absence of vacuolar H+-ATPase pump in the collecting duct of a patient with hypokalemic distal renal tubular acidosis and Sjögren's syndrome. J Am Soc Nephrol. 1995;6(2):295–301.
13. Ren H, Wang WM, Chen XN, Zhang W, Pan XX, Wang XL, et al. Renal involvement and follow up of 130 patients with primary Sjögren's syndrome. Rheumatol. 2008;35(2):278-84.
14. Goules A, Masouridi S, Tzioufas AG, Ioannidis JP, Skopouli FN, Moutsopoulos HM, et al. Clinically significant and biopsy-documented renal involvement in primary Sjögren syndrome. Medicine. 2000;79(4): 241-9.
DOI:10.1097/00005792-200007000-00005.
15. Price EJ, Rauz S, Tappuni AR, Sutcliffe N, Hackett KL, Barone F, et al. The British Society for Rheumatology Guideline for the management of adults with primary Sjogren's Syndrome. Rheumatol. 2017;56:1643-7.
DOI: 10.1093/rheumatology/kex166.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/73869