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Renal Involvement in Sjögren Syndrome: A Case Report

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Abstract **Case Report**

Sjögren syndrome (SS) is an autoimmune disorder that characterized by chronic inflammation of exocrine glands. However extra-glandular involvement is sometimes observed. The onset of Sjögren syndrome is insidious and its clinical manifestations are extremely diverse. Lymphocytic infiltration and tissue damage of the affected organs are the histopathological features in Sjögren syndrome. In the cases of renal involvement, tubulointerstitial nephritis (TIN) followed by glomerulonephritis are frequently found in renal biopsies. The prognosis of glomerular disease in Sjögren syndrome is usually favorable but the risk of developing chronic kidney disease (CKD) is remains high among patients with TIN.

Keywords: Autoimmune Disorder, Glomerulonephritis, Renal Involvement, Sjögren Syndrome.

INTRODUCTION

Sjögren syndrome (SS) is a rare autoimmune disorder that may occur alone (as primary Sjögren syndrome) or sometimes associated with other autoimmune diseases like- systemic lupus erythematosus (SLE), rheumatoid arthritis [1]. It is characterized by chronic inflammation of exocrine glands like lacrimal and salivary glands, which typically manifest as dry eyes and dry mouth [1]. However, extra-glandular involvement in Sjögren syndrome is not uncommon, particularly kidneys and liver are often affected [2, 3]. Typically, Sjögren syndrome affects middle aged women but children, adult male and elderly person also may affect [4, 5]. It was reported that Sjögren syndrome affects approximately 0.05% to 0.23% of the adult population [5]. Histologically, Sjögren syndrome is characterized by infiltration of lymphocytes along with aggressive tissue damage in the affected organs [6]. Usually, patients with Sjögren syndrome have cryoglobulinemia and low serum complement levels which have a high risk of developing lymphoma and/or glomerulonephritis [7]. Renal involvement in Sjögren syndrome is a rare complication affecting around 10% of all patients with Sjögren syndrome and tubulointerstitial nephritis (TIN) is the commonest histological abnormality in renal biopsies followed by glomerulonephritis secondary to cryoglobulinemia [5, 7]. Electrolyte disturbances are common as renal distal tubular acidosis may occur in Sjögren syndrome [7]. The prognosis of glomerular disease in Sjögren syndrome is usually favorable but the risk of developing chronic kidney disease (CKD) is remains high among patients with TIN [7]. The onset of Sjögren syndrome is insidious and its clinical manifestations are extremely diverse, therefore Sjögren syndrome is misdiagnosed and often missed. Herein we repot a case of Sjögren syndrome that had renal involvement.

CASE REPORT

A-28- years old female presented with dry eye and dry mouth along with swelling of leg for 6 months

and recurrent abdominal pain for last 8 months. She has developed dryness of mouth, which is- insidious in onset, gradually progressive, initially patient needs water to swallow dry food but gradually the dryness is so severe that she needs water to swallow any type of foods. She also complains of dryness of eye which is evidenced by occasional foreign body sensation and redness of eyes. She has developed swelling of legs for 6 months, which was- recurrent, mild, and gradual in onset more marked in the morning. She has passage of frothy urine with mild reduction in volume of urine; the colour of urine was normal but that was not foul smelling. She also complaints of occasional abdominal pain for 8 months which was mostly around umbilicus, colicky in nature, mild to moderate intensity, persists for few minutes to hours, not related to food intake, sometimes relieved by defecation. She gives history of dyspareunia for 1 year. She also gives history of oral ulceration for 4 years which was present on the dorsal surface of the tongue and that was painless. She had history of recurrent parotid swelling since 2016 and treated by local physician with analgesics but there was no improvement. On query, she had history of fetal loss at 32 weeks of gestation in 2016. She had a history of acute calculus cholecystitis and underwent laparoscopic cholecystectomy on August 2023. After evaluation in hospital, she was diagnosed as a case of suspected Sjögren syndrome along with renal tubular acidosis type1 (hypercholraemic normal anion gap metabolic acidosis), hypokalemia, with renal impairment. Her renal biopsy was done to evaluate the renal impairment. She had no history of such type of illness (auto-immune disease) in her family.

On examination, all vital signs of the patient were found within normal limit and her higher mental functions were intact. She was not pale rather ill-looking. Her oral cavity was dry and oral ulceration was present on the dorsal surface of the tongue and that was painless, she had mild leg oedema and no lymphadenopathy. Her musculo-skeletal, alimentary, cardiovascular, respiratory and nervous system examinations reveal no abnormality. Her temperature was 98.6°F, blood pressure was 120/80 mm of Hg, pulse rate 72 beat per minute, respiratory rate 16 breaths per minute, but her bed-side deep stick urine test was found positive for protein.

Initial laboratory investigation revealed that her haemoglobin level was 11.6 gm/dl, serum creatinine was 1.92 mg/dl, on serum electrolytes analysis; sodium (Na^+) was- 134 mmol/L, potassium (K^+) was- 2.8 mmol/L, chloride (Cl^-) was- 104 mmol/L and total carbon dioxide (TCO_2) was- 14 mmol/L; her serum albumin level was- 31 mg/dl (Table- 1). Urine routine microscopic examination showed specific gravity was 1.010, P^H was 7.0, RBC- nil/HPF, WBC- 4-8/HPF, sugar- nil, protein- 1+, cast- nil. Her urinary protein was 35.0 mg/dl, urinary creatinine was 51.7 mg/dl and urinary protein creatinine ratio was 0.68. While her urine electrolytes analysis revealed that; 24 hours urinary sodium (Na^+) was- 113.4 mmol/L, 24 hours urinary potassium (K^+) was- 54.6 mmol/L, 24 hours urinary chloride (Cl^-) was- 149.1 mmol/L, 24 hours urinary total protein was 1.2 gm/24 hours and 24 hours total urinary volume was 1600 ml (Table- 2).

Table-1: Laboratory investigations of the patient

Tests	Results	Reference range
Haemoglobin (gm/dl)	11.6	13-17 (male); 11.5-16 (female)
Serum creatinine (mg/dl)	1.92	0.6-1.3
Na^+ (mmol/L)	134	135-145
K^+ (mmol/L)	2.8	3.5-5.5
Cl^- (mmol/L)	104	95-107
T-CO_2 (mmol/L)	14	22-30
Serum albumin (mg/dl)	31	35-45

Table-2: Urine examination findings of the patient

Tests	Results	Reference range
Urine specific gravity	1.010	1.010-1.030
Urine P^H	7.0,	5-7.5
Urinary protein (mg/dl)	35.0	0-14
Urinary creatinine (mg/dl)	51.7	0.5-1.2
Urinary protein creatinine ratio	0.68	<0.2
24 hours urinary sodium (mmol/L)	113.4	39-258
24 hours urinary potassium (mmol/L)	54.6	60-80
24 hours urinary chloride (mmol/L)	149.1	38-210
24 hours urinary total protein (gm/24 hours)	1.2	<0.02

On arterial blood gas (ABG) analysis; P^H- was 7.342, PCO_2 was- 28.2 mmHg, PO_2 was- 111 mmHg, TCO_2 was- 16.2 mom/L, HCO_3 was- 15.3 mmol/L. Serological marker of autoimmune panel showed that

her anti nuclear antibody (ANA) was strongly positive but anti-double stranded DNA (anti-ds DNA) antibody was negative, while pANCA, cANCA, complements (C_3 and C_4) levels were within normal limits. Analysing an extractable nuclear antigen (ENA) profile showed U1-SM/RNP positive, SS-A/RO positive and SS-B/LA positive suggested to Sjögren syndrome (Figure-1).

Her ammonium chloride loading test was done that revealed urine pH remained 7; indicated an inability to acidify the urine in spite of a low serum HCO_3. Her unstimulated salivary flow test and schrimer's tests were positive, which goes in favour of Sjögren syndrome (Figure-2).

Her thyroid function tests were within normal limits. Her X- ray chest and X-ray KUB region revealed no abnormality. No other abdominal organ abnormality except slightly echogenic kidneys on whole abdomen ultrasonography indicated early renal parenchymal disease (Figure 3A, 3B). Erosive gastritis was detected in her upper gastrointestinal endoscopy but colonoscopy finding was normal (Figure-4). Her renal biopsy was done following standard procedure that reveled diffuse membranoproliferative glomerulonephritis (Figure-5).

Her viral markers for hepatitis B and hepatitis C were negative. Her coagulation profile was within normal limits. Her routine liver function tests were within physiological limits. Her electrocardiogram (ECG) and echocardiography yielded with normal findings.

She was treated with tablet mycophenolate mofetil 500 mg 12 hourly and oral prednisolone 30 mg daily along with other supportive management.

ENA PROFILE

Slip ID : 1,025
Patient Name : [redacted]
Ref By :

Specimen Receiving Date : 27-Feb-2023
Report Delivery Date : 28-Feb-2023
Sex : F **Age** : 28 Y, 0 M, 0 D

Specimen : Bood
Test Advised : ENA Profile
Method : LIA

Test Name		Result	Reference
ENA Profile	Nucleosome	Negative	
	Histone	Negative	
	SmD1	Negative	
	U1-SM/RNP	Positive	
	SS-A/Ro60KD	Positive	
	SS-A/Ro52KD	Positive	
	SS-B/La	Positive	
	Scl70	Negative	
	CENP-B	Negative	
	Jo-1	Negative	
	Po (RPP)60	Negative	
	PCNA	Negative	
	PM-Scl	Negative	
	Mi-2	Negative	
	Ku	Negative	
	AMA-M2	Negative	

Figure-1: Extractable nuclear antigen (ENA) profile of the patient

DEPARTMENT OF RHEUMATOLOGY

বঙ্গবন্ধু শেখ মুজিব মেডিক্যাল বিশ্ববিদ্যালয়

Bangabandhu Sheikh Mujib Medical University

Shahbagh, Dhaka -1000.

Tel: 8611307, PABX: 86145 45-9 / 4237, 4640

Name of the Patient: [redacted]		Date: 02 / 10 /23
Age: 28 years	Sex: Female	Reg: 2023021002

Unstimulated Salivary Flow: 0.014 ml/min

Interpretation: Positive

Unstimulated Salivary Flow rate ≤ 0.1 ml/ min is considered as indicator for salivary hypofunction

Schirmer's Test:

Schirmer's test	
Right Eye	Left Eye
03 mm/ 5 min	02 mm/ 5 min

Interpretation: Positive

Schirmer's test ≤ 5 mm / 5min in at least one eye is considered as objective marker of dry eye.

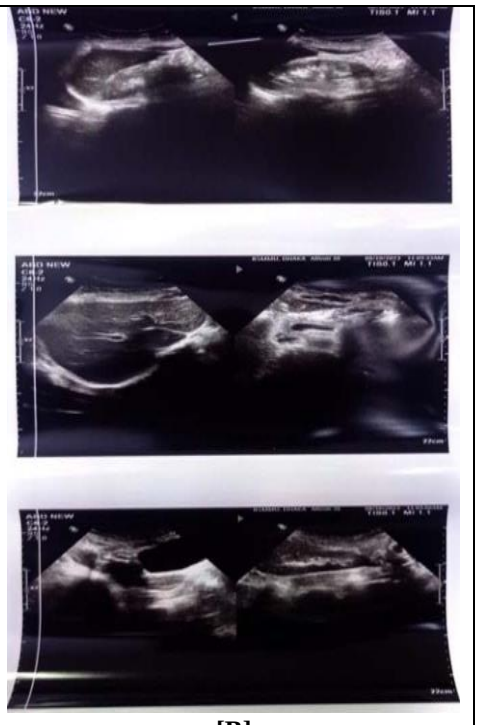
Figure-2: Unstimulated salivary flow test and schrimer's test findings of the patient

ULTRASONOGRAM REPORT

Id no :	125783		08/Oct/2023		
Patient Name:	[redacted]	AGE:	28	YRS	SEX: F
Examined :	USG OF WHOLE ABDOMEN				

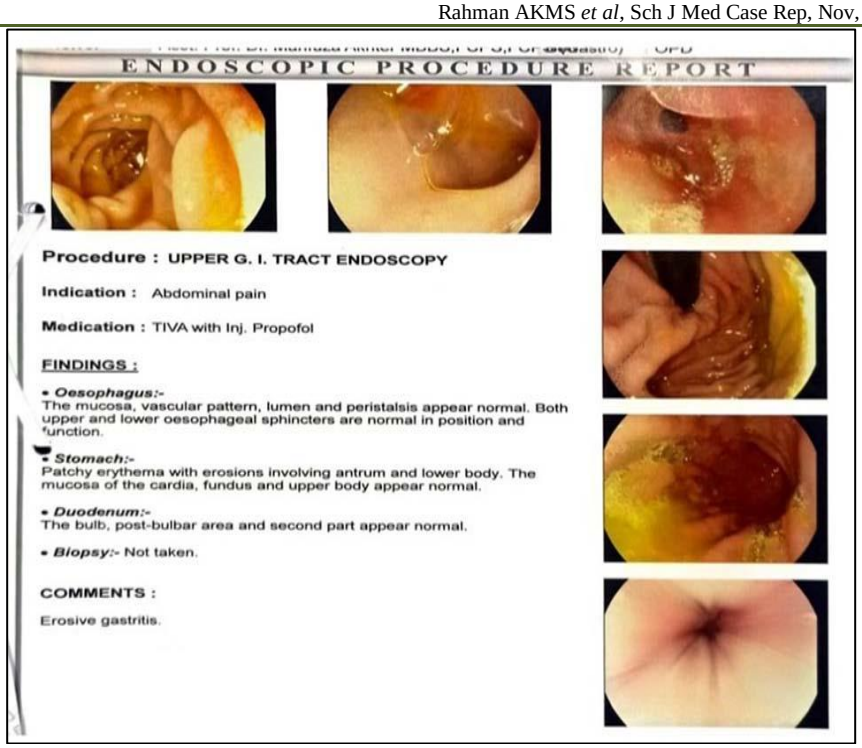
Liver	:	Liver is normal in size with homogeneous in echotexture. No focal lesion is seen in the liver.
Biliary channel	:	Intra hepatic biliary channel are not dilated.
CBD	:	CBD is not dilated.
Gall bladder	:	Is not visualized (H/O operation)
Pancreas	:	Pancreas is normal in size. MPD is not dilated.
Spleen	:	Normal in size & uniform echopattern.
Both Kidneys	:	Both kidneys are normal in size & shape. **Cortical echogenicity is increased. Cortico medullary differentiation is maintained.** Pelvicalyceal systems of both kidneys are not dilated.
Urinary bladder	:	Well-filled & regular in outline. No intravesical calculus is seen.
Uterus	:	Normal in size & anteverted in position with uniform is myometrial echotexture. No focal lesion is seen. Uterine cavity is empty.
Adnexae	:	Both adnexal regions are normal.
Cul-de-sac	:	No fluid collection is noted in the cul-de-sac.
Impression	:	**Bilateral early renal parenchymal disease.**

[A]



[B]

Figure-3: Whole abdomen ultrasonogram report of the patient [A, B]



ENDOSCOPIC PROCEDURE REPORT

Procedure : UPPER G. I. TRACT ENDOSCOPY

Indication : Abdominal pain

Medication : TIVA with Inj. Propofol

FINDINGS :

- ***Oesophagus:-***
The mucosa, vascular pattern, lumen and peristalsis appear normal. Both upper and lower oesophageal sphincters are normal in position and function.
- ***Stomach:-***
Patchy erythema with erosions involving antrum and lower body. The mucosa of the cardia, fundus and upper body appear normal.
- ***Duodenum:-***
The bulb, post-bulbar area and second part appear normal.
- ***Biopsy:-*** Not taken.

COMMENTS :

Erosive gastritis.

Figure-4: Upper gastrointestinal endoscopy finding of the patient

Renal Biopsy Report

Specimen: K-939/23: Renal tissue for histopathology, DIF-1026/23: Renal tissue for DIF

Gross description:

K-939/23: Specimen was received in formalin with proper patient's identification and consists of two cores of renal tissue, the larger one is measuring 1.8 cm in length. Embedded as such in one block.

Microscopic description: (H&E and PAS stains)

Sections reveal two cores of renal medulla and cortical tissue containing 23 glomeruli. All glomeruli are enlarged and hypercellular with mild to moderate degree of mesangial hypercellularity with increase of mesangial matrix and infiltration of few neutrophils. There is moderate thickening of capillary basement membrane. No histologic evidence of crescent formation, tuft necrosis or intracapillary thrombi is present.

Renal tubules reveal mild cytoplasmic vacuolar change with patchy acute tubular injury. Scattered hyaline granular casts are also present in some renal tubules.

Foci of tubular atrophy with interstitial fibrosis are noted covering about 10% of cortical renal parenchyma. There are few tiny foci of interstitial lymphocytic infiltration.

Arteries show mild medial thickening and arterioles reveal foci of hyalinosis in the wall.

Direct immunofluorescence report

DIF - 1026/23: Single core of renal tissue, measuring 1.6 cm in length

Antibody	Site of deposit	Pattern of deposit	Intensity
IgA	-	-	0
IgG	-	-	0
IgM	-	-	0
C3	-	-	0
C1q	-	-	0

Summary of positive finding:

1. Glomerular hypercellularity with capillary basement membrane thickening
2. Patchy acute tubular injury
3. Foci of tubular atrophy and interstitial fibrosis
4. Mild arterial medial thickening
5. DIF: Negative

Diagnosis: Kidney (Biopsy): **Diffuse membranoproliferative glomerulonephritis**

Figure-5: Histopathological findings of renal tissue of the patient

DISCUSSION

Sjögren syndrome (SS) is an autoimmune disorder characterized by secretory glands dysfunction resulting in dryness of main mucosal surfaces like- mouth, eyes, nose, pharynx, larynx and vagina [8]. Although, Sjögren syndrome particularly affects middle aged women, but elderly people, men and children may also affect [4]. Sjögren syndrome may be a primary disorder or secondary to other autoimmune diseases. Among autoimmune illnesses, primary SS is the second most common cause of renal impairment, affecting less than 10% of cases, after systemic lupus erythematosus [7]. The exact cause of Sjögren syndrome is still unknown, it is postulated that genetic and environmental factors may play role [8]. A little over half of patients presented with intermittent parotid swelling, and pain affecting one or both sides, while 70% to 80% of patients complain of dry mouth [9]. Sjögren syndrome may be a serious condition with a high mortality resulted from lymphoproliferative malignancy [9] Low level of serum C_3 and/or C_4 at the time of diagnosis is the strongest indicator of an adverse outcome [9].

The diagnose of Sjögren's syndrome is challenging, especially when the initial presentation is different from the exocrine manifestation of dry mouth and eyes. The diagnostic criteria emphasize on oral and ocular findings. Four of the six criteria included in the American-European Consensus Classification Criteria; ocular or oral symptoms, objective ocular or oral indicators, lip biopsy histology, and the presence of autoantibodies- must be met in order to diagnose primary Sjögren's disease [10]. Our patient had only satisfied three of the requirements- dry eyes and mouth for longer than three months with positive anti-SS-A and anti-SS-B antibodies; primary Sjögren's syndrome was assumed to be the cause. Renal biopsy results can be helpful even though they are not included in the Sjögren's syndrome diagnostic criteria [10]. Based on renal histopathology reports or biochemical impairment, the incidence of renal involvement in Sjögren's syndrome ranges from 0.3% to 27% [11, 12]. It was documented that, the most common renal involvement of Sjögren's syndrome is renal tubular acidosis (11%) followed by glomerulonephritis (<5%), interstitial cystitis (<5%) and recurrent renal colic due to renal stones (<5%) [4]. Usually, patients with Sjögren syndrome have cryoglobulinemia and low serum complement levels [7]. Renal glomerular involvement in Sjögren syndrome is less frequent but commonly takes the form of membranoproliferative glomerulonephritis secondary to cryoglobulinemia [7].

In our patient serum complements levels were with in normal limit, her renal biopsy report revealed diffuse membranoproliferative glomerulonephritis. Electrolyte disturbances are common as renal distal tubular acidosis may occur in Sjögren syndrome, in our patient persistent hypokalemia with metabolic acidosis was observed. Finally, she was diagnosed as a case of Sjögren syndrome, renal tubular acidosis type1 (hypercholraemic normal anion gap metabolic acidosis), hypokalemia, with renal impairment.

The prognosis of glomerular disease in Sjögren syndrome is usually favorable but the risk of developing chronic kidney disease (CKD) is remains high among patients with TIN [7].

To enable the early identification of renal complications in patients with systemic Sjögren syndrome, appropriate screening needs to be carried out at least once a year. Determination of autoantibodies to Ro/SS-A and La/SS-B antigens that are positive in 50-70% of patients, must be included in immunological study; these antigens are the only immunological parameters that included in the current criteria although the sensitivity of these antigens is low (33-46%) but the specificity is 100% [10]. In addition, serum complement (C_3/C_4) levels, serum monoclonal band, and cryoglobulins are other parameters that should be examined or ruled out [13, 14]. Despite being invasive, salivary gland biopsy has 82% sensitivity and 86% specificity for diagnosing Sjögren syndrome that is recommended particularly for those patients who have negative anti-Ro/La antibodies [15]; the distinctive histopathological feature is focal lymphocytic sialadenitis, which is defined by aggregates of more than 50 lymphocytes [4]. But in our patient anti-Ro and anti-La were positive, therefore salivary biopsy was not done.

CONCLUSION

The findings of this case suggest that patients with hypokalemia should pay attention to the symptoms including dry mouth, dry eye and renal tubular acidosis. Renal involvement (GN) and the medical history of female patients should be considered in order to confirm the diagnosis of primary Sjögren syndrome. This is because renal involvement in primary Sjögren syndrome is an under diagnosed condition that can manifest in a number of subtle and varied ways.

Ethical Implications

In this case report, only clinical effects of disease were observed, no experiments were performed. Therefore, ethical approval from any ethical committee was not required.

Consent

This article only observed the disease progression and did not report any unconventional treatment options. Hence patient consent was not an ethical issue.

Conflicts of Interest: All authors declared that they have no conflict of interest regarding this publication.

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