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Case based Review

Minimal Change Disease and Primary Sjogren Syndrome Concurrence: Case-Based review

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Abstract

Primary Sjogren's syndrome is a chronic autoimmune disease with glandular and extraglandular features. Renal involvement is less frequent when compared with other systemic manifestations. Glomerulonephritis is a relatively rare manifestation of primary Sjogren's syndrome. Among all types of glomerular manifestations, minimal change disease is rarely identified, and there are only a few cases in the literature. Herein, we present a 53-year-old male patient who was diagnosed with primary Sjogren's syndrome and minimal change disease while searching for the etiopathogenesis of nephrotic syndrome. The patient had edema, dyspnea, hypertension, and 12 g/day proteinuria at admission. Serum albumin level was 1.82 g/dL, and renal function tests were within normal ranges. Renal biopsy findings were consistent with minimal change disease. At the same time, he was diagnosed with primary Sjogren's syndrome based on dry eyes demonstrated with Schirmer's test, positive antinuclear antibody, anti-SS-A, and anti-SS-B antibodies. Hydroxychloroquine with methylprednisolone 1 mg/kg (64 mg/day) was started, and methylprednisolone was slowly tapered. His proteinuria regressed to 79.2 mg/day, creatinine level was 0.83 mg/dL, and serum albumin level increased to 3.88 g/dL on the second week of the glucocorticoid treatment. In this case-based review, we present our case with 5 other reports of minimal change disease associated with primary Sjogren's syndrome. Our aim was to increase the awareness of this rare concurrence both among rheumatologists and nephrologists in light of the literature review.

Keywords: Sjogren's syndrome, proteinuria, glomerulonephritis, minimal change disease

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Introduction

Sjogren's syndrome is a relatively common, chronic autoimmune disease with glandular and extraglandular features.[1] Sjögren's syndrome can occur as primary Sjögren's syndrome (PSS) or in association with connective tissue diseases such as rheumatoid arthritis and systemic lupus erythematosus as secondary Sjogren's syndrome.[2] Even though the etiopathogenesis of PSS is still unclear, B lymphocyte infiltration in glandular and extraglandular epithelia is demonstrated.[2] This results with keratoconjunctivitis sicca and xerostomia.[3] Extraglandular manifestations occur in about 25% of the patients and include arthralgia, arthritis, myalgia, fatigue, purpura, interstitial pneumonia, pericarditis, pulmonary hypertension, nephritis, and neuropathy.[3-5] Renal involvement in PSS is known since 1960s.[2] Compared with other systemic manifestations, renal involvement is a less frequent feature of PSS.[5] The reported prevalence of renal manifestations in PSS varies from 2% to 67% and is mostly learned from case reports or retrospective analysis.[3,4] Renal symptoms usually appear in patients aged more than 50.[6] Two different pathogenetic mechanisms cause renal pathology resulting in interstitial nephritis or glomerulonephritis.[6,7]

The most common renal involvement in PSS is tubulointerstitial nephritis (TIN) and usually occurs before or near the beginning of sicca symptoms.[5] On the contrary, glomerulonephritis (GN) is rare and occurs as a late finding of PSS.[7] Tubulointerstitial nephritis is characterized by an inflammatory infiltrate in the kidney interstitium mainly composed of CD4+ T cells.[8] The most common type of GN in PSS is membranoproliferative glomerulonephritis.[6] Other glomerular diseases described in patients with PSS are immunoglobulin A (IgA) nephropathy (1%-22%), focal segmental glomerulosclerosis (FSGS, 1%-8%), and minimal change disease (MCD) (2%-4%).[4] Minimal change disease in PSS is rarely identified with a few case reports in the literature.

The aim of this study is to describe a patient with PSS and MCD, additionally to review similar cases in the literature.

Patients and Methods

To address the concurrence of PSS and MCD, we searched websites such as Pubmed, Web of Science, Scopus, and Google Scholar using keywords such as "primary Sjogren's syndrome and renal involvement" and "primary Sjogren's syndrome and minimal change disease" in September 2020. The search was performed by one of the authors. English and non-English literature which included English abstracts were selected for the review. All retrieved articles were screened by title and abstract, and the related ones were kept for full-text review, if accessible. Case reports and case series that described renal biopsy findings of PSS cases with MCD were considered for inclusion. Finally, 5 cases were obtained for review as illustrated in the flowchart (Figure 1).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the patient included in this report.

Case

A 53-year-old male patient was admitted to the hospital with dyspnea, edema, and hypertension for 20 days in January 2020. On medical history, he did not have any chronic illness, exposure to allergens, and he was not receiving any medicine. On physical examination, his blood pressure was 150/100 mm/Hg, and he had pretibial edema bilaterally. Laboratory tests revealed 12 g/day proteinuria, creatinine 0.9 mg/dL, blood urea nitrogen 21 mg/dL, total protein 4.93 g/dL, and albumin 1.82 g/dL. The complete blood count was normal. Urinalysis showed a pH of 6, the specific gravity of 1.021, red blood cell <1/high power field, leucocyte 4/high power field, and proteinuria (protein 3+). Erythrocyte sedimentation rate (ESR) was 100 mm/h, and C-reactive protein level was 1.4 mg/dL (0-5). Serologic tests for hepatitis B, C, and human immunodeficiency virus were negative. Total and free prostate-specific antigens were within normal ranges. The abdominal ultrasound and chest x-ray were normal. He was diagnosed with nephrotic syndrome, and renal biopsy was performed. The specimen contained 19 glomeruli. There was focal minimal chronic inflammatory cell infiltration in the interstitium without fibrosis. In focal areas, there were rare atrophic tubules. Vascular structures were in normal appearance. There was no amyloid deposition with crystal violet and congo red staining. The immunofluorescence examination did not show a reaction to any of the Ig G, Ig A, Ig M, C3c, C1q, fibrinogen, kappa, and lambda. We were unable to perform an electron microscopic examination. These findings were consistent with MCD (Figure 2). Methylprednisolone 1 mg/kg (64 mg/day) was started and slowly tapered. While the biopsy results were pending, anti-nuclear antibody (ANA) tests that were required for investigating the etiology of nephrotic syndrome resulted positive in 1/320-1/1000 titer with speckled patern. Anti-dsDNA was negative, serum complement levels were within normal ranges (C4: 0.396 g/L [0.1-0.4] and C3: 1.424 g/L [0.9-1.8]), and anti-SS-A and anti-SS-B antibodies were positive. Other components of extractable nuclear antibody test (anti SM, anti Jo-1, antiScl-70, anti SM/RNP, and anti Ro-52) were negative. Cryoglobulin was also negative. Serum IgG, IgA, and IgM levels were within normal ranges, and protein electrophoresis was consistent with polyclonal gammopathy. Schirmer's test was performed, and it was compatible with dry eyes. He was diagnosed as PSS. Unfortunately, minor salivary gland biopsy was not performed due to COVID-19 pandemic restrictions. Hydroxychloroquine (HCQ) was started for PSS. His proteinuria regressed to 79.2 mg/day, and creatinine level was 0.83 mg/dL, blood urea nitrogen was 24 mg/dL, total protein was 5.94 g/dL, and albumin level increased to 3.88 g/dL on the second week of the glucocorticoid treatment. Glucocorticoid treatment was stopped at the end of the sixth month. He is receiving HCQ alone and is in complete remission since then.

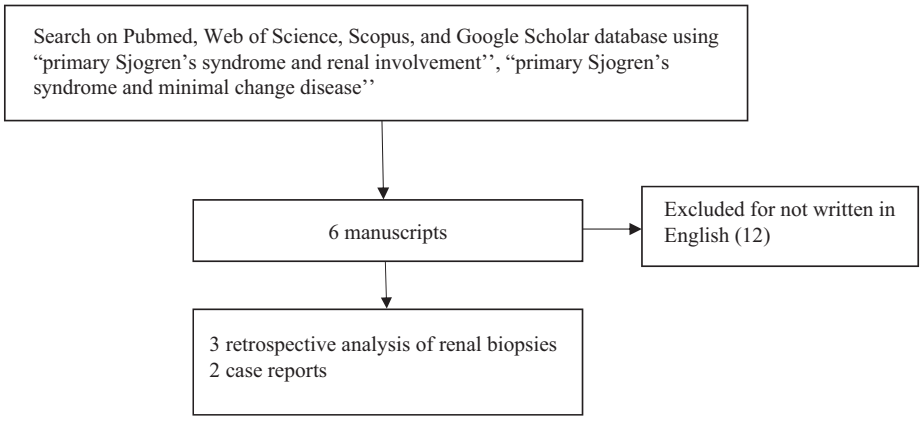

Figure 1. Flowchart of the literature review methodology.

Review of the Literature

We have searched the literature and reached 8 patients with PSS and MCD; 4 patients in a retrospective study from China,[1] 1 patient in a retrospective study from the United States,[3] 2 case reports,[4,9] and 1 in a study from the United Kingdom.[10] Also, there were records of patients in a study about kidney biopsy findings of PSS findings, but we were not able to reach the patient information in that manuscript.[11]

The first case in the literature was reported by Mon et al.[9] In that case, the nephrotic syndrome was supposed to be related to increased serum

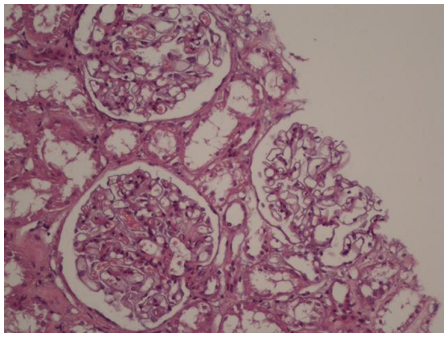

Figure 2. The glomeruli appear normal without an increase in cellularity or an increase in capillary wall thickness (H&E ×200).

Main Points

- Glomerulonephritis is a relatively rare manifestation of primary Sjogren's syndrome (PSS).
- Among all types of glomerular manifestations, minimal change disease (MCD) is rarely identified in PSS.
- Minimal change disease may be the diagnostic feature of PSS. Minimal change disease and PSS may be diagnosed concurrently.
- Minimal change disease as a clinical feature of PSS, responds well to glucocorticoids.

Table 1. General Features of Cases in the Literature

	Age/Gender	Initial Presentation	Kidney Biopsy	Treatment	Autoantibodies
Yang et al[1]	-	-	-	-	-
Maripuri et al[3]	66/F	Nephrotic ranged	MCD + arteriolosclerosis	Hydroxychloroquine + glucocorticoid	-
Yang et al[5]	40/F	Dry mouth, nephrotic syndrome	MCD + TBMN	Glucocorticoid	Anti SS-A (+) Anti SS-B (+)
Mon et al[9]	-	-	-	-	-
Kidder et al[10]	39/F	Proteinuria	MCD	Hydroxychloroquine + glucocorticoid (?)	-
Current case	53/M	Proteinuria	MCD	Glucocorticoid	ANA (+) Anti SS-A (+) Anti SS-B (+)

MCD, minimal change disease; TBMN, thin basement membrane nephropathy; ANA, anti-nuclear antibody.

CA 19-9. Unfortunately, the article was in Spanish, and we could not reach the details of the case. Only limited data obtained from the English abstract were assessed.

The second case was from Taiwan. The patient was a 40-year-old female and presented with dry mouth and nephrotic syndrome. The biopsy findings were consistent with MCD and thin basement membrane nephropathy (TBMN), and nephrotic syndrome regressed after glucocorticoid treatment.[4] This patient had TBMN findings in addition to MCD. Similar to our case, this patient had a PSS diagnosis simultaneously with MCD, and nephrotic syndrome resolved with glucocorticoid therapy in both patients.

In a study by Kidder et al.[10] biopsy findings of 25 PSS patients were evaluated, and only 1 female patient aged 39 years had MCD. Additional 8 cases had other types of GN, and 13 patients had TIN. The patient had proteinuria and hematuria in admission and was treated with HCQ.[10] This patient was younger than ours and did not need glucocorticoid therapy. But we were not able to reach the detailed laboratory tests and treatment data of this patient.

There was 1 case in a retrospective analysis of 7276 PSS patients' renal biopsies.[3] The study included renal biopsy findings of 24 PSS patients and only 1 female patient, aged 66 years, who had MCD and arteriolosclerosis simultaneously. The remaining patients mostly had TIN (n = 17). The patient was admitted with proteinuria in nephrotic ranges with normal creatinine levels, and after HCQ and prednisolone treatment she was in remission.

The last study was from China[1] in which 103 PSS patients' renal biopsy findings were analyzed. This study included 4 patients with MCD. But there were not any data about the specific clinical features of these 4 patients.[1]

The limited data of these published cases are summarized in Table 1.

Discussion

This is an unusual case with PSS having nephrotic syndrome and MCD. Renal involvement is an extraglandular manifestation of PSS, although the real prevalence of renal disease is not known.[4] Although TIN is the main type of renal involvement in PSS, GN may be detected in a small number of patients. Clinical features of glomerular involvement include dysmorphic erythrocytes in urine, proteinuria, or nephrotic syndrome. Common glomerular diseases seen in PSS are membranoproliferative GN, membranous nephropathy, and mesengioproliferative GN. Immunoglubulin A nephropathy and FSGS are less frequent glomerular findings in PSS.[4] Minimal change disease, just as our case, is only reported in a few cases in the literature. Glomerular involvement usually presents in patients with older age and higher morbidity and mortality.[7] The current patient was aged more than 50, and he had nephrotic syndrome. He was diagnosed as MCD with biopsy-proven findings. Concurrently, the possible causes of the nephrotic syndrome were investigated, and the ANA test was determined to be positive. Then we investigated the possible causes for ANA positivity, and he was diagnosed as PSS concomitant with MCD. Interestingly, this patient did not have any of the sicca complaints. Also, GN is usually expected to be a late finding of PSS but this patient was diagnosed after the nephrotic syndrome developed. This is a rare concurrence with only a few similar cases published.

Patients with PSS may have renal involvement with different clinical presentations. According to the study of Luo et al.[5] renal involvement is associated with several factors including xerophthalmia, positive histological findings of salivary gland biopsy, anti-SSA/Ro52 positivity, IgG level, reduced C3 levels, ESR level, hypoalbuminemia, and anemia ($P < .05$, for all). The current patient had xerophthalmia, anti-SSA positivity, increased ESR levels, and hypoalbuminemia. Luo et al[5] reported a negative association with renal involvement,anti-SSA/Ro52 positivity, and xerophthalmia. But none of the patients in that study had MCD.

The pathogenesis of renal involvement in PSS is unclear. Different mechanisms are supposed to play a role in the development of TIN or GN. Circulating immune complexes, mixed cryoglobulinemia, or decreased C4 levels were thought to be related with glomerular disease.[4] Our case did not show any clinical finding of cryoglobulinemia, and the C4 level was normal. The limited number of patients and low frequency of this concurrence retain us from a generalization. But B cells play a pivotal role in the pathogenesis of both MCD and PSS, and this may be a hint for the pathogenesis of these 2 events. But there are still question marks about the pathogenesis of glomerular involvement in PSS, and we did not find any detailed data about the pathogenesis in our literature search.

Recognition of glomerular involvement and treatment with immunosuppressants, especially with glucocorticoids, may provide remission. Maripuri et al[3] have suggested that PSS patients with renal involvement should receive corticosteroids as first-line treatment. But unlike other rheumatologic conditions, the need for long-term steroid-sparing immunosuppressive agents for the treatment of renal disease remains largely unknown. This is an area for further research. However, based on the literature review, treatment should be tailored to each patient's clinical, laboratory, and histopathological findings.

In conclusion, we present a case that was diagnosed with MCD and PSS simultaneously. Even GN is a rare type of renal involvement, MCD is much rarer in PSS. Minimal change disease may be one of the clinical findings of PSS, or there may be a coincidence between MCD and PSS resulting from the shared pathogenesis of these 2 events. Reporting such rare patients may provide more information about the causality of these 2 situations.

Informed Consent: Informed consent was obtained from the patient included in this report.

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