A case of Sjögren syndrome and anti-neutrophil cytoplasmic antibody-associated vasculitis

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SUMMARY

Sjögren's syndrome (SS) is a rare disease with the highest reported prevalence of 0.01-0.09%. Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) is another rare auto-immune disease (prevalence of 0.0009-0.01%). The co-occurrence of these two separate clinical entities in one patient might rarely be encountered as an overlap syndrome. Here, we present the case of a 60-year-old female patient who had complaints of headache, nausea, weakness, gritty sensation in her eyes, and dry mouth [unstimulated saliva production of 0.033 mL/minute (normal; >0.1 mL/minute)] with a blood pressure of 190/110 mmHg, hypertensive retinopathy, proteinuric kidney disease, positivity of myeloperoxidase anti-neutrophil cytoplasmic antibodies, anti-Ro-52, anti-Ro, and anti-La antibodies. Pauci-immune crescentic proliferative glomerulonephritis was found in a kidney biopsy and successfully treated with cyclophosphamide and methylprednisolone. The co-occurrence of these diseases was first reported in 1992 by Böttinger *et al*. Since then, nearly 37 cases of SS and AAV have been reported. By reporting this case of primary SS and AAV, we emphasize the importance of auto-antibody tests in searching for the etiology of patients with proteinuria.

Key words: *Antibodies, antineutrophil cytoplasmic, dry eye syndromes, renal insufficiency*.

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INTRODUCTION

Sjögren's syndrome (SS) is a rare disease with a reported prevalence of 0.01-0.09% (1). Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is another rare auto-immune disease (prevalence of 0.0009-0.01%) (2). The co-occurrence of these conditions was first reported in 1992 by Böttinger et al. (3). Since then, nearly 37 cases of SS and AAV have been reported in the literature (4-12). Kidney involvement has been observed in 2-67% of patients with SS, in 18% of those with AAV at presentation, and in 64% (24 of the 37 patients) of patients with co-occurrence of SS and AAV (2, 4-20). In these predominantly older and female patients, the emergence of AAV was usually documented approximately 5-15 years later than the diagnosis of SS (4, 14).

Here, we present the case of a 60-year-old female patient who had complaints of headache, sicca syndrome, nausea, and weakness resulting from the co-occurrence of AAV and SS.

CASE REPORT

A 60-year-old female patient had a medical history of untreated asthma for four years. She did not take any medication except nonsteroidal anti-inflammatory drugs. The main complaints were nocturia, headaches, gritty sensation in her eyes, and dry mouth. Physical examination revealed blood pressure of 190/110 mmHg and hypertensive retinopathy (grade 2). Schirmer test showed wetting of 8 mm in the right eye and 7 mm in the left eye. Unstimulated saliva production was measured at 0.5 mL/15 minutes. Laboratory tests showed increased serum creatinine level (1.72 mg/dL), anemia (hemoglobin: 10.6 g/dL), and hypoalbuminemia (33.6 g/L). Urine sediment evaluation revealed hematuria without casts. Analysis of 24-hour urine collection revealed proteinuria (3.48 g/day) and albuminuria (2.45

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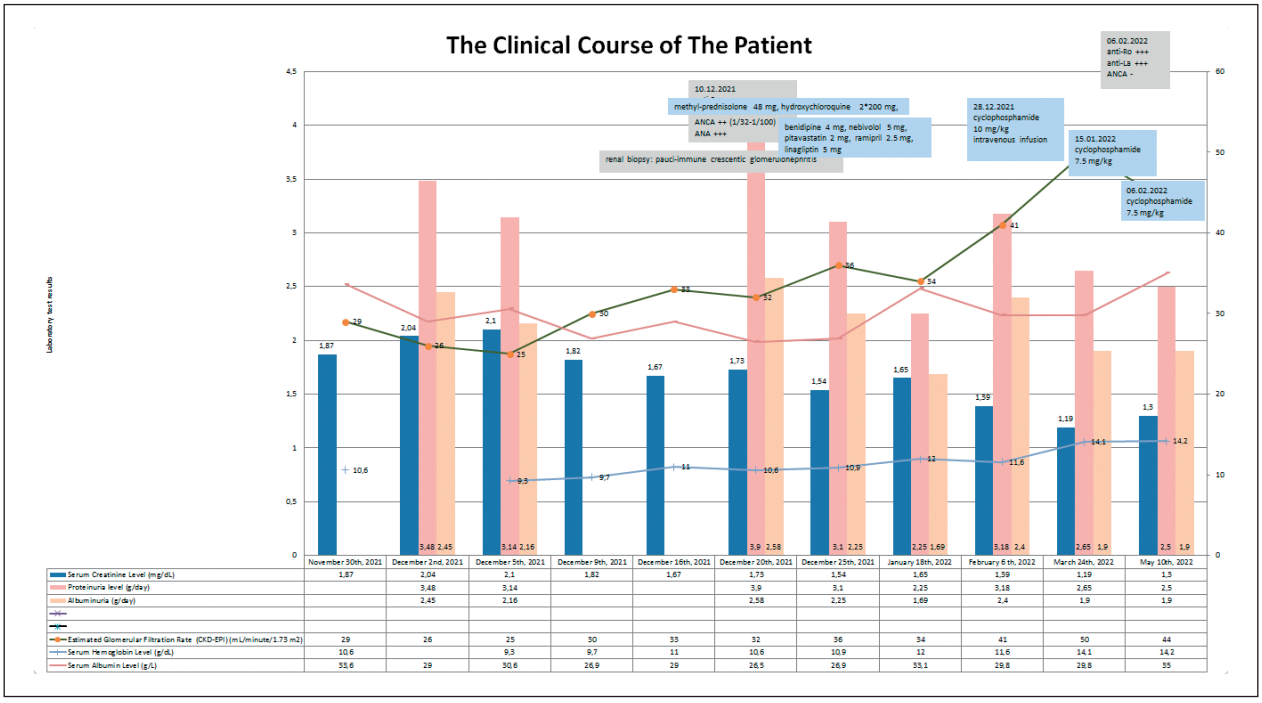

Figure 1 - Clinical course of the patient.

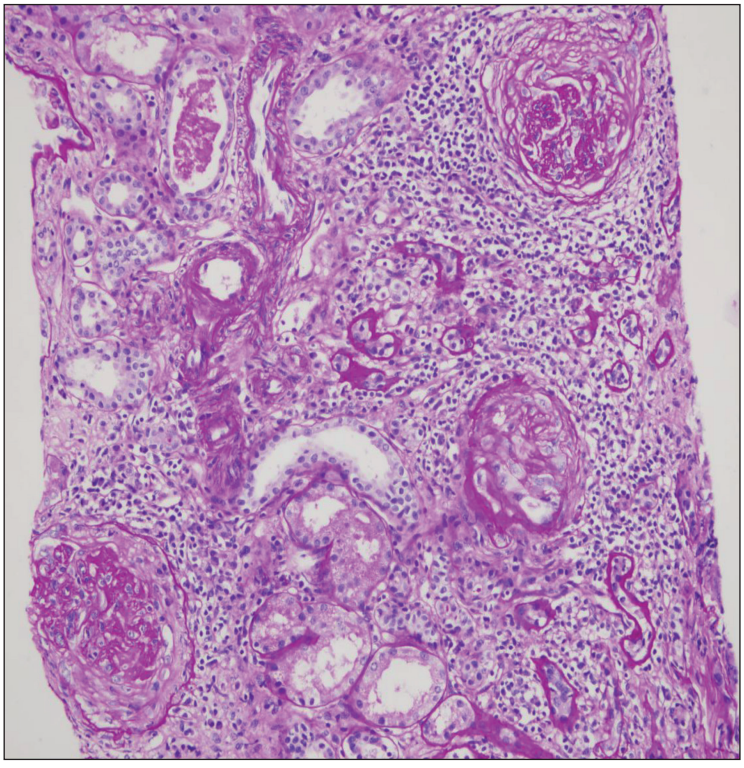

Figure 2 - Kidney biopsy showing full-moon fibrocellular crescent, diffuse mesangial cellular proliferation and matrix expansion with lobulation, interstitial inflammation by light microscopy, periodic acid Shiff × 400.

g/day) (Figure 1). Tests for auto-antibody panel resulted in positive antinuclear antibodies with nuclear-speckled pattern (titer of 1/1000-1/3200), myeloperoxidase anti-neutrophil cytoplasmic antibodies (MPO-ANCA) (titer of 1/32-1/100), high titer anti-Ro-52 antibodies, anti-Ro/SSA and anti-La/SSB antibodies. Benidipine (4 mg/day), nebivolol (5 mg/day), and ramipril (2.5 mg/day) were administered based on the presence of high blood pressure and hypertensive target organ damage (retinopathy and left ventricular hypertrophy). The size of the right kidney was 98×50 mm, and the left kidney was 82×46 mm with mildly increased (grade 1) echogenicity. A kidney biopsy was performed because of nephrotic-level proteinuria with decreased glomerular filtration rate (GFR). Chronic kidney disease epidemiology collaboration cre-based formula for GFR revealed 29 mL/min/m^2. Global sclerosis in 2 out of 16 glomeruli, full-moon fibrocellular crescents in 9 glomeruli, diffuse mesangial cellular proliferation and matrix expansion with lobulation in the rest of the glomeruli, and interstitial inflammation (75-80%)

were found by light microscopy (Figure 2). No necrosis and segmental sclerosis were noticed. No depositions of immunoglobulin (Ig) G, IgM, IgA, C3, C1q, amyloid A, and light chains were detected by immunofluorescence microscopy except fibrin depositions (Figure 2). Labial salivary gland biopsy (sample is 1 cm in size, glandular area: 3 mm^2, focus score:0, glandular area <4 mm^2, suboptimal evaluation) did not reveal sialadenitis. High-resolution computed tomography revealed ground-glass opacities in the lower lobes of the lungs bilaterally reflecting lymphoid interstitial pneumonitis and multiple lung cysts (Figure 3). The patient satisfied the American College of Rheumatology/European Alliance of Associations for Rheumatology (2022) classification criteria for AAV (microscopic polyangiitis) and SS (1, 15).

Methylprednisolone (1 mg/kg/day, 64 mg/day) and cyclophosphamide (renal dose of 10 mg/kg every two weeks, a total of 6 doses) together with mercaptoethane sulfonate were administered to the patient. Hydroxychloroquine (for pulmonary involvement) was prescribed to treat SS. After 3 months, serum creatinine levels and proteinuria decreased to 1.39 mg/dL and 3.1 g/day, respectively, and MPO-ANCA antibodies and ground-glass appearance in the lungs disappeared. As the induction therapy, the final (6^{th}) dose of cyclophosphamide (dose decreased by 375 mg due to previous adverse effects of leukopenia) was administered on April 16, 2022. The serum creatinine level was 1.3 mg/dL, and serum albumin level was 35 g/L by then and she was well without symptoms under the maintenance treatment of azathioprine and low-dose methylprednisolone for AAV and hydroxychloroquine for SS.

DISCUSSION AND CONCLUSIONS

SS might be underrecognized among physicians due to its low prevalence and incidence rates, as in our case despite the presence of gritty sensation in her eyes and dry mouth. An abnormal salivary function was seen in our patient based on her unstimulated saliva production of 0.033 mL/minute (normal: >0.1 mL/minute). In addition, abnormal specific serologic tests for SS (antibodies to SSA/Ro and SSB/La) and typical lung involvement of SS (ground-glass opacities in the lower lobes and cysts) were also found allowing us to make the diagnosis of SS (1, 16). Lung involvement in SS patients includes ground-glass opacification (92%), subpleural small nodules (78%), non-septal linear opacities (75%), interlobular septal thickening (55%), bronchiectasis (38%), and cysts (30%) (17). However, patients with AAV also develop interstitial lung disease (usually nodules, infiltrates, hilar adenopathies, and masses). In addition, non-specific interstitial pneumonia may present with ground glass opacification in

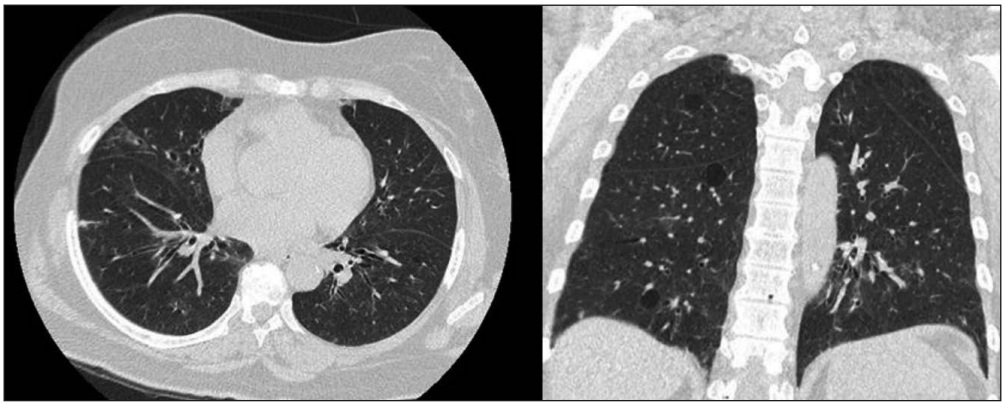

Figure 3 - Axial and coronal images of high-resolution computed tomography showing ground glass opacities and multiple lung cysts.

the lungs. Bronchoalveolar lavage may be needed in differential diagnoses with infection or malignancy (2). Kidney disease in SS commonly occurs in the form of interstitial nephritis (including distal tubular acidosis, nephrogenic diabetes insipidus) rather than glomerulonephritis. When glomerular diseases are found in SS patients, the reported forms are often membranous glomerulopathy, membranoproliferative glomerulonephritis, IgA nephropathy, and minimal change diseases (13).

Pauci-immune crescentic glomerulonephritis with MPO-ANCA, which is the kidney disease form occurring in almost all patients with AAV, was found in our patient's kidney biopsy (2). It is very unusual to find anti-Ro, anti-La, and anti-Ro-52 antibodies in the serum of patients with AAV unless co-occurrence of SS is also present, as in our case. Until now, 37 patients with the co-existence of primary SS and AAV, which mostly had MPO-ANCA, have been reported (14, 18-23). Proteinase-3 AAV was also found in patients with SS (4).

Primary SS patients with MPO-ANCA positivity and neuropathy without kidney disease were also reported (4, 20). Kidney involvement was detected in 24 of the overall 37 cases. Almost all of them had crescentic proliferative glomerulonephritis which responded well to the treatment with methylprednisolone and cyclophosphamide, as in our case. Plasma exchange was reported to be an addition to treatment in some instances (19, 23). The combination of methylprednisolone and mycophenolate mofetil was shown to be an effective therapy in one patient (18).

In conclusion, we would like to emphasize the importance of auto-antibody testing by reporting this case of primary SS with MPO-ANCA-associated pauci-immune crescentic proliferative glomerulonephritis in the evaluation of patients with proteinuria. Especially when the glomerular type of proteinuria (albuminuria) is present, renal involvement in SS requires a careful diagnostic workup, including exclusion of AAV.

Contributions

All authors have read and agreed to the final manuscript. KK, participated in the conception, design, interpretation of data, drafting and revision of the article; BG, contributed to the design, interpretation of data, and drafting of the article; AŞ, reviewed the literature and participated in the writing of the manuscript; SM, contributed to the interpretation of the pathological findings of patient's kidney biopsy.

Conflict of interest

The authors declare no potential conflict of interest.

Patient consent for publication

Informed consent was obtained from the patient.

Availability of data and materials

Data and materials are available from the corresponding author upon request.

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