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Case Report

Anti-neutrophil Cytoplasmic Antibody-associated Pauci-immune Crescentic Glomerulonephritis Complicating Sjögren's Syndrome

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Sjögren's syndrome is a chronic autoimmune disease, characterized by specific autoimmune antibodies anti-Ro and anti-La, and it can involve multiple organs, such as the kidneys, lungs, muscles, and nervous system. The most common renal complication of Sjögren's syndrome is tubulointerstitial nephritis, and glomerulonephritis is relatively uncommon. We report the case of an 86-year-old man presenting with recurrent fever, poor appetite, decreased salivary secretion, and body weight loss. Laboratory investigation revealed that serum creatinine was 4.2 mg/dL, proteinuria was 3+, and there was microscopic hematuria. Positive perinuclear anti-neutrophil cytoplasmic antibody, anti-Ro, and anti-La antibodies were detected. Renal biopsy showed crescentic glomerulonephritis with scanty immune complex deposition. The patient was diagnosed with primary Sjögren's syndrome complicated with rapidly progressive glomerulonephritis with positive anti-neutrophil cytoplasmic antibody. Unlike the patients of other case reports, our patient's renal function did not recover after immunosuppressant treatment, and he finally received long-term hemodialysis. Pauci-immune glomerulonephritis is a rare renal complication of Sjögren's syndrome, and progress to renal failure in such patients is possible.

Key Words: anti-neutrophil cytoplasmic antibodies, crescentic glomerulonephritis, Sjögren's syndrome

Sjögren's syndrome (SS) is a chronic autoimmune disease in which the exocrine glands are attacked and infiltrated by lymphocytes, thus causing xerostomia and xerophthalmia. Other regions, such as musculoskeletal, pulmonary, vascular, renal, dermatological, and neurological systems, can also be involved in patients with Sjögren's syndrome. The specific autoantibodies to Sjögren's syndrome in diagnostic criteria revised in 2002[1] are anti-Ro and anti-La, but some atypical autoantibodies, such as anti-DNA antibodies, anti-Smith antibodies, and anti-neutrophil cytoplasmic antibodies (ANCA), can also be found. We present the case of a patient diagnosed with Sjögren's syndrome with pauci-immune crescentic glomerulonephritis, characterized by positive perinuclear ANCA (p-ANCA), and review the literature.

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Case Report

An 86-year-old Taiwanese man presented to our hospital for recurrent fever, poor appetite, decreased salivary secretion, and body weight loss. He had a history of a cerebrovascular accident with left hemiplegia for more than 10 years. He did not previously have diabetes mellitus, renal insufficiency or hypertension, and his baseline creatinine (Cre) level was 1.2 mg/dL 3 months prior to the current event. On physical examination, his blood pressure was 122/68 mmHg and he had coarse breath sounds bilaterally without rhonchi or wheezing. He had no oral ulcers, lymphadenopathy, or skin rash, but skin turgor was decreased. Laboratory investigation revealed the following: serum Cre, 4.2 mg/dL; blood urea nitrogen, 56 mg/dL; serum potassium, 5.2 mmol/L; and hemoglobin, 9.1 g/dL. A urinary study showed 3+ proteinuria, a daily urine protein loss of 1.31 g and microscopic hematuria (red blood cells: 25–50/high power field) without cast or crystals. A renal sonogram showed that the right kidney was 9.6 cm and the left kidney was 10.7 cm in size, as well as renal parenchymal disease with a left renal stone. Because of the clinical suspicion of rapidly progressive glomerulonephritis, the autoimmune profile was further investigated. The complement 3 level was 92 mg/dL, complement 4 level was 22 mg/dL, and anti-double strand DNA antibody and rheumatoid factor were both negative. However, high titers of antinuclear antibody (ANA = 1280×), positive p-ANCA (anti-myeloperoxidase, anti-MPO, > 20×), anti-Ro (65 U/mL, normal range < 10 U/mL), and anti-La (74 Ul/mL, normal range < 10 U/mL) antibodies were detected. Shirmer's test was positive and a lip biopsy showed increased lymphocyte infiltration with gland atrophy (Figure 1), compatible with Sjögren's syndrome. In a renal biopsy, glomeruli showed a change in crescents without deposits (Figure 2). The interstitium showed chronic inflammation and fibrosis, focal tubulitis and moderate tubular atrophy. Arterioles showed atherosclerosis without vasculitis. Pauci-immune crescentic glomerulonephritis was confirmed. The patient received cyclophosphamide pulse therapy (7 mg/kg) with oral prednisolone 20 mg per day, and 1 month later, a second cyclophosphamide therapy of the same dose plus intravenous methylprednisolone 600 mg was performed. However, severe sepsis occurred during the second treatment course and his renal function progressed to anuria with a Cre of 4.7 mg/dL. After recovery from the episode of infectious complications, the family declined further immunosuppressive treatment, including plasmapheresis, and he started hemodialysis 5 months after the initial presentation.

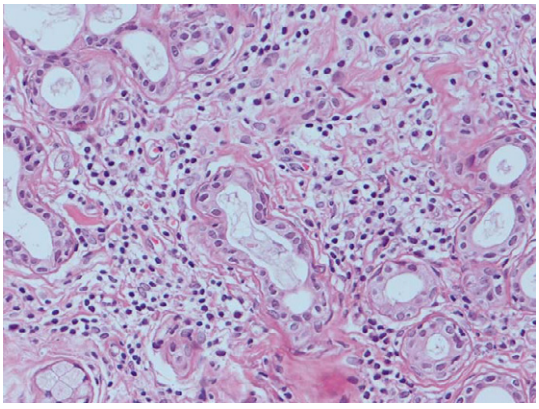

Figure 1. A large amount of lymphocytes are infiltrated over the small salivary gland with gland atrophy (hematoxylin-eosin stain, 200×).

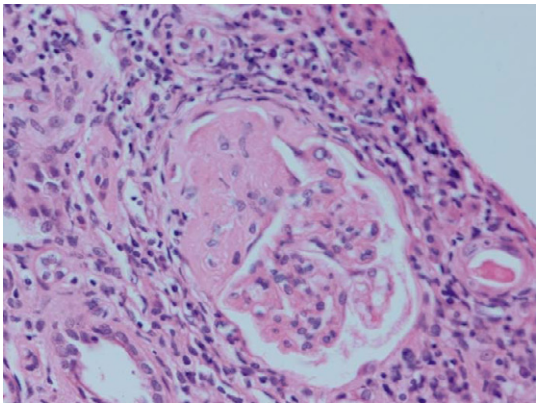

Figure 2. A glomerulus is shown with crescentic change and fibrosis. The interstitium is infiltrated with lymphocytes (hematoxylin-eosin stain, 200×).

Discussion

ANCAs are autoantibodies against antigens in cytoplasmic granules of neutrophils and monocytes,

classified as perinuclear (p-ANCA), cytoplasmic (c-ANCA), and an atypical pattern. There are a multitude of antigens recognized by p-ANCA, including MPO, lactoferrin, elastase, and cathepsin G, and there are many conditions associated with the presence of ANCA, such as connective tissue disorders (e.g. systemic lupus erythematosus and systemic vasculitis), gastrointestinal disorders (e.g. inflammatory bowel disease and autoimmune hepatitis), infections, neoplasia, and drugs.[2] It is difficult to differentiate the target antigens in various clinical conditions by immunofluorescence alone. However, MPO is recognized as the only one of clinical significance among p-ANCAs, specific to ANCA-associated vasculitides (AAV), after the advent of the enzyme-linked immunosorbent assay.[3] Most of the p-ANCAs present in diseases other than AAV are those besides MPO, and their clinical significance is still unclear.

The presence of ANCA in patients with Sjögren's syndrome is uncommon. Ramos-Casals et al surveyed atypical autoantibodies in 402 patients with primary Sjögren's syndrome,[4] and only 13 patients (3.2%) presented with positive ANCA. The presence of p-ANCA was detected in 12 of the patients, and only one patient presented with atypical ANCA. Five of the 13 patients presented with anti-MPO antibodies, but anti-proteinase 3 antibody was not detected. Such discriminating results are comparable with another study. Nishiya et al followed 60 primary Sjogren's syndrome patients,[5] and 10 patients (16.7%) presented with positive ANCA, and all were p-ANCA. Four of them presented with anti-MPO antibody. Our case also presented with anti-MPO antibody of p-ANCA, but c-ANCA was not detected. In previous studies of ANCA-positive primary Sjögren's syndrome patients, a higher prevalence of extra-glandular manifestations, such as pulmonary, renal, vascular, and neurological involvement, was noted in this subgroup of patients. However, there was less incidence of ANCA-related vasculitis, and the probability of evolving to microscopic polyangiitis was small. In the study by Ramos-Casals et al,[4] only one patient evolved to microscopic polyangiitis after being followed up for more than 7 years.

Renal involvement in primary Sjögren's syndrome, which is approximately 20–30%, may be overt or latent and consists primarily of tubulointerstitial nephritis with interstitial infiltration by lymphocytes, tubular atrophy, and fibrosis. Some patients with tubulo-interstitial nephritis presented as distal type renal tubular acidosis. Glomerulonephritis is a relatively rare pathological finding, and most patients have late sequelae in the course of the disease.[6] The majority of glomerulopathies are membranous glomerulonephritis and membranoproliferative glomerulonephritis, mainly associated with cryoglobulinemia with a low complement 4 level. In a study by Dussol et al following 21 Sjögren's syndrome patients with glomerulonephritis,[7] 13 of them presented with membranoproliferative nephritis, and six patients presented with membranous nephropathy. Cryoglobulinemia was detected in eight of 13 patients examined for cryoglobulin. ANCA-related pauci-immune glomerulonephritis is the most rare case, and to our knowledge, only two cases have been reported in the English literature.[8,9] Our case was an older man, with higher creatinine levels at the initial presentation compared with previous patients (Table), and he was negative for rheumatoid factor. Other systemic manifestations, such as pulmonary and neurological involvement, were less than those in the other cases. However, we could not compare the ANCA level of each case, because of different methods for ANCA measurement.

The combination of cyclophosphamide with prednisolone is the standard induction therapy for AAV-related glomerulonephritis, and we therefore chose this regimen for our patient. Other immunosuppressants, such as azathioprine, methotrexate, and mycophenolate mofetil, are used as alternatives or cyclophosphamide-sparing agents. Therapies currently under investigation are intravenous immunoglobulin, high-dose myeloablative chemotherapy, and various biological agents, including tumor necrosis factor blockers, and anti-B-cell and anti-T-cell agents.[10]

The renal function of most of the previous cases of Sjögren's syndrome complicated with rapidly

Table. Comparison of three patients with Sjogren's syndrome with anti-neutrophil cytoplasmic antibody positive crescentic glomerulonephritis

	Hernandez et al[8]	Kamachi et al[9]	Our case
Age/sex	74/F	67/F	86/M
Race	Spanish	Japanese	Taiwanese
Systemic disease	Cerebrovascular accident, aortic stenosis	Chronic renal insufficiency	Cerebrovascular accident
Hemoglobin (g/dL)	8.8	5.2	9.1
BUN (mg/dL)	81	33	56
Cre (mg/dL)	2.6	2.8	4.2
Urine protein (g/day)	1.6	0.43	1.31
ANA	1,280×, speckled	320×, speckled	1,280, speckled
C3/C4 (mg/dL)	normal/normal	NA/NA	92/22
RF	50 U	Positive	Negative
p-ANCA	59 U (EIA)	603 U/mL (ELISA)	> 20× (ELISA)
c-ANCA	Negative	Negative	Negative
Anti-DNA Ab	Negative	NA	Negative
Anti-Smith Ab	Negative	NA	Negative
Anti-RNP Ab	Negative	NA	Negative
Anti-Ro (U/mL)	Positive	32.5	> 10
Anti-La (U/mL)	Positive	NA	> 10
Cryoglobulin	Traces	Type III	NA
HBV surface Ag	Negative	NA	Negative
HCV antibodies	Negative	NA	Negative
Renal biopsy result	Sclerosed and some cellular crescent glomeruli; moderate focal infiltration by lymphocytes and plasma cells	Sclerosed glomeruli with fibrocellular crescents; mesangial sclerosis, interstitial infiltration of lymphocytes	Crescentic glomerulonephritis, lymphocyte infiltration in the interstitial tissue
Therapy	Intravenous MTP, oral prednisolone	Intravenous MTP, plasma exchange, oral prednisolone, and cyclophosphamide	Oral prednisolone, cyclophosphamide pulse therapy
Outcome	Improved renal function	Improved renal function	Long-term hemodialysis

BUN = blood urea nitrogen; Cre = creatinine; ANA = antinuclear antibody; C3 = complement 3; C4 = complement 4; RF = rheumatoid factor; p-ANCA = perinuclear anti-neutrophil cytoplasmic antibody; c-ANCA = cytoplasmic anti-neutrophil cytoplasmic antibody; EIA = enzyme immunoassay; ELISA = enzyme-linked immunosorbent assay; NA = not applicable; HBV = hepatitis B virus; HCV = hepatitis C virus; MTP = methylprednisolone.

progressive glomerulonephritis fully recovered, but our case did not. It's still unclear why results differ among cases, but old age and poor initial renal function might be involved. Since case reports are rare, further information is required for detailed analyses. A better renal recovery rate by plasma exchange compared with intravenous methylprednisolone (58% *vs*. 32%) was demonstrated in a randomized control trial, "MEPEX",[11] in which the Cre levels of patients with AAV were greater than 5.7 mg/dL. Therefore, the guidelines[12] recommend plasma exchange as adjunctive therapy for severe AAV-related acute renal failure (Cre > 500 μmol/L). Despite the finding that there was a lower Cre level in our patient compared with that in the guidelines, plasma exchange might have improved renal function of our patient. However, his family hesitated about the use of

plasma exchange with concurrent oral immunosuppressants, which is still the cornerstone of treatment, and we hold this management.

In conclusion, ANCA is an uncommon autoantibody detected in Sjögren's syndrome patients as opposed to the common autoantibodies, such as anti-Ro and anti-La. Most of the detected ANCAs in Sjögren's syndrome patients are p-ANCA, predominantly anti-MPO antibody. Extra-glandular involvement is more commonly presented in this subgroup of patients compared with ANCA-negative patients, but the incidence of evolvement to ANCA-associated vasculitis is low. Nephropathy associated with Sjögren's syndrome is predominantly interstitial nephritis. Glomerulonephritis is uncommon, and pauci-immune crescentic glomerulonephritis is rare.

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