

[ CASE REPORT ]

## Emergence of Smoldering ANCA-associated Glomerulonephritis during the Clinical Course of Mixed Connective Tissue Disease and Sjögren's Syndrome

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### Abstract:

A 67-year-old woman presented with hematuria and proteinuria 16 and 11 months ago, respectively. She had been followed up as mixed connective tissue disease and Sjögren's syndrome for over 19 years. Blood chemistry showed no elevated serum creatinine or C-reactive protein but did reveal myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) of 300 U/dL. A kidney biopsy showed pauci-immune focal necrotizing glomerulonephritis. She was treated with prednisolone and rituximab, resulting in normal urinalysis and decreased MPO-ANCA. The complication of ANCA-associated glomerulonephritis should not be overlooked when abnormal urinalysis findings appear in the course of connective tissue disease, irrespective of the presence of rapidly progressive glomerulonephritis.

**Key words:** ANCA-associated glomerulonephritis, mixed connective tissue disease, Sjögren's syndrome

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### Introduction

Connective tissue diseases can be associated with a variety of renal diseases. Renal involvement in primary Sjögren's syndrome (pSS) is common and the most frequent renal lesion in pSS is tubulointerstitial nephritis (1). Glomerulonephritis, such as membranoproliferative glomerulonephritis (MPGN) with or without cryoglobulinemic glomerulonephritis and membranous nephropathy, has been reported to occur in pSS (1-3). Glomerulonephritis was found in 2% of 261 patients with pSS over a 3.6-year follow-up period (4). In mixed connective tissue disease (MCTD), the rate of occurrence of glomerulonephritis, such as membranous glomerulonephritis and mesangial proliferative glomerulonephritis, was reported to range from 0% to 37% (5-8). Patients with MCTD were also found to be fre-

quently associated with secondary Sjögren's syndrome (9).

The rate of antineutrophil cytoplasmic antibody (ANCA) positivity in patients with pSS by an indirect immunofluorescence is reported to range from 3.2% to 16.7% and most cases show P-ANCA positivity (10-12). However, the rate of ANCA positivity in patients with MCTD is not known. Typical renal manifestation of ANCA-associated glomerulonephritis is rapidly progressive glomerulonephritis (RPGN) characterized by a rapid loss of the renal function (usually a 50% decline in the glomerular filtration rate within several weeks to months) with nephritic urinalysis. Although rare, patients with pSS or MCTD have also been reported to be accompanied by RPGN due to ANCA-associated glomerulonephritis (Table).

We herein report a patient with ANCA-associated glomerulonephritis during the clinical course of MCTD and Sjögren's syndrome and summarize a review of the English

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**Table. Clinical Features of Patients with MCTD Or Sjögren's Syndrome Presenting with Rapidly Progressive Glomerulonephritis Due to ANCA-associated Glomerulonephritis.**

References	Reported year	Age (years/gender)	MCTD	pSS	Interval (months)	MPO/PR3-ANCA	Cr (mg/dL)	Proteinuria	Microscopic hematuria	Therapy	Outcome
25	2000	58/F	+	-	192	+/-	1.5	0.77 g/day	+	mPSL, PSL, CYP	imp
26	2006	47/F	+	-	228	+/	2.7	6.5 g/day	+	mPSL, PSL, CYP	imp
27	2006	42/F	+	+, #	168	+/-	6.0	+	+	mPSL, PSL, CYP, PE	dead
28	2011	68/F	+	-	48	*+/-	0.58	2+	+	PSL	dead
29	2013	42/F	+	-	36	+/-	0.9	11 g/day	+	PSL, CYP	imp
30	2014	35/F	+	-	8	+/	0.95	4.1 g/day	+	mPSL, PSL, CYP	imp
31	1992	63/F	-	+	7	+/-	2.3	2.07 g/day	+	PSL, mPSL, CYP	imp
32	1996	74/F	-	+	36	+/-	2.6	1.60 g/day	+	mPSL, PSL	imp
33	1999	67/F	-	+	7	+/-	2.8	0.43 g/day	+	mPSL, PSL, CYP, PE	imp
34	2000	49/F	-	+	24	+/-	1.3	1.20 g/day	+	mPSL, PSL	imp
35	2009	49/F	-	+	12	+/-	1.2	0.48 g/day	+	mPSL, PSL, MMF	imp
36	2011	86/M	-	+	0	+/-	4.2	1.31 g/day	+	PSL, CYP	ESRD
37	2014	66/F	-	+	72	+/-	2.8	2.40 g/day	+	PSL	imp
38	2015	64/M	-	+	528	+/-	2.22	1.97 g/day	+	mPSL, PSL, CYP, AZA	imp
38	2015	71/F	-	+	101	+/-	2.04	1.70 g/day	+	mPSL, PSL, CYP	imp
38	2015	57/M	-	+	12	+/-	3.77	6.50 g/day	+	mPSL, PSL, CYP	death
39	2015	65/F	-	+	94	+/-	1.6	1.6 g/day	+	mPSL, PSL, AZA	imp
40	2016	71/F	-	+	1	+/+	2.9	1.68 g/day	+	mPSL, PSL, CYP	imp
Our case		67/F	+	+	228	+/-	0.82	0.58 g/gCr	+	mPS, PSL, RTX	imp

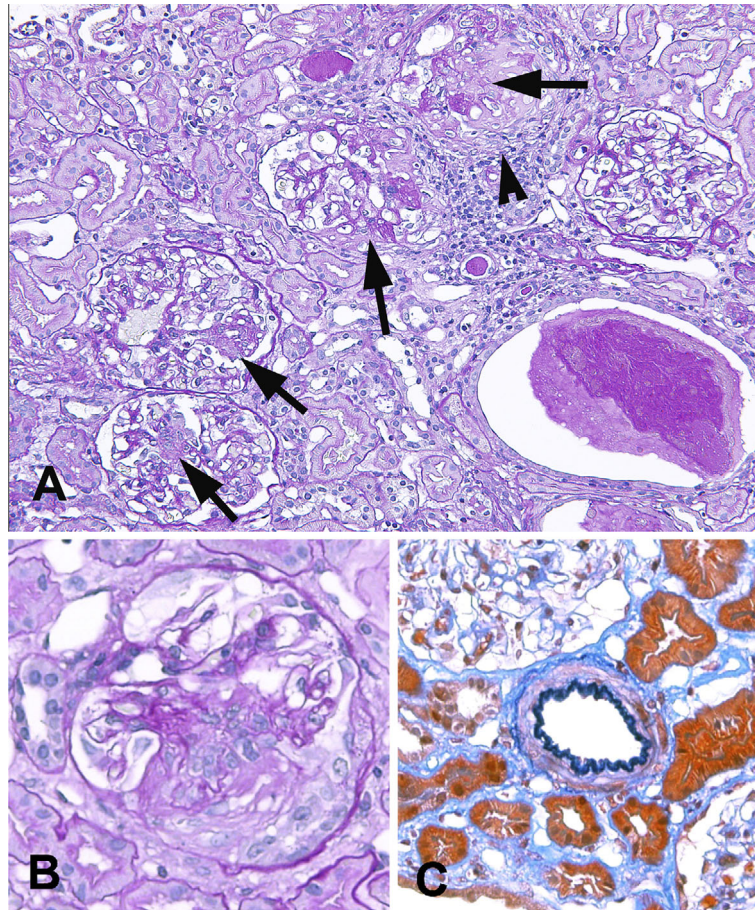
Interval: interval between the first symptoms of Sjögren's syndrome or MCTD and presentation of RPGN, +: presence or positive, -: absence or negative. #: secondary Sjögren's syndrome, \*: MPO-ANCA related crescentic glomerulonephritis and immune complex glomerulonephritis. imp: improvement, ESRD: end stage renal disease, mPSL: methylprednisolone pulse, PSL: oral prednisolone, CYP: cyclophosphamide, PE: plasma exchange, MMF: mycophenolate mofetil, AZA: azathioprine, RTX: rituximab

literature. In contrast to RPGN as the typical renal manifestation of ANCA-associated glomerulonephritis, the patient showed a smoldering clinical course, atypical renal manifestation of ANCA-associated glomerulonephritis with long-term nephritic urinalysis and little or no renal insufficiency. This case may provide an important diagnostic implication of ANCA in patients with MCTD or Sjögren's syndrome presenting with nephritic urinalysis.

### Case Report

A 67-year-old woman presented with proteinuria and hematuria. She had a medical history of MCTD and Sjögren's syndrome at the age of 48. At the diagnosis, her subjective symptoms were characterized by skin eruption, a fever, arthralgia, Raynaud's phenomenon, face erythema, swelling of the fingers of both hands and sicca symptom with keratoconjunctivitis. Laboratory tests showed elevated levels of

anti-nuclear antibody (speckled pattern), anti-U1-RNP antibody and anti-SS-B antibody and leukopenia. A Schirmer tear test and rose bengal test were found to be positive. A lip biopsy was not performed. After initiation of 20 mg/day of prednisolone (PSL), her clinical condition became stable. She had presented with microscopic hematuria 16 months earlier and 1+ proteinuria 11 months earlier at a dose of 8 mg/day of PSL. Three months before admission, a urinary examination showed increased proteinuria of 1.01 g/g creatinine, red cell casts and alpha1-microglobulin of 16.1 mg/L. Blood chemistry showed serum creatinine (Cr) of 1.03 mg/dL, C-reactive protein (CRP) of 0.11 mg/dL and MPO-ANCA of 300 U/mL. The test of ANCA positivity had not been conducted before. Although MPO-ANCA was positive, the patient did not show RPGN or elevated CRP. Therefore, her nephritic urinalysis was suspected to have been caused by Sjögren's syndrome and/or MCTD-associated glomerulonephritis rather than MPO-ANCA-associated glomeru-



**Figure 1.** Light microscopic findings of the kidney biopsy. **A.** Light micrograph shows glomeruli with focal segmental necrotizing lesions (arrows). There are proteinaceous cast formations and mononuclear cell infiltration around a glomerulus with extensive dissolution of the Bowman's capsule (arrow head). Tubulointerstitial nephritis with lymphoplasmacytic infiltration is not observed. (PAS staining)  $\times 200$ . **B.** A glomerulus with fibrinoid necrosis and fibrocellular crescent formation (PAS staining)  $\times 400$ . **C.** A small artery shows no vasculitis (Elastica-Masson staining)  $\times 400$ . PAS: periodic acid-Schiff

lonephritis.

On admission, she had no objective symptoms and no pulmonary or skin lesions. Laboratory examinations showed urinary protein of 0.58 g/g Cr, RBC 30-40/HPF and RBC casts in urinary sediments, serum Cr of 0.82 mg/dL, CRP of 0.16 mg/dL, anti-nuclear antibody of  $\times 320$ , anti-U1-RNP antibody of 11.6 U/mL, anti-SS-A antibody of 1.8 U/mL, anti-SS-B antibody of 0.5 U/mL, MPO-ANCA of 262 U/mL and cryoglobulin (-). A kidney biopsy revealed 1/3 to circumferential fibrocellular to fibrous crescents, with segmental fibrinoid necrosis in 11 out of 37 glomeruli (Fig. 1A and B). However, small crescent formation was predominantly found. Tubulointerstitial nephritis and arteritis were not observed (Fig. 1A and C). An immunofluorescence study showed no immune reactant. Pauci-immune focal segmental necrotizing crescentic glomerulonephritis due to MPO-ANCA-associated vasculitis was diagnosed.

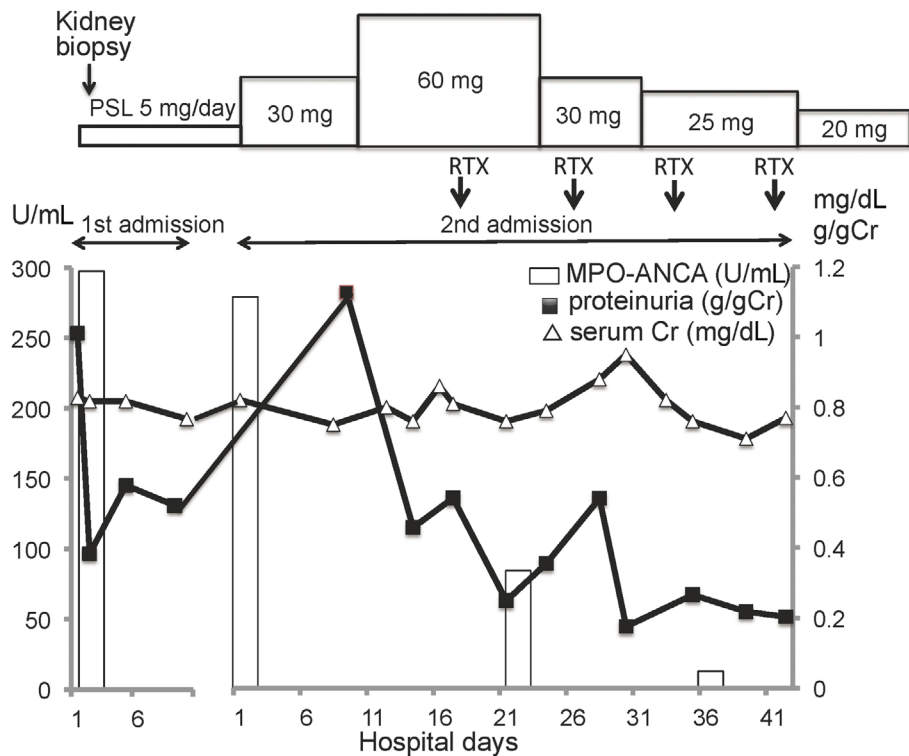
The clinical course is shown in Fig. 2. The patient was treated with 30 mg/day of PSL; however, 1 month after the treatment, her laboratory data had not improved. Thus, the

dose of PSL was raised to 60 mg/day in combination with intravenous rituximab 560 mg every week for a total of 4 doses.

The clinical condition was improved 5 weeks after the therapy, and the patient was discharged with proteinuria (-), hematuria (-) and MPO-ANCA of 7.4 U/mL. One year after the discharge, the patient's status was stable, and clinical remission of ANCA-associated glomerulonephritis had been maintained at a dose of 10 mg/day of PSL.

## Discussion

We reported a patient with MCTD and secondary Sjögren's syndrome presenting with a smoldering clinical course of ANCA-associated glomerulonephritis. Her nephritic urinalysis was suspected to be caused by glomerulonephritis, such as MPGN or mesangial proliferative glomerulonephritis, which are rarely reported in patients with MCTD or pSS (1-7) before a kidney biopsy, because she showed year-long nephritic urinalysis without elevated



**Figure 2.** Clinical course. PSL: prednisolone, RTX: 560 mg rituximab, MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibody, Cr: creatinine

serum creatinine and elevated CRP despite MPO-ANCA positivity.

The characteristic feature of ANCA-associated glomerulonephritis is a focal necrotizing glomerulonephritis associated with crescent formation, and the typical renal manifestation is RPGN with hematuria, proteinuria and elevated serum creatinine (13). The renal manifestation in a smaller subset of patients is a smoldering, remitting and relapsing course, and the pathology shows glomerular sclerosis either alone or accompanied by focal active lesions with necrosis and crescents (14, 15). Our case may therefore be an instance of the latter renal manifestation, which does not necessarily indicate a favorable prognosis. Extra-renal manifestations, such as vasculitis allergica cutis (16) or arthralgia (17), have been reported to be an opportunity to identify patients with either a smoldering course or a slowly progressive course of ANCA-associated glomerulonephritis. However, if such patients do not show any extra-renal manifestations, then the presence of proteinuria and/or hematuria, as identified by routine urine tests, are thus thought to be symptoms which indicate the early phase of the disease.

The serum Cr level may not have increased in our patient due to there being less glomerular injury at the time of the kidney biopsy than in characteristic ANCA-associated glomerulonephritis. This may be due in part to the low activity of nephritogenic MPO-ANCA and/or the anti-inflammatory action of low-dose corticosteroid treatment.

Connective tissue diseases have been reported to be occasionally associated with ANCA-associated glomerulonephritis during the clinical course. However, no causal relation-

ship between connective tissue diseases and ANCA-associated vasculitis has been found. Various factors have been proposed to be involved in ANCA-associated vasculitis, including heredity, environment, infection and cellular or humoral immunity (18). One explanation for the development of ANCA-associated vasculitis in some MCTD/SS patients may be an infectious trigger caused by the relatively immunosuppressed condition associated with systemic autoimmune diseases and their treatments (19). B-cell depletion therapy is a well-established therapeutic option for inducing and maintaining remission in patients with ANCA-associated vasculitis (20). Recent reports have also shown that B-cell depletion brought about favorable results with regard to reducing the systemic disease activity in patients with MCTD (21, 22) and pSS (23, 24). Thus, increased B-cell-associated autoimmunity might lead to an excessive production of immunoglobulins and various autoantibodies, which is shared as a common mechanism of pathogenesis between MCTD/SS and ANCA-associated vasculitis. Our patient was successfully treated with high-dose PSL and rituximab as B-cell depletion therapy after insufficient effect of 30 mg/day of PSL.

The reported cases of MCTD or pSS presenting with pauci-immune ANCA-associated glomerulonephritis are listed in the Table. There was only one case report in which ANCA-associated glomerulonephritis occurred in a patient with both MCTD and Sjögren's syndrome. All cases showed proteinuria, hematuria, MPO-ANCA positivity and RPGN. The mean interval between the first symptoms of pSS or MCTD and presentation of RPGN was 94.8 months.

Three of the 18 cases died of organ failure or infection, and 1 developed end-stage renal disease despite immunosuppressive treatment. None of the reported cases were treated with rituximab. Our case showed smoldering ANCA-associated glomerulonephritis at the later clinical course of MCTD and Sjögren's syndrome and was successfully treated with high-dose PSL and rituximab.

In summary, the determination of ANCA is necessary in patients with MCTD or Sjögren's syndrome who present with nephritic urinalysis even without RPGN, as ANCA-associated glomerulonephritis can be a complication of MCTD or Sjögren's syndrome. In addition, renal pathology is essential for obtaining the correct diagnosis and appropriately managing ANCA-associated glomerulonephritis.

**The authors state that they have no Conflict of Interest (COI).**

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