

Case Report

# Sjögren Syndrome-Related Membranous Glomerulonephritis Progressing to Membranoproliferative Glomerulonephritis

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## Keywords

Membranous glomerulonephritis · Membranoproliferative glomerulonephritis · Sjögren syndrome · Hyperthyroidism

## Abstract

We report a case of glomerulopathy in a 36-year-old Japanese woman with primary Sjögren syndrome (pSS). The first renal biopsy suggested membranous glomerulonephritis. However, repeat biopsy was performed after 16 years because of increased proteinuria, revealing membranoproliferative glomerulonephritis with mesangial deposits, subendothelial deposits, and subepithelial deposits. Immunofluorescent studies showed predominant deposition of IgG2 and IgG4. This patient was positive for antinuclear antibody and anti-SS-A antibody.

Sicca syndrome was confirmed by a positive Schirmer test and positive Rose Bengal test. Therefore, pSS-related glomerulopathy was considered to be the most likely diagnosis.

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## Introduction

In patients with primary Sjögren syndrome (pSS), renal involvement is frequent. Tubulointerstitial nephritis is the most common renal manifestation of pSS, while glomerulonephritis is unusual [1]. Membranous glomerulonephritis (MGN) is reported to be one of the most common pathological findings in patients with pSS-related glomerulonephritis [2]. Systemic lupus erythematosus (SLE) is generally diagnosed on the basis of clinical criteria. However, serological data are important for suggesting the possibility of SLE, since antinuclear antibodies (ANA) are closely associated with this condition, including anti-double-stranded DNA (anti-dsDNA) antibody and anti-Smith (anti-Sm) antibody [3, 4]. In patients without these antibodies who meet the diagnostic criteria for SLE, making an accurate diagnosis of lupus becomes more difficult and further investigation is needed [5].

We report a patient who was considered to have MGN for many years, but in whom the final diagnosis was glomerulonephritis associated with pSS. The relation between hyperthyroidism and exacerbation of proteinuria in this patient is also discussed.

## Case Report

In March 2015, a 36-year-old Japanese woman was admitted to our hospital for exacerbation of proteinuria. She first presented to another hospital with massive proteinuria at the age of 19 years. ANA was positive, and the complement titer was low. A renal biopsy specimen containing 20 glomeruli was obtained. Light microscopy showed no global sclerosis and no definite spike formation on the glomerular basement membrane (GBM) (Fig. 1), but immunofluorescence revealed fine granular deposits of IgG and C1q along the GBM. IgG subclasses were not evaluated at that time. Subepithelial electron-dense deposits (EDD) were detected by electron microscopy (EM), but there were no mesangial EDD or tubuloreticular inclusions. MGN was diagnosed.

She was commenced on prednisolone (PSL) at 50 mg daily, and also received steroid pulse therapy (intravenous methylprednisolone at 0.5 g daily for 3 consecutive days) and addition of cyclosporine A (CyA) at 75 mg daily (Fig. 2). Proteinuria subsided and PSL was tapered. Proteinuria relapsed (4 g daily) temporarily during pregnancy, but thereafter decreased to less than 0.5 g daily. In November 2014, proteinuria increased again to over 1 g daily. The dose of CyA was increased to 150 mg daily, but proteinuria became worse. She had no allergies. She did not drink alcohol, but had smoked 1 pack of cigarettes daily for 16 years from 20 years old. There was no family history of SLE or kidney disease.

On admission in 2015, the patient was 153 cm tall and weighed 54 kg. Her blood pressure was 139/78 mm Hg. She had acne on the bilateral malar regions. Joint pain, neurologi-

cal symptoms, and lupus-related skin lesions were all absent. There was no edema of the lower limbs.

Laboratory findings were as follows (Table 1): white blood cell count, 4,100/ $\mu$ L; red blood cell count, 3.67/ $10^6$ / $\mu$ L; hemoglobin, 9.5 g/dL; platelet count, 24.0/ $10^4$ / $\mu$ L; total protein, 5.8 g/dL; albumin, 2.7 g/dL; serum urea nitrogen, 19 mg/dL; serum creatinine, 0.59 mg/dL; total cholesterol, 119 mg/dL; and CRP, 0.0 mg/dL. Immunological tests revealed that ANA was 40.0 (normal: <20.0). She was positive for anti-SS-A (Ro) antibodies at a titer of 1:8, but anti-dsDNA antibody, anti-Sm antibody, anti-ribonucleoprotein (RNP) antibody, anti-phospholipid antibodies (including lupus anticoagulant and anticardiolipin antibodies), the direct Coombs test, and anti-SS-B (La) antibody were all negative. Cryoglobulin was weakly positive. Serum C3 was 46 mg/dL (normal: >86 mg/dL), C4 was 7 mg/dL (normal: >18 mg/dL), and CH50 was 26 U/ml (normal: >30 U/mL). The serum level of IgG was 1,217 mg/dL, IgA was 255 mg/dL and IgM was 68.1 mg/dL. Both hepatitis B virus antibody and hepatitis C virus antibody were negative. The urinary sediment contained 5–10 erythrocytes and 1–5 leukocytes per high-power field. In addition, 24-h protein excretion was 4.65 g and creatinine clearance was 111 ml/min.

#### *Second Renal Biopsy*

Light microscopy of the biopsy specimen contained 13 glomeruli, among which only 1 showed global sclerosis. Diffuse thickening of the GBM and mesangial cell proliferation were revealed by periodic acid-Schiff staining, while GBM spike formation was recognized on periodic acid methenamine-silver staining (Fig. 3). There was mild lymphoid cell infiltration in the interstitium. Immunofluorescence revealed granular deposits of IgG, IgA, IgM (faint staining), C3, C4, and C1q along the GBM. Analysis of IgG subclasses showed that IgG2 and IgG4 were predominant. On EM, in addition to the previous subepithelial EDD, new mesangial and subendothelial EDD were noted. There were also broad EDD extending from the subepithelium to subendothelium. However, tubuloreticular inclusions and ultrastructural evidence of cryoglobulins were not detected.

#### *Clinical Diagnosis*

Although MGN was diagnosed in 1997, membranoproliferative glomerulonephritis (MPGN) with predominance of IgG2 and IgG4 deposits was revealed by the second renal biopsy. Also, this patient was consistently negative for anti-dsDNA antibody and anti-Sm antibody, while being positive for anti-SS-A antibody. Sicca syndrome was a definite diagnosis, because she had a positive Schirmer test (4 mm after 5 min in both eyes) and a positive Rose Bengal test.

pSS could also be diagnosed in this patient since her hypocomplementemia could be explained as due to cryoglobulinemia, because cryoglobulin was consistently positive at a low titer. However, renal biopsy did not show the typical histologic features of cryoglobulinemic glomerulopathy with predominance of IgM deposits.

#### *Clinical Course*

The total cholesterol level usually increases in proportion to the level of proteinuria, but this patient's total cholesterol decreased from 256 mg/dL (2 years previously) to 119 mg/dL and showed an inverse relationship to proteinuria (Fig. 2). Thyroid function tests gave the

following results: thyroid-stimulating hormone (TSH), 0.003  $\mu$ IU/mL (normal:  $>0.54$ ); free thyroxine (FT4), 3.44 ng/dL (normal:  $<1.52$ ); free triiodothyronine, 12.31 pg/ml (normal:  $<4.17$ ); anti-TSH receptor antibody, 20.0 IU/l (normal:  $<2.0$ ). Hyperthyroidism due to Graves' disease was diagnosed. Treatment with methimazole was started on March 16, but was discontinued after 2 weeks because of mild rash and leukopenia. Subsequently, total thyroidectomy was performed on June 19. On August 3, thyroid function was normalized (FT4: 1.08 ng/dL). Even after surgery, she remained in a euthyroid state without thyroid hormone supplementation. Urinary protein decreased to 0.4 g daily, serum C3 was 53 mg/dL, C4 was 14 mg/dL, and CH50 was 30 U/mL. PSL was tapered from 7.5 to 4 mg daily, and CyA was also reduced from 150 mg to 75 mg daily. As of December 2015, her proteinuria remains under 0.5 mg daily. It seems likely that hyperthyroidism developed at 34 years old (two years before diagnosis) when the total cholesterol level decreased.

## Discussion

Patients with SLE can be positive for various autoantibodies, including ANA, anti-dsDNA antibody, anti-Sm antibody, anti-RNP antibody, anti-Ro antibody, and anti-La antibody. Among these, anti-ds DNA antibody is most commonly associated with lupus nephritis (LN), and its titer is usually correlated with disease activity [6]. Anti-Sm antibody has also been reported to show a relation with renal disease, and this association is stronger when anti-Sm antibody is positive together with anti-dsDNA antibody [7]. LN has not been reported in patients negative for both anti-dsDNA and anti-Sm antibodies.

Imai et al. [8] analyzed IgG subclasses in patients with MPGN, MGN, and LN. They concluded that IgG1 and IgG3 are positive in patients with typical LN. Our patient had no deposits of IgG1 and IgG3, which was inconsistent with typical LN.

Anti-SS-A (Ro) antibody is more commonly associated with pSS, although it is also detected in patients with LN. Bossini et al. [2] evaluated the prevalence of renal involvement in 60 patients with pSS. Renal biopsy was done in 9 patients and 3 of them had chronic glomerulonephritis, including MGN, mesangioproliferative glomerulonephritis with C3 deposits, and cryoglobulinemic glomerulonephritis with IgM deposits. Cortez et al. [9] reported a 31-year-old Caucasian woman with pSS who developed nephrotic syndrome. Renal biopsy revealed type I MPGN with fine granular deposits of IgM and C3, while EM demonstrated scattered subendothelial granular dense deposits. However, this case differs from our patient who showed predominance of IgG deposition, including IgG2 and IgG4. Ren evaluated 130 patients with pSS. Renal biopsy was done in 41 patients, among whom 1 had MGN and 2 had mesangial proliferative nephritis. Deposition of IgG, IgM, and C3 was noted, but EM findings were not reported [10]. Skopouli et al. [11] performed a prospective cohort study of 261 patients with pSS, and reported that palpable purpura, a decrease in C4 level, and mixed monoclonal cryoglobulinemia were significant predictors of glomerulonephritis in patients with pSS. Moreover, MPGN with deposition of IgM and C3 has been reported in 6 patients. According to these previous reports, cryoglobulinemic glomerulopathy with predominant deposition of IgM were the typical features of glomerulonephritis in patients with pSS, but IgG subclass staining was not done in patients with glomerulopathies such as MGN and MPGN.

Only a few case reports have described treatment using corticosteroids with or without cyclophosphamide for pSS with renal disease, but such regimens have generally achieved good clinical outcomes [12]. Our patient had hyperthyroidism that responded to total thyroidectomy. Hyperthyroidism is considered to promote proteinuria, and Vargas reported that hyperthyroidism may be related to glomerular hyperfiltration, since it resolved after treatment of the thyroid disease [13]. There has also been a case report that Graves' disease can induce MGN [14].

In conclusion, we evaluated glomerulonephritis in a patient with pSS. Renal biopsy at the onset of nephrotic range proteinuria revealed MGN, but repeat renal biopsy at the relapse of heavy proteinuria 16 years later showed MPGN with mesangial and subendothelial deposits as well as subepithelial deposits. In addition, IgG subclass analysis identified predominant deposition of IgG2 and IgG4. Furthermore, this patient was consistently negative for anti-dsDNA antibody and anti-Sm antibody, while she was positive for anti-SS-A antibody. This patient's nephropathy was considered to be closely related to pSS. Because her proteinuria subsided soon after remission of hyperthyroidism, it seems that hyperthyroidism also contributed to exacerbation of proteinuria, probably via acceleration of hyperfiltration.

### Acknowledgement

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### Statement of Ethics

The present report adhered to the Declaration of Helsinki, and the patient gave her consent for the case report to be published.

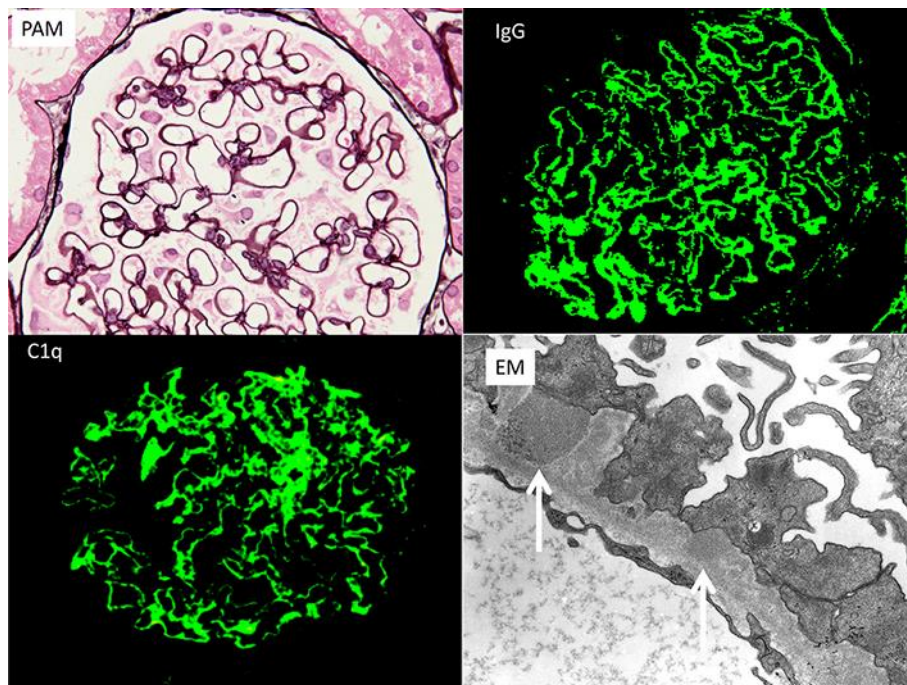
### Disclosure Statement

The authors report no conflicts of interest.

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**Fig. 1.** First renal biopsy specimen. PAM: No definite spike formation in GBM. IgG and C1q: Immunofluorescence reveals fine granular deposits of IgG and C1q along the GBM. EM: Subepithelial EDD are seen (arrows).

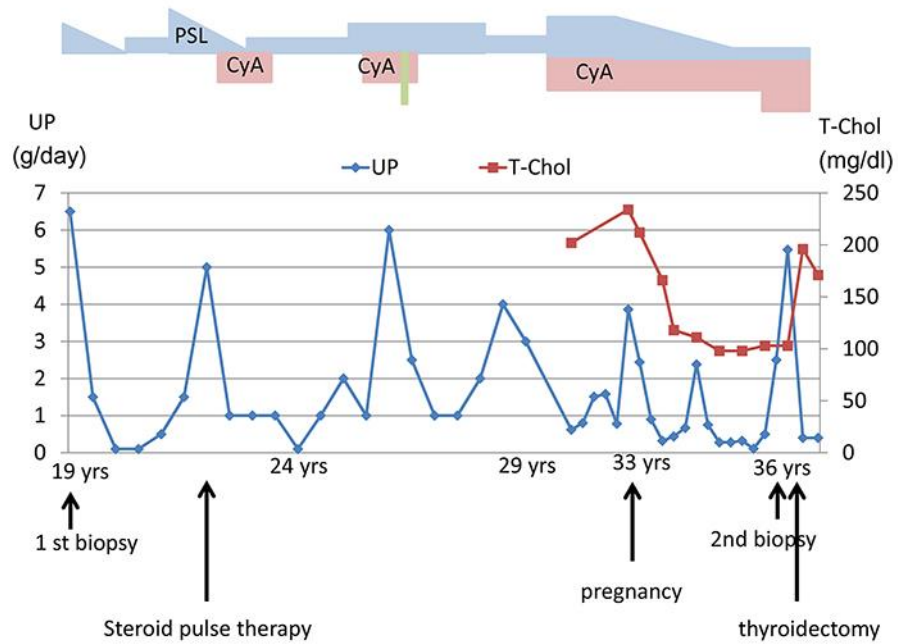
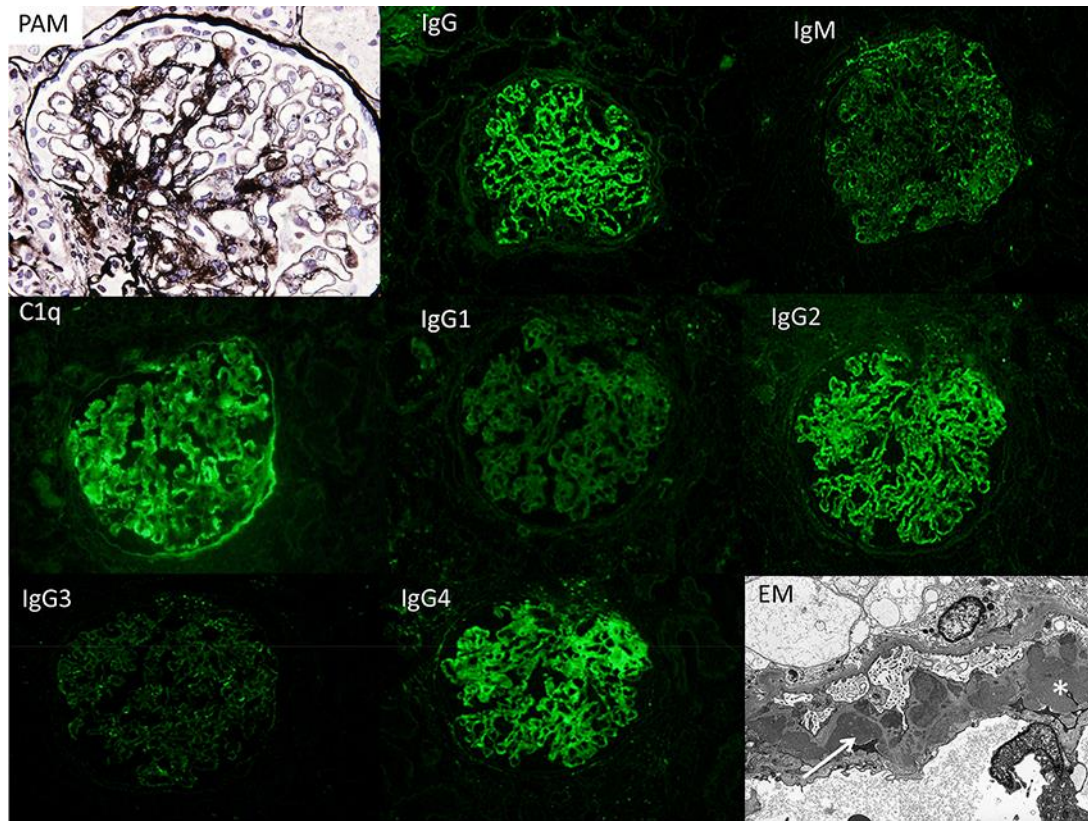


Fig. 2. Clinical course. PSL, prednisolone; CyA, cyclosporine A; yrs, years.





**Fig. 3.** Second renal biopsy specimen. PAM: There is a spike in the GBM. Immunofluorescence microscopy revealed granular deposits of IgG, IgM (faint staining) and C1q along the GBM. IgG deposits were predominantly IgG2 and IgG4. On EM, in addition to subepithelial electron dense deposits (EDD), mesangial and subendothelial (arrow) EDD were noted, along with broad EDD extending from the subepithelium to subendothelium (asterisk).

**Table 1.** Laboratory findings on admission

	On admis- sion	Normal range		On admission	Normal range
White blood count, $\mu\text{L}$	4,100	3,400–9,200	IgG, mg/dL	1,217	870–1,700
Red blood cells, $\times 10^4 \mu\text{L}$	367	400–566	IgA, mg/dL	248	110–410
Hemoglobin, g/dL	9.5	13.0–17.0	IgM, mg/dL	50	35–220
Hematocrit, %	28.5	38.2–50.8	C3, mg/dL	46	86–160
Platelets, $\times 10^4 \mu\text{L}$	24	14.1–32.7	C4, mg/dL	7	17–45
Total protein, g/dL	5.8	6.9–8.4	CH50, U/mL	26	30–50
Albumin, g/dL	2.7	3.9–5.2	ANA	positive (speckle)	negative
Total bilirubin, mg/dL	0.5	0.3–1.1	Anti-ds-DNA	negative	negative
AST, IU/L	33	13–33	Anti-RNP	negative	negative
ALT, IU/L	36	8–42	Anti-Sm	negative	negative
LDH, IU/L	181	119–229	Anti-SS-A (Ro)	positive	negative
CPK, IU/L	39	62–287	Anti-SS-B (La)	negative	negative
ALP, IU/L	213	117–350	Anti-phospholipid	negative	negative
$\gamma\text{GTP}$ , IU/L	49	9–109	Anti-centromere	negative	negative
ChE	184	220–495	Anti-mitochondria	negative	negative
T-Chol	119	120–240	Cryoglobulin	positive	negative
TG	81	30–150	Anti-TSH receptor	20.0 IU/L	<2.0
HbA1c	5.6	4.6–6.2	HCV	negative	negative
UN, mg/dL	19	8–12	HBV	negative	negative
Creatinine, mg/dL	0.59	0.65–1.06	CRP, mg/dL	0.1	0.0–0.3
eGFR	91	>100	Urinalysis		
Urinary acid, mg/dL	6.5	2.5–7.0	Sediment		
Na, mmol/L	142	139–146	RBC/HPF	5–10	<1
K, mmol/L	4.2	3.7–4.8	WBC/HPF	1–5	<1
Cl, mmol/L	110	101–108	Cast	5–10	<1
TSH, $\mu\text{IU/mL}$	0.003	>0.54	Protein, g/day	4.65	<0.1
F-T3, pg/mL	12.3	<4.17	Glucose	negative	negative
F-T4, ng/mL	3.4	<1.52	NAG, IU/day	16.3	0.8–5.0
			$\alpha_1$ -MG, mg/day	20.5	0.6–8.8
			$\beta_2$ -MG, mg/day	390	14–329

ANA, antinuclear antibody; anti-RNP, anti-ribonucleoprotein antibody; HCV, hepatitis C virus; HBV, hepatitis B virus.