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Coexistence of Anti-Glomerular Basement Membrane Glomerulonephritis and Membranous Nephropathy in a Female Patient with Preserved Renal Function

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Renal prognosis for anti-glomerular basement membrane (GBM) glomerulonephritis is poor. The greater the amount of anti-GBM antibody binding the antigen (type IV collagen of the glomerular basement membrane), the greater the number of crescents that develop in glomeruli, resulting in progression of renal impairment. Immunofluorescence staining reveals linear IgG depositions on glomerular capillary walls. Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in middle-aged to elderly patients. Immune complex is deposited in the sub-epithelial space of the glomerulus resulting in the development of a membranous lesion. Immunofluorescence staining reveals granular IgG depositions on glomerular capillary walls. Coexisting anti-GBM glomerulonephritis and MN are rare and, here we report a case of coexisting anti-GBM glomerulonephritis and MN with preserved renal function. There are some cases of coexisting anti-GBM glomerulonephritis and MN do not show severely decreased renal function. A 76-year-old Japanese woman presented with nephrotic syndrome, microscopic hematuria, and was positive for anti-GBM antibody. Kidney biopsy revealed linear and granular IgG depositions in glomerular capillary walls, crescent formations, and electron-dense deposits in the sub-epithelial space. She was diagnosed with anti-GBM glomerulonephritis and MN. Steroid and cyclosporine therapy achieved complete remission, and kidney function was preserved. In conclusion, coexisting anti-GBM glomerulonephritis and MN can have preserved renal function. IgG subclass of deposited anti-GBM antibody may be associated with the severity of anti-GBM glomerulonephritis. In addition, in the case of nephrotic syndrome with hematuria, we should consider the possibility of coexisting anti-GBM glomerulonephritis and MN.

Keywords: anti-glomerular basement membrane glomerulonephritis; hematuria; linear and granular IgG depositions; membranous nephropathy; nephrotic syndrome
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Introduction

The renal prognosis for anti-glomerular basement membrane (GBM) glomerulonephritis is poor. The development of anti-GBM glomerulonephritis is strongly affected by anti-GBM antibody. Anti-GBM antibody binds to type IV collagen in the GBM. The greater the amount of anti-GBM antibody binding the antigen (type IV collagen), the greater the number of crescents that develop in glomeruli, resulting in an increase in serum creatinine and progression of renal impairment (Zhao et al. 2009a).

Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in middle-aged to elderly patients. The development of MN requires an antigen of some variety to create an immune complex. This immune complex is then deposited in the sub-epithelial space of the glomerulus resulting in the development of a membranous lesion. With regard to the response to treatment and renal prognosis, 42% of idiopathic MN patients achieve complete remission, and the renal survival rate of idiopathic MN patients is about 60% after 20 years (Shiiki et al. 2004).

Several cases of coexisting anti-GBM glomerulonephritis and MN have been reported (Klassen et al. 1974; Troxell et al. 2006; Nayak and Satish 2007; Patel et al. 2010; Mori et al. 2012; Tan et al. 2013; Bandak et al. 2014;

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Jia et al. 2014). Some reports suggest cases in which there is preserved renal function (Troxell et al. 2006), despite the development of anti-GBM glomerulonephritis. Here we report a case of coexisting anti-GBM glomerulonephritis and MN that was treated successfully and showed preserved renal function.

Case Presentation

A 76-year-old Japanese woman presented with edema from the toes to the lower abdomen, and leg purpura. No other skin lesions or joint pain were detected. Her weight had increased by 7 kg. Her blood pressure was 168/84 mmHg and she had no fever. Hemoptysis was not observed. Urinary examination revealed urinary protein of 22.4 g/gCr and hematuria was detected (30-49 per high-power field). Urinary β2 microglobulin was elevated at 10,600 μg/L and N-acetyl-beta-D-glucosaminidase was elevated at 22.9 U/L. Blood examination revealed that renal function was almost preserved. Her serum creatinine was 0.83 mg/dL and blood urea nitrogen was 19.9 mg/dL. Total protein was 6.4 g/dL and serum albumin was 1.7 g/dL. Anemia was not detected. Mild inflammation was detected (C-reactive protein 1.23 mg/dL). She was diagnosed with nephrotic syndrome. Anti-nuclear antibody and anti-GBM antibody were positive (anti-GBM antibody titer was 17.2 U/mL), while anti-double strand DNA antibody, MPO-ANCA, and PR3-ANCA were negative (Main laboratory data are shown in Table 1). No lung abnormalities were detected with computed tomography.

A kidney biopsy was performed (Fig. 1A-F). The kidney biopsy specimen included 14 glomeruli, with one showing global sclerosis. Spike or double contour lesions

Table 1. Laboratory data.

Urinary examination			IgG	2361	mg/dL
Protein	3+		IgA	361	mg/dL
(U-TP/U-Cr)	22.4	g/gCr	IgM	164	mg/dL
Hematuria	3+		C3	68	mg/dL
(RBC)	30-49	/HPF	C4	19	mg/dL
Glucose	-		CH50	44.5	U/mL
NAG	22.9	U/L	ANA	x320	
β2MG	10600	μg/L	(Homogenous pattern)		
BJP	Negative		MPO-ANCA	Negative	
			PR3-ANCA	Negative	
Blood examination			Anti-GBM antibody	17.2	U/mL
WBC	8780	/μL	Cryoglobulin	Negative	
Hb	12.2	g/dL	SAA	Negative	
Plt	18.6×10^4	/μL			
TP	6.4	g/dL	Selectivity Index	0.15	
Alb	1.7	g/dL			
BUN	19.9	mg/dL			
Cr	0.83	mg/dL			
Na	143	mEq/L			
K	4.2	mEq/L			
Cl	109	mEq/L			
TC	205	mg/dL			
TG	193	mg/dL			
CRP	1.23	mg/dL			
HbA1c	5.0	%			

U-TP, urinary-total protein; U-Cr, urinary creatinine; RBC, red blood cells; NAG, N-acetyl-β-D-glucosaminidase; β2MG, beta2 microglobulin; BJP, Bence Jones protein; WBC, white blood cells; Hb, hemoglobin; Plt, platelet; TP, total protein; Alb, albumin; BUN, blood urea nitrogen; Cr, creatinine; Na, sodium; K, potassium; Cl, chloride; TC, total cholesterol; TG, triglyceride; CRP, c reactive protein; HbA1c, hemoglobin A1c; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; C3, complement 3; C4, complement 4; CH50, complement hemolytic activity assay; ANA, anti-nuclear antibody; MPO-ANCA, myeloperoxidase-anti-neutrophil cytoplasmic antibody; PR3-ANCA, proteinase 3-anti-neutrophil cytoplasmic antibody; GBM, glomerular basement membrane; SAA, serum amyloid A.

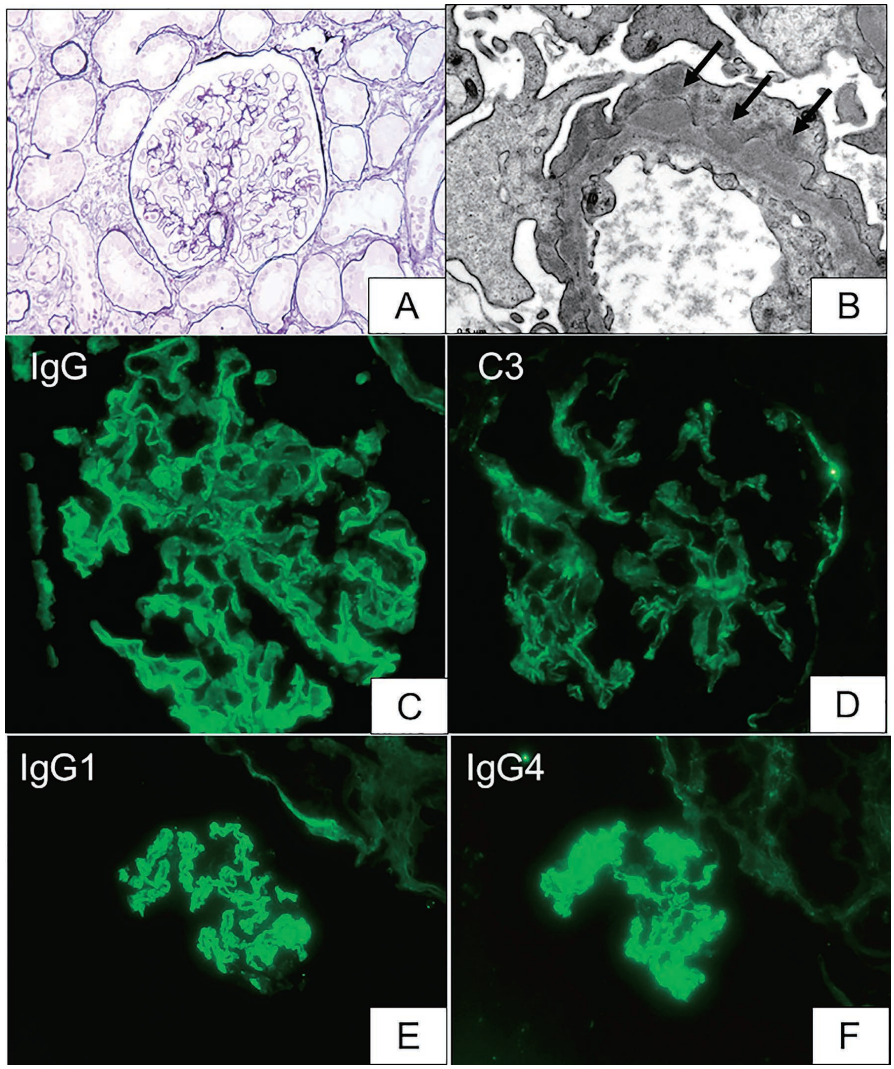

Fig. 1. Histological findings of the first kidney biopsy.
Kidney specimen stained with periodic acid-methenamine silver did not reveal any membranous lesions such as spike formation or double contour lesions (A). Electron microscopy revealed electron-dense deposits in the sub-epithelial space (arrows) (B). Immunofluorescence staining revealed linear and granular patterns of IgG depositions on glomerular capillary walls, while being negative for C3 (C, D). Immunofluorescence staining of IgG subclass revealed IgG1 and IgG4 depositions on glomerular capillary walls (E, F).

were not detected in the GBM. Immunofluorescence staining revealed linear and granular IgG depositions on glomerular capillary walls (IgA, IgM, C3, and fibrinogen were negative). In addition, immunofluorescence staining of IgG subclass analysis revealed linear and granular patterns of IgG1 and IgG4 depositions on glomerular capillary walls. Electron microscopy revealed electron-dense deposits in the sub-epithelial space. These pathological findings suggested that she had MN and anti-GBM glomerulonephritis. MN was diagnosed as stage I (Ehrenreich-Churg classification).

Steroid therapy (methylprednisolone 500 mg/day for 3 days and oral dose prednisolone 30 mg/day) was started. She became negative for anti-GBM antibody but her urinary protein level did not reduce. Cyclosporine was added to the steroid therapy. Although steroid and cyclosporine therapies were continued for 2.5 months, nephrotic syndrome did not achieve clinical remission and a large amount of proteinuria (about 3.0 g/gCr) remained.

A second kidney biopsy was performed (Fig. 2A-H). The kidney biopsy specimen included 19 glomeruli, with six showing global sclerosis, and a fibro crescent being detected in one glomerulus. Spike formation and sub-epithelial deposits were detected on capillary walls, and immunofluorescence staining revealed linear and granular IgG depositions on glomerular capillary walls. In addition, granular C3 and fibrinogen depositions were also observed. Immunofluorescence staining of IgG subclass revealed linear and granular IgG1 depositions on glomerular capillary walls. Electron microscopy revealed electron-dense deposits in the sub-epithelial space, and irregular thickened GBM was observed. The stage of MN had progressed from the first kidney biopsy, and MN was diagnosed as stage III

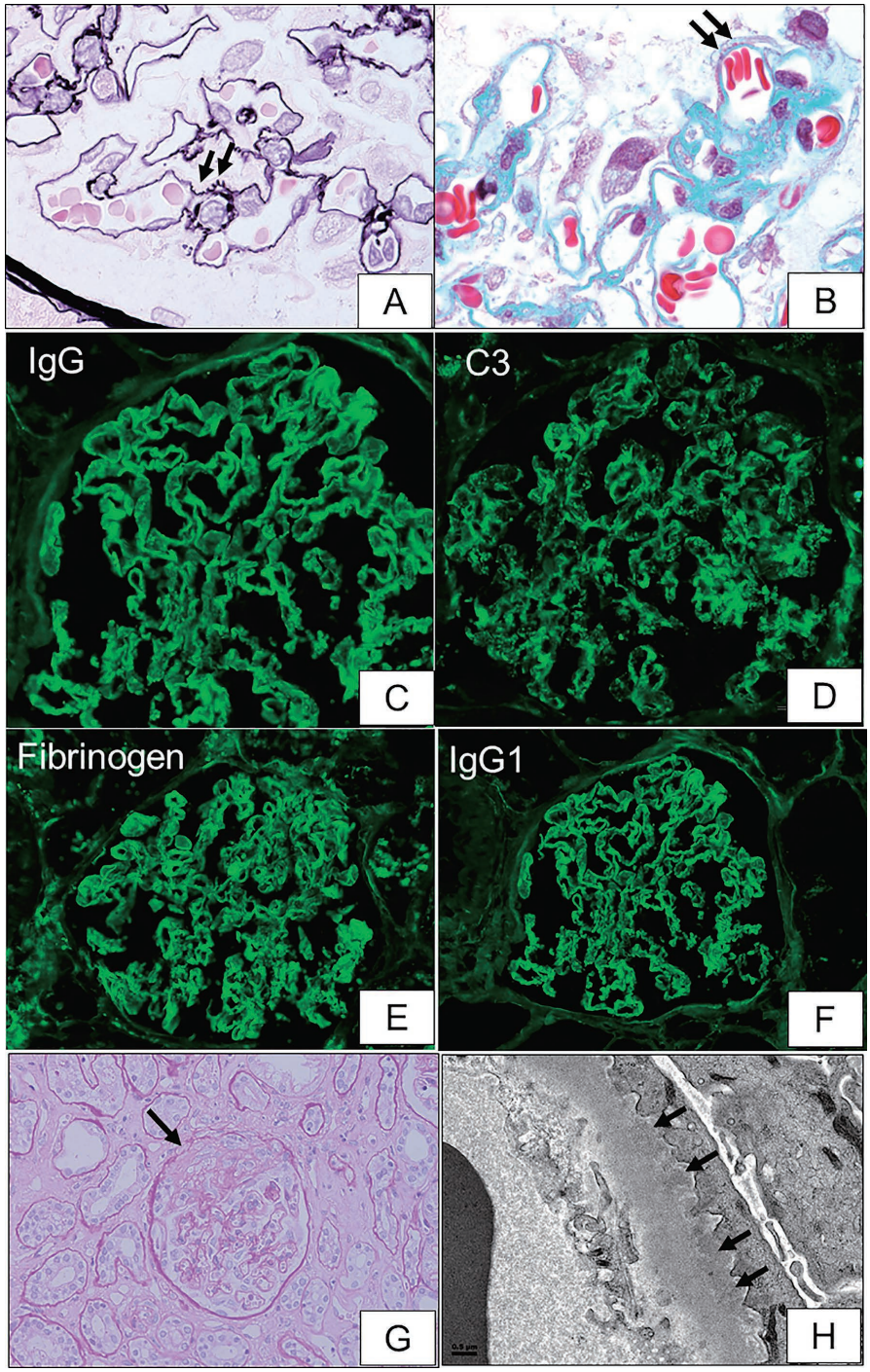

Fig. 2. Histological findings of the second kidney biopsy.
Kidney specimen stained with periodic acid-methenamine silver revealed a spike formation (arrows) in the glomerular basement membrane (A). Kidney specimen stained with Masson's trichrome revealed deposition of immune complexes in the sub-epithelial space (arrows) (B). Immunofluorescence staining revealed linear and granular patterns of IgG depositions on glomerular capillary walls (C). Immunofluorescence staining also revealed granular patterns of C3 and fibrinogen depositions (D, E). Immunofluorescence staining of IgG subclass revealed linear and granular patterns of IgG1 depositions on glomerular capillary walls (F). Kidney specimen stained with periodic acid-Schiff revealed a fibro crescent formation (arrow) in the glomerulus (G). Electron microscopy revealed electron-dense deposits (arrows) in the sub-epithelial space (H).

(Ehrenreich-Churg classification). These findings supported that diagnosis of coexisting MN and anti-GBM glomerulonephritis.

Her urinary protein gradually decreased and hematuria disappeared. Finally, her nephrotic syndrome achieved complete remission 9 months later. Renal function was

preserved and her serum creatinine level was about 1.0 mg/dL.

Discussion

The renal prognosis of anti-GBM glomerulonephritis is extremely poor because crescent formation rapidly progresses, resulting in severe injury to glomeruli (Zhao et al. 2009a). Here we report a case of coexisting anti-GBM glomerulonephritis and MN with preserved renal function.

Previous studies have reported 40 cases of coexisting (not including the current case) anti-GBM glomerulonephritis and MN (Klassen et al. 1974; Troxell et al. 2006; Nayak and Satish 2007; Patel et al. 2010; Mori et al. 2012; Tan et al. 2013; Bandak et al. 2014; Jia et al. 2014). Jia et al. (2014) compared eight cases of coexisting anti-GBM glomerulonephritis and MN with 30 cases of anti-GBM glomerulonephritis alone and found that the incidences of oliguria/anuria and gross hematuria were lower in cases of coexisting anti-GBM glomerulonephritis and MN compared with anti-GBM glomerulonephritis alone. Also, the amount of urinary protein was greater in cases of coexisting anti-GBM glomerulonephritis and MN compared with anti-GBM glomerulonephritis alone. The levels of serum creatinine on diagnosis were higher in cases of anti-GBM glomerulonephritis alone compared with cases of coexisting anti-GBM glomerulonephritis and MN.

The clinical characteristics of 32 cases are presented in Table 2 (Klassen et al. 1974; Troxell et al. 2006; Nayak and Satish 2007; Patel et al. 2010; Mori et al. 2012; Tan et al. 2013; Bandak et al. 2014; Jia et al. 2014), excluding the eight cases reported by Jia et al. (2014), because we were unable to obtain the detail data. Median age of the 32 cases is 47 years and median serum creatinine level is 3.4 mg/dL. Gross hematuria was observed in 63% of cases. Almost all patients were treated with steroid-based immune suppressive therapy. More than half the patients underwent plasma exchange. With regard to prognosis, 56% resulted in death or end-stage renal disease, and 41% had preserved renal function including complete remission. As a previous Japanese study reported a renal survival rate of only 20%, it is thought that the incidence here of preserved renal function in cases of coexisting anti-GBM glomerulonephritis and MN is relatively high (Hirayama et al. 2008).

Of the 32 cases examined, 11 presented with hemoptysis, which were suspected to be caused by alveolar hemorrhage (Table 2). For their prognosis of these 11 cases, five ended with end-stage renal disease and underwent dialysis or died, five showed improved kidney function, and the prognosis for one patient was unknown (Klassen et al. 1974; Troxell et al. 2006; Nayak and Satish 2007; Patel et al. 2010; Mori et al. 2012; Tan et al. 2013; Bandak et al. 2014).

Troxell et al. (2006) examined the relationship between the order of onset of two diseases (anti-GBM glomerulonephritis and MN) and renal prognosis. Five cases developed MN that clearly preceded anti-GBM glomerulonephritis. These patients had a poor renal prognosis and developed end-stage renal disease. Four of five cases, which developed anti-GBM glomerulonephritis that clearly preceded MN, had preserved renal function. The clinical characteristics of the patients had an age range of 17 to 20 years and serum creatinine was normal to 1.4 mg/dL, except for one case.

In the current case, pathological findings of both MN and anti-GBM glomerulonephritis were detected at the first kidney biopsy, and pathological findings of MN were clearly observed at the second kidney biopsy. Although it is unknown which glomerular disease (MN or anti-GBM glomerulonephritis) developed first in the current case, the preserved renal function suggests that anti-GBM glomerulonephritis preceded MN. However, we should also consider the possibility of the simultaneous occurrence of anti-GBM glomerulonephritis and MN. At onset, severe hematuria and heavy proteinuria, which indicated anti-

Table 2. Clinical characteristics, symptoms, treatment, and prognosis of 32 cases of coexisting anti-GBM glomerulonephritis and membranous nephropathy.

Number of cases	32	
Age	47	16-71
Sex (male: female : unknown)	21:10:1	
Serum creatinine (mg/dL)	3.4	0.7-25.0
Gross hematuria (n, %)	20	63
Proteinuria (g/day)	3.0	0.1-27.9
Hemoptysis (n, %) (suspected alveolar hemorrhage)	11	34
Treatment		
PSL + CP + PE (n, %)	13	41
PSL + PE (n, %)	5	16
PSL + CP (n, %)	3	9
PSL + AZA (n, %)	3	9
PSL (n, %)	3	9
other (n, %)	5	16
Prognosis		
Death or ESRD (n, %)	18	56
preserved renal function (n, %)	13	41
unknown (n, %)	1	3

Continuous variables are presented with median and range, categorical variables are presented with number (n) and percentage. The data of the selected 32 cases were taken from the following reports (Klassen et al. 1974; Troxell et al. 2006; Nayak and Satish 2007; Patel et al. 2010; Mori et al. 2012; Tan et al. 2013; Bandak et al. 2014; Jia et al. 2014).

AZA, azathioprine; CP, cyclophosphamide; ESRD, end stage renal disease; PE, plasma exchange; PSL, prednisolone.

GBM glomerulonephritis and MN, respectively, were observed. In addition, pathological findings from the first kidney biopsy included linear IgG depositions in the GBM and granular IgG depositions in the sub-epithelial space, indicating anti-GBM glomerulonephritis and MN, respectively. Although almost all cases of simultaneous anti-GBM glomerulonephritis and MN have a poor renal prognosis, some cases have been reported in which patients did have a good renal outcome (Troxell et al. 2006). Therefore, the current case is not inconsistent with previously reported cases. It is possible that anti-GBM glomerulonephritis was at a very early stage.

In addition, the patient here had severe edema stemming from nephrotic syndrome caused by MN. After admission to hospital, she underwent a kidney biopsy and was diagnosed with anti-GBM glomerulonephritis. It is possible that the observed nephrotic syndrome could be used as a clue to help diagnose and initiate treatment in early-stage anti-GBM glomerulonephritis. Nephrotic syndrome with hematuria and linear IgG depositions in the GBM indicated possible coexistence of anti-GBM glomerulonephritis and MN. If anti-GBM glomerulonephritis is diagnosed at an early stage, successful treatment and preserved renal function may be possible. The clinical course in the current study had a good renal prognosis, which is different from typical cases of anti-GBM glomerulonephritis alone.

A possible reason for why anti-GBM glomerulonephritis and MN coexist is that with anti-GBM glomerulonephritis, injury to podocytes results in increased antigens that leads to immune complex deposits in the sub-epithelial space (Nasr et al. 2003). In an experiment in which mercuric chloride was injected into rats, IgG first appeared as deposits in a linear pattern in the GBM and then in a granular pattern in the sub-epithelial space (Fukatsu et al. 1987).

A possible reason for why coexisting anti-GBM glomerulonephritis and MN does not result in severely decreased renal function could be through the response of anti-GBM antibody to the C-terminal of the $\alpha 3$ chain of type IV collagen in the GBM (Kalluri et al. 1995; Zhao et al. 2009a; Nasr et al. 2016). It is reported that anti-GBM antibody responds to the $\alpha 1$-$\alpha 5$ chains in anti-GBM glomerulonephritis alone, while anti-GBM antibody responds only to the $\alpha 3$ chain in coexisting anti-GBM glomerulonephritis and MN (Kalluri et al. 1995; Zhao et al. 2009a; Nasr et al. 2016). In addition, Jia et al. (2014) reported that renal survival in cases of coexisting anti-GBM glomerulonephritis and MN was better than that in anti-GBM glomerulonephritis alone. The reason given was that the target antigen spectrum of circulating anti-GBM antibody was narrower in cases of coexisting anti-GBM glomerulonephritis and MN compared with anti-GBM glomerulonephritis alone. It was suggested that sera in most cases of coexisting anti-GBM glomerulonephritis and MN recognize the $\alpha 3$ chain of type IV collagen in GBM alone, while sera in most cases of anti-GBM glomerulonephritis alone recognize more than one type of α chain of type IV collagen (Jia et al. 2014). The greater the anti-GBM antibody response to the antigen, the greater the number of crescents that develop in glomeruli. Therefore, coexisting anti-GBM glomerulonephritis and MN has fewer crescent formations, and some cases show a good renal prognosis.

We performed immunofluorescence staining of IgG subclass in the current case. First kidney biopsy revealed linear and granular IgG1 and IgG4 deposition. Granular IgG1 and IgG4 deposition indicated idiopathic MN. Previous reports have suggested that IgG1 and IgG4 deposition were mainly observed in cases of anti-GBM glomerulonephritis (Bowman et al. 1987; Noël et al. 1988). In addition, Zhao et al. (2009b) has investigated the relationship between IgG subclass and clinical feature of anti-GBM glomerulonephritis. They suggested that IgG1 and IgG3 subclasses of anti-GBM antibodies influence to the progression of renal damage of anti-GBM glomerulonephritis (Zhao et al. 2009b). The reason that glomerular IgG3 deposition was negative in the current case, might be associated with a good renal prognosis.

In the current case, there was no C3 deposition observed with the first kidney biopsy but the deposition was detected with the second kidney biopsy. These findings are important. Because serum anti-GBM antibody was negative at the time of the second kidney biopsy, it was thought that the observed C3 depositions were not associated with anti-GBM glomerulonephritis. MN had progressed from stage I to stage III (Ehrenreich-Churg classification). These findings suggested that C3 depositions at the second kidney biopsy reflected the disease severity of MN. And because severe proteinuria remained, this supported the progression of MN stage.

Unfortunately, no studies have examined whether C3 is deposited in the GBM in cases of coexisting anti-GBM glomerulonephritis and MN; however, 50-90% of cases of anti-GBM glomerulonephritis alone show C3 depositions in the GBM (Fischer and Lager 2006; Ma et al. 2014).

The relationship between anti-GBM glomerulonephritis and complemental activity has been studied, suggesting that classical and alternative complement pathways are associated with inflammation and disease severity in anti-GBM glomerulonephritis (Sheerin et al. 1997; Ma et al. 2014). In animal experiments, glomerular injury and kidney dysfunction are attenuated in C3- and C4-deficient mice compared with wild-type mice after the development of anti-GBM glomerulonephritis (Sheerin et al. 1997). In the current case, C3 deposition was not detected at the first kidney biopsy, and we thought that inflammation due to anti-GBM glomerulonephritis had not progressed, resulting in a good renal prognosis.

In conclusion, coexisting anti-GBM glomerulonephritis and MN can contribute to preserved renal function. In addition, in the case of nephrotic syndrome with hematuria, we should consider the possibility of coexisting anti-GBM glomerulonephritis and MN. More case reports are required

to increase our understanding of the coexistence of anti-GBM glomerulonephritis and MN.

Consent for Publication

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images.

Conflict of Interest

The authors declare no conflict of interest.

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