

[ CASE REPORT ]

## The Sequential Development of Antiglomerular Basement Membrane Nephritis and Myeloperoxidase-antineutrophil Cytoplasmic Antibody-associated Vasculitis

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### Abstract:

A 55-year-old woman presented with deafness, increased levels of myeloperoxidase (MPO)-antineutrophil cytoplasmic antibody (ANCA), and renal insufficiency with proteinuria and hematuria. Renal biopsy revealed crescentic glomerulonephritis with the linear deposition of immunoglobulin G along the glomerular basement membrane (GBM) and peritubular capillaritis. The anti-GBM antibody levels on admission and 10 days after admission were 11.7 U/mL and 127 U/mL, respectively. These results indicated the sequential development of anti-GBM nephritis and MPO-ANCA-associated vasculitis. This report shows that anti-GBM nephritis may be caused by MPO-ANCA-associated vasculitis because of preceding otitis media, the sequential anti-GBM antibody titers, and the findings of peritubular capillaritis.

**Key words:** anti-glomerular basement membrane nephritis, myeloperoxidase-antineutrophil cytoplasmic antibody-associated vasculitis, sensory deafness, peritubular capillaritis

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### Introduction

Antiglomerular basement membrane (anti-GBM) nephritis is a necrotizing and crescentic glomerular disease caused by anti-GBM antibodies. The target antigen of anti-GBM antibodies is known to be the NC1 domain of the  $\alpha3$  chain of type IV collagen (1). The normal structural configuration of type IV collagen hexamers in the GBM prevents antigen-antibody interactions. Hydrocarbon exposure, smoking, and infections, such as flulike illness, are associated with the disclosure of the hidden antigen (2, 3). Anti-GBM nephritis is possibly caused by antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis because ANCA has a strong membrane-disordering action. Some case reports have already indicated the sequential development of anti-GBM nephritis and ANCA-associated vasculitis (4, 5). To the best of our knowledge, there are no reports on anti-GBM nephritis induced by ANCA-associated vasculitis in the clinical set-

ting. We herein report a possible case of the sequential development of anti-GBM nephritis due to myeloperoxidase (MPO)-ANCA-associated vasculitis in the clinical setting.

### Case Report

A 55-year-old woman with no history of diabetes mellitus complained of bilateral earache and was treated by an otorhinolaryngological practitioner in November 2014. Although her serum creatinine (sCr) level was within the normal limits (0.61 mg/dL), her C-reactive protein (CRP) level was slightly elevated (0.61 mg/dL), and her urine test results were as follows: protein, 1+; occult blood, 3+; and urinary sediment of red blood cells, 300/ $\mu$ L, from the beginning of February 2015. The patient was referred to the Department of Otorhinolaryngology in our hospital after her bilateral earache became aggravated in late February 2015. MPO-ANCA-associated otitis media was suspected because of sensory deafness and a high MPO-ANCA titer (>300 U/mL)

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**Table. Laboratory Findings on Admission.**

Hematology		Blood Chemistry		Immunology	
WBC	13,410/ $\mu$ L	Na	135 mEq/L	CRP	8.75 mg/dL
RBC	402 $\times$ 10 <sup>4</sup> / $\mu$ L	K	3.7 mEq/L	C3	74 mg/dL
Hb	11.7 g/dL	Cl	97 mEq/L	C4	29 mg/dL
Hct	36.1%	Ca	8.9 mg/dL	CH50	60 U/mL
Pt	34.2 $\times$ 10 <sup>4</sup> / $\mu$ L	Pi	2.4 mg/dL	IgG	2,039 mg/dL
		BUN	10.8 mg/dL	IgA	497 mg/dL
		sCr	1.10 mg/dL	IgM	82 mg/dL
		UA	4.7 mg/dL	ANA (<40)	160 $\times$
		T-Bil	0.7 mg/dL	MPO-ANCA (<3.5)	>300 U/mL
		AST	16 U/L	PR3-ANCA (<3.5)	<1.0 U/mL
		ALT	10 U/L	Urinalysis	
		LDH	148 U/L	Protein	2+
		CPK	32 U/L	Protein excretion	1.51 g/gCr
		ALP	179 U/L	Sugar	–
		ChE	174 U/L	Occult blood	3+
		TP	7.7 g/dL	Sediment of RBC	411 / $\mu$ L
		Alb	3.1 g/dL	NAG (0.7-11.2)	17.2 U/mL
		HbA1c	5.3%	$\beta$ 2 MG (<230)	29,622 $\mu$ g/L

The data in parentheses means normal range in each laboratory finding.

BUN: blood urea nitrogen, sCr: serum creatinine, UA: uric acid, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CPK: creatine phosphokinase, ALP: alkaline phosphatase, ChE: choline esterase, TP: total protein, Alb: albumin, HbA1c: hemoglobin A1c, CRP: C-reactive protein, CH50: complement activity, Ig: immunoglobulin, ANA: antinuclear antibody, ANCA: antineutrophil cytoplasmic antibody, MPO: myeloperoxidase, PR3: proteinase 3, NAG: N-acetyl- $\beta$ -D-glucosaminidase,  $\beta$ 2 MG:  $\beta$ 2-microglobulin

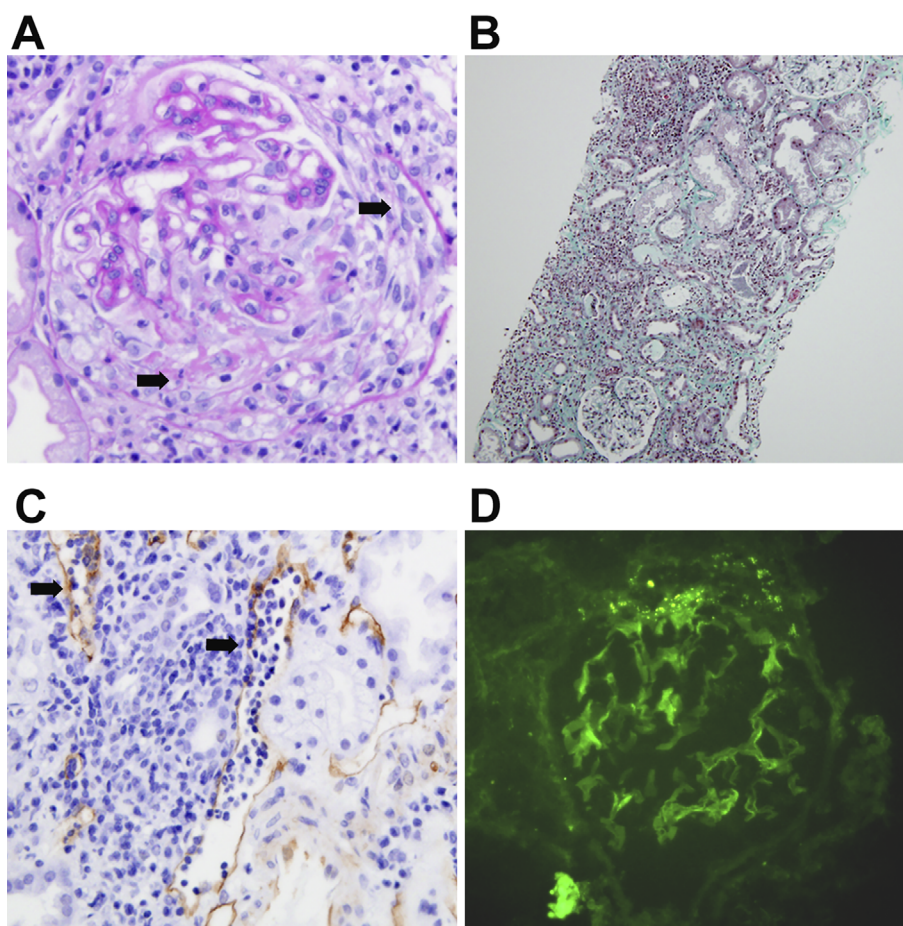
(normal range, <3.5 U/mL). The patient was referred to our Department of Nephrology and was admitted in the beginning of March 2015 because of renal insufficiency (sCr, 0.89 mg/dL) with CRP level elevation (4.99 mg/dL), proteinuria (3+), and hematuria (3+).

On admission, her blood pressure was 123/76 mm Hg and she had a regular pulse rate (105 beats/min). Her height and body weight were 151 cm and 55.5 kg, respectively. Her body temperature was slightly elevated (37.7°C). With the exception of bilateral hearing loss, the findings of physical examination were unremarkable. A serum analysis revealed the following findings: white blood cells, 13,410/ $\mu$ L; hemoglobin, 11.7 g/dL; platelets, 34.2 $\times$ 10<sup>4</sup>/ $\mu$ L; urea nitrogen, 10.8 mg/dL; sCr, 1.10 mg/dL; CRP, 8.75 mg/dL; albumin, 3.1 g/dL; hemoglobin A1c, 5.3%; MPO-ANCA, >300 U/mL, and proteinase 3 (PR3)-ANCA, <1.0 U/mL (normal range, <3.5 U/mL). Her urine test results were as follows: protein, 2+; daily urinary protein excretion, 1.51 g/gCr; occult blood, 3+; urinary sediment of red blood cells, 411/ $\mu$ L; urinary N-acetyl- $\beta$ -D-glucosaminidase (NAG), 17.2 U/mL, and urinary  $\beta$ 2-microglobulin, 29,622  $\mu$ g/L (Table). Although chest computed tomography did not show alveolar hemorrhage, a slight reticular shadow was detected in the bilateral lower lungs.

MPO-ANCA-associated vasculitis was considered based on the systemic inflammatory findings (fever and an increased serum CRP level), the presence of otitis media, the reticular shadow in her lungs and rapidly progressive glomerulonephritis, and her high MPO-ANCA titer. Thus,

steroid therapy [oral prednisolone (40 mg, daily)] was initiated a day after admission. Renal biopsy was performed 9 days after admission and revealed cellular crescents in 41% of the glomeruli with segmental fibrinoid necrosis (Fig. 1A). Widespread tubular atrophy and interstitial fibrotic changes were present with diffuse mononuclear cell infiltration (Fig. 1B), and peritubular capillaritis was occasionally observed (Fig. 1C). Immunofluorescence microscopy showed linear deposits of immunoglobulin G along the GBM (Fig. 1D). No C3 staining was found in the immunological examination (data not shown). The anti-GBM antibody level in a remaining serum sample that had been collected on the admission day was 11.7 U/mL (normal limits, <3.0 U/mL). In addition, the anti-GBM antibody level was remarkably elevated to 127 U/mL at 10 days after admission. The reticular shadow in the lungs was not aggravated in parallel with the increase in the patient's anti-GBM antibody. In contrast, the patient experienced rapidly progressive renal dysfunction caused again when an increase in the anti-GBM antibody titer was detected. The sequential development of anti-GBM nephritis and MPO-ANCA-associated vasculitis was diagnosed.

Steroid pulse therapy [methylprednisolone (1,000 mg, daily for three consecutive days)] and plasma exchange followed by double-filtration plasmapheresis were initiated at 25 days after admission. Moreover, oral cyclophosphamide was administered at 1 month after admission. Subsequently, the anti-GBM antibody and CRP levels decreased to within normal limits, and the MPO-ANCA titer, proteinuria, and



**Figure 1.** Light and immunofluorescence microscopic examinations of the renal biopsy specimens. Light microscopy of the renal biopsy specimen reveals cellular crescents in half of the glomeruli along Bowman's capsule (indicated by arrows) (periodic acid-Schiff staining,  $\times 400$ ) (A), widespread tubular atrophy, and interstitial fibrotic changes with diffuse mononuclear cell infiltration (Masson's trichrome staining,  $\times 100$ ) (B) and peritubular capillaritis showing the accumulation of polymorphonuclear and mononuclear cells in the peritubular capillary with the disruption of the capillary walls (anti-CD34 antibody staining; indicated by arrows; original magnification  $\times 400$ ) (C). Immunofluorescence microscopy shows linear deposits of immunoglobulin G along the glomerular basement membrane (original magnification  $\times 400$ ) (D).

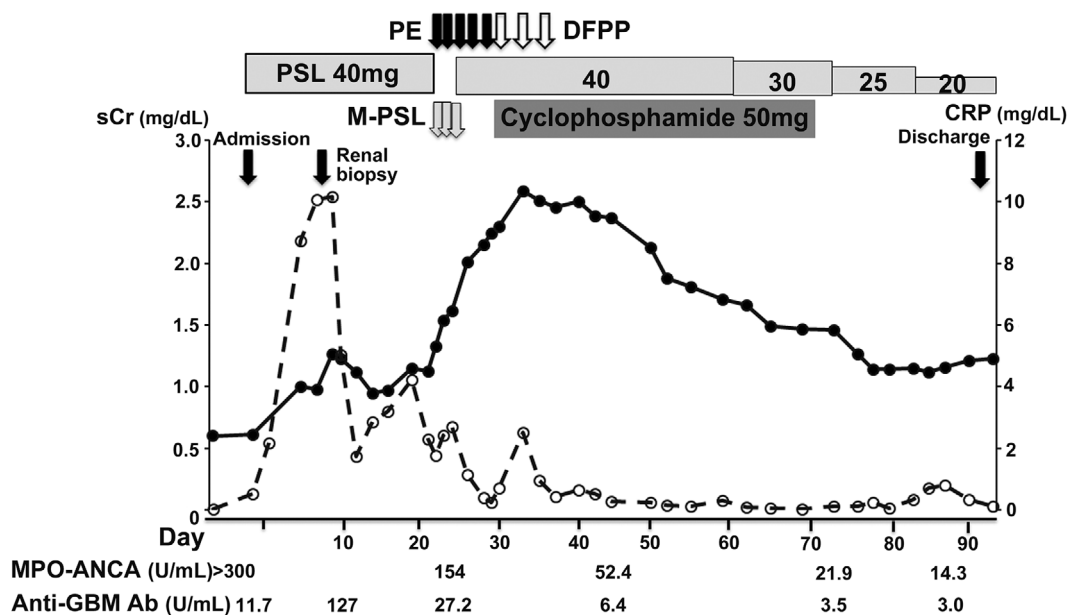
hematuria returned to levels that were almost within the normal limits. Although the patient's renal function did not completely improve, the sCr levels returned to approximately 1.2 mg/dL (Fig. 2). Moreover, the patient's sensory deafness was ameliorated, and the reticular shadow in the bilateral lower lungs was partially resolved.

## Discussion

Some previous reports have already demonstrated the relationship between elevated levels of ANCA and anti-GBM antibodies. A single-center study of 205 patients with anti-GBM nephritis reported that 30.7% of the patients showed elevated ANCA levels. Similarly, a composite of 11 previous studies, which included 727 patients with anti-GBM nephritis, reported that 31.5% of the patients showed elevated ANCA levels (6, 7). However, serious concern has been raised regarding these reports: whether both ANCA-

associated vasculitis and anti-GBM nephritis are simply complications or whether they have a cause-and-effect relationship is unclear.

ANCA has a strong membrane-disordering action. In addition, when serum samples of patients with anti-GBM nephritis were investigated repeatedly, a greater percentage were found to have a detectable level of ANCA before they had a detectable anti-GBM antibody level in comparison to those that had a detectable anti-GBM antibody level before they had a detectable level of ANCA (before anti-GBM antibody, 40% vs. after anti-GBM antibody, 0%,  $p < 0.001$ ) (8). Thus, ANCA-associated vasculitis has been widely considered to be the cause of anti-GBM nephritis. Moreover, some case studies have reported the sequential development of anti-GBM nephritis after ANCA-associated glomerulonephritis (4, 5). However, clearly stating that anti-GBM nephritis is induced by ANCA-associated vasculitis in the clinical setting is impossible because anti-GBM nephritis was caused



**Figure 2.** The time course after admission. The solid line with closed circles indicates the serum creatinine (sCr) levels; the dashed line with open circles indicates the C-reactive protein (CRP) levels. PSL: prednisolone, m-PSL: methyl-prednisolone, PE: plasma exchange, DFPP: double filtration plasmapheresis, MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibody, anti-GBM Ab: anti-glomerular basement membrane antibody, sCr: serum creatinine, CRP: C-reactive protein

after a long period of ANCA-associated vasculitis, and no evidence shows that ANCA-associated vasculitis caused the pathological lesions of glomerular or alveolar basement membrane to expose the NC1 domain of the  $\alpha 3$  chain of type IV collagen. In this case, the anti-GBM antibody level on the day of admission (11.7 U/mL) was not within the normal range ( $<3.0$  U/mL). Moreover, we did not have the information that the first renal biopsy showed crescentic formation without linear immunoglobulin (Ig) G deposition along the GBM or that repeated renal biopsy showed crescentic formation with linear IgG deposition along the GBM. Thus, proving that anti-GBM nephritis was caused by MPO-ANCA-associated vasculitis is difficult. However, this patient had fever, an increased serum CRP level, and otitis media. Although the fever and increased serum CRP levels may be explained as systemic inflammatory findings of anti-GBM nephritis, the finding of otitis media in a patient with anti-GBM nephritis is impossible to explain. Thus, it is clear that ANCA not only existed in, but also induced systemic vasculitis. In addition, peritubular capillaritis was observed in this case. Peritubular capillaritis is not caused by anti-GBM nephritis because type IV collagen is not a constituent of the peritubular capillary. In contrast, the peritubular capillary is one of the target vessels of ANCA-associated vasculitis (9). Thus, ANCA-associated vasculitis has been considered to play an important role in pathological damage of the kidney. Namely, ANCA could cause not only peritubular capillaritis, but also necrotizing crescentic glomerulonephritis, and that hidden antigen was exposed in the damaged glomeruli. As a result, anti-GBM antibodies were produced and anti-GBM nephritis was induced. Moreover, the anti-

GBM antibody titer reflects the disease activity of anti-GBM nephritis (10). In this case, rapidly progressive renal dysfunction was caused again when the increase in the anti-GBM antibody titer was detected. It is possible that the hidden antigen was extensively exposed by ANCA at this point.

The reticular shadow in the bilateral lower lungs was considered to have been caused by MPO-ANCA-associated vasculitis because this lung disease already existed in the patient with MPO-ANCA-associated vasculitis before admission. This lung disease was not originally severe, and it was not aggravated, even when the disease activity of MPO-ANCA-associated vasculitis increased in the kidney after admission. Based on these points, it seems difficult to suggest that anti-GBM antibody production was induced by the exposure of a hidden antigen because of the destruction of the alveolar basement membrane by MPO-ANCA. In addition, because the anti-GBM antibody titer has been reported to reflect the disease activity of Goodpasture syndrome (10), and because the lung disease was not aggravated even when the kidney disease activity increased, it would be difficult to attribute this lung disease (including the kidney disease) to Goodpasture syndrome.

In conclusion, we reported a possible case of the sequential development of anti-GBM nephritis due to MPO-ANCA-associated vasculitis in the clinical setting.

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

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