

An Elderly Patient with Diabetic Nephropathy Complicated by ANCA-associated Nephritis

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Abstract

A 67-year-old man, on oral therapy for type 2 diabetes mellitus since 1990, had sustained proteinuria since 2005. When hematuria was first discovered in 2008, renal dysfunction [creatinine (Cr), 1.2 mg/dL], inflammation [C-reactive protein (CRP), 12 mg/dL] and high myeloperoxidase anti-neutrophil cytoplasmic antibodies (MPO-ANCA) levels [546 ELISA units (EU)] were observed. Renal biopsy showed the diagnosis of ANCA-associated nephritis combined with diabetic nephropathy. For this patient, there was pathological proof of the combination of diabetic nephropathy and ANCA-associated vasculitis.

Key words: ANCA-associated nephritis, type 2 diabetes mellitus, diabetic nephropathy

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Introduction

There has been a steady increase in diabetic nephropathy in recent years, which has been caused by increased numbers of diabetic patients and interruptions in follow-up. Since 1998, diabetic nephropathy has been the primary cause of the initiation of dialysis in Japan; the management of diabetic nephropathy is therefore very important from the standpoint of prognosis. Approximately 20% to 30% of diabetic nephropathy cases are also complicated by non-diabetic nephropathy, particularly IgA nephropathy and membranous nephropathy (1). Thus, complication by another nephrotic syndrome should be considered when there is worsening of renal dysfunction or abnormal urinalysis that does not concur with the natural course of diabetic nephropathy.

To date, there have been 9 reported cases of diabetic nephropathy complicated by nephritis and associated with anti-neutrophil cytoplasmic antibodies (ANCA) (2-9), including the present case, but only 3 of these cases have shown pathological evidence of diabetic nephropathy. The present case is a rare case of nephropathy in which patho-

logical examination proved the co-existence of ANCA-associated nephritis and diabetic nephropathy. ANCA-associated nephritis, which is often seen in the elderly, can present with a high rate of rapidly progressive glomerulonephritis (RPGN), leading to renal failure; therefore, early diagnosis and treatment are very important.

In the current case, the patient presented with the pathophysiological characteristics of RPGN during the course of diabetic nephropathy; the pathological findings of a renal biopsy sample confirmed that the patient had diabetic nephropathy in combination with ANCA-associated nephritis.

Case Report

The patient was a 67-year-old man with primary complaints of hematuria and proteinuria. Although there was nothing noteworthy in the family history, there was a past incident of cerebral infarction in the left basal ganglia in June 2007. The patient had a history of smoking 20 cigarettes a day (from age 20 to 67 years), but no history of drinking alcohol.

Type 2 diabetes mellitus was first noted in 1990, and medication was started. Proteinuria had been seen since

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Table 1. Laboratory Data on Admission

Urine		Others			
Occult blood	3+	BUN	21 mg/dL	IgG	1870 mg/dL
Sugar	-	Cre	1.9 mg/dL	IgA	483 mg/dL
Protein	2+	TP	6.7 g/dL	IgM	88.2 mg/dL
Proteinuria	1.8 g/day	Alb	2.9 g/dL	ANF	×80
RBC	80-100/HPF	LDH	185 IU/L	HBs antigen	(-)
WBC	5-10/HPF	AST	16 IU/L	HCV antibody	(-)
Granular Cast	1-3/HPF	ALT	11 IU/L	C3	112.0 mg/dL
Hemogram		T-chol	160 mg/dL	C4	19.6 mg/dL
WBC	5700/mm ³	TG	109 mg/dL	CH50	49.7 U/mL
Hb	10.6 g/dL	CRP	3.7 mg/dL	MPO ANCA	476 EU
Plt	27×10 ⁴ /mm ³	HbA1c	9.7%	PR3 ANCA	<10 EU
		eGFR	28.7 mL/min	Anti-GBM antibody (-)	
				Anti-GAD antibody (-)	

Abbreviations: RBC: red blood cell, WBC: white blood cell, Hb: hemoglobin, Plt: platelet, BUN: blood urea nitrogen, Cre: creatinine, TP: total protein, Alb: albumin, LDH: Lactate Dehydrogenase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, T-chol: total cholesterol, TG: triglyceride, CRP: C-reactive protein, HbA1c: hemoglobin A1c, eGFR: estimated glomerular filtration rate, ANF: antinuclear factor, MPO ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibodies, PR3 ANCA: Proteinase-3 anti-neutrophil cytoplasmic antibodies, GBM: glomerular basement membrane, GAD: Glutamic Acid Decarboxylase.

2005 and progressed to 2+ to 3+; there was also evidence of diabetic retinopathy. In 2007, assessment of renal function showed that the serum creatinine (Cr) was 0.8 mg/dL, and the estimated glomerular filtration rate (eGFR) was 74.0 mL/min ($eGFR=194 \times Cr^{-1.094} \times age^{-0.287}$) (10). Hematuria (occult blood in the urine 3+) was first seen on the beginning of March 2008 upon admission by a previous doctor for glyce-mic control. At the same time, severe inflammation and renal dysfunction were observed: white blood cell (WBC) count, 10,700/ μ L; C-reactive protein (CRP), 12 mg/dL; serum Cr, 1.2 mg/dL; and high myeloperoxidase anti-neutrophil cytoplasmic antibodies (MPO-ANCA) level, 546 ELISA units (EU). On the basis of the above findings, the patient was believed to have anti-neutrophil cytoplasmic antibodies (ANCA)-associated nephritis and was admitted to our hospital in mid-March 2008 for examination and treatment.

The patient's height was 171.7 cm, and his weight was 71.2 kg. The patient's body temperature was 36.8°C, and his blood pressure was 120/64 mmHg. Cardiac and respiratory sounds were normal, and abdominal examination was normal. There was no evidence of lower extremity edema. Neurological findings included confirmation of decreased deep sensation bilaterally.

Test results on admission are shown in Table 1. Qualitative findings from urinalysis showed occult blood 3+, protein 2+. The sediment was confirmed to contain hematuria red blood cell (RBC) count, 80-100/high power field (HPF) and granular casts. Urinary protein level was 1.8 g/day. Peripheral blood tests showed poor glycemic control, hemoglobin A1c (HbA1c), 9.7%, deterioration of renal function, with serum Cr of 1.9 mg/dL (eGFR, 28.7 mL/min), and inflammation (CRP, 3.70 mg/dL). On serological testing, anti-nuclear antibodies were increased 80 times, and MPO-ANCA levels were high (476 EU). Proteinase-3 (PR3)-

ANCA and anti-glomerular basement membrane (GBM) antibodies tested negative.

Chest X-ray confirmed a bilateral lower lung field interstitial pattern, and chest computed tomography (CT) confirmed reticular shadowing, which was thought to be due to interstitial pneumonia at the same site. KL-6, SP-A, and SP-D were all high on testing after admission; these findings were consistent with interstitial pneumonia. Abdominal CT revealed a low density area that was thought to be caused by renal cysts and calcification of the renal arteries. There was slight swelling of the kidneys. No tumors or hydronephrosis was observed.

The underlying pathogenesis was suspected to be diabetic nephropathy based on the 10-year history of diabetes, the presence of diabetic retinopathy, and proteinuria over the past several years. Because the appearance of hematuria suggested that the diabetic renal disease had been complicated by MPO-ANCA-associated nephritis, based on the rapidly progressive renal dysfunction and the high MPO-ANCA levels, steroid pulse therapy (1 g/day of methylprednisolone for 3 days) was started on the day after admission, followed by oral administration of 50 mg/day of prednisolone (PSL). The patient's clinical course is shown in Fig. 1.

On day 12 after admission, a renal biopsy was performed to obtain a definitive diagnosis on which to base a treatment plan. Light microscopy findings showed global glomerulosclerosis in four of the 26 observed glomeruli, advanced segmental glomerulosclerosis in another two, an increase in the mesangial matrix, and nodular lesions (Fig. 2A, D). Eleven of the non-hyalinized glomeruli also showed cellular and fibrocellular crescent formations (Fig. 2B, C). These crescent formations were present in more than half of the non-hyalinized glomeruli. The interstitium showed a moderate degree of cellular infiltration and fibrosis accompanied by tubular atrophy (Fig. 2D). Intimal thickening of the inter-

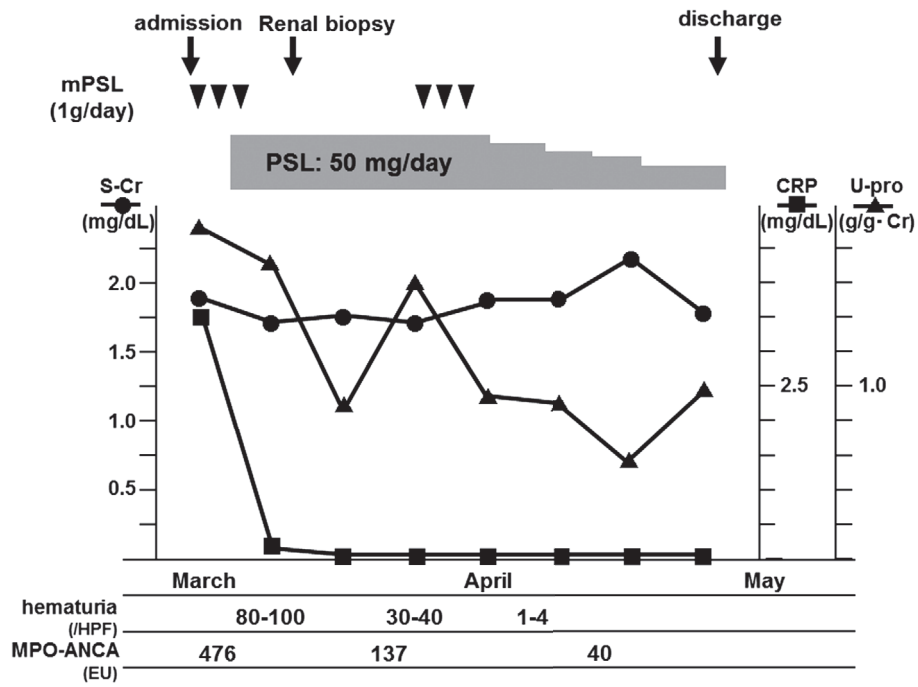


Figure 1. Clinical course

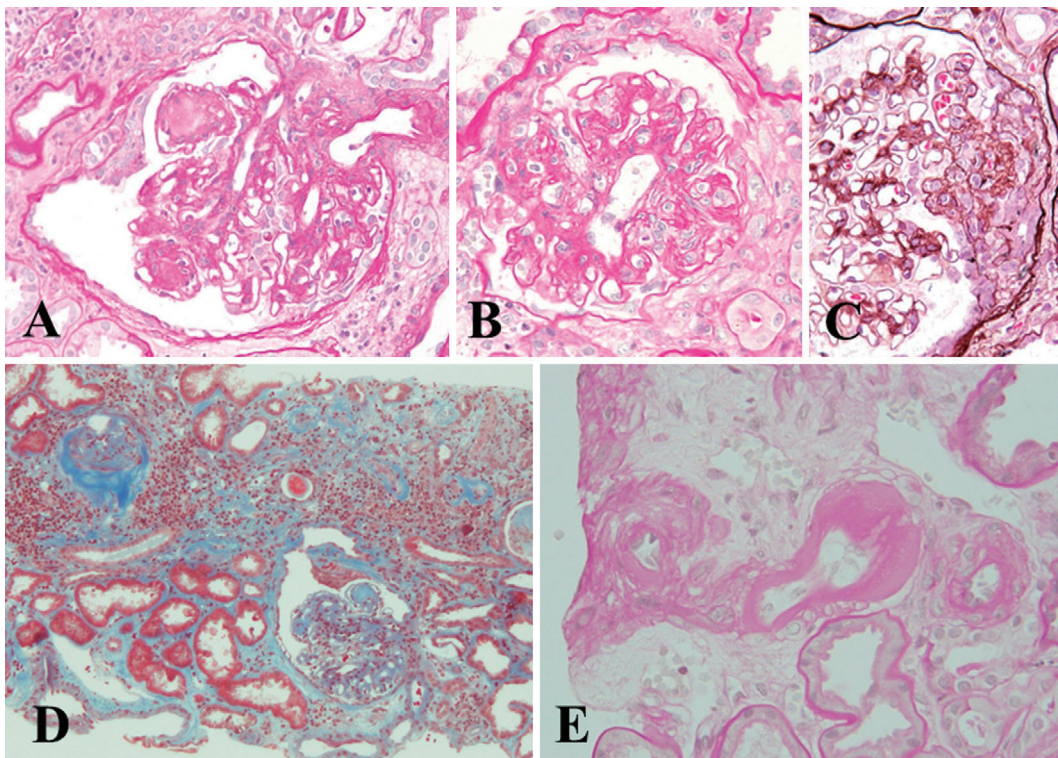


Figure 2. Light microscopy of a renal biopsy sample. A) Nodular lesions characteristic of diabetic glomerulosclerosis are shown (Periodic acid Schiff (PAS) staining, $\times 400$). B) and C) A glomerulus with fibrocellular crescent formation is shown (B: PAS staining, C: Periodic acid-methenamine-silver (PAM) staining, $\times 400$). D) Cellular infiltration and fibrosis in interstitium and a sclerotic glomerulus are shown (Masson's trichrome staining $\times 400$). E) Hyaline thickening of the arteriole is shown (PAS staining $\times 400$).

lobular artery and hyaline thickening of the arterioles were also observed (Fig. 2E). Immunofluorescence staining showed only slight deposition of IgM in the mesangial re-

gion. Electron microscopy showed diffuse thickening of the glomerular basement membrane and fibrinous dense material in Bowman's space. (Fig. 3). On the basis of the clinical

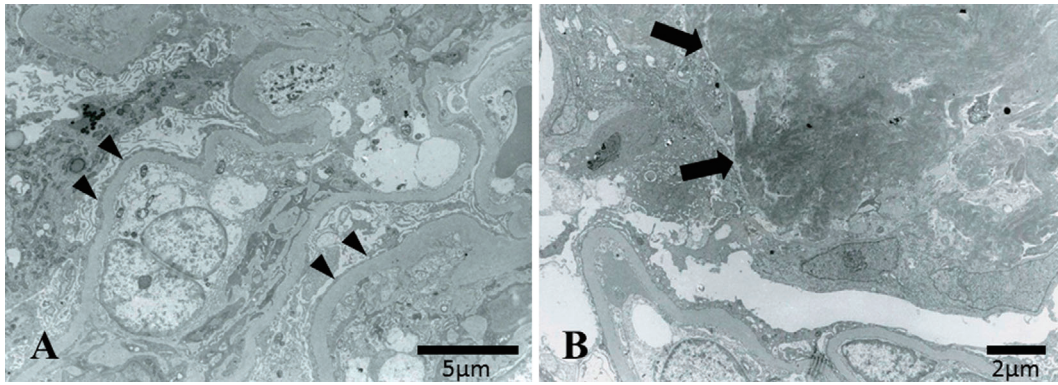


Figure 3. Electron microscopy of a renal biopsy sample. A) The effacement of the foot process is apparent. The glomerular basement membrane is diffusely thickened (arrowheads). B) Fibrinous dense material (arrow) is in Bowman's space. No electron dense deposits are observed.

course and pathological results, the renal dysfunction was diagnosed as diabetic nephropathy complicated by MPO-ANCA-associated nephritis.

After steroid pulse therapy was started, the inflammation improved (CRP, 0.62 mg/dL) by day 4. Furthermore, the MPO-ANCA level decreased to 137 EU by day 21. Additionally, the Cr was 1.7 mg/dL, and the urinary protein was around 0.5-1.5 g/day, but hematuria persisted at levels of 30-40 RBC/HPF. Since there appeared to be sustained vasculitis activity, steroid pulse treatment was repeated on day 26 after admission (1 g/day of methylprednisolone for 3 days). Although proteinuria persisted at around 0.5-1.0 g/day after the treatment, hematuria was negative, and Cr was about 1.7-2.0 mg/dL. PSL was administered orally for 1 month at 50 mg/day and then reduced to 30 mg/day after 3 weeks. When the CRP level was less than 0.5 mg/dL, the hematuria was negative, the urinary protein was around 0.5 g/day, and there was no observed aggravation of the ANCA-associated nephritis, the patient was discharged on day 56 after admission. He was confirmed to be negative for ANCA at an outpatient procedure performed in early July.

During the clinical course, because his blood pressure control was poor with 20 mg/day of nifedipine, telmisartan at a dosage of 20 mg/day was added on day 9 after admission. With regard to diabetes mellitus, despite intensive insulin therapy, his HbA1c level was 9.7% on admission. As his blood glucose level increased due to corticosteroid therapy, we increased the dose of insulin. As a result, his HbA1c level improved to 8.8% on day 26 after admission. In addition, pulmonary findings with interstitial pneumonia did not change after steroid therapy.

Discussion

The incidence of diabetic nephropathy has increased steadily over the past few years. In Japan, it is the disease for which dialysis is most commonly required (approximately 40% of cases). The prognosis is especially poor for patients receiving dialysis due to the diabetic nephropathy rather than other diseases; the 5-year survival rate for these

patients is about 50%. In contrast, in ANCA-associated nephritis, ANCAs, which are observed in the serum, are believed to be involved in the pathogenesis of the nephritis. ANCA-associated nephritis is classified into two types according to the corresponding type of antigen, MPO-ANCA-associated nephritis and PR3-ANCA-associated nephritis. There have been reports of nephritis cases that have tested positive for other types of ANCAs. In Japan, MPO-ANCA-associated nephritis accounts for more than 80% of the cases, with a predilection for people in their 60s and 70s; people over 80 years of age account for about 10% of the total number of cases (11).

The frequency of non-diabetic glomerulonephritis with diabetes has been reported to be 22%, and the rate of each type of nephritis with diabetes has been reported as follows: 10.4% for mesangial proliferative nephritis, 4.9% for membranous nephropathy, 3.0% for intratubular proliferative nephritis, 2.4% for membranous proliferative glomerulonephritis, and 1.2% for minimal change nephrotic syndrome (12). Clinical differential points for suspecting a new nephritis during the course of diabetic nephropathy include: 1) persistent hematuria of greater than a moderate degree (more than 50 RBC/HPF); 2) the appearance of proteinuria or nephrotic syndrome in the early stage of diabetes (5-10 years); 3) rapid deterioration of renal function; and 4) proteinuria or renal failure despite a lack of any other observable microangiopathy (12-16). These findings provide a reason to perform a renal biopsy for differential diagnosis. Both moderate hematuria and rapid deterioration of renal function were applicable in the present case, which had high levels of MPO-ANCAs on close inspection, and the results of the renal biopsy revealed that the diabetic nephropathy had been complicated by MPO-ANCA-associated nephritis.

There have not been many reports to date of MPO-ANCA-associated nephritis complicating diabetic nephropathy; 9 case reports were identified in the literature (Table 2). The patients' ages ranged from 50 to 88 years old, with 5 male patients and 4 female patients. The duration of diabetes tended to be long, and all cases exhibited proteinuria and hematuria. Hemodialysis was initiated in 3 of the 9 cases,

Table 2. Patients Reported to have Diabetic Nephropathy Complicated by ANCA-associated Glomerulonephritis

No.	Age (years)/Sex	Duration (years)	R	ANCA (EU)	Proteinuria (g/day)	Hematuria (/HPF)	Outcome
1 ²⁾	64M	16	(-)	548	1.3	Many	Improved
2 ³⁾	55F	25	(+)	531	1.5	60-80	Improved
3 ⁴⁾	78M	30	(+)	196	4.0	Many	ESRD (HD)
4 ⁵⁾	65M	13	(-)	8.4(U/mL)	NA	+	ESRD (HD)
5 ⁶⁾	67F	3	(+)	240	4.2	250	ESRD (HD)
6 ⁷⁾	72F	10	NA	NA	5.4	+	Improved
7 ⁸⁾	50M	7	(-)	903.5		Many	Improved
8 ⁹⁾	88M	30	(-)	767.2		50-99	Died
This case	67M	17	(+)	546	1.9	80-100	Improved

Abbreviations: R#: reference number, Duration: duration of diabetes mellitus, R: diabetic retinopathy, ANCA: antineutrophil cytoplasmic antibody, ESRD: end-stage renal failure, NA: not available

and 1 case resulted in death.

Accardo-Palumbo et al. in 1996, reported a relationship between diabetes and MPO-ANCA-associated nephritis, and compared to healthy patients, type 1 diabetes mellitus patients had a particularly high rate of MPO-ANCA positivity (17). Chronic activation of polymorphonuclear neutrophils in type 1 diabetes mellitus, which results from the absolute lack of insulin and subsequent deregulation of glucose metabolism, is believed to be the cause, but the details remain unclear (18). The relationship between type 2 diabetes and MPO-ANCA-associated nephritis is unknown.

With the object of pulmonary findings, although the reasons for ineffectiveness of steroid therapy were not clear in the present case, we considered that chronic interstitial change which was resistant to steroid therapy might exist or a smoking-induced interstitial lung abnormality would affect the pulmonary findings. With regard to the relationship between smoking habits and ANCA positivity, there are conflicting reports. One report shows a higher prevalence of smoking in patients with ANCA-associated nephritis (19). On the other hand, there are studies showing no association between smoking status and ANCA-associated vasculitis (20, 21). Thus, we could not determine whether the smoking habit influenced ANCA positivity in the present case.

The present case showed increases and nodular lesions of the mesangial matrix, as well as cellular crescents, on light microscopy. Findings from the fluorescent antibody technique confirmed only small IgM deposits in the mesangial region, a finding consistent with ANCA-associated nephritis with pauci-immunity. Electron microscopy findings showed diffuse thickening of the basal membrane, a characteristic diabetic nephropathy transformation, and fibrinous dense material in Bowman's space, which is characteristic of inflammatory changes caused by ANCA-associated nephritis. Of the 9 reported cases of combined diabetic nephropathy and ANCA-associated nephritis, diabetic nephropathy was pathologically confirmed by electron microscopy in only 3 cases; we believe that confirmation of nephropathy in combination with ANCA-associated nephritis is rare.

We suggest that, even in elderly diabetic patients with a long history of illness, when a rapid deterioration of renal function or a high degree of microscopic hematuria is observed, complication by a renal disease other than diabetic nephropathy must be considered and dealt with promptly, including renal biopsy.

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

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