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AN ELDERLY PATIENT WITH TYPE 2 DIABETES MELLITUS COMPLICATED WITH DIABETIC NEPHROPATHY AND LUPUS NEPHRITIS

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We report a 76-year-old man with type 2 diabetes mellitus (DM) complicated with diabetic nephropathy and lupus nephritis. The patient had a 7-year history of DM without renal dysfunction. He was referred to our hospital for severe arthralgia and right chest pain. Laboratory examination indicated urinary granular casts, but not proteinuria. Systemic lupus erythematosus (SLE) was suspected based on symptoms and further laboratory findings such as serum autoantibodies including anti-DNA antibody, antinuclear antibody and perinuclear anti-neutrophil cytoplasmic antibody. Finally, renal biopsy revealed mesangial sclerosis, subendothelial deposit of electron dense material and necrotic vasculitis, which were interpreted as diabetic nephropathy and lupus nephritis, respectively. Treatment with oral prednisolone ameliorated serological abnormalities as well as clinical symptoms. These findings indicate that renal biopsy is indispensable for a definite diagnosis of nephropathy in diabetic patients without proteinuria but with active urine sediments.

Key words: type 2 diabetes mellitus, diabetic nephropathy, lupus nephritis, late onset SLE

INTRODUCTION

Systemic lupus erythematosus (SLE) is a disease in which tissues and cells are damaged by pathogenic autoantibodies and immune complexes. Most patients are young women, usually of child-bearing age, whereas men and the elderly can be rarely affected (1). Diabetes mellitus (DM) is the most common endocrine disease, which is characterized by metabolic abnormalities and by long-term complications involving the eyes, kidneys, nerves, and blood vessels. DM is now classified into type 1, type 2, other specific types and gestational diabetes according to the American Diabetes Association Classification in 1997 (2). Among them, type 2 DM is the most prevalent form of the disease and the prevalence increases with age, although development of type 2 DM is influenced by genetic factors and environmental factors, including obesity and decreased physical activity. In contrast, type 1 DM is characterized by an insulin deficiency secondary to ß-cell destruction, in which autoimmune mechanisms may be involved.

We report an elderly male patient with type 2 DM complicated with diabetic nephropathy and lupus nephritis, which were revealed by renal biopsy. This is a rare case although it was previously reported that SLE may simultaneously occur in elderly patients with diabetic nephropathy (3,4).

CASE REPORT

This patient was diagnosed as type 2 DM on a regular health check-up at the age of 69. Since then, plasma glucose levels had been modestly controlled by diet and exercise. He was admitted to our hospital for the first time for the cerebral infarction at the age of 73. One and a half year later, he was referred again to our clinic for severe arthralgia and right chest pain. He had not taken hydralazine, isonicotinic acid hydrazide or procainamide.

Physical examination on the second admission showed body temperature, 36.8℃; pulse rate, 80 beats/min, regular; respiration rate, 22/min; arterial blood pressure, 142/70 mmHg. No eruption was found on the face. Heart sounds were normal, but breath sounds were not fully audible at the right

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Table 1. Laboratory findings of the patient on the second admission.

《Peripheral Blood》			《Blood chemistries》			《Serological tests》		
WBC	7700	/μl	TP	7.0	g/dl	IgG	1804	mg/dl
RBC	349 x 10^4	/μl	Alb	3.3	g/dl	IgA	420	mg/dl
Hb	10.5	g/dl	T.Bil	0.3	mg/dl	IgM	130	mg/dl
Ht	30.2	%	GOT	18	IU/l	C3	125	mg/dl
Plt	42.4 x 10^4	/μl	GPT	19	IU/l	C4	25.4	mg/dl
			LDH	141	IU/l	CH50	50.7	Unit/ml
《Coagulation》			ALP	409	IU/l	CRP	6.8	mg/dl
PT	12.9	sec	γ-GTP	96	IU/l	Anti GAD Ab	<1.3	U/ml
APTT	37.4	sec	ChE	200	IU/l	Anti DNA Ab	13.1	IU/ml
			CK	12	IU/l	ANA (diffuse)	x1280	
《Urinalysis》			Amy	93	IU/l	RF	<10	IU/ml
Glucose	+		ZTT	9.6	K.U	LE cell	+	
Protein	0.2	g/day	TTT	1.7	K.U	Anti Sm Ab	(-)	
Blood	(-)		T-Cho	178	mg/dl	Immune Complex	(-)	
Ketone	(-)		TG	108	mg/dl	Anti CLß$_2$GPIAb	<1.2	U/ml
			HDL-Cho	41	mg/dl	Lupus anticoagulant	(-)	
《Sediments》			BUN	22	mg/dl	C-ANCA	<10	EU
RTEC	10-29	/HF	Cr	0.8	mg/dl	P-ANCA	12	EU
HCAST	1-4	/HF	Na	144	mEq/l			
GCAST	3	/HF	K	4.0	mEq/l	u-CPR	54	μg/day
			Cl	104	mEq/l	s-CPR	1.3	ng/ml
《Renal function》			FBS	134	mg/dl			
Ccr	38	ml/min	HbA1c	6.6	%	ESR	140	mm/h
U-NAG	21.2	U/day	Fe	44	μg/dl			
U-Alb	144	mg/day	TIBC	193	μg/dl			
U-ß$_2$MG	838.8	μg/day	Ferritin	311	μg/ l			

HF: high power field, RTEC: renal tubule epithelial cast, HCAST: hyaline cast, GCAST: granular cast, U-NAG: urinary N-acetyl-ß-D-glucosaminidase, U-ß$_2$MG: urinary ß$_2$microglobulin, TIBC: total iron binding capacity, AntiCLß$_2$-GPIAb: anticardiolipin ß$_2$-glycoprotein I antibody, C-ANCA:cytoplasmic antineutrophil cytoplasmic antibody, P-ANCA: perinuclear antineutrophil cytoplasmic antibody, u-CPR: urinary connecting peptide immunoreactivity, s-CPR: serum connecting peptide immunoreactivity

lower lung field. Limited excursion was observed in the hand, wrist and knee joint of both sides, but there was no deformity. Ophthalmologic examination revealed nonproliferative diabetic retinopathy.

Laboratory data are summarized in Table 1. Urinalysis showed no protein but hyaline and granular casts in the sediment. Urinary microalbumin excretion was increased to 144 mg/day, and N-acetyl-ß-D-glucosaminidase and ß$_2$-microglobulin levels were also increased to 21.2 IU/L and 838 mg/L, respectively. Serum chemistry revealed hypoalbuminemia, slightly elevated urea nitrogen and normal levels of creatinine and electrolytes. Creatinine clearance was decreased to 38 ml/min. Serological tests showed high ESR, increased CRP and the presence of perinuclear antineutrophil cytoplasmic antibody (P-ANCA), antinuclear antibody and anti-DNA antibody, but no cytoplasmic ANCA. Chest X-ray demonstrated pleural effusion in the right lower lung field. There was no remarkable change in the kidneys on ultrasonography.

A renal biopsy was performed to diagnose the renal lesion suspected in the patient, after obtaining an informed consent. The specimen contained seven glomeruli available for microscopic evaluation. All glomeruli showed global glomerular changes; consisting of nodular diffuse mesangial sclerosis, thickening of the capillary walls and mesangio-capillary proliferation (Fig. 1A). In addition to the glomerular changes, necrotic vasculitis and fibrinoid necrosis were apparent in the small-sized vessels (Fig. 1B). Electron microscopic examination of glomeruli identified the presence of subendothelial electron dense deposits and thickening of the basement membrane (Fig. 2). No material was available for immunofluorescence study.

These findings in the renal biopsy were interpreted as follows: The mesangial sclerotic changes, both diffuse and nodular forms, were compatible with diabetic nephropathy. Changes in the capillary wall and

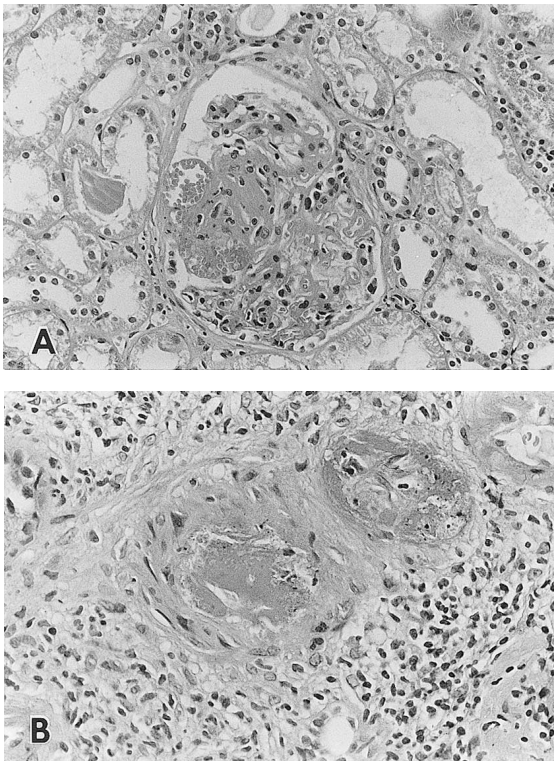

Fig. 1. Light microscopic findings of renal specimen biopsied from the patient. Panel A shows diabetic nodular glomerulosclerosis and mesangial proliferation (HE stain, ×200). Panel B shows necrotizing vasculitis in interstitial region (HE stain, ×400).

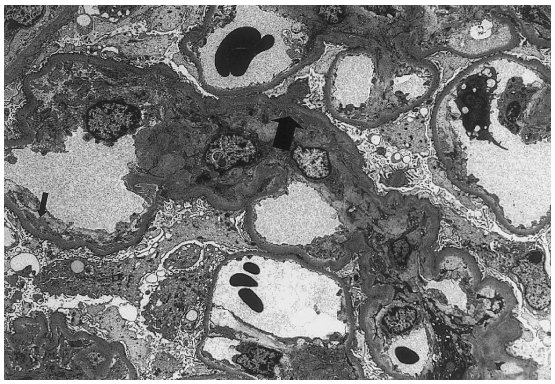

Fig. 2. Electron microscopic findings of renal specimen biopsied from the patient. Mesangial and subendothelial dense are shown by large and small arrows, respectively (×1800).

mesangio-capillary region were due to lupus nephritis, since the clinical symptoms and signs included 5 out of 11 used to define SLE, according to the American Rheumatism Association-1982. Necrotic vasculitis was not primary but rather secondary to lupus nephritis.

The patient was treated with oral prednisolone, starting at a dose of 0.7 mg/kg/day. Clinical symptoms dramatically improved and both serum P-ANCA and anti-DNA antibodies became negative after one month. The dose of prednisolone was tapered slowly without relapse.

DISCUSSION

We investigated an elderly patient with type 2 DM. DM had been modestly controlled by diet and exercise in the patient for 7 years until he was admitted for arthralgia and right chest pain at the age of 76. Physical examination and laboratory data on admission suggested that he was suffered from arthritis, serositis, renal dysfunction with active urinary sediments and serum autoantibodies including P-ANCA that might relate to vasculitis (5).

A renal biopsy was performed to elucidate the renal lesion before starting the treatment. Two types of glomerular lesions were identified, suggesting the coexistence of diabetic and lupus glomerulopathies. In addition to the glomerular changes, necrotic vasculitis and fibrinoid necrosis were apparent in the small-sized vessels. Considering the clinical course of DM, it seems that the lupus lesion including vasculitis was superimposed on that of diabetic nephropathy. There have been a limited number of case reports in which lupus nephritis was superimposed on diabetic nephropathy (4,6). It is also noted that the onset of SLE after 50 year is very unusual and that clinical symptoms in elderly patients with SLE are considerably different from those in younger patients since the major organ was less involved in the late onset SLE (7).

Non-diabetic renal disease does not seem to be common in DM. However, recent publications suggest a considerable prevalence of non-diabetic renal disease in type 2 DM. Several reports described the presence of idiopathic membranous glomerulonephritis, immunoglobulin A glomerulonephritis, Henoch-Schönlein nephritis, membranoproliferative glomerulonephritis, postinfectious glomerulonephritis, minimal change glomerulonephritis, focal glomerulosclerosis, crescentic glomerulonephritis and anti-glomerular basement membrane nephritis in patients with DM (3). It is noteworthy that the above conditions are diseases of immune-based pathogenesis. Although the occurrence of lupus nephritis in DM is rare, it can be categorized into such a group.

It was previously reported that SLE was present in a large proportion of patients with insulin resistance due to autoantibodies to insulin receptors(8). Insulin resistance was not found in the present case since serum C-peptide was within the normal range. Deterioration of immune regulatory mechanism due to aging or DM might explain the development of such non-diabetic renal disease in elderly patient with type 2 DM.

Histopathological diagnosis of the renal lesion is especially important, since treatable glomerulonephritis could be superimposed in patients with diabetic nephropathy. Treatment with corticosteroids and/or immunosuppressive agents should be critically considered even in diabetic patients with renal insufficiency. Our present experience is quite valuable since definite diagnosis by renal biopsy led to proper treatment of the late-onset complication and prevented the development of severe clinical symptoms in the patient. These findings support the proposal of Ahuja et al. (3) that renal biopsy should be performed in patients with DM when they develop systemic symptoms suggestive of vasculitis and show active sediment in the urine even if without proteinuria.

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