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A Case of NSAIDs-Induced Nephrotic Syndrome Associated with Renal Tubular Injury in the Course of Diabetic Nephropathy

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A 66-year old man with type 2 diabetes mellitus has maintained good plasma glucose level with insulin therapy. His diabetic nephropathy was classified in G3aA2 stage of chronic kidney disease. He was administrated flurbiprofen after gastrectomy because of gastric cancer, and after that his urinary protein creatinine ratio was increased, in line with increase in both U-NAG and U-β2MG levels. We diagnosed NSAIDs-induced nephrotic syndrome to start predonisolon. After starting steroid therapy, proteinuria and renal tubular injury were rapidly improved. When proteinuria is suddenly increased in the course of diabetes mellitus, kidney diseases other than diabetic nephropathy should be considered.

Key words: Nephrotic syndrome, NSAIDs, drug-induced nephropathy, renal tubular injury, Diabetes mellitus

INTRODUCTION

Non-steroid anti-inflammatory drugs（NSAIDs）are well-known causes of acute kidney injury（AKI）. In NSAIDs-induced AKI, either acute allergic interstitial nephritis or nephrotic syndrome is responsible for renal failure. In addition, NSAIDs-induced nephrotic syndrome is mostly associated with tubulointerstitial lesions［1］. In diabetic nephropathy, nephrotic syndrome sometimes occurs independent of serum creatinine（Cr）level and renal failure rapidly progresses in cases with severe proteinuria［2］.

We experienced a case of sudden-onset nephrotic syndrome associated with severe renal tubular injury in the course of diabetic nephropathy. NSAIDs were highly suspected in the pathophysiology of kidney injury. Since steroid therapy improved sustained renal tubular injury and nephrotic syndrome, we would report this case to review NSAIDs-induced nephrotic syndrome.

CASE REPORT

A 66-year old Japanese man was diagnosed as type 2 diabetes mellitus about 30 years ago, and started intensive insulin therapy after 20 years of diagnosis. In recent years, his HbA1c levels were 6-7% and he has maintained good plasma glucose level. His diabetic retinopathy was A2 stage in Fukuda's classification. Serum creatinine levels have been 1.1-1.3 mg/dL for the past 7 years to our knowledge. Urinary albumin（Alb）levels were 86.2, 95.2, and 277 mg/g・Cr at 4 years ago, 1 year ago, and before operation for gastric cancer, respectively. His albuminuria was gradually getting worse over time and his diabetic nephropathy was classified in G3aA2 stage of chronic kidney disease before operation. He underwent total gastrectomy for gastric cancer. Postoperative histopathological findings were early stage adenocarcinoma（stageIA）without metastasis. He was administrated 50 mg/day of flurbi-

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profen for 6 days after gastrectomy. After operation, urinary protein/Cr ratio was markedly increased from 0.7 to 6.8 g/g・Cr, whereas serum Alb level was markedly decreased to 0.5 g/dL. Therefore, he was referred to our university hospital.

His family members do not have any kidney diseases and allergic histories. He had 163.3 cm in height and 58.3 kg in weight before surgery. On admission, he was alert with general malaise and anasarca. His blood pressure was 130/72 mmHg. He was afebrile and had moist rale in the right lower chest and marked pitting edema in the extremities. The CT scan showed pulmonary infiltration in the right lower lung with bilateral pleural effusion and ascites.

The laboratory data are shown in Table 1. Marked proteinuria, hyaline casts and waxy casts were shown in the urine examination. Elevated white blood cell（WBC）and C-reactive protein（CRP）were probably caused by the aspiration pneumonia. Very low serum protein and Alb levels with severe proteinuria indicated nephrotic syndrome. Serum Cr level was elevated partly because of intravascular volume depletion. Selectivity index was 0.36, suggesting that classical minimal-change nephrotic syndrome was not plausible. Both hepatitis B surface（HBs）antigen and hepatitis C virus（HCV）antibody were negative. Antinuclear antibody as well as anti-neutrophil cytoplasmic antibody（ANCA）was also negative. Serum immunogloburin levels were within normal range except IgE and there was no abnormal finding in the electrophoresis of urinary protein. Proteinuria and hypoalbuminemia became acutely worse because of sustained massive proteinuria after gastrectomy. In addition, both urinary N-acetyl-β-D-glucosaminidase（NAG）and β2-microglobulin（β2MG）were also markedly increased after operation（U-NAG; 8.7 IU/g・Cr to 51.6 IU/g・Cr, U-β2MG; 5.0 μg/g・Cr to 8666.2 μg/g・Cr, respectively）. The kidney size was 101.5 mm and 108.6 mm in the diameter of the right and left kidnies. There was no atrophy, infection or hydronephrosis. The renal biopsy was not performed because his consent was not obtained due to dementia.

He suffered from neither type B hepatitis nor

Table 1. Laboratory findings on admission

《Urinalysis》			《Blood chemistry》			《Immunology》		
pH	5.5		TP	4.2	g/dL	IgG	903	mg/dL
Protein	(+3)		Alb	0.6	g/dL	IgA	345	mg/dL
Occult Blood	(+)		BUN	39.4	mg/dL	IgM	66	mg/dL
Glucose	(+)		Cre	2.45	mg/dL	IgE	2552.0	IU/L
Sediments			UA	5.2	mg/dL	C3	150	mg/dL
RBC	10-19	/HPF	Na	138	mEq/L	C4	29.4	mg/dL
WBC	20-29	/HPF	K	2.9	mEq/L	CH_{50}	44.6	U/mL
Hyaline Cast	5-9	/ HPF	Cl	104	mEq/L	RF	< 40	×
Waxy Cast	50-99	/ LPF	TC	175	mg/dL	ANA(nucleolar)	< 40	×
			TG	111	mg/dL	MPO-ANCA	< 10	EU
《Complete Blood Count》			HDL-C	21	mg/dL	PR3-ANCA	< 10	EU
WBC	11,220	/μl	LDL-C	126	mg/dL			
Neutro.	81.3	%	CRP	7.15	mg/dL	《Renal function》		
Eos.	3.1	%	FPG	115	mg/dL	U-NAG	51.6	IU/g·Cr
Lymph.	10.1	%	HbA1c	7.7	%	U-β_2MG	8866.2	μg/g·Cr
RBC	286×10^4	/μl				Proteinuria	6.8	g/g·Cr
Hb	8.8	g/dl	《Serological examination》					
PLT	49.1×10^4	/μl	HBs-Ag	(−)		Selectivity index	0.36	
			HCV-Ab	(−)				

WBC; white blood cell, CRP; C-reactive protein, HBs-Ag; hepatitis B surface antigen, HCV-Ab; hepatitis C virus antibody, RF; rheumatoid factor, ANA; antinuclear antibodies, MPO-ANCA; myeloperoxidase-anti-neutrophil cytoplasmic antibody, PR3-ANCA; proteinase-3-anti-neutrophil cytoplasmic antibody, U-NAG; urinary-N-acetyl-β-D-glucosaminidase, U-β_2MG; urinary-β2 -microglobulin

type C hepatitis which causes glomerulonephritis such as membranous nephropathy. His gastric cancer was totally cured. In addition, he did not have an immune deficiency disease or myeloproliferative disease. Although it could not be completely ruled out that his nephrotic syndrome was caused by diabetic nephropathy, we considered NSAID was the most likely cause of his nephrotic syndrome because it occurred after flurbiprofen usage. Three months later of his taking flurbiprofen, the renal tubular damage progressed and proteinuria persisted. Furthermore, he needed an intravenous administration of albumin preparation at monthly intervals to attenuate anasarca. Therefore, we started oral administration of predonisolon (PSL) at 40 mg/day and its dosage was reduced every two weeks. After starting steroid, severe proteinuria and renal tubular injury were rapidly improved. Serum Alb level was maintained around 1.5 g/dL without the administration of albumin preparation (Fig. 1). We controlled glucocorticoid-induced hyperglycemia by increasing the insulin dose.

DISCUSSION

We experienced a diabetic patient associated with nephrotic syndrome and severe renal tubular injury after operation of gastric cancer. Based on the clinical course and laboratory examination, flurbiprofen might be the most responsible for the pathophysiology, even though kidney biopsy had not been performed due to dementia. In spite of the presence of type 2 diabetes, we decided to start steroid therapy and found the effectiveness.

NSAIDs-induced nephropathies include acute kidney injury, acute allergic interstitial nephritis, and nephrotic syndrome [1]. In general, NSAIDs-induced nephrotic syndrome mostly presents minimal-change disease (MCD) with renal tubular damage to various extents. In case of NSAIDs-induced membranous nephropathy, the renal tubular and interstitial lesions are reported to be scarce [3]. In this case, however, the patient showed nephrotic syndrome associated with marked renal tubular damage. Thus, we speculated that his nephrotic syndrome was most

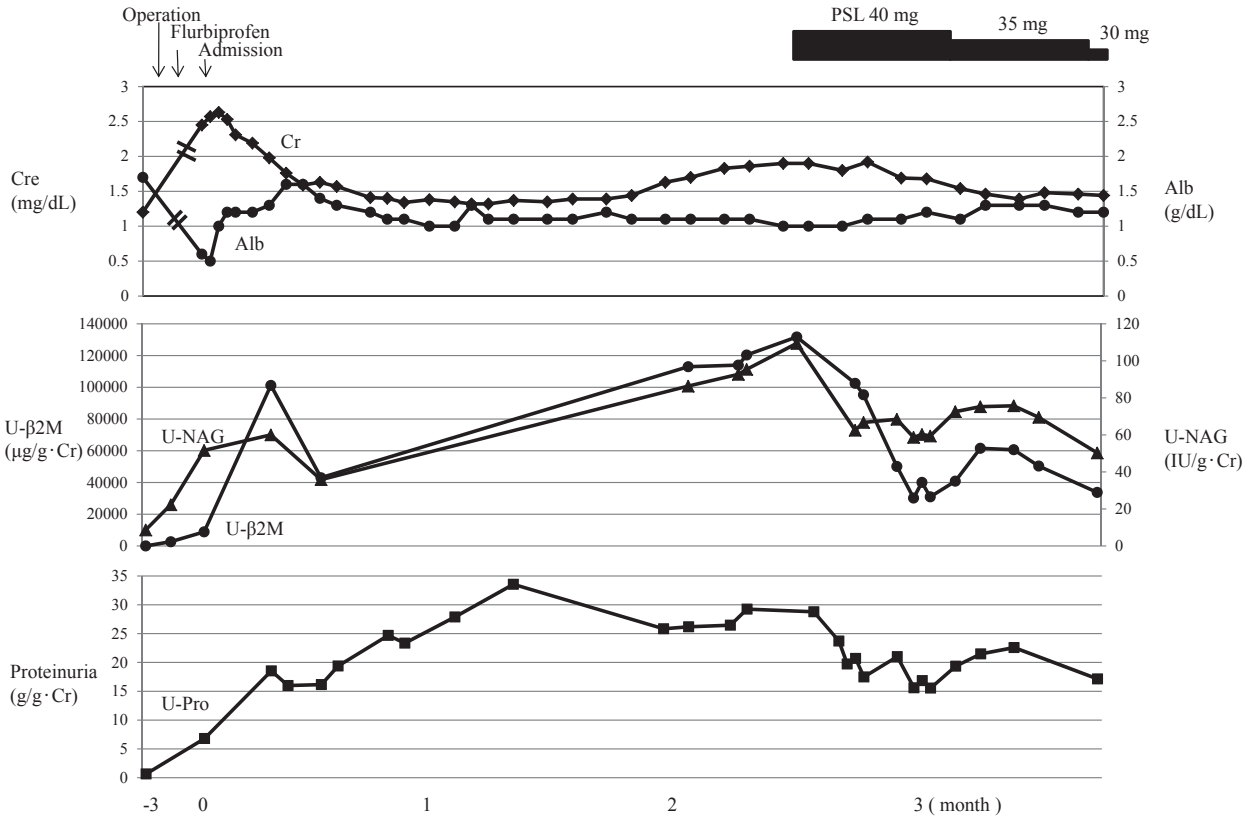

Fig. 1. Clinical course of the patient.

probably MCD accompanied with severe tubulointerstitial nephritis instead of low selectivity index of proteinuria. Although MCD generally shows high selectivity, some cases of adult-onset MCD with low selectivity index have been reported [4]. Therefore, we considered that the present case was NSAIDs-induced MCD with low selectivity index, although aggravation of diabetic nephropathy could not be completely ruled out. It is well known that diabetic nephropathy is a major cause of nephrotic syndrome. However, it remains unsolved whether NSAIDs apt to induce nephrotic syndrome in patients with diabetic nephropathy.

NSAIDs-induced acute renal tubular interstitial damage was thought to be caused by all of type I-IV allergy [5]. In this case, he had an increase of serum IgE level related to type I allergy. The pathogenesis of NSAIDs-induced nephrotic syndrome was generally considered to be depressed production of prostaglandin. NSAIDs depressed production of prostaglandin through inhibiting cyclooxigenase in the arachidonic acid metabolism pathway. PGE2, PGI2 and thromboxane A2 are decreased, while leukotriene, a leukocyte chemotactic factor, is produced. This leads to the enhancement of T-lymphocytes function and the lymphokine production, followed by an increase in permeability of the glomerular basement membrane and by aggravated proteinuria. Diminished production of prostaglandin caused by NSAIDs also leads to a decrease in renocortical blood flow [6]. Both prostaglandin and angiotensin have strong effects on pathological condition of renal dysfunction. Therefore, in patients with fever, diarrhea, states of dehydration including appetite loss, renal dysfunction and heart failure, administration of NSAIDs accelerates the decline of renal function [7]. In this case, NSAIDs usage shortly after operation could have led to nephrotic syndrome. In addition, the volume depletion due to hypoalbuminemia might be involved in the development of AKI.

Renal function generally improves within a month after the cease of an offending drug. But, in some patients, more than 1 year takes to recover from proteinuria. Corticosteroid therapy is an option for patients in whom proteinuria is not significantly reduced after discontinuation of NSAIDs [8,9]. Since massive proteinuria with severe tubular injury persisted 3 months after discontinuation of NSAIDs, we decided to start corticosteroid therapy. The reported cases of NSAIDs-induced nephrotic syndrome are shown in Table 2. According to the previous reports, severe proteinuria (*e.g.* 8-17.5 g/day) sometimes occurs in patients with NSAIDs-induced nephrotic syndrome [10-15]. In some patients after discontinuation of NSAIDs, proteinuria has been improved by the use of steroid [11,12,14,15]. In most patients who developed NSAIDs-induced nephrotic syndrome, NSAIDs were repeatedly administered for 3 months to 3 years [11-15]. On the other hand, nephrotic syndrome occurs after the administration of NSAIDs for a few days or just twice [10,15]. Thus, nephrotic syndrome may occur independent of the duration of NSAIDs administration.

We experienced a case of NSAIDs-induced tubulointerstitial nephritis and nephrotic syndrome associated with diabetic nephropathy. When proteinuria is suddenly increased in the course of diabetes mellitus, kidney disorders other than diabetic nephropathy should be considered. Steroid was effective for NSAIDs-induced tubular injury and proteinuria, although the dosage of insulin administration was increased. Thus, in addition to stop offending drugs, steroid therapy could be of value when tubular injury and proteinuria persist.

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

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Table 2. Reported cases of NSAIDs-induced Nephrotic Syndrome

Case	Age /sex	NSAID /Dose, Duration of Use	Proteinuria (g/day)	Histologic Diagnosis	Therapy	Recovery time /Proteinuria (g/day)	References
1	60/M	Meloxixam, 15 mg, few days	17.2	MC	Follow-up	1 month 0.34	Mihovilovic K, 2011[9]
2	73/F	Diclofenac 75 mg, 6 months	9.5	IN, MC	Hemodialysis PSL	1 month 0.2	Inoue M, 2008[10]
3	59/M	Celecoxib 100-200 mg, 1 year	10.6	IN, MC	PSL	ND ND	Alper AB, 2002[11]
4	68/F	Diclofenac 150 mg, 2-3 years	10.8	MN	Follow-up	22 months 0.05	Radfold MG, 1996[12]
5	36/M	Tolmetin 400 mg, 1 year	23.8	MN	Follow-up	16 months 0.42	Radfold MG, 1996[12]
6	43/M	Flurbiprofen 160-320 mg, 22 months	14.0-17.5	IN	PSL	ND ND	Tazoe N, 1987[13]
7	70/F	Diclofenac 100 mg, 3 months	14.0	MC	Follow-up	7 weeks ND	Beun GDM, 1987[14]
8	56/F	Dicrofenac 151 mg, twice times	11.0	MC	PSL	ND ND	Beun GDM, 1987[14]

MC; Minimal Change Nephropathy, IN; interstitial nephritis, MN; Membranous nephropathy,PSL;Predonisolone, HD;hemodialysis, ND;not described

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