CASE REPORT

Partial remission by cyclosporine monotherapy in a patient with membranous nephropathy superimposed diabetic nephropathy

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Abstract It has been noted that cyclosporine A (CsA) is an effective drug for membranous nephropathy (MN). Diabetes is a common disease that sometimes causes nephrotic syndrome. We report the case of an 89-year-old woman with type 2 diabetes mellitus who exhibited nephrotic syndrome. Examination of a renal biopsy indicated MN and she was prescribed CsA as monotherapy. Her edema subsided and she achieved partial remission. This is the first report of a patient in diabetic condition with MN having achieved partial remission after CsA monotherapy without steroid therapy. The use of steroid in patients with diabetes may worsen their diabetic condition, especially if they are of very advanced age. CsA monotherapy may be useful for diabetic patients with MN.

Keywords Cyclosporine · Diabetes · Membranous nephropathy

Introduction

Membranous nephropathy is a common cause of nephrotic syndrome in the elderly. Diabetes mellitus (DM) is a major cause of chronic kidney disease (CKD) and DM may lead to nephrotic syndrome. Indeed, MN often occurs in patients with DM [1]. Differential diagnosis of MN or diabetic nephropathy is clinically difficult, as generally renal biopsy

is not performed in old patients, least of all in old diabetic patients.

A previous study suggested that corticosteroid monotherapy was not effective in patients with idiopathic MN (IMN). These results suggested that combination therapy using a corticosteroid and immunosuppressive drugs should be considered as the first-line of treatment for IMN patients with nephrotic syndrome [2]. However, steroid therapy worsens the diabetic condition. This far there has been no report of the efficacy of CsA monotherapy for IMN in patients with DM. Here, we report the case of an old diabetic patient who developed MN and was successfully treated with CsA monotherapy.

Case report

The patient was an 89-year-old Japanese woman who had been under treatment for hypertension and DM for the previous 8 years. Her blood pressure (BP) was controlled at about 120/80 mmHg. HbA1c was 5.7–6.1 %. Her renal function was stable (serum Cr between 1.2 and 1.4) before admission to our hospital. She had been medicated with amlodipine 2.5 mg, irbesartan 100 mg, mitiglinide 30 mg, and voglibose 0.6 mg/day. Leg edema suddenly appeared and she went to a local hospital 20 days before being admitted to our hospital. The cause of her edema was suspected to be nephrotic syndrome. The physical examination on admission showed that she was 145 cm tall, body weight was 62 kg, BMI was 29.5, blood pressure was 120/60 mmHg, body temperature was 36.9 °C, and her pulse rate was 84 beats/minute and regular. She had received laser therapy for proliferative retinopathy. We could not detect the neuropathy causing her leg edema. Laboratory findings on admission are shown in Table 1.

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Table 1 Laboratory data on admission

Blood cell count				Urinalysis	
WBC	5000/ μ L	Na	142 mEq/L	PH	7.0
RBC	277×10^4 / μ L	K	4.4 mEq/L	Protein	3+
Hb	8.6 g/dL	Cl	101 mEq/L	Occult blood	1+
Ht	26.6 %	Ca	8.2 mg/dL	RBC	10–19/HPF
Plat	26.5×10^4 / μ L	P	3.9 mg/dL	WBC	10–19/HPF
Blood chemistry		HbA1c	5.4 %	Hyaline cast	30–49/HPF
TP	4.7 g/dL	CRP	0.75 mg/dL		
Alb	2.0 g/dL	Serological test			
AST	21 U/L	IgG	601 mg/dL		
ALT	10 U/L	IgA	320 mg/dL		
T-cho	218 mg/dL	IgM	64 mg/dL		
UA	7.2 mg/dL	C3	101 mg/dL		
BUN	37.5 mg/dL	C4	37.1 mg/dL		
Cr	1.28 mg/dL	CH50	46.0 U/mL		
		ANA	$\times 160$		
		PR3-ANCA	3.3 EU		
		MPO-ANCA	<1.3 EU		

Fig. 1 a Light microscopic features of the kidney (periodic acid methenamine silver $\times 200$) The glomeruli showed increase of the mesangial (see arrow). **b** Light microscopic features at a higher magnification (periodic acid methenamine silver $\times 1000$) Spike formations are seen on the sub epithelial glomerular basement membrane (see arrow)

Red blood cell count (RBC) 277×10^4 / μ L, platelet count 26.5×10^4 / μ L, hemoglobin (Hb) 8.6 g/dL, hematocrit (Ht) 26.6 %, white blood cell count (WBC) 5000/ μ L, plasma glucose 107 mg/dL, HbA1c 5.4 %. Total cholesterol 218 mg/dL, serum albumin (Alb) 2.0 g/dL, serum creatinine (Cr) 1.28 mg/dL, blood urea nitrogen (BUN) 37.5 mg/dL, blood uric acid (UrA) 7.2 mg/dL, C-reactive protein (CRP) 0.75 mg/dL, serum sodium 142 mEq/L, serum potassium 4.5 mEq/L, serum chloride 112 mEq/L, serum calcium 8.2 mg/dL, serum phosphate 3.9 mg/dL, proteinuria 4.7 g/day, hematuria 10–19/HPF. Albumin accounted for 63.6 % of total proteinuria. Her proteinuria was nonselective. Renal pathological examination was performed using the open renal biopsy technique. Under light microscopy, the specimen showed 180 glomeruli, and 110 of them showed global sclerosis. The other glomeruli showed no proliferation of either intra or extra glomerular mesangial cells. Still, there was focal proliferation of the mesangial matrix. Spike formations were seen in the sub

epithelial glomerular basement membrane (Fig. 1a, b). Interstitial lesion showed focal fibrosis and focal infiltration of inflammatory cells. Immunofluorescence microscopy showed IgG and C3 deposits on the glomerular capillary wall (Data are not shown). Examination of the type of MN (IgG1–4) was not performed. Electron microscopy revealed sub-epithelial electron dense deposits (Fig. 2) and thickening of the glomerular basement membrane. Given these observations, this patient was diagnosed as having MN including diabetic nephropathy. No malignant tumor was detected. Generally, therapy for MN consists of a steroid and immunosuppressive drugs. Because of the age of our patient and the risk of the various side effects of steroid therapy, we selected CsA and irbesartan. The starting dose of CsA was 50 mg/day. At a dose level of 75 mg/day, the blood concentration of CsA was 600–900 ng/mL at 2 h after its administration. The mean proteinuria decreased to 1.4 g/day per week, the mean serum albumin concentration increased to 2.7 g/day per

Fig. 2 Electron microscopic findings $\times 6000$. Higher electron dense deposit is seen on the sub epithelial space on the glomerular basement membrane. Thickening of GBM is also seen

week (Fig. 3), and serum Cr remained unchanged at 1.2 mg/dL. Her leg edema subsequently subsided.

Discussion

In this patient DM was assumed to be type 2 DM, because although we did not measure her insulin secretion, her BMI was 29.5, and her diabetes was controlled (HbA1c 5.4 %) with mitiglinide 30 mg and voglibose 0.6 mg/day.

Diabetic nephropathy is the most common cause of chronic renal failure. Renal involvement in DM is mostly diabetes nephropathy. However, diabetic patients often develop non diabetes nephropathy [1]. MN is the most common probable cause of primary glomerulonephritis in

adults with nephrotic syndrome. And the most common non diabetic renal pathology in diabetic patients is MN [3]. Thus, our patient is not a rare case. However, it is generally uncommon to perform renal biopsy and provide steroid therapy to elderly patients because of potential risks, especially if they have DM. We thought this patient had a nephrotic condition, and treatment would improve her quality of life. Her pathologic diagnosis was MN; however, increase of mesangial matrix and GBM thickening may also be due to diabetic nephropathy. In general, proteinuria increases gradually in patients with diabetic nephropathy. In our patient, edema appeared suddenly and was thought to be due not only to diabetic nephropathy but to MN too. Decrease of proteinuria and improvement of serum Alb concentration were confirmed after treatment with CsA and irbesartan. Besides, serum Cr was almost normal (Fig. 3). Patients with MN generally have a good prognosis. Prednisolone, either alone or combined with an immunosuppressive drug, seems to be useful in Japanese patients. Indeed, steroid therapy is effective not only in inducing a remission of nephrotic syndrome but also in preserving renal function [4]. However, Hogan et al. [5] demonstrated a lower 5-year renal survival rate in the steroid/no-therapy group than in patients receiving the steroid and alkylating agents. Thus they did not recommend therapy with steroids alone for patients with MN. These results suggest therapy and prognosis of MN are different in Japan and American or European countries. Recently, it was reported that 6 months' therapy with prednisolone and chlorambucil, but not with Cs A monotherapy, was effective for maintaining renal function in patients with IMN, and thus CsA monotherapy should be avoided in MN [6]. Nevertheless, in this study we administered our patient CsA as

Fig. 3 Clinical course of the patient

The amount of proteinuria is written by the average value for a week.

monotherapy. In Japan, the standard therapy is steroid or steroid plus an immunosuppressive drug. The main immunosuppressive drugs used in Japan are cyclophosphamide, CsA, and mizoribine. As for MN in patients with steroid resistant nephrotic syndrome, CsA therapy proved effective, proteinuria decreased from 8.5 g/day (mean value) before CsA therapy to 2.8 g/day (mean value) after 3 months, and the patients did not develop any side effect for a period of 12–24 months [7]. Those results proved the efficacy and safety of CsA therapy. It has also been reported that CsA monotherapy effectively induces remission in most nephrotic patients with MN [8]. As for our patient, we also used an angiotensin receptor antagonist (ARB). This drug may have contributed to the decrease of proteinuria. Indeed, ARB is recommended for MN. In about 30 % of the patients with MN remission occurs spontaneously [9]. After the start of treatment, proteinuria decreased in our patient; however, we cannot completely deny the possibility of spontaneous remission.

In conclusion, we experienced a case of MN in a diabetic patient of very old age with nephrotic syndrome. CsA mono-therapy may be effective and safe in a patient at a high risk for serious adverse effects.

Compliance with ethical standards

Conflict of interest The authors have declared that no Conflict of interest exists.

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