Case Report

A Case of Nephrotic Syndrome Associated with Renovascular Hypertension Successfully Treated with Candesartan

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A sixty eight-year-old man was referred to our hospital for evaluation of hypertension and hypokalemia. His chief complaints were fatigability and weakness of the lower extremities. Atrophy of the right kidney was noted on computed tomography. The laboratory findings demonstrated massive proteinuria, markedly elevated plasma renin activity, hypokalemia, and renal insufficiency. Angiography showed total occlusion of the right renal artery. The patient was diagnosed as having nephrotic syndrome associated with renovascular hypertension. Treatment with candesartan, an angiotensin-II-receptor blocker (ARB), controlled both hypertension and proteinuria satisfactorily without worsening of his renal function. This is the first report on the effect of ARB on nephrotic syndrome associated with renovascular hypertension. Based on the results, ARB can be considered a promising agent for the treatment of patients with renovascular hypertension with massive proteinuria and renal insufficiency. (Hypertens Res 2003; 26: 123–127)

Key Words: renin-angiotensin system, proteinuria, candesartan

Introduction

Renovascular hypertension is not a common cause of nephrotic syndrome, although there are several reported cases of the two conditions existing simultaneously (1–9). The mechanism of massive proteinuria in patients with renovascular hypertension is not clear. Since resolution of proteinuria has frequently been observed after nephrectomy (3, 4, 6), reconstruction of the affected renal artery (7), or administration of an angiotensin-converting enzyme (ACE) inhibitor (8, 9), the increased activity of the renin-angiotensin system may play an important role in this mechanism. We report a case of a 68-year-old man with nephrotic syndrome associated with renovascular hypertension which was successfully treated with candesartan, an angiotensin-II-receptor blocker (ARB).

Case Report

A sixty eight-year-old man was referred to our hospital for evaluation of hypertension and hypokalemia. Hypertension had been discovered incidentally 2 months before admission by his family doctor, who started treatment with nifedipine-CR 40 mg/day. However, blood pressure remained uncontrolled and his condition was complicated with hypokalemia, for which spironolactone was started on May 1. Finally, he was referred to our hospital for further evaluation in June 2001. The patient reported a history of smoking one pack of cigarettes a day for 50 years. He had no history of hypertension or renal disease. His parents were not hypertensive. During the preceding 3 months, he had noticed easy fatigability and weakness of the lower extremities. Results of physical examination on admission showed: height, 165 cm; weight, 55 kg; blood pressure, 192/124 mmHg; and pulse,
88/min and regular. Results of a cardiopulmonary examination were normal. Abdominal bruit was not audible and there was no peripheral edema. Optic fundi showed a hypertensive retinopathy of Keith-Wagener grade 3. The laboratory findings on admission are presented in Table 1. In summary, urinalysis showed massive proteinuria and no hematuria. In addition, laboratory findings such as a serum creatinine concentration of 1.5 mg/dl (132.6 µmol/l), a creatinine clearance of 33.8 ml/min, a serum potassium level of 3.4 mmol/l, and a plasma renin activity of 51.9 ng/ml/h suggested renovascular hypertension. Conditions causing secondary glomerular diseases such as diabetes, systemic lupus erythematosus (SLE), neoplasm, hepatitis B or C, amyloidosis, and drugs were excluded. Computed tomography revealed atrophy of the right kidney (Fig. 1). 99m Tc-mercaptoacetyltriglycine (99m Tc-MAG3)-renography revealed a marked decrease in the effective renal plasma flow of the right kidney (right side, 19.8 ml/min; left side, 209.4 ml/min) (Fig. 2). Magnetic resonance arteriography revealed occlusion of the right renal artery.
artery. Digital subtraction aortography showed occlusion of the right renal artery and collateral arteries from the right lumbar arteries (Fig. 3). Renal vein sampling showed marked laterality of plasma renin activity (right, 203 ng/ml/h; left, 53 ng/ml/h). In order to improve blood pressure control, we started candesartan 4 mg/day on July 6; the dosage was increased to 6 mg/day 2 weeks later. The clinical course of the patient is shown in Fig. 4. After treatment with candesartan, his blood pressure fell to 120/80 mmHg, and his urinary protein excretion decreased gradually to the level of 1.2 g/day by the end of July. The patient’s creatinine clearance did not change significantly, though his serum creatinine concentration showed a transient increase from 1.6 mg/dl to 1.9 mg/dl. His serum total protein and albumin levels returned to normal. Laboratory findings including serum electrolyte levels and peripheral blood examination remained stable, and he was discharged on July 27.

**Discussion**

Nephrotic-range proteinuria in a patient with renovascular hypertension is uncommon. Berlyne et al. first reported the association of nephrotic syndrome with renovascular hypertension in three patients, although the mechanism responsible for the coexistence of these conditions was unclear (1). It seems likely, however, that this mechanism involves the ef-

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**Fig. 2.** $^{99}$mTc-mercaptoacetyltriglycine ($^{99}$mTc-MAG3)-renography revealing a marked decrease in the effective renal plasma flow of the right kidney.

**Fig. 3.** A: Digital subtraction aortography showing occlusion of the right renal artery and collateral arteries from the right lumbar arteries. B: Left renal arteriography showing atherosclerotic changes.
 Effects of angiotensin II on the glomerular permeability, combined with the effects of severe hypertension. Angiotensin II exerts multiple actions on renal function through angiotensin type 1 (AT1) receptors, including: 1) afferent and efferent artery vasoconstriction; 2) mesangial cell contraction and proliferation; 3) stimulation of aldosterone release; and 4) activation of cytokines and growth factors (10). Therefore, it is possible that massive proteinuria is induced by not only the hemodynamic but also the non-hemodynamic effects of angiotensin II on renal function (11). Recently, Halimi et al. (12) demonstrated that nephrotic-range proteinuria could result from atherosclerotic renovascular disease. They showed that such patients carried a poor prognosis for renal function and mortality compared to patients with glomerulonephritis. Interestingly, patients with nephrotic-range proteinuria associated with renovascular disease share the following characteristics: an age of 50 years or greater, a current smoking habit or a history of smoking, increased likelihood of atherosclerotic vascular disease, lower serum potassium levels, and in most cases, complete obstruction of the renal artery. The clinical characteristics of the present patient were consistent with Halimi’s study, although our patient showed no signs of other atherosclerotic diseases, such as coronary artery or cerebrovascular disease.

Based on the patient’s medical history and arteriographic results, we suspected that the cause of the renovascular disease was atherosclerosis. The results of renal vein sampling suggested that the right kidney caused the systemic hyperreninemia in the present case. It is possible that the right kidney with renal artery occlusion is more ischemic than that with renal artery stenosis, and thus that the former releases much more renin. This would lead to greater plasma levels of angiotensin II, and higher blood pressure and hyperfiltration of the left kidney. In addition, angiotensin II releases aldosterone and often causes hypokalemia in patients with renovascular hypertension (6). Since the right kidney of our patient seemed to be non-functioning, we did not perform a biopsy for the contralateral kidney. It is possible that our patient had a superimposed renal disease, such as focal segmental glomerulosclerosis. There have been case reports of renovascular hypertension with biopsy-proven focal segmental glomerulosclerosis of the contralateral kidney (4, 5). However, Bhowmik et al. (5) speculated in their case report that the focal segmental glomerulosclerosis in the contralateral kidney was due to hyperfiltration secondary to the increased angiotensin II level. Since our patient had shown no abnormality in urinalysis until 1 year before admission, it would appear that he had not suffered from a primary glomerular disease.

Some cases of renovascular hypertension with massive proteinuria have been treated successfully by administration of an ACE inhibitor (8, 9). Because our patient had renal insufficiency, we chose an ARB, which is mainly metabolized in the liver, for control of his blood pressure and proteinuria. Treatment with candesartan satisfactorily controlled both the hypertension and proteinuria without worsening of his renal function. ARBs lower blood pressure by blocking the action of angiotensin II at its AT1 cellular receptor site. Since these drugs interfere with the renin-angiotensin system (10), they might be expected to be highly effective in renovascular hypertension. The antiproteinuric effect of ARB has been established for mesangial cell proliferative renal diseases such as IgA nephropathy (13) and diabetic nephropathy (14). However, this is the first report on the effect of ARB on nephrotic syndrome associated with renovascular hypertension. In the present case, the antiproteinuric effect of ARB may be attributable to a reduction in blood pressure. However, such a favorable reduction in blood pressure and urinary protein excretion could not have been achieved by other non-renin-angiotensin inhibiting drugs, because the activity of the patient’s renin-angiotensin system was markedly increased. In addition, Lewis et al. demonstrated that an ARB was effective in protecting against the progression of nephropathy due to type 2 diabetes, and that this protection was independent of the reduction in blood pressure (15). As some authors have pointed out (16, 17), we should consider the possible efficacy of combined treatment with an ARB and a calcium channel blocker. In any case, we must consider combination therapy with an ACE inhibitor and right nephrectomy when a patient’s blood pressure or proteinuria, or both, is not adequately controlled by ARB.

In conclusion, our results indicate that ARB is a promising agent for the treatment of patients with renovascular hypertension with massive proteinuria and renal insufficiency.

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References