Case Report

Renovascular Hypertension: A Unique Cause of Unilateral Focal Segmental Glomerulosclerosis

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A 48-year-old man presented with malignant hypertension and massive proteinuria. Renal angiography showed complete obstruction of the left renal artery and ^{99m}Tc-mercaptoacetylglycine (MAG_3) renography showed a nonfunctioning left kidney. Percutaneous transluminal renal angioplasty of the left renal artery was unsuccessful; hence, the patient underwent left nephrectomy because of uncontrolled hypertension and proteinuria. Histological examination of a right kidney specimen revealed lesions of focal segmental glomerulosclerosis with benign nephrosclerosis. In contrast, histology of the left kidney showed typical ischemic kidney with hypertrophy of arteriolar smooth muscle cells. The patient responded favorably to the nephrectomy, as his blood pressure and urinary protein dramatically decreased with no antihypertensive medication. This case illustrates the heterogeneous effect of the renin-angiotensin system on either kidney in patients with renovascular hypertension due to unilateral renal artery stenosis. (*Hypertens Res* 2006; 29: 203–207)

***Key Words*: renovascular hypertension, renal artery stenosis, angiotensin II, focal segmental glomerulosclerosis, nephrotic syndrome**

Introduction

Nephrotic syndrome in patients with renovascular hypertension (RVHT) is uncommon, and it raises the different diagnosis of focal glomerulosclerosis (FSGS) or malignant hypertension. While activation of the renin-angiotensin system is clearly responsible for the hypertension in patients with renal artery stenosis, its direct role in the pathogenesis of renal pathology in either kidney remains largely speculative.

Only a few cases of renal artery stenosis associated with FSGS in the contralateral kidney have been reported (*1–3*). In those cases, a detailed histological assessment of the ipsilateral kidney was not provided. We here report the case of a patient with RVHT and nephrotic syndrome, in whom histological examination of the contralateral kidney revealed lesions of FSGS with benign nephrosclerosis, while histological examination of the poststenotic kidney showed typical ischemic findings and unexpected results in the intra-renal resistance arteries.

Case Report

A 48-year-old, previously healthy male patient was hospitalized because of disturbed consciousness, dysarthria and blurred vision. On admission, he was found to have a blood pressure of 210/116 mmHg, bilateral grade IV hypertensive retinopathy and central retinal vein occlusion. There were no focal neurological signs. All peripheral pulses were intact and no peripheral edema or audible bruits were detected. Urine examination showed 1+ hematuria with normal sediments, and a 24-h excretion of 6.80 g protein. The blood urea nitro-

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Table 1. Comparison of the Plasma Renin and Aldosterone Levels at Three Different Points throughout the Patient's Clinical Course

	Reference value	On admission	Pre-operative*	Post-operative†
Blood pressure (mmHg)	—	210/116	180/126	130/60
Plasma renin (pg/ml)	2.5–21.4	2,440	669	8.9
Plasma aldosterone (pmol/l)	83–555	2,713	186	43.3
Urinary protein (g/day)	0	6.8	2.6	1.0

*Five months after commencing angiotensin blocking agents. †Three weeks after nephrectomy.

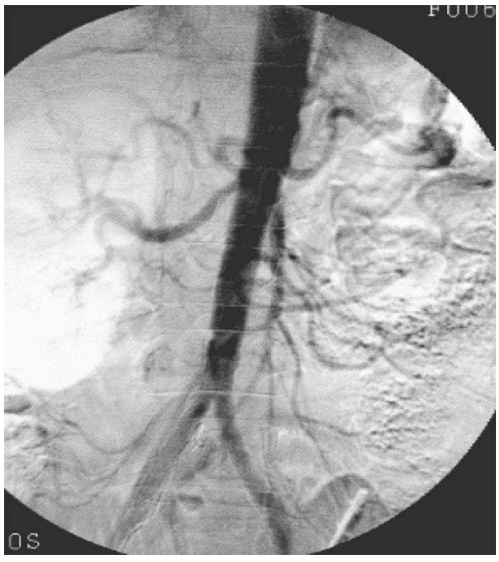

Fig. 1. *Angiography showing the normal aorta and right renal artery with a normal nephrogram on the right side. There is total occlusion of the left renal artery and the atrophic left kidney is faintly visible through collaterals.*

gen was 3.6 mmol/l (10.1 mg/dl), and the serum creatinine was 86.63 μmol/l (1.04 mg/dl) with a glomerular filtration rate of 47.7 ml/min. The serum total protein was 53 g/l, the albumin 30 g/l, the cholesterol 11.16 mmol/l (372 mg/dl), and the triglycerides 2.24 mmol/l (224 mg/dl). The results of serological evaluation for immunoglobulins, complement, antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), hepatitis B and C virus and human immunodeficiency virus (HIV) antibodies were negative. The plasma renin and aldosterone levels were very high (Table 1) and the catecholamine levels were normal. The chest X-ray results were normal, but cardiac echo showed mild concentric hypertrophy of the left ventricular wall. Brain MRI depicted edematous change of the brainstem, consistent with the clinical diagnosis of hypertensive encephalopathy. Ultrasound examination of the abdomen revealed asymmetrical kidneys: the right was 10.5 cm and the left 8.6 cm in length, a finding that was confirmed by computed tomography. ^{99m}Tc-mercaptoacetylglycine (MAG_3) scintigraphy showed that the left kidney was nonfunctioning. A renal arteriogram (Fig. 1) showed that the left renal artery was totally occluded, and the atrophic left kidney was faintly visible through some collaterals. The right renal artery appeared normal, as did the aorta. Percutaneous transluminal angioplasty was attempted, but the catheter failed to pass through the orifice of the left renal artery. Selective blood sampling for measurement of plasma renin activity from each renal vein confirmed the laterality of renin secretion with a left-to-right ratio greater than 4:1. Moreover, the level of renal venous blood draining from the uninvolved right kidney was similar to that draining from the inferior vena cava below the entrance of the renal veins.

Upon admission, antihypertensive medications were begun, including benidipine 4 mg/day, losartan 50 mg/day, and temocapril 2 mg/day. The blood pressure fell to 135/90 mmHg, but proteinuria remained in the nephrotic range (3.5 g/24-h). Five months later, the blood pressure rose again to 180/126 mmHg despite adding doxazosin 1 mg/day to the therapeutic regimen. At this point, the plasma renin and aldosterone levels were 669 pg/ml and 186 pmol/l, respectively. Left nephrectomy was done, and an intraoperative biopsy was taken from the right kidney to determine the cause of the continued proteinuria. Three weeks after the operation, the blood pressure, plasma renin and aldosterone levels became normal without antihypertensive medication (Table 1), and the proteinuria decreased to 1.0 g/24-h and remained low.

Macroscopically, the nephrectomized kidney was grossly atrophic with very thin cortex on cross section (Fig. 2). The specimen of the left renal artery showed a severe atheromatous lesion involving almost 90% of the arterial lumen. On light microscopy of the left kidney (Fig. 3), over 90 glomeruli were examined and showed ischemic collapse and 5% global sclerosis. There was no mesangial matrix expansion. The juxtaglomerular bodies showed hyperplastic changes. There was diffuse interstitial fibrosis with marked tubular atrophy. The small arteries were unremarkable, but the arterioles, including both the afferent and efferent arterioles, were severely narrowed by hypertrophy of the vascular smooth muscle cells without hyalinosis. An immunofluorescence study showed no specific staining.

Histology of the right kidney (Fig. 4) showed global sclerosis in 8 out of 38 glomeruli. The remaining 24 glomeruli showed mild segmental expansion of the mesangial matrix without mesangial cell proliferation, and FSGS lesions with

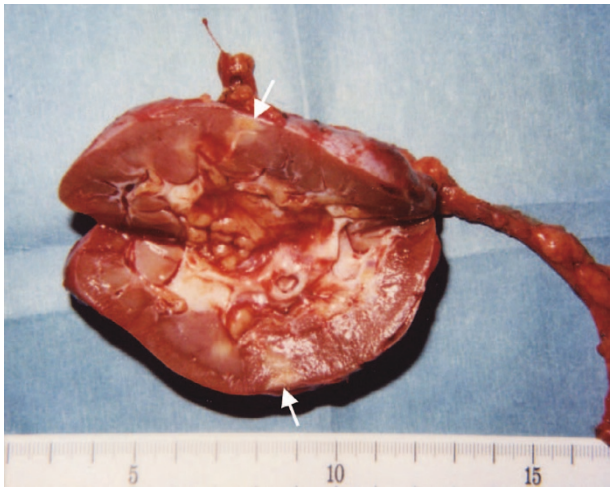

Fig. 2. *Longitudinal section of the nephrectomized kidney showing general renal atrophy, thinning of the renal cortex and triangular pale cortical areas (arrows) due to severe ischemia.*

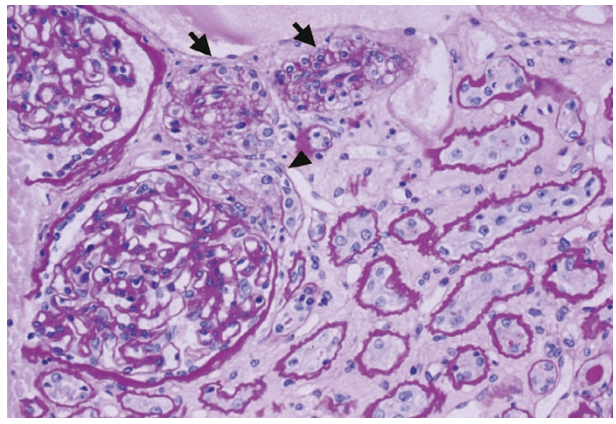

Fig. 3. *Biopsy of the left kidney showing collapsing changes of glomeruli, hyperplasia of the juxtaglomerular apparatus (arrowhead) and marked hypertrophy of arteriolar smooth muscle cells (arrows). There is diffuse interstitial fibrosis with marked tubular atrophy (periodic acid–Schiff staining; original magnification, ×66).*

capsular adhesions in 6 glomeruli. The tubulointerstitial area displayed mild patchy tubular atrophy with interstitial fibrosis, intimal fibrosis of the arteries and arteriolar hyalinosis. The results of the immunofluorescence study were negative. The final diagnosis was RVHT due to occlusion of the left renal artery with FSGS of the right kidney.

Discussion

Significant proteinuria (>300 mg/24-h) is an uncommon finding in patients with benign nephrosclerosis. In contrast, malignant hypertension often causes proteinuria, which can reach the nephrotic range due to the severe vasculoendothelial damage. Nephrotic syndrome in association with RVHT has been a subject of growing interest in recent years. A preliminary report on 59 elderly patients with FSGS suggested that FSGS may be an under-diagnosed etiology of significant proteinuria in patients with renal vascular disease (*4*). Subsequently, there have been few reports of patients with unilateral renal artery stenosis presenting with nephrotic syndrome that turned out to be due to FSGS of the contralateral kidney (*1–3*).

Two mechanisms have been proposed for the development of FSGS in patients with renovasculopathies. While hyperfiltration-induced FSGS is the most well-established mechanism, Meyrier *et al*. (*5*) suggested that ischemia is another possible contributor to the development of FSGS. In our patient, the poststenotic kidney showed normal glomeruli, suggesting that ischemia *per se* and the local activation of renin-angiotensin were insufficient factors to cause FSGS, and that protection from hyperfiltration was provided by the presence of high-grade stenosis. A similar finding has been previously reported (*6*). Although FSGS has rarely been

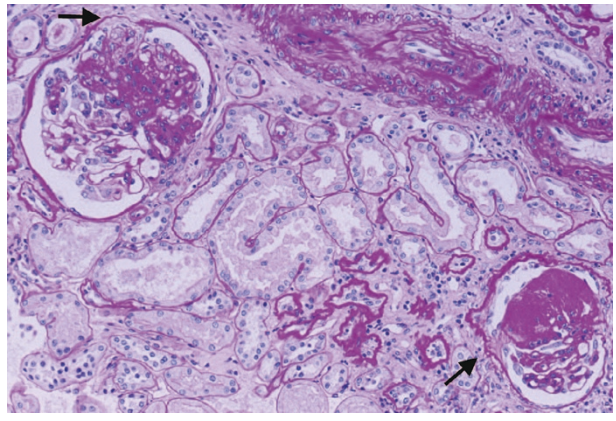

Fig. 4. *Biopsy of the right kidney showing two glomeruli with segmental sclerosis and capsular adhesions (arrows), fibrous intimal thickening of the small arteries and a focal area of tubular atrophy (periodic acid–Schiff staining; original magnification, ×50).*

observed in the stenotic kidney (*7*), such cases might be secondary to hyperfiltration in groups of glomeruli under control of the collateral arteries. In fact, we have recently experienced a patient with renovascular hypertension due to renal artery stenosis in one of the two main renal arteries to the right kidney, in whom FSGS lesions were found in the portion of the kidney supplied by the patent artery, but not in the remaining atrophic portion (data not shown). This difference may also be related to the time course and grade of stenosis—*i.e.*, the more abrupt and more severe the obstruction in the renal artery, the less likely that there will be FSGS in the poststenotic kidney.

Hypertensive arterial and arteriolar lesions are conspicuously absent in the clipped kidney in the experimental models of renovascular hypertension, and this has given rise to the concept of the "protected kidney" (*8*). Interestingly, our patient showed hyperplasia of the arteriolar smooth muscle cells in the poststenotic kidney, which was probably related to ischemia rather than hypertension. Although all blood vessels distal to the obstruction should generally be affected by ischemia, it seems that the smaller arterioles are more sensitive to the mitogenic effect of angiotensin II, which has been shown to induce replication of smooth muscle cells in the carotid arteries and type I and III mesenteric microvessels independent of blood pressure (*9*).

The few reports of nephrotic syndrome occurring in association with renal artery stenosis implicate renin and angiotensin as common etiological factors. By multivariate analysis of 96 patients with hypertension secondary to complete renal artery occlusion, active renin concentration and contralateral kidney length were the only factors independently linked to the severity of proteinuria (*10*). In RVHT, angiotensin II constricts the efferent arterioles in the unaffected kidney, causing an increase in the intraglomerular pressure and filtration fraction. Angiotensin II also acts directly on the endothelial cells to cause widening of the intra-endothelial gaps and an increase in glomerular capillary permeability. In addition, angiotensin II has been shown to stimulate extracellular matrix synthesis through induction of transforming growth factor β in rat mesangial cells (*11*), and infusion of angiotensin has been shown to induce glomerulosclerosis in rats (*12*). These overwhelming evidences for the central role of renin-angiotensin in the development of glomerulosclerosis and proteinuria dictate the use of angiotensin II inhibitors. Takahashi *et al*. (*13*) reported a case of nephrotic syndrome associated with renovascular hypertension successfully treated with candesartan, an angiotensin-II–receptor blocker. We assume that the activated renin-angiotensin system could not be overcome by angiotensin II inhibitors in our patient, especially at the tissue level, even though there was a marked reduction in serum aldosterone concentration. Recent studies have reported that intrarenal angiotensin II content and angiotensin II concentrations in the proximal tubular fluid and renal interstitial fluid are much greater than the circulating angiotensin II levels (*14*). The high intrarenal angiotensin II levels contribute to the development of hypertension and long-term proliferative effects leading to renal injury, and explain the mechanism by which renal artery occlusion causes hypertension which is unresponsive to angiotensin II inhibitors but can be completely corrected by nephrectomy. Alkhunaizi *et al*. (*2*) reported the first case to show resolution of nephrotic syndrome and renal insufficiency through repair of the renal artery stenosis. Unfortunately, an attempt to recanalize the stenotic lesion in our patient was a failure. It has been suggested that renal vein renin measurements can be used as a predictive test for surgically correctable renal disease when the ischemic kidney has a significantly higher venous plasma renin activity than the normal kidney, by a factor of ≥1.5 (*15*). Our patient had straightforward lateralizing data and responded as expected to the nephrectomy, showing normalization of the blood pressure and renin and aldosterone levels.

In conclusion, the present case serves as a reminder that the association of FSGS and renovascular disease should be considered in patients with malignant hypertension and nephrotic-range proteinuria. It also illustrates the importance of hemodynamic factors in the pathogenesis of FSGS in humans. Finally, it indicates that both blood pressure control and inhibition of the renin-angiotensin system are essential therapeutic strategies for nephrotic syndrome secondary to FSGS.

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