Renal artery stenosis, nephrotic-range proteinuria, and focal and segmental glomerulosclerosis[1]

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Two patients with renal artery stenosis, secondary to atherosclerosis and nephrotic-range proteinuria, underwent renal biopsies. The results indicated focal and segmental glomerulosclerosis. The relationship between focal and segmental glomerulosclerosis proteinuria and glomerular sclerosis is discussed.

Index terms: Arteriosclerosis • Glomerulonephritis • Proteinuria • Renal artery obstruction

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The association between renal artery stenosis and hypertension has been documented in numerous series. Yet, the association between renal artery stenosis and the nephrotic syndrome or nephrotic-range proteinuria is unusual.[1–9] In most cases, renal tissue had been obtained by biopsy, a nephrectomy had been performed, or an autopsy was done; however, evaluation was limited to light microscopy and did not include immunohistochemistry, immunofluorescence, or electron microscopy.[1–4,6–9] The results of one biopsy from a patient with renal artery stenosis and nephrotic-range proteinuria showed no evidence of immunofluorescent or ultrastructural deposits.[3] Biopsy results from a kidney contralateral to the renal artery stenosis demonstrated only segmental IgM in glomeruli and normal glomeruli, as evaluated by light and electron microscopy.[5] The relationship between elevated levels of renin/angiotensin and induced proteinuria in experimental animals has been demonstrated.[10–12] The relationship of elevated

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renin/angiotensin levels to nephrotic-range proteinuria in man has also been reported.[3,5]

Materials and Methods

Two patients with renal artery stenosis were identified as part of a study of 27 consecutive patients whose renal biopsy specimens were found to have the light microscopic, immunohistochemical, and electron microscopic features of focal and segmental glomerulosclerosis. The biopsy specimens were processed for light microscopy, immunohistochemistry, and electron microscopy as previously described.[13] The patients' charts, including clinical and laboratory data, as well as appropriate angiograms, were reviewed.

Case reports

Case 1. A 54-year-old white man presented at the Cleveland Clinic in June 1979 with hypertension, heavy proteinuria without edema, and congestive heart failure. He had no history of diabetes mellitus. In 1974, the patient was discovered to be hypertensive. Since 1974, the diastolic blood pressure varied from 90 to 110 mm Hg, and the systolic pressure varied from 190 to 210 mm Hg. Medications included digoxin, a thiazide diuretic, furosemide, methyldopa, and aspirin. During that period, atherosclerotic stenosis of the left and right carotid arteries developed; endarterectomies were required. The chest radiograph, obtained on admission, was normal. Hemoglobin and hematocrit levels, the red blood cell count, red blood cell indexes, the platelet count, and the white blood cell count were normal. The differential white blood cell count was also normal. VDRL was negative. Results of the lupus erythematosus (LE) preparation were negative. Urine contained oval fat bodies. The urine sediment included hyaline casts, but no other casts, and only rare white and red blood cells. The serum total protein value was 6.6 g/dl; albumin value, 3.6 g/dl; and cholesterol value, 215 mg/dl. Glucose, calcium, inorganic phosphate, total bilirubin, alkaline phosphatase, creatinine phosphokinase, lactic dehydrogenase, and glutamic-oxalate transaminase levels were normal. Other laboratory values were: sodium, 135 mEq/l; potassium, 3.4 mEq/l; chloride, 95 mEq/l; and carbon dioxide (CO_2), 32 mEq/l. The 24-hour urine protein excretion value was 10.0 g. The serum creatinine level was 1.5 mg/dl. The blood-urea-nitrogen (BUN) level was 34.0 mg/dl. The iodothalamate clearance was 63.0 ml/min/1.73 m^2. Tomograms showed that the left kidney measured 7.0 cm in length and the right kidney measured 16.5 cm in length. Inferior venacavography was not performed. Angiograms demonstrated stenosis of the right and left renal arteries (*Fig. 1A*). A perfusion scan showed that the left kidney was not functioning. Percutaneous transluminal angioplasty of the right renal artery was performed to increase renal blood flow to the only functioning kidney. This resulted in normalization of blood pressure; however, during the following year (July 1980), proteinuria persisted (7.9 g/24 hr), the serum creatinine level increased to 2.6 mg/dl, and iodothalamate clearance decreased to 29.0 ml/min/1.73 m^2. A right renal angiogram demonstrated patency of the right renal artery, with possible stenosis at the aortic origin. Transluminal percutaneous angioplasty was attempted, but the catheter could not be passed through a tight right artery orifice. At that time, the right kidney measured 14.0 cm.

An open biopsy of the right kidney was performed to determine the degree of scarring of the renal parenchyma, as well as the type of nephropathy associated with nephrotic-range proteinuria. If most of the glomeruli had not been sclerotic, revascularization of the renal kidney would have been undertaken. The light microscopic sections contained 41 glomeruli. Seventeen glomeruli were normal. Two glomeruli exhibited segmental sclerosis, and 22 glomeruli exhibited global sclerosis (*Fig. 1B*). Arterioles were unremarkable. Patchy interstitial fibrosis and tubular atrophy were evident. Immunoperoxidase with the periodic acid Schiff (PAS) counterstain contained seven glomeruli. Granular deposits of IgM and C3 were identified in segmentally sclerotic areas of glomeruli. The glomeruli were negative for IgG and IgA. Granular deposits of C3 were present in arterioles and rare segments of tubular basement membranes. Electron microscopy of three glomeruli demonstrated extensive collapse; dense deposits were identified in the areas of collapse. There was no amyloid deposit. Peripheral glomerular basement membranes did not appear thickened; however, the extensive degree of collapse rendered evaluation of the membrane thickness difficult (*Fig. 1C*). An angiogram obtained in October 1980 demonstrated coronary atherosclerosis with moderate generalized impairment of left ventricular function. The celiac artery was 80% stenotic. Because of these findings and the extent of glomerular sclerosis, revascularization of the right kidney was not attempted. The patient remained normotensive on continuing hypertensive medication (methyldopa, a thiazide diuretic, furosemide), but progressive renal failure subsequently developed, requiring chronic hemodialysis. The patient died of renal failure in April 1981. An autopsy was not performed.

Case 2. A 62-year-old white man presented at the Cleveland Clinic in February 1981 with a history of severe hypertension (detected in March 1980 [200/100 mm Hg]) and azotemia. He had a history of hypertension for the previous five to six years, but no evidence of diabetes mellitus. At admission, his blood pressure was 164/100 mm Hg. There was no edema. Medications included methyclothiazide, furosemide, and prazosin hydrochloride. The chest radiograph was unremarkable, with the exception of cardiomegaly and a pleural scar. Anemia was evident (hematocrit, 24%). The result of the direct Coombs test was negative. The white blood cell count and platelet count were normal. The differential white blood cell count was normal. Other laboratory values were: serum total protein, 5.2 g/dl; albumin, 2.6 gm/dl; calcium, 7.6 mg/dl; cholesterol, 308 mg/dl (normal, 150–240 mg/dl); and creatinine phosphokinase, 205 units/l (normal, 20–180 units/l). Inorganic phosphate, glucose, uric acid, total bilirubin, alkaline phosphatase, lactic dehydrogenase, glutamic-oxalate transaminase, sodium, potassium, chloride, and CO_2 levels were normal. VDRL was negative. Urine contained 5–10 red blood cells and 3–5 white blood cells per high power field, as well as granular and hyaline casts. The 24-hour urine protein secretion value was 9.5 g. The serum creatinine level was 5.8 mg/dl. (In March 1980, the serum creatinine level had been 2.5 gm/dl.) The BUN value was 70 mg/dl. The iodothalamate

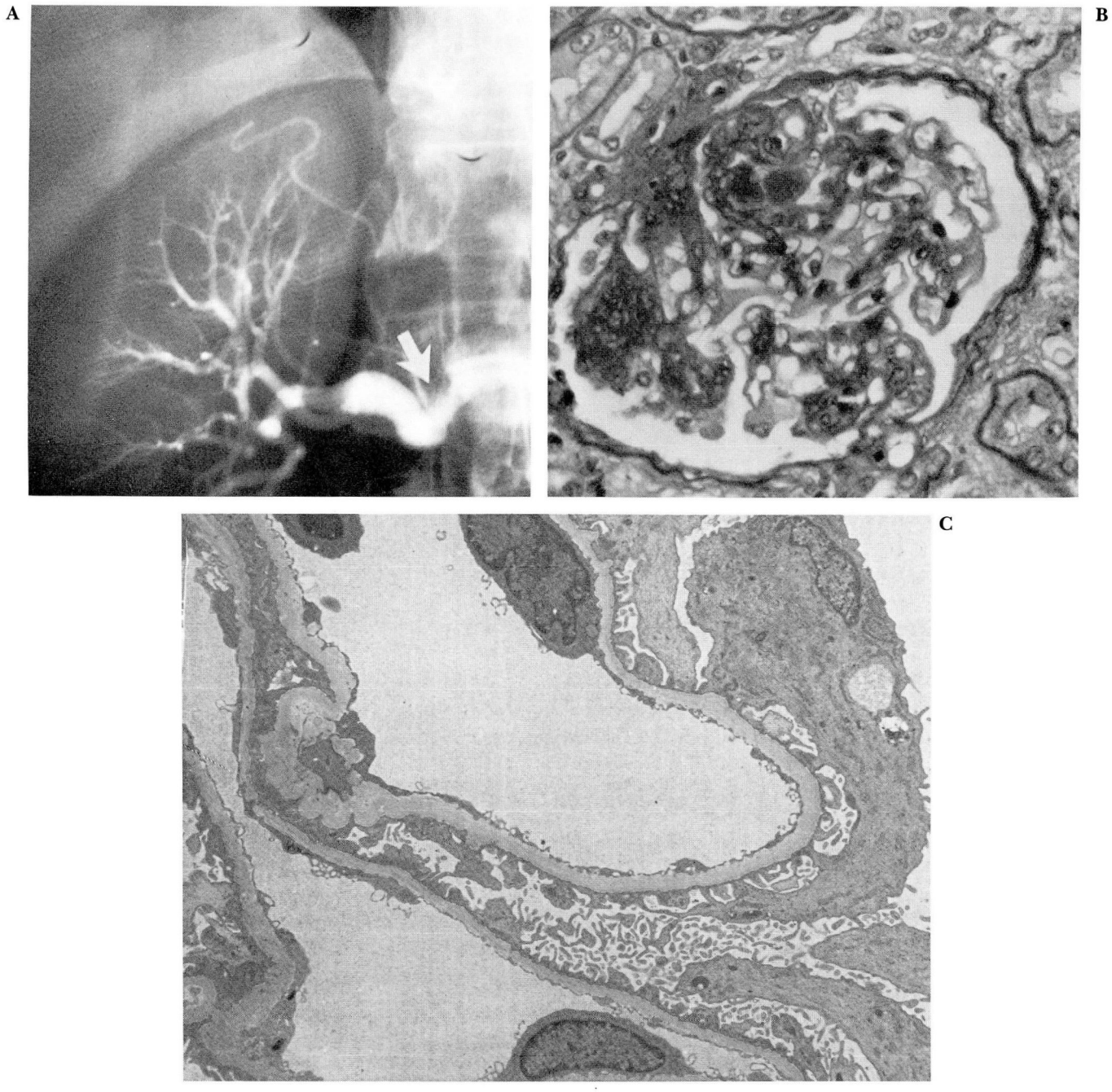
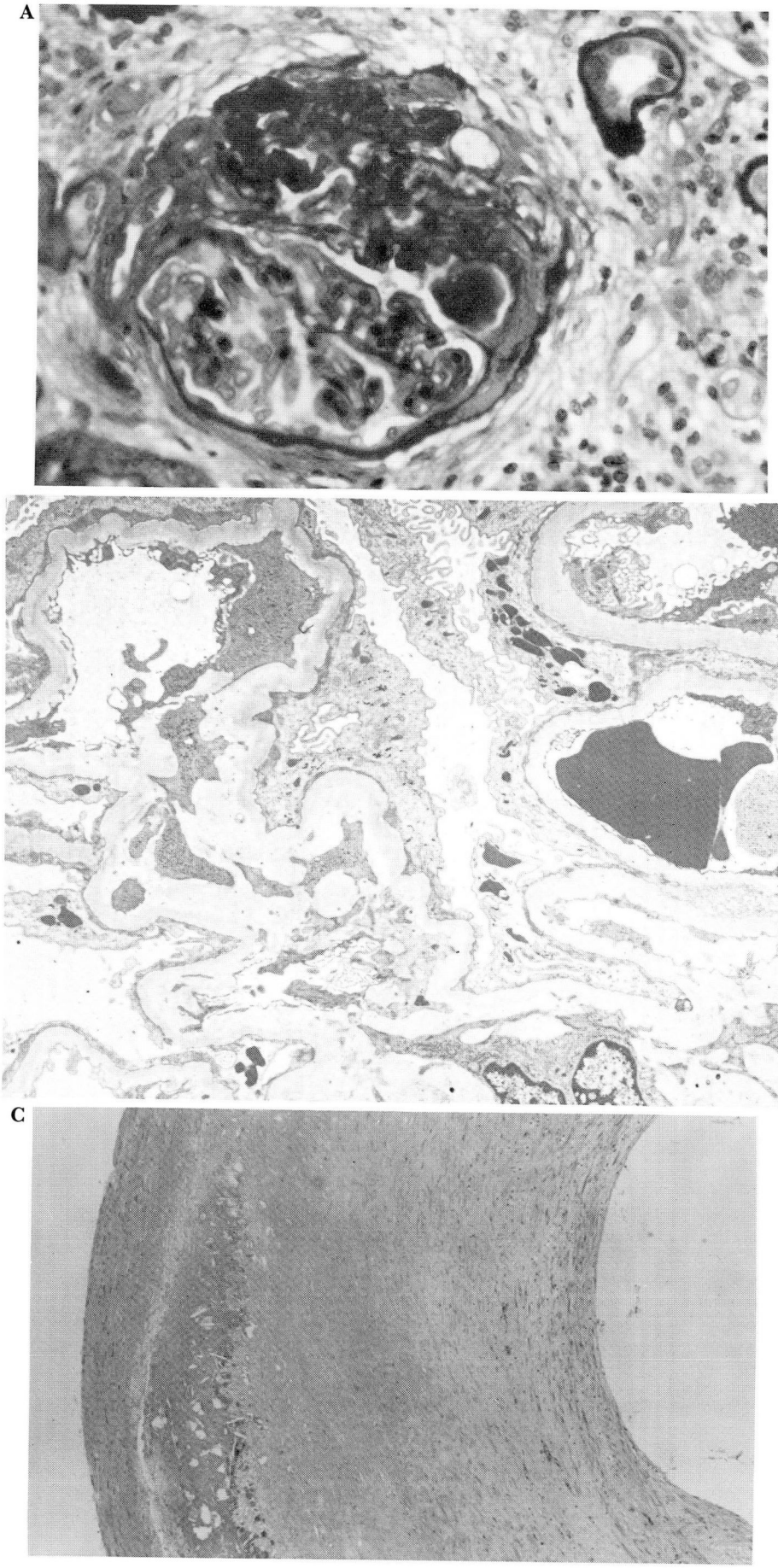


Fig. 1. Case 1
A. Right renal angiogram demonstrates stenosis (*arrow*). Narrowing was also present in the left renal artery.
B. PAS stain. Glomerulus with segmental sclerosis is shown. (× 100)
C. Electron micrograph shows no dense deposit in the glomerular basement membrane or mesangium. (× 4,500)

glomerular filtration rate was 9.0 ml/min/1.73 m^2. The antinuclear antibody titer was negative. Renal tomograms demonstrated a right kidney that was 12.5 cm in length and a left kidney that was 13.5 cm in length. The electrocardiogram demonstrated a remote myocardial infarct. Serum CH50, C3, and C4 were normal. The rheumatoid factor was slightly elevated. The result of the assay for circulating immune complexes was not elevated. An open biopsy of the right kidney was performed. Light microscopic sections contained 44 glomeruli. Ten glomeruli were normal. Five glomeruli exhibited segmental sclerosis (*Fig. 2A*); 29 glomeruli showed global sclerosis. Marked interstitial fibrosis and tubular atrophy were noted. The arterioles and small arteries exhibited mild thickening. Immunoperoxidase with PAS counterstain contained six glomeruli. Granular deposits of IgG, IgM, and C3 were demonstrated in segmentally



sclerotic areas of glomeruli. Granular deposits of C3 were detected in arterioles and segments of tubular basement membranes. Electron microscopy of two glomeruli demonstrated no dense deposit. The glomeruli exhibited no collapse. No amyloid deposit was evident. The peripheral glomerular basement membrane was not thickened (*Fig. 2B*). Hypertension was initially controlled and methyclothiazide was discontinued; however, hypertension recurred one month later and persisted (206–107/110–60 mm Hg supine and 190–146/110–68 mm Hg standing) despite adding propranolol hydrochloride and clonidine hydrochloride to the therapeutic regimen. Chronic renal failure subsequently developed (serum creatinine level, 9.9 mg/dl), and the patient died in December 1981 while being considered for chronic hemodialysis. An autopsy was performed; remote and recent myocardial infarcts of the left ventricle and interventricular septum were apparent. A 70%–100% atherosclerotic stenosis of the left anterior descending, right mid-coronary, and left mid-circumflex coronary arteries, with recent and old myocardial infarcts, cardiomegaly, and left ventricular hypertrophy were found. The right proximal renal artery exhibited a 60% atherosclerotic stenosis. The abdominal aorta showed moderate atherosclerosis. A right superior branch of the renal artery demonstrated up to 100% atherosclerotic narrowing (*Fig. 2C*). The left distal renal artery demonstrated 80% atherosclerotic stenosis. The inferior vena cava and renal veins had no thrombus. The right kidney weighed 150 g, and the left kidney weighed 130 g. No discrete cortical or papillary scar was evident, although the cortex was uniformly diminished in thickness. The ureters, pelves, and calyces were normal. Microscopically, both kidneys exhibited segmentally and globally sclerotic glomeruli. The liver and pulmonary edema, as well as the lungs, were congested.

Discussion

The association between renal artery stenosis and the nephrotic syndrome has been reported,[1–9] but is unusual. We have described two patients with renal artery stenosis: one diagnosed by angiography (Case 1) and one diagnosed at autopsy (Case 2). The autopsied patient had no thrombus in the renal veins or inferior vena cava. The other patient had not undergone inferior venacavography. Biopsy specimens from the kidneys ipsilateral to the renal artery stenosis demonstrated light microscopic, immunohistochemical, and electron microscopic findings typical of focal and segmental glomerulosclerosis. Membranous glomerulonephritis, diabetic nephropathy, amyloid nephropathy, mesangial glomerulonephritis, or membranoproliferative glomerulonephritis was not evident. Whether the sclerotic lesions in the glomeruli represented changes secondary to ischemia or an intrinsic process similar to patients with focal and segmental glomerulosclerosis without renal artery stenosis was difficult to determine since focal and segmental sclerosis is commonly associated with the nephrotic syndrome.[14–16] Reflux nephropathy may be associated with proteinuria and produce lesions identical to focal and segmental glomerulosclerosis.[17,18] Excretory urography, sonography, and tomography demonstrated no abnormality in the functioning kidney, which underwent a biopsy, of our first patient (Case 1). The autopsy of the second reported patient (Case 2) demonstrated no ureteral, renal pelvic, or calyceal abnormality. These findings did not exclude reflux, but indicated that it was unlikely.

The two patients described here did not undergo renin/angiotensin assays; therefore, we cannot comment on the relationship of elevated renin/angiotensin levels and proteinuria, which has been demonstrated in experimental animals.[10–12] Yet, increased renin/angiotensin levels probably did not contribute to the heavy proteinuria of the first patient (Case 1) because blood pressure was well controlled. In some humans with renal artery stenosis, elevated renin/angiotensin levels have been related to nephrotic-range proteinuria.[3,5]

Two of 27 consecutive patients with renal biopsy evidence of focal and segmental glomerulosclerosis had atherosclerotic renal artery stenosis demonstrated by renal angiography (Case 1) and autopsy (Case 2). This represents an incidence of 7.4%; however, renal angiography was only performed in that one instance (Case 1). Only these 2 patients died; one (Case 1) did not undergo autopsy, but the other patient (Case 2) did. The true incidence of renal artery stenosis in patients with renal biopsy evidence of focal and segmental glomerulosclerosis is, therefore, unknown. The association of renal artery stenosis, nephrotic-range proteinuria, and focal and segmental glomerulosclerosis may be coincidental since the nephrotic syndrome and hypertension are common manifestations of focal and segmental sclerosis. The hypertension associated with idiopathic focal and segmental glomerulosclerosis is usually assumed to be secondary to azotemia rather than renal artery stenosis.

Renal artery stenosis did not appear to exert a protective effect on the renal parenchyma in our

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Fig. 2. Case 2

A. PAS stain. Glomerulus with segmental sclerosis is evident (× 100)

B. Electron micrograph shows no dense deposit in the glomerular basement membrane or mesangium. (× 7,100)

C. During the postmortem examination, an atherosclerotic plaque was found in the right artery. (Hematoxylin-eosin stain, × 10)

two patients reported here. In both cases, biopsy specimens of the kidneys ipsilateral to the renal artery stenosis demonstrated extensive glomerular sclerosis, and progressive renal failure developed. In one instance (Case 1), this was complicated by a contralateral nonfunctioning kidney with arterial stenosis, and in the other instance (Case 2), bilateral renal artery stenosis was evident. Therefore, it is difficult to speculate on the role of renal artery stenosis and the occurrence and progression of glomerular disease, which has been demonstrated experimentally[19] and in humans.[20]

Conclusion

Because not only nephropathies other than focal and segmental glomerulosclerosis may be diagnosed,[21] but more importantly, revascularization of kidneys with extensive parenchymal scarring will be avoided,[22] we believe that a renal biopsy should be considered for patients with renal artery stenosis and nephrotic-range proteinuria to determine the nature of the renal disease.

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