KIDNEY BIOPSY TEACHING CASE

A Rare Cause of Posttransplantation Nephrotic Syndrome

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INDEX WORDS: Transplantation; nephrotic syndrome; lipoprotein.

THE MAJOR CAUSES of posttransplantation nephrotic syndrome are transplant glomerulopathy, de novo glomerular disease, and recurrent glomerular disease.[1] Renal allograft biopsy and clinical correlation with native biopsy findings are necessary to distinguish between these entities, guiding therapy and providing valuable insights into pathogenetic mechanisms. We describe a case of posttransplantation nephrotic syndrome caused by recurrence of a rare glomerular disease that was uncovered by allograft biopsy.

CASE REPORT

The patient, a 42-year-old American-born man of Chinese descent, presented with graft dysfunction and nephrotic-range proteinuria 2 years after cadaveric renal transplantation. Details of his native kidney disease and preoperative clinical course have been reported previously.[2] In brief, the subject developed end-stage renal disease after 8 years of nephrotic-range proteinuria, hypertension, hypertriglyceridemia, and progressive deterioration in renal function. Serological test results for antinuclear antigen, cryoglobulin, hepatitis B surface antigen, C3, and C4 were negative or within normal limits. There was no history of diabetes. After transplantation, the postoperative course was uneventful and serum creatinine levels were stable, in the range of 1.4 to 1.6 mg/dL (123.8 to 141.1 μmol/L). Immunosuppressive medications consisted of cyclosporine, 75 mg twice daily; mycophenolate mofetil, 500 mg twice daily; and prednisone, 5 mg/d.

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Received August 16, 2004; accepted in revised form August 26, 2004.

Originally published online as doi:10.1053/j.ajkd.2004.08.048 on May 3, 2005.

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0272-6386/05/4506-0021$30.00/0

doi:10.1053/j.ajkd.2004.08.048

Two years after transplantation, serum creatinine level was noted to be elevated at 2.0 mg/dL (176.8 μmol/L; normal range, 0.6 to 1.2 mg/dL [53 to 106 μmol/L]). Urinalysis showed 4^+ protein, 8 to 10 red blood cells/high-power field, occasional hyaline casts, and no cellular casts. A 24-hour urine collection contained 4.921 g of protein. Serum albumin level was 2.9 g/dL (29 g/L). No graft tenderness was noted, and the patient was asymptomatic, without edema. Doppler ultrasound showed good blood flow in the renal artery and vein and no evidence of outflow obstruction. A renal biopsy was performed, and the specimen was examined using light microscopy.

Biopsy Findings

Sections showed 1 core of renal cortex with 6 glomeruli, none of which showed global or segmental sclerosis. There was marked accentuation of glomerular lobularity with prominent aneurysmal dilatation of capillary lumina containing weakly eosinophilic acellular material that did not stain with periodic acid–Schiff (Fig 1), stained pale blue with Masson trichrome, and was Congo red negative. This material had a faintly laminated appearance under high-power magnification. Entrapped erythrocytes were seen at the periphery of some capillary loops. Peripheral capillary walls were diffusely thickened, with frequent duplication of glomerular basement membranes and focal mesangial interposition. There was moderate diffuse mesangial hypercellularity. The tubulointerstitium showed a mild patchy mononuclear inflammatory infiltrate with rare foci of mild tubulitis (1 to 4 mononuclear cells/tubular cross-section), suspicious for acute cellular rejection (Banff 97 schema). There was no significant tubular atrophy or interstitial fibrosis. Arterioles and medium-sized arteries showed no significant histological abnormalities. Immunofluorescence microscopy was not performed, and no glomeruli were identified for electron microscopic examination in the remaining deparaffinized formalin-fixed tissue.

Differential Diagnosis

The most common cause of posttransplantation nephrotic syndrome is transplant glomerulopathy, a manifestation of chronic rejection at the level of the glomerulus. Although the possibility of transplant glomerulopathy was suggested by the presence of membranoproliferative features, including double contours of the glomerular capillary walls and segmental mesangial interposition, the abundant intracapillary material, absence of mesangiolysis, and absence of marginated intracapillary leukocytes argued against this possibility. The major light microscopic finding was engorgement of the glomerular capillary lumina by pale eosinophilic acellular material. Differential diagnosis of this intracapillary material includes fibrin thrombi, immune deposits, amyloid, or other storage material. Fibrin thrombi and immune deposits

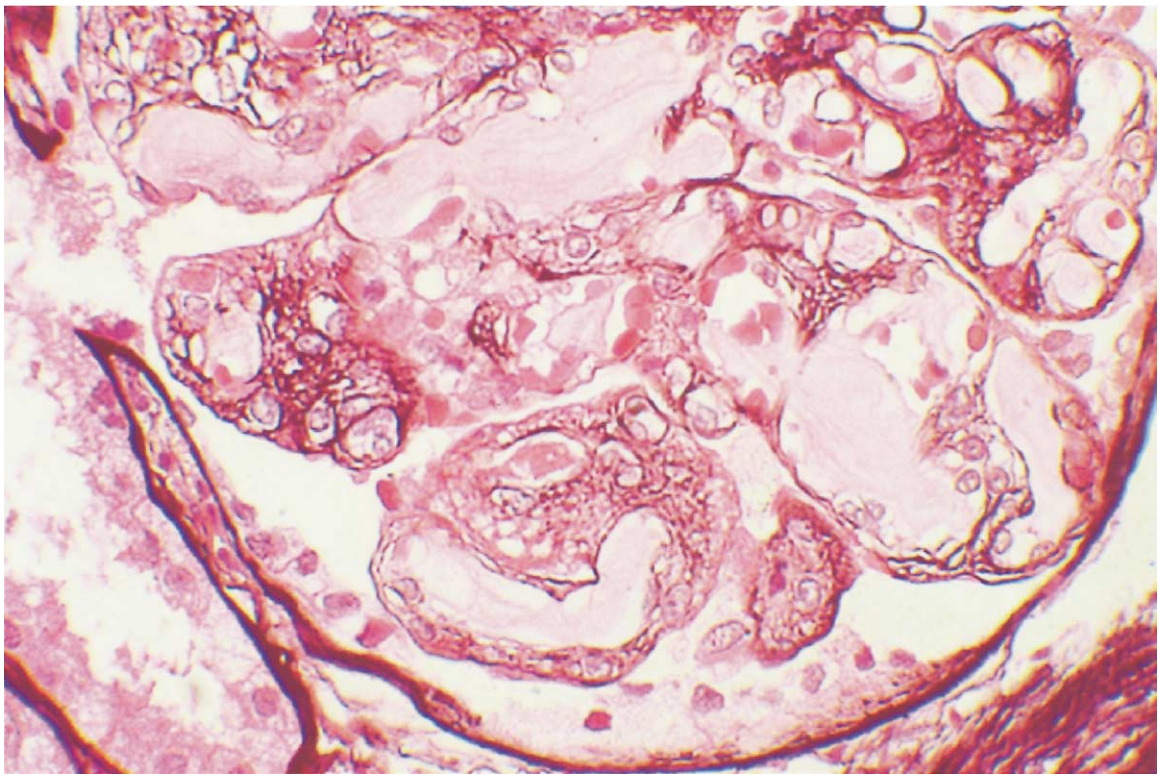

Fig 1. Glomerular capillary lumens are markedly dilated and contain pale-staining, weakly eosinophilic, thrombus-like material. This material has a finely lamellar pattern. There is marked thickening of the peripheral capillary wall, with duplication of glomerular basement membranes and focal cellular interposition (Jones silver methenamine stain; original magnification ×40).

typically stain fuchsinophilic (red) with trichrome stain. In this case, the pale blue appearance with trichrome stain indicated a composition other than fibrin or immune deposits. Congo red negativity ruled out amyloidosis. Thus, by process of elimination, the possibility of a storage product was entertained.

The material seen in this biopsy specimen stained pale with eosin, weakly with periodic acid–Schiff, and pale blue with trichrome, all features strongly suggestive of renal lipidosis.[3] Identical glomerular findings were seen in the native kidney biopsy specimen, obtained 8 years before transplantation (Fig 2). In cryosections of the native kidney biopsy specimen, glomerular material stained strongly with oil red O for fat (Fig 3). Immunofluorescence microscopy showed no specific staining for immunoglobulin G (IgG), IgM, IgA, C3, C1q, fibrinogen, or κ and λ light chains. However, there was intense staining of glomerular capillary contents for apolipoprotein (apo) E and apo B, but not for apo A-I, apo A-II, or apo J.[2] Electron microscopy showed concentrically layered, finely vacuolated material within capillary lumina (Fig 4) and focally in the mesangium and subendothelial sites. This constellation of distinctive pathological findings is characteristic of lipoprotein glomerulopathy (LPG),[4] a diagnosis supported by the clinical findings of hypertriglyceridemia and elevated plasma apo E levels. Lipid electrophoresis before transplantation had shown increased pre–β-lipoprotein, and isoelectric focusing showed a heterozygous E2/3 apoE phenotype. Subsequent molecular testing performed on peripheral-blood DNA (vide infra) showed the presence of apoE-Kyoto variant (Fig 5). Based on histological similarity to native kidney findings, recurrent LPG (with coexistent borderline acute cellular rejection) was diagnosed in the renal allograft.

Characterization of the ApoE Genotype

Genomic DNA was isolated from the patient's peripheral-blood leukocytes, the apoE gene was amplified by using polymerase chain reaction, and nucleotide sequencing analysis of the genomic apoE gene was performed as previously described.[5] Sequencing analysis identified a heterozygous missense mutation (C $\rightarrow$ T) leading to an amino acid substitution Cys (TGC) for Arg (CGC) at codon 25 (Fig 5), consistent with heterozygous apoE-Kyoto genotype. Results were confirmed by means of restriction fragment length polymorphism analysis with *Aor*51HI to eliminate sequencing error resulting from misincorporation during polymerase chain reaction, as previously described.[5]

Postbiopsy Clinical Course

After the renal allograft biopsy, the patient was administered an intravenous bolus of corticosteroids for borderline