Recurrence of lipoprotein glomerulopathy after renal transplantation

P. A. Andrews¹, P. J. O’Donnell², S. A. Dilly³, S. A. Snowden¹ and M. Bewick¹

¹Department of Nephrology, St George’s Hospital, ²Department of Histopathology, King’s College Hospital, ³Department of Histopathology, St George’s Hospital, London, UK

Key words: lipoprotein glomerulopathy; recurrent disease; renal transplantation

Introduction

Lipoprotein glomerulopathy is a rare condition characterized by abnormal lipoprotein deposition in glomeruli, usually with lipoprotein thrombi distending and occluding glomerular capillary lumina, and with a variable degree of mesangial proliferation [1]. First described and most frequently reported in Japan [1–5], it has been increasingly recognized in other racial groups and in Europe over the past 10 years [6,7]. The usual presentation is with proteinuria or nephrotic syndrome together with moderate renal impairment, often with hypertension, and progressing in many cases to renal failure.

The aetiology of the condition is uncertain, although it has been associated with increased apolipoprotein E2/E3 phenotype, and with variable increases in serum cholesterol and triglycerides [1,3–5]. One report suggests a familial predisposition [1]. It is clearly distinct from other causes of lipid accumulation within glomeruli, such as Gaucher’s disease and other hereditary sphingolipidoses. Immunohistochemical analysis indicates that the lipid deposits are composed mainly of β/β lipoprotein and that they represent accumulation of VLDL and/or remnants of VLDL derived from the plasma [6]. The factors which determine abnormal deposition/accumulation are, however, unknown.

Most reports suggest that the pathogenesis of the condition is likely to be humoral in origin, rather than specific to the kidney, although no other organ systems have yet been shown to be affected. Given this, the recurrence of lipoprotein deposits and renal disease following renal transplantation would be of great interest. An abstract presented to the Japanese Society of Nephrology in 1989 suggested that this might indeed occur, but few details were provided [8]. More recently, Djamali et al. [9] reported a case of recurrent disease in a French recipient of a renal allograft. We now describe a third such case, the first to be reported in the English literature.

Case report

A 16-year-old man presented with a 7-day history of headache. Direct questioning revealed a 1-month history of tiredness, breathlessness on exertion, ankle oedema, and blurred vision. There was no relevant past medical history. Family history was unremarkable apart from insulin-dependent diabetes mellitus and mild hypertension diagnosed in his father when aged 36. His parents were from Jamaica, but he had lived all his life in the United Kingdom. Examination showed a fit, well muscled man. Blood pressure was 268/168 on repeated measurement. Fundoscopy showed bilateral papilloedema with haemorrhages. There was bilateral pitting oedema to the knees, small pleural effusions, and moderate left ventricular hypertrophy. Urinalysis showed 3+ protein and 1+ blood. Remainder of examination was unremarkable.

Initial investigation showed sodium 134 mmol/l, potassium 6.5 mmol/l, bicarbonate 16 mmol/l, urea 39.9 mmol/l, and creatinine 1859 μmol/l. Creatinine phosphokinase and random glucose were not elevated. He was appropriately anaemic with haemoglobin 8.7 g/dl, and normochromic normocytic indices. Blood films showed minor fragmentation but no evidence of haemolysis. White cell count was normal, platelets 92 x 10⁹/l. ESR was 71 mm in the first hour, C reactive protein <4 u (normal <10 u), uric acid 0.63 mmol/l. Tests of liver function and coagulation were normal apart from an albumin of 31 mmol/l. He was nephrotic with 6.4 g/24-h proteinuria. Chest and abdominal radiographs were unremarkable, while ECG showed concentric left ventricular hypertrophy, confirmed on echocardiography. Renal ultrasound showed 9.0-cm unobstructed kidneys with increased cortical echogenicity, and a small amount of ascitic fluid. Serological tests including antinuclear, antineutrophil cytoplasmic, and antiglomerular basement membrane antibodies

Correspondence and offprint requests to: Dr Peter A. Andrews, Renal Unit, St Helier Hospital, Wrythe Lane, Surrey SM5 1AA, UK.

© 1997 European Renal Association–European Dialysis and Transplant Association
were negative. Complement and immunoglobulin levels were normal. Infective and viral screens were negative.

Initial management consisted of control of hypertension with calcium antagonists, haemofiltration, optimization of fluid status, and insertion of a peritoneal dialysis catheter. He became oliguric despite adequate intravascular hydration. Catecholamine, steroid, and carcinoid screens were negative. Renal arteriograms showed no evidence of renovascular stenosis.

Percutaneous renal biopsy was performed on day 7. The findings were initially felt to be consistent with severe hypertension and long-standing ischaemic damage. On review, however, the diagnosis of lipoprotein glomerulopathy was established through special staining and a comparison with previously reported cases. Twenty-five glomeruli were present in the biopsy, 15 of which were totally sclerosed. The remainder showed expansion of the glomerular tuft by lipid-laden cells, variable mesangial expansion, and a minor degree of accumulation of lipid deposits in tubular epithelial cells (Figures 1 and 2). There were no interstitial foam cells. Blood vessels showed marked hypertensive changes with areas of intraglomerular thrombosis and necrosis but no vasculitis, whilst the tubulointerstitial compartment showed severe chronic damage with cellular casts and tubular atrophy. Amyloid staining and immunofluorescence for IgG, IgA, IgM, C3, and fibrin were negative. Electron-microscopy confirmed arterial hypertrophy, lipid-laden macrophages in glomeruli, and an absence of immune deposits.

The patient was established on continuous ambulatory peritoneal dialysis, his blood pressure controlled, and he was worked up for transplantation. Over this period, persistent mild eosinophilia was noted, with an absolute eosinophil count 0.5–1.0 × 10^9/l. No cause for this was determined. Investigations of his lipid status showed fasting cholesterol 3.6 mmol/l, triglycerides 0.7 mmol/l, and apolipoprotein E3/3 phenotype. Fasting glucose was 3.9 mmol/l. He was blood group O+, with tissue type A 1,23 B 7 Bw 6 Cw 2 DR 3,7 Dw 52,53 DQ2. Lecithin–cholesterol aclytransferase activity was within the normal range and other lipoidoses were excluded by history and clinical examination.

Five months after presentation, the patient received a cadaveric renal transplant. The donor was a 29-year-old man who had died from partially treated bacterial meningitis. Immunosuppression was with tacrolimus, prednisolone, and azathioprine. Initial function was excellent, with a nadir creatinine of 105 μmol/l, while proteinuria fell to 1.9 g/24 h. Subsequently the patient developed insulin-dependent diabetes and two episodes of unexplained abdominal pain, both of which were attributed to tacrolimus. From 4 months onwards, there was a gradual rise in serum creatinine from 110 to 135 μmol/l. Increasing proteinuria was also recorded, peaking at 7.7 g/24 h, and suggesting the possibility of a recurrent disease process. There was no haematuria.

Transplant biopsy was performed 7 months after transplantation. A small sample of cortex contained five glomeruli. There was no evidence of glomerulonephritis, amyloid, or rejection. Three glomeruli showed increased mesangial matrix, giving a rather solid appearance with a proliferation of cells at the periphery of the tuft and in Bowman’s space (Figure 3). The remaining two glomeruli showed increased cellularity throughout the tuft, with a lesser increase in matrix. The cells in Bowman’s space had foamy cytoplasm, with fat demonstrable in the glomerular tuft using Oil Red O staining. These changes had not been present in a donor biopsy taken the time of transplantation. The tubules and blood vessels were unremarkable. There was a mild focal lymphoid infiltrate, but no tubulitis. Immunofluorescence was
negative. Overall, the appearances were very similar to those seen in the original biopsy, and were interpreted to reflect recurrence of the original disease process. The patient is well at 12 month follow-up. He remains insulin dependent with normal albumin and liver function, trough tacrolimus levels 5–6 ng/l, and serum cholesterol which has risen to 6.4 mmol/l. Renal function is impaired and gradually declining, with urea currently 6.4 mmol/l, creatinine 156 μmol/l, and 4.8 g/24 h proteinuria.

**Discussion**

This case represents the first case in the English literature of recurrent renal disease in a patient with lipoprotein glomerulopathy. Taken together with the two previous case reports [8,9], it indicates that the aetiology of this condition is systemic, not renal. Given this, a second issue arises, of whether the disease has other, extrarenal manifestations. To date, no specific extrarenal features have been noted, but it is possible that other organs might be damaged by the accumulation of lipid deposits over the longer term, analogous for example to the multisystem manifestations of Gaucher’s disease. If so, appropriate tissue biopsies or post-mortem examination might detect similar lipoprotein deposition in other organs, indicating occult (asymptomatic) disease. The only data at present comes from Meyrier et al. [7], who reported a patient with an incidental finding of a normal liver biopsy, and concluded that the pattern of lipid abnormalities suggested a disease whose expression was restricted to the kidney. This apart, examination of extrarenal tissue and long-term follow-up have not yet been reported and are clearly required.

Alternatively, if lipoprotein deposition is confined to the kidney, it remains to be determined what factors determine the propensity for and sites of localization. For example, it is unknown whether immunological factors such as HLA typing are associated with disease incidence or progression. These details are provided in our patient for future reference.

Optimal treatment for lipoprotein glomerulopathy remains uncertain. Trials of immunosuppression, anti-platelet drugs, fibrinolytics, lipid-lowering drugs, and glucocorticoids have all proved ineffective, albeit in very small numbers of patients [2,6,7,9]. Although one case report suggests that probucol may be effective in minimizing disease progression, the patient described had coincident IgA nephropathy and an unusual apolipoprotein E phenotype [10]. A second patient treated with probucol showed no improvement, and the majority of case reports have shown no response to this or other lipid-lowering agents. Given this, the efficacy of any form of therapy or prophylaxis has yet to be confirmed, and our patient received no specific treatment other than our normal post-transplant immunosuppression.

This case is instructive in two other respects. The post-transplant course of this patient shows that the condition is not prevented by moderate immunosuppression, with implications for therapy and transplantation; and that it may develop rapidly despite relatively normal plasma lipids, measured on several occasions. This latter feature makes screening for disease problematic, even within family groups, and may caution against the use of living related transplant donors. Much remains to be determined about both the natural history and the early presentation of this condition, and further well-documented reports are required.

**References**


Received for publication: 18.6.97
Accepted: 20.6.97

---

**Fig. 3.** Transplant biopsy. Increased cellularity and matrix formation within the glomerular tuft and numerous lipid-laden cells (arrows). Periodic Acid Schiff stain. Bar represents 100 μm.