Clin Kidney J (2014) 7: 396–398
doi: 10.1093/ckj/sfu058
Advance Access publication 17 June 2014

Clinical Report

CKJ

Long-term outcome of kidney transplantation in a patient with coexisting lipoprotein glomerulopathy and fibrillary glomerulonephritis

Chi Yuen Cheung[1]*, Angel O.K. Chan[2], Gordon P.T. Chan[3], Heidi Y.P. Iu[3], Chi Chung Shek[3] and Ka Foon Chau[1]

[1]Department of Medicine, Queen Elizabeth Hospital, Hong Kong, [2]Department of Pathology and Clinical Biochemistry, Queen Mary Hospital, Hong Kong and [3]Department of Pathology, Queen Elizabeth Hospital, Hong Kong

Correspondence and offprint requests to: Chi Yuen Cheung; E-mail: simoncycheung@gmail.com

Abstract

Both lipoprotein glomerulopathy (LPG) and fibrillary glomerulonephritis (FGN) are rare causes of end-stage renal disease (ESRD), and the literature concerning the outcome of kidney transplant in patients with LPG or FGN is scarce. We report a patient who suffered from ESRD with coexisting FGN and LPG and received deceased kidney transplant >10 years ago did not reveal any clinical features of disease recurrence during follow-up. Our case shows that the prognosis of patients with LPG component who received kidney transplant can be good. Kidney transplantation remains a viable therapeutic option for patients with ESRD secondary to FGN with LPG.

Keywords: fibrillary glomerulonephritis; kidney transplant; lipoprotein glomerulopathy

Background

Both lipoprotein glomerulopathy (LPG) and fibrillary glomerulonephritis (FGN) are rare causes of end-stage renal disease (ESRD). LPG is a rare disease of renal lipoidosis, first described by Saito *et al.* in 1989 [1]. To date, ∼150 cases of LPG have been reported in the literature, with most of them in Japan and East Asian countries [2, 3]. It has been shown that half of the patients with LPG eventually develop ESRD at 1–27 years after onset of symptoms [3]. However, the literature concerning the outcome of kidney transplantation in patients with LPG was scarce. Only five kidney transplants have been reported and LPG recurred early in all the transplanted allografts [4–8]. While usually cases without complications are less likely to be reported, it is noteworthy that cases without LPG recurrence have yet been described.

On the other hand, FGN is also a rare deposition disease comprising only ∼1% of native kidney biopsies [9, 10]. It is characterized by the deposition of organized microtubules, measuring 16–24 nm in diameter and arranged in a parallel fashion [9]. FGN usually progresses to ESRD within months to a few years but the risk of recurrence in kidney transplant is low according to the limited number of cases [10].

Herein we report a patient with coexisting LPG and FGN, who underwent deceased kidney transplant >10 years ago and did not reveal any clinical features of recurrence of diseases after long-term follow-up.

Case history

A 34-year-old Chinese man first presented to our hospital with 1-year history of ankle swelling. He had no relevant drug history and no family history of renal disease. His blood pressure was 140/90 mmHg. Laboratory investigations revealed a 24-h urinary protein excretion >10 g per day, serum albumin 21 g/L, serum creatinine 123 μmol/L, total cholesterol 10.1 mmol/L and triglyceride 4.7 mmol/L. Ultrasound-guided renal biopsy was performed. Light microscopy revealed 13 out of 36 glomeruli showing advanced sclerosis and another six showing segmental sclerosis. The capillary lumens were markedly dilated and showed occasional fibrin caps. Immunofluorescence studies revealed capillary deposits of IgM and C3 without IgG or IgA. Electron microscopy showed abundant non-branching fibrillary material ranging from 16–19 nm in diameter in the mesangium. Electron-lucent areas were noted in the subendothelial space with fragmented filamentous material ranging from 11–16 nm in diameter (Figure 1A). The diagnosis was FGN. He was put on accupril and atorvastatin. His renal function gradually deteriorated but he defaulted follow-up thereafter.

Three years later, he presented with uremic symptoms and blood tests showed urea nitrogen 46 mmol/L, creatinine 2011 μmol/L, albumin 28 g/L, hemoglobin 7.5 g/dL with normochromic normocytic indices. Autoimmune markers including antinuclear, antineutrophil cytoplasmic and anti-glomerular basement membrane antibodies were all negative. Renal ultrasound showed bilateral small kidneys. He was put on hemodialysis support. Three months later, he received deceased kidney transplant and immunosuppression included prednisolone, tacrolimus and mycophenolate mofetil. The postoperative course was unremarkable. His serum creatinine remained stable (at ∼120 μmol/L) without any significant proteinuria. His serum cholesterol was 5 mmol/L and triglyceride was 1.8 mmol/L.

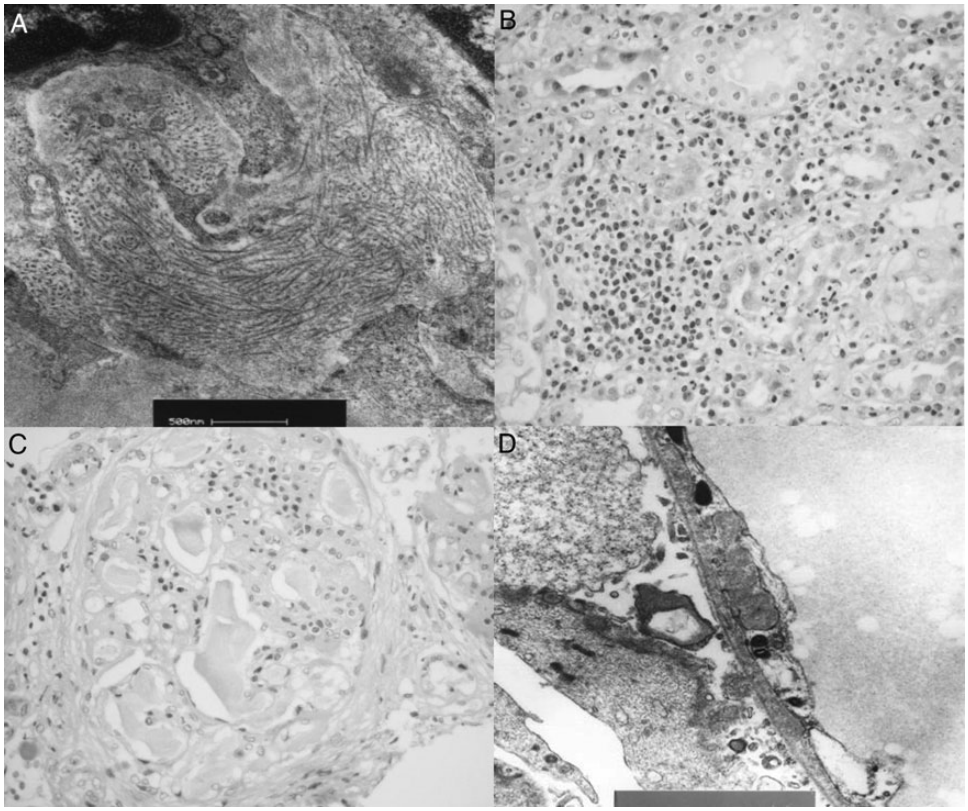

Fig. 1. (**A**) Electron microscopy showing abundant non-branching fibrillary material in the subendothelial space. (**B**) Light microscopy showing marked interstitial inflammation consisting of a large amount of polymorphs in the graft kidney specimen. (**C**) Light microscopy showing some vacuolated and stringy materials inside the dilated capillary lumens in the native kidney specimen. (**D**) Electron microscopy showing the intraluminal materials composed of fine granular material with small lipid vacuoles, consistent with lipoprotein thrombi.

He suffered an episode of acute kidney injury with serum creatinine reaching 201 μmol/L during follow-up at 18-months post-transplant. There was neither fever nor urinary symptoms. Renal graft biopsy was performed and light microscopy revealed marked interstitial inflammation consisting of a large amount of polymorphs which were also noted within the tubular lumens (Figure 1B). All these features were suggestive of infective etiology. A course of ceftriaxone was given and the serum creatinine gradually returned to baseline. He continued to have regular follow-ups in our clinic with unremarkable course.

However, subsequent review of his native kidney biopsy specimen showed that in addition to features of FGN, components of LPG which were characterized by some vacuolated and stringy materials inside the dilated capillary lumens (Figure 1C) were also seen. These materials were weakly eosinophilic, weakly periodic acid–Schiff (PAS) positive and stained pale blue under Chromotrope-Aniline Blue (CAB) stain. On electron microscopy, these intraluminal materials contained fine granular material with small lipid vacuoles, consistent with lipoprotein thrombi (Figure 1D). These features were not present in the graft biopsy specimen obtained 18 months after transplant. Mutational analysis of the apolipoprotein (*APOE*) gene by polymerase chain reaction and direct DNA sequencing revealed an E3/E3 genotype and a heterozygous mutation c.480_488del, which is predicted to result in deletion of Leu-Arg-Lys at codons 162–164 (reference sequences NM_000041.2 and NP_000032.1). This is a known mutation called *APOE* Tokyo causing LPG [11]. A familial genetic study on his son at 18 years of age showed that he also carries the same mutation, though there was no biochemical evidence of proteinuria or renal disease at the time of testing.

His maintenance immunosuppressive regimen remained prednisolone, tacrolimus and mycophenolate mofetil while he was also put on diltiazem and lisinopril for blood pressure control. After >10 years post-transplant, his latest serum biochemistry and other laboratory examination revealed no significant abnormality. These included serum creatinine 125 μmol/L, serum albumin 42 g/L, total cholesterol 4.8 mmol/L, triglyceride 1.2 mmol/L and 24-h urinary protein excretion <0.1 g.

Discussion

FGN and LPG are both uncommon causes of ESRD. The native kidney histology of our patient showed coexisting features of FGN and LPG. Subsequent mutational analysis revealed the presence of *APOE* Tokyo. LPG is found to be due to mutations of the *APOE* gene. Up till now, 12 mutations have been reported in the Human Gene Mutation Database (version 27 September 2013) to result in LPG (http://www.hgmd.org/). The more common ones include *APOE* Sendai (Arg145Pro) [12] and *APOE* Kyoto (Arg25Cys) [13]. Most patients are asymptomatic. The usual presentation includes proteinuria on routine screening examination and renal impairment. Most patients also have hyperlipidemia with

predominance of triglycerides. Nevertheless, hyperlipidemia appears not to be an essential prerequisite as LPG has been reported in patients with normolipidemia [4]. A high serum concentration of apoE is another characteristic feature in patients with LPG. However, serum apoE level was not available in our patient because of a lack of apoE quantitation service in Hong Kong. As a result, renal biopsy is important for diagnosis. Once the histopathological diagnosis of LPG has been made, mutational analysis on the *APOE* gene can be carried out to confirm the diagnosis.

Since half of the patients with LPG might eventually develop end-stage renal disease, kidney transplantation should be considered in these patients. However, the long-term outcome of kidney transplantation in patients with LPG still remains uncertain. Only five kidney transplants have been reported in the literature to date. Unfortunately all of them had LPG relapse which was confirmed by renal graft biopsy within 2 years after transplantation. Among them, one patient had persistent proteinuria and developed graft failure 1 year later [4]. Two patients developed nephrotic-range proteinuria within 6 months after transplant [5, 8]. One patient had nephrotic syndrome with serum creatinine level reaching 176 μmol/L 2 years after transplant [7] while the last case revealed histological recurrence by protocol biopsy ∼15-month post-transplant in an asymptomatic patient with proteinuria of 300 mg/day [6]. It seems that LPG recurrence in a transplanted kidney is inevitable which is also associated with poor prognosis. In our patient, renal graft biopsy was performed at 18-months post-transplant which only showed infective component as the cause of acute deterioration in renal function. No recurrence of LPG or FGN could be demonstrated histologically. Since there was no significant proteinuria all along during follow-up, renal graft biopsy was not repeated. In addition, his serum cholesterol and triglyceride levels remained normal. While early relapse had been ruled out by histology at 18-months post-transplant, no biochemical features of LPG or FGN recurrence could be demonstrated in our patient despite having a follow-up for >10 years. Our case shows that the prognosis of patients with coexisting FGN and LPG who have received a kidney transplant can be good. Prior studies illustrated that the location of *APOE* mutations is an important determinants for the development of LPG. However, the relationship between various *APOE* mutations and LPG recurrence in the kidney graft is not well established because of the limited number of patients. Moreover, family studies showed that LPG occurs in some members but not in others even with the same phenotypic and genotypic *APOE* abnormalities [5, 14]. As a result, it has been postulated that some other possibilities such as local mechanisms in the glomeruli or environmental factors in addition to the *APOE* genotype are required for disease expression. Further studies are thus required for clarification of the exact pathogenic mechanism of LPG.

In conclusion, our experience shows that kidney transplantation remains a viable therapeutic option for patients with ESRD secondary to FGN with LPG. However, close monitoring of renal function and proteinuria for any recurrence is essential.

Conflict of interest statement. None declared.

References

1. Saito T, Sato H, Kudo K *et al*. Lipoprotein glomerulopathy: glomerular lipoprotein thrombi in a patient with hyperlipoproteinemia. *Am J Kidney Dis* 1989; 13: 148–153
2. Saito T, Matsunaga A, Ito K *et al*. Topics in lipoprotein glomerulopathy: an overview. *Clin Exp Nephrol* 2014; 18: 214–217
3. Saito T, Matsunaga A, Oikawa S. Impact of lipoprotein glomerulopathy on the relationship between lipids and renal diseases. *Am J Kidney Dis* 2006; 47: 199–211
4. Saito T, Sato H, Oikawa S *et al*. Lipoprotein glomerulopathy. Report of a normolipidemic case and review of the literature. *Am J Nephrol* 1993; 13: 64–68
5. Mourad G, Djamali A, Turc-Baron C *et al*. Lipoprotein glomerulopathy: a new cause of nephrotic syndrome after renal transplantation. *Nephrol Dial Transplant* 1998; 13: 1292–1294
6. Miyata T, Sugiyama S, Nangaku M *et al*. Apolipoprotein E2/E5 variants in lipoprotein glomerulopathy recurred in transplanted kidney. *J Am Soc Nephrol.* 1999; 10: 1590–1595
7. Foster K, Matsunaga A, Matalon R *et al*. A rare cause of post-transplantation nephrotic syndrome. *Am J Kidney Dis* 2005; 45: 1132–1138
8. Andrews PA, O'Donnell PJ, Dilly SA *et al*. Recurrence of lipoprotein glomerulopathy after renal transplantation. *Nephrol Dial Transplant* 1997; 12: 2442–2444
9. Mitwalli A, Shah I, Hammad D *et al*. Recurrence of fibrillary glomerulonephritis in a renal transplant recipient. *Int Urol Nephrol* 2013; 45: 1527–1532
10. Czarnecki PG, Lager DJ, Leung N *et al*. Long-term outcome of kidney transplantation in patients with fibrillary glomerulonephritis or monoclonal gammopathy with fibrillary deposits. *Kidney Int* 2009; 75: 420–427
11. Konishi K, Saruta T, Kuramochi S *et al*. Association of a novel 3-amino acid deletion mutation of apolipoprotein E (Apo E Tokyo) with lipoprotein glomerulopathy. *Nephron* 1999; 83: 214–218
12. Oikawa S, Matsunaga A, Saito T *et al*. Apolipoprotein E Sendai (arginine 145–>proline): a new variant associated with lipoprotein glomerulopathy. *J Am Soc Nephrol* 1997; 8: 820–823
13. Matsunaga A, Sasaki J, Komatsu T *et al*. A novel apolipoprotein E mutation, E2 (Arg25Cys), in lipoprotein glomerulopathy. *Kidney Int* 1999; 56: 421–427
14. Han J, Pan Y, Chen Y *et al*. Common apolipoprotein E gene mutations contribute to lipoprotein glomerulopathy in China. *Nephron Clin Pract* 2010; 114: c260–c267

Received for publication: 11.5.14; Accepted in revised form: 22.5.14