Recurrence of familial interstitial nephritis following renal transplantation

Christopher F. Wong¹, Kottarathil A. Abraham¹, Anthony M. Dorman² and J. Joseph Walshe¹

¹Department of Nephrology and Transplantation and ²Department of Renal Pathology, Beaumont Hospital, Dublin, Ireland

Keywords: familial interstitial nephritis; recurrence; renal transplantation

Introduction

Hereditary renal disease is not an uncommon cause of end-stage renal failure (ESRF) and accounts for 15.7% of the patients in the Irish dialysis population [1]. Adult polycystic kidney disease was the underlying diagnosis in the majority (68%) of these individuals. Although familial interstitial nephritis is rare, we have previously reported two siblings who developed ESRF as a consequence [2]. They also had retinitis pigmentosa but did not fit into any previously described renal-retinal syndrome. Both patients have since undergone successful cadaveric renal transplantation but have subsequently developed recurrence of their disease with ultimate graft loss. The implications of these findings are discussed.

Case 1

A 16-year-old female was admitted with worsening night blindness and renal failure in 1988. She was obese and her IQ was estimated at 130 using the Wechsler Adult Intelligence Scale (normal WAIS being 85–115). She had retinitis pigmentosa and syndactyly of the second and third digits of her hands and feet, but developed normal secondary sexual characteristics. Renal histology from a biopsy performed in 1988 showed chronic tubulointerstitial disease characterized by a patchy but almost diffuse infiltrate, predominantly comprising lymphocytes and plasma cells. The majority of the tubules showed atrophic changes. There was no evidence of crystal deposition (Figure 1). She was commenced on peritoneal dialysis. Three and a half years later, she received a cadaveric renal allograft and was commenced on quadruple immunosuppression consisting of antithymocyte globulin, cyclosporin, azathioprine and prednisolone. The patient was discharged 2 weeks later with a serum creatinine of 140 μmol/l. After 3 years of relatively stable graft function and cyclosporin levels that were consistently in the therapeutic range, she developed a subacute deterioration of kidney function from a baseline creatinine of 144 to 360 μmol/l over 5 months. Imaging of the renal transplant revealed no abnormalities. The graft was biopsied and histology confirmed recurrence of interstitial nephritis (Figure 2) with infiltrates of predominantly lymphocytes and plasma cells, similar to the histology from her native biopsy. Minimal tubulitis was noted in very occasional non-atrophic tubules. However, tubular atrophy was widespread and interstitial fibrosis involved 90% of the cortex. Seven of 15 glomeruli were sclerosed. Moderate hyaline arteriosclerosis was present with mild sclerosis in the arteries. These findings were identical to those found in the original biopsy from her native kidney. She was recommenced on peritoneal dialysis in 1995, almost 2 years after graft dysfunction began. She subsequently received another renal transplant in 1999, and, 22 months on, her serum creatinine remains stable at 120 μmol/l with a tacrolimus, mycophenolate mofetil and prednisolone based immunosuppressive regimen.

Case 2

A 19-year-old male, who is the brother of Case 1, presented with symptoms of uraemia in 1991. Renal histology confirmed tubulointerstitial nephritis with features very similar to his sister’s biopsy findings. There was a patchy, almost diffuse infiltrate of predominantly lymphocytes and plasma cells, with interstitial fibrosis affecting almost 100% of the renal cortex in the presence of normal arteries and relatively mild glomerulosclerosis. He was also obese and had retinitis pigmentosa, but his extremities, IQ and secondary
sexual characteristics were normal. He was commenced on peritoneal dialysis and 1 year later received a renal transplant. However, complications at the time of surgery resulted in graft loss. The patient received a second cadaveric renal transplant after 14 months. Induction of immunosuppression was with antithymocyte globulin, cyclosporin, azathioprine and prednisolone. The postoperative course was uncomplicated and the patient’s serum creatinine dropped from its preoperative level of 1468 to 150 μmol/l within 1 week. Three years on, similar to that seen with his sister and despite long-term therapeutic cyclosporin levels, a subacute decline in renal function was noted with a rise in serum creatinine, from a baseline of 130 to 226 μmol/l over 4 months. The renal transplant ultrasound and DTPA scans were essentially normal. A renal biopsy was performed and histology confirmed recurrence of tubulointerstitial nephritis with patchy foci of tubular atrophy. The infiltrating inflammatory cells (again mainly lymphocytes and plasma cells) were most significant in the areas of interstitial fibrosis and tubular atrophy. Occasional areas of mild tubulitis were noted in the surviving tubules. Nodular hyaline arteriosclerosis without any evidence of endotheliitis and mild arterial sclerosis without significant concentric fibrointimal proliferation were present. Only

Fig. 1. Renal histology from Case 1 showing interstitial nephritis in the native kidney (PAS stain; original magnification: ×200).

Fig. 2. Histology of the renal allograft in Case 1 (PAS stain; original magnification: ×200).
one of 10 glomeruli was sclerosed. As borderline cellular rejection could not be entirely ruled out, he was treated with high dose steroids without any improvement in renal function. He was subsequently placed back on our chronic dialysis programme, 4 years after the decline in his graft function commenced.

Discussion

Rejection and patient death with a functioning graft are the most common reasons for renal graft loss [3]. While recurrence of the original disease in the transplanted kidney is not uncommon, it leads to ESRF in ~5% of cases [4,5]. To date, there have been no reports describing the recurrence of familial interstitial nephritis as a cause of transplant loss. However, there are only four families reported (in addition to our cases) with ESRF due to interstitial nephritis in the absence of medullary cystic disease [6–9], and members of only one of these families have undergone renal transplantation [7]. Our two patients are the first to demonstrate that familial tubulointerstitial nephritis can recur in renal transplants and, more importantly, that they can be of sufficient severity to result in graft loss.

In both siblings, allograft function started to deteriorate ~3 years after transplantation. (Of note, there were no features of tubulointerstitial nephritis on the histology acquired 1 month after the sister received her latest renal transplant.) Other causes of acute interstitial nephritis, including infections, hypersensitivity, crystal deposition disorders and autoimmune disease, were ruled out in both patients by history, clinical examinations, laboratory investigations and renal histologies. In addition, there was no convincing evidence of acute rejection in our patients’ renal histologies. The long-term maintenance of cyclosporin levels within the therapeutic range and the histological findings made cyclosporin toxicity less likely, but not impossible. Chronic allograft nephropathy could also have resulted in comparable renal pathology, although the 3 years over which renal impairment occurred in our two patients would be an unusually short period for this process to cause the degree of graft dysfunction observed in them [10]. Also, despite the almost 100% interstitial fibrosis seen in our cases, arterial changes were mild and <50% of the glomeruli were sclerosed. Given this disproportionate involvement of the interstitium and tubules, the similarity of their transplant histology to the native biopsies in both cases, the time sequence and the lack of response to increased immunosuppression, we conclude that the cause of renal impairment in both our transplant recipients was recurrence of their familial interstitial nephritis.

Our patients are unique in that they developed this recurrence and also because they cannot be categorized into any previously described renal-retinal syndrome.

The clinical entity that most resembles our cases is Bardet–Biedl syndrome (BBS), an autosomal recessive condition with renal defects that are most often structural in nature [11]. Despite some similarities, our patients have many features that distinguish them from BBS cases, including normal I.Q.s and the lack of hypogenitalism or dysmorphic extremities in the male sibling. In addition, the pattern of renal disease in our cases differs from those described in BBS patients. While renal failure does occur in BBS [12], tubulointerstitial nephritis is rare [13] and has not been reported as the reason for ESRF in any BBS patient. Also, renal transplantation has been performed successfully in patients with BBS [11] without the recurrence of native disease ever being recorded.

The question remains of whether our patients represent a unique renal-retinal syndrome or form part of the spectrum of BBS. Ongoing genetic studies will hopefully clarify this issue. What is clear, however, is that familial interstitial nephritis can recur in renal transplants with sufficient severity to result in graft failure.

References


Received for publication: 5.12.01
Accepted in revised form: 6.3.02