De novo diabetes mellitus in kidney allografts: nodular sclerosis and diffuse glomerulosclerosis leading to graft failure

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Introduction

Post-transplant diabetes mellitus (PTDM) is a well-recognized clinical problem following renal transplantation, and occurs with incidence rates that range between 2.5 and 20% [1–4]. Despite this high incidence, there are very few reported cases of diabetic nephropathy of the diffuse type [5,6] and only a single report of the nodular sclerosis form [7].

We report (i) patient who developed PTDM 8 months after renal transplantation, with progression to the nephrotic syndrome and end-stage renal failure due to typical diabetic nodular sclerosis of Kimmelstiel–Wilson, and (ii) patients who developed PTDM 6 months and 2 years after renal transplantation respectively, who progressed to the nephrotic syndrome with impaired renal function due to diffuse diabetic glomerulosclerosis.

Cases

Case 1

A 48-year-old woman who was neither diabetic nor hypertensive presented with chronic renal failure. She had no family history of diabetes mellitus and her kidney ultrasound demonstrated bilateral small kidneys.

She was maintained on haemodialysis for 30 months before she had a cadaver renal transplant in May 1986. The donor was not diabetic, and a biopsy of the allograft performed during the transplant operation showed a kidney of normal histology apart from mild non-specific mesangial proliferation (Figure 1).

The patient’s graft functioned well (mean serum creatinine of 124 μmol/l) and her fasting glucose was normal (range 3.8–5.2 mmol/l) during the first 7 months after surgery. Immunosuppression consisted of cyclosporin 12 mg/kg/day and subsequently the dose was adjusted aiming at a whole-blood trough level of 600–800 ng/ml (polyclonal antibody measured by radioimmunoassay (Abbot)) for the initial 6 months and a level of 400–600 ng/ml thereafter. Prednisolone was administered at 60 mg/day for 2 days, then reduced to 30 mg/day and gradually tapered over 6 months to a maintenance dose of 10 mg/day. An initial pulse of 500 mg methylprednisolone was also given as part of our protocol.

Eight months later the patient developed PTDM manifested by persistent hyperglycaemia of more than 11 mmol/l. Glibenclamide was prescribed. Good glycemic control was achieved until 1992 when she required metformin. Her renal function remained stable with a creatinine of 120 μmol/l. She had no proteinuria.

In 1994 rejection was diagnosed clinically and the patient responded to three pulses of methylprednisolone 500 mg. Her glycemic control deteriorated for a short period, but was re-established by adjusting the oral hypoglycaemic medications.

The patient was lost to follow-up for 11 months before she presented in December 1995 with proteinuria of 3.46 g/day, serum albumin of 32 g/l, and markedly impaired renal function, i.e. serum creatinine of 340 μmol/l. There was no retinopathy on fundal examination. A graft biopsy showed advanced diabetic glomerulosclerosis with extensive interstitial fibrosis and hyaline arteriosclerosis. The glomeruli showed both diffuse and nodular sclerosis with characteristic Kimmelstiel–Wilson lesions (Figure 2) and capsular drops. There was no evidence of amyloidosis, light-chain nephropathy, or immune-complex deposits.

Three months later the graft function deteriorated further and the patient required regular haemodialysis.

Case 2

A 45-year-old man was diagnosed to have chronic renal failure with bilateral small kidneys in 1979. He
Fig. 1. Baseline renal allograft biopsy of case 1 showing a virtually normal looking glomerulus. The glomerular tuft shows patent thin-walled capillary loops with only a few small foci of increased mesangium.

Fig. 2. Renal allograft biopsy of case 1 after 9 years. This glomerulus, in sharp contrast to Fig. 1, shows a well-developed Kimmelstiel–Wilson lesion, with nodular sclerosis of the glomerular tuft.

was hypertensive but not diabetic. His mother had non-insulin-dependent diabetes.

In September 1981 he had a live-related renal transplant from his brother. Graft function was good with serum creatinine of 60–65 μmol/l. Immunosuppression consisted of azathioprine and prednisolone. There was no other complication on follow-up apart from hypertension, which was well controlled.

In March 1983 the patient was found to be diabetic, but with no proteinuria or retinopathy. He was started on glibenclamide with good control of his blood sugar. In November 1989 he was investigated for elevated
liver enzymes, and his liver biopsy showed chronic active hepatitis. Azathioprine was stopped and cyclosporin introduced instead. Consequently his blood sugar went out of control, requiring insulin. Still there was no proteinuria and he continued to have a normal graft function.

In April 1992 the patient was evaluated for chest pain, and coronary angiography showed extensive 3-vessels disease. Later he was discovered to be positive for hepatitis C virus, and a repeat liver biopsy showed chronic active hepatitis. In December 1995 he developed proteinuria of 1.3 g/day which progressed slowly until May 1998 when he presented with massive proteinuria of 15 g/day. He underwent a renal graft biopsy that showed changes of diabetic nephropathy with diffuse mesangial proliferation and expansion in addition to hyaline fibrin caps. Immunofluorescence revealed IgM, IgG, and C3 deposits on immunofluorescence. The patient's creatinine remained stable; her diabetes is controlled with glibenclamide.

Case 3

A non-diabetic 56-year-old woman with hypertensive nephrosclerosis had a second cadaver transplant in April 1988. She was maintained on azathioprine, prednisolone, and cyclosporin. She had a well-functioning graft with a serum creatinine of 90–100 μmol/l. Six months after transplantation she developed persistent hyperglycaemia and she was started on glibenclamide.

In October 1993, the patient became positive for hepatitis C virus and accordingly azathioprine was stopped while the dose of cyclosporin was increased without any alteration of glycaemic control. There was no proteinuria. In October 1996, she developed mild ankle oedema and significant protein excretion of 2.1 g/day. She had no retinopathy or peripheral sensory neuropathy; graft function remained stable.

In September 1997, the patient developed proteinuria of 3.65 g/day. Her renal function showed some deterioration as reflected by an increase in serum creatinine concentration from 100 to 150 μmol/l. She underwent a renal graft biopsy that showed features of diabetic nephropathy with mesangial proliferation, arteriolar hyaline deposits, and moderate fibrosis with tubular atrophy on light microscopy, mesangial proliferation, diffuse thickening of the glomerular basement membrane, and absence of dense deposits on electron microscopy and deposits of C3 and IgG on immunofluorescence. The patient’s creatinine remained stable at 150 μmol/l, and her diabetes is controlled with glibenclamide.

Discussion

Despite the increasing incidence of PTDM, there are few reported cases of de novo diabetic nephropathy in renal allografts [5–7]. The classic lesion of nodular diabetic glomerulosclerosis is rare after renal transplantation. In recurrent diabetic nephropathy, Hariharan et al. [8] found it in two of 14 cases compared to diffuse glomerulosclerosis, which was observed in nine of 14 cases.

A single case of de novo diabetic nodular sclerosis was reported by Schwarz et al. [7], in a woman on maintenance azathioprine and prednisolone. She developed diabetes 8 months after transplantation. Sixteen years after transplantation she was observed to have retinopathy, neuropathy, peripheral vascular disease, and nephropathy with non-nephrotic range proteinuria (<1 g/day). Within few months she progressed to maintenance dialysis.

Our case 1 also developed diabetes 8 months after transplantation. She developed severe nephrotic syndrome with rapid progression to end-stage renal failure 9 years after transplantation. Nodular diabetic glomerulosclerosis (Kimmelstiel–Wilson lesions) was documented by histology. Remarkably, there was no retinopathy.

There are some reports in the literature concerning diffuse diabetic glomerulosclerosis in graft recipients. Gimenez et al. [5] reported a man who developed PTDM 9 months after transplantation and nephrotic syndrome with progressive renal impairment 11 years later. Sharma et al. [6] reported a man on maintenance azathioprine and prednisolone, and who developed PTDM 2 years after the transplant, and developed proteinuria of 2 g/days in the absence of retinopathy; with progression to end-stage renal failure 10 years later.

Our two patients with de novo diffuse diabetic glomerulosclerosis developed PTDM at 6 months and at 2 years post-transplantation, both were maintained on cyclosporin and prednisolone when they developed their diabetes and they progressed to nephrotic syndrome with functional impairment of renal function at 9 and 16 years respectively.

Earlier reports commented that graft failure from diabetic lesions was rare. In the report of Maurer et al. [9] diabetic glomerular changes were demonstrated within 2 years of transplanting normal kidneys into diabetics, but graft failure was thought to be rare at least before the 10th year after transplant. On the other hand Hariharan et al. [8] studied 14 patients with recurrent diabetic nephropathy, and found severe advanced morphological changes after a mean of 8 years, in some cases even after no more than 41 months post-transplant.

Our patients developed PTDM at a mean time of 13 months, all had nephrotic syndrome with functional impairment of graft function, and case 1 had a rapid progression to end-stage renal failure after 9 years, indicative of the progressive nature of this disease. This finding is supported by a recent study by Miles et al. [10] of 40 post-transplant diabetics, in which they found a statistically significant impaired long-term graft survival at 5 years compared to controls.

In the large Diabetes Control and Complications
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Trial (DCCT) [11], of 1441 patients, intensive insulin therapy reduced the occurrence of microalbuminuria and of albuminuria. One can expect similar benefit in PTDM if tight glycaemic control is adhered to. In addition the use of angiotensin-converting enzyme inhibitor has been shown in a large multicentre trial [12] to protect against deterioration of renal function in insulin-dependent diabetic nephropathy.

Steroids, cyclosporin, and FK506 are diabetogenic [13]. Before newer immunosuppressive agents are considered, more data is needed to evaluate their action on the incidence of PTDM.

In summary, PTDM carries the same adverse prognosis as in non-transplant diabetics, and as such it necessitate tight glycaemic control. The value of new immunosuppressive agents in reducing the high incidence of PTDM remains to be seen.

References


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