Renal failure from diabetic glomerulosclerosis three decades after allograft transplantation

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Key words: diabetic nephropathy; long-term graft survival; renal transplantation

Introduction

Diabetic nephropathy is one of the major causes of end stage renal disease (ESRD). In patients with ESRD due to diabetic nephropathy, the incidence of typical diabetic lesions in the renal allograft is nearly 100% at 2 years after transplantation [1]. The incidence of de novo diabetic nephropathy in previously non-diabetic renal allograft recipients varies between 2 and 5% [2–4]. Here we report an unusual case of steroid-induced diabetic nephropathy in a renal allograft recipient, which resulted in ESRD and resumption of haemodialysis 29 years after allogenic renal transplantation.

Case

A 62-year-old Caucasian woman with ESRD due to recurrent bacterial tubulointerstitial nephritis (no biopsy performed) had received a cadaveric renal allograft in 1968. In addition, there was a history of hypertension and pre-eclampsia during her third pregnancy of five. Throughout 29 years, she had stable graft function with serum creatinine levels ranging between 80 and 100 µmol/l. Mild hypertension was treated with diuretics and/or calcium antagonists. Chronic hepatitis C was first documented in 1968. Ten years ago, hyperglycaemia was noted for the first time (fasting glucose levels >140 mg/dl, 1 h postprandial C-peptide level 20 ng/ml). This was regarded as a side-effect of maintenance immunosuppression, which consisted of prednisolone (15–20 mg/day) and azathioprine (25–75 mg/day). From 1988 until 1991, the patient was treated with a strict diet regimen. In 1991, antidiabetic medication with oral glibenclamide was started. At the same time, proteinuria appeared and remained stable around 0.5 g/day until the end of 1996. Insulin therapy became necessary in 1994. In 1997, proteinuria increased slightly to more than 1 g/day, indicating progressive diabetic nephropathy [5]. Proteinuria further increased during the following months, despite ACE-inhibitor medication (Figure 1). However, renal function remained stable until July 1997, when the patient was admitted to our clinic with a rise in serum creatinine from 120 to 190 µmol/l (Figure 1). Current medication consisted of azathioprine (50 mg/day), methylprednisolone (16 mg/day), digitoxin (0.07 mg/day), furosemide (20 mg/day), minoxidil (0.2 mg/day), fosinopril (10 mg/day), and a combination of long-acting insulin (28 IU/day) and short acting insulin (30 IU/day). Physical examination revealed high blood pressure (180/100 mmHg), bilateral ankle oedema, a systolic murmur over the apex, and signs of early peripheral diabetic polyneuropathy.

Urinalysis was positive for glucose and protein (5.5 g/day). Ultrasound examination showed a normally sized graft with moderately increased echodensity of the parenchyma. Duplex ultrasound revealed normal resistance indices (RI 0.75). Laboratory findings were normal except for elevations in serum creatinine (202 µmol/l), urea (20.6 µmol/l) and γGT (2.1 µmol/l). There was no evidence for acute infection. Without a biopsy, she was empirically treated with steroid pulse therapy (250 mg methylprednisolone/day, i.v., for 3 days). Thereafter, serum creatinine levels remained elevated around 200 µmol/l and she was discharged.

Two weeks later the patient presented with further deterioration of renal function (rise of serum creatinine from 200 to 260 µmol/l) and was hospitalized again. A core biopsy of the renal allograft was performed which revealed no signs of rejection, but clear evidence for diabetic nephropathy (Figure 2). During the following weeks, renal function declined continuously (serum creatinine >300 µmol/l, and urea >50 µmol/l).
and the patient developed symptoms of uraemia. As renal function did not recover, she finally returned to regular maintenance haemodialysis, 29 years after allogenic renal transplantation.

**Discussion**

In diabetic patients, microalbuminuria develops within 10–15 years of the onset of hyperglycaemia and progresses to proteinuria (>0.15 g/day) within the following 3–7 years. The time interval between the onset of proteinuria and a detectable decline in GFR is quite variable. Usually the average duration of this period is 5–7 years. In most patients, hypertension also supervenes and is a marker of disease progression. In primarily diabetic renal allograft recipients, histological signs of diabetic nephropathy appear as early as 2 years after transplantation [6], showing thickening of glomerular basement membrane and mesangial expansion. About 4 years after transplantation, hyalinization of afferent and efferent arterioles occur [7].

There are no sufficient data concerning the time interval between the onset of diabetes mellitus and the onset of overt proteinuria (>1 g/day). According to the literature, progression from overt proteinuria to ESRD takes several years [8]. Therefore graft loss due to diabetic nephropathy usually occurs in the second decade after transplantation [9]. The incidence of de novo diabetes mellitus after renal transplantation averages around 2.5% [10]. It was suggested that the number of steroid pulse courses might be a crucial factor for the onset of post-transplant diabetes mellitus [9]. However, some investigators could not detect a significant correlation between the occurrence of post-transplant diabetes mellitus and the cumulative dose of steroids or the type of immunosuppression employed [10].

In the patient described here, the onset of post-transplant diabetes mellitus was nearly 20 years after renal transplantation. To our knowledge, such a late manifestation of post-transplant diabetes mellitus has not been described previously. The time interval between the detection of hyperglycaemia (1988) and the onset of proteinuria (1991) was unusually short and the progression from overt proteinuria to ESRD was unusually fast (9 months). Therefore, progression from hyperglycaemia to ESRD was quicker compared to other patients [8]. As there were no signs for rejection throughout 29 years, non-immunological cofactors may have accelerated the course of diabetic nephropathy in this patient. The fast progression of diabetic nephropathy indicates that the longevity of renal allografts may be particularly susceptible to the harmful effects of diabetes mellitus.

Histopathology showed focal segmental nodular glomerulosclerosis and mild mesangial thickening, arteriolosclerosis and atherosclerosis, interstitial fibrosis, and mild lymphocyte infiltration. There was no evidence of chronic rejection (absence of tubulitis, endovasculitis, endothelial cell enlargement, and reduplication of the basement membranes; only mild interstitial lymphocyte infiltration; negative immunofluorescence with IgG, IgM and C3), amyloidosis (negative Congo-red staining), light-chain nephropathy (negative immunofluorescence staining with kappa and lambda light-chains) and membranoproliferative glomerulonephritis (no mesangial hypercellularity; no peripheral reduplication of glomerular basement membranes; negative immunofluorescence staining with IgG, IgM, IgA, C3, C4, C1q). All these conditions are
known to cause nodular glomerulosclerosis, but were excluded by the above studies. Apart from that, diabetes-like lesions including nodular glomerulosclerosis may occur in patients without glucose intolerance. Recently, Rivera et al. [11] reported on a non-diabetic renal allograft recipient with nodular glomerulosclerosis in the allograft. This entity, which is called ‘idiopathic lobular glomerulonephritis’ or ‘idiopathic nodular mesangial sclerosis’ was primarily described in non-diabetic patients with native kidneys [12,13]. Although these patients form a rather heterogeneous group, it has been postulated that some of them have latent diabetes with minimal disturbances of carbohydrate metabolism or positive family histories. This implies that some factors other than hyperglycaemia are responsible for renal damage in diabetes. As the patient described here suffered from manifest diabetes mellitus and as all other causes of nodular glomerulosclerosis were adequately excluded, histopathology confirmed the clinical diagnosis.

Because of the introduction of new immunosuppressive agents, renal allograft survival is expected to increase further in the future. However, as the immunosuppressive protocols in most transplantation centres still include corticosteroids, the incidence of post-transplant diabetes mellitus is expected to increase simultaneously. Therefore the question of how to deal with post-transplant diabetes mellitus will become more important. Recently Kim et al. [14] demonstrated in a prospective study that deflazacort, an oxazoline derivative of prednisolone, permits better control of post-transplant diabetes mellitus than prednisolone. In 43% of renal allograft recipients with post-transplant diabetes mellitus who received deflazacort, a dose reduction of more than 50% in blood-glucose-lowering agents was possible without seriously affecting the immunosuppressive activity (no higher rates of graft dysfunction or acute rejection). In addition, powerful new immunosuppressants, including FK506, cyclosporin A, mycophenolate mofetil, or rapamycin, may permit alternative immunosuppressive regimens without long-term corticosteroids.

References


Received for publication: 15.7.98
Accepted in revised form: 9.12.98