Nodular glomerulosclerosis in a renal allograft of a non-diabetic recipient

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Introduction

Sclerotic mesangial nodules are a highly characteristic but not specific finding of diabetic nephropathy. In addition to diabetes mellitus, nodular mesangial sclerosis may occur in monoclonal immunoglobulin (usually light chain) deposition disease, advanced membranoproliferative glomerulonephritis (MPGN) and rarely in congenital cyanotic heart disease. However, the constellation of nodular mesangial sclerosis with glomerular hyalinosis (fibrin cap or exudative lesion), Bowman’s capsular drops, diffuse glomerular basement membrane thickening and prominent hyalin arteriolopathy can be considered fairly specific of diabetic nephropathy. We report a case which is unique because nodular glomerulosclerosis developed in association with other changes characteristic of diabetic nephropathy in the renal allograft of a non-diabetic recipient 21 years following transplantation.

Case

A 56-year-old white male was found to have proteinuria and haematuria on a routine urinalysis in 1964, when he was 23 years old. His renal function gradually deteriorated and he was started on haemodialysis in April, 1974. He underwent a bilateral nephrectomy because of uncontrolled hypertension in July, 1974. Light and electron microscopy were consistent with advanced type I MPGN with abundant immunotype electron-dense deposits in the mesangium and glomerular capillary loops (Figure 1). In 1975 he received a renal allograft from a 15-year-old previously healthy donor who died following an automobile accident. The recipient had no diabetes, hypertension or obesity. There was no family history of diabetes. A post-perfusion biopsy of the graft showed normal renal parenchyma except for mild preservation injury. The HLA phenotype of the donor was A2, A10, B2, B12 (DR typing was not available at that time) and of the recipient A2, A26, B8, B38, DR17 and DQB0201 (DR typing was performed later). The initial immunosuppressive therapy was azathioprine 150 mg/kg/day and prednisone 60 mg (1 mg/kg/day) which were tapered to 125 and 10 mg, respectively, 3 months after transplantation. The patient did well until November 1996 when he presented with fatigue and shortness of breath. His serum creatinine was 460.5 μmol/l which was an increase from 123.7 μmol/l at his last check up 6 months before. The creatinine clearance was 17 ml/min. On physical examination, the 55-year-old patient with a weight of 60 kg and a height of 167 cm had an average blood pressure of 110/50 mmHg without any antihypertensive therapy. Serum and urine electrolytes were normal. His fasting blood sugar levels ranged from 4.16 to 5.00 mmol/l. Urinalysis was normal and glycosuria was absent. A renal transplant biopsy was performed in December, 1996.

Fig. 1. Nephrectomy specimen of the native kidney showing advanced MPGN. Note the prominent lobularization of the glomeruli. PAS, × 100.
1996 which showed acute rejection and changes suggestive of diabetic nephropathy. Following the renal biopsy, an oral glucose tolerance test was performed which showed the following values: 0 min, 4.9 mmol/l; 30 min, 8.99 mmol/l; 60 min, 8.43 mmol/l; 90 min, 6.66 mmol/l; 120 min, 6.06 mmol/l. HgA1c was 6.5 (normal, 5.6–7.7%). Retinal fluorescein angiography was unremarkable. The 24-h urine collection contained 300 mg of protein. Total serum protein and albumin were 65 and 42 g/l respectively. Blood and urine immunofixation studies and serum complement levels were normal. He was negative for anti-nuclear antibodies, cryoglobulin, hepatitis B virus and human immunodeficiency virus (HIV). He was positive for hepatitis C virus but had normal liver function. Following anti-rejection (intravenous Solumedrol) and anti-viral (intravenous and oral gancyclovir) therapy, the patient’s renal function started to improve. A second biopsy in January 1997 showed decreasing interstitial infiltrate and tubular injury with similar glomerular and vascular changes to those seen in the biopsy performed 1 month earlier.

**Renal biopsy findings**

The first biopsy performed in December 1996 contained up to 35 glomeruli per section. Twenty percent of the glomeruli were globally sclerotic. In the remaining glomeruli, a variable degree of mesangial expansion was noted, with sclerotic mesangial nodules (identical in appearance to the Kimmelstiel–Wilson nodules of diabetic glomerulosclerosis) in two of them (Figure 2). Arteriolar hyalin change was present in afferent arterioles. A mild focal interstitial fibrosis was also seen. Congo red stain was negative. A prominent acute tubular injury with interstitial mononuclear cell infiltrate and tubulitis, consistent with a late acute rejection episode, was noted. Because the patient had a flu-like disease prior to the acute renal failure, a virus-induced interstitial, nephritis was also considered and immunohistochemistry and in situ hybridization for cytomegalovirus, adenovirus, herpesvirus and BK virus were performed with negative results. Immunofluorescence was performed on frozen sections containing four glomeruli. Reactions with antibodies to IgM and C3 showed mild segmental mesangial fluorescence. A mild linear glomerular capillary staining was noted for IgG and albumin. Reactions with antibodies to IgA, C1q, fibrinogen and kappa and lambda light chains were negative. The electron micrographs showed increased mesangial matrix and diffusely thickened glomerular basement membranes (546 nm (range 442–720 nm)). No immune-type electron dense deposits were identified (Figure 3).

The second biopsy in January, 1997 contained only eight glomeruli. A moderate diffuse mesangial expansion with a tendency to nodularity was noted. In two glomeruli, capsular drops were present (Figure 4). There was prominent hyalin change in some arterioles. A mild to moderate focal interstitial fibrosis was present. The interstitial inflammatory cell infiltrate and the acute tubular injury were diminished compared with the previous biopsy. Frozen sections for immuno-fluorescence contained two glomeruli; the immunofluorescence findings were identical to those in the first graft biopsy. Thick sections for electron microscopy contained one glomerulus with mesangial expansion, but ultrastructural examination was not performed because no relevant findings could be expected in addition to what was seen in the biopsy a month before.

**Comment**

The light microscopy in our case was strongly suggestive of diabetic nephropathy because, in addition to the nodular glomerular sclerosis, other renal changes characteristic of diabetes, such as Bowman’s capsular drops, diffuse mesangial expansion and diffuse thickening of the glomerular basement membranes, were also noted. Arteriolar hyalinosis was seen in the afferent arterioles. In a typical case of diabetic nephropathy, both afferent and efferent arterioles are involved by hyalin change; however, this finding is not always seen (particularly not in a renal biopsy). Despite these pathological findings, the patient had normal blood glucose levels, and repeated oral glucose tolerance tests were normal. Thus, the condition cannot be called de novo diabetic glomerulosclerosis or de novo diabetic nephropathy in a renal allograft.

The patient’s native kidney disease was MPGN; thus, a recurrent MPGN has to be considered in the differential diagnosis. In advanced MPGN, the sclerosing glomeruli may have a nodular appearance, but this nodularity is quite uniformly present in every glomerulus. In our case, only occasional glomeruli contained sclerotic nodules, the remaining glomeruli showed mild to moderate diffuse mesangial expansion, just as it is seen characteristically in diabetic nephropathy. The immunofluorescence and electron microscopy were not

![Fig. 2. First allograft biopsy 21 years post-transplant. Note the sclerotic mesangial nodule consistent with a Kimmelstiel–Wilson nodule in this glomerulus. H&E, × 200.](image)
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Fig. 3. Ultrastructure of a glomerular capillary from the first allograft biopsy. Note the diffusely thickened glomerular basement membranes and the absence of electron-dense deposits. Uranyl acetate–lead citrate, original magnification ×5000.

consistent with an immune complex glomerulonephritis (such as MPGN) either. A further argument against the possibility of recurrent MPGN is the fact that a recurrent glomerulonephritis usually manifests within the first months or years post-transplant, whereas in the present case the post-transplant interval was 21 years.

Other diseases in which nodular glomerulosclerosis may occur include monoclonal immunoglobulin deposition disease, congenital cyanotic heart disease and idiopathic lobular glomerulonephritis. Clinical, laboratory and morphological findings were not consistent with any of these. Idiopathic lobular glomerulonephritis (nodular mesangial sclerosis) is a rare and ill-defined condition, with very similar morphology to advanced sclerosing MPGN [1]. Immunofluorescence and electron microscopy in idiopathic nodular glomerulonephritis do not show immune deposits, still, the disease may merely represent an advanced ‘burned-out’ form of MPGN. The morphological findings were not consistent with transplant glomerulopathy either. Transplant glomerulopathy appears in certain renal allografts with chronic rejection, and resembles changes in MPGN and/or thrombotic microangiopathy. Chronic rejection-related changes, though present,

Fig. 4. Second allograft biopsy. Note the capsular drop (arrow)—a hyalin lesion on the Bowman’s capsule protruding into the Bowman’s space—which is another highly characteristic lesion of diabetic nephropathy. H&E, ×400.
were not prominent in the patient’s biopsies. The patient has never been treated with cyclosporin and had a normal blood pressure without medication; thus, the arteriolar hyaline change cannot be attributed to these factors. Amyloidosis was excluded based on negative Congo red stain and the absence of amyloid fibrils by electron microscopy.

Numerous patients with renal changes identical to those seen in diabetic nephropathy in the absence of diabetes mellitus have been reported [2–9]. Some of these cases (particularly those from the older literature) may have represented undiagnosed monoclonal immunoglobulin deposition disease; however, in more recent reports, this was excluded. An undetectable mild abnormality of carbohydrate metabolism and genetic susceptibility were considered in the pathogenesis of these diabetic nephropathy-like changes.

Several studies indicate that in addition to the diabetic metabolic environment, other factors, such as genetic susceptibility, are important in the pathogenesis of diabetic complications [10–12]. It has been suggested that in patients with genetic susceptibility to diabetes mellitus, the degree of hyperglycaemia necessary to induce diabetic microangiopathic changes may be less than that required for the diagnosis of diabetes by glucose tolerance test. Hyperinsulinaemia, which occurs with conventional injectable preparations of insulin, has also been proposed as an aetiological factor in the pathogenesis of diabetic complications. Both in vivo and in vitro studies have shown that hyperinsulinaemia may be related to the development of sclerotic mesangial nodules similar to Kimmelstiel–Wilson nodules [13,14]. Since the association of hyperinsulinaemia with steroid treatment is well known, it is worthwhile considering the role of chronic hyperinsulinaemia in the pathogenesis of diabetic nephropathy-like changes in this transplanted kidney.

In summary, our case provides further evidence that factor(s) other than hyperglycaemia may play a role in the pathogenesis of changes characteristic of diabetic nephropathy. Ours is the first case to show that such histological changes, including nodular glomerulosclerosis, may occur not only in native kidneys but also in long surviving renal allografts in the absence of diabetes mellitus.

References