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Nephrology
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Teaching Point
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The normoglycaemic patient with nephrotic syndrome

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Case report

A 54-year-old man was admitted to the nephrology outpatient clinic because of suspected nephrotic syndrome. He was a non-smoker with an unremarkable personal history; his father had had non-insulin dependent diabetes mellitus (NIDDM). The patient had been under the care of a practicing internist for more than a year because of hypertension, overweight and oedema of the lower extremities. Initially he had presented with normal serum creatinine (103 μmol/l), normoglycaemia, and marked (+ + +) proteinuria on dipstick urinalysis. His blood pressure was lowered to normal values with an ACE inhibitor, a thiazide diuretic, and spironolactone. The patient reduced his body mass index (BMI) from 37.8 kg/m^2 to 32 kg/m^2. Three months after initial presentation, transient elevation of blood glucose levels was noted; glycosylated haemoglobin C (HbA1c) was 7.5%.

With weight reduction and transient administration of glibenclamide, both fasting plasma glucose and HbA1c levels normalized within 7 months and subsequently remained normal without medication. Serum creatinine had risen from 103 μmol/l (initial visit) to 185 μmol/l prior to admission. Oedema of the legs persisted, and proteinuria of 12 g/24 h was documented. Immunoelectrophoresis of the urine failed to reveal paraproteinuria.

Upon admission, the patient was overweight (BMI 33 kg/m^2), blood pressure was 215/99 mmHg, and physical examination was notable only for marked oedema of the legs. Serum creatinine was 216 μmol/l, BUN 20.2 mmol/l, creatinine clearance 47.9 ml/min, sodium 143 mmol/l, potassium 5.8 mmol/l, phosphate 1.3 mmol/l, albumin 35 g/l, plasma glucose 5.6 mmol/l, and HbA1c 5.5%. Urinalysis showed proteinuria of 9 g/24h; repeated immunoelectrophoresis of urine and serum showed no paraprotein. Renal biopsy revealed nodular sclerosis of the mesangium, thickening of the basement membrane of Bowman's capsule, low-grade interstitial inflammation, and atherosclerosis (Figure 1, panel A). Electron microscopy confirmed the diagnosis of nodular glomerulosclerosis, with capsular deposits and fusion of podocytes (Figure 1, panels B and C). Immunofluorescence microscopy with antibodies against IgM and complement factor C3 showed unspecific staining (not shown). These findings were consistent with diabetic nephropathy, and the patient was treated with furosemide and an ACE-inhibitor. Later, simvastatin, atenolol, amlodipin, and metolazone were added. Blood pressure was lowered, but ambulatory 24-h recordings repeatedly demonstrated mild to moderate elevation of both systolic and diastolic measurements, with a lack of the normal nocturnal blood pressure dip. Over the next 34 months, glucose and HbA1c levels remained normal, but creatinine levels rose to above 300 μmol/l and creatinine clearance fell to 25 ml/min; proteinuria remained high with a maximum value of 15 g/24 h. Computed analysis of heart rate variability demonstrated autonomous neuropathy. An ophthalmological examination disclosed diabetic retinopathy with microaneurysms, hard exsudates, cotton-wool lesions and a suspected small vascular proliferation.

Discussion

At the end of the 20th century, diabetic nephropathy is by far the most common cause of end-stage renal disease and accounts for 30–50% of all patients entering chronic renal replacement therapy. Generally, both in type I and type II diabetes, the disease is present for many years before nephropathy occurs, but hyperglycaemia often goes unnoticed in NIDDM [1]. Thus, as many as 8–30% of patients newly diagnosed

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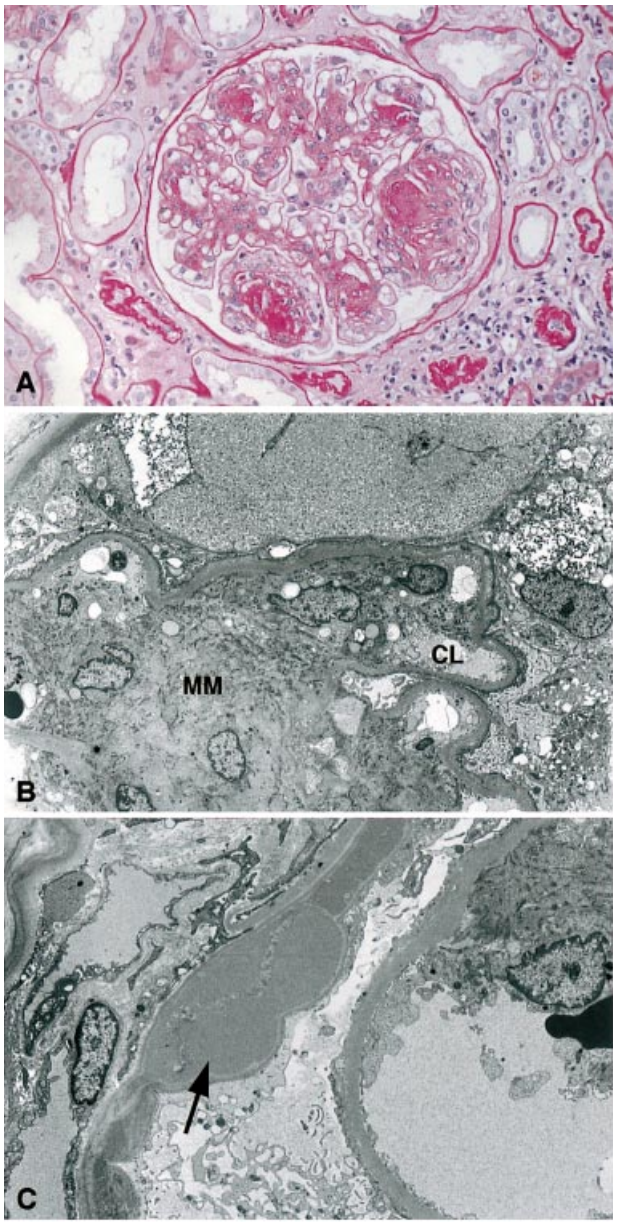

Fig. 1. (A) Light microscopical photomicrograph showing rounded, hypocellular mesangial nodules (Kimmelstiel-Wilson-lesions) characteristic for diabetic glomerulosclerosis. (haematoxylin-eosin, ×300). (B) Low-power electron micrograph (×2100) of a glomerulus showing a diffusely thickened glomerular basement membrane and excess of mesangial matrix (MM). The capillary lumen (CL) is narrowed. (C) Low-power electron micrograph (×2100) showing a large 'capsular drop' in Bowman's capsule (arrow).

with NIDDM present with micro- or macroalbuminuria [2–6]. On the other hand, the percentage of patients progressing from microalbuminuria to overt proteinuria (albumin excretion >300 mg/24 h) is smaller in type II than in type I diabetes [7].

The initial finding in our patient of full blown nephrotic syndrome despite normal creatinine and fasting glucose values is unusual and deserves comment. Diabetic glomerulosclerosis in the absence of biochemical diabetes has rarely been reported [8–13]. The pathogenesis of these renal lesions remained controversial, but in retrospect many of these observations may be explained by light chain deposit disease, which may closely imitate diabetic glomerulosclerosis by light microscopy but not by immunohistology. Good metabolic control has unequivocally been shown to reduce the risk of appearance and progression of retinopathy, neuropathy and nephropathy in IDDM [14] as well as in NIDDM [15]. It is not clear, however, whether a chronic 'prediabetic state' alone can lead to diabetic late complications. In some of the reported cases, azotaemia may indirectly have improved glycaemic control by lowering insulin clearance and leading to reduced food-intake; our patient had a normal serum creatinine value when first seen by the referring physician. In others, additional risk factors for the development and/or progression of diabetic nephropathy, such as hypertension, smoking, or genetic predisposition [6,16–21], might also have contributed to an unfavourable course of nephropathy despite adequate metabolic control. Our patient, despite a quadruple antihypertensive therapy, persistently showed mildly elevated blood pressure and a pathological pressure profile during 24-h monitoring, and the duration of his hypertension before he sought medical advice is unknown. In the absence of overt diabetes, other potential causes of nodular glomerular lesions, such as light-chain deposits, amyloidosis, or membranoproliferative glomerulonephritis [7] had to be evaluated but were not found upon renal biopsy. In our patient, persistent hypertension very likely hampered therapeutic efforts to slow renal deterioration while only transient elevation of HbA1c was documented and fasting glucose values remained normal for 34 months of follow-up. A pathologic oral glucose tolerance test was documented 18 months after admission, however. These findings emphasize that fasting glucose and HbA1c measurements may be quite insensitive and must be interpreted with caution. As shown by others, even standard oral glucose tolerance testing may be normal in some patients with histologically documented nodular glomerulosclerosis [8,10]. If other underlying causes can be excluded, concomitant retinopathy is the most valuable hint on a diabetic aetiology of the renal pathology.

In conclusion, we presume that our patient and most of the earlier reported cases of 'normoglycaemic diabetic nephropathy' had long-standing asymptomatic and hence undiagnosed type II diabetes prior to presentation, most likely with undocumented intermittent or persistent hyperglycaemic periods, and were initially studied during an interval of good metabolic control. Our patient underscores the notion that there is no such thing as 'mild diabetes mellitus'.

Teaching point

Even if normoglycaemia over prolonged follow-up, normal HbA1c levels or normal glucose tolerance seem to exclude the diagnosis of NIDDM, microvascular

organ damage caused by diabetes mellitus is by no means excluded. Previous disturbances of carbohydrate metabolism must always be considered in the initial differential diagnosis of nephrotic syndrome.

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