The Interesting Case

Antiglomerular basement membrane antibody-mediated nephritis in two patients with type II diabetes mellitus

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Introduction

Since Epstein’s first report in 1961 [1] of a patient with diabetic glomerulosclerosis and acute postinfectious glomerulonephritis, several cases have been published of various glomerulonephritides superimposed on diabetic glomerulosclerosis (DGS). The most commonly reported forms of glomerulonephritis complicating DGS are membranous glomerulonephritis [2] and acute postinfectious glomerulonephritis [1–4]. In some reports, the prevalence of non-diabetic renal lesions has been reported to be much higher in selected series of proteinuric type II diabetics (about 30%) as compared with proteinuric type I diabetics (ca. 5%) [2,3,5,6].

Until now, only two cases of antiglomerular basement membrane antibody-mediated nephritis in association with DGS have been reported [4,7]. We here present two further cases of patients with type II diabetes mellitus developing an acute change in renal function, in which the renal biopsy disclosed the presence of anti-glomerular basement membrane antibody-mediated nephritis.

Case reports

Case 1

A 78-year-old female was admitted with severe hypoglycaemia and renal failure; 3 days before admission she had had diarrhoea. She had a previous history of type II diabetes mellitus of 18 years’ duration and recurrent urinary-tract infections, and a staghorn calculus had been detected in her right kidney 3 years previously. One year before admission, a routine analysis had shown serum creatinine 1.6 mg/dl (141.4 μmol/l).

On admission, the patient’s blood pressure was 160/70 mmHg, heart rate 84/min, and temperature 36.8°C; there was moderate diabetic retinopathy. The lung fields were clear, and the heart and abdomen were normal. Peripheral oedema was present (+++).

Laboratory values were: haemoglobin 8.7 g/dl (5.39 mmol/l), WBCs 7850/mm³ (neutrophils 88%, lymphocytes 7%, monocytes 5%), platelets 206 000/mm³; BUN 104 mg/dl (37.1 mmol/l), creatinine 11.7 mg/dl (1034 μmol/l), Na 136 mmol/l, K 5.6 mmol/l, CO₂H⁻ 14.3 mmol/l, Ca 7.5 mg/dl (1.87 mmol/l), P 11 mg/dl (3.55 mmol/l). Arterial blood gases: pH 7.23, PaO₂ 96 mmHg, PaCO₂ 31 mmHg, and CO₂H⁺ 13 mmol/l. The 24-h urine output was 600 ml, with Na 66 mmol/l, creatinine 21 mg/dl (1856 μmol/l), and protein 3.4 g/l. The urinary sediment showed microhaematuria. A selective renal angiography ruled out renal arterial disease. Serum immunoelectrophoresis showed IgG 1636 mg/dl, IgA 308 mg/dl, IgM 56 mg/dl, and C3 and C4 levels within normal ranges. The anti-ANA, anti-sDNA, anti-RNP, anti-SSb, anti-SSa, antineutrophil cytoplasmic antibodies, cryoglobulins, and circulating immune complexes were negative; the antiglomerular basement membrane antibodies were positive (1/428 U/ml). Hepatitis A, B and C and HIV serologies were negative.

In the abdominal ultrasound scan, the left kidney was 10.8 cm long with normal features; the right kidney was 6 cm long, with a staghorn calculus occupying the pelvis and calyceal systems.

A renal biopsy was performed and revealed, by light-microscopy, diffuse pronounced mesangial expansion with nodular changes in the glomeruli. The sample contained 25 glomeruli, four of them were completely obsolescent and the remainder showed diffuse parietal epithelial proliferation with crescent formation (Figure 1). Typical changes of diabetic glomerulosclerosis Kimmelstiel–Wilson’s type was found (Figure 2). Red-cell casts were present on the tubules, and the tubular basement membranes were focally
Fig. 1. Three glomeruli, in two of them epithelial crescents and increase of mesangial matrix with nodular formation are seen. The third glomerulus showed features of nodular and diffuse diabetic glomerulosclerosis and arteriolar hyalinosis. (Masson’s trichrome × 20.).

Fig. 2. Epithelial crescent and Kimmelstiel–Wilson’s nodule. (Masson’s trichrome × 66.).
thickened. There was hyalinization of the arterioles. A percutaneous renal biopsy disclosed moderate diffuse increase of the mesangial matrix, mesangial proliferation and thickened basement membrane; epithelial crescents were present in 90% of the glomeruli. Periglomerular monocyte and lymphocyte infiltration with rupture of Bowman’s capsule was present in several glomeruli, and there was also parcellar necrosis on some glomerular tufts. The arterioles were hyalinized, and there was marked interstitial fibrosis with inflammatory cell infiltrates. The immunofluorescence studies showed diffuse linear parietal deposits of IgG and C3; IgM and C1q were also detected in the mesangium, and fibrinogen in the crescents (Figure 3).

Immunosuppressive therapy was instituted after the renal biopsy (cyclophosphamide 75 mg/day and prednisone 70 mg/day), with pulsed methylprednisolone (1 g for 3 days). Plasmapheresis was carried out (14 sessions) until the antiglomerular basement membrane antibodies became negative.

The renal function did not improve, and the patient was admitted into a periodic haemodialysis programme.

Discussion

The growing number of reports of glomerulopathies superimposed on DGS has led some authors to consider these forms as a separate entity among glomerular diseases [4,8]. Most patients with clinical diabetes presenting with renal abnormalities will have DGS alone, but there are some patients, particularly in the case of type II diabetes mellitus, with other renal disease [2,5,7].

Reported types of glomerulonephritis associated with DGS are summarized in Table I. A sudden increase of protein excretion, an atypical urinary sediment or a rapid deterioration of renal function all suggests the possibility that a superimposed glomerular injury has occurred.

The prevalence of non-diabetic kidney diseases in proteinuric non-insulin-dependent diabetes mellitus patients has been reportedly high, but this finding is based on studies [2,5,6] in which the selection criteria would lead to an overestimation of the real prevalence.

Table 1. Reported glomerulonephritides associated with diabetic glomerulosclerosis

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<td>Minimal-change nephropathy</td>
<td>2,3,5</td>
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<tr>
<td>Focal segmental glomerulosclerosis</td>
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<td>IgA nephropathy</td>
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<td>Schönlein–Hench purpura</td>
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<td>Crescentic glomerulonephritis</td>
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<td>Membranous glomerulonephritis</td>
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<tr>
<td>Membranoproliferative glomerulonephritis</td>
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<td>Amyloidosis</td>
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<td>Cryoglobulinaemic glomerulonephritis</td>
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of non-diabetic glomerulopathies. Parving et al. [5] performed a kidney biopsy in 35 non-insulin dependent diabetes mellitus patients with persistent albuminuria and found that in 23% of cases had a variety of non-diabetic glomerulopathies. However, the autopsy study of Waldherr et al. [9] did not show an excess of glomerular disease in type II diabetes. The difference between those reports may reflect selection bias, since Parving et al. [5] examined diabetics suffering from persistent proteinuria, that is, with renal pathology already present. Diabetes is a frequent disease, and it is possible that by chance alone two renal diseases may coexist.

On the other hand one should consider the possibility that, in diabetes mellitus, the glomerulus exhibits functional and structural changes that may predispose to superimposed glomerulonephritis in this disease. These modifications are:

1. Impairment of the mesangial capacity for processing macromolecules or immune complexes.
2. Hyperfiltration and intraglomerular hypertension that might increase the risk of immune-complex deposition.
3. Non-enzymatic glycosylation might be important in the development of immune-mediated glomerulonephritis [11]. The glomerular basement membrane lacks glycosaminoglycans and is readily available for interaction with circulating, charged macromolecules or macromolecular aggregates which could well be antigens or immune complexes [12]. Positively charged sites could justify the linear binding of IgG4 and albumin to the glomerular capillary wall [12]. Such charged sites may also facilitate the binding of charged antigens or complexes.
4. Abnormal turnover of the glomerular basement membrane [13].
5. Immunological abnormalities [14] predisposing to infections and immune-complex nephritis. In addition, it is conceivable that functional and biochemical changes in DGS might facilitate the localization of immunoreactants.

Considering the above alterations, it would seem that the glomerulus in the diabetic patient is predisposed to the deposition of circulating immune complexes, and possibly to an in situ interaction of antibodies with local or circulating antigens [11].

Observations suggest that in genetically susceptible individuals infection may lead to antibody production and to development of antiglomerular basement membrane antibody-mediated nephritis [15], and it should be acknowledged that, as pointed out above, diabetics show a tendency to develop infections. Several studies have shown that, in diabetic patients, the serum and urine concentrations of type IV collagen are increased as compared to control subjects [16], and in diabetic patients antibodies to the M28 (non-collagenous monomer of alpha-3 type IV collagen) and Alport peptides react intensively with the thickened glomerular base-
ment membrane [17]. Thus it is possible that the damage of the glomerular basement membrane in diabetic patients might lead to the development of an autoimmune response and to the appearance of a secondary form of antiglomerular basement membrane antibody-mediated nephritis. This could explain the high incidence of membranous glomerulonephritis in diabetics, taking into account that some authors [18] consider immune complex glomerulonephritis and antiglomerular basement membrane antibody-mediated glomerulonephritis to be the extremes of a continuum.

In summary, we report the development of anti-glomerular basement membrane antibody-mediated nephritis in two patients with pre-existing nephropathy due to type II diabetes mellitus. Diabetes is so common that by chance alone two diseases may occur. At any rate, however, we wish to remind nephrologists that rapid deterioration in renal function requires evaluation, including kidney biopsy, to exclude the possibility of superimposed, non-glomerular pathology.

References