Case Report

Two different glomerular diseases in the same patient at an interval of 7 years

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Introduction

Overlapping of different glomerulopathies has already been observed in renal biopsies from diabetic as well as non-diabetic patients [1]. Unlike other reports, the present paper describes a patient where two distinct forms of immunological glomerulonephritis with a different histological and clinical picture occurred separately at some years' interval from each other. This finding suggests an individual susceptibility of the patient to immunological renal injury and gives food for speculation on the pathogenesis of glomerulonephritis.

Case

The patient here described was born in Southern Italy in 1966. Family investigation proved negative for glomerular diseases, renal failure, arterial hypertension and diabetes mellitus. In 1991, when he was 25 years old, he had an episode of macroscopic haematuria during an upper airways infection, and this recurred in November 1994, at the age of 28. At that time, urinalysis revealed haematuria and non-nephrotic proteinuria (1 g/day) with normal renal function (serum creatinine 0.9 mg/dl, creatinine clearance 118 ml/min/1.73 m²); serum immunological tests, including complement levels and immunoglobulins, were within the normal range; autoantibodies were not detected. BP was 120/80 mmHg.

Renal tissue obtained by percutaneous biopsy was processed for light, immunofluorescence and electron microscopy by standard techniques. The histological diagnosis was ‘IgA nephropathy’. By immunofluorescence, typical IgA deposits (3+) involving all 13 glomeruli in the specimen were seen in the mesangial areas along with C3 (3+); scanty fibrinogen deposits (1+) were also observed, while IgG, IgM and C1q proved negative (Table 1). Electron microscopy observation of four additional glomeruli showed a mild mesangial expansion with both matrix and mesangial-cell increase, and many electron-dense deposits in mesangial and paramesangial areas; no deposits were seen along the GBM and the podocyte foot-processes were normal. Light microscopy showed a mild to moderate increase in mesangial cellularity and mesangial matrix expansion in all glomeruli examined; two of 12 glomeruli were totally sclerotic, and focal tubular atrophy was observed near the sclerotic glomeruli.

The patient underwent a course of low-dose steroids (prednisolone at an initial dosage of 0.3 mg/kg/day, then tapered to 0.15 mg/kg/day) for 12 months when proteinuria disappeared. A mild haematuria was occasionally seen by microscopic examination of urinary sediment during regular checks carried out in subsequent years.

In October 2000 (at 34 years) a nephrotic syndrome suddenly appeared without any sign of systemic or infectious disease. The patient denied any drug taking or exposure to toxic substances or reaction to environmental factors.

Laboratory investigations showed: non-selective proteinuria of 14 g/day, without monoclonal components, and microscopic haematuria; serum creatinine 0.8 mg/dl; creatinine clearance 127 ml/min/1.73 m²; total serum protein 3.9 g%; platelets 294 000/mm³; WBC 8800/mm³ with normal differential count; erythrocyte sedimentation rate 51; CRP was negative, as were rheumatic and immunological tests, including autoantibodies and...
serum complement activity. No alteration of hepatic enzymes was detected and serology for HBV and HCV proved negative. No clinical or laboratory signs suggestive of haematological or neoplastic disease were found. The patient failed to respond to treatment with steroids (prednisolone at initial dosage 1 mg/kg/day) combined with angiotensin-converting enzyme inhibitor (ramipril), and 5 months later he underwent a second renal biopsy that revealed a stage II–III membranous glomerulonephritis.

Immunofluorescence examination of renal tissue showed diffuse, finely granular IgG deposits (4+) on the capillary wall in all glomeruli [5] along with less intense C3 deposition with the same pattern (3+); segmental granular and pseudo-linear fibrinogen deposits were also observed on the capillary walls (2+); IgA proved completely negative, as did IgM and C1q (Table 1). Electron microscopy showed diffuse thickening of the glomerular capillary walls with extensive sub-epithelial electron-dense deposits and diffuse fusion of podocyte foot-processes; deposits in the mesangial area were no longer detectable.

By light microscopy, homogeneous thickening of glomerular capillary walls was seen, with typical ‘spikes’ at silver stain; one of 14 glomeruli was sclerotic; a mild focal interstitial infiltrate of lymphomonocytes and occasional hyaline changes to the arteriolar wall were also observed.

### Table 1. Immunofluorescence findings on renal tissue (mes, mesangial deposits; cap, deposits along the glomerular capillary walls)

<table>
<thead>
<tr>
<th>Renal biopsy (year)</th>
<th>IgG</th>
<th>IgA</th>
<th>IgM</th>
<th>C3</th>
<th>C1q</th>
<th>Fibrinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>2001</td>
<td>++++</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>+++</td>
</tr>
</tbody>
</table>

Discussion

To the best of our knowledge, this is the first report of two different forms of immunological glomerulonephritis occurring separately in one patient at some years' interval.

Different glomerulopathies coexisting in the same subject (so-called ‘double glomerular diseases’) have already been observed in several cases.

They frequently consist of an immunological nephropathy superimposed on a non-immune disease, such as diabetic nephropathy [1], thin basement membrane disease [2] or Alport syndrome [3], where it has been suggested that the alteration of renal tissue structure may favour the subsequent deposition of circulating macromolecules.

A second group of double glomerulopathies includes cases where both lesions are immunological in nature, arising either from an autoimmune reaction against unmasked renal antigens or from an immune response to various antigens acting either simultaneously or at different times, or alternatively from a single complex antigen capable of eliciting a multiple antibody response, thus leading to the formation of various immune complexes. An example of the former is anti-GBM nephritis superimposed on a membranous GN [4], while the second mechanism has been demonstrated in hepatitis-B-induced glomerulonephritis [5]. In some cases, however, IgA deposits superimposing on minimal-change [6] or membranous nephropathy [7] at a later stage of the disease may simply be the consequence of macromolecule overload in the mesangium.

On the contrary, in the patient here described, the two glomerulonephritides occurred as separate entities from the clinical as well as histological point of view. Indeed, the IgAN found when the patient presented recurrent intra-infective macroscopic haematuria subsequently went into remission, as confirmed by the complete absence of IgA deposits in the second biopsy carried out 7 years later, when the patient showed a nephrotic syndrome, as well as by the resolution of mesangial deposits at electron microscopy.

This observation, while in accordance with other reports that IgAN may completely resolve [8], seems to exclude the possibility that IgAN per se may have facilitated the onset of the membranous GN.

Transition from one histological pattern of glomerular lesions to another is a frequent event in autoimmune diseases, but it usually occurs without any significant variation in immunoglobulin deposit composition. Moreover, for many years the patient we studied did not show any clinical or laboratory signs suggesting a systemic disease. Thus, it is clear that a second antigenic stimulus must have occurred.

We were not able to identify any toxic, infectious or environmental factor that could have induced the second glomerulonephritis, and no sign of neoplasia was detected in the investigations carried out.

There are several reports on the association of IgAN and membranous GN [9,10]. Although these are the most frequently occurring primary glomerulonephritides, it seems unlikely that they should develop in a single person by chance alone, and the obvious suspicion is that these forms of glomerulonephritis may share some common pathogenetic mechanism.

The time elapsing between the two glomerulonephritides in the patient here described, and their clear-cut distinctness from the clinical and histological point of view, suggest an individual susceptibility to glomerular diseases rather than an interrelationship between the two forms of nephritis. This proneness to developing a glomerulonephritis could be essentially due to three mechanisms: the first is some specific feature of the immune response leading to nephritogenic macromolecules. Recent studies on the pathogenesis of IgAN have focused attention on the altered glycosylation of IgA molecule as a decisive factor for IgA mesangial deposition. By analogy, a
structural abnormality involving other immunoglobulins as well as IgA could be hypothesized. A second possible mechanism is the increased affinity of renal tissue for macromolecules. A third hypothesis—that the clearance of immune complexes may be defective—seems unlikely, since the current view on the pathogenesis of membranous GN favours the in situ immune-complex formation rather than deposition of already aggregated complexes from circulation.

Finally, as far as clinical practice is concerned, this case once more emphasizes the importance of repeating a renal biopsy whenever the clinical course of patients shows any unusual or unexplained feature.

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References


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