LONG TERM STUDY OF MESANGIAL PROLIFERATIVE GLOMERULONEPHRITIS WITH IgM DEPOSITS

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Summary

Twenty-six cases of Mesangial Proliferative Glomerulonephritis and diffuse IgM deposits were studied. Nine had nephrotic syndrome; 8 minimal urinary abnormalities; 7 asymptomatic proteinuria; 2 recurrent haematuria.

Immunofluorescence revealed granular mesangial deposits in 14 cases and interrupted linear deposits in the others, chiefly along the capillary walls. In the latter group the clinical picture was mainly nephrotic syndrome or asymptomatic proteinuria. The clinical course is favourable: 7 cases recovered; 12 improved; 7 did not show any change. No progression of renal lesions was observed. Despite uniform histological features, this nephropathy is unlikely to be a unique disease, but in our opinion it should be considered separately from other glomerulopathies.

Introduction

'Mesangial Proliferative Glomerulonephritis' is an accepted term in the current classification of glomerular nephropathies. However this lesion has been described in a variety of clinical situations [1], often associated with a wide range of histo-immunological patterns. Owing to the differing criteria employed in selecting case material, it is still controversial whether mesangial proliferative lesions with IgM deposits exist as a specific form of glomerulonephritis.

This report deals with the clinical picture and course of 26 patients with pure mesangial proliferative glomerulonephritis (GN) associated with isolated IgM deposits. Only cases with a clinico-histological follow-up longer than three years were included in the present study.

Patients and methods

Twenty-six patients (17 males and 9 females), aged from 7 to 42 years (mean 18) were studied. The follow-up period lasted from 3 to 15 years (mean 6). Cases of
post-infectious GN, systemic disease, or a family history of nephropathies were excluded. A percutaneous biopsy was performed in all cases at the onset of clinical signs and repeated 8 months to 3 years later. Twelve patients underwent a third biopsy after 4 to 12 years. All specimens were processed for light microscopy (EE, PAS, PASM and Masson's trichrome) and immunofluorescence (IgG, IgA, IgM, C3, C4, fibrinogen). In 14 cases electron microscopy was also performed.

The histological and histoimmunological criteria for admission of patients included the absence of: 1) focal and/or segmental sclerosis; 2) polymorphs in the capillary loops; 3) thickening of capillary walls and deposits inside the basement membrane.

Results

**Light microscopy**  All cases showed pure diffuse mesangial proliferation, ranging from 1+ to 3+, with a variable increase in the mesangial matrix. Small deposits were observed in the mesangium by trichrome stain in 18 out of 26 cases. The capillary walls had a normal appearance while double contours or deposits inside the basement membranes were never seen.

**Immunofluorescence**  showed diffuse IgM deposits involving all glomeruli. Two main patterns were observed: (i) 14 cases had granular deposits, generally located in the mesangial areas, and sometimes also along the capillary walls; (ii) in the other 12 cases interrupted linear deposits were seen, mainly along the capillary walls. C3 deposits were present in 80% of cases and C1q in 27%, whether the pattern was granular or interrupted linear. Fibrinogen was observed in 5 cases with granular deposits and 9 cases with interrupted linear deposits.

**Electron microscopy**  revealed an increase in mesangial cells and matrix and only occasionally electron-dense deposits, located in the mesangial area. Deposits were always absent inside the basement membranes which sometimes showed a slight enlargement of the lamina rara interna. Fusion of podocyte foot processes was observed. In one case small electron-dense particles, about 1,000 Å in diameter were located inside the basement membrane, probably as a consequence of abnormal permeability.

**Clinical picture**  Despite the apparent uniformity in the morphological picture, associated clinical signs varied: 9 cases (34%) had a nephrotic syndrome; 8 (31%) minimal urinary abnormalities; 7 cases (27%) persistent asymptomatic proteinuria; 2 cases (8%) recurrent gross haematuria. Only those cases with minimal urinary abnormalities showed a statistically significant relationship (p < 0.01) between immunofluorescence and clinical picture (Table I). However, an outstanding fact was that most cases with interrupted linear pattern presented with the nephrotic syndrome or persistent proteinuria. Only four cases had high serum IgM levels, but no correlation with the clinical or histoimmunological picture was found.

**Course**  All patients received steroids. Six out of the 9 cases with nephrotic syndrome were steroid dependent, 3 steroid resistant. They underwent therapy with
TABLE I. Correlation between clinical picture and immunofluorescence patterns

<table>
<thead>
<tr>
<th>Deposits</th>
<th>GH</th>
<th>MUA</th>
<th>PP</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granular (14 c)</td>
<td>1 (7%)</td>
<td>7 (50%)*</td>
<td>2 (14%)</td>
<td>4 (28%)</td>
</tr>
<tr>
<td>Interrupted linear (12 c)</td>
<td>1 (8%)</td>
<td>1 (8%)*</td>
<td>5 (42%)</td>
<td>5 (42%)</td>
</tr>
</tbody>
</table>

* p < 0.01

GH = Gross Haematuria; MUA = Minimal Urinary Abnormalities; PP = Persistent Proteinuria; NS = Nephrotic Syndrome

cyclophosphamide. After 3 to 15 years GFR was within the normal range in all cases, and none developed hypertension. Clinico-morphological recovery was documented in 7 cases (27%) between 2 and 5 years after the withdrawal of therapy; 12 cases (46%) improved; 7 cases were unchanged (Table II).

TABLE II. Outcome of the reported cases

<table>
<thead>
<tr>
<th></th>
<th>GH</th>
<th>MUA</th>
<th>PP</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases (number)</td>
<td>26</td>
<td>2</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Recovery</td>
<td>7 (27%)</td>
<td>-</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Improvement</td>
<td>12 (46%)</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>No change</td>
<td>7 (27%)</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

GH = Gross Haematuria; MUA = Minimal Urinary Abnormalities; PP = Persistent Proteinuria; NS = Nephrotic Syndrome; S = steroids; Cy = cyclophosphamide

Discussion

The clinical morphological nosology of the cases here reported is still unclear. This mostly refers to the relationship among mesangial proliferative glomerulonephritis with IgM deposits, minimal change nephropathy and focal segmental glomerular sclerosis. A slight increase in mesangial cells and matrix and even IgM deposits, most frequently focal and segmental in distribution, have also been found in cases referred to as ‘minimal change’ [2].

However, the cases reported in the present study are unlikely to be confused with minimal change nephropathy, because of the quite obvious mesangial proliferation. Focal segmental glomerulosclerosis is generally described [3] as being without any increase in glomerular cellularity; and the IgM deposits are observed in a focal and segmental pattern, corresponding to the sclerotic lesions [4]. However, cases of focal segmental glomerulosclerosis associated with diffuse mesangial hypercellularity have been reported [5, 6] as well as cases without hypercellularity, but immunofluorescent studies, when performed, showed

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typical focal and segmental deposits.

In our cases, we never observed sclerotic lesions even in biopsies carried out many years after the first observation and immunofluorescence always showed diffuse IgM deposits involving all glomeruli. It thus seems likely that these cases should be considered apart from focal segmental glomerulosclerosis.

Waldherr et al [6] reported cases of nephrotic syndrome in whom renal biopsy revealed pure diffuse mesangial proliferation. By serial biopsies they observed a progression from 'minimal change' to 'diffuse proliferative GN' and vice versa, and from both to focal segmental sclerosis. They suggested there was a close relationship between 'diffuse mesangial proliferative GN' and 'minimal change'. Such cases, however, were not homogeneous from the histoimmunological point of view (pattern and type of deposits).

The histological and histoimmunological lesions we observed in repeated biopsies were uniform, nor did we note any progression towards other histological pictures. Until it has been shown whether immunofluorescent deposits are specific or not, cases presenting various histoimmunological patterns should probably be grouped according to immunofluorescent findings, since they may indicate different pathogenic mechanisms. Mesangial proliferative GN with IgM deposits, despite the uniform histological features, is probably not a unique form of glomerular disease, being associated with various clinical pictures and histoimmunological patterns (granular IgM deposits or interrupted linear deposits). Different patterns may suggest different pathogenetic mechanisms and it is noteworthy that there are differences in the clinical picture according to the different immunofluorescent findings.

The clinical course was favourable and only 7 patients out of all cases studied failed to show any change at the end of follow-up; moreover, no case presented reduction in GFR or developed hypertension and worsening of histological lesions was never seen. Since all our cases received some treatment, we cannot exclude the possibility of spontaneous remission.

In conclusion: Mesangial proliferative GN with IgM deposits shows uniform histological features, and various histoimmunological and clinical patterns.

Even though it is probably not a unique disease, it seems appropriate to consider it separately from other glomerulopathies.

References

4 Hyman LR, Burkholder PM. Lab Inv 1973; 28: 533
Open Discussion

MANGANELLA (Paris) I would like to know whether you have observed on light microscopy or immunofluorescence if there is any sign of vascular damage in these biopsies, as the other glomerulonephritis with vascular damage associated with IgM deposition is focal glomerulosclerosis? I would like to know whether you have observed any damage in the afferent arteries.

FRASCA Never.

PARSONS (London) Could I ask you if the only immunoglobulin you saw was IgM. Was there never any IgG?

FRASCA Never — only IgM.