Clinical features, predictors of disease progression and results of renal transplantation in fibrillary/immunotactoid glomerulopathy

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Abstract

Background. The clinical manifestations of fibrillary-immunotactoid glomerulopathy are still being appreciated. It is unclear whether fibrillary-immunotactoid glomerulopathy represents two distinct clinicopathological entities, fibrillary glomerulopathy (FG) and immunotactoid glomerulopathy (ITG), or a single disease with different ultrastructural variants.

Methods. To address these issues, we analysed the clinical features of 186 patients with fibrillary-immunotactoid glomerulopathy referred to our institutions (25 patients) or reported in the literature (161 patients). In separate analyses, patients were subclassified as having fibrillary glomerulopathy (FG) or immunotactoid glomerulopathy (ITG) according to fibril diameter (FG ≤ 30 nm, ITG > 30 nm) or arrangement (FG, random; ITG, focally organized).

Results. Proteinuria (FG ~100%, ITG ~100%), nephrotic syndrome (FG ~71%, ITG ~82%), haematuria (FG ~71%, ITG ~64%), hypertension (FG ~67%, ITG ~45%), and renal insufficiency (FG ~54%, ITG ~42%) were frequent clinical correlates of both FG and ITG, irrespective of the ultrastructural criteria for diagnosis. Twenty-five patients presenting to our institutions (24 FG, 1 ITG) were divided into three groups based on rate of decline of GFR (mean slope of 1/serum creatinine versus time: group 1 −0.103 ± 0.238; group 2 0.121 ± 0.040; group 3 0.466 ± 0.318) in an attempt to identify clinical predictors of progression at presentation. Rapid progressors (Group 3) had an increased incidence of nephrotic syndrome and tended to have higher blood pressure than patients with milder disease, but did not differ from other groups in age, prevalence of haematuria or degree of renal insufficiency. The number of patients requiring dialysis was 0/10 in group 1, 2/6 in group 2, and 2/4 in group 3 over a follow-up period of 47 ± 46, 55 ± 32, and 19 ± 19 months respectively; two predialysis deaths being recorded in group 3. Four patients received five renal allografts (one patient being transplanted twice) and were followed for 4–11 years. Whereas recurrence of FG was documented in three allografts undergoing post-transplant biopsy, the rate of deterioration of GFR was invariably slower in allografts than native kidneys (mean slope of 1/Cr versus time: 0.036 ± 0.01 versus 0.301 ± 0.18 respectively). The strength of association between FG-ITG and lymphoproliferative malignancy varied depending on whether patients with monoclonal-gammopathy-associated fibrillary deposits were included or excluded from the analysis.

Conclusions. We contend that patients presenting with Congo-red-negative fibrillary deposits on renal biopsy should be evaluated carefully for monoclonal gammopathy and cryoglobulins, but that there is insufficient published data, as yet, to justify subclassification of FG and ITG as distinct clinicopathological entities. Indeed, we argue that it remains to be determined if FG-ITG represents a unique condition or a forme fruste of cryoglobulin- or monoclonal-gammopathy-associated renal disease. Although the optimal treatment for FG-ITG has not been determined, renal transplantation appears an attractive option in patients with end-stage renal failure.

Key words: amyloid; cryoglobulinaemia fibrils; fibrillary glomerulonephritis; fibrillary glomerulopathy; glomerulonephritis; immunotactoid glomerulopathy; kidney diseases; lymphoma; leukaemia; multiple myeloma; transplantation

Introduction

Fibrillary-immunotactoid glomerulopathy is a relatively recent addition to the family of glomerular deposition diseases [1–6]. This pathological entity is characterized by extracellular deposition of non-branching microfibrils or microtubules within the mesangium and capillary walls of renal glomeruli [2–6].
The microfibrils and microtubules do not stain with Congo red or thioflavin T, distinguishing them from the fibrils of amyloid. By definition, glomerular deposits are found in the absence of circulating cryoglobulins, another major cause of Congo-red-negative fibril deposition [2–6]. It has been proposed [4,6,7], albeit without general agreement [3,5], that fibrillary-immunotactoid glomerulopathy represents at least two distinct clinicopathological entities: (a) fibrillary glomerulopathy, characterized by intraglomerular deposition of smaller (≤30 nm in diameter) randomly arranged microfibrils or microtubules (usually the former) and a lower incidence of associated lymphoproliferative malignancy and (b) immunotactoid glomerulopathy, typified by intraglomerular deposition of larger (>30 nm in diameter) microfibrils or microtubules (usually the latter) focally organized into parallel bundles and more commonly associated with lymphoproliferative malignancy. In the present study, 186 patients with fibrillary-immunotactoid glomerulopathy were categorized as having fibrillary glomerulopathy or immunotactoid glomerulopathy on the basis of the diameter or arrangement of their microfibrils and microtubules to determine if these pathological ultrastructural definitions are associated with different clinical presentations. In a subgroup of 25 patients referred to our institutions, presenting clinical features were correlated with the rate of decline in glomerular filtration rate in an attempt to identify predictors of disease progression. We report on the outcome of five cadaveric renal transplants in patients with fibrillary-immunotactoid glomerulopathy, since there is limited published data on allograft survival in this setting.

Subjects and methods

Patient characteristics

A retrospective review was performed of the case records of 25 patients referred to our institutions between 1986 and 1993 whose renal biopsy specimens revealed prominent Congo-red-negative extracellular fibrillary glomerular deposits in the absence of detectable circulating cryoglobulins. In addition, we analysed the clinical presentations of 161 reported cases of fibrillary-immunotactoid glomerulopathy, identified by computerized search of the MEDLINE database from 1977 to June 1994 [1,4,7–37]. Since pathologists can differ in their criteria for diagnosis of FG and ITG, two separate analyses were performed in which patients were classified as having fibrillary glomerulopathy (FG) or immunotactoid glomerulopathy (ITG) on the basis of either the diameter (FG <30 nm, ITG >30 nm) or arrangement (FG, random; ITG, focally organized) of the microfibrils and microtubules. Patients with cryoglobulinemia, diabetes mellitus or systemic lupus erythematosus, or other potential causes of Congo-red-negative fibrillary glomerular deposits were excluded. Renal insufficiency was defined as a serum creatinine of ≥1.5 mg/dl, hypertension as systemic arterial blood pressure of ≥140/90 mmHg, proteinuria as urinary protein excretion of ≥150 mg/24 h and nephrotic syndrome as urine protein excretion of ≥3.5 g/24 h. Unless stated otherwise, the finding or a serum or urinary paraprotein was defined as evidence of underlying lymphoproliferative malignancy.

Structural studies

Renal biopsy tissue from the 25 patients referred to our institutions was prepared for routine light-microscopy, immunofluorescence, and electron-microscopy according to conventional techniques [16]. For electron-microscopy, portions of biopsy specimens were fixed in glutaraldehyde–paraformaldehyde mixture, postfixed in osmium tetroxide, and embedded in epoxy resin. Thin sections were stained with uranyl acetate–lead citrate and examined by transmission electron-microscopy. Fibril thickness was measured on a calibrated electron-micrograph.

Statistics

Clinical parameters in the 25 patients comprising three groups of patients with FG-ITG were assessed by analysis of variance (one-way ANOVA), and Bonferroni’s, Scheffe’s and Tukey’s t tests for comparisons between groups.

Results

Table 1 shows the age, sex, and clinical presentation of 186 patients with fibrillary-immunotactoid glomerulopathy who were subclassified as having either fibrillary glomerulopathy or immunotactoid glomerulopathy on the basis of either fibril diameter or arrangement. The presenting age varied widely in fibrillary and immunotactoid glomerulopathy. Patients with fibrillary glomerulopathy were more likely to be female, whereas a slight preponderance of males was observed in the immunotactoid group. Caucasians outnumbered blacks by 9:1 among patients with fibrillary glomerulopathy and there was insufficient data to comment meaningfully on the racial mix among patients with immunotactoid glomerulopathy. A similar spectrum of renal abnormalities was noted with both ultrastructural patterns: proteinuria being an almost universal finding and frequently nephrotic, and most patients having microscopic haematuria, hypertension and impairment of glomerular filtration. The demographics and clinical presentations were almost identical when fibrillary and immunotactoid glomerulopathy were segregated on the basis of fibril diameter or arrangement.

Twenty-five patients presenting to our institutions were stratified into three groups according the slope of 1/serum creatinine (1/Cr) versus time to search for presenting clinical features that might predict the subsequent rate of decline of glomerular filtration rate (Table 2). Twenty-four patients had fibrillary glomerulopathy and one had immunotactoid glomerulopathy, as defined by fibril diameter and arrangement. Group 1 comprised 10 patients with stable GFR or slow progression (mean slope 1/Cr —0.103 ±0.238); group 2 consisted of nine patients whose progression of renal disease was intermediate (mean slope 0.121 ±0.040); and group 3 represented those with the most rapid decline in renal function (mean slope 0.465 ±0.318).
The groups did not differ in age, the prevalence of haematuria or proteinuria, or the level of serum creatinine at presentation (Table 2). However, patients with more rapidly progressive renal dysfunction were notable for a higher incidence of nephrotic syndrome and a tendency towards worse hypertension and increased mortality, when compared to patients with less severe disease (Table 2).

Five renal transplants were performed in four of our patients presenting with fibrillary glomerulopathy (one patient being transplanted twice) and followed for 4–11 years. Whereas recurrence of fibrillary deposits was noted in all three patients having a post-transplant renal biopsy, the rate of deterioration of renal function was invariably slower in allografts than native kidneys (mean slope 1/Cr versus time: allografts 0.036 ± 0.01; native kidneys 0.301 ± 0.18; Table 3). Two of the allografts have maintained normal renal function at 4 and 8 years post-transplant. Furthermore, allografts have maintained sufficient function to negate the need for dialysis for 6–11 years even in patients with biopsy evidence of recurrence of fibrillary deposits.

The strength of association between fibrillary-immunotactoid glomerulopathy and lymphoproliferative malignancy has been the subject of debate [2–6]. Much of the controversy has focused on whether monoclonal-gammopathy-associated Congo-red-negative fibrillary deposits represent a clinicopathological entity distinct from fibrillary-immunotactoid glomerulopathy, and therefore should be excluded from studies of the latter condition. To address this issue, we assessed the incidence of lymphoproliferative malignancy in patients with fibrillary-immunotactoid glomerulopathy with inclusion or exclusion of patients with monoclonal gammopathy (Table 4). When patients with a circulating or urinary paraprotein were included, the incidence of malignancy was markedly higher in patients with immunotactoid (~33%) than with fibrillary glomerulopathy (~7%). In contrast, when patients with monoclonal gammopathy were

### Table 1. Demographics and presenting clinical features of 186 patients with fibrillary or immunotactoid glomerulopathy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 ± 12</td>
<td>48 ± 12</td>
<td>50 ± 16</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>131 ± 23</td>
<td>132 ± 24</td>
<td>130 ± 22</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>78 ± 14</td>
<td>79 ± 15</td>
<td>77 ± 13</td>
</tr>
<tr>
<td>Proteinuria (no. pts)</td>
<td>4/10</td>
<td>2/4</td>
<td>2/6</td>
</tr>
<tr>
<td>Haematuria (no. pts)</td>
<td>6/10</td>
<td>4/6</td>
<td>2/4</td>
</tr>
<tr>
<td>Nephrotic syndrome (no. pts)</td>
<td>6/10</td>
<td>4/6</td>
<td>2/4</td>
</tr>
<tr>
<td>Renal Insufficiency</td>
<td>35/186</td>
<td>17/93</td>
<td>18/93</td>
</tr>
</tbody>
</table>

* In this analysis, fibrillary (FG) and immunotactoid (ITG) glomerulopathy were separated on the basis of either the diameter (FG <30 nm, ITG >30 nm) or arrangement (FG, random; ITG, focally organized) of microfibrils and microtubules. ** Fibril size was not reported in this analysis.

### Table 2. Clinical predictors of progression and outcome in 25 patients with fibrillary or immunotactoid glomerulopathy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>P &lt; *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean slope 1/Cr versus time</td>
<td>-0.103 ± 0.238</td>
<td>0.121 ± 0.304</td>
<td>0.466 ± 0.318</td>
<td>0.0002</td>
</tr>
<tr>
<td>Number of patients</td>
<td>10</td>
<td>9</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50 ± 12</td>
<td>48 ± 15</td>
<td>51 ± 19</td>
<td>0.88</td>
</tr>
<tr>
<td>Proteinuria (no. pts)</td>
<td>10/10</td>
<td>9/9</td>
<td>6/6</td>
<td>-</td>
</tr>
<tr>
<td>Proteinuria (g/24 hours)</td>
<td>6.6 ± 4.7</td>
<td>7.9 ± 6.7</td>
<td>6.2 ± 0.9</td>
<td>0.82</td>
</tr>
<tr>
<td>Nephrotic syndrome (no. pts)</td>
<td>5/10</td>
<td>6/5</td>
<td>3/5</td>
<td>-</td>
</tr>
<tr>
<td>Haematuria (no. pts)</td>
<td>9/10</td>
<td>9/9</td>
<td>6/6</td>
<td>-</td>
</tr>
<tr>
<td>Initial sCr (mg/dl)</td>
<td>2.85 ± 3.70</td>
<td>1.36 ± 0.53</td>
<td>1.97 ± 1.06</td>
<td>0.42</td>
</tr>
<tr>
<td>Last sCr (mg/dl)</td>
<td>2.33 ± 1.28</td>
<td>6.71 ± 3.92</td>
<td>6.62 ± 3.83</td>
<td>0.0089</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>145 ± 11</td>
<td>151 ± 32</td>
<td>167 ± 24</td>
<td>0.25</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>88 ± 12</td>
<td>87 ± 14</td>
<td>104 ± 20</td>
<td>0.17</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>47 ± 46</td>
<td>55 ± 32</td>
<td>19 ± 19</td>
<td>0.17</td>
</tr>
<tr>
<td>Dialysis (no. pts)</td>
<td>0/10</td>
<td>2/6</td>
<td>2/4</td>
<td>-</td>
</tr>
<tr>
<td>Mortality (no. pts)</td>
<td>0/10</td>
<td>2/9</td>
<td>2/6</td>
<td>-</td>
</tr>
</tbody>
</table>

* One-way ANOVA. Study population consisted of 25 cases referred to our institutions. Twenty-four patients had fibrillary glomerulopathy (FG) and one had immunotactoid glomerulopathy (ITG), as defined by either the diameter (FG <30 nm, ITG >30 nm) or arrangement (FG, random; ITG, focally organized) of microfibrils and microtubules.

** In this analysis, fibrillary (FG) and immunotactoid (ITG) glomerulopathy were separated on the basis of either the diameter (FG <30 nm, ITG >30 nm) or arrangement (FG, random; ITG, focally organized) of microfibrils and microtubules. *** Fibril size was not reported in this analysis.
ultrastructural patterns are observed on electron-fibrils and microtubules [7-37]. Two characteristic pathognomonic deposits of Congo-red-negative microcent formation or membranous nephropathy. These are typically observed to have a lumen under routine microscopy. The majority of patients have deposits composed of microfibrils of 15–25 nm in diameter that are usually not observed to have a lumen under routine magnifications (fibrillary glomerulopathy). These microfibrils are larger than those of amyloid, the latter being typically 6–10 nm in diameter, and are usually randomly arranged in the mesangium and glomerular capillary wall. A minority of patients have larger microfibrils of > 30 nm in diameter (immunotactoid glomerulopathy). These are typically observed to have a lumen (and therefore termed microtubules) and are focally arranged in parallel bundles. It is argued by some investigators that these distinct ultrastructural patterns may result from different pathophysiological processes or portend different clinical courses [4,6,7]; however, the validity of this subclassification is disputed [3,5] and remains to be definitively established.

The results of the present analysis indicate that fibrillary-immunotactoid glomerulopathy may present at any age and suggest a slight female preponderance among patients with the fibrillary ultrastructural variant and a slight male preponderance among patients with the immunotactoid variant (Table 1). These observations are in keeping with analyses of smaller populations of patients by other investigators [7-14]. The fibrillary variant was more common in Caucasians than blacks (ratio of 9:1), a notable trend given previous observations by Iskander et al. [8] that the incidence of associated lymphoproliferative malignancy was similar in both conditions (≤7%). As with other clinical features, the incidence of malignancy did not differ when fibrillary and immunotactoid glomerulopathy were defined according to fibril diameter or arrangement (Table 4).

Discussion

Fibrillary-immunotactoid glomerulopathy, originally described by Rosenmann and Eliakim in 1976 [1], is an increasingly recognized cause of glomerular disease [2-6]. The diagnosis is made in approximately 1% of renal biopsies in adults and equals the incidence of antiglomerular basement membrane antibody disease in several large series [7,8]. The light-microscopy findings are non-diagnostic, showing patterns that may be seen with other glomerulonephritides [7–37]. These include mesangial hypercellularity, mesangial expansion with amorphous PAS-positive material, a membranoproliferative pattern, and in some cases crescent formation or membranous nephropathy. Immunofluorescence microscopy is usually positive for IgG and C3 whose distribution correlates with the pathognomonic deposits of Congo-red-negative microfibrils and microtubules [7–37]. Two characteristic ultrastructural patterns are observed on electron-microscopy. The majority of patients have deposits composed of microfibrils of 15–25 nm in diameter that are usually not observed to have a lumen under routine magnifications (fibrillary glomerulopathy). These microfibrils are larger than those of amyloid, the latter being typically 6–10 nm in diameter, and are usually randomly arranged in the mesangium and glomerular capillary wall. A minority of patients have larger microfibrils of > 30 nm in diameter (immunotactoid glomerulopathy). These are typically observed to have a lumen (and therefore termed microtubules) and are focally arranged in parallel bundles. It is argued by some investigators that these distinct ultrastructural patterns may result from different pathophysiological processes or portend different clinical courses [4,6,7]; however, the validity of this subclassification is disputed [3,5] and remains to be definitively established.

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preponderance of caucasians over blacks among their patients with this entity exceeds the caucasian:black ratio in their total renal biopsy population. In our analysis, patients with fibrillary and immunotactoid ultrastructural patterns presented with equivalent impairment of glomerular filtration and barrier function, as determined by assessments of proteinuria, haematuria and serum creatinine (Table 1). Thus, deposition of microfibrils and microtubules of different sizes or arrangements does not appear to predict differential disruption of renal function at presentation. Although not addressed specifically in our analysis, Fogo et al. [7] suggest that the subsequent rate of decline in renal function may be more rapid in patients with the fibrillary than immunotactoid features. This potential difference in natural history warrants further investigation.

Whereas it is clear that patients with fibrillary-immunotactoid glomerulopathy frequently progress to end-stage renal failure, there is limited information on the suitability of these patients for renal transplantation. Our series suggests that renal transplantation is a useful treatment option in this setting, albeit based on a small number of patients (Table 4). This conclusion is supported by five cases reported by other investigators [12,16,32,38]. Although the sum of these experiences suggests that fibril deposition recurs in at least 50% of patients, the allografts functioned satisfactorily for over 5 years in the majority of cases. These results are in stark contrast to those reported for primary amyloidosis, where allograft and patient survival is notoriously poor [5,6,39]. It is interesting that the rate of decline in renal function in allografts was slower than in native kidneys in our series, suggesting that immunosuppressive therapy may prolong renal survival in some patients or that this disease may spontaneously remit with time. Definitive demonstration of a benefit of immunosuppressive therapy will require formal testing in prospective, randomized controlled trials.

As discussed above, many investigators advocate that subclassification of non-cryoglobulinemic Congo-red-negative fibrillary glomerulopathy into fibrillary glomerulopathy and immunotactoid glomerulopathy on the basis of fibril ultrastructure is useful for identifying a subgroup of patients (immunotactoid) with a higher incidence of monoclonal gammapathy and/or lymphoproliferative malignancy, and provides clues to the mechanism of fibril formation [4,6,7]. Others argue that this subclassification is without a clinical basis, that patients with monoclonal-gammapathy-associated fibrillary deposits represent a separate clinical entity from fibrillary-immunotactoid glomerulopathy, and that the term immunotactoid glomerulopathy should be applied to patients with Congo-red-negative fibrillary deposits without cryoglobulinaemia or monoclonal gammapathy because the microfibrils invariably contain IgG [3,5]. Unfortunately this controversy has generated more heat than light. While each approach clearly has merit, we contend that both may obscure the true clinical correlates and pathological basis of the fibrillary glomerulopathies. As discussed above, both ultrastructural morphologies appear to induce a similar pattern of clinical renal injury. As illustrated in Table 2, the strength of the association of the fibrillary and immunotactoid variants with lymphoproliferative malignancy hinges on the criteria by which patients are included in the analysis. Whereas several intriguing observations point to an immune basis for fibril formation (reviewed in [6]), it has yet to be definitively determined if the IgG associated with fibrils represents an integral component of fibrils or binding of IgG to a fibril component by virtue of electrical charge or other physiochemical characteristics. Indeed, given the marked overlap in ultrastructural and immunohistochemical features among the various fibrillary glomerulopathies (reviewed in [5]), it is still conceivable that fibrillary-immunotactoid glomerulopathy represents a form fruste of cryoglobulin- and paraprotein-associated disease and have a common pathophysiological basis.

Given the limited understanding of the pathogenesis of the fibrillary glomerulopathies, we urge caution against overclassifying these disorders and employing nomenclature which prematurely suggests mechanisms of fibril formation. It seems reasonable to conclude only that the vast majority of patients with extracellular fibrillary deposits within the glomerulus can be assigned to one of four categories: [1] amyloid-associated fibrillary glomerulopathy (Congo red positive with green dichroism), [2] Congo-red-negative fibrillary glomerulopathy in association with cryoglobulinaemia, [3] Congo-red-negative fibrillary glomerulopathy in association with monoclonal gammapathy and [4] Congo-red-negative idiopathic fibrillary glomerulopathy without measurable cryoglobulins or monoclonal gammapathy. We suggest that the finding of Congo-red-negative extracellular fibrillary deposits on renal biopsy should prompt a search for monoclonal gammapathy or cryoglobulins. A definitive answer as to whether patients with isolated Congo-red-negative fibrillary deposits represent a form fruste of cryoglobulin- or paraprotein-associated disease or a distinct syndrome(s) will require longitudinal assessments for circulating cryoglobulins or abnormal para-proteins, the development of more sensitive assays for detection of cryoglobulins and paraproteins, and ultimately the elucidation of the molecular basis for fibril formation.

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