Fibrillary Glomerulonephritis and Immunotactoid Glomerulopathy

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CASE PRESENTATION

The patient was a 48-yr-old man who had a history of hypertension, hyperlipidemia, obesity, and chronic renal insufficiency and was referred for evaluation of proteinuria. The patient's history was notable for a myocardial infarction 5 yr previously.

Physical examination revealed an obese man with BP of 168/89 mmHg and no other notable findings. Urinalysis revealed 4+/H₁₁₀₀₀₁ protein and 2+/H₁₁₀₀₀₁ glucose and rare red and white blood cells and no casts. A 24-h urine collection revealed 8 g of protein. Other relevant laboratory data included serum albumin of 2.8 mg/dl, creatinine of 4.2 mg/dl, and total cholesterol of 204 mg/dl. Liver function tests were within normal limits. Serologic tests for evidence of autoimmune disease were not obtained.

A renal biopsy showed cortex containing 16 glomeruli, seven of which were completely sclerosed and three of which were segmentally sclerosed. The remaining glomeruli revealed marked expansion of mesangial stalks and irregular thickening of capillary walls as a result of infiltration and accumulation of silver negative and periodic acid-Schiff–positive acellular material (Figure 1). There was neither significant increase in mesangial cellularity nor basement membrane “spike” formation. There was a background of patchy interstitial fibrosis and tubular atrophy and associated interstitial inflammation. Arterial vessels showed mild intimal sclerosis. Staining with the Congo Red reagent for amyloidosis was negative.

Immunofluorescence microscopy demonstrated confluent mesangial and glomerular capillary wall staining for IgG (3+) and κ and λ light chain (each trace). There was no significant staining of the glomeruli for IgA, IgM, C3, C1q, fibrinogen, or albumin. Ultrastructural examination of two glomeruli revealed expansion of the mesangial stalks and capillary walls as a result of extracellular accumulation of haphazardly arranged fibrils measuring approximately 16 nm in thickness. Podoocyte foot processes were diffusely effaced. There was no evidence of fibrillary deposits in the tubular basement membranes or interstitium. The diagnosis of fibrillary glomerulonephritis was established on the basis of the ultrastructural findings in conjunction with the negative Congo Red stain and typical histologic and immunohistochemical features.

FIBRILLARY GLOMERULONEPHRITIS

Fibrillary glomerulonephritis is a morphologically defined entity characterized by glomerular accumulations of nonbranching, randomly arranged fibrils that are ultrastructurally indistinguishable from amyloid fibrils but differ from amyloid by virtue of their larger size and lack of reactivity with Congo Red and other reagents that are histochemically reactive with amyloid.1–4 As in our case, this diagnosis requires electron microscopic identification of characteristic infiltrating fibrils within glomerular structures. It has been identified in approximately 0.5 to 1.0% of native
kidney biopsies in at least three large biopsy series reported to date.3–5 It is distinct from other, much rarer processes involving deposition of glomerular fibrils such as occur with fibronectin glomerulopathy and collagenofibrotic glomerulopathy.6

Clinically, fibrillary glomerulonephritis most often presents in middle-aged to older patients (mean age 55 to 60 yr), although the age range is wide and this disease has rarely been reported in the pediatric population. Patients typically present with proteinuria, 50% within nephrotic range. Hematuria and hypertension are also common presenting conditions (60 and 77%, respectively, in some series).5 No clinical laboratory findings are specific for this condition; all of the usual serologies obtained for the workup of various forms of glomerulonephritis are typically negative and/or normal; however, there was a report of several patients who had features of fibrillary glomerulonephritis and concomitant infection with hepatitis C virus.7

The outcome for patients with this disease is frequently poor. Progression to end-stage renal disease occurs in approximately half of the patients within several years of diagnosis.4,5 There are no known established therapeutic regimens for this disease, and no organized clinical trials have tested the efficacy of any proposed clinical approach.8 Several studies have documented the recurrence of this disease in renal transplants, which in some cases has resulted in nephrotic syndrome and/or allograft loss.1,6–10

**DIAGNOSIS OF FIBRILLARY GLOMERULONEPHRITIS**

The histologic appearance of fibrillary glomerulonephritis is somewhat heterogeneous. Common histologic patterns include those of a membranoproliferative glomerulopathy, diffuse proliferative glomerulonephritis, mesangial proliferative glomerulopathy and a smaller number of cases in which the pattern and distribution of the fibrillary deposits is similar to that of membranous nephropathy.3 In many cases, a pattern of infiltration of glomerular structures by amorphous acellular material is the most striking feature unaccompanied by prominent cellular proliferation (Figure 1). This material can be seen to infiltrate mesangial regions and peripheral capillary walls, although in rare cases there may be no detectable histologic alterations and the glomerular appearance may be indistinguishable from minimal-change disease. Some studies have suggested that as many as 20% of cases may be accompanied by crescent formation,4,8 although this number is high in our experience and the crescents are rarely a dominant feature. Most often, the glomeruli are without prominent inflammatory cell infiltration. Essential to the diagnosis, as already indicated, is the absence of reactivity with Congo Red or other agents typically used for the histochemical demonstration of amyloid in tissues. Immunofluorescence findings most often reveal polyclonal deposits of immunoglobulin (Ig), typically IgG, and light chains, but a small percentage of these patients have monoclonal or oligoclonal Ig deposition characterized by deposits of Ig heavy-chain and one light-chain subclass (e.g., κ light chain) but not the other.1–3 When studied by IgG subclass typing sera, deposition of IgG4 and IgG1 predominates in fibrillary glomerulonephritis, a finding of uncertain pathophysiologic significance.4,5 The characteristic ultrastructural finding is an amyloid-like process in which glomerular structures are infiltrated by randomly arranged, nonbranching fibrils that typically measure 12 to 24 nm in diameter, with measurements most frequently being approximately 18 to 20 nm (Figure 2).1–4 This contrasts with the usual fibril size in amyloid (typically reported as being between 8 and 15 nm, but with the most typical measurements being 8 to 12 nm).2 Fibrils in fibrillary glomerulonephritis are often enmeshed in regions in which there is electron lucency. Granular electron-dense deposits, sim-
ilar to conventional immune deposits, may also be present and admixed among the accumulations of fibrils.

Fibrillary glomerulonephritis, as the name suggests, is primarily a disorder involving glomeruli. Uncommonly, the fibrillar deposits may also involve tubular basement membranes. There are scattered case reports of concomitant deposition of fibrillary deposits in extrarenal sites such as heart and lung, but inspection of published illustrations suggests to us that these reports be interpreted with caution.

FIBRILLARY GLOMERULONEPHRITIS VERSUS IMMUNOTACTOID GLOMERULONEPHRITIS

An entity that is often considered within the spectrum of renal diseases as fibrillary glomerulonephritis is immunotactoid glomerulopathy. In the view of some, immunotactoid glomerulopathy is a unifying term for cases of glomerular deposition of both the amyloid-like fibrils described as fibrillary glomerulonephritis and cases in which the glomerular deposits consist of larger microtubular structures that also fail to react with histochemical stains for amyloid in tissue sections. These microtubular structures often measure >30 nm in diameter with most reported cases having measurements ranging from 34 to 49 nm.2-3 We and others have taken the approach that immunotactoid glomerulopathy is a term best used in a more restricted sense, to define a morphologic entity characterized by glomerular deposits of Ig organized as large microtubules.2,3,5,14 The diagnosis requires ultrastructural demonstration of these microtubules, which are generally but not invariably >30 nm in diameter. When so defined, immunotactoid glomerulopathy is a rare entity, occurring one tenth as frequently as fibrillary glomerulonephritis.4 Like fibrillary glomerulonephritis, this entity occurs in an older population, with most reported patients >50 yr of age. Patients typically present with nephrotic syndrome (50% in one series5) but may also have features of hematuria and renal insufficiency (five out of six patients in one of the largest series reported to date5). Specific therapeutic approaches have not been established. Recurrent disease has been reported in renal allografts.

There are clinical features that also support the notion that the morphologic entity of immunotactoid glomerulopathy is best considered as a distinct clinical entity. These patients have a greater predisposition to an underlying lymphoplasmacytic disorder,2,3,5,13,14 This is supported by immunofluorescence studies on renal biopsies in which clonality (i.e., restriction to one light-chain subclass) of the deposits frequently can be demonstrated by immunofluorescence microscopy. The characteristic organized nature of the microtubular deposits is a feature that is also occasionally encountered in patients with cryoglobulinemia and/or systemic lupus erythematosus, and the morphologic findings of microtubular deposits in a renal biopsy should prompt consideration of these clinical possibilities.

Although there has been a spirited discussion among members of the renal community over the issue of whether fibrillary glomerulonephritis and immunotactoid glomerulopathy are best considered as one entity or two, this issue of classification seems less important than the recognition that both of these entities can and should be morphologically distinguished from amyloidosis and that the recognition of these morphologic patterns can suggest important clinical disease considerations that should be evaluated in affected patients, such as cryoglobulinemia, systemic lupus, and perhaps hepatitis C virus infection.2,5,11,13

Table 1 provides key features for distinguishing amyloidosis, fibrillary glomerulonephritis, and immunotactoid glomerulopathy.

DIFFICULTIES IN DIAGNOSIS

Despite the clear definitions for classic manifestations of these entities provided in Table 1, there are cases in which the differential diagnosis of fibrillary glomerulonephritis and immunotactoid glomerulopathy poses difficult challenges for the pathologist. These entities can be overlooked when electron microscopy is not performed on a renal biopsy; there is no other means of establishing this diagnosis. This is a particular problem when the infiltrating fibrils of fibrillary glomerulonephritis are confined to subepithelial portions of the glo-

Table 1. Clinicopathologic features that distinguish fibrillary glomerulonephritis from morphologically similar immunopathologic features of fibrillar/microtubular glomerulopathies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Amyloid</th>
<th>Fibrillary Glomerulonephritis</th>
<th>Immunotactoid Glomerulopathy</th>
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<tbody>
<tr>
<td>Appearance</td>
<td>Fibrils</td>
<td>Fibrils, rarely microtubular</td>
<td>Microtubules</td>
</tr>
<tr>
<td>Fibril/microtubule size (nm)</td>
<td>8 to 15 (most often 8 to 12)</td>
<td>12 to 24 (most often 18 to 20)</td>
<td>&gt;30 (most often 34 to 49)</td>
</tr>
<tr>
<td>Fibril arrangement in tissues</td>
<td>Random</td>
<td>No</td>
<td>Often organized in parallel arrays</td>
</tr>
<tr>
<td>Reactions with histochemical dyes Congo Red and Thioflavin T</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ig deposition</td>
<td>Monoclonal light chains in AL type amyloid only</td>
<td>Usually polyclonal, occasionally oligoclonal or monoclonal IgG</td>
<td>Monoclonal or oligoclonal IgG</td>
</tr>
<tr>
<td>Association with lymphoplasmacytic disorders</td>
<td>Yes, if AL type</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
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merular capillary walls, giving an appearance of membranous glomerulopathy by immunofluorescence microscopy and thus obviating the need for ultrastructural examination in the minds of some. A second source of error is not to measure the fibrils or, just as important, not to measure them accurately with a properly calibrated electron microscope. A more difficult challenge is finding fibrils or microtubules of a measured size at the far ends of the accepted spectrums. In those uncommon cases of fibrillary glomerulonephritis with smaller fibrils, there is overlap with amyloid, and in these circumstances, in which diagnostic certainty may not be achievable, it is our practice to rely heavily on the results of Congo Red staining (or staining with other dyes that identify amyloid, such as Thioflavine T) to make a diagnostic distinction. Sometimes the fibrils may have an atypical ultrastructural appearance: they may be curved rather than straight, and some fibrils may appear “hollow” when viewed on end. In these unusual cases, it must be acknowledged that the best judgment of the pathologist will be as important as published criteria in reaching or excluding this diagnosis.

One additional consideration is the substructural organization of Ig deposits in certain systemic disorders. Deposits of cryoglobulins can be microtubular and indistinguishable from those of immunotactoid glomerulopathy; for this reason, cryoglobulinemia should be a diagnostic consideration whenever such deposits are encountered. Ig deposits in lupus nephritis can demonstrate substantial organization with a “fingerprint” appearance that is not easily confused with fibrillary glomerulonephritis; however, the immune deposits in lupus nephritis can occasionally have a randomly arranged fibrillary substructure indistinguishable from fibrillary glomerulonephritis, particularly lupus membranous glomerulonephritis, and it is only by clinicopathologic correlation that the correct diagnosis of lupus nephritis may be achieved in these cases.

PATHOGENESIS

The pathogenesis of fibrillary glomerulonephritis is unknown. Investigations into pathogenesis have been hampered by the absence of an animal model. One clue to the pathogenesis of this disease has been the immuno-electron microscopic localizations of IgG; the complement component C3 and amyloid P component to individual fibrils; but not labels for matrix and microfibrillar proteins including collagen type IV, heparan sulfate proteoglycan, fibronectin, and fibrillin. These studies provide the best evidence to date that the fibrils in this disorder are composed of Ig, although they do not conclusively prove this proposition because it remains possible that the Ig identified is secondarily bound to a fibrillar protein not recognized by the antisera used. To our knowledge, the fibrils of fibrillary glomerulonephritis have not been extracted from biopsy, nephrectomy, or autopsy tissues; therefore, biochemical approaches to characterize the involved proteins have yet to be attempted.

DISCLOSURES

None.

REFERENCES