Glomerulonephritis With Associated Hypocomplementemia and Crescents: An Unusual Case of Fibrillary Glomerulonephritis

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ABSTRACT

Fibrillary glomerulonephritis is an unusual, but not rare, cause of glomerulonephritis. Hypocomplementemia in association with fibrillary glomerulonephritis has been reported only once previously. A patient with hypocomplementemia and fibrillary deposits as demonstrated by electron microscopy is reported. The clinical and pathologic features of fibrillary glomerulonephritis and immunotactoid glomerulopathy are reviewed.

Key Words: Glomerulonephritis, hypocomplementemia

Fibrillary glomerulonephritis is an uncommon, but not rare, cause of nephrotic syndrome. Some investigators have divided this disease into two subclasses: fibrillary glomerulonephritis and immunotactoid glomerulopathy. Depressed serum complement levels are unusual in both of these disorders (1,2). In considering the differential diagnosis in a patient presenting with hematuria and proteinuria, one should consider this entity. However, because there are no specific findings in the patient’s history, physical examination, or laboratory evaluation, the diagnosis must be established by renal biopsy, with the particular finding of fibrillary deposits as identified by the use of electron microscopy. We report here a case that has the pathologic characteristics of fibrillary glomerulonephritis and that has depressed serum complement levels.

CASE REPORT

C.S. is an 80-yr-old man who was in generally good health. His past medical history is significant for
tuberculosis 4 yr previously that had been treated with a 1-yr course of ethambutol and rifampin. In the summer of 1993, he presented to his primary-care physician with a complaint of 3 wk of leg swelling and urinary frequency. Other symptomatology at that initial visit included a 1-wk complaint of decreased appetite as well as nausea and vomiting. Vital signs taken at the time of physical examination were notable for a blood pressure of 138/78 mm Hg. Of note on physical examination was 2+ to 3+ pitting edema of the lower extremities, but no appreciable ascites. Serum chemistries were significant for a BUN level of 44 mg/dL, a creatinine level of 5.2 mg/dL, and an albumin level of 2.5 g/dL. Urinalysis revealed 3+ protein, trace glucose, and an unremarkable microscopic examination. He was subsequently referred to the Department of Nephrology for further evaluation of nephrotic syndrome.

On evaluation in our clinic, further history was significant only for nocturia three times per night that had been present for several years. Vital signs were notable for a seated blood pressure of 140/72. Physical examination revealed a cachectic-appearing elderly gentleman. There was no appreciable adenopathy; his lungs were without rales, but diffuse bronchial breath sounds were noted. A prominent S2 was present on cardiac auscultation, as well as a harsh III/VI holosystolic murmur. No pericardial rub or gallop rhythm was appreciated. His abdomen was soft and nontender without hepatosplenomegaly. The lower extremities had 2+ to 3+ pitting edema.

Urinalysis demonstrated a specific gravity of 1.020, pH of 5.5, trace blood, 1+ glucose, and 4+ protein. The microscopic examination revealed 10 to 20 red blood cells per high-power field, many of which were crenated, and an occasional granular cast. Quantitation of proteinuria revealed 20.7 g/24 h.

Blood chemistries were obtained and were noted to be within normal limits for electrolytes and liver enzymes. The C3 component of complement was reduced to 66 (83 to 177) mg/dL whereas the C4 component was reduced to the lower limits of normal at 15 (15 to 45) mg/dL. Other serologies included an antinuclear antibodies of 1:20, negative cryoglobulins, negative hepatitis C antibody, and an hemoglobin A1C of 6.5%. Serum protein electrophoresis was unremarkable, and the urine immunofixation was negative for monoclonal immunoglobulins.

A renal biopsy was performed. Light microscopy demonstrated mesangial expansion producing an accentuated lobular appearance, resembling membranoproliferative glomerulonephritis (Figure 1). The basement membranes appeared focally thickened with occasional double contours, as demonstrated by periodic acid-Schiff and Jones silver staining. Crescent formation was also present (Figure 1) involving 50% of the glomeruli. Also noted were extensive interstitial fibrosis and tubular atrophy with thickening of the tubular basement membrane. A Congo Red stain for amyloid was negative. Immunofluorescence microscopically demonstrated weak but definite granular fluorescence in the mesangium after staining with the anti-immunoglobulin (Ig) G and anti-IgM fluorescein-labeled antibody conjugates. There was moderately intense mesangial staining for C3 and C1q, with less intense staining along the glomerular capillary loops. Electron microscopy demonstrated effacement of the epithelial foot processes, marked thickening and duplication of the glomerular capillary loops, and disruption of the basement membrane architecture by randomly arranged fibrillary deposits (Figure 2). These fibrils, with an average diameter of 20 nm, were slightly larger than those found in amyloidosis. Within the mesangium and basement membrane, the fibrils were distributed uniformly rather than forming discrete deposits. However, the fibrils located in the subepithelial region formed triangular projections in which the orientation of the fibrils was perpendicular to the axis of the basement membrane (Figure 2). The final diagnosis was fibrillary glomerulonephritis.

**REVIEW**

In 1977, Rosenmann and Eliakim (3) described a form a glomerulonephritis characterized by fibrillary deposits seen by electron microscopy that failed to stain with Congo Red. Since that time, over 100 cases of fibrillary glomerulonephritis have been described, characterized by these unique histologic features. Indeed, after reviewing their experience, two different groups have estimated that fibrillary glomerulonephritis represents about 1% of all glomerulonephritides observed in their renal biopsy experience (1,4). Various names have been applied to this entity, including fibrillary glomerulonephritis, immunotactoid glomerulopathy, and Congo Red-negative, amyloid-like glomerulopathy (5). The most characteristic finding is the presence of fibrillary glomerular deposits, ranging from 8 to 70 nm in diameter (5). Typically, the smaller diameter fibrils are randomly arranged, whereas the larger diameter fibrils tend to form par-
allel tubular arrays. Some investigators believe that fibrillary glomerulonephritis and immunotactoid glomerulopathy are distinct entities (4–7), whereas others believe that they are variations on a theme (8,9). The distinction between fibrillary glomerulonephritis and immunotactoid glomerulopathy is based largely on fibrillary size and arrangement.

The clinical presentation can be quite varied. In one review (1), in which the investigators separated fibrillary glomerulonephritis from immunotactoid glomerulopathy, 26 cases of the former entity and 6 cases of the latter were evaluated. In the cases defined as fibrillary glomerulonephritis, the average age at biopsy was 50 yr and the female: male ratio was about 2:1. Most patients presented with the triad of hematuria, proteinuria, and hypertension, with no other systemic manifestations. The serum creatinine was elevated in approximately 50% of these patients, with an average creatinine of 3.2 (±0.5) mg/dL. Hematuria was invariably present, but all patients had proteinuria, often in the nephrotic range. Antinuclear antibodies were absent in 15 of 16 of the patients in this study, and complement levels when measured were normal in all but 1 patient, who had a low C3 with a normal C4. Approximately 50% of patients progressed to ESRD, usually within 2 to 4 yr.

In contrast, in the group of six patients designated as having immunotactoid glomerulopathy, the female: male ratio was 1:1. The average serum creatinine was 1.7 mg/dL, with only one patient having a significant elevation. Proteinuria was invariably present, whereas hematuria was present in two of six patients. Antinuclear antibodies were present in two of four patients, and complement levels were low in three of five patients. None of these six patients had progression of their renal disease.

In general, fibrillary deposits in these disorders have been limited to the kidney. Recently, however, two case reports of pulmonary hemorrhage associated with fibrillary glomerulonephritis (10,11) have been described. Electron microscopy showed prominent deposition of fibrillar material in the alveolar-capillary interstitium, which was morphologically similar to that found in the glomerular mesangium and capillary basement membrane. There have also been rare reports of skin involvement manifesting as leukocytoclasis, vasculitis (2) in patients with documented fibrillary deposits in the kidney, but no other systemic manifestations.

PATHOLOGY

A summary of pathologic findings in fibrillary glomerulonephritis is shown in Table 1. Iskander et al. (4) evaluated 31 renal biopsies from 28 patients diagnosed with fibrillary glomerulonephritis. Light microscopy was most notable for the presence of mesangial matrix expansion and hypercellularity. Other investigators have described a lobular appearance of the glomerular tufts, similar to that observed in mem-

Figure 2. (a) Electron photomicrograph of a glomerular capillary loop showing intramembranous fibrillar deposits, particularly on the subepithelial aspect of the basement membrane (uranylacetate, original magnification, ×8000). (b) High-power view of the basement membrane demonstrating random and perpendicular fibrils in the basement membrane (uranylacetate, original magnification, ×31,500).
TABLE 1. Pathologic findings in fibrillary glomerulonephritis

<table>
<thead>
<tr>
<th>Light Microscopy (% Cases)</th>
<th>Immunofluorescence Microscopy</th>
<th>Electron Microscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Findings are quite variable</td>
<td>Predominantly mesangial staining</td>
<td>Randomly arranged fibrils in fibrillary glomerulonephritis (100)</td>
</tr>
<tr>
<td>Capillary wall thickening (95)</td>
<td>Moderate to Intense IgG, usually IgG₄ (97-100)</td>
<td>Parallel arrays of fibrils in immunotactoid glomerulopathy (23)</td>
</tr>
<tr>
<td>Mesangial matrix expansion (95)</td>
<td>Weaker C3 staining (97)</td>
<td>Predominantly located in mesangium</td>
</tr>
<tr>
<td>Crescent formation (19)</td>
<td>Kappa light chain staining (96)</td>
<td>Fibrils can be located in any or all glomerular compartments</td>
</tr>
<tr>
<td>Involving 10 to 80% of glomeruli</td>
<td>Lambda light chain staining (84)</td>
<td></td>
</tr>
<tr>
<td>Obsolescent glomeruli (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variable lymphocytic interstitial infiltrate</td>
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</tbody>
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References
1. 1
4. 4

TABLE 2. Morphologic characteristics of glomerular fibrillar deposits

<table>
<thead>
<tr>
<th>Fibril</th>
<th>Fibril Diameter (nm)</th>
<th>Arrangement</th>
<th>Location of Deposit</th>
<th>Congo Red Staining</th>
<th>Cryoglobulins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid</td>
<td>8-10</td>
<td>Random</td>
<td>Mesangium, capillary loop</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Fibrillary</td>
<td>10-18</td>
<td>Random</td>
<td>Mesangium,  &gt;subendothelial,  Subepithelial</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Immunotactoid Glomerulopathy</td>
<td>16-90</td>
<td>Parallel arrays</td>
<td>Subepithelial,  &gt;subendothelial,  mesangium</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>20-40</td>
<td>Parallel arrays</td>
<td>Mesangial, capillary loop, intraluminal Capillary loop</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9-12</td>
<td>Random of parallel</td>
<td></td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Taken from References 1 and 4, with permission.

branoproliferative glomerulonephritis. Significantly, Iskander et al. reported a 19% incidence of crescent formation involving 10 to 80% of the glomeruli. Variable degrees of interstitial fibrosis and mononuclear cell infiltration were also described, often correlating with the degree of impairment of renal function. In the study by Fogo et al. (1), predominant mesangial deposits of IgG and C3 were found in fibrillary glomerulonephritis, whereas in immunotactoid glomerulopathy, deposits of IgG and C3 were primarily along the glomerular capillary wall. However, most investigators have described mesangial deposits consistently in both fibrillary glomerulonephritis and immunotactoid glomerulopathy. Immunofluorescence studies were carried out on all 31 specimens in the study by Iskander et al. (4). The deposits contained principally IgG. Those cases designated as fibrillary glomerulonephritis frequently contain polyclonal IgG4 as the main immunoglobulin. Anti-C3 staining was also highly prevalent, noted in 97% specimens, and was graded as moderately intense. Other immunoglobulins have also been identified in the glomeruli by immunofluorescence microscopy but at a lower frequency and decreased intensity. In general, the pattern of immunofluorescence reflects the distribution of fibrillar deposits noted by electron microscopy, as well as the pattern of mesangial and capillary loop pathology observed by light microscopy.

Electron microscopy is crucial in making the diagnosis of fibrillary glomerulonephritis. The characteristic ultrastructural findings consist of randomly arranged fibrillar deposits in the glomeruli, with marked variability in fibril diameter from case to case. Those cases typically designated as fibrillary glomerulonephritis are distinguished by fibrils slightly larger than those of amyloidosis, ranging in size from 10 to 18 nm in diameter. The fibrils are most abundant in the mesangium, but may involve the glomerular capillary loops as well. As noted in the study by Fogo et al. (1), both subendothelial deposits and occasionally subepithelial deposits were identified. In comparison, the fibrillary deposits in cases classified as immunotactoid glomerulopathy are larger than those of fibrillary glomerulonephritis, with diameters of 16 to 90 nm. The orientation of these deposits is often nonrandom, forming parallel tubules or cylinders. These characteristics have prompted the designation of these fibrils as microtubules and the immunotactoid nomenclature.

DISCUSSION

Although the fibrillary glomerulonephritis appear to represent a distinct entity, there are many systemic diseases in which fibrillary glomerular deposits can be
observed, including diabetes (12), cryoglobulinemia, amyloidosis, and various paraproteinemias (Table 2; Figure 3). Immunohistochemical evaluation of these deposits has demonstrated the variety of proteins capable of forming fibrillar deposits. For example, in the AL form of amyloidosis, the amyloid fibrils consist of polymers of light chain variable regions. However, morphologically identical fibrils can be produced in a variety of nonimmune conditions as well, in which the fibrils are composed of the phase reactant serum amyloid A protein. Immunohistochemical staining in cryoglobulinemia has demonstrated that the fibrillar deposits in this disorder are either immune complexes (Types II and III) or polymers of a monoclonal immunoglobulin (Type I). Thus, immunoglobulin fragments, immune complexes, and in some instances, other proteins are capable of forming fibrillar deposits in the right environment.

In amyloidosis, the physicochemical properties of the deposits are such that β-pleated sheets are formed, which after Congo Red staining, show apple-green birefringence when examined microscopically with polarized light. In contrast, Congo Red staining is negative by definition in fibrillary glomerulonephritis (or nonamyloid glomerulopathy). As a result, some cases of fibrillary glomerulonephritis initially were labeled "atypical amyloidosis." Korbet et al. (5,8) make a strong argument for differences in the physicochemical properties of the deposits that in turn result in differences in the fibril diameter and arrangement. Of interest is that the size of the fibrils in each particular case remains fairly constant, although the case-to-case variation is quite high. When the course of renal transplantation in immunotactoid glomerulopathy was evaluated in four patients (13), recurrence of disease was found in two of four patients, emphasizing the importance of systemic factors in the development of this disorder. What is of notable interest is that the size of the fibrils found in the transplanted kidney was similar to the size of the fibrils observed in the native kidneys. One could speculate that the size consistency between native disease and recurrent disease could be a result of the specific physicochemical properties of the immunoglobulins, or fragments found, in a particular patient, rather than a difference in the stimulus leading to fibril deposition. Other authors have speculated that the fibrils are composed of fibronectin to which immunoglobulins have become attached. Fibronectin has been demonstrated in some fibrillar deposits, but this has not been a consistent finding.

The localization of deposits in the glomerulus in both immunotactoid and fibrillary glomerulonephritis is quite variable. In the majority of cases, the deposits are noted in the mesangium, with lesser degree of deposition within the capillary wall. There is no consistent cause associated with the process of fibril formation, and it is as yet not clear whether these fibrils represent circulating immune complexes, in situ formation of immune complexes, or polymerization of immunoglobulin fragments. Furthermore, Churg and Venkatesh (14) recently reported two cases of fibrillary glomerulonephritis in which the fibrils were composed of a protein other than immunoglobulins. Rarely, cases of pulmonary hemorrhage (9,10) in association with fibrillar deposits in the kidney have been reported. These findings lead one away from the supposition that fibrillogenesis is due to local factors in the kidney and raises the suspicion that circulating factors may be responsible for promoting fibril formation.

There is considerable overlap between fibrillary glomerulonephritis and immunotactoid glomerulopathy with respect to serologic studies. Typically, both entities have normal ANA and normal serum complement levels. A normal serum complement level does not exclude the possibility that complement activation is occurring in the glomerulus and contributing to the pathology. Complement has been demonstrated to play a variety of roles in the mediation of glomerular immune injury (15). It is known that complement activation plays a major role in cytokine release and other intercellular signaling mechanisms. Recruitment of neutrophils and platelets may occur, as well as the formation of the membrane attack complex, followed by the clearance of immune complexes. The terminal complement components are also capable of producing direct injury to the basement membrane and adjacent cells. Most cases of glomerulonephritis associated with fibrillary deposits have reported normal serum complement levels, although there has been one report of fibrillary glomerulonephritis associated with low complement levels. In a previously reported case of immunotactoid glomerulonephritis associated with hypocomplementemia (2), it was postulated that the low C3 levels may have contributed to the delayed clearance of immune complexes, which in turn allowed for fibril deposition. The case reported

![Diagram](https://example.com/diagram.png)

**Figure 3. Algorithm for the evaluation of patients with fibrillary glomerulopathy.** CLL, chronic lymphocytic leukemia; LCDD, light chain deposition disease. Reprinted with permission from Korbet et al. (5).
here represents a second case of fibrillary glomerulonephritis associated with hypocomplementemia. Crescent formation has usually been associated with fibrillary glomerulonephritis, as demonstrated in this case. The distinction between fibrillary glomerulonephritis and immunotactoid glomerulopathy is quite blurred. For those who separate the two, fibril size is the most distinguishing feature. Other characteristics, such as the presence of crescents on renal biopsy and the location of the fibrillar deposits, display a significant degree of overlap (Table 2). This case underscores the fact that depressed serum complement levels also overlap, further blurring the distinction between fibrillary glomerulonephritis and immunotactoid glomerulopathy.

Various approaches to treatment have been attempted without success. These have frequently included steroid therapy, occasionally with a very brief stabilization, soon followed by deterioration of the patient's status. Other approaches have included plasmapheresis and cytotoxic therapy, neither of which has provided sustained remission. Until the mechanisms resulting in fibril formation and glomerular injury are better understood, effective therapy is likely to remain elusive.

In summary, fibrillary glomerulonephritis remains a descriptive diagnosis based on the histologic findings. However, other entities with similar histologic findings must first be ruled out. Shown in Figure 3 is an algorithm for the evaluation of fibrillary glomerulonephritis. The clinical presentation can be quite varied but typically consists of hematuria, proteinuria, and hypertension. Serologic studies are not helpful in establishing the diagnosis. Progression to ESRD appears to occur in approximately 50% of patients. Attempts at treatment with steroids, cytotoxic agents, and plasmapheresis have not demonstrated any consistent degree of improvement or stabilization of renal function. The pathophysiology of fibril deposition remains to be unraveled. Given the degree of overlap in fibril size, serologic findings, the morphologic abnormalities, and variable patient outcome, it is reasonable to consider fibrillary glomerulonephritis and immuno-tactoid glomerulopathy as manifestations of a disease spectrum as opposed to distinct entities.

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