Immunotactoid Glomerulopathy (Fibrillary Glomerulonephritis)

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Immunotactoid glomerulopathy first was described in 1977, when Rosenmann and Eliakim (1) reported an unusual glomerular lesion in a 45-yr-old woman who presented with the nephrotic syndrome and renal insufficiency. The electron microscopy was remarkable for organized electron-dense deposits in the form of randomly arranged fibrils that measured 10 nM in diameter. The deposits were associated with mesangial expansion and immune deposits of IgG, IgM, and C3 in a mesangial pattern. Congo red stain of the deposits was negative, and there was no clinical or serologic evidence of a systemic disease. They interpreted the deposits to be “amyloid-like” and speculated that they might represent a “preamyloid” state. In 1980, Schwartz and Lewis (2) reported a case of a 49-yr-old man who presented with the nephrotic syndrome and no evidence of systemic disease and had a similar renal lesion: Immune aggregates were associated with highly organized electron-dense deposits that were composed of microtubules that were arranged in parallel bundles. During 7 yr of follow-up, the patient progressed to renal failure but never demonstrated any clinical or serologic evidence of a systemic disease. To distinguish this lesion from other disorders that differ significantly from that of ITG, these disorders compose the family of histopathologic lesions that are referred to as the fibrillary glomerulopathies (Figure 1). The disorders that are included in this classification are defined histochemically. In this schema, ITG represents one of the nonamyloid, Ig-mediated fibrillary glomerulopathies of which there is a differential diagnosis with diseases, which must be excluded before the diagnosis of ITG is made. Many of the diseases that are associated with the fibrillary glomerulopathies have specific therapies and prognoses that differ significantly from that of ITG. As a result, it is critical that the clinician use a combined histologic, clinical, and serologic approach in reaching the correct diagnosis.

One Entity or Two?

It has been suggested that ITG should be separated into two categories on the basis of arbitrary ultrastructural criteria regarding fibril size and/or organization. The proponents of subdividing ITG suggest that the diagnosis of ITG be reserved for cases with larger (>30 nM diameter), parallel microtubules (Figure 2A) and that FGN be applied to cases with smaller (<30 nM diameter), randomly arranged fibrils (Figure 2B) (9,10,13). The rationale for this subdivision is that the two morphologic categories have significantly different clinical implications (9,10,14,15). In a review of the literature in 1992, Alpers (13) first proposed that such a distinction was clinically important when he found that six (54.5%) of 11 patients with microtubules that were >30 nM in diameter had associated dysproteinemia or lymphoproliferative disorder compared with only one (1.2%) of 86 patients with smaller microtubules. In 1993, Fogo et al. (10), on the basis of their own experience, found that patients with organized arrays of larger microtubules were more likely to...
have a hematopoietic disorder than patients with small, randomly oriented fibrils. In patients with the larger microtubules, four (66%) of six were said to have a hematologic disorder (one with chronic lymphocytic leukemia and an associated monoclonal gammopathy and two with Sjögren’s syndrome [one of these had a monoclonal gammopathy], and one patient was included because of a bone marrow biopsy showing 3% plasma cells) compared with only one (4%) of 26 patients with smaller fibrils (the patient had myeloma). Most recently, Rosenstock et al. (5), in a study of 61 patients with randomly oriented fibrils that were $\geq 30$ nM and six patients with hollow, stacked microtubules that were $\geq 30$ nM found the presenting clinical features were indistinguishable between the two groups. However, at presentation, patients with the larger microtubules were more likely to have an associated lymphoproliferative disorder (two [33%] of six versus one [1.6%] of 61 patients; $P = 0.02$) and a paraproteinemia (four [66%] of six versus seven of [15%] 46; $P = 0.014$). What is consistent with all of these studies is that although they excluded patients with cryoglobulinemia (despite this claim, in one study, 56% of patients were not even serologically evaluated for the presence of cryoglobulinemia [5]), they chose to include patients with paraproteinemias.

We find a number of problems with separating ITG into two categories. First, this approach assumes that morphologic divisions are distinct when in fact they are not. Pronovost et al. (3) found that when ITG was defined on the basis of fibril size of $>30$ nM, 6.5% of 186 cases reviewed had ITG but that when they defined ITG on the basis of having parallel arrangement, the prevalence doubled (12%). Second, in one of the largest and most thorough reviews on the topic to date, Pronovost et al. (3) found no difference in the clinical features (hypertension, hematuria, nephrotic syndrome, or renal insufficiency) at presentation when the diagnosis of ITG was subdivided on the basis of differences in fibril size ($>30$ versus $\leq 30$ nM) or arrangement (random versus parallel bundles). They also recognized that any association with a lymphoproliferative disorder very much depended on the criteria used for study. When, as in the previous studies, patients who were known to have paraproteins were included in the analysis, they, too, found that patients with larger microtubules were more likely to have an associated lymphoproliferative disorder (33% of patients) compared with patients with the smaller fibrils (0%). However, when they...
excluded patients who were known to have paraproteins (our approach and theirs in diagnosing ITG), the association of a lymphoproliferative disorder was not different between the groups: 3% in patients with larger microtubules and 7% in those with smaller fibrils. Finally, there is no pathogenic or biochemical basis to justify such a division. Therefore, in our view, on the basis of the existing literature, there is no compelling reason to diagnose ITG and FGN separately on the basis of morphology alone, because it has not been demonstrated clearly that the ultrastructural features have significant pathogenic or clinical implications (8). As a result, we agree with the conclusion of Brady that “it would be folly to subclassify patients on the basis that the variants look different” (4).

It is understandable why a nephropathologist when faced with a lesion such as ITG might want to make a morphologic distinction in the absence of clinical or serologic information. Clearly, the diagnosis of ITG, a diagnosis of exclusion in our practice, requires communication between the nephropathologist and the nephrologist and a thorough clinical and serologic evaluation. We continue to use the diagnosis of ITG (or fibrillary glomerulonephritis if one prefers) to describe patients with organized Ig deposits that are Congo red negative and not associated with a cryoglobulinemia or a paraproteinemia, irrespective of the size or the orientation of the fibrils. We reserve the term fibrillary glomerulopathy to denote the broader category of diseases (Figure 1) that are characterized morphologically by fibrils that are seen by electron microscopy without regard to their biochemical composition (7).

Clinical and Laboratory Features

There is nothing unique about the clinical or laboratory presentation or course of ITG that would allow one to distinguish it from other primary glomerulopathies. Patients with ITG range in age from 10 to 81 yr, but, on average, they have been 44 yr of age at presentation (3,4,6,7,9). More than 90% of the patients are white, and men compose from 47 to 61% of cases (3,6,11). Proteinuria is the presenting feature in all patients, with nephrotic syndrome being described in 60 to 70% of cases. Hypertension and microscopic hematuria are common and present in >65 and >70% of patients, respectively. Renal insufficiency is seen at the time of diagnosis in >45% of patients (3,6,9).

In our approach to the diagnosis of ITG, the serologic evaluation for cryoglobulins and paraproteins (by immunoelectrophoresis or immunofixation of serum and urine) is, by definition, negative in ITG. Serum complement levels generally are normal. However, up to 19% of patients may have a low titer antinuclear antibody, often in a speckled pattern (3,9,16). Nonetheless, patients with ITG do not have clinical SLE and, in general, have no evidence of a systemic disease process.

Extrarenal involvement in ITG is extremely rare, with organized Ig deposits having been described in only four cases (17–20). Liver involvement was described in two cases (18,19), and lung (17) and cardiac involvement (20) was found in the remaining two cases. In each instance, there was clinical evidence of disease. Unlike amyloidosis and monoclonal Ig deposition diseases, deposits have not been demonstrated in clinically uninvolved organs studied at autopsy (21). On the basis of the lack of evidence for systemic involvement in the overwhelming majority of cases, ITG invariably presents as a primary glomerulopathy.

Although some have suggested that ITG may be associated with an underlying lymphoproliferative disorder, the overall prevalence of a lymphoproliferative malignancy in patients with ITG is <3% when patients with cryoglobulinemia and paraproteinemia are excluded (3). Furthermore, patients with ITG rarely develop clinical or serologic evidence of a systemic disease or a dysproteinemia (6). Thus, the pathogenic process in ITG primarily involves the glomeruli, which distinguishes the lesion from the other Ig-derived FGN (7).

Pathology

The primary pathology of ITG is confined almost exclusively to the glomeruli, reflecting the location of the microfibrils in the mesangium and the glomerular capillary walls (6,12). By light microscopy, mesangial expansion by periodic acid–Schiff–positive material with only a mild mesangial hypercellularity is observed in up to 95% of cases (4,8,9). Glomerular capillary wall pathology also is observed in 95% of cases, may be focal or diffuse, and consists of thickening and complex staining patterns that are seen with methenamine silver–periodic acid–Schiff (Jones) stain, including reticular patterns, spikes, and double contours. Proliferative glomerulonephritis with cellular and fibrocellular crescents and segmental necrotizing lesions have been described in up to 30% of patients (4,5,9,22,23). However, we have not seen these lesions in ITG when systemic diseases such as cryoglobulinemia, paraproteinemia, and SLE have been excluded (6,8,16). Most important, the glomeruli, tubulointerstitium, and vessels are negative for amyloid by Congo red and thioflavin-T stains. Evaluation of extraglomerular structures demonstrates no specific vascular or tubulointerstitial lesions in ITG.

The principal findings by fluorescence microscopy are the presence of Ig and complement in a pattern that precisely reflects the distribution of the fibrils by electron microscopy and glomerular mesangial and capillary wall pathology by light microscopy (6,12). The capillary wall deposits are either diffuse and coarsely granular or discontinuous and pseudolinear. Tubular basement membrane, interstitial, and vascular deposits, determined by fluorescence microscopy, have not been observed. The Ig class that is seen in the majority of cases is IgG (IgG 94%, IgA 60%, IgM 29%), and in 80% of cases, both κ and λ light chains are seen. Despite the absence of a paraprotein, monoclonal Ig deposits have been seen in approximately 20% of cases of ITG studied with light-chain antisera, and κ light-chain restriction was present in all cases, usually in combination with IgG heavy chain (8). A study of IgG subgroups found IgG4 as the dominant subclass with weak staining for IgG1 and absent IgG2 and IgG3 (9), and monoclonal IgGκ was reported in one case, not associated with a paraproteinemia, with 35 nM microtubular deposits (2).

The ultrastructural appearance of ITG is characterized by the glomerular deposition of extracellular elongated, nonbranching microfibrils/microtubules that have neither periodicity nor.
logenesis in ITG may be analogous to amyloidosis but without the presence of amyloid P component raises the possibility that fibril-associated (fibronectin and fibrillin) proteins (24,25). The presence of amyloid-associated, basement membrane–associated (type IV collagen as well as amyloid P component but do not contain other proteins) deposits that involve the tubular basement membrane or interstitium are rare and have been demonstrated in <2% of cases of ITG (16,22,23).

The size of the fibrils varies from being slightly larger than those seen in amyloid (10 to 12 nM) to as large as 49 nM (Figure 2A). However, in almost 50% of cases, the fibril diameters have a mean value of 18 to 22 nM (Figure 2B) (8). Although there is variability of fibril size among cases, the fibrils in a given case are remarkably consistent in appearance wherever they appear in the glomerulus. The cross-sectional appearance varies from a solid dot to microtubules with either a thin or a thick wall. Examination of the fibrils at high magnification reveals a central core and a wall of varying thickness. Fibrils have a variable length and can appear long and straight or short and curved. They usually are present within a granular, electron-dense matrix, suggesting that only part of the deposit is aggregated into fibrils. In the majority of cases, the microtubules are arranged randomly on cross-section (Figure 2B), whereas in other cases, the microtubules seem to be in tightly packed parallel bundles (Figure 2A).

Pathogenesis and Pathophysiology

The composition of the fibrils in ITG has been evaluated carefully using immunoelectron microscopy. With the use of this technology, it has been shown that the fibrils in patients with ITG contain Ig (both heavy and light chains) and complement as well as amyloid P component but do not contain other amyloid-associated, basement membrane–associated (type IV collagen and heparan-sulfate proteoglycans) or microfibril-associated (fibronectin and fibrillin) proteins (24,25). The presence of amyloid P component raises the possibility that fibrillogenesis in ITG may be analogous to amyloidosis but without resulting in the critical β-pleated sheet formation.

In the usual physiologic environment, intact normal Ig do not crystallize readily. In ITG, the propensity to form microtubular structures or tactoids suggests that the deposits are composed of a uniform substructure with strong intermolecular attraction. Therefore, one can speculate that the formation of immunotactoid deposits is the result of immune complexes’ having a uniform structure or an abnormal production of monoclonal Ig that perhaps have an unusual or abnormal structure. These may be produced in such small quantities that they escape detection with standard serologic evaluation, because patients with ITG, by definition, do not have evidence of a circulating cryoglobulin or a paraprotein. The deposition of the Ig within the glomerulus along the filtration surface of the glomerular capillary wall may be a consequence of the unique environment that is created by the ultrafiltration of plasma (6,16). The increased concentration of protein that occurs along the glomerular capillary as a consequence of ultrafiltration may account for the tendency of the deposits to form exclusively within the kidney.

Structural alterations along the filtration surface of the glomerulus also may be important and predispose to fibril formation. In mice, absence of CD2-associated protein, a protein that binds to nephrin and is important in the function of the podocyte slit diaphragm, results in congenital nephrotic syndrome and glomerular ultrastructural pathology similar to that seen in ITG in humans (26–29). Thus, glomerular deposits in ITG may result from acquired defects in critical podocyte cellular functions that are involved in the clearance of filtered and retained Ig.

Although the cause of ITG is unknown, the heterogeneity of the immunopathology suggests that more than one cause is responsible for the production of fibrils with a common morphologic appearance. In this respect, it may be similar to amyloidosis, which is widely known to have various disease states that are capable of producing different proteins that have in common the capacity to form the highly organized β-pleated sheet structure. Because immunotactoids may be composed of either immune complexes or monoclonal proteins, which are capable of forming tactoids or microtubules, the variability in the size and the orientation of the tactoids from one patient to another may be a result of concentration or biochemical composition of the protein similar to that described in cryoglobulinemia. Alternatively, the variability in ultrastructural morphology among patients with ITG may be analogous to the morphologic heterogeneity in hemoglobin S described in the hemoglobinopathy of sickle cell anemia (30). The morphology of deoxygenated hemoglobin S in sickle cell disease depends on the concentration of hemoglobin S and the rate of tactoid formation. Under circumstances in which they form slowly, the tactoids are aligned in parallel, forming a paracrystalline structure. In contrast, the more rapidly the tactoids are formed, the more random the orientation to one another (30). Consistent with this theory is a recent report of a patient who had ITG and was found to have biochemically identical fibrils in the glomeruli and in a serum precipitate that formed after 4 mo in cold storage (31). However, the ultrastructural morphology differed significantly between the fibrils. The fibrils in the glomeruli were 15 to 20 nM in diameter and arranged randomly, whereas those in the serum precipitate were 70 nM and organized in parallel bundles. Therefore, as in hemoglobin S, the variability in morphology that is observed among patients with ITG may result from physicochemical factors that are involved in fibrillogenesis.

The pathogenesis of ITG may be immunochemically diverse, with the unifying feature being the ultrastructural organization of the deposits. In the appropriate setting, immune complexes or Ig are capable of forming fibrils or microtubules (tactoids) in...
the glomerular capillary wall or mesangium. Unfortunately, the disease(s) responsible for the production of the immune material in the tactoids of ITG has not been determined in the patients who have been described to date.

**Prognosis and Treatment**

The clinical course of patients with ITG is one of progressive renal failure. More than 50% of patients progress to ESRD over 2 to 5 yr (3,5,6,9). This is similar to other primary glomerulopathies but is distinct from that of the other fibrillary glomerulopathies, which induce a more rapid decline to ESRD (7). Patients who present with hypertension, nephrotic syndrome, and renal insufficiency are at greatest risk for progression to ESRD (3,5,6,16). Histologically, patients with more extensive glomerular deposits, those with crescentic or necrotizing lesions, and those with advanced interstitial disease have a poorer prognosis (5,16).

The response to treatment in ITG generally has been poor. A recent report described three nephrotic patients who had normal serum creatinines and mesangial proliferative ITG and achieved a remission in proteinuria with the use of prednisone (1 mg/kg per d for 6 to 15 mo) (32). However, therapeutic trials with steroids alone, steroids with cytotoxic agents, and steroids with plasmapheresis, reported in 33 patients, have resulted in clinical remission of proteinuria in <10% of patients (8).

Patient survival in ITG is quite good, as one might expect with a primary glomerulopathy: The 1-yr survival rate is 100%, and >80% of patients are alive at 5 yr (6,8,16). As a result of the favorable patient survival, renal transplantation should be a treatment consideration for patients with ITG. The outcome of renal transplantation has been reported in 14 patients with ITG with 2 to 13 yr of posttransplantation follow-up (10,21,23,33,34). Recurrence of ITG has been demonstrated in six (43%) of these patients from 2 to 9 yr after transplantation, and in three cases, this resulted in the loss of the graft. In the remaining patients with recurrent disease, renal function continued to be adequate after 5 to 11 yr of follow-up (3,21,23). The rate of deterioration in renal function in patients with recurrent disease has been shown to be slower than with their original disease (3). One possible explanation for the slower progression is a result of the effect of immunosuppression (3). In patients with recurrent disease, the ultrastructural morphology in the transplants was similar to that originally seen in the native kidneys (21,23,34). Therefore, although recurrent disease does occur in ITG, it usually occurs late after transplantation and does not result inevitably in graft loss.

**References**


