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Immunotactoid Glomerulopathy of 10-Years' Duration: Insights Gained From Sequential Biopsies

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INTRODUCTION

Immunotactoid glomerulopathy (ITG) is a rare entity, occurring in 0.06% to 0.1% of native kidney biopsies.[1] The distinctive feature of ITG is the presence of glomerular deposits of Ig, most often of the monoclonal or oligoclonal type, with a distinctive substructural organization as microtubules, which in most cases are 30 to 50 nm in diameter as revealed by electron microscopy.[1] Underlying medical conditions such as lymphoid malignancy, diabetes, alcoholic cirrhosis, psoriasis, and rheumatoid arthritis have been reported in association with ITG.[2,3] ITG may have a better prognosis than other paraprotein-related renal lesions.[3,4] However, due to the rarity of this renal disease and limited duration of follow-up in most reported cases, few data are available regarding long-term outcomes. We describe a case of ITG in a patient with relatively stable renal function and histopathologic findings over a 10-year course but with persistent proteinuria, until the development of rapidly progressive renal failure due to a superimposed antineutrophil cytoplasmic antibody (ANCA)–associated crescentic glomerulonephritis. The sequential biopsy specimens showed comparable diagnostic ultrastructural features, but a changing and evolving pattern of glomerular deposition of Ig light chains over time not previously recognized for this disorder.

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CASE PRESENTATION

A 56-year-old Alaska Native woman with a 5-year history of rheumatoid arthritis was referred to a nephrologist for the management of nephrotic syndrome. The patient's history was notable for hypertension and hypothyroidism secondary to remote thyroiditis. At the initial diagnosis, her rheumatoid arthritis met 4 of 7 of the American College of Rheumatology 1987 criteria: hand/wrist involvement, bilateral symmetry of the arthritis, >3 joints involved, and a circulating rheumatoid factor.[5] The treatment for her rheumatoid arthritis included methotrexate (discontinued soon after initiation due to nausea and vomiting), hydroxycloroquine, and etanercept (a tumor necrosis factor-α inhibitor). She was noted to have lower extremity edema; the remainder of her physical examination was unremarkable. Laboratory studies showed the following values: serum creatinine, 0.6 mg/dl, hemoglobin, 11.1 g/dl; hematocrit, 32.4%; white blood cell count, 7.6 $\times$ 10^3/μl; platelet count, 341.000/μl; serum albumin, 1.7 g/dl; serum total protein, 5.5g/dl; and normal liver function test results (Table 1). Urine studies revealed microscopic hematuria and a urine protein-creatinine ratio of 13 g/g with measured proteinuria of 10.7 g/24 h. Serologic tests were negative for antinuclear antibody, anti–double-stranded DNA antibody, ANCA, antiglomerular basement membrane antibody, anti-HIV, and anti–hepatitis B and C virus antibodies. Rheumatoid factor was highly positive (1230 IU/ml). Complement levels were normal. Serum and urine protein electrophoresis and immunofixation study results were negative for a monoclonal

Table 1. Initial laboratory findings at first presentation

Parameter	Value (reference range)
Creatinine (mg/dl)	0,6 (0.6–1.2)
Hemoglobin (g/dl)	11.1 (12–16)
Hematocrit (%)	32.4 (37–47)
White blood cell count (×103/μl)	7.6 (4.5–13.5)
Platelet count (/μl)	341,000 (150,000–400,000)
Serum total protein (g/dl)	5.5 (6.4–8.0)
Serum albumin (g/dl)	1.7 (3.2–5.5)
Spot urine protein-creatinine ratio (g/g)	13 (<0.3)
Proteinuria (g/d)	10.7 (<0.2)
Rheumatoid factor (IU/ml)	1230 (<15)
Antinuclear antibody	Neg (neg)
Anti–double-stranded DNA antibody	Neg (neg)
Anti–neutrophil cytoplasmic antibody	Neg (neg)
Anti–glomerular basement membrane	Neg (neg)
Hepatitis C antibody	Neg (neg)
Serum protein electrophoresis	No M-spike
Urine protein electrophoresis	No M-spike
Serum cryoglobulins	Neg (neg)

Neg, negative.

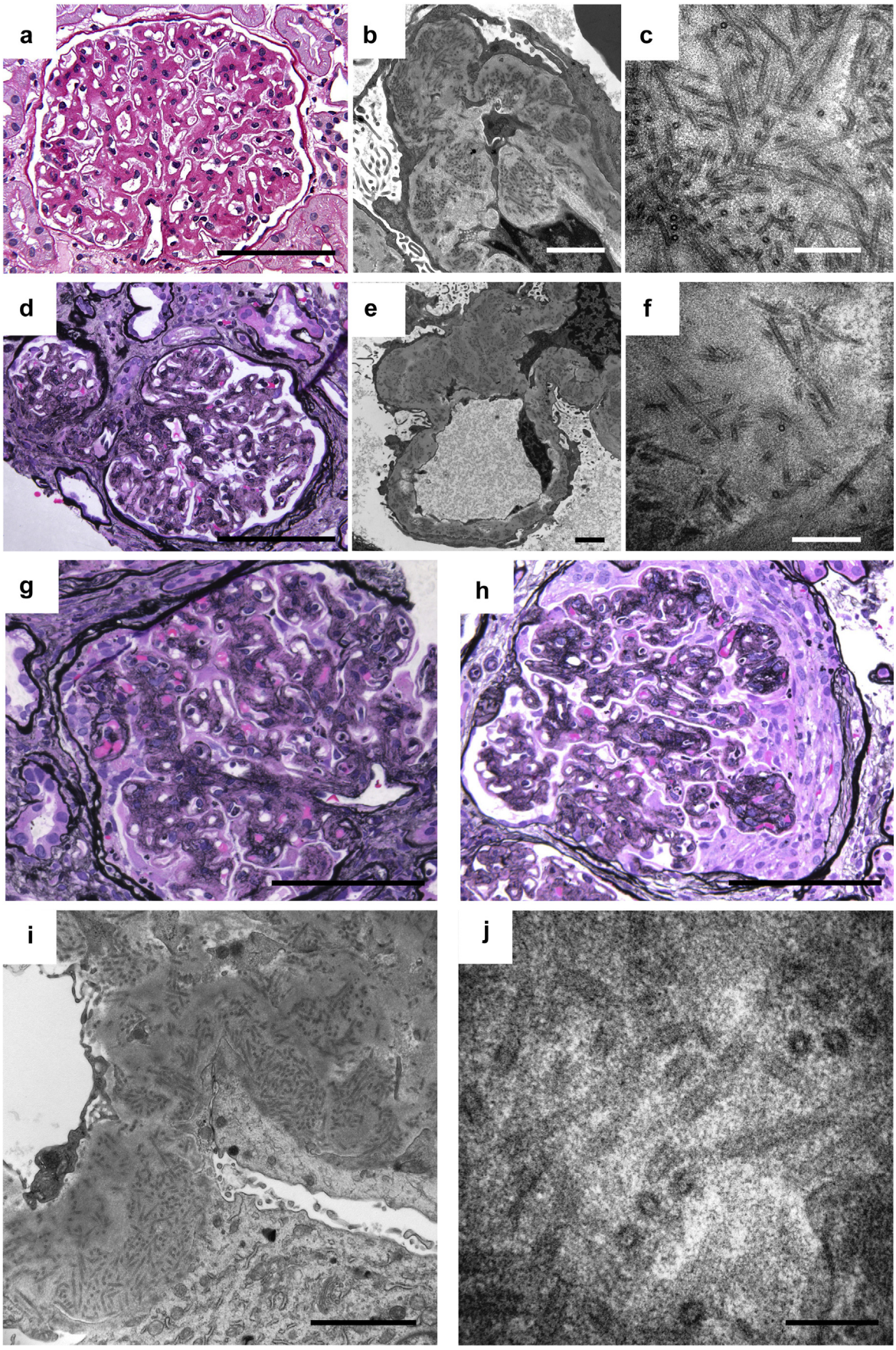
protein. Testing for circulating cryoglobulins was negative.

A kidney biopsy specimen showed abnormal glomeruli due to diffuse infiltration of the capillary walls and mesangium by silver-negative and periodic acid–Schiff–positive acellular material (Figure 1a). The glomerular capillary walls were diffusely thickened and exhibited focal and segmental glomerular basement membrane duplication, conferring a membranoproliferative pattern of injury. Immunofluorescence (IF) microscopy revealed confluent granular staining, predominantly of capillary walls but also involving the mesangium, for IgG (4+), C3 (3+), κ light chains (4+), and λ light chains (4+). Staining of significantly lesser intensity but with a comparable pattern was observed in glomeruli for IgA and IgM. There was no significant glomerular staining of C1q and fibrinogen. Electron microscopy showed diffuse thickening of the capillary loops due to massive accumulation of organized electron-dense deposits (Figure 1b and c). The deposits were predominantly intramembranous but also extended into subepithelial spaces and mesangial regions. The deposits had a microtubular configuration and were focally arranged in parallel arrays. These microtubules measured ~30 nm in diameter on high-power examination. The diagnosis at that time was ITG, despite the evidence of polyclonal Ig deposits, which are uncommon in cases in which characteristic immunotactoids are present.

Following biopsy, in the absence of a monoclonal Ig deposition disorder, the patient was started on conservative therapy with lisinopril (20 mg/d), which led to a partial remission of the proteinuria. After 1 year of therapy, the patient's protein excretion was reduced to 0.95 g/24 h with a serum albumin of 2.8 g/dl. Four years later, she presented with relapse of the nephrotic syndrome and was then treated with oral prednisone with a progressive tapering dose and tacrolimus; etanercept treatment was temporarily suspended. Although the patient initially showed a good response, with the urine protein-creatinine ratio decreasing to 1.7 g/g, she never reached a complete remission of the proteinuria.

Eight years later, the patient presented again with a relapse of the nephrotic syndrome and a recrudescence of her rheumatoid arthritis with recurrent swelling of the right knee and pericarditis. Serum creatinine remained stable at 0.5 mg/dl. Notably, serum protein electrophoresis now demonstrated an IgG-κ monoclonal protein, and testing for cryoglobulins revealed a trace cryoprecipitate with a measured cryocrit of 0.1%. A bone marrow biopsy showed normocellular marrow with no evidence of a plasma cell or lymphoproliferative disorder. A repeat kidney biopsy (biopsy 2, Figure 1d–f), showed persistent ITG, although this time, a partial bias of glomerular staining for κ over λ light chains (2+ vs. 1+) was observed by IF patterns with distributions of κ and λ similar to IgG (staining intensity 3–4+) and C3 (3+) and similar to the pattern seen on biopsy 1 (Figure 2a). Electron microscopy again demonstrated numerous electron-dense deposits, organized as microtubules with an average measured diameter of 38 nm, present in glomerular capillary walls in subendothelial and intramembranous locations and in mesangial regions (Figure 1e and f). Tacrolimus was stopped, and she was treated with rituximab infusions (3 doses of 1000 mg each, with the third dose given 1 year after the first). This regimen resulted in improvement of her rheumatoid arthritis symptoms, but no significant effect on her proteinuria, which persisted in the nephrotic range.

Ten years after the initial episode of nephrotic syndrome, worsening kidney function developed (serum creatinine of 3.1 mg/dl). Urinalysis revealed hematuria with dysmorphic red blood cells, and the urine protein-creatinine ratio was 9.7 g/g. Serologic studies were notable for the presence of circulating perinuclear ANCA (titer not reported), rheumatoid factor >1200 IU/ml, and a strongly positive cyclic citrullinated peptide antibody. SPEP revealed biclonal IgG-κ and IgG-λ paraproteins. The serum-free light-chain ratio was 1.33 (normal values, 0.26–1.65). A repeat kidney biopsy (biopsy 3) at this time contained up to 17 glomeruli per level section, of which 1 to 2 were globally sclerosed. The biopsy revealed a focally crescentic glomerulonephritis superimposed on the previously observed findings of ITG (Figure 1g and h). Two to 3 glomeruli per level section (12%–18% of the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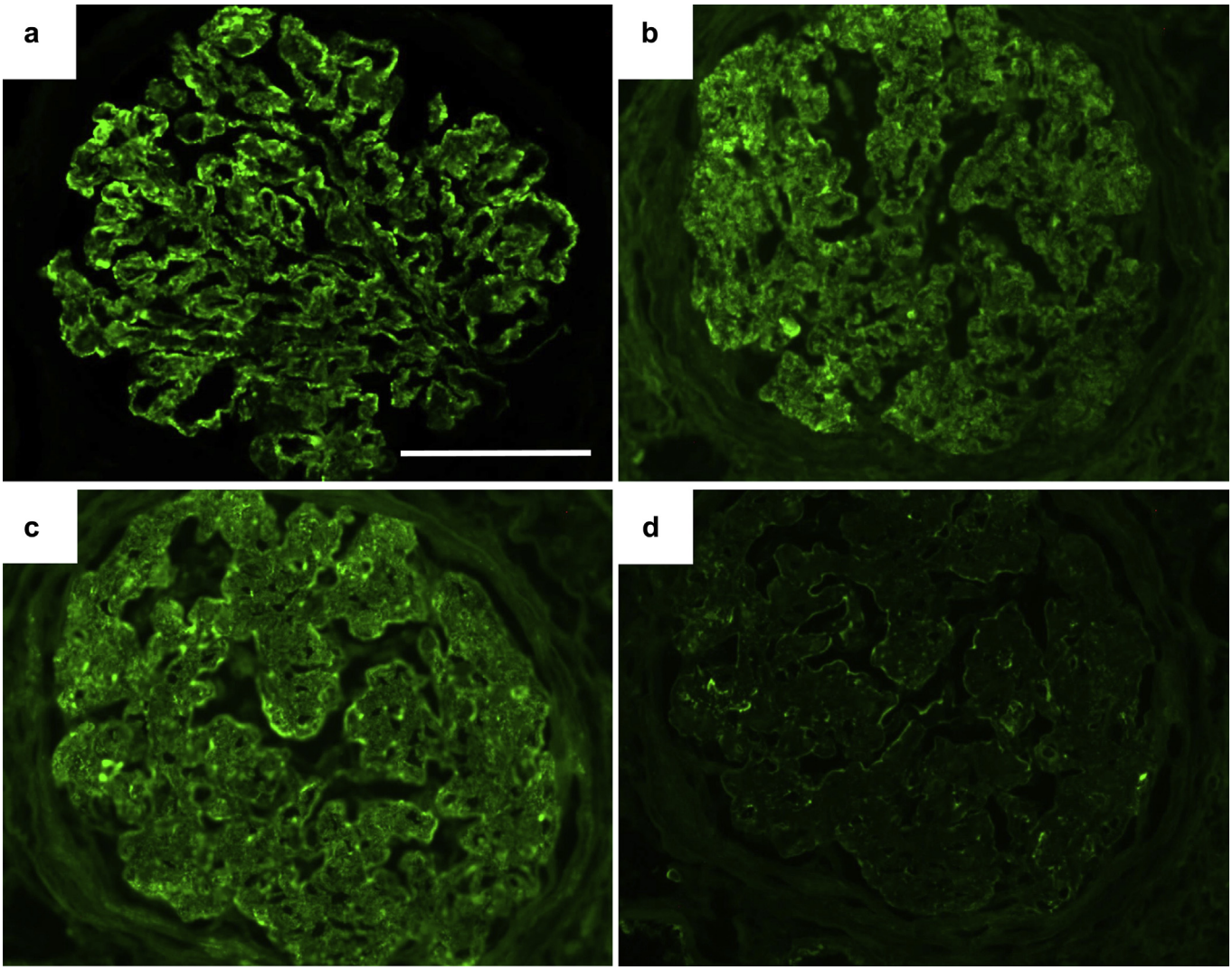

Figure 2. Immunofluorescence studies: intense granular staining in the mesangial areas and peripheral capillary walls for IgG in the 8-year (a) and 10-year (b) follow-up biopsies. A biased glomerular staining for κ (c) over λ (d) light chains was present in the 10-year follow-up biopsy (a similar but slighter bias in light-chain staining was observed in the 8-year biopsy [not shown here]). Bar = 100 μm.

intact glomeruli) were involved by cellular crescents without concurrent segmental necrosis of the glomerular tufts. No fibrous/fibrocellular crescents were seen. Five pecent to 10% of the glomeruli per level section were globally sclerosed. The remaining glomeruli showed diffuse thickening of capillary walls due to accumulation of silver-negative eosinophilic material and diffuse endocapillary hypercellularity with prominent leukocyte influx into glomerular capillaries. A strongly biased glomerular staining for κ (2+) over λ light chains (absent staining) was demonstrated by IF, and there was persistent staining of IgG (3+) in a distribution equivalent to that of the staining for κ light chain (Figure 2b–d). Electron microscopy again

Figure 1. Histologic findings of the initial biopsy (a–c) and the biopsy at 8-year (d–f) and 10-year (g–j) follow-up. (a) Light microscopy of the initial kidney biopsy specimen showed diffuse thickening of mesangial regions and glomerular capillary walls due to accumulation of extracellular material. Diffuse endocapillary hypercellularity with leukocyte influx was also present. Similar histologic findings were present at 8-year (d) and 10-year (g) follow-up, although in the last renal biopsy, 15% to 40% of the glomeruli per level section were involved by cellular crescents (h). Electron microscopy showed massive accumulation of organized immune-type deposits in both capillary loops and mesangial regions. On high-power examination, the deposits had a characteristic microtubular configuration and were focally arranged in parallel arrays. These ultrastructural findings were present on the initial biopsy (b,c) and at 8-year (e,f) and 10-year follow-up (i,j). (a) Periodic acid–Schiff stain, original magnification ×480. (d,g,h) Jones silver stain, original magnification ×480. (b) Original magnification ×12,000. (c) Original magnification ×54,800. (e) Original magnification ×4800. (f) Original magnification ×49,000. (i) Original magnification ×11,000. (j) Original magnification ×98,000. Bars = 100 μM (a), 2 μm (b), 500 nM (c), 100 μM (d), 2 μM (e), 500 nM (f), 100 μM (g,h), 2 μM (i), and 200 nM (j).

showed glomerular microtubular deposits similar in size, appearance, and distribution to those identified in the previous biopsies (Figure 1i and j). Extraglomerular deposition of immunotactoids was not detected in this or any of the previous biopsies. The patient was treated with oral prednisone (20 mg/d) and rituximab infusions (2 doses of 1000 mg and 590 mg, respectively). Her renal function improved, and the serum creatinine level at hospital discharge was 1.7 mg/dl.

Two months after discharge, she was readmitted with shortness of breath, bilateral pleural effusion, and anasarca, likely a manifestation of her persistent nephrotic syndrome (urine protein-creatinine ratio at that time was 10 g/g). At this time, an ANCA screen by immunofluorescence was negative for perinuclear ANCA and cytoplasmic ANCA, and testing for myeloperoxidate and proteinase-3 antibody was negative by enzyme-linked immunosorbent assay. Thoracentesis showed a transudate. Anti–glomerular basement membrane antibody titers were not obtained at this time.

DISCUSSION

ITG is a glomerular disease characterized by the accumulation of Congo red–negative deposits with a characteristic ultrastructural morphology of thick microtubules, measuring in most cases 30 to 50 nm in diameter[1,4,6,7] and typically staining for IgG and complement component C3 by IF. The majority of cases indicate the deposition of monoclonal or oligoclonal Igs based on staining of the deposits for either κ or λ light chains, but not both (69% of cases in the series of Nasr *et al*. [3]). Initial descriptions of ITG by some groups also encompassed a pattern of glomerular injury that is now recognized as a separate entity (fibrillary glomerulonephritis). When defined as a more limited entity with deposits of microtubules, ITG is a rare condition, occurring one-tenth as frequently as fibrillary glomerulonephritis.[2,8]

In terms of pathologic findings, 56% of the patients from the largest series showed a membranoproliferative pattern of glomerular injury by light microscopy.[3] On IF, 88% of cases from the same study showed glomerular positivity for IgG, including 12% of cases that also showed glomerular positivity for IgM of similar intensity (2+). ITG occurs in an older population, with most reported patients older than 50 years of age. More than one-half of the patients present with nephrotic syndrome, but many also have a nephritic presentation with features of microscopic hematuria and renal insufficiency, occurring, respectively, in 80% and 50% of cases in the study of Nasr *et al.*,[3] the largest series reported to date.[2,3] These patients have a significant predisposition for an underlying lymphoplasmacytic disorder (38% in the study of Nasr *et al.*[3] and 33% in the study of Rosenstock *et al.*[2]), with several additional patients in the series of Rosenstock *et al.*[2] showing a circulating monoclonal protein without other overt features of lymphoplasmacytic neoplasia; it is unknown whether subsequently on further follow-up, overt neoplasia developed in any of these patients. This predisposition is supported by IF studies on renal biopsy specimens in which clonality of the deposits can often be demonstrated. Different concomitant medical conditions have been reported in patients affected by ITG, such as diabetes, psoriasis, alcoholic cirrhosis, and melanoma.[2–4] To our knowledge, there is just 1 report describing concomitant ITG and rheumatoid arthritis.[9]

On initial presentation with nephrotic syndrome, our patient lacked evidence of a concurrent lymphoplasmacytic disorder by either biopsy or by serologic studies. Curiously, in our case, although the first renal biopsy specimen demonstrated the absence of staining restricted to 1 light-chain subclass by IF, the second and third biopsy specimens, obtained 8 and 10 years after initial presentation, showed a biased glomerular staining for κ over λ light chains. That finding was accompanied by an IgG-κ paraprotein newly detected in the serum, in the absence of an underlying lymphoproliferative disorder.

This case provides the unique opportunity to describe the evolution of ITG, a rare disease, over a 10-year period of observation after the initial biopsy. Due to the lack of large studies, data on long-term outcome and appropriate therapy for ITG are limited. In the study of Nasr *et al.*,[3] only 17% of patients with ITG progressed to end-stage renal disease after a mean follow-up of 48 months. In those patients with underlying lymphoma, the remission of the nephrotic syndrome was achieved in some after successful treatment of the hematologic malignancy. The rest of the patients reported by Nasr *et al.*[3] showed a very variable disease course; 1 patient maintained renal function after 83 months of follow-up.

Our case demonstrates that ITG may follow an indolent disease course. Despite the relative inefficacy of the immunosuppressive therapies in controlling the proteinuria in our patient, her excretory renal function remained stable for many years. The histologic manifestations correspondingly demonstrated little evidence of progressive chronic kidney disease over this time. The third biopsy this patient demonstrated only 1 to 2 globally sclerosed glomeruli of the 6 to 17 glomeruli that were present per level section. The interstitial fibrosis and tubular atrophy were judged mild to moderate and relatively stable compared with the previous biopsy. However, rapid progression of the renal insufficiency due to a superimposed

ANCA-related crescentic glomerulonephritis prompted the last biopsy. Although focal cellular crescents were detected in 2 cases (13%) in the series of Nasr *et al.*,[3] crescents were not identified in the ITG cases in the series of Rosenstock *et al.*,[2] and crescents overall are not a common feature of ITG. In conjunction with the rapid change in the course and the presence of a circulating ANCA, it is highly likely that the crescents in this third biopsy were due to a superimposed ANCA-associated glomerulonephritis and not a manifestation of the long-standing ITG.

The evolving pattern of immunofluorescence findings in our case also provides a caveat for our diagnostic understanding of these cases. The development of an overt pattern of monoclonality of the light chain deposits evolved over an extended period of time. This case demonstrates that the finding of a specific immunofluorescence pattern in a kidney biopsy performed at a single time point may be misleading in characterizing the overall disease process, as the findings of biopsy 1 showed a polyclonal deposition process, whereas biopsies 2 and 3, performed 10 years later, revealed deposits that were clearly characterized as monoclonal or oligoclonal in nature. Yet it is typical for affected patients to undergo only a single diagnostic biopsy, which is accepted as providing an immutable characterization of deposited immunotactoids as monoclonal or not.

CONCLUSIONS

In summary, this patient with biopsy-proven ITG had a long and relatively indolent clinical course until it was interrupted by superimposed crescentic glomerulonephritis. Lessons that may be drawn from this case study include the following: (i) the diagnosis of ITG does not necessarily lead to end-stage renal disease, (ii) associated lymphoplasmacytic disorders commonly identified in patients with ITG may manifest years after the initial renal appearance of ITG, (iii) the manifestations of ITG may evolve over time with transformation from an initial composition of polyclonal Igs to 1 of oligoclonal or monoclonal deposits, and (iv) in the absence of an overt lymphoplasmacytic disorder, it is possible that relatively conservative therapy may be sufficient to control the functional abnormities consequent to the Ig deposition process.

DISCLOSURE

All the authors declared no competing interests.

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