EXCEPTIONAL CASE

Histologic regression of fibrillary glomerulonephritis: the first report of biopsy-proven spontaneous resolution of disease

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Abstract

Fibrillary glomerulonephritis (FGN) is a rare immune complex type glomerulonephritis characterized by glomerular deposition of randomly oriented fibrils measuring 10–30 nm in thickness, and typically presents with proteinuria with or without renal insufficiency and hematuria. We present a case in which a patient initially presented at age 41 years with nephrotic-range proteinuria and hypertension; a kidney biopsy showed FGN. The patient was treated with angiotensin receptor blockage only, without immunosuppression as per patient preference, and the level of protein in the urine improved. During the follow-up period of 17 years, the patient developed type 2 diabetes mellitus. The patient re-presented with nephrotic-range proteinuria 17 years later, at the age of 58 years. A kidney biopsy was performed and showed diffuse diabetic glomerulosclerosis with secondary focal segmental glomerulosclerosis and related vascular changes. There was no evidence of FGN by immunofluorescence or electron microscopy. Although FGN has been rarely reported to regress clinically, this is the first documented case of histologic regression of FGN. The potential for FGN fibrils to regress spontaneously is important in the management of FGN patients considering that currently available immunosuppressive agents have limited efficacy, and is an encouraging finding for future studies aiming to find a cure for the disease.

Key words: diabetic nephropathy, fibrillary glomerulopathy, immune complex glomerulonephritis, immunosuppressive therapy, kidney biopsy

Background

Fibrillary glomerulonephritis (FGN) has an incidence of 0.6–1% amongst native kidney biopsies, and typically presents between 46 and 65 years of age [1, 2]. The pathogenesis of FGN, while not entirely elucidated, is considered to be secondary to glomerular localization of immune complexes that deposit and form fibrillary substructures [3, 4]. FGN is idiopathic in most cases; however, concurrent autoimmune disease, malignancy and infection have been associated with FGN [5]. Histopathologic features characteristic for FGN include mesangial expansion or hypercellularity with occasional duplication of the glomerular basement membrane (GBM) [5–7]. The deposited material is usually strongly periodic acid–Schiff (PAS) but can be weakly PAS positive, and is Congo red negative [1]. Endocapillary proliferation, crescent formation and necrosis can been observed less frequently [5]. By electron microscopy (EM), electron-dense deposits can form in the GBM and/or mesangium, have fibrillary substructure haphazardly arranged, and fibril thickness ranging

from 10 to 30 nm. We present a case in which a patient is diagnosed with FGN, and managed without immunosuppressive therapy for 17 years. The patient then re-presented in a nephrotic state, and a subsequent kidney biopsy showed no histologic evidence of FGN. While there are data to show patients attaining clinical remission of disease without immunosuppressive therapy, this is the first example of histologic regression of FGN.

Case report

Clinical history and initial laboratory data

A non-Hispanic/Latino White male patient was initially referred to the Mayo Clinic at the age of 41 years for further evaluation of nephrotic syndrome and hypertension. The patient had a 5–6 year history of hypertension with poor control in light of regimen adjustments (managed with quinapril hydrochloride, atenolol and furosemide), and had developed dyspnea on exertion, marked lower extremity edema and was obese (body mass index of 40 kg/m^2). No other findings were noted on physical examination. Pertinent laboratory values included serum creatinine of 1.2 mg/dL, 24-h urine protein of 13.7 g/day, serum albumin of 2.3 g/dL and serum C3 of 92.5 mg/dL. Serologic studies were negative for hepatitis B viral surface antigen, hepatitis C viral antibody, anti-dsDNA, anti-nuclear antibody, antiphospholipid antibody, cryoglobulins and a monoclonal protein via protein electrophoresis. A kidney biopsy was obtained at the outside institution soon before being reviewed at our institution.

First kidney biopsy

In all, 14 glomeruli were present, one of which was globally sclerosed. Light microscopic evaluation showed mildly enlarged glomeruli, generalized glomerular capillary loop thickening with compromised lumina, fuchsinophilic deposits along capillary loop basement membranes as seen on the trichrome stain and segmental splitting and remodeling of peripheral capillary loop basement membranes by silver stain (Figure 1). GBM spikes or spicules were not present. The mesangium was diffusely expanded by eosinophilic material that was weakly PAS positive. Crescents, endocapillary proliferation and necrosis were absent. There was minimal interstitial fibrosis or tubular atrophy, with focal areas of lymphocytic infiltration and rare foam cells. Mild hyalinosis of arteries and arterioles was present. A Congo red stain was negative for amyloid.

Immunofluorescence (IF) microscopy showed smudgy granular capillary wall and mesangial deposits staining for IgG (4+ diffuse, on a 0–4+ scale), C3 (2+), C1q (1–2+), and kappa and lambda light chains (3+). There was trace patchy staining of capillary walls for IgA. IgM staining was absent.

EM was notable for thickening of the GBM with deposition of randomly oriented fibrillary material (Figure 1E and F). Deposition of similar fibrillary material was found in the mesangium. The mean fibril diameter was 15 nm with a standard deviation of ± 0.3 nm, as calculated after the measurement of 21 fibrils. The podocyte foot processes were diffusely effaced. Tubular basement membranes were thickened but without electron dense deposits.

Diagnosis

A diagnosis of FGN was made.

Clinical follow-up

After pathologic examination of the patient's kidney biopsy and clinical evaluation by the nephrology service at our institution, the patient was given the option but elected not to undergo an immunosuppressive treatment regimen. Atenolol was replaced by labetalol, and the angiotensin-converting enzyme inhibitor quinapril hydrochloride was continued. Within the following month the patient's serum creatinine increased to 2.0 mg/dL, however renal functional indices improved over 3 months with serum creatinine decreasing to 1.6 mg/dL, serum albumin increasing to 3.8 g/dL and 24-h urine protein decreasing to 2.9 g/day. The patient's renal function would stabilize and would remain so for ~17 years. There was no evidence of malignancy at this juncture, and after almost 17 years of follow-up no evidence of malignancy would be detected either.

The patient, now 58 years old, presented for re-evaluation after stable renal function over the elapsed period, now having developed nephrotic syndrome characterized by peripheral edema, slightly low serum albumin (3.4 mg/dL), increased proteinuria with a urine protein to creatinine ratio of 6.0 g/g and trace blood on urinalysis. The serum creatinine had been stable at ~1.6 mg/dL for the prior 12 years, but with a recent increase to 2.4 mg/dL. During the elapsed period the patient also was diagnosed with type 2 diabetes mellitus 7 years after the initial kidney biopsy. A second kidney biopsy was performed to determine the etiology of the increased proteinuria and worsening of renal function.

The second kidney biopsy showed features compatible with diffuse diabetic glomerulosclerosis with secondary focal segmental glomerulosclerosis and severe vascular disease (arteriosclerosis and arteriolar hyalinosis) (Figure 1). A Congo red stain was negative for amyloid. What was notable after review with all microscopic imaging modalities was the absence of evidence of FGN. Glomeruli were negative for IgA, IgG, C1q, fibrinogen, and kappa and lambda light chains by IF microscopy, and IgM (1+) and C3 (1–2+) stained only scarred portions of glomeruli. EM examination of two glomeruli showed an expanded mesangial matrix and thickened GBMs but did not show any fibrillary substructure within the mesangium or GBMs (Figure 1J).

Discussion

The presented case is the first report to describe histologic regression of FGN, and in this case in the setting of not having received immunosuppressive therapy. In the case series by Nasr et al., of 16 FGN patients that had not received any disease-directed therapy, a single patient had 'complete clinical remission' of disease and seven patients had 'partial clinical remission' of disease [5]. Complete clinical remission was defined as proteinuria of <500 mg/day with normal renal function. Partial clinical remission was defined as a reduction of proteinuria by at least 50% and to <2 g/day with stable renal function characterized by not >20% increase in serum creatinine [5]. However, in those instances biopsy-provided evidence of histologic regression of disease was not available. Risk factors for worse outcomes in patients with FGN include higher serum creatinine and 24-h urine protein at the time of biopsy, older age and a greater proportion of globally sclerosed glomeruli [5]. Of these risk factors, our patient only had one: a 24-h urine protein excretion of 13.7 g/day. As such, one could have possibly anticipated at the time of diagnosis a less rapid progression to end-stage kidney disease as seen with this patient.
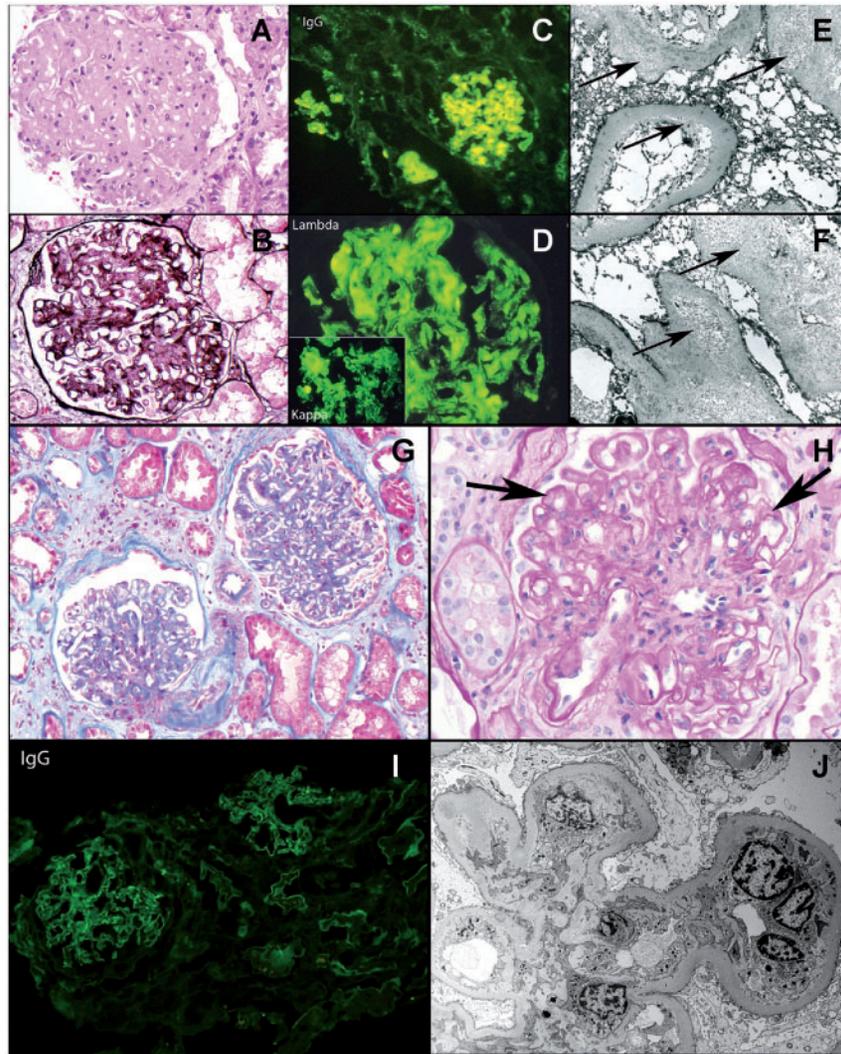
Fig. 1. First kidney biopsy (**A–F**). By light microscopy, the glomerular capillary loops show marked thickening and there is mesangial matrix expansion (hematoxylin and eosin (A); the expanded mesangium stains negatively or weakly on a silver stain, and there is segmental GBM duplication or remodeling [Jones methenamine silver, (B)]. By IF, the glomeruli show bright mesangial and capillary loop smudgy mesangial staining for IgG (C), C3 (not shown), and kappa and lambda light chains (D). By EM, fibrillary deposits are seen along the GBMs and within the mesangium (E and F, arrows). Second kidney biopsy (**G–J**). By light microscopy, the glomeruli show thickened capillary loops and mesangial matrix expansion; arteriolar hyalinosis is present as well [Masson trichrome, (G)]. On a PAS-stained section, GBM duplication and remodeling is still seen (arrows) and there is weakly PAS-positive mesangial matrix expansion [PAS, (H)]. By IF, there is linear glomerular and tubular basement membrane staining for IgG but the glomeruli show minimal granular staining for IgG (I), C3, and kappa and lambda light chains (not shown). By EM, the GBMs are thickened and there is mesangial matrix expansion, without fibrillary deposits (J). Original magnifications for A–C, G and I at $\times 200$; for D and H at $\times 400$; for E and F at $\times 20\,000$; for J at $\times 6000$.

The diagnosis of FGN typically portends a poor prognosis, with approximately half of the patients progressing to end-stage kidney disease within a few years [1, 3, 5]. Unfortunately there is no established therapy specific for FGN, but the therapy generally consists of immunosuppression. Immunosuppressive treatments for FGN have included corticosteroids, cyclophosphamide, cyclosporine, mycophenolate mofetil, melphalan hydrochloride, lenalidomide, rapamune, azathioprine and rituximab [1, 5]. Renin angiotensin system (RAS) blockade also has been used as part of the management of FGN patients, and in the case series by Nasr *et al.* 'complete clinical remission' was achieved with RAS blockade alone in 2 of 16 patients [5]. Renal transplantation is a therapeutic option with end-stage kidney disease, and while the risk of FGN recurrence in the allograft should be considered, this does not seem to necessarily correlate with loss of allograft function [8]. A range of 36% to almost half of transplanted kidneys

redevelop primary disease, and recurrence seems to be greater in patients with associated hematologic dyscrasias [5, 8, 9]. A case report describing the usage of plasmapheresis in the management of a patient with FGN showed at least immediate decrease of proteinuria, though no larger studies to date have thoroughly examined this therapeutic procedure in the setting of FGN [10]. Recent studies have vetted the efficacy of rituximab-based treatment regimens, with the largest group of patients retrospectively analyzed showing halt of disease progression in 4 of the 12 patients [11, 12]. The true efficacy of rituximab containing therapies will need to be determined with properly structured clinical trials.

It is apparent that in certain instances FGN can have a benign course with clinical remission, and as illustrated in our case, the possibility of histologic regression, which appears to be different from immunoglobulin-derived amyloidosis in which amyloid fibrils do not regress even after successful therapy [13–15]. The

underlying pathologic process that drives this glomerular disease—whether it is idiopathic, or associated with malignancy, autoimmune disease or infection—likely contributes to the course of FGN progression. In the current case, no associated condition was identified, and so FGN may have resulted from an abnormal immune response. The underlying driver(s) of each individual case of FGN likely contributes to that case's responsiveness to therapy or even propensity to self-resolve in the absence of immunotherapy. If a causative underlying immune response spontaneously normalizes, then the glomerulonephritis may resolve itself as well.

Authors' contribution

All authors were involved and approved the final manuscript.

Conflict of interest statement

None declared.

References

1. Rosenstock JL, Markowitz GS, Valeri AM *et al*. Fibrillary and immunotactoid glomerulonephritis: distinct entities with different clinical and pathologic features. *Kidney Int* 2003; 63: 1450–1461
2. Fogo A, Qureshi N, Horn RG. Morphologic and clinical features of fibrillary glomerulonephritis versus immunotactoid glomerulopathy. *Am J Kidney Dis* 1993; 22: 367–377
3. Alpers CE, Kowalewska J. Fibrillary glomerulonephritis and immunotactoid glomerulopathy. *J Am Soc Nephrol* 2008; 19: 34–37
4. Yang GC, Nieto R, Stachura I *et al*. Ultrastructural immunohistochemical localization of polyclonal IgG, C3, and amyloid P component on the Congo red-negative amyloid-like fibrils of fibrillary glomerulopathy. *Am J Pathol* 1992; 141: 409–419
5. Nasr SH, Valeri AM, Cornell LD *et al*. Fibrillary glomerulonephritis: a report of 66 cases from a single institution. *Clin J Am Soc Nephrol* 2011; 6: 775–784
6. Iskandar SS, Falk RJ, Jennette JC. Clinical and pathologic features of fibrillary glomerulonephritis. *Kidney Int* 1992; 42: 1401–1407
7. Pronovost PH, Brady HR, Gunning ME *et al*. Clinical features, predictors of disease progression and results of renal transplantation in fibrillary/immunotactoid glomerulopathy. *Nephrol Dial Transplant* 1996; 11: 837–842
8. Samaniego M, Nadasdy GM, Laszik Z *et al*. Outcome of renal transplantation in fibrillary glomerulonephritis. *Clin Nephrol* 2001; 55: 159–166
9. Czarnecki PG, Lager DJ, Leung N *et al*. Long-term outcome of kidney transplantation in patients with fibrillary glomerulonephritis or monoclonal gammopathy with fibrillary deposits. *Kidney Int* 2009; 75: 420–427
10. Pliquett RU, Mohr P, El Din Mukhtar B *et al*. Plasmapheresis leading to remission of refractory nephrotic syndrome due to fibrillary glomerulonephritis: a case report. *J Med Case Rep* 2012; 6: 116
11. Hogan J, Restivo M, Canetta PA *et al*. Rituximab treatment for fibrillary glomerulonephritis. *Nephrol Dial Transplant* 2014; 29: 1925–1931
12. Collins M, Navaneethan SD, Chung M *et al*. Rituximab treatment of fibrillary glomerulonephritis. *Am J Kidney Dis* 2008; 52: 1158–1162
13. Zeier M, Perz J, Linke RP *et al*. No regression of renal AL amyloid in monoclonal gammopathy after successful autologous blood stem cell transplantation and significant clinical improvement. *Nephrol Dial Transplant* 2003; 18: 2644–2647
14. Yamazaki O, Ubara Y, Suwabe T *et al*. Successful treatment of primary AL amyloidosis by VAD therapy, high-dose melphalan, and autologous peripheral stem cell transplantation. *Clin Exp Nephrol* 2009; 13: 522–525
15. Safadi S, Saad A, Quint PS *et al*. Disappearance of immunoglobulins from persistent renal amyloid deposits following stem cell transplantation for heavy-and light-chain amyloidosis. *Nephrol Dial Transplant* 2015; 30: 1151–1155