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

Miroslav Sekulic1, Samih H. Nasr2, Joseph P. Grande2 and Lynn D. Cornell2

1Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA and
2Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

Correspondence and offprint requests to: Miroslav Sekulic; E-mail: sekul002@umn.edu

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 blocker 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 be 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

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from 10 to 30 nm. We present a case in which a patient is diag-
osed with FGN, and managed without immunosuppressive
therapy for 17 years. The patient then re-presented in a nep-
hotic state, and a subsequent kidney biopsy showed no histo-
logic evidence of FGN. While there are data to show patients
attaining clinical remission of disease without immunosuppres-
sive 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 exer-
tion, marked lower extremity edema and was obese (body mass
index of 40 kg/m²). No other findings were noted on physical exa-
namination. Pertinent laboratory values included serum creati-
nine of 1.2 mg/dL, 24-h urine protein of 15.7 g/day, serum albu-
min 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
virus antibodies, anti-dsDNA, anti-nuclear antibody, antiphos-
pholipid antibody, cryoglobulins and a monoclonal protein via
viral antibody, anti-

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 evi-
dence 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 pro-
teinuria 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 deter-
mine 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 seg-
mental glomerulosclerosis and severe vascular disease (arte-
riosclerosis 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 micro-
scopy, 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 1).

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 func-
tion. Partial clinical remission was defined as a reduction of pro-
teinuria by at least 50% and to <2 g/day with stable renal
function characterized by not >20% increase in serum creati-
nine [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 pro-
tein 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.

First kidney biopsy
In all, 14 glomeruli were present, one of which was globally scler-
osed. Light microscopic evaluation showed mildly enlarged
glomeruli, generalized glomerular capillary loop thickening
with compromised lumina, fuchsinophilic deposits along capil-
lar 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 posi-
tive. Crescents, endocapillary proliferation and necrosis were
absent. There was minimal interstitial fibrosis or tubular atro-
phy, 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 gran-
ular 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 mesan-
gium. The mean fibril diameter was 15 nm with a standard devi-
ation 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 elec-
tron dense deposits.

Diagnosis
A diagnosis of FGN was made.
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].
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.

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