Fibrillary Glomerulonephritis: A Report of 66 Cases from a Single Institution

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Summary

Background and objectives Fibrillary glomerulonephritis (FGN) is a rare primary glomerular disease. Most previously reported cases were idiopathic. To better define the clinical-pathologic spectrum and prognosis, we report the largest single-center series with the longest follow-up.

Design, setting, participants, & measurements The characteristics of 66 FGN patients who were seen at Mayo Clinic, Rochester, between 1993 and 2010 are provided.

Results The mean age at diagnosis was 53 years. Ninety-five percent of patients were white, and the female: male ratio was 1.2:1. Underlying malignancy (most commonly carcinoma), dysproteinemia, or autoimmune disease (most commonly Crohn's disease, SLE, Graves' disease, and idiopathic thrombocytopenic purpura), were present in 23, 17, and 15% of patients, respectively. Presentation included proteinuria (100%), nephrotic syndrome (38%), renal insufficiency (66%), hematuria (52%), and hypertension (71%). The most common histologic pattern was mesangial proliferative/sclerosing GN followed by membranoproliferative GN. During an average of 52.3 months of follow-up for 61 patients with available data, 13% had complete or partial remission, 43% had persistent renal dysfunction, and 44% progressed to ESRD. The disease recurred in 36% of 14 patients who received a kidney transplant. Independent predictors of ESRD by multivariate analysis were older age, higher creatinine and proteinuria at biopsy, and higher percentage of global glomerulosclerosis.

Conclusions Underlying malignancy, dysproteinemia, or autoimmune diseases are not uncommon in patients with FGN. Prognosis is poor, although remission may occur in a minority of patients without immunosuppressive therapy. Age, degree of renal impairment at diagnosis, and degree of glomerular scarring are predictors of renal survival.

Clin J Am Soc Nephrol 6: 775–784, 2011. doi: 10.2215/CJN.08300910

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Introduction

Fibrillary glomerulonephritis (FGN) is a rare primary glomerular disease first described by Rosenmann and Eliakim in 1977 (1). It is defined by the ultrastructural finding of haphazardly arranged, straight fibrils measuring 10 to 30 nm in thickness. The fibrils are deposited in the mesangium, glomerular basement membranes (GBM), or both. On immunofluorescence (IF), the deposits typically stain for polyclonal IgG and complement, indicating immune complex deposition (2–6). The light microscopic features are heterogenous; most cases exhibit mesangial expansion/hypercellularity with or without duplication of the GBMs (2,3). Less commonly reported morphologic patterns included endocapillary proliferative glomerulonephritis (EPGN) and crescentic glomerulonephritis (CGN) (2,7). By definition, the glomerular deposits in FGN are Congo red–negative, which distinguishes it from amyloid. FGN is encountered in 0.5 to 1% of native kidney biopsies (2,4). Most previously reported cases were idiopathic and occurred in the absence of other systemic diseases (2–5). Patients with FGN typically present with proteinuria (usually nephrotic), hematuria, renal insufficiency, and hypertension. The prognosis is poor, with close to one half of patients progressing to ESRD within a few years after diagnosis (2,6), despite the administration of steroids and cytotoxic agents.

Most investigators advocate separating FGN from immunotactoid glomerulopathy (2,4,6,8). The latter, which is 10-fold rarer than FGN, is characterized by glomerular deposition of larger microtubular structures (usually >30 nm in diameter) that have focal parallel alignment. In contrast to FGN, patients with immunotactoid glomerulopathy frequently have hypocomplementemia and underlying dysproteinemia, and the glomerular deposits are usually monoclonal (2,6).

There have been several studies addressing the clinical-pathologic characteristics of FGN, all of

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which, with the exception of the study by Rosenstock *et al.* (61 patients), included <30 patients (2–5,9). Furthermore, the mean duration of patient follow-up in all previous studies with >10 patients was ≤24 months, except for the series by Pronovost *et al.* of 24 patients that were followed for a mean time of 43 months (2–5). Here, we report our experience with 66 patients with FGN that were followed for a mean time of 52 months. The longer follow-up and larger cohort of patients in this study has the advantage of allowing us to better define the disease's demographics, associated conditions, presenting features, histologic findings, poor prognostic indicators, and outcome.

Materials and Methods

Seventy-two Mayo Clinic patients with a diagnosis of FGN were identified by retrospective review of all native renal biopsies evaluated in the Renal Pathology Laboratory at Mayo Clinic, Rochester, from 1993 to 2010. Six patients were excluded from this study because of the lack of glomeruli for IF. The remaining 66 patients that were included in this study fulfilled the following diagnostic criteria of FGN: glomerular deposition of fibrils that (*1*) were randomly oriented; (*2*) lacked hollow centers at magnification of <30,000; (*3*) were Congo red negative; and (*4*) stained with antisera to immunoglobulins by IF.

Thirty-seven of the 66 patients had their kidney biopsies performed and interpreted at an outside institution. At the request of the treating nephrologist at Mayo Clinic, the original biopsy materials were sent for second opinion to the Renal Pathology Laboratory at the Mayo Clinic. The remaining 29 patients underwent kidney biopsies at the Mayo Clinic. Standard processing of renal biopsies included light microscopy (LM), IF, and electron microscopy. For LM, all cases were stained with hematoxylin and eosin, periodic acid-Schiff, Masson's trichrome, and Jones methenamine silver. Standard IF on frozen tissue was performed in 63 biopsies with available glomeruli. In the remaining three biopsies, glomeruli were lacking on frozen tissue, and therefore, IF was performed on pronase-digested paraffin-embedded tissue (10). For IF, 3-μm cryostat sections were stained with polyclonal FITC-conjugated antibodies to IgG, IgM, IgA, C3, C1q, kappa, and lambda. Clinical data, including demographic information, presenting clinical and laboratory findings, medical history, treatment and follow-up, were obtained from patients' electronic medical records and telephone interviews with the referring nephrologist. The following clinical definitions were used: (*1*) nephrotic-range proteinuria, ≥3.0 g/d; (*2*) hypoalbuminemia, serum albumin <3.5 g/dl; (*3*) renal insufficiency, serum creatinine >1.2 mg/dl; (*4*) nephrotic syndrome, nephrotic-range proteinuria with hypoalbuminemia and peripheral edema; and (*5*) hypertension, systolic BP >140 mmHg, diastolic BP >90 mmHg, or ongoing treatment with anti-hypertensive medications. Quantification of proteinuria was performed by 24-hour collection or by spot urine protein-to-creatinine ratio when 24-hour urine collection was not performed. Tubular atrophy and interstitial fibrosis were graded on a semiquantitative scale based on an estimate of the percentage of renal cortex affected and recorded as 0 (none), 1 to 25% (mild), 26 to 50% (moderate), or >50% (severe).

For the purpose of outcome analysis, the following definitions were used: (*1*) complete remission (CR), remission of proteinuria to <500 mg/d with normal renal function; (*2*) partial remission (PR), reduction in proteinuria by ≥50% and to <2 g/d with stable renal function (no more than a 20% increase in serum creatinine); (*3*) persistent renal dysfunction (PRD), failure to meet criteria for either CR or PR but not reaching ESRD, including patients with unremitting proteinuria or progressive chronic kidney disease; and (*4*) ESRD, requiring renal replacement therapy or undergoing preemptive transplant.

Continuous variables are reported as the mean ± SD. Statistical analysis was performed using SPSS for Windows, version 16.0 (SPSS, Chicago, IL). Analysis was performed using nonparametric exact statistical methods. Univariate analysis was performed using the Mann-Whitney-Wilcoxon test, the Kruskal-Wallis test, and the Fisher-Freeman-Halton exact test, as appropriate for variable type. Survival analysis for progression to ESRD was performed by the method of Kaplan and Meier using the log rank test for univariate analysis and the Cox proportional hazards model for multivariate analysis. Statistical significance was assumed at $P < 0.05$.

The study was approved by the Institutional Review Board of Mayo Clinic Foundation.

Results

Clinical Features

Ninety-five percent of patients were white, and there was a slight female predominance (female:male ratio, 1.2:1; Table 1). The mean age at biopsy was 53 years (range, 19 to 81 years), and 18% were elderly (>64 years of age). Fifteen patients (23%) had an associated malignancy discovered 15 years before to 10 years after the clinical onset of renal disease, including multiple myeloma (MM; $n = 6$; Durie-Salmon stage IIIB in one, stage IIB in one, and stage IB in four; one of whom also had chronic myelomonocytic leukemia) (11) thyroid carcinoma ($n = 2$; papillary in one and follicular in one), hepatocellular carcinoma ($n = 1$), breast carcinoma ($n = 1$), uterine carcinoma ($n = 1$), prostate carcinoma ($n = 1$), colon carcinoma ($n = 1$), renal cell carcinoma ($n = 1$), and melanoma ($n = 1$). Ten patients (15%) had a history of autoimmune disease, including Crohn's disease ($n = 3$), SLE ($n = 2$) with no evidence of lupus nephritis histologically, Graves' disease ($n = 2$), idiopathic thrombocytopenic purpura ($n = 2$), primary biliary cirrhosis ($n = 1$), ankylosing spondylitis ($n = 1$), and Sjögren's syndrome ($n = 1$). History of chronic hepatitis C infection was present in two patients (3%). Other coexistent conditions included diabetes mellitus in 20% of patients, coronary artery disease in 9% of patients, and chronic obstructive pulmonary disease in 5% of patients.

On standard serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) with immunofixation electrophoresis (IFE) performed in 63 patients, 11 (17%) had a monoclonal spike (M-spike): in both serum and urine in 7, in the serum only in 3, and in the urine only in 1 (Table 2). Thirty-one of these 63 patients underwent serum free light-chain assay, which showed a normal kappa:lamnda ratio in 28 patients. Of the remaining three patients, two (who had lambda M-spike on SPEP/IFE) had a decreased kappa:lambda ratio and one (who had negative SPEP/UPEP/IFE)

Table 1. Demographics and associated medical conditions (66 patients)

	No. of Patients (%)
Female:male	36/30 (55/45)
Age (years; mean ± SD)	53 ± 12
15 to 24	1 (2)
25 to 34	4 (6)
35 to 44	9 (14)
45 to 54	17 (26)
55 to 64	23 (35)
>64	12 (18)
Race	
white	63 (95)
Hispanic	2 (3)
black	1 (2)
Associated medical conditions	
diabetes mellitus	13 (20)
malignancies	15 (23)
multiple myeloma[a]	6 (9)
nonhematologic[b]	9 (14)
autoimmune disease[c]	10 (15)
hepatitis C infection	2 (3)
coronary artery disease	6 (9)
chronic obstructive pulmonary disease	3 (5)

[a]Durie-Salmon stage IIIB in one, stage IIB in one, and stage IB in four; one of whom also had chronic myelomonocytic leukemia.
[b]Thyroid carcinoma ($n = 2$; papillary in 1 and follicular in 1), hepatocellular carcinoma ($n = 1$), breast carcinoma ($n = 1$), uterine carcinoma ($n = 1$), prostate carcinoma ($n = 1$), colon carcinoma ($n = 1$), renal cell carcinoma ($n = 1$), and melanoma ($n = 1$).
[c]Crohn's disease ($n = 3$), systemic lupus erythematosus ($n = 2$), Graves' disease ($n = 2$), idiopathic thrombocytopenic purpura ($n = 2$), primary biliary cirrhosis ($n = 1$), ankylosing spondylitis ($n = 1$), and Sjögren's syndrome ($n = 1$).

had a slightly elevated kappa:lambda ratio. Bone marrow examination, performed in 27 patients (including 9 of the 11 patients with a positive serum or urine M-spike), showed <5% plasma cells in 21 patients and 10 to 40% lambda-restricted plasma cells in 6 patients. All of the latter six patients had a positive serum and/or urine M-spike. Of the 11 patients with positive M-spike, 5 showed positive IF staining for IgG and lambda with negative kappa (all had IgG lambda M-spike, including 3 with MM); 3 patients showed positive IF staining for IgG, kappa, and lambda (1 of whom had MM); and 3 patients showed positive IF staining for IgG with negative kappa and lambda (2 of whom had MM).

Serum cryoglobulin was positive in only 1 of the 38 patients (3%) tested, which was type III. Only 1 of the 49 patients (2%) tested for serum complement had hypocomplementemia (low C4 with normal C3). Hepatitis C antibody, tested in 47 patients, was negative in 45 and positive in 2, both of whom had positive hepatitis C virus RNA by PCR. Hepatitis B antigen was negative in all 43 patients tested. Testing for HIV antibody, performed in 25 patients, was negative. Antinuclear antibody (ANA) was positive in 7 of 49 patients tested (weakly positive in 5 and strongly positive in 2). At the time of biopsy, one of the two patients with a known history of SLE had a high titer ANA (1:2516) and the other one had a negative ANA titer. Antineutrophil cytoplasmic antibody (ANCA) testing was performed in 36 patients and was negative in 34, equivocal in 1 (MPO-ANCA; 9% crescents on biopsy), and positive in 1 (P-ANCA; 50% crescents on biopsy). Total serum IgG level, tested in 28 patients, was normal in 16, decreased in 11, and elevated in 1.

At the time of biopsy, all patients had proteinuria (Table 2). The mean 24-hour urine protein was 5.62 g (range, 0.2 to 20.4 g). Proteinuria was in the nephrotic range in 55% of patients, and 38% had full nephrotic syndrome. Microhematuria was documented in 52% of patients, whereas gross hematuria was present in only 5% of patients. Renal insufficiency was present in two thirds of patients, with 46% of patients having a serum creatinine >2 mg/dl. The mean serum creatinine was 2.1 mg/dl (range, 0.5 to 8.3 mg/dl). The mean serum albumin was 3.2 g/dl (range, 1.5 to 4.8 g/dl), and peripheral edema was present in 59% of patients. Hypercholesteremia was present in 63% of patients.

Pathologic Findings

Light microscopy. Sampling for LM included 16 glomeruli (range, 2 to 46 glomeruli). A mean of 25% of glomeruli were globally sclerotic (Table 3). The most common histologic pattern, seen in 47 cases (71%), was mesangial proliferative/sclerosing glomerulonephritis (MesGN), with variable degrees of mesangial hypercellularity, sclerosis, and expansion by immune deposits (Figure 1). Two of these cases also showed segmental membranous features with segmental spike formation on silver stain. The second most common pattern was membranoproliferative glomerulonephritis (MPGN), characterized by segmental or global double-contoured glomerular capillary walls with mesangial cell interposition and mesangial expansion by increased mesangial cell number and matrix. Four cases (6%) exhibited EPGN, characterized by endocapillary hypercellularity and leukocyte infiltration causing luminal occlusion, without duplication of the GBMs. All of these four cases also exhibited mild to moderate mesangial sclerosis and hypercellularity. CGN defined by the presence of crescents and/or necrosis affecting ≥50% of glomeruli (two cases) or crescents and necrosis in the absence of mesangial sclerosis/hypercellularity, endocapillary hypercellularity, or GBM duplication (one case) was present in only three cases (5%), one of which was associated with P-ANCA seropositivity. One case (2%) exhibited exclusively membranous-like glomerulonephritis (MGN), characterized by global glomerular capillary wall thickening and global subepithelial deposits in the absence of mesangial sclerosis/hypercellularity, endocapillary hypercellularity, or GBM duplication. Diffuse sclerosing glomerulonephritis (DSGN)

Table 2. Clinical characteristics at biopsy (66 patients)

	No. of Patients (%)
Hypertension	47 (71)
Edema	38/64 (59)
Mean 24-hour urine protein (range)	5.62 g (0.2 to 20.4)
proteinuria <1 g/24 h	5/64 (8)
proteinuria 1 to 3 g/24 h	24/64 (38)
proteinuria 3.1 to 10 g/24 h	26/64 (41)
proteinuria >10 g/24 h	9/64 (14)
Hypoalbuminemia	38/61 (62)
Full nephrotic syndrome	24/64 (38)
Hypercholesteremia	32/51 (63)
Hematuria (microscopic or macroscopic)	33/64 (52)
Macroscopic hematuria	3 (5)
Leukocyturia	17/59 (29)
Mean serum creatinine (range)	2.1 mg/dl (0.5 to 8.3)
creatinine ≤1.2 mg/dl	22/65 (34)
creatinine 1.2 to 2 mg/dl	13/65 (20)
creatinine >2 mg/dl	30/65 (46)
Low serum complements	1/49 (2)
Positive serum cryoglobulin	1/38 (3)
Positive ANA	7/49 (14)
Presence of monoclonal protein on electrophoresis/ immunofixation	11/63 (17)
in both serum and urine	7
in the serum only	3
in the urine only	1

(100% of glomeruli showing global sclerosis) was seen in one case (2%). On statistical analysis, the MesGN pattern correlated with lower serum creatinine ($P = 0.001$) and absence of nephrotic syndrome ($P = 0.014$) at biopsy, and the MPGN and CGN patterns correlated with immunomodulatory (IM) therapy ($P = 0.039$). The glomerular deposits were glassy and stained eosinophilic on hematoxylin and eosin, periodic acid-Schiff–positive, silver-negative (Figure 1), and trichrome blue or gray. By definition, the deposits were Congo red negative in all 66 cases.

Crescents were present in 11 cases (17%; Table 3). When present, the crescents affected a mean of 25% of glomeruli. Three cases (5%) showed fibrinoid necrosis. Fifty-five cases (83%) showed interstitial inflammation, which was predominantly focal. The degree of tubular atrophy and interstitial fibrosis ranged from absent (6% of cases) to mild (51%) to moderate (33%) to severe (9%). Arteriosclerosis ranged from absent (23% of cases) to mild (45%) to moderate (29%) to severe (3%). One patient with recently diagnosed IgG lambda MM had both FGN and myeloma cast nephropathy. On IF, the glomerular fibrillary deposits stained for IgG and lambda with negative kappa, and the myeloma casts stained for lambda with negative kappa.

Immunofluorescence. By IF, all 66 cases showed glomerular positivity for IgG, with a mean intensity of 2.5+ (on a scale of 0 to 3+; Figure 2; Table 4). Twenty-eight percent of cases were positive for IgA (mean intensity of positive cases, 1.0+), and 47% of cases were positive for IgM (mean intensity of positive cases, 1.0+). The glomerular staining for IgM and IgA was weaker than IgG in all cases except one, in which IgA staining was stronger than IgG. In a similar distribution to the IgG deposits, glomerular deposition of C3 was detected in 92% of cases (mean intensity, 2.0+) and C1q in 60% of cases (mean intensity, 0.8+). Glomeruli were present in the sections incubated with antibodies against kappa and lambda light chains in 61 cases (92%). The glomerular deposits stained for both kappa and lambda light chains in 51 cases (84%). In seven cases (11%), they stained for only one light chain (lambda only in five cases and kappa only in two cases). SPEP/IFE performed in six of these seven patients showed monoclonal IgG-lambda protein in four (who had monoclonal IgG lambda glomerular deposition), monoclonal lambda light chain in one (who had monoclonal IgG lambda glomerular deposition), and no monoclonal protein in one. In the remaining three patients (5%), the glomerular IgG deposits were negative for both kappa and lambda light chains. All of these three patients had monoclonal protein on SPEP/IFE (two IgG lambda and one IgG kappa). In addition to the glomerular staining, nine cases (14%) showed focal, segmental tubular basement membranes staining for IgG. The texture of tubular basement membrane deposits was semilinear in five and smudgy in four. Vessel wall positivity for IgG was not seen in any case.

Electron microscopy. The fibrillary deposits were seen infiltrating the mesangium in 65 cases (98%; Figure 3A) and the lamina densa of the GBMs in 56 cases (85%; Figure 3B). In the single case with MGN pattern on LM, the fibrillary deposits were present globally in the lamina densa and subepithelial zone of the GBMs associated by spike formation, without mesangial deposits. In all 66 cases, the fibrils were randomly oriented, straight,and nonbranching (Figure 3C). The mean diameter of fibrils, mea-

Table 3. Light microscopic findings

Pathologic Findings	No. of Patients (%)
Mean number of glomeruli	16
Mean percent of globally sclerotic glomeruli	25
Glomerular pattern of injury	
mesangial	47 (71)
membranoproliferative	10 (15)
endocapillary proliferative	4 (6)
crescentic and necrotizing[a]	3 (5)
membranous	1 (2)
diffuse sclerosing[b]	1 (2)
Crescents	11 (17)
Interstitial inflammation: none/focal/diffuse[c]	11/52/3 (17/79/5)
Tubular atrophy and interstitial fibrosis: none/mild/moderate/severe[d]	4/34/22/6 (6/51/33/9)
Arteriosclerosis and arteriolar hyalinosis: none/mild/moderate/severe	15/30/19/2 (23/45/29/3)
Concurrent myeloma cast nephropathy	1 (2)

[a]Defined by the presence of crescents and/or necrosis affecting ≥50% of glomeruli or crescents and necrosis in the absence of other patterns.
[b]100% of glomeruli with global sclerosis.
[c]Focal <50% of cortical surface area; diffuse ≥50%.
[d]Mild (0 to 25% of cortical surface area); moderate (26 to 50%); severe (>50%).

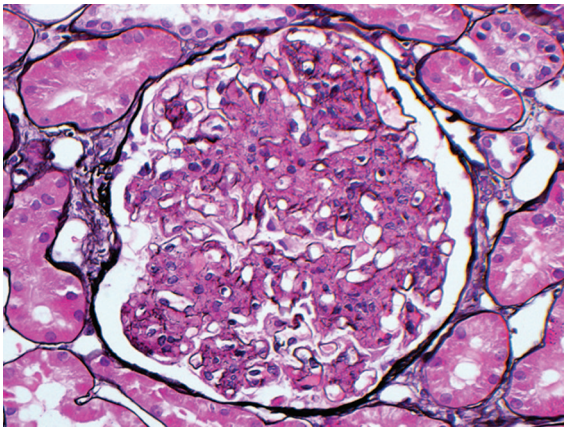

Figure 1. | There is prominent global mesangial expansion and segmental glomerular basement membrane thickening by Silver-negative immune material. Mild global mesangial hypercellularity is also present (Jones methenamine silver, ×400).

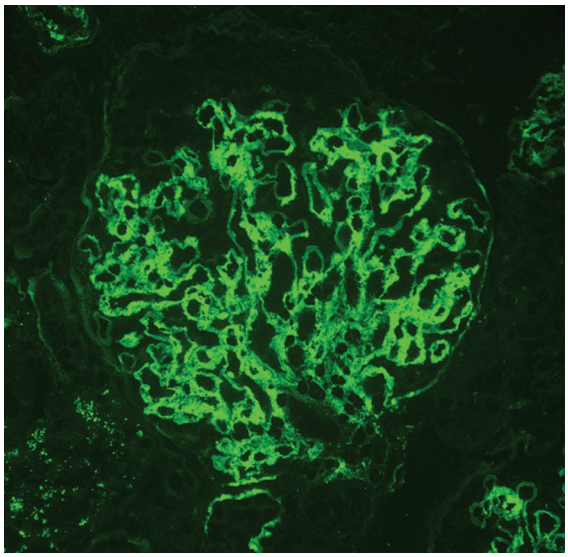

Figure 2. | An immunofluorescence image shows global, flocculent mesangial, and glomerular capillary wall staining with an antiserum specific for IgG (×400).

Table 4. Glomerular findings on immunofluorescence

	No. of Positive Cases (%)	Mean Intensity When Positive[a]
IgG	66/66 (100)	2.5+
IgM	30 of 65 (47)	1.0+
IgA	18/65 (28)	1.0+
C3	59/64 (92)	2.0+
C1q	38/63 (60)	0.8+
Kappa	52/61 (85)	2.0+
Lambda	55/61 (90)	2.0+

[a]Scale: trace (0.5+), 1 to 3+.

sured in 51 cases (77%), was 18.1 nm (range of means, 9 to 26 nm). Fibrillar deposits were identified focally in tubular basement membranes in two cases, which were among the nine cases that showed tubular basement membrane positivity on IF. No case showed interstitial or vascular fibrillar deposits. None of the cases showed large organized microtubular deposits typical of immunotactoid glomerulopathy, deposits with annular-tubular substructure commonly seen in cryoglobulinemic glomerulonephritis, or punctate, ribbon-like deposits along the GBM and tubular basement membranes characteristic of Randall type monoclonal Ig deposition disease. The biopsies from the two SLE patients lacked any characteristic histologic feature of lupus nephritis on IF or electron microscopy, such as full house immunostaining (with negative staining for IgA and C1q), extraglomerular deposits, "tissue ANA," granular electron dense deposits ultrastructurally, or endothelial tubuloreticular inclusions.

Clinical Outcome

Clinical follow-up was available in 61 patients (92%). The mean duration of follow-up for the entire cohort was

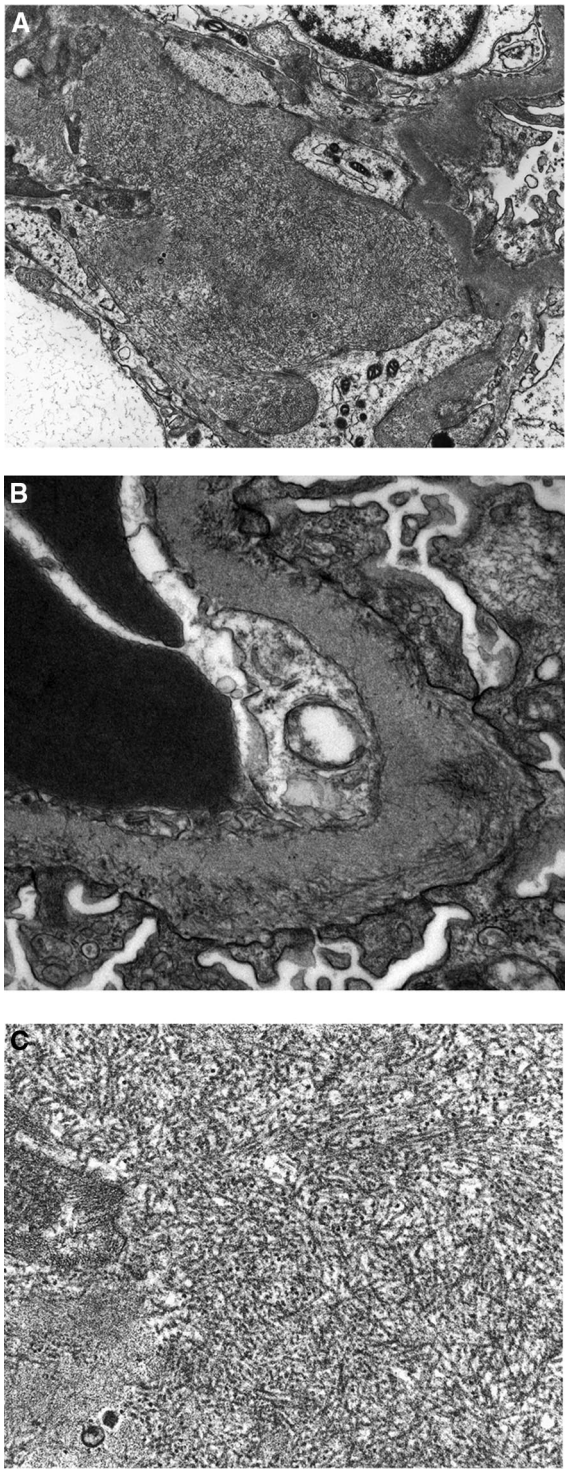

Figure 3. | Electron micrographs exhibit fibrillar deposits in the mesangium (A) and the subepithelial zone of the glomerular capillary walls (B). On higher magnification, the glomerular deposits are composed of randomly oriented, straight, nonbranching fibrils (C). (A, ×10,000; B, ×24,500; C, ×46,000).

52.3 months (range, 2 to 209 months). On follow-up, 3 patients (5%) had CR, 5 patients (8%) had PR, 26 patients (43%) had PRD, and 27 patients (44%) progressed to ESRD (Table 5). Of the 27 patients who reached ESRD, 14 received kidney transplant (pre-emptive in 5; 11 of whom were part of our previous study that focused on recurrent FGN) (12). After a mean post-transplant follow-up of 51 months (range, 5 to 156 months), five patients (36%) had biopsy-proven recurrence of FGN. Two of these patients lost their allograft because of recurrent disease and subsequently received a second transplant that was lost again because of recurrent disease in one, whereas the second patient had no recurrence. Twelve of the 61 patients with follow-up (20%; 11 with ESRD and 1 with PRD) died: 2 of sepsis, 1 of metastatic hepatocellular carcinoma, 1 of leukemia, 1 of chronic obstructive pulmonary disease, 1 of ischemic bowel disease, 1 of stroke, 1 of cardiac arrhythmias, and 4 of unknown cause.

Table 5. Treatment and outcome (61 patients)

Parameter	No. of Patients	Percent of Patients
Duration of follow-up [months; mean (range)]	52.3 (2 to 209)	
Treatment		
none	16	26
RAS blockade alone	16	26
immunosuppressive therapy	29	48
steroids	24	39
cyclophosphamide	9	15
mycophenolate mofetil	6	10
rituximab	3	5
melphalan hydrochloride	3	5
cyclosporine	2	3
lenalidomide	2	3
rapamune	1	2
azathioprine	1	2
Outcome		
complete remission	3	5
partial remission	5	8
persistent renal dysfunction	26	43
ESRD	27	44
kidney transplantation	14	23
disease recurrence	5	36
death	12	20

The correlates of reaching ESRD by the Kaplan-Meier survival estimates on univariate analysis were the presence of MPGN (*versus* MesGN) pattern on LM ($P = 0.045$) and greater degree of tubular atrophy and interstitial fibrosis ($P = 0.0027$) and arteriosclerosis ($P = 0.0370$). Gender, type of therapy, the presence of M-spike on SPEP or UPEP, presence of underlying malignancy, and presence of underlying autoimmune disease did not correlate significantly with outcome.

By Cox regression, predictors of reaching ESRD on univariate analysis (Table 6) were older age ($P = 0.011$), higher creatinine at biopsy ($P < 0.001$), higher proteinuria at biopsy ($P = 0.003$), higher percent global glomerulosclerosis ($P = 0.001$), and greater degree of tubular atrophy and interstitial fibrosis ($P = 0.001$), interstitial inflammation

Table 6. Predictors of reaching ESRD on univariate analysis by Cox regression

Factor	Hazards Ratio	95% Confidence Interval	*P*
Age	1.056	1.013 to 1.101	0.011
24-hour urine protein at biopsy	1.114	1.036 to 1.196	0.003
Serum creatinine at biopsy	1.543	1.231 to 1.933	<0.001
Percent of globally sclerotic glomeruli	1.031	1.012 to 1.051	0.001
Tubular atrophy and interstitial fibrosis	2.729	1.514 to 4.919	0.001
Interstitial inflammation	3.584	1.279 to 10.043	0.015
Arteriosclerosis	1.919	1.186 to 3.104	0.008
MPGN *versus* MesGN pattern on LM	2.48	0.99 to 6.24	0.054

Table 7. Predictors of reaching ESRD on multivariate analysis by Cox regression

Factor	Hazards Ratio	95% Confidence Interval	*P*
Age	1.124	1.051 to 1.202	0.001
24-hour urine protein at biopsy	1.116	1.026 to 1.214	0.011
Serum creatinine at biopsy	1.948	1.309 to 2.900	0.001
Percent of globally sclerotic glomeruli	1.036	1.012 to 1.060	0.003

($P = 0.015$), and arteriosclerosis ($P = 0.008$). The presence of MPGN (*versus* MesGN) pattern on LM did not quite reach statistical significance ($P = 0.054$). Using the Cox proportional hazards model, the independent predictors of the rate of progression to ESRD on multivariate analysis were older age ($P = 0.001$), higher creatinine at biopsy ($P = 0.001$), higher 24-hour urine protein at biopsy ($P = 0.011$), and higher percent global glomerulosclerosis ($P = 0.003$; Table 7).

Treatment

Sixteen patients (26%) were not treated (Table 5). On follow-up, one of them had CR, seven had PRD, and eight developed ESRD. Sixteen patients (26%) were treated with renin angiotensin system blockade alone (angiotensin-converting enzyme inhibitor alone in 13, angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker in 2, and angiotensin II receptor blocker alone in 1). Of these 16 patients, 2 had CR, 2 had PR, 8 had PRD, and 4 progressed to ESRD. The remaining 29 patients (48%) received IM therapy, of whom 3 had PR, 11 had PRD, and 15 had ESRD. IM therapy consisted of steroids alone in eight patients, of whom four developed PRD and four developed ESRD. Of the remaining 21 patients, 16 were treated with steroids and one or more additional immunosuppressive agents (cyclophosphamide [CYT] in 7, mycophenolate mofetil [MMF] in 4, melphalan in 3, lenalidomide in 2, rapamune in 1, and azathioprine in 1), and 5 were treated with immunosuppressive agents without steroids (cyclosporine alone in 2, MMF alone in 1, CYT alone in 1, and MMF and CYT in 1). Rituximab was used in combination with steroids in one patient who developed ESRD, in combination with steroids and CYT in one patient who had PRD, and in combination with CYT and MMF in one patient who had PRD (Table 5).

Of the 53 patients who eventually developed PRD or ESRD, 3 (2 with PRD and 1 with ESRD) had an initial response to IM therapy: 2 were treated with steroids alone, which resulted in an initial decline in proteinuria from 14 to 2 g/d and from 8 to 1.7 g/d, and the third one was treated with steroids and CYT, which resulted in an initial improvement of serum creatinine from 8 to 1.7 mg/dl.

IM therapy did not slow progression to ESRD by the Kaplan-Meier survival estimate (0 = 0.341). The MPGN and CGN patterns correlated with IM therapy ($P = 0.039$). Because patients with the MPGN pattern progressed to ESRD faster than those with the MesGN pattern ($P = 0.045$), we looked at the effect of IM therapy stratified by histology (using both MesGN *versus* all other patterns and MesGN *versus* MPGN), and neither analysis was significant ($P = 0.432$ and 0.717, respectively). Histology stratified by IM therapy lost some significance but remained close to significant, with MesGN patients progressing to ESRD slower than the MPGN patients, regardless of whether IM therapy was used ($P = 0.051$).

Discussion

This study reports our experience with a series of 66 patients with FGN. To our knowledge, this is the largest clinical-pathologic series of FGN with the longest follow-up. Our data indicate that FGN can present over a wide range of ages, although most cases are diagnosed between 45 and 65 years of age. The strong white racial predominance and slight female predominance in our patient population are in agreement with prior studies (2–4).

In contrast to prior series of FGN in which most cases were idiopathic (2–5,9), one third of our cases occurred in patients with history of malignancy (most commonly carcinoma) or autoimmune diseases (most commonly Crohn's disease, SLE, Graves' disease, and idiopathic thrombocytopenic purpura). There have also been rare single case reports in the literature of FGN in association with SLE, rheumatoid arthritis, primary biliary cirrhosis, hemolytic anemia, HIV infection, essential thrombocytosis, Castleman's disease, gastric adenocarcinoma, and metastatic hepatocellular carcinoma (13–20). Therefore, we believe that FGN should not be assumed as "idiopathic," and a

Table 8. Characteristics of patients with complete or partial remission

	Age	Serum Creatinine (mg/dl) at Biopsy	24-Hour Urine Protein (g/d) at Biopsy	Nephrotic Syndrome	Associated Conditions	Percent of Glomeruli with Global Sclerosis	Degree of Tubular Atrophy and Interstitial Fibrosis	Treatment	Duration of Follow-Up (months)
Patients with complete remission									
1	38	0.8	2.7	No	Melanoma	0	None	ACE I	87
2	48	1.1	1.4	No	None	14	Mild	ACE I	13
3	37	0.8	1.5	No	None	17	Mild	None	81
Patients with partial remission									
1	57	2.5	2	No	Multiple myeloma	0	Mild	Steroids/ lenalidomide/ apheresis[a]	13
2	59	2.3	7.5	Yes	None	25	Mild	Steroids/CYT/MMF	22
3	58	0.8	4.4	No	None	0	Mild	ACE I	19
4	30	0.8	3	No	SLE	0	Mild	Steroids/ azathioprine/ MMF	19
5	37	0.9	3	No	None	13	Mild	ACE I	17

ACE I, angiotensin-converting enzyme inhibitor; CYT, cyclophosphamide; MMF, mycophenolate mofetil.
[a]This patient has concurrent myeloma cast nephropathy.

thorough investigation of FGN patients is warranted. Because of the universal presence of IgG and complement components in the glomerular deposits, the pathogenesis of FGN is thought to result from glomerular localization of immune complexes that have the ability to undergo fibrillogenesis (6). The chronic stimulation of the immune system associated with autoimmune diseases potentially plays a role in the pathogenesis of FGN. The pathogenetic link between FGN and carcinoma is less clear and remains to be proven; thus far, no tumor antigens have been shown in the glomerular fibrillar deposits. Only two of our patients (3%) had chronic hepatitis C infection, which has been previously reported in few patients (7,21,22). Positive M-spike on SPEP and/or UPEP was present in 17% of our patients, including six who fulfilled the diagnostic criteria for MM, and in 15% of patients in the series by Rosenstock *et al.* (2), justifying the need to exclude an underlying dysproteinemia in all patients who are diagnosed with FGN. Of note, the total number of Mayo Clinic patients with MM who underwent kidney biopsy during the study period was 190. This indicates that the incidence of FGN among our MM patients who undergo kidney biopsy is 3.2%.

Our findings confirm the poor prognosis of FGN. After a mean follow-up of 52.3 months, 44% of our patients progressed to ESRD and 43% had PRD. Similar to prior studies (2,3), we were unable to show a statistical benefit of IM treatment in this uncontrolled retrospective study. This could be simply because the current therapeutic agents are ineffective in treating this condition or because of the tendency for patients with a higher creatinine and nephrotic syndrome to be offered IM therapy and the fact that multiple immunosuppressive drug regimens were used over time in this population. Prospective, multicenter, controlled study of FGN is needed to determine the optimal therapeutic regimen. Notably, remission occurred in eight of our patients (13%). The clinical and pathologic characteristics of these patients are listed in Table 8. These patients were relatively young (50% of them <40 years of age), 75% had normal serum creatinine at biopsy, only one had nephrotic syndrome, and all had no more than mild chronicity on biopsy. Only three of these patients received IM therapy.

We particularly sought to identify the features associated with poor renal outcome, an aspect of the disease that is not adequately addressed in the literature. We identified several independent predictors of ESRD by multivariate analysis, including older age, higher creatinine at biopsy, higher 24-hour urine protein at biopsy, and higher percentage of globally sclerotic glomeruli. In the study by Rosenstock *et al.* (2), the only previous study that included multivariate analysis, the independent predictors of progression to ESRD were higher serum creatinine at biopsy and the severity of interstitial fibrosis. The above data reflect the importance of age, serum creatinine and degree of proteinuria at biopsy, and the degree of parenchymal scarring as predictors of renal survival in this disease.

Multiple histologic patterns of glomerular injury have been described in patients with FGN, including MesGN, MPGN, EPGN, CGN, and DSGN (2,3,7). In one study, 44% of patients had MPGN, followed by MesGN (21%), EPGN (15%), DSGN (13%), and MGN (7%) (2). In our experience, the MesGN pattern was by far the most frequent, seen in 71% of patients, followed by the MPGN pattern (15% of patients). EPGN, CGN, MGN, and DSGN were seen in only 14% of cases, attesting to the rarity of these patterns in patients with FGN. Not surprising, the MesGN pattern correlated with lower serum creatinine and absence of nephrotic syndrome at biopsy. In the study by Rosenstock *et al.* (2), the mean time to ESRD by the Kaplan-Meier survival analysis was shorter in patients with DSGN, MPGN, and EPGN patterns than in those with the MesGN or MGN patterns. In our study, the mean time to ESRD was shorter in patients with the MPGN pattern compared with those who had the MesGN pattern. The DSGN, EPGN, and MGN patterns in our study did not correlate with outcome, possibly because of small sample size of these subgroups of patients.

In summary, FGN is most common in adults 46 to 65 years of age. Close to one quarter of cases are associated with malignancy, most commonly carcinoma, and 15% are associated with autoimmune disease. Most patients present with nephrotic-range proteinuria with or without renal insufficiency and hematuria. Prognosis is poor, with nearly one half of patients progressing to ESRD within 4 years. Disease remission, however, occurs in a minority of patients and does not seem to be influenced by IM therapy. Features associated with poor renal outcome include older age, higher creatinine at biopsy, higher 24-hour urine protein at biopsy, and higher percentage of globally sclerotic glomeruli. A prospective, multicenter, controlled study of this condition is needed to determine the optimal therapeutic regimen.

Disclosures

None.

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Received: September 19, 2010. **Accepted:** November 29, 2010

Published online ahead of print. Publication date available at www.cjasn.org.

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