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Fibrillary and immunotactoid glomerulonephritis: Distinct entities with different clinical and pathologic features

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Fibrillary and immunotactoid glomerulonephritis: Distinct entities with different clinical and pathologic features.

Background. Controversy surrounds the relatedness of fibrillary glomerulonephritis (FGN) and immunotactoid glomerulonephritis (IT).

Methods. To better define their clinicopathologic features and outcome, we report the largest single center series of 67 cases biopsied from 1980 to 2001, including 61 FGN and 6 IT. FGN was defined by glomerular immune deposition of Congo red–negative randomly oriented fibrils of < 30 nm (mean, 20.1 ± 0.4 nm). IT was defined by glomerular deposition of hollow, stacked microtubules of ≥ 30 nm (mean, 38.2 ± 5.7 nm).

Results. FGN comprised 0.6% of total native kidney biopsies and IT was tenfold more rare (0.06%). Deposits in FGN were immunoglobulin G (IgG) dominant and polyclonal in 96%. IgG subtype analysis in 19 FGN cases showed monotypic deposits in four (two IgG1 and two IgG4) and oligotypic deposits in 15 (all combined IgG1 and IgG4). In IT, deposits were IgG dominant in 83% and monoclonal in 67% (three IgG1κ and one IgG1λ). FGN patients were a mean age of 57 years, 92% were Caucasian, and 39% were male. At biopsy, FGN patients had the following clinical characteristics (mean, range): creatinine 3.1 mg/dL (0.5 to 14), proteinuria 6.5 g/day (0.8 to 25), 60% microhematuria, and 59% hypertension. Histologic patterns of FGN were diverse, including diffuse proliferative glomerulonephritis (DPGN) (nine cases), membranoproliferative glomerulonephritis (MPGN) (27 cases), mesangial proliferative/sclerosing (MES) (13), membranous glomerulonephritis (MGN) (four), and diffuse sclerosing (DS) (eight). The more proliferative (MPGN and DPGN) and sclerosing (DS) forms presented with a higher creatinine and greater proteinuria compared to MES and MGN. Median time to end-stage renal disease (ESRD) was 24.4 months for FGN and mean time to ESRD varied by histologic subtype: DS 7 months, DPGN 20 months, MPGN 44 months, compared to MES 80 months and MGN 87 months. There was no statistically significant effect of immunosuppressive therapy (given to 36% of FGN patients). By Cox regression (hazard ratio, confidence interval, *P* value), independent predictors of progression to ESRD were creatinine at biopsy [2.05 (1.55 to 2.72) $P < 0.001$] and severity of interstitial fibrosis [2.01 (1.05 to 3.85) $P = 0.034$]. Although IT had similar presentation, histologic patterns, and outcome compared to FGN, it had a greater association with monoclonal gammopathy ($P = 0.014$), underlying lymphoproliferative disease ($P = 0.020$), and hypocomplementemia ($P = 0.032$).

Conclusion. FGN is an idiopathic condition characterized by polyclonal immune deposits with restricted gamma isotypes. Most patients present with significant renal insufficiency and have a poor outcome despite immunosuppressive therapy, and outcome correlates with histologic subtype. By contrast, IT often contains monoclonal IgG deposits and has a significant association with underlying dysproteinemia and hypocomplementemia. Differentiation of FGN from the much more rare entity IT appears justified on immunopathologic, ultrastructural, and clinical grounds.

Key words: fibrillary glomerulonephritis, immunotactoid glomerulonephritis.

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Organized fibrillar or microtubular glomerular deposits may be encountered in a variety of renal disorders, including amyloidosis, cryoglobulinemic glomerulonephritis, lupus nephritis, collagen glomerulopathies, and the entities of fibrillary and immunotactoid glomerulonephritis. Fibrillary glomerulonephritis (FGN) is a distinctive but controversial glomerulopathy first reported by Rosenmann and Eliakim in 1977 [1]. This rare disorder comprises less than 1% in renal biopsy series and usually presents with renal insufficiency, nephrotic range proteinuria, and microhematuria [2, 3]. It is characterized pathologically by the deposition in glomeruli of fibrillar deposits that generally range from 16 to 24 nm in diameter [2, 3]. These fibrils usually stain for immunoglobulin G (IgG) and C3, with more variable and weaker positivity for other immunoglobulins [2]. By definition, the glomerular deposits are Congo red–negative, allowing their differentiation from amyloid. Hence, synonyms for FGN include "nonamyloidotic fibrillary glomerulonephritis" and "Congo red–negative amyloidosis-like glomerulopathy" [4–6].

There is considerable debate about the relationship of FGN to immunotactoid glomerulonephritis (IT), an

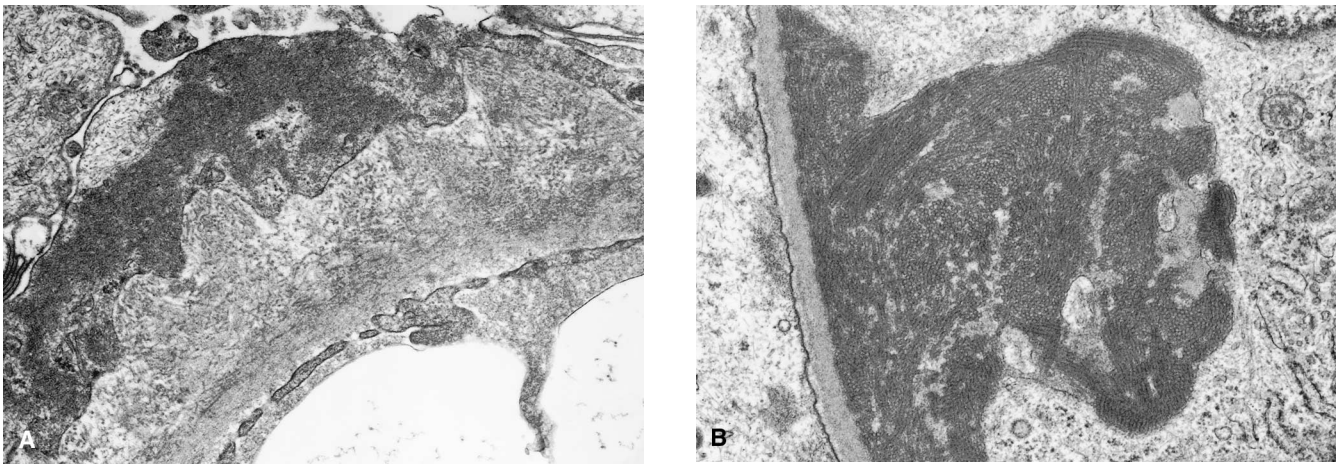

Fig. 1. Electron microscopic features of fibrillary glomerulonephritis (FGN) and immunotactoid glomeronephritis (IT). (*A*) An example of FGN displays intramembranous, randomly oriented fibrils of mean 20 nm diameter that infiltrate and thicken the glomerular basement membrane. The fibrils lack hollow centers and parallel stacking. Magnification ×15,000. (*B*) An example of IT exhibits subendothelial accumulation of microtubules of 35 nm diameter with hollow centers arranged in parallel stacks. The microtubules do not infiltrate the glomerular basement membrane. Magnification ×15000.

entity with larger microtubular deposits, usually >30 nm in diameter, which are often hollow and arranged in parallel or stacked arrays [3, 7–12]. Proponents of the view that FGN and IT are related entities have argued that morphologic differences, such as hollow centers and parallel bundling, are merely a function of fibril diameter and the resolution of the electron microscope rather than their intrinsic physicochemical properties or etiologic differences [12]. The identification of underlying dysproteinemia or autoimmune disorders in a subgroup of patients with the IT pattern has led some investigators to continue to split IT from FGN, an entity in which most patients have no underlying systemic disorder [9]. Yet, other investigators prefer to use the term IT for both entities, insisting that there is insufficient knowledge about differences in pathogenesis to justify their distinction on morphologic grounds alone [7, 8, 12].

In order to enlarge our understanding of the morphologic and clinical features of these controversial entities, we report the results of renal biopsies from 61 patients with FGN and from six patients with IT. Our findings underscore a more diverse histologic spectrum of FGN than previously recognized. Based on the clinical, immunopathologic, and ultrastructural differences between these entities, we advocate the continued segregation of FGN from the more rare entity of IT.

METHODS

Renal biopsies from 60 patients with FGN and six patients with IT were identified retrospectively from among 10,108 native kidney biopsies in the files of the Columbia University Renal Pathology Laboratory over a period of two decades (1980 to 2001). The single case of FGN identified in a renal allograft was also included in the study. FGN was defined as the glomerular deposition of fibrils that were (*1*) randomly oriented; (*2*) lacked hollow centers at magnifications of <30,000×; (*3*) measured <30 nm in diameter; (*4*) were Congo red–negative; and (*5*) stained with antisera to immunoglobulins by routine immunofluorescence (Fig. 1A). IT was defined as glomerular microtubular deposits that were (*1*) oriented in stacked or parallel arrays; (*2*) had hollow centers at magnifications of <30,000×; (*3*) measured ≥30 nm in diameter; (*4*) were Congo red–negative; and (*5*) stained with antisera to immunoglobulins by routine immunofluorescence (Fig. 1B). For a single case with microtubules measuring less than 30 nm in diameter, a designation of IT was given because the microtubules had hollow centers and formed parallel arrays. Biopsies with a clinicopathologic diagnosis of amyloidosis (defined as Congo red–positive fibrils of 8 to 12 nm diameter), cryoglobulinemic glomerulonephritis, lupus nephritis, and collagen glomerulopathy were excluded.

Renal biopsies were processed by standard techniques for light microscopy, immunofluorescence, and electron microscopy. For immunofluorescence, 3 μm cryostat sections were stained with fluorescein isothiocyanate (FITC)-conjugated rabbit antihuman IgG, IgM, IgA, C3, C1q, kappa light chain and lambda light chain (Dako Corporation, Carpenteria, CA, USA). IgG subtypes (studied in 19 FGN and four IT cases with residual archival frozen tissue) were analyzed by direct immunofluorescence using polyclonal FITC-conjugated antibodies to IgG1, IgG2, IgG3 and IgG4 (The Binding Site, Birmingham, UK) at concentrations standardized by the manufacturer. Electron microscopy was performed with a Philips 300 (Am-

sterdam, The Netherlands) or JEOL 100S electron microscope (Tokyo, Japan). Fibril diameter was measured with a hand-held magnification graticule (Graticules Ltd., Tonbridge, UK) by averaging the measurements in 10 high-power fields and correcting for the magnification of the negative and the factor of print enlargement. Only fibrils with distinct borders cut in cross-section were measured.

Clinical data were gathered retrospectively by review of hospital charts and office charts of the referring nephrologists. Follow-up information was obtained on all but four cases. The following clinical definitions were used. Renal insufficiency was defined as serum creatinine $\geq$1.5 mg/dL; hypertension as blood pressure >140 mm Hg systolic or >90 mm Hg diastolic; nephrotic syndrome as 24-hour urinary protein $\geq$3.5 g accompanied by edema and serum albumin <3.5 gm/dL; microhematuria as >5 red blood cells (RBC)/ high-power field on urinalysis.

Statistical analysis was performed using nonparametric exact statistical methods, including the Fisher exact test and the Kruskal-Wallis test for categorical variables and the Mann-Whitney test for continuous variables, where appropriate. Comparison among multiple groups with normally distributed data was performed by one-way ANOVA with post-hoc analysis using tests where equal variance is not assumed (Tamhane's T2 and Dunnett's T3). Multivariate analysis was performed by logistic regression analysis with end-stage renal disease (ESRD) as the dependent variable and by the Cox proportional hazards model with risk of progression to ESRD over time as the dependent variable. Survival analysis was performed by the method of Kaplan-Meier using the log-rank test for analysis of statistical significance. Analysis was performed using SPSS v11.0 (SPSS, Chicago, IL, USA) and STATXact v5.0 (Cytel Software Corp., Cambridge, MA, USA). Statistical significance was assumed at $P < 0.05$.

RESULTS

Clinical features of FGN

The diagnosis of FGN was made in 0.6% of 10,108 native kidney biopsies accessioned by the Renal Pathology Laboratory of Columbia University from 1980 to 2001. The single case of FGN identified in a renal allograft was also included in the study. Patients with FGN included 24 males and 37 females (total, 61 patients) age 28 to 81 years old (mean, 56.8 $\pm$ 1.6 years). These included 56 Caucasian, three African American, and two Hispanic patients. Associated medical conditions and serologic findings are summarized in Table 1. There was a low incidence of underlying nonhematologic malignancies (5%) (including one each of lung, colon, and renal cell carcinomas), lymphoproliferative disease (2%), myeloproliferative disease (2%), vasculitis (3%), and hepatitis or cirrhosis (5%). A single patient had history of systemic lupus erythematosus, but lacked renal biopsy findings of lupus nephritis. Other autoimmune or inflammatory conditions included thyroiditis in three patients, rheumatoid arthritis in one patient, temporal arteritis in one patient, gout in two patients, bronchiectasis in one patient, and intravenous drug abuse in two patients. No patient had clinical or serologic evidence of human immunodeficiency (HIV) infection. One patient who had undergone a kidney transplant 12 years earlier for ESRD of unknown etiology developed FGN in her transplanted kidney, although it could not be ascertained whether this represented de novo or recurrent disease. The incidence of diabetes mellitus was 20%; however, no patient had renal biopsy findings of diabetic nephropathy. Although 17% of patients tested had antibodies to hepatitis C, only three patients (5%) had clinical evidence of active hepatitis. Fifteen percent of those tested had a monoclonal protein identified in the serum or urine. Sixteen percent had a positive antinuclear antibody (ANA), which was of low titer (<1:160) in all but two cases and was never accompanied by hypocomplementemia. A single patient had hypocomplementemia (reduced serum C3). One patient had a positive test for serum cryoglobulins. No patient with FGN had clinical or pathologic evidence of systemic involvement by fibrillary deposition.

Renal manifestations at the time of biopsy (Table 1) included renal insufficiency in 44 of 61 (72%) patients, with mean serum creatinine 3.1 $\pm$ 0.34 mg/dL (range, 0.5 to 14 mg/dL). Thirty-six patients (59%) were hypertensive at presentation. All patients presented with proteinuria, with mean urinary protein 6.48 $\pm$ 0.60 g/day (range, 0.84 to 25 g/day). Among the 53 patients for whom adequate data are available, 28 (52%) had full nephrotic syndrome. Mean serum albumin was 3.14 $\pm$ 0.09 g/dL (range, 1.3 to 4.4 g/dL) and mean serum cholesterol was 256 $\pm$ 9.61 mg/dL (range, 146 to 421 mg/dL). Hematuria was present in 60% (33/55) of patients with documented urinalysis, including two patients with gross hematuria.

Clinical features of IT

IT comprised only 0.06% of all native kidney biopsies. Of the six patients with IT, five were female (83%) and five were Caucasian. Other medical conditions and serologic findings are summarized in Table 1. Renal findings at presentation were similar to those of FGN; however, patients with IT had a significantly higher incidence of serum or urine monoclonal gammopathy, (67% vs. 15%) ($P = 0.014$), underlying lymphoproliferative disease ($P = 0.020$) and hypocomplementemia (33% vs. 2%) ($P = 0.032$) (Table 1). Of the four patients with monoclonal gammopathy, one had chronic lymphocytic leukemia; two had negative bone marrow biopsies; and one had

Table 1. Clinical parameters

Initial clinical parameters	Fibrillary ($N = 61$)	Immunotactoid ($N = 6$)	P value
Age *years*	56.8 (28–81)	66.3 (44–86)	NS
Female	37 (61%)	5 (83%)	NS
Race			
Caucasian	56 (92%)	5 (83%)	NS
African American	3 (5%)	1 (20%)	NS
Hispanic	2 (3%)	0	NS
Renal insufficiency	42 (69%)	5 (83%)	NS
Creatinine *mg/dL*	3.1 (0.5–14)	2.1 (1.4–3.8)	NS
24-hr urine protein *gm/day*	6.4 (.84–25)	8.7 (2.3–24)	NS
Proteinuria > 2 *gm/day*	52/57 (91%)	6/6 (100%)	NS
Edema	41 (67%)	4 (67%)	NS
Serum albumin *g/dL*	3.1 (1.3–4.4)	2.7 (1.1–3.7)	NS
Serum cholesterol *mg/dL*	256 (146–421)	236 (188–293)	NS
Nephrotic syndrome	28/53 (52%)	3 (50%)	NS
Hypertension	47 (77%)	3 (50%)	NS
Hematuria	33/55 (60%)	5 (83%)	NS
Associated medical conditions			
Diabetes mellitus	12 (20%)	1 (17%)	NS
Lymphoproliferative disease[a]	1 (2%)	2 (33%)	= 0.020
Carcinomas	3 (5%)	0	NS
Systemic lupus erythromatosus	1 (1.6%)	1 (17%)	NS
Autoimmune/vasculitis	2 (3%)	1 (17%)	NS
Cirrhosis/hepatitis	3 (5%)	0	NS
HIV	0	1 (17%)	NS
Positive serologies			
Hepatitis C	6/34 (17%)	1/5 (20%)	NS
Monoclonal spike (SPEP)	6/45 (13%)	4/6 (67%)	= 0.006
Monoclonal spike (UPEP)	4/35 (11%)	2/5 (40%)	NS
SPEP or UPEP	7/46 (15%)	4/6 (67%)	= 0.014
Antinuclear antigen	7/44 (16%)	0/4 (0%)	NS
Cryoglobulins	1/27 (4%)	0/6 (0%)[b]	NS
Low complements	1/46 (2%)	2/6 (33%)	= 0.032

All results reported as mean (range) or number (%). Abbreviations are: SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.
[a] Defined as lymphoproliferative disorder confirmed by bone marrow biopsy
[b] One case of immunotactoid glomerulonephritis subsequently developed cryoglobulinemia several months after the renal biopsy

mild plasmacytosis on bone marrow biopsy, but did not meet criteria for multiple myeloma. One of the IT patients with hypocomplementemia had known HIV and hepatitis C virus co-infection and had had two negative cryoglobulin determinations at the time of renal biopsy. However, a mixed cryoglobulin was identified on a third determination performed 2 months later.

Renal biopsy findings

Light microscopy. FGN biopsies manifested diverse histologic patterns (Table 2). The most common pattern, found in 44% of biopsies, was membranoproliferative glomerulonephritis (MPGN) defined by mesangial expansion with foci of mesangial interposition and replication of glomerular basement membrane (Fig. 2A). Twenty-one percent of biopsies had exclusively mesangial proliferation or sclerosis (MES) (Fig. 2B). Fifteen percent of patients had a diffuse proliferative (DPGN) pattern characterized by endocapillary proliferation including focal infiltrating leukocytes (Fig. 2C). A relatively uncommon pattern was membranous (MGN) (7%), featuring predominantly subepithelial fibrillar deposits separated by well-formed basement membrane spikes, with little or no mesangial hypercellularity (Fig. 2D). Transmembranous penetration of fibrils, which can mimick membranous glomerulopathy by light microscopy, was considered insufficient to qualify as the MGN pattern. Thirteen percent of biopsies had a nondescript diffuse sclerosing pattern (DS), defined as glomerular sclerosis obliterating >70% of glomeruli (Fig. 2E). In the DS group, a mean of 87% of glomeruli exhibited advanced sclerosis. For all histologic subgroups, the glomerular deposits typically exhibited tinctorial properties resembling amyloid with routine stains [glassy and weakly eosinophilic, weakly periodic acid-Schiff (PAS)–positive, gray-purple on trichrome stain, and nonargyrophilic]; however, all cases were Congo red–negative.

Thirty-one percent of all FGN cases had cellular or fibrocellular crescents. Crescents were most frequently identified in the DPGN subgroup, in which crescents involved mean 25% (range, 0% to 57%) of glomeruli. Crescents also involved mean 4.7% of glomeruli with MPGN pattern, 3.5% of glomeruli with MGN pattern, but no example of MES. Interstitial disease was most severe in the DS subgoup, in which all biopsies (100%) displayed moderate to severe interstitial fibrosis, fol-

Table 2. Histologic findings and clinical correlations in fibrillary glomerulonephritis (FGN)

Histologic pattern	No. of cases (%) ($N = 61$)	Mean creatinine ($N = 61$)	Mean proteinuria *gm/day* ($N = 57$)	Nephrotic ($N = 53$)	Serum albumin ($N = 54$)	Hematuria ($N = 55$)	Hematocrit ($N = 46$)	% Crescents ($N = 61$)	Moderate/severe interstitial disease
MPGN	27 (44%)	3.3 (±0.55)	8.2 (±1.10)	17/23 (74%)	3.0 (±0.09)	15/25 (60%)	33.6 (±0.91)	4.7%	20/27 (74%)
MES	13 (21%)	1.7(±0.28)	3.6 (±0.84)	1/13 (8%)	3.8 (±0.13)	6/11 (55%)	37.0 (±1.84)	0.0%	8/13 (61%)
DPGN	9 (15%)	4.1 (±0.95)	6.7 (±0.93)	5/7 (71%)	2.4 (±0.32)	6/8 (75%)	32.9 (±2.96)	25.0%	5/9 (56%)
MGN	4 (7%)	0.8 (±0.09)	4.7 (±1.13)	1/3 (33%)	3.5 (±0.28)	1/4 (25%)	41.4 (±1.35)	3.5%	1/4 (25%)
DS	8 (13%)	5.1 (±1.0)	5.7 (±0.78)	4/7 (57%)	3.1 (±0.09)	5/7 (71%)	32.2 (±2.61)	5.4%	8/8 (100%)
P value (ANOVA)		<0.001	0.027	0.001[a]	<0.001	NS	NS	0.009	0.009
Post-hoc analysis		DS > MES, MGN	MPGN > MES	MPGN, DPGN, DS > MES	MES > MPGN DPGN, DS			MPGN, DPGN > MES	DS > MPGN, MES, DPGN, MGN

Abbreviations are: MPGN, membranoproliferative glomerulonephritis; MES, mesangial proliferative/sclerosing; DPGN, diffuse proliferative glomerulonephritis; MGN, membranous glomerulonephritis; and DS, diffuse sclerosing.

[a] By Fisher exact test

lowed by MPGN (74%), MES (61%), DPGN (56%), and MGN (25%).

Of the six cases of IT, three (50%) had an MPGN pattern (one with associated membranous features) and three (50%) exhibited a DPGN pattern (of which two had associated membranous features) (Fig. 2F). Crescents were not identified in any IT case.

Immunofluorescence microscopy. Among the FGN cases, all stained with antisera to immunoglobulins and 96% displayed glomerular positivity for IgG, with mean intensity of 2.19 (scale 0 to 3+). Fifty-two percent of cases were reactive for IgM (mean intensity of positive cases, 1.04), 30% for IgA (mean intensity, 0.72). C3 was detected in 83% of cases (mean intensity, 1.76), compared to 41% reactivity for C1q (mean intensity, 0.98). In 96%, there was staining for both kappa and lambda light chains, without evidence of light chain predominance. However, in one case, only kappa light chain was identified, and in another only lambda light chain was identified, each with 1+ intensity. The texture of the staining by immunofluorescence was typically smudged without distinct linearity or granularity.

Among the IT cases, all six displayed glomerular positivity for IgG (mean intensity, 2.20), three of six for IgM (mean intensity of positive cases, 1.17), two of six for IgA (mean intensity, 0.75), six of six for C3 (mean intensity, 1.33), and four of six for C1q (mean intensity, 1.13). Four cases (66%) showed monoclonal IgG deposition with light chain restriction (three kappa, one lambda). All four of these patients had a monoclonal protein (3 IgGκ and 1 IgGλ) identified in their serum, and two also had free kappa light chain in the urine. The other two cases had glomerular staining for both kappa and lambda light chains, without evidence of light chain predominance. One of the latter cases was a patient with hypocomplementemia and co-infection with HIV and hepatitis C virus, who was later documented to have a circulating mixed cryoglobulin.

Electron microscopy. The mean diameter of the glomerular fibrils was 20.1 ± 0.4 nm (range, 13 to 29 nm) in the 61 cases with FGN. Fibrils were most commonly detected in the mesangium (98%) or within the glomerular basement membrane (92%), with subepithelial or subendothelial distribution in only 13% of cases. Fibrillar deposits were identified in the tubular basement membranes in only 5% of cases. In no case were fibrils identified in Bowman's capsule or the walls of arteries or interstitial capillaries. In all cases the fibrils were randomly arranged and closely intermingled with the matrix material of the mesangium or glomerular basement membrane. Fibrils were often deposited on a background of more granular, amorphous electron dense deposits.

In IT, the mean diameter of the microtubules was 38.2 nm ± 5.7 (range, 20 to 55 nm). One case with microtubules of 20 nm diameter was classified as IT

rather than FGN because of the presence of hollow centers and arrangement of the microtubules in parallel arrays. Among the six IT cases, five had mesangial deposits, three had intramembranous deposits, six had subendothelial deposits, and three had subepithelial deposits. No microtubules were identified in the tubular basement membranes, Bowman's capsule, or walls of blood vessels or interstitial capillaries.

IgG subtyping. Staining for the IgG subtypes was performed on 19 FGN cases for which residual frozen tissue was available. Monotypic deposits composed of a single gamma subtype were found in four cases (two IgG1 and two IgG4). Oligotypic deposits (containing both IgG1 and IgG4, but not IgG2 or IgG3) were found in the remaining 15 cases (Fig. 3 A to D). All 19 had apparently polyclonal deposits (with equivalent staining for kappa and lambda light chain). By contrast, among a control group of 80 biopsies with lupus nephritis, 81.3% stained for IgG1, 88.8% for IgG2, 96.3% for IgG3, and 36.3% for IgG4. No lupus nephritis case had staining for IgG1 alone or IgG4 alone. Moreover, no lupus case had copositivity for IgG1 and IgG4, with negativity for IgG2 and IgG3.

Among the five cases of IT with frozen tissue available for IgG subtype staining, four cases contained monoclonal deposits of IgG1 subclass (including three IgG1 kappa and one IgG1 lambda) (Fig. 3 E and F). One of these four cases had monoclonal (3+) staining for IgG1 kappa in a membranous pattern in the single non-sclerotic glomerulus sampled, however there was 1+ IgG1, 1+ IgG2, trace IgG3, and trace IgG4 in several globally sclerotic glomeruli. Interestingly, this patient was known to have had a past history of systemic lupus and biopsy-documented lupus nephritis in 1993, 7 years before the development of monoclonal IgG κ monoclonal gammopathy and the repeat biopsy containing microtubular deposits of monoclonal IgG κ. The fifth case with HIV and hepatitis C virus co-infection had oligotypic deposits of IgG2 and IgG3, with negativity for IgG1 and IgG4.

Clinicopathologic correlations at presentation

In FGN, histologic pattern correlated with both the severity of renal insufficiency and the amount of proteinuria at presentation (Table 2). Presenting mean serum creatinine was higher in the DS, DPGN, MPGN cases (5.1 mg/dL, 4.1 mg/dL, and 3.3 mg/dL, respectively) when compared with MES and MGN (1.7 mg/dL and 0.8 mg/dL). Mean proteinuria was higher in the patients with MPGN, DPGN, and DS (8.2 g/day, 6.7 g/day, 5.7 g/day, respectively) when compared with MES and MGN (4.7 g/day and 3.6 g/day). Seventeen of 23 (74%) patients with MPGN had full nephrotic syndrome, followed by five of seven (71%) patients with DPGN, four of seven (57%) patients with DS, one of three (33%) of those with MGN, and only one of 13 (8%) of those with MES.

For IT, cases were too few to permit analysis of correlations between histologic findings and presenting clinical features.

Outcome

Of the patients with FGN, five patients were lost to follow-up. The remaining 56 patients were followed for a mean of 23 months (0 to 128 months). Twenty-five patients (45%) developed ESRD. While only 18% of patients who presented without renal insufficiency (creatinine <1.5 mg/dL) progressed to ESRD, 72% (23/32) of patients who presented with a creatinine ≥ 2.0 mg/dL reached ESRD. The median time to ESRD was 24.4 ± 15.2 months (mean, 57.6 ± 9.49 months). Mean time to ESRD varied according to histologic subtype ($P = 0.001$), (Fig. 4). The histologic subgroups of DS, DPGN, and MPGN progressed more rapidly to ESRD (mean, 7 months, 20 months, and 44 months, respectively) compared to MES and MGN (mean, 80 months and 87 months, respectively). On univariate analysis, outcome correlated significantly with a number of factors, including histologic subtype ($P < 0.001$) (Table 3). On multivariate Cox regression analysis, only serum creatinine at biopsy ($P < 0.001$) and severity of interstitial fibrosis ($P = 0.034$) correlated with outcome (Table 4).

The six patients with IT were followed for a mean of 10 months (2 to 20 months). One patient who presented with a creatinine of 2.2 mg/dL progressed to ESRD in 2 months. The other patients have persistent, significant renal insufficiency, without progression to ESRD. The mean renal survival for the IT group was 17.2 months. The number of IT patients is too small to analyze statistically the differences in outcome between IT and FGN.

Treatment

Among FGN patients, 20 of 56 (36%) received immunosuppressive therapy, including steroids alone in 16%, cyclophosphamide (with or without steroids) in 14%, and cyclosporine in 5%. The type of immunosuppressive therapy offered was generally tailored to histologic subtype. Steroids alone or cyclophosphamide were offered only to patients with DPGN (22% received steroids alone and 56% received cyclophosphamide), MPGN (15% received steroids alone and 4% received cyclophosphamide), MES (15% received steroids alone and 15% received cyclophosphamide). Cyclosporine was offered to patients with MGN (50%) and DS (13%).

The use of immunosuppressive therapy did not correlate with outcome parameters, including incidence of ESRD or time to ESRD in any histologic subgroup. Nevertheless, an apparent partial response to therapy was found in several individuals. In one FGN patient with DPGN, serum creatinine fell from 6.2 mg/dL to 2.6 mg/dL following an 8-month course of intravenous cyclophosphamide and prednisone, although he ulti-

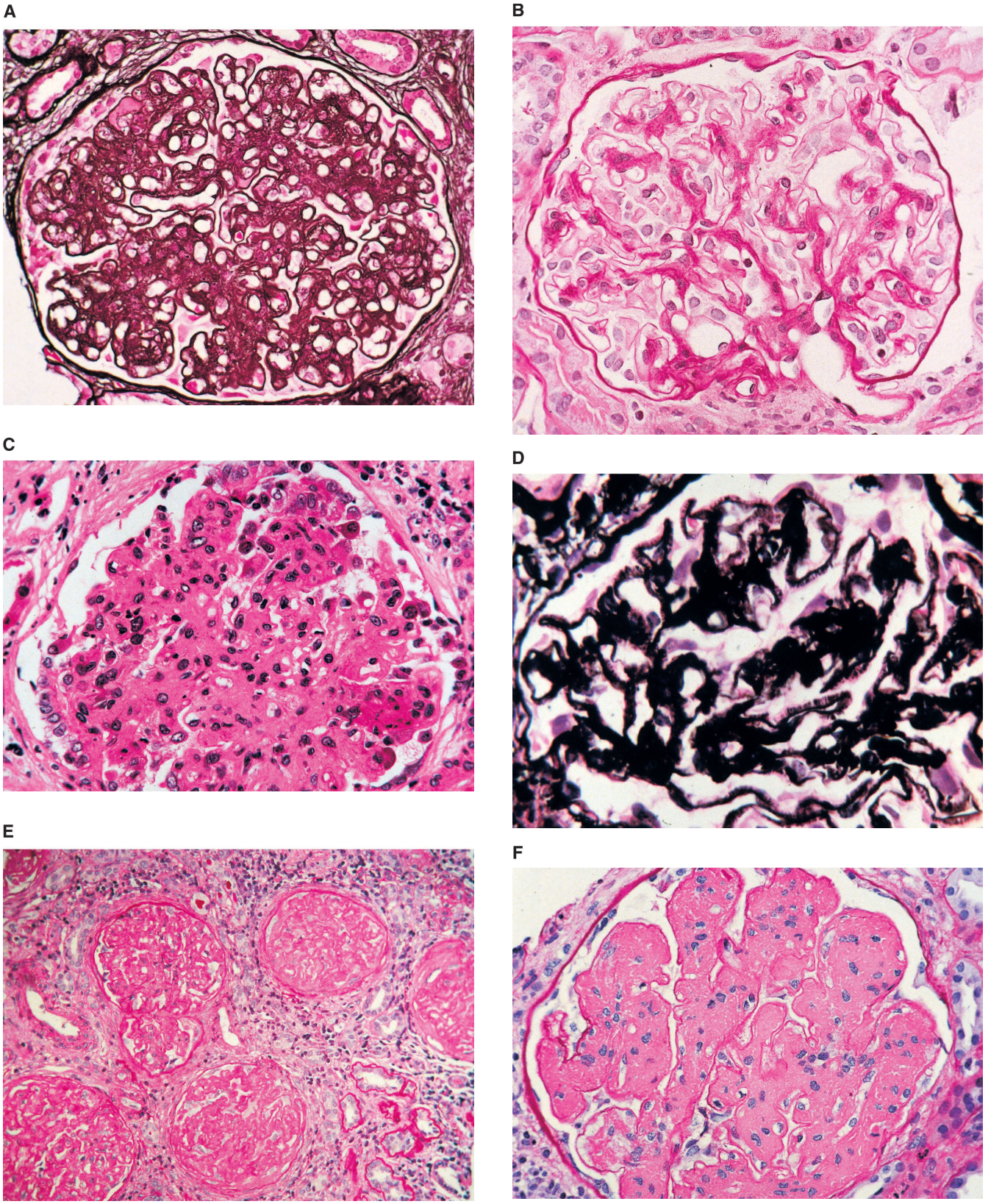

Fig. 2. Light microscopic features of fibrillary glomerulonephritis (FGN) and immunotactoid glomeronephritis (IT). (*A*) The most common histologic pattern of FGN is membranoproliferative glomerulonephritis, with mesangial proliferation and increased mesangial matrix, double contours of the glomerular basement membrane, and mesangial interposition (Jones methenamine silver, ×400). (*B*) The mesangial pattern of FGN is characterized by mild mesangial expansion composed of mesangial cells and matrix. The glomerular capillary lumina are patent and glomerular

mately progressed to ESRD despite a second course of immunosuppressive therapy. In a second FGN patient with MPGN pattern, creatinine fell from 7.3 mg/dL to 4.8 mg/dL following 6 months of intravenous cyclophosphamide and prednisone. A patient with DS was treated with 5 months of cyclosporine followed by a fall in her proteinuria from 5.8 g/day to 2.0 g/day; however, creatinine rose from 1.9 mg/dL to 2.7 mg/dL during the treatment period. One FGN patient with MGN pattern, normal serum creatinine, and the nephrotic syndrome had a partial response to steroids with a fall in proteinuria from 6.3 g/day to 3.2 g/day, followed by a further decline to 1.3 g/day following an 18-month course of cyclosporine.

Three patients with IT who had monoclonal IgG deposits (two IgG κ and one IgG λ) and monoclonal gammopathy received treatment for their hematologic disease. One patient was treated with melphalan and prednisone and one with prednisone and immuran, followed by cellcept. Both of these patients did not show any obvious response to therapy as measured by stabilization of renal function or decrease in proteinuria**.** However a third patient with CLL was treated with a course of fludarabine and had a decrease in proteinuria from 7.8 g/day to 1.8 g/day and a fall in creatinine from 3.8 mg/dL to 1.7 mg/dL 3 months later.

Transplantation

Two patients received cadaveric kidney transplants during the follow-up period. One patient had no clinical evidence of recurrence after 8 years, with normal serum creatinine and no proteinuria. The other patient died 4 years after transplantation due to colon cancer with a stable creatinine of 2.2 mg/dL at the time of death. Because of stable graft function and absence of proteinuria, neither patient was subjected to allograft biopsy.

One patient was diagnosed with FGN in her allograft after having received a living-related donor transplant 12 years prior. The cause of her initial renal failure was unknown. Because her native kidney disease had its clinical onset at age 11, it is unlikely that her original renal disease was FGN. She experienced progressive graft failure despite the addition of oral cyclophosphamide to treat her FGN.

DISCUSSION

Our series represents the largest single-center series on FGN and IT published to date. Our data on FGN confirm a number of observations from earlier, smaller published series. The incidence of FGN of 0.6% of renal biopsies is similar to the incidence of 1% reported by Iskandar, Falk, and Jennette [2] and Fogo, Qureshi, and Horn [10]. We found a slight female preponderance (male:female ratio, 1.0:1.5) similar to the ratio of 1.0:1.3 in a compilation of reported cases reviewed by Brady [3]. Our strong Caucasian racial predominance of 11:1 is also similar to the 9:1 ratio reported by Brady [3]. The mean age at presentation of 57 years is only slightly higher than the mean ages of 49 to 51 years reported in other series [2, 10, 11].

Patients presented with high-grade proteinuria (mean, 6.5 g/day) at biopsy, similar to that reported in several other series [2, 10, 11]. Fifty-two percent of our patients had full nephrotic syndrome and 60% had hematuria, slightly less than the rates of 71% and 70%, respectively, reported by others [3]. Renal insufficiency was identified at presentation in 72% of cases, and the mean serum creatinine of 3.1 is similar to that reported by several groups [2, 10, 11].

Our findings confirm the high risk of ESRD in FGN, with a median renal survival in our patients of only 24 months from the time of biopsy. Our series is the first to document the utility of subcategorizing the diverse light microscopic patterns of FGN. MPGN was the most frequent histologic pattern (44%), followed by MES (21%), DPGN (15%), DS (13%), and MGN (7%). The predominant histologic pattern on biopsy correlated with clinical features on presentation including the severity of renal insufficiency, the amount of proteinuria, and the incidence of nephrotic syndrome. We also found that clinical outcomes, in terms of the percentage of patients reaching ESRD and the mean time to ESRD, correlated with histologic pattern. Not surprisingly, patients who had advanced sclerosis (DS) or severe proliferative features (DPGN or MPGN) had the worst prognosis. Conversely, patients with MGN and MES had both a lower risk of progression to ESRD and a slower rate of progression. The diversity of histologic subtypes and correlation with outcome is reminiscent of the pleomorphic renal pathologic findings in lupus nephritis. We believe that classifying FGN patients in a manner analogous to the World Health Organization (WHO) classification for lupus nephritis is useful to estimate risk of progression [13]. A mesangial or membranous lesion would be considered

basement membranes are of normal thickness [periodic acid-Schiff (PAS), ×400]. (*C*) The diffuse proliferative pattern of FGN has global endocapillary proliferation, including infiltrating leukocytes. There is segmental fibrinoid necrosis with karyorrhexis. An early, segmental cellular crescent is seen (at top) [hematoxylin and eosin (H&E), ×400]. (*D*) The membranous pattern of FGN has a normocellular tuft with global thickening of glomerular capillary walls, which contain spike-like projections of glomerular basement membrane material (Jones methenamine silver, ×650). (*E*) The diffuse sclerosing pattern exhibits diffuse and global solidification of the glomerular tuft by glassy PAS-positive material, with loss of cellular elements (PAS, ×120). (*F*) An example of IT displays mixed membranoproliferative and membranous pattern with lobular accentuation, marked mesangial expansion by cells and weakly PAS-positive deposits, and glomerular basement membrane thickening (PAS, ×400).

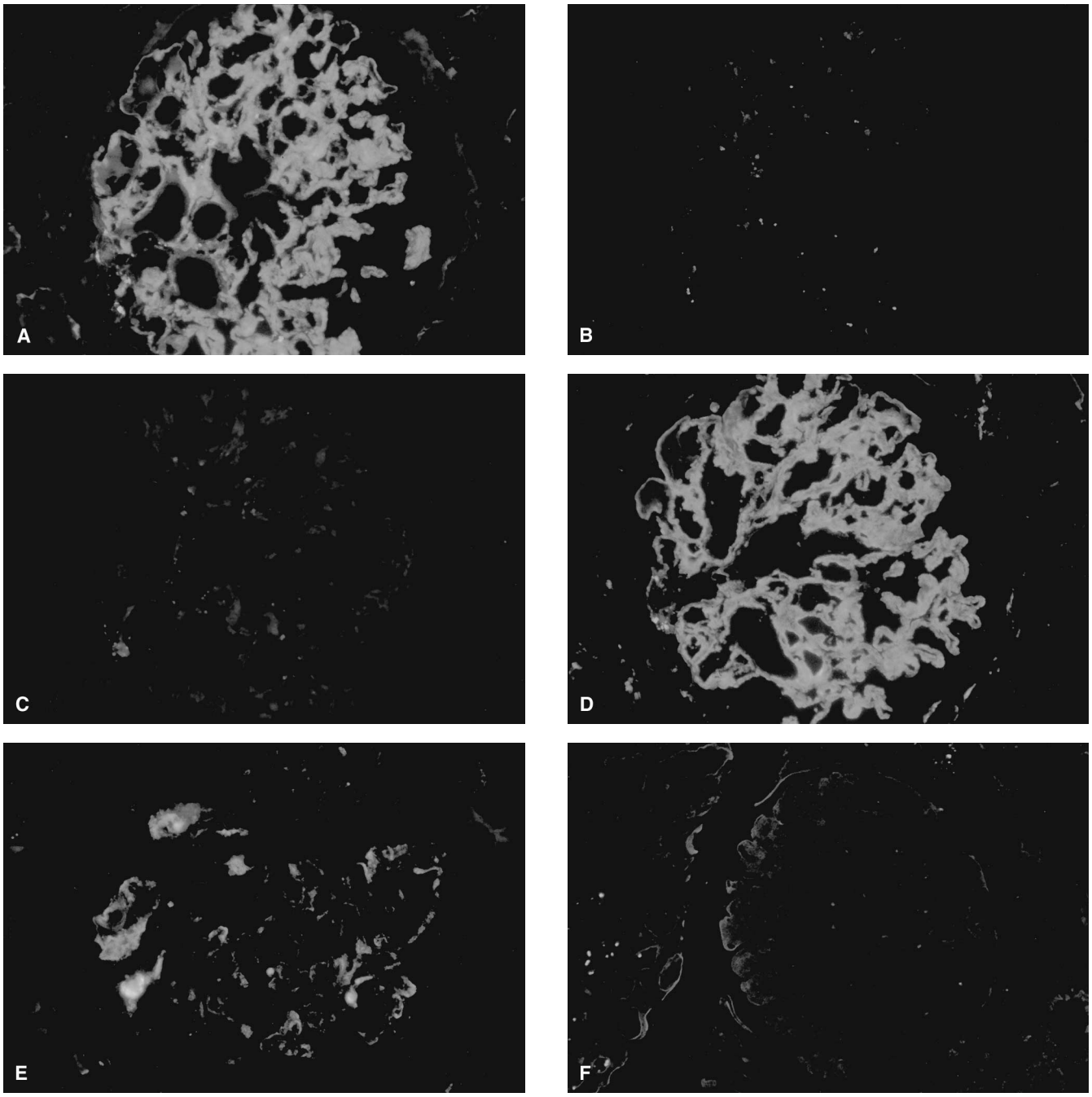

Fig. 3. Immunoglogulin G (IgG) subtyping in fibrillary glomerulonephritis (FGN) and immunotactoid glomeronephritis (IT). Representative glomerulus from a case of FGN shows high intensity, global mesangial and capillary wall positivity for IgG1 (*A*), negativity for IgG2 (*B*) and IgG3 (*C*), and similar high intensity positivity for IgG4 (*D*). The texture of the staining is "smudgy," without distinct granularity or linearity. A case of IT with monoclonal IgG lambda deposits shows positivity for IgG1 (*E*) in a mesangial and capillary wall distribution. There was negativity for IgG2 (*F*), IgG3 (not shown), and IgG4 (not shown) (all magnifications ×400).

analogous to class II and V lupus nephritis, with a lower risk of progressive renal failure than those with proliferative histologies akin to class III and IV lupus nephritis. Similarly, the DS form can be considered analagous to advanced lupus nephritis class VI. It is likely that the observed differences in outcome between these histologic subtypes are not a function of intrinsic differences in disease biology, but rather reflect differences in activity and chronicity.

We could not demonstrate a statistical benefit of treatment in this uncontrolled retrospective analysis. It is likely that the advanced degree of renal damage, as indi-

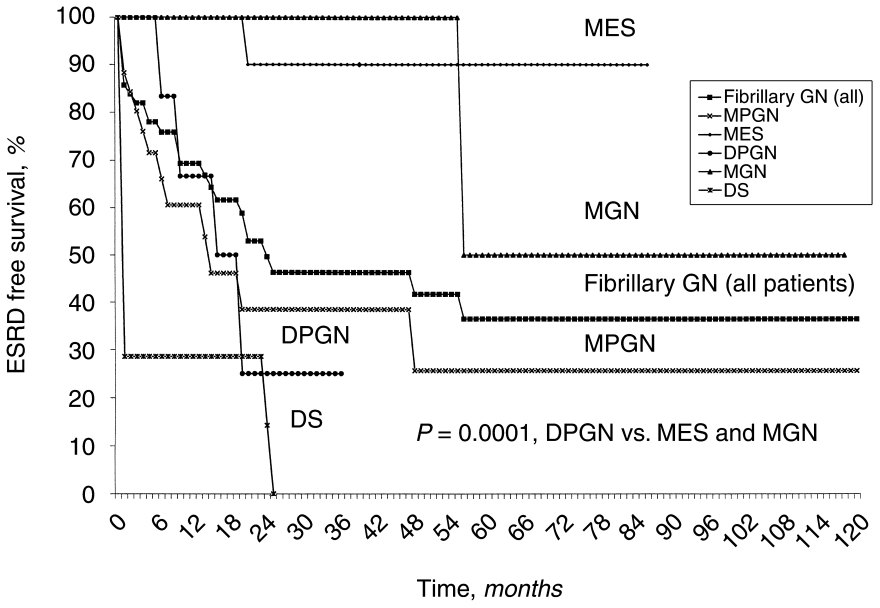

Fig. 4. Kaplan-Meier survival analysis in fibrillary glomerulonephritis (FGN) and its histologic subtypes. Abbreviations are: ESRD, end-stage renal disease; MPGN, membranoproliferative glomerulonephritis; MES, mesangial proliferative/sclerosing; DPGN, diffuse proliferative glomerulonephritis; MGN, membranous glomerulonephritis; and DS, diffuse sclerosing.

Table 3. Correlates of end-stage renal disease (ESRD) in fibrillary glomerulonephritis (FGN)—Univariate analysis

	P value
Histologic subtype	<0.001
Nephrotic syndrome	0.007
Severity of interstitial disease	<0.001
Presence of crescents	<0.001
Percentage of crescents	<0.001
Hematocrit	0.007
Proteinuria	0.001
Serum creatinine	<0.001
Serum albumin	0.001
Percentage of glomerulosclerosis	0.009

Abbreviations are: SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

Table 4. Correlates of end-stage renal disease (ESRD) in fibrillary glomerulonephritis (FGN)–Multivariate Cox regression

	P value
Serum creatinine	<0.001
Interstitial disease	0.034

cated by the mean serum creatinine of 3.1 mg/dL in FGN, contributed to the poor therapeutic response. However, several of our FGN patients had a transient response to therapy with cyclophosphamide or cyclosporine. Most dramatically, one patient with IT and underlying CLL, who had monoclonal glomerular deposition of IgG lambda, exhibited an impressive response to treatment with fludarabine, a nucleoside analog and potent antilymphocyte agent. This case is of particular interest given our recent observations of favorable response to fludarabine in patients with type 2 cryoglobulinemia and glomerulonephritis [14]. Prospective controlled study of a larger group of FGN and IT patients pooled from multiple centers is needed to determine the potential benefit of therapy and to define the optimal therapeutic regimen.

There is considerable controversy about the relationship of FGN to IT. Our series attests to the extreme rarity of IT (0.06%) compared to FGN (0.6% of native kidney biopsies), an entity that is approximately tenfold more common, but nonetheless rare. Although presenting renal characteristics were similar between FGN and IT, there were statistically significant differences with respect to the incidence of associated monoclonal gammopathy, hematologic malignancy, and hypocomplementemia. These differences are reflected in the differing immunopathologic composition of the glomerular deposits, which consisted of monoclonal IgG in 67% of IT cases. Whereas some investigators have argued that monoclonal gammopathy should be an exclusion criterion for IT [3, 8, 11], we disagree with that approach. How should cases of monoclonal microtubular deposits be classified, if not as IT? Microtubules are not a defining feature of Randall's type monoclonal immunoglobulin deposition disease [15]. The large diameter and Congo red–negativity of the organized deposits is inconsistent with renal amyloidosis. Finally, all six patients lacked an identifiable cryoglobulin at the time of renal biopsy, disqualifying them from categorization as a form of cryoglobulinemic glomerulonephritis, (although the single case with oligotypic deposits of IgG2 and IgG3 was demonstrated to have a mixed cryoglobulin months later). The category of IT appears most appropriate for this group and serves the useful purpose of identifying patients with a high probability of underlying dysproteinemia or occult cryoglobulinemia.

Cases of IT had microtubules that varied from 20 to 55 nm in diameter, and all but one case had microtubules

of ≥30 nm. Thus, although the range of microtubule diameter in IT overlapped slightly with that of FGN at its lowest reaches, more important criteria for distinguishing IT from FGN were the presence of hollow centers and the formation of parallel arrays in IT.

To our knowledge, only 15 patients with FGN undergoing transplant have been reported to date [11, 16–18]. A high incidence of recurrence (47% of allografts) has been reported [17], supporting the role of a circulating or systemic factor. Only three patients lost their allografts due to recurrent disease 5 to 13 years after transplant, whereas the others maintained stable or normal renal function up to 8 years posttransplant, indicating a relatively indolent course of recurrent FGN in the allograft [17]. Of the two patients in our series who were transplanted due to known FGN, neither was rebiopsied and neither had clinical evidence of recurrence. A third case probably represents the first example of de novo FGN in the allograft, (although a single case of de novo IT in the allograft has been reported) [19].

Our findings confirm that the glomerular deposits in FGN have dominant staining for IgG and C3, with weaker and more variable positivity for IgM, IgA, and C1q. The staining for both kappa and lambda light chain in all but two cases supports the polyclonal nature of the deposits [20]. These findings are in agreement with the immunoelectron microscopic observations by Yang et al [21] showing decoration of individual fibrils with immunogold labeling for IgG, kappa and lambda light chains, as well as amyloid P component, which may play a role in fibrillogenesis or resistance to proteolysis. Iskandar, Falk, and Jennette [2] noted that the immune deposits in FGN were almost exclusively composed of the IgG4 subclass, with few cases also staining weakly for IgG1. Our data confirm that the IgG deposited in FGN is subclass-restricted; however, we found only 10.5% of cases to be composed exclusively of monotypic IgG1 or IgG4 and 78.9% to have oligotypic deposits of both IgG1 and IgG4. This was in dramatic contrast to the findings in diffuse proliferative lupus nephritis where all four IgG subclasses were represented and IgG4 was never dominant. The homogeneous nature of the IgG deposition with respect to subclass may promote fibrillogenesis through the deposition of immunoglobulin proteins with similar structural and physicochemical properties. The homogeneous physical properties of the IgG deposits may prevail despite the apparently polyclonal composition of the immune deposits.

The source of immune stimulation in FGN remains obscure. On review of clinical data, no distinctive clinical profile emerges, although some patients with FGN had diverse underlying inflammatory, autoimmune, or neoplastic processes that could have served as sources of chronic antigenic stimulation. Of particular interest is hepatitis C virus infection, which was identified in 17% of FGN patients [22], and raises the question of a "slow cryoglobulin," a concept proposed by Rostagno et al [23]. Some cryoglobulins may be difficult to detect because they require longer than four days at 4°C for precipitation [23], or because they require the unique microenvironment of the glomerular filter. Fibril deposition in both IT and FGN is generally limited to the kidney, although there have been rare reports of fibrils found in other tissues, including lung, liver, and bone marrow [24–26]. No patient in our series had clinical evidence of fibril deposition in other organs, and only 5% had evidence of tubular basement membrane deposits. The renal-limited, and exclusively glomerular, deposition observed in the vast majority of cases of FGN suggests the potential importance of glomerular sieving to concentrate circulating immune reactants at the level of the glomerular capillary, where unique matrix interactions with fibronectin or other basement membrane components may occur. Of interest, one of our patients with FGN and MPGN pattern developed purpura due to leukocytoclastic vasculitis several months after initial renal biopsy, with negative serologies (including ANA, ANCA, hepatitis C virus, and cryoglobulins). To our knowledge this is the first association of vasculitis with FGN, although there are rare reports of vasculitis associated with IT [27, 28].

CONCLUSION

FGN is an idiopathic glomerular disease characterized by randomly arranged Congo red–negative fibrils of mean 20 nm diameter. Glomerular deposits are predominantly composed of polyclonal IgG and C3, with strong evidence of monotypic or oligotypic IgG subclass restriction. IT is defined by glomerular deposition of generally larger microtubules that are composed of monoclonal IgG in the majority of cases. Although renal presentation of FGN and IT are similar, patients with IT are more likely to have dysproteinemia, hypocomplementemia, and occult cryoglobulinemia. Based on these important clinical and immunopathologic distinctions and their implications for patient management, we believe the differentiation of FGN from IT is useful and well justified.

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