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Fibrillary glomerulonephritis with a favourable prognosis of 26 years

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ABSTRACT

Fibrillary glomerulonephritis (FGN) is a rare glomerular disease. The prognosis is usually unfavorable with nearly half of patients progressing to end-stage renal disease within 4 years. We report a case of biopsy-proven FGN characterized by an unusual benign clinical course in which a kidney biopsy, repeated after an extended follow-up of 26 years, confirmed the presence of fibrils deposition. In 1993, a 32-year-old Caucasian man was admitted to our nephrology ward because of macroscopic hematuria. Renal function was normal. Kidney biopsy displayed an FGN with mesangial pattern. The patient was treated with lisinopril, titrated for blood pressure; the therapy was maintained during 26 years of follow-up. The yearly slope of estimated glomerular filtration rate was -3.17 mL/min. Starting from March 2018, a rapid worsening of renal function was observed and proteinuria increased up to a nephrotic range. We planned a second renal biopsy to assess the cause of the rapid change of clinical course. The diagnosis of FGN on advanced sclerosis was made, and the severity of glomerular sclerosis. We report a case of FGN with an unusually benign clinical course, characterized by a slow progression to end-stage renal disease over a very extended follow-up time; thus, to better clarify the reason for renal function worsening, a second renal biopsy was performed. The persistence of fibrils deposition confirmed the initial diagnosis of FGN, and a histological pattern characterized by global glomerular sclerosis and interstitial fibrosis has been observed.

Implication for health policy/practice/research/medical education:

Fibrillary glomerulonephritis (FGN) is an uncommon disease, since diagnosis in the past required electron microscopy and the prognosis of the disease was really unfavorable. Here, we described an unusual case of FGN with 26 years of prognosis without progression to end-stage renal disease and not required dialysis.

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Introduction

Fibrillary glomerulonephritis (FGN) is a rare glomerular disease (less than 1% of glomerulonephritis) (1-4) characterized by the deposition of randomly distributed non-amyloid fibrils in the mesangium and capillary basement membrane (5,6). The prognosis is usually unfavorable with nearly half of patients progressing to end-stage renal disease (ESRD) within 4 years (1-4). The pathogenesis is still unclear, while studies highlighted

a possible association with autoimmune disease, malignancy, or hepatitis C infection (4,7,8). Recently, a potential role of DNA homolog subfamily B member 9 (DNAJB9) in causing FGN has been reported (5,9,10). The glomerular deposits usually stain for polyclonal IgG, mostly subtypes IgG1 and IgG4 (3,11). In this disease, immunoelectron studies have shown the co-localization of polyclonal IgG to the FGN fibrils (2,12,13). The clinical feature is usually a therapy-resistant nephrotic syndrome,

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hematuria, arterial hypertension and a progressive renal impairment, which is present in 50% of all cases of FGN at the time of diagnosis (3,4,8,14).

Here, we report a patient with biopsy-proven FGN characterized by an unusual benign clinical course in which a kidney biopsy, repeated after an extended follow-up of 26 years, confirmed the presence of fibrils deposition.

Case Presentation

In 1993, a 32-year-old Caucasian man was admitted to our nephrology ward because of macroscopic hematuria. Main laboratory tests are reported in Table 1. Serum creatinine (Scr) was 0.9 mg/dL with an estimated glomerular filtration rate (eGFR) of 112 mL/min/1.73m². Urinalysis showed 20-40 RBC and 1-2 granular casts in high-power field (HPF) with 24-hour urinary protein excretion of 0.6 g. Serum electrophoresis revealed no abnormalities, and Bence-Jones protein was not detected in the urine sample. Serum C3, C4, and total Ig levels were normal. Additionally, ANA, ANCA, extractable nuclear antigen, and cryoglobulins were absent. Serology markers for hepatitis B and C were negative. Clinical history, as well as the physical examination, was negative. A percutaneous renal biopsy was carried out. Light microscopy showed 10 glomeruli with diffuse mesangial matrix expansion and thickened capillary walls. The arteries displayed mild intimal fibrosis, while arterioles, tubules, and interstitium were normal. Immunofluorescence investigation on frozen sections (5 glomeruli) showed granular mesangial deposition of IgG (2+), C3 (1+), k and l light chains (++) . Congo red staining was negative. Electron microscopy revealed randomly arranged non-branching fibrils of approximately 15 nm in diameter in the mesangium and sub-endothelial space (Figure 1A, 1B) with diffuse foot process effacement (Table 1).

Tangri kidney failure risk equation (16) resulted at 0.2% of risk to progression to ESRD over 5 years.

The patient was treated with lisinopril, titrated for blood pressure. The therapy was maintained during 26 years of follow-up. The yearly slope of eGFR was -3.17 mL/min). Starting from March 2018, a rapid worsening of renal function was observed (Scr 2.1 mg/dL, eGFR 35 mL/min/1.73m²) (Figure 2) and proteinuria increased up to a nephrotic range (9.8 g/24 h) despite an optimal blood pressure control (<130/80 mm Hg). Immunological tests were still negative, and serum complement profile was average. No paraproteins were detected in serum and urine electrophoresis. Renal ultrasound showed normal-sized kidneys. We planned a second renal biopsy to assess the cause of the rapid change of clinical course (i.e., superimposed glomerulonephritis versus FGN progression) and to evaluate the indication for emergent treatment strategies (e.g., rituximab) (7,15). Light

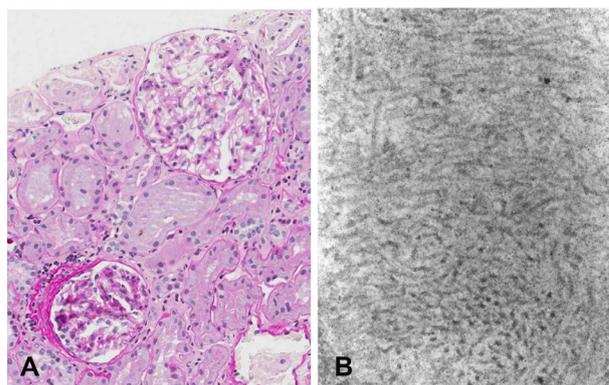


Figure 1. (A) in 1993 Kidney biopsy specimen shows diffuse mesangial matrix expansion and thickened capillary walls. (B) electron microscopy revealed randomly arranged non-branching fibrils of approximately 15 nm in diameter in the mesangium and sub-endothelial space with diffuse foot process effacement.

microscopy displayed 15 glomeruli; 12 globally sclerosed, 3 with diffuse mesangial matrix increase associated in 2 of them with global fibrotic crescents. The arteries displayed narrowing of the lumens with wall fibrosis. Some hyaline casts were detected inside the tubules. Polymorphic infiltrates and area of fibrosis were present in the interstitial space. Immunofluorescence examination on paraffin showed segmental, granular deposition of IgG (1+), IgM (1+), fibrinogen (1+) along the capillary walls. Congo red staining was negative. The staining for IgG4 was positive. Ultrastructural investigation revealed randomly arranged non-branching fibrils of approximately 15 nm in diameter in the mesangium (Figure 2A, B, C, D; Table 1).

Tangri kidney failure risk equation (16) resulted in 77.6% in risk to progression to ESRD over two years.

The diagnosis of FGN on advanced sclerosis was made, and the severity of glomerular sclerosis discouraged us to treat the patient with rituximab.

Discussion

We report a case of FGN with an unusually benign clinical course, characterized by a slow progression to ESRD over a very extended follow-up time. Indeed, in our patient an advanced chronic kidney disease was evident after 26 years from initial diagnosis; thus, to better clarify the reason for renal function worsening, a second renal biopsy was performed. The persistence of fibrils deposition confirmed the initial diagnosis of FGN, and a histological pattern characterized by global glomerular sclerosis and interstitial fibrosis has been observed.

As a rule, FGN has a relentless progression towards ESRD, since 40-50% of patients require dialysis after an average of two years from the diagnosis (2-4,15). In a case series from Columbia University, including 61 patients with FGN, the median time to ESRD was 24.4±15.2

Table 1. Laboratory and histological findings at first renal biopsy and at the time of the second kidney biopsy

	1993	2019
Laboratory data		
Serum creatinine (mg/dL)	0.9	3.32
Urinary protein excretion (g/24 h)	0.6	10.2
eGFR (mL/min/1.73 m ²)	112	19
BUN (mg/dL)	19.2	46.7
Total serum proteins (g/dL)	7.3	4.8
Serum albumin (g/dL)	3.12	2.6
Hemoglobin (g/dL)	14.3	11.3
RBC (U/ μ l)	4.950.000	3.740.000
WBC (U/ μ l)	6.700	5.830
PLTs (U/ μ l)	194.000	226.000
Urinary sediment	RBC 40 hpf	RBC 10-20 hpf
Biopsy findings		
Glomeruli #	10	15
Crescents #	None	2 (fibrotic)
Sclerosis and/or hyalinosis #	None	12
Mesangial matrix increase#	10	3
Tubular atrophy/interstitial fibrosis	None	Diffuse
Congo red stain	neg	neg
Immunofluorescence	IgG (2+), C3 (1+), e C1q (0/1+)	IgG, IgM, Fibrinogen (+)
Deposit type (EM)	Fibrils 15 nm	Fibrils 15 nm
Deposit location (EM)	M, BM	M, BM

months (3). Average time to ESRD varied according to histologic subtype with the worst renal outcome associated with membranous proliferative, diffuse proliferative and diffuse sclerosing patterns; in particular, time to ESRD ranged from 80 months in mesangial pattern to only 7 months in sclerosing glomerulonephritis (3). Furthermore, multivariate analysis selected sCr at the time of biopsy and severity of interstitial fibrosis as the main prognostic factors (3). In a series from the Mayo Clinic, including 66 patients for an average follow-up period of 52.3 months, 44% of patients reached ESRD during the observation period; main independent predictors of the rate of progression to ESRD were higher percentage of global glomerulosclerosis, older age, higher creatinine, and higher 24-hour urine protein excretion at the time of biopsy (4).

Progressive damage secondary to the deposition of fibrils was generally considered due to the release of profibrotic cytokines as transforming growth factor-beta associated with activation of the NOTCH1 pathway [S8, S9]. Recently, Nasr et al proposed a pathogenic role for DNAJB9, a heat-shock protein that acts as co-chaperone

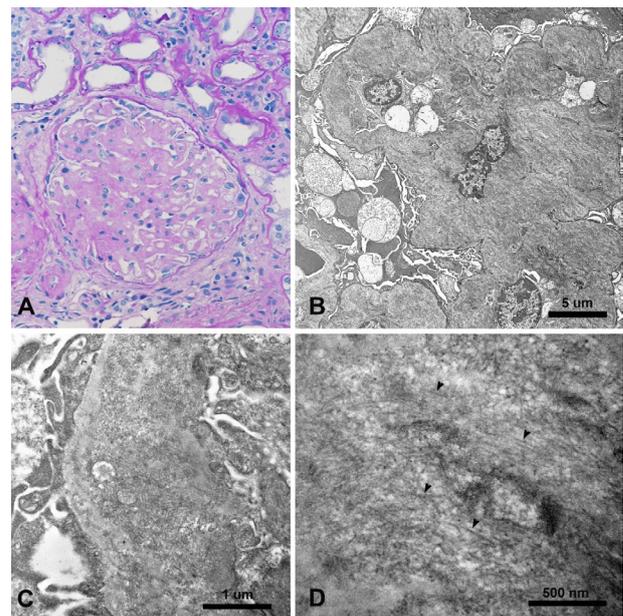


Figure 2. In 2019 kidney biopsy specimen shows diffuse mesangial matrix increase associated with global fibrotic crescents (PAS \times 40). (B, C and D) EM revealed deposition of randomly arranged non-branching fibrils of approximately 15 nm in diameter in the mesangium.

and co-localizes with IgG and components of the complement pathway (5). In particular, DNAJB9 may be pivotal in recognition of misfolded proteins and activate the unfolded protein reaction determining endothelial reticulum stress and inflammation (5). Andeen et al, pointing out the absence of demonstration of other unfolded protein response beside DNAJB9, proposed an alternative hypothesis. The co-localization of DNAJB9 as antigen with IgG and complement fractions suggests autoimmune pathogenesis (10). Thus, questions arise about the therapeutic strategy to adopt in patients with FGN, first of all, the potential role of immunosuppressive treatment.

Our patient has been treated with an angiotensin-converting enzyme inhibitor alone for the entire follow-up, and the presence of positive prognostic factors could explain the long dialysis-free period at the time of diagnosis (i.e., normal renal function, low-grade proteinuria and mesangial pattern). For the absence of definitive evidence on its clinical effectiveness, immunosuppressive therapy has not been taken into consideration after the first renal biopsy.

Different experiences regarding immunosuppressive use in FGN have been later reported. In the above-described cohort, 36% (3) and 48% of patients (4) received immunosuppressive therapy (steroids, rituximab or cyclophosphamide) in various combinations without evidence of a slower progression to ESRD. A subsequent study, including 27 patients with FGN in conservative

treatment with renin-angiotensin system (RAS) inhibitors, showed that the addition of immunosuppressive therapy with different protocols in 13 out of 27 patients (rituximab-based therapy in 7 cases), resulted in partial remission (>50% decrease in 24-hour proteinuria with <15% decrease in eGFR compared to the baseline value) in about 46% of cases (7). The authors highlighted that those responders were characterized by a higher eGFR at the start of immunosuppressive treatment if compared to non-responders (76 versus 42 mL/min/1.73 m²) (7). More recently, in the more extensive published case series of FGN patients treated with rituximab (n=12), 4 patients, characterized by a median basal eGFR of 71 mL/min/1.73 m², showed a stable or improved sCr with a minimum of 1-year follow-up (non-progressors), while the remaining 8 patients (median basal eGFR 28 mL/min/1.73 m²) showed a progressive renal disease (ESRD in 5 patients after a median follow-up of 17 months) (15). Thus, the therapeutic strategy in FGN remains poorly defined; although it appears reasonable to adopt RAS inhibitors treatment in all patients. The start of an immunosuppressive regimen remains debated and at the same time worthy of further evaluation in well selected and appropriately extended case series.

Conclusion

In conclusion, we could speculate that the benign clinical course observed in our patient, characterized by the maintenance of renal function for more than 25 years, could be explained by a subtype of FGN disease with favourable histologic and clinical prognostic factors along with the protective effects of RAS block (17,18).

Authors' contribution

DM wrote the paper and revisited the case. KG and EM, as the pathologists, read and reported the first and the second biopsies, respectively. ART was the electron microscopist who read TEM; VP and SM were the physicians of the patient from 1993 to 2018. IS performed the second kidney biopsy. All authors read and signed the final paper.

Conflicts of interest

The authors declare no competing interests.

Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors. The patients gave his consent to publish as a case report.

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