

Familial Fibrillary Glomerulonephritis in Living Related Kidney Transplantation



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INTRODUCTION

Glomerular diseases characterized by deposits of non-amyloid fibrils include fibrillary glomerulonephritis (FGN), fibronectin glomerulopathy, immunotactoid glomerulonephritis, and some cryoglobulins-associated glomerulonephritis. Perhaps the most common form of these rare glomerulopathies, FGN is identified by smudgy glomerular staining for IgG by immunofluorescence and accumulation of randomly oriented, nonbranching fibrils with a diameter of 15 to 25 nm.^{1,2} Although FGN is typically polyclonal, monoclonal forms of FGN have been described.^{S1} A proportion of FGN patients may have had an associated autoimmune disease, malignancy, or viral hepatitis. Recently, the presence of DNAJ homolog subfamily B member 9 (DNAJB9) in the glomerular deposits was found to be highly sensitive and specific for FGN.^{3,S2,S3}

Although fibronectin glomerulopathy is known to have strong clustering within certain families,^{S4–S6} only 3 case reports of 4 families with FGN have so far been reported.^{4–6} A fifth affected family was additionally mentioned in the context of a large series of FGN.^{S7} We report the first case of donor-transmitted familial FGN in the renal allograft and review the literature on familial FGN.

CASE PRESENTATION

A 49-year-old African American man was found to have nephrotic-range proteinuria (urine protein/creatinine 6 g/g) on a routine health insurance examination,

with normal serum creatinine (sCr) of 1.0 mg/dl. Serologic workup was negative for monoclonal gammopathy, autoimmune diseases, malignancy, and hepatitis B and C. He had no known family history of kidney disease. A renal biopsy performed at an outside hospital (retrospectively reviewed at our institution) revealed, on light microscopy, a membranoproliferative pattern of injury (Figure 1a). Congo red stain was negative. Immunofluorescence microscopy revealed smudgy glomerular staining for IgG (3+), C3 (3+), lambda (3+), and kappa (2+). Electron microscopy displayed randomly arranged fibrils in the mesangium and in the glomerular basement membrane, with an average diameter of 16 nm. Immunohistochemical staining for DNAJB9 (details in [Supplementary Material on Immunostaining](#)), which was performed later at our institution, was strongly positive in the glomeruli (Figure 1b). Despite treatment with long-term low-dose prednisone, angiotensin-converting enzyme inhibitors, and diuretics, kidney function deteriorated progressively. The patient eventually presented to Columbia University Irving Medical Center 5 years later with stage V chronic kidney disease (CKD-V). Prednisone was discontinued, and after he underwent further evaluation, which included a negative serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), immunofixation of urine, normal kappa/lambda ratio in the serum, and negative serology for hepatitis B and C, he agreed to proceed with a living-related kidney transplantation.

The donor, the patient's biological son, was a 35-year-old African American man with no known history of kidney disease, hypertension, diabetes,

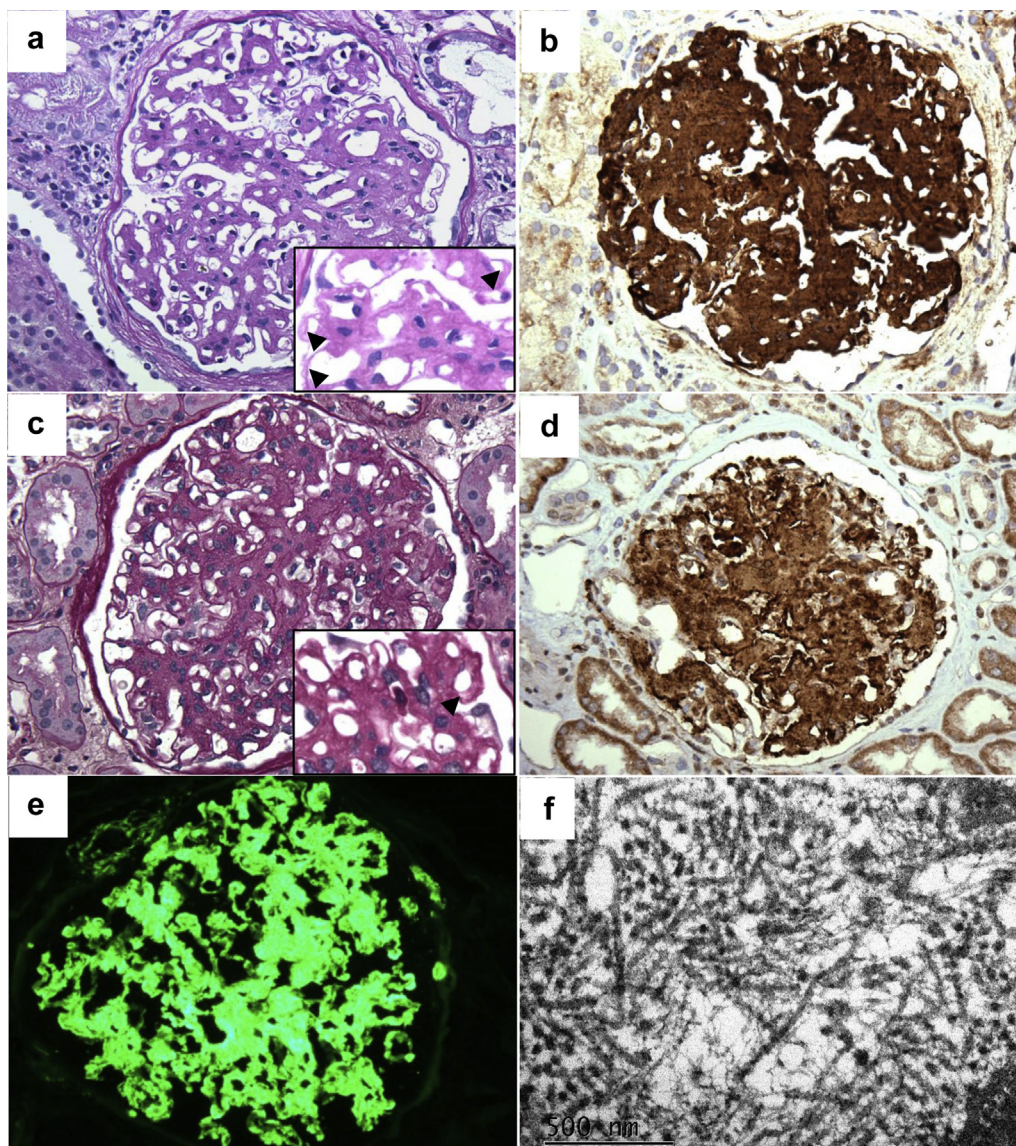


Figure 1. Pathology findings in the recipient's native kidney biopsy specimen. (a) Mild mesangial proliferation, mild to moderate mesangial expansion, and segmental glomerular capillary double contours (periodic acid–Schiff, original magnification $\times 400$; double contours [arrowheads] are best seen in the inset [original magnification $\times 600$]). (b) Positive immunoperoxidase staining for DNAJB9 (original magnification $\times 400$). Pathology findings in the donor tissue detected in post-reperfusion biopsy sample: (c) mild mesangial proliferation, mild mesangial expansion, and occasional short glomerular capillary double contours (periodic acid–Schiff, original magnification $\times 400$; double contours [arrowheads] are best seen in the inset [original magnification $\times 600$]). (d) Positive immunoperoxidase staining for DNAJB9 (original magnification $\times 400$). (e) Smudgy global mesangial and segmental glomerular capillary wall staining for IgG (immunofluorescence IgG, original magnification $\times 400$). (f) Randomly oriented fibrils, 18 nm (electron microscopy performed on paraffin-embedded sample; original magnification $\times 80,000$).

proteinuria, or hematuria. His physical examination showed blood pressure of 126/82 and a body mass index of 32, and he was otherwise normal with no edema in the lower extremities. Laboratory workup revealed serum creatinine (sCr) of 0.9 mg/dl and urinalysis (UA) with trace blood and negative protein, with urine albumin:creatinine ratio of 30 $\mu\text{g}/\text{mg}$. Urine microscopy revealed no red blood cells (RBCs)/hpf. Repeat UA again showed trace blood with 3 RBCs/hpf (reference range 0–4 RBC/hpf), with 30 mg/dl proteinuria (albumin:Cr ratio not quantified). A third urinalysis was performed, which was negative for blood and protein,

with 0 RBC/hpf on microscopy. Urine albumin:Cr ratio was 20 $\mu\text{g}/\text{mg}$, with total protein quantified as <40 mg/dl. Given that he met the requirement for kidney donation with 2 UAs without evidence of microscopic hematuria and urine albumin:creatinine ratio of 30 $\mu\text{g}/\text{mg}$ or less, additional evaluation with a pretransplantation kidney biopsy was not performed. The patient had preformed class-II circulating donor-specific antibodies (anti-HLA-DQ6: 2000 MFI).

At age 56 years, the patient underwent 1-haplotype match living-related kidney transplantation from his son and received induction therapy with thymoglobulin.

Table 1. Published cases of familial fibrillary glomerulonephritis (FGN)

Authors, year, reference	Subjects	Age at Dx	Presenting symptoms	Fibrils by EM (nm)	DNAJB9 stain	Treatment	Outcome	Other notes
Chan et al., 1998 ⁵	Sister	36	Proteinuria	20–30	No	Steroids, CP	F (3 yr)	
	Brother	38	Proteinuria	20–30 ^a	No	Steroids, CP	F (2 yr)	
Ying et al., 2015 (family 1) ⁶	Father	64	Elevated sCr, hematuria	10–15	No	ACE-i	F (10 mo)	
	Daughter	43	Proteinuria, hematuria	10–15	No	ACE-i, steroids, CP	ESKD (1.5 yr)	
Ying et al., 2015 (family 2) ⁶	Mother	61	NS	15 ^b	No	ACE-i	ESKD (2 yr)	Grandfather died of "Bright's disease"; no Bx performed
	Son	40	NS	Diameter N/A ^b	No	ACE-i	F (5 yr)	
Watanabe et al., 2017 ⁴	Brother	35	Proteinuria	EM N/A ^c	No	Steroids + CP	F (5 yr)	Father died with NS; no Bx performed
	Brother	40	Proteinuria	20 ^c	No	ARB	F (7 mo)	
Andeen et al., 2019 ³	Mother	N/A	N/A	N/A	No	N/A	ESKD (time N/A)	
	Daughter	N/A	N/A	N/A	Yes	N/A	ESKD (time N/A)	
Jeyabalan et al., 2020 (this report)	Father	49	Proteinuria	16	Yes	Adjusting IS	Preemptive Tx (7 yr)	
	Son	35	Essentially asymptomatic	18	Yes	No treatment	F (~1.5 yr)	

ACE-i, Angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; Bx, biopsy; CP, cyclophosphamide; Dx, diagnosis; EM, electron microscopy; ESKD, end-stage kidney disease; F, functioning; IS, immunosuppression; N/A, not available; NS, nephrotic syndrome; sCr, serum creatinine; Tx, transplant.

^aAtypical features for FGN were found in brother with immunofluorescence staining for kappa but negative for lambda.

^bAtypical features for FGN were found in mother with negative immunofluorescence staining for kappa and lambda, and in son with immunofluorescence staining only for lambda and C1q.

^cAtypical features for FGN were found in 35-year-old brother, with stronger immunofluorescence staining for C3 compared to IgG; for 40-year-old brother, there was only trace immunofluorescence staining for kappa and negative staining for lambda.

Light microscopic evaluation of the intraoperative formalin-fixed, paraffin-embedded, post-reperfusion biopsy specimen showed mild membranoproliferative features, manifested as mild mesangial proliferation, mild mesangial expansion, and scattered double contours (Figure 1c). The sample showed 5% tubulointerstitial scarring and minimal vascular sclerosis. Congo red stain was negative and immunoperoxidase staining for DNAJB9 was positive in the glomeruli (Figure 1d). Immunofluorescence, performed on frozen tissue, revealed smudgy global mesangial and segmental glomerular capillary wall staining for IgG (2+), C3 (1-2+), C1q (1+), kappa (2+), and lambda (2+) (Figure 1e). Immunofluorescence also showed focal staining in blood vessels. Immunostaining for IgG subclasses revealed dominant staining for IgG1 (3+) and IgG4 (2-3+). Electron microscopic evaluation, which was performed on paraffin-embedded tissue, demonstrated randomly oriented fibrils within the mesangium and rarely in glomerular basement membrane with a mean diameter of 18 nm (Figure 1f). Taken together, these findings were diagnostic of donor-transmitted FGN, indicating a familial form of FGN affecting both the father and son.

Follow-Up

The recipient was initially maintained on tacrolimus and mycophenolate mofetil, and his transplantation course was complicated by unexplained pruritus. Therefore, tacrolimus was discontinued, cyclosporine was initiated, and the patient was also started on chronic low-dose prednisone because of pruritus.

One and a half months after transplantation, the patient presented with subnephrotic proteinuria.

Laboratory workup revealed sCr of 1.1 mg/dl, urine protein/creatinine of 1.1 g/g, serum albumin of 4.0 g/dl, and 1+ blood in the urine (8 red blood cells/hpf). An allograft biopsy demonstrated FGN with 20% tubulointerstitial scarring. The 6-month protocol biopsy showed similar findings (FGN and 20% tubulointerstitial scarring). No convincing evidence of significant resolution of the fibrils was seen on the 6-month protocol biopsy by immunofluorescence or electron microscopy. The 1-year protocol biopsy, performed in the settings of sCr of 1.2 mg/dl, urine protein/creatinine of 0.5 g/g, and trace blood in the urine, demonstrated FGN and 60% to 65% tubulointerstitial scarring. The unusually high scarring in the latest allograft biopsy was attributed to sampling issues, given the minimally affected kidney function.

One year later (~2 years after transplantation), the patient had an sCr of 1.6 mg/dl, urine microalbumin/creatinine of 0.4 g/g, and bland urine sediment. The last urinalysis, performed 20 months after transplantation, revealed trace blood. The asymptomatic son was not treated, given his minimal proteinuria. Approximately 16 months after kidney donation, he had a stable sCr of 1.4 mg/dl, urine protein/creatinine of 0.5 g/g, and trace blood in the urine.

Given the familial nature of this FGN, we were able to evaluate the recipient's mother and his other son. Although the 77-year-old mother had an sCr of 1.0 mg/dl with negative protein and negative blood in the urine, the 30-year-old son had trace protein in the urine without blood and with an sCr of 1.0 mg/dl. Whole-exome sequencing of both the donor and recipient did not reveal any genetic defects.

Table 2. Teaching points

Familial FGN can occur in rare instances.
Donors with a family history of FGN with even minimal UA abnormalities should be considered for kidney biopsy as part of pretransplantation evaluation to rule out asymptomatic disease state.

FGN, fibrillary glomerulonephritis; UA, urinalysis.

DISCUSSION

FGN is encountered in ~1.0% of adult native kidney biopsies.⁵¹ It is more often seen in White individuals in their fifth or sixth decade of life, where it manifests commonly as proteinuria and less frequently as renal insufficiency or micro-hematuria.⁷ FGN is usually associated with a poor prognosis. A recent large study revealed that half of the patients reach end-stage kidney disease (ESKD) or death within 2 years after biopsy.⁵⁷ Notably, that study revealed that males have worse outcomes than females. Recurrent glomerular disease in the allograft due to FGN, said to occur in up to 50% of patients, has been found to be less common when staining for DNAJB9 excludes atypical patients.⁸

The pathogenesis of FGN is incompletely understood. Although FGN is often idiopathic in nature, it may be associated with secondary causes such as autoimmune diseases, hepatitis C infection, and malignancies.⁵⁸ On the other hand, evidence of inherited risk factors for FGN are sparse. A recent study has shown an association between FGN and each of HLA-DR7 and HLA-B35 antigens.⁹ However, to date, only 3 case reports of 4 families with FGN have been published.^{4–6} A fifth affected family was mentioned in a large series of FGN cases.⁵⁷ Details of these cases are presented in [Table 1](#). Looking at the table, some patterns emerge: most families show FGN affecting parents and offspring of both sexes. These findings raise the possibility of an autosomal pattern of inheritance. In contrast to what has been described in FGN in general, most females developed ESKD during follow-up, whereas most males did not. However, the latter finding should be interpreted with caution, given the small sample size and the variable duration of follow-up. Notably, half of the reported families have unusual FGN features, including monotypic immunofluorescence staining of the light chains, negative staining for both light chains, or more intense staining for complement 3 (C3) compared to IgG. Finally, these cases predated the discovery of DNAJB9 marker. As such, the DNAJB9 stain was never performed in all affected family members.

In our case, FGN was detected in both the father, who presented with nephrotic-range proteinuria, and his son, who was essentially asymptomatic despite significant glomerular infiltration by fibrils. Both kidney biopsy specimens showed typical polyclonal IgG

staining, randomly oriented fibrils of appropriate size, and positive DNAJB9 staining in the glomeruli. Immunostaining for IgG subclasses revealed intense staining for IgG1 (3+) and IgG4 (2-3+), similar to what was described in the literature for FGN in large series, where most studies showed a predominance of IgG4,^{59,510} whereas others showed a predominance of IgG1.⁵¹¹ Notably, our post-reperfusion biopsy specimen also showed focal IgG staining in blood vessels. Such staining is observed in a minority of patients with FGN.⁵⁷

In summary, we have presented the first known case of familial FGN discovered in a kidney allograft. The diagnosis was confirmed by the presence of glomerular DNAJB9 staining in the kidney tissue from the recipient (father) and the donor (son). Because the donor was essentially asymptomatic, even transient microhematuria or minimal elevations of urinary protein excretion should warrant renal biopsy of potential donors to family members with ESKD due to FGN ([Table 2](#)).

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

[Supplementary Material on Immunostaining.](#)

[Supplementary References.](#)

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