Glomerular Diseases

Case Report

Glomerular Dis 2022;2:95–99
DOI: 10.1159/000520071

Received: July 12, 2021
Accepted: September 30, 2021
Published online: October 7, 2021

Immunoglobulin-Negative Fibrillary Glomerulonephritis Masked in Diabetic Nephropathy: A Case Report and Discussion of a Diagnostic Pitfall

Gabriel B.W. Lerner[a] Gary G. Singer[b] Christopher P. Larsen[c] Tiffany N. Caza[c]

[a]Departments of Pathology and Laboratory Medicine, Yale University School of Medicine, New Haven, CT, USA; [b]Midwest Nephrology Associates, Saint Peters, MS, USA; [c]Arkana Laboratories, Little Rock, AR, USA

Keywords
Fibrillary glomerulonephritis · Nephrotic syndrome · DnaJ homolog subfamily B member 9 · Diabetes · Glomerular diseases · Renal biopsy

Abstract
Introduction: Fibrillary glomerulonephritis (FGN) is a rare glomerular disease with poor prognosis, characterized by deposition of randomly arranged fibrillar material measuring 10–30 nm in diameter. This diagnosis is confirmed with DNAJB9 immunohistochemistry as well as ultrastructural examination. Ultrastructurally, the fibrillary material seen in this entity may be confused with diabetic fibrillosis occurring in diabetic nephropathy. ***Case Presentation:*** We present a case of a 63-year-old African American male with remote hepatitis C virus (HCV) infection and type II diabetes mellitus who presented with chronic kidney disease and nephrotic range proteinuria. A kidney biopsy revealed PAS-positive mesangial matrix expansion consistent with diabetic nephropathy and focal randomly oriented fibril deposition on ultrastructural examination. Immunofluorescence for immunoglobulin G and light chains was negative by both routine and paraffin immunofluorescence. Immunohistochemistry for DNAJB9 was diffusely positive, confirming co-existing FGN. ***Discussion/Conclusion:*** Patients with diabetic nephropathy and FGN have similar clinicopathologic presentations with a slowly progressive onset of kidney failure and proteinuria. In diabetic patients with fibrillary deposits under ultrastructural examination, concurrence of these disease entities must be considered. In this patient with remote HCV infection that was successfully treated years before, it is possible that in the absence of an FGN trigger, there was a loss of antigenicity with a loss of immunoglobulin staining. Therefore, we recommend DNAJB9 immunostaining for patients with remote HCV infection to avoid this diagnostic pitfall. Further studies are needed to determine the potential role of HCV infection in the initiation and etiopathogenesis of FGN.

Introduction

Fibrillary glomerulonephritis (FGN) is a rare form of glomerulonephritis characterized by glomerular deposition of distinctive randomly oriented fibrillar material measuring 10–30 nm in diameter under ultrastructural examination. Overall prognosis is poor, with approximately 50% of patients progressing to end-stage kidney disease within 4

karger@karger.com
www.karger.com/gdz

Correspondence to:
Tiffany N. Caza, tiffany.caza@arkanalabs.com

years of diagnosis [1]. Initially identified using laser-capture microdissection and subsequent mass spectrometry, the heat shock protein DnaJ homolog subfamily B member 9 (DNAJB9) has been identified as a highly sensitive and specific diagnostic marker in this disease [2].

Light microscopy of FGN cases reveals varying degrees of mesangial hypercellularity and mesangial expansion by PAS-positive, nonargyrophilic material, with varying amounts of mesangial sclerosis [3]. However, diverse histopathologic patterns may be seen, including nodular glomerulosclerosis, proliferative or membranoproliferative glomerulonephritis, and membranous-like glomerulonephritis, among others [3]. Morphologically, PAS-positive mesangial expansion may be seen in both FGN and much more commonly in diabetic nephropathy, making the latter an important differential diagnosis. Immunofluorescence reveals smudgy and rarely pseudo-linear mesangial and glomerular capillary wall staining for IgG and C3, and the diagnosis can be clinched by DNAJB9 immunohistochemistry.

However, rare cases have been reported without immunoglobulin deposition, termed immunoglobulin-negative FGN [4]. Here, we present a case of immunoglobulin-negative FGN with concurrent nodular diabetic glomerulosclerosis in a patient with a history of treated hepatitis C virus (HCV) infection. This case highlights the diagnostic pitfalls of a collision of 2 sources of nodular glomerulosclerosis to consider FGN in diabetic patients with a history of current or prior HCV infection.

Case Presentation

A 63-year-old African American male with hypertension, type II diabetes mellitus, obesity, hyperlipidemia, and hepatic steatosis was referred to the nephrology department for management of chronic kidney disease stage III. Additional past medical history included HCV infection successfully treated 4 years prior to presentation. The HCV viral load was undetectable 4 months prior to presentation. Physical exam was unremarkable. Laboratory work-up revealed impaired kidney function with an elevated serum creatinine (1.94 mg/dL) and a low glomerular filtration rate (36 mL/min), nephrotic range proteinuria (9.0 g/day) with a normal serum albumin of 3.7 g/dL, and a hemoglobin level of 12.4 g/dL. To assess the extent of injury, a kidney biopsy was performed.

Kidney Biopsy

The biopsy contained 48 glomeruli, 8 of which were globally sclerotic. The remaining glomeruli displayed nodular PAS-positive mesangial matrix expansion and segmental mesangial hypercellularity, with frequent Kimmelstiel-Wilson nodules. Jones silver staining revealed argyrophilic mesangial areas, without spikes, holes, or double contour formation (shown in Fig. 1a). Focal glomeruli showed microaneurysm formation. Six glomeruli showed perihilar segmental sclerosis. There was moderate interstitial fibrosis and tubular atrophy involving 30% of the cortex. A Congo red stain was negative. Direct immunofluorescence performed on frozen tissue was negative for immunoglobulins (IgA, IgG, IgM, kappa, and lambda) and complement (C3 and C1q). Paraffin immunofluorescence was performed on the paraffin-embedded tissue after protease digestion and was negative for IgG, kappa, and lambda light chains (shown in Fig. 1b). By electron microscopy, there was moderate foot process effacement and no electron-dense immune complex deposits. Randomly arranged fibrils were identified within the glomerular mesangium (shown in Fig. 1c), which were accompanied by positive DNAJB9 staining (shown in Fig. 1d). Randomly oriented small fibrils also showed variable extension through glomerular basement membranes (shown in Fig. 1e), with corresponding DNAJB9 staining (shown in Fig. 1f). Together, this confirms a diagnosis of immunoglobulin-negative FGN within a background of diabetic nephropathy (Renal Pathology Society Class III).

Following the biopsy, the patient was started on an SGLT2 inhibitor (empagliflozin) in addition to prior ACE inhibitor antiproteinuric therapy (lisinopril). He had a reduction in proteinuria from 9.0 g/g to 4.9 g/g with stable kidney function (Cr 1.99 mg/dL) after 3 months of treatment.

Discussion/Conclusion

The clinicopathologic findings present in this case of immunoglobulin-negative FGN bring up several important points. Under light microscopic examination, the patient's biopsy revealed predominant changes of diabetic nephropathy, including prominent PAS-positive nodular mesangial expansion, glomerular capillary wall thickening, and arteriolar hyalinosis. Patients with FGN and diabetic nephropathy have similar clinical presentations, including chronic kidney disease and slowly progressive proteinuria. Given the lack of characteristic "smudgy" immunoglobulin staining by immunofluorescence, the presence of a concurrent FGN could easily have been overlooked if not for the identification of characteristic deposits on electron microscopy, which prompted DNA-

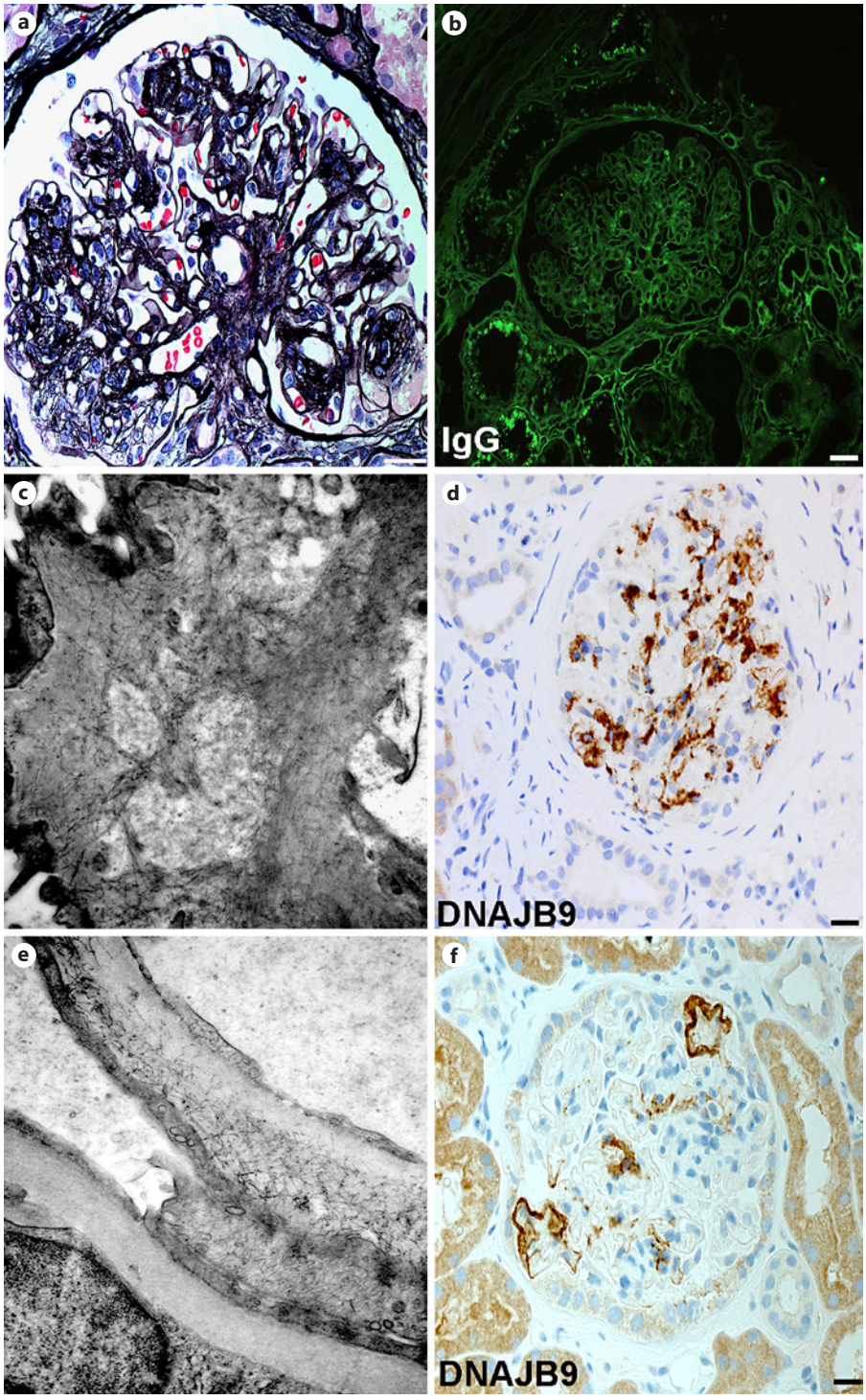

Fig. 1. Histopathologic findings in immunoglobulin-negative FGN occurring within a background of diabetic nephropathy. Agyrophilic nodular mesangial matrix expansion within a glomerulus (characteristic of diabetic nephropathy) (**a**), Jones methenamine silver, ×400. Immunofluorescence performed on paraffin-embedded tissue after pronase digestion was negative for immunoglobulin G (**b**), ×400. Ultrastructural photomicrograph showing small randomly arranged fibrils within the glomerular mesangium (**c**). Positive DNAJB9 immunostaining within the glomerular mesangium (**d**). Ultrastructural photomicrograph demonstrating small randomly oriented fibrils extending through a glomerular capillary loop (**e**). DNAJB9 immunohistochemistry showing positive staining in a segmental distribution along capillary loops (**f**). All scale bar, 20 μm. FGN, fibrillary glomerulonephritis.

JB9 immunostaining and identification of concurrent fibrillary glomerulopathy. The presence of fibrils in the mesangium of glomeruli with diabetic nephropathy is well described and commonly referred to as diabetic fibrillosis [5]. The fibrils commonly seen in the setting of diabetic glomeruli are considerably smaller, with a diameter of approximately 10 nm, compared to those seen in FGN that typically show a diameter of 20–30 nm [5] and DNAJB9 staining is negative. Negative DNAJB9 immunostaining was previously shown in diabetic fibrillosis in

10 cases, along with negativity in multiple other glomerular diseases [2]. An additional pitfall in differentiating FGN from diabetic glomerulopathy is the frequent presence of linear accentuation of IgG along glomerular basement membranes in cases of diabetic glomerulopathy, where even if the FGN is not IgG negative, it may be difficult to identify. For indeterminate cases of diabetic nephropathy with fibrillosis, DNAJB9 immunostaining is helpful for a concurrent diagnosis of FGN, as it is a sensitive and specific marker for the disease [2].

Within this patient, identification of FGN in addition to diabetic glomerulopathy did not change management. While it is likely that the patient's HCV infection provided the trigger for disease development, it cannot be conclusively determined. Given the patient's viral hepatitis was effectively treated and in long-term remission, no changes in management were made. However, it is important to recognize the FGN lesion histologically, as this could prompt a clinical workup to examine for occult disease, such as viral hepatitis or a hematologic disorder with paraproteinemia may still be active. One patient with active HCV infection with IgG-negative FGN has been reported in the literature [6].

Immunoglobulin-negative FGN may be underreported, as many previous studies of FGN have required immunoglobulin positivity as an inclusion criterion [4]. Said and colleagues [4] reported the largest case series to date of 9 cases, with all patients presenting with proteinuria (mean 24-h protein excretion, 3 g) and hematuria. Two of 9 patients had nephrotic syndrome. No monoclonal protein was present by serum or urine immunofixation in 7 and 4 patients tested, respectively [4]. Within this series, 3 patients had an underlying carcinoma and 2 had HCV infection [4]. Of those 2 patients, 1 had active infection and required elbasvir plus grazoprevir [4]. In this case, identification of FGN led to appropriate antiviral treatment.

Although more commonly associated with entities such as cryoglobulinemic glomerulonephritis or membranous nephropathy, HCV infection has been documented in FGN [7]. Chronic immune stimulation from this viral infection has been suggested as a potential source of ongoing immune activation, possibly initiating fibrillary deposition [3]. The findings in the current case support this possibility, in that treatment of this patient's underlying viral infection may have removed the immune stimulus to DNAJB9 synthesis and subsequent deposition within the kidney. Additionally, this case demonstrates the persistence of nonantigenic fibrillary glomerular deposits, as has been documented in cases of treated AL amyloidosis without light chain staining [8, 9]. In patients with a history of multiple myeloma in remission through chemotherapy or stem cell transplantation, AH and/or AL amyloid can be negative for immunoglobulin and light chains, although can be confirmed by mass spectrometry [10–12]. This may be due to a loss of antigenicity secondary to resolution of the driver of the disease, and AL amyloidosis may be underdiagnosed due to this [10]. Alternatively, immunoglobulin negativity in FGN could result from the deposited fibrils not interacting with the polyclonal or monoclonal antibodies used for staining due to mutations or changes in conformational epitopes, resulting from an immunologically active underlying disease process. Other pathophysiologic possibilities exist, and further studies are needed to investigate these hypotheses.

Teaching Points

- As FGN and diabetic nephropathy both present with slowly progressive proteinuria with or without hematuria, a high index of suspicion for FGN is required to make the diagnosis.
- Immunoglobulin-negative FGN is a rare entity, in which we rely on electron microscopy, nonargyophilia on silver staining, and positivity for DNAJB9 to confirm the diagnosis.
- HCV has been associated with both FGN and immunoglobulin-negative FGN and may be a trigger for immunoglobulin production. Appropriate antiviral treatment may result in a loss of antigenic stimulation, cessation of immunoglobulin and DNAJB9 deposition, and the development of this entity.

Statement of Ethics

This study is written in compliance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient prior to submission of the manuscript. The study is exempt from ethics committee approval, as it is a case report in which patient consent was obtained.

Conflict of Interest Statement

The authors declare that they have no financial conflicts of interest.

Funding Sources

The authors declare that they have no relevant financial interests.

Author Contributions

G.B.W.L. wrote the initial manuscript draft. Manuscript review and commentary were provided by T.N.C., G.G.S., and C.P.L.

Data Availability Statement

This work did not involve data sets to submit to a public repository. All clinical and laboratory data analyzed during this study are included in the article. Further inquiries can be directed to the corresponding author.

References

1 Nasr SH, Valeri AM, Cornell LD, Fidler ME, Sethi S, Leung N, et al. Fibrillary glomerulonephritis: a report of 66 cases from a single institution. Clin J Am Soc Nephrol. 2011;6(4):775–84.
2 Nasr SH, Vrana JA, Dasari S, Bridoux F, Fidler ME, Kaaki S, et al. DNAJB9 is a specific immunohistochemical marker for fibrillary glomerulonephritis. Kidney Int Rep. 2018;3(1):56–64.
3 Nasr SH, Fogo AB. New developments in the diagnosis of fibrillary glomerulonephritis. Kidney Int. 2019;96(3):581–92.
4 Said SM, Rocha AB, Royal V, Valeri AM, Larsen CP, Theis JD, et al. Immunoglobulin-negative DNAJB9-associated fibrillary glomerulonephritis: a report of 9 cases. Am J Kidney Dis. 2021;77(3):454–8.
5 Herrera GA, Turbat-Herrera EA. Renal diseases with organized deposits: an algorithmic approach to classification and clinicopathologic diagnosis. Arch Pathol Lab Med. 2010;134(4):512–31.
6 Said SM, Rocha AB, Royal V, Valeri AM, Larsen CP, Theis JD, et al. Immunoglobulin-negative DNAJB9-associated fibrillary glomerulonephritis: a report of 9 cases. Am J Kidney Dis. 2020.
7 Johnson RJ, Willson R, Yamabe H, Couser W, Alpers CE, Wener MH, et al. Renal manifestations of hepatitis C virus infection. Kidney Int. 1994;46(5):1255–63.
8 Okuyama H, Yamaya H, Fukusima T, Yokoyama H. A patient with persistent renal AL amyloid deposition after clinical remission by HDM/SCT therapy. Clin Nephrol. 2013;79(3):233–6.
9 Zeier M, Perz J, Linke RP, Donini U, Waldherr R, Andrassy K, et al. No regression of renal AL amyloid in monoclonal gammopathy after successful autologous blood stem cell transplantation and significant clinical improvement. Nephrol Dial Transplant. 2003;18(12):2644–7.
10 Novak L, Cook WJ, Herrera GA, Sanders PW. AL-amyloidosis is underdiagnosed in renal biopsies. Nephrol Dial Transplant. 2004;19:3050–3.
11 Sethi S, Theis JD, Leung N, Dispenzieri A, Nasr SH, Fidler ME, et al. Mass spectrometry-based proteomic diagnosis of renal immunoglobulin heavy chain amyloidosis. Clin J Am Soc Nephrol. 2010;5(12):2180–7.
12 Safadi S, Saad A, Quint PS, Sethi S, Leung N, Kurtin P, et al. Disappearance of immunoglobulins from persistent renal amyloid deposits following stem cell transplantation for heavy-and light-chain amyloidosis. Nephrol Dial Transplant. 2015;30(7):1151–5.