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Fibrillary Glomerulopathy With Immune Complex Deposition and Superimposed Crescentic Glomerulonephritis in an Octogenarian

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Abstract

Fibrillary glomerulopathy is an uncommon cause of progressive kidney disease, and the development of superimposed crescentic glomerulonephritis creates a particularly difficult therapeutic challenge. We report an 84-year-old woman with progressive kidney dysfunction, persistent hematuria, and proteinuria. Over 12 months, serum creatinine increased from 0.99 mg/dL to 2.52 mg/dL, with estimated glomerular filtration rate declining from 57 mL/min/1.73 m² to approximately 18 mL/min/1.73 m². Serologic evaluation, including antinuclear antibody, antineutrophil cytoplasmic antibody, and complement levels, was unrevealing, and evaluation for monoclonal gammopathy was negative. Kidney biopsy demonstrated DNAJB9-negative fibrillary glomerulopathy with superimposed focal crescentic glomerulonephritis. The patient was initially treated with prednisone 80 mg daily, and avacopan was started at a dose of 30 mg twice a day two weeks after initiation of prednisone therapy. The prednisone dose was rapidly tapered, and avacopan was subsequently used as a glucocorticoid-sparing strategy. At 12 months, kidney function remained stable, with serum creatinine of 1.97 mg/dL without progression to dialysis-dependent kidney failure. Early biopsy and individualized immunosuppressive therapy are critical, and emerging agents such as avacopan may offer glucocorticoid-sparing benefits in selected cases.

Categories: Nephrology, Allergy/Immunology
Keywords: avacopan, crescentic glomerulonephritis, dnajb9, fibrillary glomerulopathy, kidney biopsy

Introduction

Fibrillary glomerulopathy is an uncommon glomerular disease characterized by deposition of randomly oriented, nonbranching fibrils within the glomeruli. Fibrillary glomerulonephritis (FGN) represents the best-characterized form of this disease and has traditionally been diagnosed by electron microscopy demonstrating fibrils generally measuring approximately 12-24 nm in diameter, together with immunoglobulin and complement deposition [1]. FGN has been reported in association with autoimmune disease, monoclonal gammopathy, solid-organ malignancy, hepatitis C infection, and diabetes mellitus [2]. Anti-neutrophil cytoplasmic antibody (ANCA)-negative pauci-immune crescentic glomerulonephritis is a recognized clinicopathologic entity and may cause rapidly progressive kidney dysfunction despite negative ANCA serology [3]. The identification of DnaJ heat shock protein family member B9 (DNAJB9) as a highly sensitive and specific tissue biomarker has substantially improved the diagnostic classification of FGN [4]. Nevertheless, atypical cases occur, including rare DNAJB9-negative and Congo-red-positive fibrillary lesions, creating potential diagnostic overlap with amyloidosis and other organized deposit diseases [5]. Crescent formation can occur in association with several glomerular diseases and indicates severe glomerular capillary injury [6,7]. When active crescentic injury occurs in a patient with an underlying fibrillary glomerulopathy, treatment decisions are particularly difficult because evidence supporting immunosuppression is limited and there are no randomized trials specifically addressing this combination. These decisions become even more challenging in elderly patients, in whom the potential benefits of suppressing active glomerular inflammation must be balanced against the substantial toxicity associated with prolonged glucocorticoid and cytotoxic therapy.

We report an 84-year-old woman with progressive kidney failure in whom biopsy demonstrated an atypical DNAJB9-negative fibrillary glomerulopathy with immune-complex deposition and superimposed acute and chronic focal crescentic glomerulonephritis. The case illustrates both the diagnostic challenges associated with atypical fibrillary deposits and the individualized therapeutic considerations involved in treating aggressive crescentic kidney injury in an elderly patient.

Case Presentation

An 84-year-old woman with a past medical history of hypothyroidism, hypertriglyceridemia, and gout presented for nephrology evaluation. Vitals were stable, and blood pressure in the office was 140/50 mmHg. She reported nausea and poor appetite, with symptoms resolving after food intake. There were no symptoms of vomiting, back pain, or systemic infection symptoms. Her medications included levothyroxine (125 mcg every morning), gemfibrozil, allopurinol, and aspirin. There were no intercurrent illnesses, such as acute

infectious processes, acute myocardial infarction, stroke, gastrointestinal (GI) bleeding, or exposure to any nephrotoxins. There was no change in the color of the urine or volume, and no significant weight loss was reported. The last mammogram done two years prior was negative. Labs are as outlined in Table *1*.

Parameters	Latest Reference Range & Units	12 Months Before Baseline	Baseline	Day 20	Day 28	Day 29
Sodium	135-146 mmol/L	138	137	135	139	137
Potassium	3.5-5.3 mmol/L	5.4 (H)	4.6	5.7 (H)	5.5 (H)	4.9
Chloride	98-110 mmol/L	104	105	105	110	106
CO_2	20-32 mmol/L	25	21	21	23	20 (L)
Blood Urea Nitrogen (BUN)	7-25 mg/dL	27 (H)	48 (H)	56 (H)	51 (H)	57 (H)
Creatinine	0.60-0.95 mg/dL	0.99 (H)	2.52 (H)	2.51 (H)	2.55 (H)	2.93 (H)
Glucose	65-99 mg/dL	83	104 (H)	87	92	92
Calcium	8.6-10.4 mg/dL	10.3	9	9.1	9.1	9.2
Total Protein	6.1-8.1 g/dL	6.8	6.2		6.1	
Albumin	3.6-5.1 g/dL	4.4	3.9	3.9	3.7	
Aspartate Transferase	10-35 U/L	22	25		22	
Alanine Transaminase	6-29 U/L	14	10		11	
Total Bilirubin	0.2-1.2 mg/dL	0.6	0.3		0.4	
Blood Urea Nitrogen/Creatinine Ratio	6-22 (calc)	27 (H)	19	22	20	19
Globulin	1.9-3.7 g/dL (calc)	2.4	2.3		2.4	
Albumin/Globulin Ratio	1.0-2.5 (calc)	1.8	1.7		1.5	
Phosphorus	2.1-4.3 mg/dL			5.3 (H)	4.3	
Alkaline Phosphatase	37-153 U/L	125	99		59	
HemoglobinA1C	<5.7%	5.5		5.2		
Erythrocyte Sedimentation Rate (mm/h)				55		
Magnesium	1.5-2.5 mg/dL			2	2	
Uric Acid	2.5-7.0 mg/dL			8.0 (H)	6.9	
eGFR*	> OR = 60 mL/min/1.73m2	57 (L)	18 (L)	18 (L)	18 (L)	15 (L)
Cholesterol, Total	<200 mg/dL	185	189	228 (H)		
Triglycerides	<150 mg/dL	139	142	148		
High-Density Lipoprotein	> OR = 50 mg/dL	58	51	59		
Low-Density Lipoprotein	mg/dL (calc)	103 (H)	113 (H)	142 (H)		
Creatine Kinase	16-215 U/L			225 (H)		
Natriuretic Peptide	<100 pg/mL			210 (H)		
Thyroid Stimulating Hormone	0.40-4.50 mIU/L	0.9	16.09 (H)			

Free T4 (Thyroxine)	0.8-1.8 ng/dL	1.1	0.9			
Hematocrit %	35.0-45.0%	37.2	31.1 (L)	30.9 (L)	32.5 (L)	
Parathyroid Hormone Intact	16-77 pg/mL			171 (H)		
Vitamin D, 25-OH, Total, IA	30-100 ng/mL			49		

TABLE 1: Laboratory findings during the clinical course

*eGFR: estimated glomerular filtration rate

Over the preceding 12 months, the patient demonstrated progressive deterioration in kidney function. Serum creatinine increased from 0.99 mg/dL to 2.52 mg/dL, with a corresponding decline in estimated glomerular filtration rate (eGFR) from 57 to approximately 18 mL/min/1.73 m^2. Blood urea nitrogen remained elevated, ranging from 27 to 57 mg/dL, with intermittent hyperkalemia. Urinalysis demonstrated persistent 3+ hematuria and persistent sub-nephrotic range proteinuria, with urine protein-to-creatinine ratios ranging from 1.7 to 2.6 mg/mg and a 24-hour urine protein excretion of 1.4 g/day. Additional laboratory findings included normocytic anemia, with hemoglobin levels of approximately 10-11 g/dL, and secondary hyperparathyroidism, with a parathyroid hormone level of 171 pg/mL. Thyroid-stimulating hormone level was elevated, with free thyroxine (T4) in the normal range, suggestive of subclinical hypothyroidism being treated with levothyroxine.

Evaluation for associated systemic conditions included negative antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody (ANCA) testing, with C3 and C4 levels within the reference ranges. Hepatitis B and C serologies were negative. Hemoglobin A1c was 5.2%, without laboratory evidence of diabetes mellitus. Quantitative serum immunoglobulin levels were within the reference ranges. Serum and urine protein electrophoresis and serum free light-chain testing showed no evidence of a monoclonal gammopathy. CT performed of the chest, abdomen, and pelvis was negative for any concern for a malignant process. Echocardiogram performed revealed normal left and right ventricular function with mild mitral and mild-to-moderate aortic regurgitation. Cytomegalovirus (CMV) polymerase chain reaction (PCR) was negative, and extensive GI evaluation, including hepatitis C (HCV) PCR, was negative. Right renal (Figure *1*) and left renal (Figure *2*) ultrasound demonstrated bilateral renal cysts and increased cortical echogenicity without evidence of obstruction.

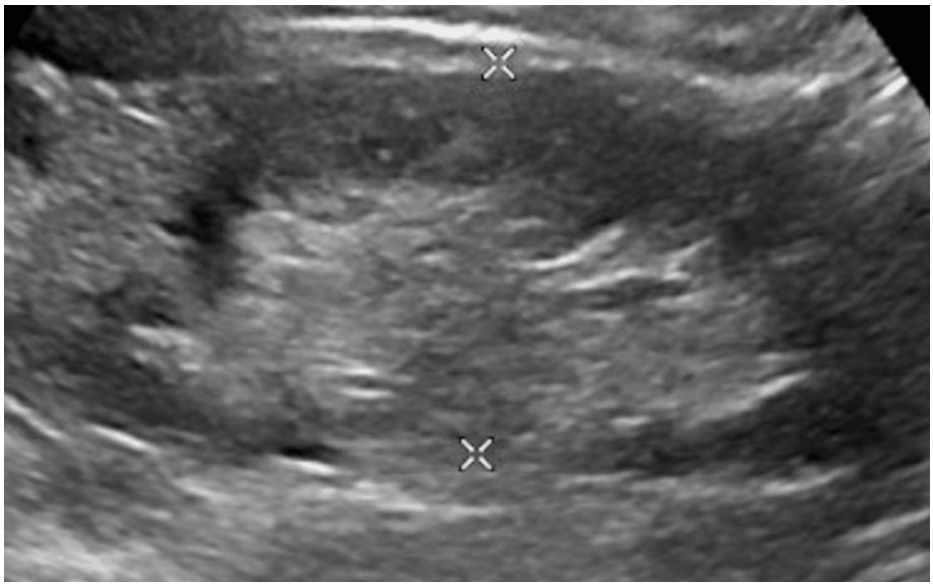


FIGURE 1: Renal ultrasound of the right kidney

Right kidney measured 10.2 x 4.0 x 4.2 cm.



FIGURE 2: Renal ultrasound of the left kidney

Left kidney measures 11.1 x 4.0 x 4.0 cm.

Given the progressive deterioration in renal function accompanied by persistent hematuria and proteinuria, a kidney biopsy was performed. The biopsy yielded an adequate specimen containing 34 glomeruli, seven of which were globally sclerotic. Fibrous crescents were identified among the chronic lesions. The tubulointerstitial compartment showed moderate-to-severe interstitial fibrosis and tubular atrophy, accompanied by tubular degenerative changes. Light microscopy demonstrated an acute and chronic focal crescentic pattern of glomerulonephritis, with active lesions involving approximately 18% of sampled glomeruli (Figure *3*).

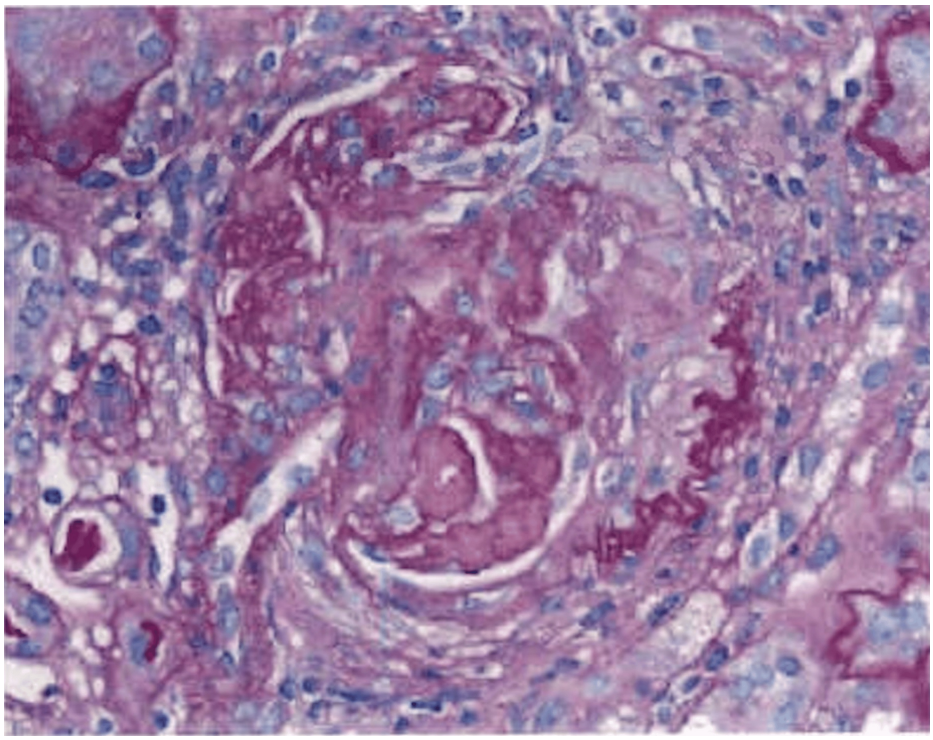


FIGURE 3: H & E staining revealing glomeruli with crescents with endocapillary leukocyte infiltration (200X magnification)

Immunofluorescence microscopy demonstrated smudgy global mesangial staining for IgG, C3, C1q, kappa, and lambda light chains, with additional staining involving small blood vessels and rare tubular basement membranes. Electron microscopy demonstrated mesangial deposits composed of randomly oriented, non-branching fibrils with a mean diameter of approximately 9 nm. Congo red staining demonstrated weakly

congophilic material within the mesangium, peritubular capillaries, tubular basement membranes, and small blood vessels, with focal weak apple-green birefringence under polarized light (Figure 4).

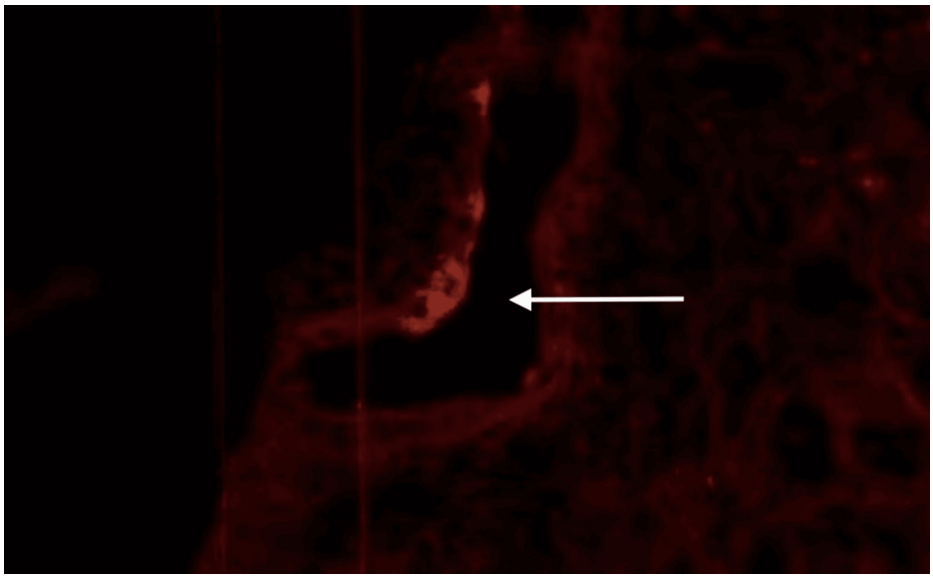


FIGURE 4: Congo red staining demonstrating a congophilic material with focal weak apple-green birefringence under polarized light (arrow pointing to blood vessel, 400X magnification)

White arrow pointing to the artery.

DNAJB9 immunohistochemistry demonstrated reactivity within peritubular capillaries but no detectable staining within the glomeruli, tubular basement membranes, or blood vessels. Because the glomerular fibrillary deposits lacked DNAJB9 immunoreactivity, the glomerular lesion was considered DNAJB9-negative. Immunohistochemical stain for serum amyloid A protein was negative. Overall proteomic features on mass spectroscopy were equivocal for amyloid. Integration of the light microscopic, immunofluorescence, ultrastructural, and immunohistochemical findings supported a diagnosis of DNAJB9-negative fibrillary glomerulopathy with superimposed acute and chronic crescentic glomerulonephritis.

Two days after biopsy results were obtained, the patient was initiated on prednisone 80 mg daily (1 mg/kg/day). She was advised on supportive measures: GI prophylaxis (famotidine), calcium/vitamin D supplementation, and infection precautions. The patient was counseled to avoid international travel due to infection risk. The patient was initially started on 80 mg of prednisone for two weeks. Given the patient's advanced age and high risk for complications from prolonged high-dose glucocorticoid therapy, an accelerated taper was planned. Avacopan was started at a dose of 30 mg twice a day two weeks after initiation of prednisone therapy. The prednisone dose was then rapidly tapered to a lower dose of 20 mg, and avacopan was subsequently used as a glucocorticoid-sparing strategy. Hepatitis B serology was confirmed to be negative before additional immunomodulatory therapy. At approximately one month, serum creatinine was 2.93 mg/dL with an eGFR below 15 mL/min/1.73 m^2. Despite the severity of initial kidney dysfunction, renal function subsequently stabilized. At 12 months of follow-up, serum creatinine was 1.97 mg/dL without progression to dialysis-dependent kidney failure. The patient has been doing well so far, with stable GFR and kidney function, a benign urinalysis, and no systemic features of amyloid. No adverse effects of avacopan therapy have been noted so far.

Discussion

This case illustrates an uncommon clinical and therapeutic challenge: an octogenarian with progressive renal failure in whom kidney biopsy demonstrated an atypical fibrillary glomerulopathy accompanied by an active crescentic pattern of injury. The biopsy was central to establishing both the underlying diagnosis and the presence of potentially treatable active glomerular inflammation. The patient's clinical and serologic evaluation did not identify the cause of her progressive kidney dysfunction. Urine analysis revealed non-nephrotic-range proteinuria. B-type natriuretic peptide (BNP) was elevated at 210 pg/mL. However, the patient had no clinical evidence of acute decompensated heart failure or significant volume overload. The elevation was interpreted cautiously in the setting of advanced kidney dysfunction. Evaluation for associated autoimmune, infectious, hematologic, metabolic, and malignant conditions was unrevealing, with no evidence of hepatitis B or C infection, diabetes mellitus, monoclonal gammopathy, or solid-organ malignancy. Kidney biopsy, however, demonstrated fibrillary deposits together with active and chronic

crescentic lesions. DNAJB9 immunoreactivity was absent from the glomerular deposits, supporting classification as a DNAJB9-negative fibrillary glomerulopathy rather than conventional DNAJB9-positive fibrillary glomerulonephritis [2]. Although ANCA-negative pauci-immune crescentic glomerulonephritis is a recognized entity, ANCA negativity alone does not establish pauci-immunity [8]. Immunofluorescence in this patient demonstrated IgG, C3, C1q, kappa, and lambda deposition. Overall proteomic features on mass spectroscopy were equivocal for amyloid. Therefore, the biopsy was not interpreted as conventional ANCA-negative pauci-immune glomerulonephritis. Instead, given the clinical presentation of acute kidney failure with nephritic presentation and rapidly declining glomerular filtration rate, our working diagnosis was active crescentic injury superimposed on an underlying fibrillary glomerulopathy.

The pathogenesis of FGN remains incompletely understood. DNAJB9 is highly enriched within the glomerular fibrillary deposits of most patients with FGN. Proteomic studies have also demonstrated IgG1 and components of the classical complement pathway within affected glomeruli, leading to the hypothesis that DNAJB9 may function as an autoantigen targeted by an IgG-mediated immune response. Another hypothesis is that DNAJB9 may become incorporated into abnormal immunoglobulin-containing deposits as a secondary binding partner or scaffold rather than functioning as the initiating antigen. FGN contains DNAJB9-associated, usually IgG-containing fibrillary deposits in the mesangium and capillary walls, and complement activation is present in these deposits. The mechanisms responsible for crescent formation in FGN are similarly uncertain. Severe immune-complex and complement-mediated glomerular injury may result in disruption of the glomerular capillary wall, leakage of plasma proteins and inflammatory mediators into Bowman's space, and subsequent extra-capillary proliferation and crescent formation. Classical complement activation has been proposed as a mediator of destructive glomerular injury in FGN.

There are no randomized controlled trials specifically evaluating treatment of DNAJB9-negative fibrillary glomerulopathy complicated by crescentic glomerulonephritis. Consequently, therapeutic decisions required cautious extrapolation from evidence involving other severe crescentic glomerular diseases, particularly ANCA-associated vasculitis. Empiric treatment with glucocorticoids and other immunosuppressive agents has produced inconsistent results, and available evidence is limited. High-dose prednisone was initiated because of the progressive kidney failure and biopsy evidence of active crescentic injury. However, prolonged high-dose glucocorticoid therapy posed substantial risk in this patient, including infection, metabolic complications, osteoporosis, muscle weakness, neuropsychiatric effects, and other glucocorticoid-related toxicities, which were of particular concern. The patient also had pre-existing short-term memory impairment for which she had undergone an extensive neurologic evaluation. Her advanced age, baseline cognitive concerns, and risk of infection were important considerations in attempting to minimize prolonged exposure to glucocorticoids and conventional cytotoxic immunosuppression.

In the plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS) trial, a reduced-dose glucocorticoid regimen was noninferior to a standard-dose regimen with respect to death or end-stage kidney disease and was associated with fewer serious infections [9]. Similarly, the low-dose glucocorticoids plus rituximab versus high-dose glucocorticoids plus rituximab for remission induction in the ANCA-associated vasculitis (LoVAS) trial demonstrated that reduced-dose glucocorticoids combined with rituximab were noninferior to a high-dose glucocorticoid regimen for remission induction [10]. Avacopan was selected as a glucocorticoid-sparing strategy in this patient. Avacopan is an oral antagonist of the complement C5a receptor and has been studied in ANCA-associated vasculitis. Contemporary KDIGO guidance incorporates avacopan as an alternative to glucocorticoids in AAV, particularly when reduction of glucocorticoid toxicity is an important clinical objective [11]. The decision to use avacopan in our patient consequently represented an individualized therapeutic strategy rather than an evidence-based treatment specifically established for fibrillary glomerulopathy. The primary objective was to facilitate rapid reduction in glucocorticoid exposure while continuing treatment of a biopsy-proven aggressive crescentic process in a patient considered particularly vulnerable to the complications of prolonged conventional immunosuppression. Hepatic abnormalities have been reported with avacopan, and rare severe hepatic complications, including vanishing bile duct syndrome, have been described [12,13]. Baseline and serial monitoring of liver function and careful review of potential drug interactions are therefore important, particularly in elderly patients receiving multiple medications. The efficacy of reduced-dose glucocorticoids and avacopan in ANCA-negative disease has not been extensively studied. Although this case report suggests that treatment strategies validated in ANCA-positive vasculitis may also be considered in ANCA-negative presentations, stabilization of renal function following treatment in our patient cannot establish treatment efficacy or causality. Once a year of avacopan treatment has been completed, rituximab as maintenance therapy every six months is a future option for our patient. Overall, individualized tapering schedules, vigilant monitoring for relapse, and proactive management of therapy-related complications remain central to optimizing outcomes. Given the rarity and heterogeneity of FGN, adequately powered randomized controlled trials of the crescentic variant will likely require international, multi-institutional collaboration. Prospective registries and collaborative research networks could facilitate successful recruitment and completion of adequately powered controlled trials specifically addressing the crescentic phenotype. These trials will determine whether immunomodulatory or complement-directed therapies improve kidney outcomes compared with supportive care or existing empiric treatment approaches.

Conclusions

We describe a case of DNAJB9-negative fibrillary glomerulopathy with superimposed acute and chronic crescentic glomerulonephritis in an 84-year-old woman with progressive kidney failure. Kidney biopsy was essential in establishing the underlying diagnosis and demonstrating an active crescentic component that influenced the decision to pursue immunosuppressive therapy despite negative ANCA and other serologic studies. High-dose prednisone was initiated for the active crescentic process, followed by an accelerated taper and use of avacopan as an individualized glucocorticoid-sparing strategy. Kidney function remained stable at 12 months. This report highlights the central role of kidney biopsy in unexplained progressive kidney disease and the need for individualized therapeutic decision-making when severe biopsy-proven glomerular injury occurs outside the populations represented in randomized clinical trials.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Vinay Kamath, Ekambaram Ilamathi

Drafting of the manuscript: Vinay Kamath, Ekambaram Ilamathi

Critical review of the manuscript for important intellectual content: Vinay Kamath, Ekambaram Ilamathi

Acquisition, analysis, or interpretation of data: Ekambaram Ilamathi

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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