Rapidly progressive glomerulonephritis due to coexistent anti-glomerular basement membrane disease and fibrillary glomerulonephritis

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Abstract

Anti-glomerular basement membrane (anti-GBM) disease is a major cause of rapidly progressive glomerulonephritis (RPGN). On the other hand, fibrillary glomerulonephritis (GN) typically presents as proteinuria, hematuria and renal insufficiency, but rarely as RPGN. Without electron microscopy, the diagnosis of fibrillary GN can be missed. We report a 68-year-old white woman who presented with RPGN with kidney biopsy demonstrating diffuse crescentic GN on light microscopy. By immunofluorescence, there was bright linear staining of the GBMs and smudgy mesangial staining for immunoglobulin G, C3, and kappa and lambda light chain. Electron microscopy revealed fibrillary deposits in the GBM and mesangium. A serum test for anti-GBM antibody was positive. To our knowledge, this is the first report of coexistence of fibrillary GN in a patient with anti-GBM disease. Electron microscopy is critical to identify the coexistence of other GN in patients presenting with crescentic GN.

Key words: anti-GBM, anti-glomerular basement membrane disease, crescentic glomerulonephritis, fibrillary glomerulonephritis, rapidly progressive glomerulonephritis

Introduction

Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome manifested by features of nephritic syndrome and rapid loss of the kidney function over a period of a few weeks to months where the main pathologic finding is a necrotizing and crescentic glomerulonephritis (GN) on kidney biopsy [1]. The general categories of the cause of RPGN are anti-glomerular basement membrane (anti-GBM) disease, pauci-immune crescentic GN [usually antineutrophil cytoplasmic antibody (ANCA)-associated] and immune complex type crescentic GN.

Fibrillary GN (FGN) is an immune complex GN characterized by glomerular staining by immunofluorescence for immunoglobulin G (IgG), complement components, and usually kappa and lambda light chains, and deposition of irregularly oriented, elongated, nonbranching fibrils, 10–30-nm thick, in the GBMs and mesangium [2–5] as seen by electron microscopy; focal
Case report
Clinical history and initial laboratory data
A 68-year-old woman was admitted with progressive weakness and altered mental status. Approximately 2 weeks prior to admission, the patient was diagnosed with an upper respiratory tract infection and was prescribed a 7-day treatment course with trimethoprim/sulfamethoxazole. Her respiratory symptoms improved. However, she developed progressive generalized weakness, nausea and altered mental status and was brought to the hospital for evaluation. Her past medical history was significant for diabetes mellitus type 2 on diet control, rheumatoid arthritis in remission, dyslipidemia and gastroesophageal reflux disease. Medications included pravastatin and ranitidine. The patient was a former smoker. There was no family history of kidney disease. Physical examination was unremarkable except for 1+ pitting edema in the lower extremities. Serum creatinine (Cr) of 1.0 mg/dL (88.4 µmol/L; estimated glomerular filtration rate, 59 mL/min/1.73 m²) was increased at 4.0 mg/dL (353.6 µmol/L) from a baseline Cr of 1.0 mg/dL (88.4 µmol/L; estimated glomerular filtration rate, 59 mL/min/1.73 m²) calculated by the four-variable equation for the Modification of Diet in Renal Disease Study. The patient was normotensive without corticosteroids. However, renal function continued to deteriorate with Cr of 5.1 mg/dL at Day 2 of hospital admission. At that time, an anti-GBM IgG antibody test was positive at 272 units/mL (reference range 0–19 units/mL). A chest X-ray revealed no pulmonary infiltration. A kidney biopsy was performed.

Kidney biopsy
Light microscopic evaluation showed two small cores of renal cortex including a small portion of medulla. The sample included seven glomeruli, two of which were globally sclerosed. Four glomeruli (57%) showed crescents, including two cellular crescents, one fibrocellular and one fibrous crescent. No necrotizing lesions were identified. The uninvolved glomeruli showed mild mesangial matrix expansion with periodic acid–Schiff positive and silver negative material. No significant mesangial or endocapillary hypercellularity was noted. There was minimal thickening of peripheral capillary loops.

Tissue submitted for immunofluorescence studies contained one glomerulus, which showed linear GBM staining and segmental smudgy mesangial staining with IgG (2–3+), C3 (2+), and kappa (2+) and lambda (2+) light chains. Fibrinogen stained glomerular crescents. IgG subclass staining was attempted, but additional sections lacked glomeruli.

Ultrastructural studies showed an expanded mesangial matrix with several areas of electron-dense to intermediately dense deposits. On higher magnification, these deposits were composed of randomly oriented fibrils, measuring mean thickness of 19 nm, range 14–25 nm. The GBMs were thickened. Fibrils were also seen within segments of glomerular capillary loops within thickened basement membranes. Podocytes showed moderate to severe foot process effacement. No tubular basement membrane deposits were seen. Representative light, immunofluorescence and electron microscopy findings are shown in Figure 1.

Diagnosis
Kidney, needle biopsy: (i) anti-GBM disease; (ii) FGN.

![Fig. 1.](https://academic.oup.com/ckj/article-abstract/9/1/97/2462511)

**Fig. 1.** Representative kidney biopsy findings showing FGN with anti-GBM disease. (A) Glomerulus with cellular crescent and mild mesangial matrix expansion. Associated interstitial inflammation is noted (periodic acid–Schiff, 40×). (B) Immunofluorescence staining with IgG demonstrates linear GBM staining as well as segmental smudgy mesangial staining. (C) Electron microscopy shows randomly oriented nonbranching fibrils distributed within mesangium as well as within the peripheral capillary loops.
Clinical follow-up

The patient was initiated on treatment with intravenous pulsed methylprednisolone 500 mg daily for 3 days followed by prednisone 60 mg daily and oral cyclophosphamide 100 mg/day. However, kidney function continued to deteriorate with Cr of 5.8 mg/dL and the patient developed hyperkalemia at 5.8 mmol/L (reference range 3.6–5.2 mmol/L). On hospital Day 5, the patient was started on hemodialysis. Following plasmapheresis, her circulating levels of anti-GBM IgG antibodies were reduced to 173 and 70 units/mL after the first and second sessions, respectively. On Day 7, the patient developed thrombocytopenia, oral candidiasis and urinary tract infection with sepsis. The patient was treated with levofloxacin, and plasmapheresis was discontinued. The patient was treated with cyclophosphamide for 3 months. Prednisone was gradually tapered to 10 mg daily. At 4 months following diagnosis, the patient remained on dialysis.

Discussion

Anti-GBM disease is an autoimmune disorder resulting from circulating antibodies against an antigen intrinsic to the alpha 3 chain of type IV collagen in the GBM [10]. Emerging evidence has demonstrated that autoreactive T cells may also play an important role in the development of anti-GBM disease [11, 12]. Anti-GBM disease is a well-known cause of RPGN. In contrast, patients with FGN typically present with proteinuria and progressive loss of kidney function [5, 6]. Nevertheless, cases of FGN presenting as RPGN have been reported [5, 7, 8, 13, 14]. The diagnosis of FGN requires the pathognomonic histologic finding of the deposition of irregularly oriented, elongated, nonbranching microfibrils 10–30 nm thick in the mesangium and along the capillary walls on electron microscopy [5, 6], with negative staining by Congo red.

The kidney biopsy findings of FGN on light microscopy are variable and include diffuse mesangial hypercellularity and matrix expansion that may be seen with other types of GN [7, 13, 14]. Less commonly, light microscopy may show crescents [5, 7, 8, 15]. Immunofluorescence microscopy is positive for mesangial polyclonal IgG and C3 staining with weaker, less often granular and irregular, capillary wall staining [7, 14, 16]; ~10% of FGN cases show monotypic IgG. The texture of the immunofluorescence staining is typically smudged without distinct linearity or granularity [13]. However, the extensive fibrillar deposits of IgG can lead to a pseudolinear staining along the GBMs, similar to that seen in anti-GBM disease [3, 16]. For this reason, there have been several reported cases of FGN presenting as crescentic GN with linear IgG staining of the glomerular capillary walls mimicking anti-GBM disease [5, 7, 8, 17] (Table 1). However, in these cases of crescentic FGN, serum anti-GBM antibodies were consistently absent [2–5]. In the present case, the highly elevated anti-GBM levels in the serum together with immunofluorescence microscopy showing both linear GBM and smudgy mesangial staining for IgG and C3, along with fibrillar deposits by electron microscopy, confirmed the coexistence of two distinct pathological processes: anti-GBM disease and FGN.

Rupture of GBM has been well known to cause the exudation of fibrin in the urinary space, leading to crescent formation [19]. In anti-GBM disease, which has recently been considered as an autoimmune ‘conformeropathy’ [20], the quaternary structure of the alpha 345 noncollagenous-1 hexamer that forms GBM undergoes a conformational change resulting in an exposure of pathogenic epitopes on the α-3 and α-5 subunits and development of a pathogenic autoantibody anti-GBM response. The GBM rupture with subsequent crescentic GN can occur due to these anti-GBM antibodies against the α-3 chain of type IV collagen in the GBM [10]. In patients with FGN, the accumulation of intra-membranous fibrils may result in the rupture of GBM leading to the development of crescents as described in glomerular crescents in renal amyloidosis cases [19, 21]. It is possible that fibril accumulation disrupts the GBM exposing the cryptogenic Goodpasture antigen. Anti-GBM nephritis typically shows a diffuse necrotizing and crescentic GN on renal biopsy, with all of the crescents of the same ‘age’ (in the absence of ANCA) [22]. The current case showed a histologic picture somewhat different from typical anti-GBM nephritis: while there were diffuse crescents by light microscopy, the crescents ranged from cellular to fibrocellular to fibrous, indicative of different ‘ages’ and a more prolonged clinical course prior to presentation with renal insufficiency. This histologic feature is an indication of a glomerular disease concurrent with anti-GBM nephritis; in this case, FGN was concurrent.

In contrast to the well-known finding of positivity of ANCA, especially anti-myeloperoxidase-ANCA, in 30–38% of patients with anti-GBM disease [23, 24], the presence of circulating anti-GBM IgG antibody in patients with FGN has been demonstrated only in one other recent case [18] (Table 1). Momose et al. [18] described a patient who presented with acute kidney injury and positive serum anti-GBM antibody; renal biopsy showed thrombotic microangiopathy and ultrastructural features of FGN. Proliferative GN pattern and global sclerosis were described on light microscopy of 17 glomeruli. Unfortunately, immunofluorescence analysis was not performed in their case. In addition, diffuse necrotizing and crescentic GN was not noted, and so the authors could not conclude the existence of anti-GBM nephritis concurrent with FGN.

It is unclear whether the current case reflects an incidental coexistence of two uncommon GNs. Electron microscopy examination is not always performed in kidney biopsy specimens for patients presenting with RPGN [25, 26], and therefore, coexisting FGN may be missed and underreported. It is also possible that pre-existing deposition of fibrils in fibrillary GN may result in exposure of the cryptic antigen in anti-GBM disease, a required step in the development of anti-GBM nephritis [27, 28]. Anti-GBM disease has been described in several conditions that may predispose to exposure of cryptic GBM antigens, including infection, inhaled hydrocarbons, cocaine use, smoking and lithotripsy [29, 30]. Similarly, anti-GBM nephritis may occur superimposed on membranous GN, which may result in cryptic GBM antigen exposure [31]. In addition to antigen exposure, genetic factors such as human leucocyte antigen (HLA)-DR15 and DR4 have also played an important role for an increased risk of developing anti-GBM disease [32].

Although there are no controlled trials to guide treatment for FGN, high-dose glucocorticoids and cyclophosphamide have been used as treatment for FGN with crescentic GN [5, 9]. Its prognosis, however, is poor, and all reported cases of FGN with the clinical presentation of RPGN required renal replacement therapy and remained dialysis dependent [5, 8, 9, 18]. Plasmapheresis in conjunction with prednisone and cyclophosphamide have been recommended for the treatment of anti-GBM disease except in patients who are dialysis dependent at presentation with 100% crescents in kidney biopsy (correlated with poor kidney survival) and do not have pulmonary hemorrhage [33]. In our case presentation of coexistent anti-GBM disease with FGN, the patient received plasmapheresis in addition to treatment with cyclophosphamide and corticosteroids. Unfortunately, plasmapheresis was discontinued due to thrombocytopenia.
<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Anti-GBM antibody</th>
<th>Light microscopy</th>
<th>Immunofluorescence</th>
<th>Electron microscopy</th>
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<tr>
<td><strong>Reported cases of FGN presenting as crescentic GN with linear IgG staining of the glomerular capillary mimicking anti-GBM disease</strong></td>
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<tr>
<td>1 [5]</td>
<td>61</td>
<td>Female</td>
<td>Negative</td>
<td>Cellular crescents in 3 of 10 glomeruli, acute tubular injury and mild to moderate mononuclear interstitial infiltrate.</td>
<td>Linear, nearly global glomerular capillary wall staining for IgG (3+), C3 (3+) and albumin (1+).</td>
<td>Fibril deposition in the GBM.</td>
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<td>2 [7]</td>
<td>50</td>
<td>Male</td>
<td>Negative</td>
<td>Cellular crescent formation with collapse of the capillaries in 12 of 17 glomeruli, interstitial nephritis and acute tubular injury.</td>
<td>Prominent linear and pseudolinear staining of the capillary walls for IgG and prominent staining for fibrin in glomeruli with areas of fibrinoid necrosis.</td>
<td>Fibrils predominantly in the subepithelial areas of the capillary walls.</td>
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<td>4 [17]</td>
<td>55</td>
<td>Male</td>
<td>Negative</td>
<td>Cellular crescents in ~30% of the glomeruli. The interstitium was infiltrated with lymphocytes and neutrophils.</td>
<td>3+ linear staining of the GBM with IgG, C3, and kappa and lambda light chains.</td>
<td>Abundant, fairly straight, nonbranching fibrils with mean diameter of 26 nm in the thickened GBM and expanded mesangial regions.</td>
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<tr>
<td><strong>Reported cases of FGN presenting as crescentic GN with positive anti-GBM antibody</strong></td>
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<td>1 [18]</td>
<td>54</td>
<td>Male</td>
<td>Positive</td>
<td>Proliferative GN pattern and global sclerosis were described on light microscopy of 17 glomeruli. Renal arterioles, both afferent and efferent, showed extensive endothelial cell edema and swelling. Renal tubules were atrophic.</td>
<td>Immunofluorescence was not performed.</td>
<td>Extensive and dense extracellular deposition of fibrillar components, larger in diameter than amyloid fibers and aggregated to form large bundles.</td>
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<tr>
<td><strong>Our case presentation</strong></td>
<td>68</td>
<td>Female</td>
<td>Positive</td>
<td>4 of 7 glomeruli (57%) showed crescents, including two cellular crescents, one fibrocellular and one fibrous crescent.</td>
<td>Linear GBM staining and segmental smudgy mesangial staining with IgG (2–3+), C3 (2+), and kappa (2+) and lambda (2+) light chains.</td>
<td>Randomly oriented fibrils, measuring mean thickness of 19 nm, range 14–25 nm, within mesangium as well as within the peripheral capillary loops.</td>
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and sepsis, and the patient remained dialysis dependent at 4-month follow-up despite treatment with immunosuppressive treatment.

In summary, we present a case of coexistent anti-GBM disease with FGN presenting as RPGN. To the best of our knowledge, this has not previously been reported.

**Authors’ contribution**

All authors were involved and approved the final manuscript.

**Conflict of interest statement**

None declared.

**References**