RESEARCH LETTER

Prognostic Value of Diffuse Crescentic Lesions in Fibrillary Glomerulonephritis

To the Editor:

Fibrillary glomerulonephritis (FGN) is a rare disease classically defined by glomerular deposition of Congo red–negative, randomly oriented fibrils that stain with antisera to immunoglobulins, although rare cases are Congo red positive or immunoglobulin negative.[1,2] Despite the recent discovery of the biomarker DNAJB9, the pathophysiology is still enigmatic.[1] Prognosis is poor and predictors of progression are older age, Scr and proteinuria levels at diagnosis, glomerular pattern (membranoproliferative vs mesangial), crescents, glomerulosclerosis, and interstitial fibrosis. Crescents are present in ~25% of cases and are usually focal (<25% of glomeruli).[1,2] Diffuse crescentic involvement is very rare, with only few cases reported.[3-8] The optimal therapy in patients presenting with rapidly progressive glomerulonephritis (RPGN) is unknown.[2,9] Herein, we report a clinicopathologic series on diffuse crescentic FGN, aiming to define its clinical characteristics, pathologic features, and outcome.

Methods are in Item S1. We retrospectively reviewed the pathology archives at Mayo Clinic and University Hospital of Poitiers from 1997 to 2021 and identified 22 patients with native kidney diagnosis of FGN with crescents involving ≥50% of glomeruli (incidence of 2.7% in biopsies of FGN).

Clinical characteristics at diagnosis are detailed in Table 1. There were 22 patients (50% female, 91% White), with a median age of 59 years. All patients presented with RPGN and 9 required dialysis at diagnosis. Eight patients had CKD stages 3-5. Associated conditions included autoimmune disease in 6 and malignancy in 3. Two patients had HCV antibodies without detectable HCV RNA.

The pathologic characteristics are detailed in Table S1 and Fig S1. A majority of glomeruli had crescents (median: 64%; 82% of nonsclerotic glomeruli). Cellular crescents were observed in all cases (accounting for 50%-100% of all crescents), fibrocellular crescents in 55%, and fibrous crescents in 32% of cases, whereas focal fibrinoid necrosis was observed in 86% of cases (involving an average of 22% of glomeruli). Glomeruli showed strong staining for DNAJB9 in all 11 tested cases. By immunofluorescence, all cases showed glomerular positivity for IgG. The texture of IgG deposits was smudgy in most cases, but 27% showed linear to semilinear GBM staining mimicking anti-GBM nephritis. IgG subclass analysis, performed in 8 cases, showed IgG4 restriction (n = 5), dominance (n = 2), or co-dominance (n = 1). On electron microscopy, all cases exhibited randomly oriented fibrils (mean thickness 17 nm) permeating the mesangial matrix and the GBM.

Of 21 patients with information on therapy, 2 received symptomatic treatment alone and 19 received immunosuppressive therapy (Table 1). Four patients had a short course of plasmapheresis. On median follow-up of 5 (range, 0.5-103) months, median kidney survival was less than 1 month (Fig 1). None of the 9 patients who required dialysis at diagnosis recovered kidney function and 9 patients reached kidney failure a median of 2 (range, 0.2-7) months after biopsy. Two patients, treated with cyclophosphamide and steroids, had CKD stage 4 at last follow-up, 4 months after biopsy. A single patient who received cyclophosphamide + steroids for 5 months followed by mycophenolate mofetil + steroids for 14 months had partial remission, with reduction in proteinuria from 7.5 to 1 g/d with stable Scr at 2.2 mg/dL 22 months after

Table 1. Clinical Characteristics at Diagnosis and Treatment of Patients With Diffuse Crescentic Fibrillary Glomerulonephritis

Parameter	Value
Male sex	11/22 (50%)
Age, y	59 (23-82)
Race: White, African American, Hispanic	20 (91%), 1 (5%), 1 (5%)
Hypertension	19/22 (86%)
Hematuria	22/22 (100%)[a]
Scr, mg/dL	4.9 (1.8-11)
Proteinuria, g/24 h	8 (1.6-22.4)
Nephrotic syndrome	17/20 (85%)
CKD stage 3 or worse	8/20 (40%)
RPGN	22/22 (100%)
Dialysis required at diagnosis	9/21 (43%)
Positive ANA	3/20 (15%)
Positive ANCA	4/21 (19%)
Positive anti-GBM antibody	1/18 (6%)
Hypocomplementemia	3/22 (14%)
Positive SPEP/SIF	3/20 (15%)[b]
Positive UPEP/UIF	0/13
Associated medical condition	
Autoimmune disease[c]	6/22 (27%)
Malignancy[d]	3/22 (14%)
HCV	2/22 (9%)
First-line therapy	
Symptomatic measures alone	2/21 (10%)
Steroids alone	3/21 (14%)
Cyclophosphamide + steroids	11/21 (52%)
Rituximab + steroids	4/21 (19%)
Rituximab + cyclophosphamide + steroids	1/21 (5%)
Plasmapheresis	4/21 (19%)

Values for continuous variables given as median (range). Abbreviations: ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CKD, chronic kidney disease; GBM, glomerular basement membrane; HCV, hepatitis C virus; RPGN, rapidly progressive glomerulonephritis; Scr, serum creatinine level; SPEP/SIF, serum protein electrophoresis/immunofixation; UPEP/UIF, urine protein electrophoresis/immunofixation.

[a]Including gross hematuria in 4 cases.

[b]Including IgGκ in 1, IgGλ in 1, and IgMκ in 1 case. None of these had light chain restriction by immunofluorescence on frozen kidney biopsy specimen.

[c]ANCA-associated vasculitis in 2, rheumatoid arthritis in 2, ankylosing spondylitis in 1, and immune thrombocytopenia in 1.

[d]Diffuse large B-cell lymphoma in 1, colon carcinoma in 1, and neuroendocrine carcinoma in 1.

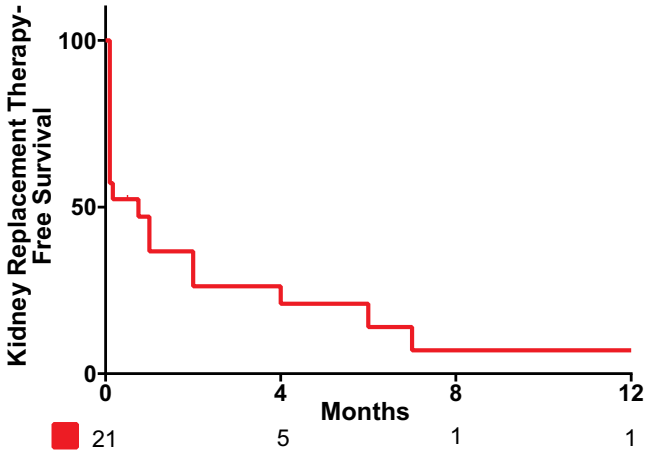

Figure 1. Kaplan-Meier analysis of kidney survival in the study cohort.

biopsy. Serious infections were recorded in 4 patients who received immunosuppressive therapy. Three patients underwent kidney transplantation without recurrence on protocol biopsies (at 4, 12, and 48 months posttransplantation), with normal Scr in 1 and stable graft function without proteinuria 18 and 56 months post transplantation in the other 2. Six patients died 1-26 months after diagnosis, 2 of neoplasia and 1 each of infection, brain hemorrhage, and acute kidney injury (cause was unknown in 1).

Mechanisms behind development of diffuse crescentic lesions in FGN remain unknown. The accumulation of fibrils may promote GBM rupture, allowing inflammatory mediators to spill into the urinary space. However, coexistent pathogenic factors are probably involved (eg, pathogenic autoantibodies, genetic factors). Interestingly, 19% of our patients had concomitant ANCA and 1 had anti-GBM antibody. The renal presentation, pathologic characteristics, and prognosis were similar in patients with and without these antibodies, so we included these cases in this study. Thus, all cases presented with RPGN with a similar percentage of glomeruli with crescents and fibrinoid necrosis. Follow-up was available for 4 of these 5 cases (3 ANCA$^+$, 1 anti-GBM$^+$). Despite treatment with steroids + rituximab in 2, steroids + cyclophosphamide in 2, and plasma exchange in 1, kidney failure occurred in 3 and 1 had CKD stage 4. ANCA or anti-GBM antibodies are likely the second "hit." However, prognosis seems mostly influenced by FGN in these cases. Half of our patients had an autoimmune disease, malignancy, or HCV, conditions previously reported in up to 40% of FGN cases.[1] There is currently no standard therapy for crescentic FGN,[4-7] and our study highlights its dismal kidney prognosis regardless of therapy type. Immunosuppressive therapy should be weighed carefully in these patients. Interestingly, none of the 3 kidney transplant recipients had evidence of recurrence despite the aggressive nature of native disease. Although ~20% of FGN patients may have recurrence posttransplant, allograft survival appears good.[10] Thus, kidney transplant is probably the best option for suitable patients with RPGN secondary to diffuse crescentic FGN.

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Supplementary Material

Supplementary File (PDF)

Figure S1; Item S1; Table S1.

Article Information

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