Anti–Glomerular Basement Membrane Glomerulonephritis
A Morphologic Study of 80 Cases

Edgar G. Fischer, MD, PhD, and Donna J. Lager, MD

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Abstract

Anti–glomerular basement membrane (anti-GBM) glomerulonephritis is a rare disease caused by IgG autoantibodies against the glomerular basement membrane. We describe clinical and pathologic findings in a series of renal biopsy specimens from 80 patients. The patients ranged in age from 16 to 87 years. The age distribution was bimodal, with one peak at a young age predominated by males and a second peak in the sixth to eighth decades with females predominating. Most patients (70 [88%]) had severe necrotizing glomerulonephritis with crescents in more that 50% of glomeruli. The fraction of crescentic glomeruli in biopsy specimens correlated well with serum creatinine levels but not with serologic titers for anti-GBM antibodies. Interstitial fibrosis was uncommon and, when present, minimal to mild. Linear IgG deposition defines this entity, but immunofluorescent costaining for other immunoglobulins and complement is found frequently. To our knowledge, this is the largest series of renal biopsy specimens with anti-GBM glomerulonephritis studied to date.

Anti–glomerular basement membrane (anti-GBM) glomerulonephritis is an autoimmune disease that clinically manifests as a rapidly progressive glomerulonephritis. When accompanied by pulmonary hemorrhage, it is designated the Goodpasture syndrome. Anti-GBM glomerulonephritis is rare, with an incidence of 0.5 to 1 case per million per year in the United States. It leads to acute renal failure and progression to end-stage renal disease in most cases.1-3 However, earlier diagnosis and better supportive care dramatically improved patient survival during the past decades. Plasmapheresis and immunosuppressive drugs are the most important treatment strategies. Two parameters have emerged as reliable predictors of adverse outcome: the fraction of crescentic glomeruli in biopsy specimens and anuria or a serum creatinine level greater than 5 mg/dL (442 µmol/L) at diagnosis.4-13

Anti-GBM glomerulonephritis is one of the few human autoimmune diseases in which the autoantigen has been identified.14 It is designated the Goodpasture antigen and comprises the noncollagenous domain (NC1) of the α-3 chain of type IV collagen.15,16 IgG autoantibodies against this antigen have been proven to be the pathogenetic agent,17 and linear IgG deposition along the GBM defines the disease. The deposited immunoglobulin is generally of the IgG1 class,1-3 although rare IgA-mediated cases have been described.9,18-21 In their seminal work, Lerner et al17 elucidated the pathogenetic role of anti-GBM antibodies in patients with glomerulonephritis by injecting eluates from kidney tissue into nonhuman primates. The authors were able to transfer the nephritis from patients to 2 monkeys, and severe proliferative glomerulonephritis developed in both monkeys. Kidneys from both monkeys showed linear basement membrane staining for IgG. The pathogenetic role of anti-GBM antibodies was
substantiated further when the nephritis recurred in patients who had received renal allografts before elimination of the autoantibody from their serum.4

Advances in our understanding of the molecular and immunologic mechanisms of the disease were reviewed recently.22,23 However, no large studies that focus on renal biopsy findings have been published recently. We reviewed the biopsy pathology of 80 patients diagnosed with anti-GBM glomerulonephritis.

Materials and Methods

Kidney biopsy specimens from 80 patients consecutively diagnosed with anti-GBM glomerulonephritis between January 1994 and December 2001 were identified from the Mayo Clinic (Rochester, MN) files. Clinical information was provided by the referring physicians, and the pathologic findings were reviewed by using routine light, immunofluorescent, and electron microscopy. Immunofluorescent stains were performed with antibodies against IgG, IgM, IgA, the complement components C3 and C1q, and κ and λ light chains. The staining intensity was scored as follows: 0+, negative; 1+, mild; 2+, moderate; or 3+, strong.

Regression analysis was performed to evaluate the correlation between the fraction of crescentic glomeruli in biopsy specimens and the serum creatinine levels. To evaluate the monthly disease distribution for seasonal clustering, a χ² goodness of fit test was performed that compared the observed disease frequency with the expected values under a uniform hypothesis.

Results

The male/female ratio among the 80 patients was 1:1.35, with a slight female predominance. The age range was 16 to 87 years (mean, 52.8 years). The age distribution showed one peak with predominance of young males in their teens and 20s and a second higher peak with predominance of females in the sixth to eighth decades of life Figure 1. Pulmonary hemorrhage was documented in 5 males 17 to 39 years of age (mean, 24.6 years). The disease distribution by month of diagnosis is shown in Table 1. A χ² goodness of fit test failed to reveal significant case clustering in any month or season (P > .5).

Light microscopy revealed that the majority of patients (70 [88%]) had severe necrotizing and crescentic glomerulonephritis, with crescent formation in more than 50% of glomeruli Figure 2. The fraction of crescentic glomeruli in biopsy specimens correlated well with the serum creatinine levels at the time of diagnosis Figure 3 (regression equation, y = 0.14 × x – 1.66; P = 2.8 × 10⁻⁵).

Glomerular changes were characterized by segmental or global necrosis of the capillary tufts with disruption of the GBM and Bowman capsule Image 1A and Image 1B. Intratubular red cell casts were present in 52 cases (65%). Interstitial edema was seen in 39 cases (49%). Interstitial inflammation with a mixed infiltrate of lymphocytes, plasma cells, and macrophages was graded as mild in 26 cases (33%), moderate in 23 (29%), and severe in 31 (39%). The intensity of chronic inflammation did not correlate with the presence of interstitial edema or interstitial fibrosis. Periglomerular accentuation of the mononuclear infiltrate was common, and periglomerular multinucleated giant cells or granulomas were found in 10 cases (13%). Vasculitis with fibrinoid necrosis of the interstitial arterioles was present in 6 cases (8%), 5 of which had crescents in all glomeruli present in the biopsy specimens. Interstitial fibrosis was absent in 48 cases (60%), minimal to mild in 26 (33%), and moderate in 5 (6%). Only 1 patient had severe interstitial fibrosis.
Immunofluorescent microscopy revealed linear GBM staining with anti-IgG antibodies in 79 cases (99%). Linear IgA staining was present in 1 exceptional case, which has been reported previously. The staining intensity for IgG ranged from 1+ to 3+ and was 2+ or stronger in most biopsy specimens (63 [80%]). In addition to the IgG deposition, linear costaining was common with antibodies against IgM, IgA, and C3 and C1q. The most frequent constellations of codeposits were C3 alone in 29 cases (36%), IgM combined with C3 in 21 (26%), and IgM with C3 and C1q in 13 (16%) (Figure 4). All 80 cases demonstrated linear deposition of κ and λ light chains, with κ staining being more intense than λ in all but 4 cases.

Glomerular fibrin deposits were detected by immunofluorescence in 90% of cases. Granular IgM labeling was found in 13 cases (16%), which always was weak and segmental (scored <1+), and granular C3 was seen in 2 cases (3%). Electron microscopy revealed that these findings were not accompanied by deposits. One patient had granular mesangial IgA and C3 deposits due to coexisting IgA nephropathy. Weak linear IgG staining of the tubular basement membranes was present in 11 cases (14%).

Ultrastructural examination demonstrated disruption of the GBM with extravasation of fibrin and inflammatory cells into the urinary space in 48 cases (60%). The Bowman capsule was disrupted in 5 cases (6%). Crescents were cellular and composed of histiocytes, lymphocytes, neutrophils, epithelial cells, and fibrin. Effacement of podocyte foot processes was present in 27 cases (34%). In 7 cases (9%), electron-dense immune complex–type deposits were seen, which were scant, subepithelial, and not detected by immunofluorescence. One patient had subepithelial immune complex–type deposits and GBM spikes due to coexisting early membranous nephropathy, but no granular deposits were found by immunofluorescence.

Serologic studies for anti-GBM antibodies were available in 32 cases (40%). They were positive in 27 cases (84%) and negative in 5 (16%). Anti-GBM antibody titers did not correlate with disease severity as evaluated by serum creatinine levels and the fraction of crescentic glomeruli in biopsy specimens (data not shown). Serologic studies for antineutrophil cytoplasmic autoantibodies (ANCAs) were positive in 10 cases (perinuclear ANCA, 5 cases; cytoplasmic ANCA, 2 cases; ANCA, not otherwise specified, 3 cases) and negative in 14 cases. Antinuclear antibodies were detected in the serum of 7 patients.

### Discussion

This study analyzed renal biopsy findings in a series of 80 patients diagnosed with anti-GBM glomerulonephritis, to our knowledge the largest biopsy series to date. In our patient population, there was a slight predominance of females, with a male/female ratio of 1:1.35. This ratio has varied from 1:1 to 9:1 in other studies (reviewed by Meyers et al). We found a bimodal age distribution (Figure 1), with a male predominance at the younger age peak and a female predominance later in life, as reported by others. Only 5 patients (6%) had clinically confirmed hemoptysis at diagnosis, and they were all males, aged 17 to 39 years. This finding is in keeping with earlier studies showing that glomerulonephritis occurs more frequently in young men, whereas glomerulonephritis...
alone is more common in older women.\textsuperscript{1,9,10} However, Goodpasture syndrome was more frequent in previous studies, ranging from 35\% to 62\%.\textsuperscript{4,8-13} The difference could be due to a predominance of older women in our patient population.

The possibility of a seasonally clustered incidence in anti-GBM disease was proposed by some authors. Savage et al\textsuperscript{9} suggested a peak incidence of anti-GBM glomerulonephritis in the spring and early summer, and Perez et al\textsuperscript{5} described a “miniepide-
mic” of 4 cases of Goodpasture syndrome during the winter. Therefore, we tested the hypothesis that there could be seasonal clustering in our patient population but found no statistically significant disease clustering by month or by season.

The majority of our patients (70 [88\%]) had severe necro-
tizing and crescentic glomerulonephritis, with more than 50\% of glomeruli affected by cellular crescents (Figure 2). The fraction of glomeruli with crescent formation in biopsy speci-
mens correlated well with serum creatinine levels (Figure 3).
The two parameters, percentage of crescentic glomeruli in biopsy specimens and serum creatinine levels at clinical diagnosis have been recognized as the most reliable predictors of renal outcome in previous studies. Serum anti-GBM autoantibody titers did not correlate with disease severity in our patient population or in other studies. Severely damaged glomeruli showed disruption of the GBM, fibrin extravasation, and obliteration of the urinary space by cellular crescents (Images 1A and 1B). Intratubular red cell casts were common. Granulomatous inflammation in the periglomerular interstitium was present in 10 (13%) of our patients, whereas others have described this finding in up to 24% of cases. Linear IgG deposition along the GBM (Image 1C) was the defining feature of anti-GBM glomerulonephritis, but codeposition of other molecules occurred frequently. Complement C3 was the most prevalent codeposit, followed by the combination of IgM and C3 (Figure 4), as described by other authors. However, we found costaining for C1q more frequently than for IgA. Staining for immunoglobulin light chains was usually stronger for \( \kappa \) than for \( \lambda \). Fibrin was detected by immunofluorescence in the majority of cases (90%), indicating the severe damage to the glomerular tuft.

Ultrastructural examination illustrated the injury to the glomerular tuft with disruption of the GBM and extravasation of blood elements into the urinary space. Crescents were cellular and composed of histiocytes, lymphocytes, neutrophils, epithelial cells, and fibrin. Most patients with GBM disruption revealed by electron microscopy had severe disease, with crescents in more than 50% of glomeruli shown by light microscopy. Electron-dense immune complex–type deposits were found in 7 cases. They were scant, not associated with deposits on immunofluorescence, and probably of no pathologic significance. Two patients in our series had pathologic evidence of a second coexisting renal disease. One patient had associated IgA nephropathy as detected by granular mesangial IgA staining by immunofluorescence. Another patient had associated early membranous nephropathy with subepithelial deposits and spike formation on the GBM.

This is largest series of renal biopsy specimens with anti-GBM glomerulonephritis to date. Our data illustrate the bimodal age distribution and the strong correlation between the fraction of crescentic glomeruli in biopsy specimens and disease severity. Statistical analysis failed to show seasonal contributions to the statistical analyses.

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References


