AJKD

Original Investigation

Membranous Nephropathy With Crescents: A Series of 19 Cases

Erika F. Rodriguez, MD,[1] Samih H. Nasr, MD,[1] Christopher P. Larsen, MD,[2] Sanjeev Sethi, MD, PhD,[1] Mary E. Fidler, MD,[1] and Lynn D. Cornell, MD[1]

Background: Membranous nephropathy (MN) with crescents is rare and, in the absence of lupus, usually is associated with anti–glomerular basement membrane (anti-GBM) nephritis or antineutrophil cytoplasmic antibody (ANCA)-positive glomerulonephritis. Only rare cases of crescentic MN without ANCA or anti-GBM have been reported.

Study Design: Case series.

Setting & Participants: 19 patients with ANCA- and anti-GBM–negative crescentic MN and no clinical evidence of systemic lupus.

Outcomes: Clinical features, kidney biopsy findings, laboratory results, treatment, and follow-up of patients with crescentic MN.

Results: Mean age was 55 (range, 5-86) years. All patients presented with proteinuria (mean protein excretion, 11.5 [range, 3.3-29] g/d) and nearly all had hematuria; 16 of 19 (84%) patients had decreased estimated glomerular filtration rates (eGFRs; mean serum creatinine, 2.9 [range, 0.4-10] mg/dL; mean eGFR, 39.7 [range, 4 to >100] mL/min/1.73 m^2). Glomeruli showed on average 25% (range, 2%-73%) involvement by crescents. All showed a membranous pattern; 7 showed mesangial and 2 showed segmental endocapillary proliferation. By immunofluorescence, all cases showed granular subepithelial immunoglobulin G (IgG) and κ and λ light chains, and all but one showed C3; 5 showed C1q or IgA. Electron microscopy revealed stages I-III MN; 38% of cases were M-type phospholipase A_2 receptor (PLA_2R) associated, indicating that at least some were primary MN. Follow-up clinical data were available for all patients (mean, 22 [range, 1.5-138] months). 14 patients received immunosuppressive therapy, and 2, only angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy. 4 patients (21%) progressed to end-stage renal disease, at 0-9 months postbiopsy. Mean serum creatinine level of those without end-stage renal disease at follow-up was 1.7 (range, 0.5-4.1) mg/dL; mean eGFR was 53.3 (range, 16-103) mL/min/1.73 m^2. 67% of patients had proteinuria with protein excretion ≥ 1 (mean, 3.2) g/d at follow-up.

Limitations: Retrospective study.

Conclusions: Crescentic MN is a rare variant of MN that usually presents with heavy proteinuria, hematuria, and decline in GFR. The prognosis is variable and the disease may respond to therapy, but most patients develop a long-term decline in GFR.

Am J Kidney Dis. ■(■):■-■.

INDEX WORDS: Crescentic glomerulonephritis; immune complex; kidney; membranous glomerulopathy; membranous glomerulonephritis; renal biopsy; case series.

Membranous nephropathy (MN) is among the most common causes of adult-onset nephrotic syndrome. It may be primary (idiopathic) or secondary to systemic autoimmune or other diseases, neoplasms, chronic infections, or drugs.[1,2] In most cases of primary MN, antibodies directed against a podocyte antigen, M-type phospholipase A_2 receptor (PLA_2R), are detected in plasma or kidney tissue.[3] Morphologically, MN is defined by subepithelial immune complex deposits that can be detected by immunofluorescence and electron microscopy, with associated diffuse podocyte foot-process effacement by electron microscopy.[4] Endocapillary proliferation, crescents, and necrosis are rare when not associated with systemic lupus erythematosus (SLE). The prognosis of MN is variable, with spontaneous complete remission in about one-third of patients. However, another one-third of patients progress to end-stage renal disease (ESRD).[5,6]

Crescent formation is a sign of severe glomerular injury that can result from various causes and pathogenic mechanisms. The percentage of compromised glomeruli usually correlates with the severity of kidney failure and other clinical manifestations. Morphologically, crescents classically are defined as extracapillary hypercellularity with 2 or more layers of cells in Bowman space.[7] Crescent formation is a rare complication of MN, with only a few cases reported in the literature in the known absence of antineutrophil cytoplasmic antibody (ANCA) or anti–glomerular basement membrane (anti-GBM) positivity.[8-14] Most

From the [1]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; and [2]Nephropathology Associates, Little Rock, AR.

Received July 17, 2013. Accepted in revised form February 6, 2014.

Address correspondence to Lynn D. Cornell, MD, Department of Laboratory Medicine and Pathology, Mayo Clinic, 200 1st St SW, Rochester, MN 55905. E-mail: cornell.lynn@mayo.edu

0272-6386/$36.00

http://dx.doi.org/10.1053/j.ajkd.2014.02.018

reported cases have a superimposed glomerulonephritis attributable to ANCA[8,13,15-19] or anti-GBM antibodies[20-24] or results of ANCA testing were not available, particularly because many cases were described prior to the established association in the mid-1980s of ANCA and crescentic glomerulonephritis.[9,14,23,25-36] In the present study, we report a series of patients with crescentic MN who have negative ANCA and negative anti-GBM antibodies and no evidence of SLE and examine the clinicopathologic features and outcomes in these patients.

METHODS

This study was approved by the Mayo Clinic Institutional Review Board. The pathology database at our institution was searched for cases from January 1, 1994, to January 1, 2013, that showed MN. Pathology reports were reviewed for a description of cellular crescents. Any case of MN with glomeruli present on light microscopy material and at least one cellular or fibrocellular crescent was considered for inclusion. Only patients with known negative ANCA, anti-myeloperoxidase (anti-MPO), and anti–proteinase 3 antibodies at the time of kidney biopsy were included. In addition, patients with MN and concurrent linear GBM staining for immunoglobulin G (IgG) were excluded, and patients with a known positive anti-GBM titer were excluded. Also excluded were patients with a history of SLE at the time of kidney biopsy or an identified likely cause of crescentic MN (eg, syphilis or concurrent postinfectious glomerulonephritis). Patients' medical records were reviewed for evidence of systemic vasculitis, medication history, and laboratory results including ANCA, anti-GBM, antinuclear antibody (ANA), serum C3 and C4, serum creatinine, serum albumin, and quantitative urinary protein studies. Estimated glomerular filtration rate (eGFR) was calculated by the 6-variable MDRD (Modification of Diet in Renal Disease) Study equation for non–African American adult patients and the one adolescent patient and by the bedside Schwartz equation for the one child patient.[37,38] Race information was available for only 8 of 19 patients; for the other patients, the non–African American eGFR calculation was used. Decreased eGFR was defined as <60 mL/min/1.73 m^2.

Standard processing of kidney biopsies processed at the Mayo Clinic included light microscopy, immunofluorescence, and electron microscopy. For light microscopy, biopsy specimens were stained with hematoxylin-eosin, periodic acid–Schiff, Masson trichrome, and Jones methenamine silver. For immunofluorescence, 4-μm cryostat sections were stained with polyclonal fluorescein isothiocyanate (FITC)-conjugated antibodies to IgG, IgM, IgA, C3, C1q, κ and λ light chains, fibrinogen, and albumin (Dako), as per routine clinical testing. Two biopsy specimens were external slides reviewed at Mayo Clinic and did not have κ and λ light chain staining reported. Immunofluorescence was scored by the pathologist on a scale of 0-3+. Electron microscopy was performed as per clinical routine.

Biopsies were stained for PLA_2R by immunofluorescence on pronase-digested paraffin sections as previously described,[39,40] using a rabbit anti-PLA_2R1 primary antibody (Sigma-Aldrich) and polyclonal goat anti-rabbit IgG (Life Technologies) as the secondary antibody. Biopsies of primary MN were used as controls for PLA_2R staining with each staining run. PLA_2R antibody staining was considered positive if it showed 3+ granular GBM staining (scale, 0-3+) in the same pattern as the IgG.

RESULTS

Clinical and Laboratory Features

A total of 5,108 native kidney biopsies showing MN, both primary and secondary, were identified at Mayo Clinic from January 1, 1994, to January 1, 2013. Of these, 20 biopsies (0.39%) from 19 patients had ANCA- and anti-GBM–negative crescentic MN. An additional 19 patients had MN with crescents but did not have ANCA, anti-MPO, and anti–proteinase 3 test results available to us, and these patients therefore were excluded from analysis. Clinical features are summarized in Table 1. Mean age at diagnosis was 55 (range, 5-86) years; 8 (42%) were female. All patients presented with proteinuria (mean protein excretion, 11.5 [range, 3.3-29] g/d) and 89% had hematuria. Of 15 patients with sufficient clinical information available, 80% had full nephrotic syndrome, including hypoalbuminemia and peripheral edema. Sixteen of 19 (84%) patients had decreased eGFR with serum creatinine levels above the normal range or increased from a previous measurement (mean serum creatinine, 2.8 [range, 0.4-10] mg/dL; eGFR, 39.7 [range, 4-119] mL/min/1.73 m^2). No patient had a previous diagnosis of MN or symptoms of nephrotic syndrome in the past. No patient had extrarenal evidence of vasculitis at the time of biopsy or in the follow-up period, except for one patient who later developed temporal arteritis. No patient developed SLE in the follow-up time period after the biopsy. Four patients (nos. 1, 6, 10, and 13) had positive or transiently positive ANA test results, whereas others had negative ANA results. No patient had positive test results for anti–double-stranded DNA, hepatitis B or C virus, or HIV (human immunodeficiency virus) infection. Of patients with available laboratory values, 94% had normal or slightly increased serum C3 and C4 levels. Serum C3 level was low (56 mg/dL) in one patient (no. 5) and C4 level was low (<5 mg/dL) in another patient (no. 3).

Light Microscopy

See Table 2 for a summary of biopsy features. By light microscopy, the average number of glomeruli was 23 (range, 5-52) per biopsy, with an average of 18% (range, 0%-61%) global glomerulosclerosis. On average, glomeruli showed 25% (range, 3%-73%) involvement by crescents or necrosis. Nine biopsy specimens (47%) showed glomerular tuft necrosis or necrosis associated with cellular crescents, whereas the others showed cellular crescents without glomerular tuft necrosis. Four of 19 (21%) cases showed $\geq$50% crescents. All biopsy specimens showed a membranous pattern, which was global in 18 cases (95%) and segmental in one case. Seven biopsy specimens showed mild mesangial hypercellularity and 2 showed segmental endocapillary proliferation (1 biopsy specimen showed both features). Infiltrating neutrophils were not conspicuous. The degree of interstitial fibrosis and tubular atrophy ranged from none or mild (n = 15) to moderate (n = 4) to severe