Membranous Nephropathy With Crescents

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Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults and can be primary or secondary. Primary MN is most commonly associated with anti-M-type phospholipase A2 receptor (PLA2R) antibodies and is usually IgG4 dominant, whereas secondary MN can be seen in the setting of malignancies, infections, autoimmune diseases, or as a side effect of certain medications or...
| Case | Sex  | Age (yr) | Ethnicity | Baseline Cr (mg/dl) | Cr at biopsy (mg/dl) | GFR at diagnosis (ml/min per 1.73 m²) | Proteinuria at biopsy | Follow-up proteinuria | Albumin (g/dl) | Edema | Lung symptoms | Medical comorbidities | Antibodies | Other relevant labs | Treatment | Dialysis | Transplant | Cr at last follow-up (mg/dl) | GFR at follow-up (ml/min per 1.73 m²) | Follow-up duration (mo) |
|------|------|----------|-----------|---------------------|---------------------|---------------------------------------|----------------------|---------------------|------------------|-------|--------------|------------------------|------------|----------------------|-----------|----------|-----------|----------------------------|--------------------------|----------------------|
| 1    | F    | 68       | White     | 1.6                 | 9                   | 4                                    | 3+                   | 4 g/24 h            | NA               | 2.5   | Yes          | SOB                    | Rheumatoid arthritis, NSAID use | MPO        | NA                   | Cyclophosphamide, prednisone complicating aspergillus pneumonia | Yes         | Yes       | NA         | NA                         | NA                       | 12                    |
| 2    | F    | 21       | White     | NA                  | 15                  | 3                                    | Anuric               | ESRD               | NA               | NA    | NA           | DAH, acute respiratory failure | NA         | Anti-GBM             | PLEX, prednisone, and cyclophosphamide | Yes         | No        | ESRD       | ESRD                       | 98                       | 13                    |
| 3    | M    | 65       | White     | 0.9                 | 2.2                 | 30                                    | >100 RBCs/HPF        | 2.88 g/24 h         | ESRD             | 3.7   | No           | Hemoptysis            | Raynaud syndrome | pANCA, MPO | ANA 1:80              | Yes                   | Yes       | Yes       | ESRD (5.38) | after transplant nephrectomy | ESRD                       | 12                    |
| 4    | F    | 64       | AA        | 2                   | 2.5                 | 24                                    | Moderate, 20–29 RBCs/HPF | 1.6 g/24 h          | 1.1 g UPC         | 2.2   | Yes          | Hemoptysis, DAH      | Diabetes, hep C cirrhosis, HCC | pANCA, MPO | PR3                  | Prednisone and cyclophosphamide then MMF | No          | None      | 4.33       | Deceased                   | 13                       | 41                    |
| 5    | F    | 62       | Asian     | NA                  | 1.09                | 51                                    | NA                   | 16.9 g/24 h         | NA               | 0.6   | Yes          | Liver dysfunction | Pulmonary nodule | NA         | NA                   | None                   | NA         | NA        | 1.14       | 49                         | 79                       | 10                    |
| 6    | F    | 61       | AA        | 0.8                 | 9                   | 5                                    | Few RBCs             | 8 g UPC             | 1.6 g/24 h        | 1.4   | Yes          | HTN, CKD, heavy smoker | NA         | NA                   | Prednisone and cyclophosphamide | No          | No        | 1.32       | 49                         | 10                       | 14                    |
| 7    | F    | 66       | AA        | 1.3                 | 2.9                 | 20                                    | NA                   | 3.5 g UPC           | NA               | NA    | NA           | Bladder cancer, MGUS | NA         | NA                   | NA                   | NA         | NA        | NA         | NA                         | NA                       | 14                    |
| 8    | M    | 70       | White     | 1.3                 | 2.35                | 28                                    | >20 RBCs/HPF         | 2 g/24 h            | 1.3 g UPC         | 3.4   | No           | Cough                  | Previous MN with crescents, MGUS, resected pancreatic neoplasm, metastatic sarcomatoid carcinoma, HTN, DM | pANCA, MPO | PR3                  | Prednisone and cyclophosphamide | No          | No        | 1.99       | 33                         | 14                       | 11                    |
| 9    | M    | 79       | White     | 1.5                 | 3                   | 21                                    | 21–30 RBCs/HPF       | 1 g UPC             | 0.2 g UPC         | 4.5   | No           | None                   | HTN, MGUS, diabetes | pANCA, MPO | None                 | Cyclophosphamide, prednisone, then MMF | No          | No        | 2.02       | 32                         | 46 mo                     | 12                    |
| 10   | M    | 56       | AA        | 1.07                | 1.07                | >60                                    | Large                | 4.7 g/24 h          | 0.7 g/24 h        | 2.7   | Yes          | None                   | Diabetes, HTN | NA         | None                 | Cyclophosphamide | No          | No        | 0.83       | >60                        | 49 mo                     | 10                    |
| 11   | F    | 42       | NA        | 1                   | 1.8                 | NA                                    | >60 RBCs/HPF         | 1.8 g UPC           | 0.2 g UPC         | 1.7   | NA           | NA                      | Prior MPO-ANCA cutaneous vasculitis, history of cocaine abuse, positive MISA skin culture | MPO        | Positive ANA and anti-SSB | Prednisone, MMF | NA          | NA        | 0.8        | >60                        | 41 mo                     | 14                    |
| 12   | M    | 26       | White     | NA                  | 18.6                | 3                                     | Large                | 2.8 g/24 h          | 0.07 g UPC        | 3.6   | None         | Hemoptysis            | Obesity | Anti-GBM >8             | PLEX, steroids, cyclophosphamide | Yes         | Yes       | 2.01       | 39                         | 38 mo                     | 11                    |

(Continued on next page)
The occurrence of crescents in MN is extremely rare, with a prevalence estimated between 0.39% and 0.26%. Crescents can be seen in both primary and secondary MN or in association with a superimposed disease process, such as anti–neutrophil cytoplasmic antibody (ANCA)–associated glomerulonephritis or anti–glomerular basement membrane (GBM) disease. Previous series in the United States have either focused on cases of MN with crescents in the absence of ANCA or anti–GBM antibodies, or in association with ANCA. In light of the recently published series of MN with crescents from the United Kingdom, and given the rarity of this entity, we analyzed its prevalence and its clinical and pathological characteristics in biopsy findings reviewed at our institution.

A total of 14,800 native and transplant renal biopsy specimens were received at the Ohio State University from 2010 to 2019. Of these, 15 cases (0.1%) showed MN with crescents (fibrous crescents only; 3; diffuse crescents [in >50% of glomeruli]; 3; focal crescents [in <50% of glomeruli], 9). In addition, 3 cases had only segmental subepithelial deposits (segmental MN).

Cases of lupus nephritis were excluded. PLA2R staining was performed retrospectively in 7 cases.

There were 8 female and 7 male patients. Two had anti–GBM antibodies (Figure 1a–d). 9 had ANCA (8 MPO, 2 both MPO and PR3), and 4 showed anti–PLA2R–positive deposits in the biopsy specimen (Figure 1e–g), including 1 with positive serum anti–PLA2R. Of note, not all of these antibodies were checked in all patients. Clinical features are summarized in Table 1 and pathological features in Table 2. One patient had prior ANCA–associated cutaneous vasculitis, and 1 patient had prior biopsy–proven infection–related glomerulonephritis; both had a history of cocaine use. Potential secondary causes of MN included solid organ malignancies (n = 3), hepatitis C (n = 2), and rheumatoid arthritis (n = 1). Three patients had a monoclonal gammapathy of undetermined significance, and 5 patients had positive autoantibodies (4 anti–nuclear antibodies, 2 anticytoplasmic antibodies, and rheumatoid arthritis). Eight patients had pulmonary symptoms, including hemoptysis in 3 and documented diffuse alveolar hemorrhage in 2. Twelve patients had hematuria, which was usually significant, and 14 had proteinuria (1 patient was anuric). Proteinuria was measured by spot urine protein–to–creatinine ratio or 24-hour collection and was >3 g in 7 of the 14 patients. Median creatinine at presentation was 2.9 mg/dl (1.07–18.6). Two patients had normal renal function on presentation (1 patient had a single fibrous and the other a single cellular crescent). The remaining 13 patients had estimated glomerular filtration rate of <60 ml/min per 1.73 m². Eleven patients...
### Table 2. Pathological characteristics

| Case | Final diagnosis | Total glomeruli | Crescents/FN | GS | % Active lesions<sup>a</sup> | IFTA% | Immunofluorescence<sup>b</sup> | lgG1 | lgG2 | lgG3 | lgG4 | PLA2R | EM stage | Mesangial deposits | TRIs | Extraglomerular deposits |
|------|----------------|----------------|--------------|----|---------------------------|------|-----------------------------|------|------|------|------|--------|----------|----------------------|------|------------------------|
| 1    | ANCA-associated crescentic and necrotizing GN; membranous GN | 16 | 4 | 8 | 25 | 25 | lgG, IgA, C3, kappa, lambda GBM | 1 | 0 | 1.5 | 0.5 | Negative | NA | NA | NA | 0 |
| 2    | Diffuse crescentic and necrotizing anti-GBM disease; segmental MN | 21 | 18 | 0 | 85 | 0 | Linear GBM IgG, kappa, lambda GBM and IgG, kappa, lambda TBM | 2.5 | 1.5 Linear | 0 | 3 Linear | Negative | 1 | 0 | 0 | 0 |
| 3    | Focal crescentic GN with MN | 30 | 1 | 10 | 3 | 35 | lgG, IgA, C3, kappa, lambda GBM and IgG, kappa, lambda TBM | 1.5 | 1 | 0 | 0.5 | Negative | 0 to 2 | 1 | 0 | TBM deposits by IF |
| 4    | MN with fibrous crescents; underlying diabetic glomerulosclerosis | 24 | 4 (Fibrous) | 10 | 0 | 60-70 | IgG, IgA, C3, kappa, lambda GBM and IgG, kappa, lambda GBM | 1.5 | 0.5 | 0.5 | 2 | Positive | 3 to 4 | 0 | 0 | TBM deposits by IF |
| 5    | MN with fibrous crescents | 34 | 1 (Fibrous) | 9 | 0 | 20 | IgG, C3, kappa, lambda GBM | 3 | 2 | 0 | 2 | Negative | 2 | 0 | 0 | 0 |
| 6    | MN with focal crescents | 13 | 3 | 0 | 23 | 20-25 | IgG, IgA, IgM, C3, kappa, lambda GBM | 2 | 1 | 2 | 3 | Weak and segmental | 2 to 3 | 0 | 0 | 0 |
| 7    | ANCA-associated crescentic and necrotizing GN with MN | 33 | 8 | 12 | 24 | 60 | IgG, IgM, C3, kappa, lambda GBM | 2 | 1 | 0.5 | 3 | Positive | 2 to 3 | 0 | 0 | 0 |
| 8    | ANCA-associated crescentic and necrotizing GN; membranous GN | 12 | 6 | 0 | 50 | 30 | IgG, C3, kappa, lambda GBM | 1.5 | 0.5 | 1 | 0 | Negative | 0 to 4 | 0 | 0 | 0 |
| 9    | ANCA-associated necrotizing and crescentic GN with MN and TBM deposits | 5 | 1 | 0 | 20 | 35 | lgG, kappa, lambda GBM and IgG, C1q, kappa, lambda TBM (focal) | 1 | 0.5 | 0 | 2 | Negative | 1 to 3 | 0 | 0 | TBM deposits by IF and EM |
| 10   | MN with focal crescents | 12 | 1 | 2 | 8 | 5 | IgG, C3, kappa and lambda | 3 | 1 | 2 | 3 | Positive | 2 | 0 | 0 | 0 |
| 11   | Immune-complex GN with segmental MN and focal necrotizing lesions | 13 | 2 | 0 | 15 | 10 | IgG, IgM, C3, kappa and lambda GBM and segmented mesangial | 2 | 0.5 | 0.5 | 0 | Negative | 2 | Rare | 1 | 0 |
| 12   | Diffuse crescentic and necrotizing anti-GBM disease; segmental MN | 23 | 18 | 0 | 78 | 25 | Linear IgG, IgA, C3, kappa and lambda | 2 | Linear | 1 Linear | 1 Linear | Negative | 1 to 2 | 0 | 0 | 0 |
| 13   | MN with focal crescents | 42 | 1 | 7 | 2 | 20 | IgG, C3, kappa and lambda GBM | 2 | 1 | 0.5 | 2 | Negative | 1 to 2 | 0 | 0 | 0 |
| 14   | Advanced chronic renal injury with underlying MN; acute TMA | 32 | 5 (Fibrous) | 29 | 0 | 90 | IgG, IgM, C3, kappa and lambda GBM and segmented mesangial | 1 | 0.5 | 0.5 | 0 | Negative | 2 | 1 | 0 | 0 |
| 15   | MN with focal crescents | 9 | 3 | 0 | 33 | 20 | IgG, C3, kappa and lambda GBM and mesangial | 3 | 1 | 2 | 3 | Positive | 2 to 4 | 1 | 1 | 1 |

<sup>a</sup>Active lesions include cellular or fibrous – cellular crescents and areas of glomerular segmental fibrinoid necrosis.

<sup>b</sup>Deposits are granular unless otherwise specified.

ANCA, anti-neutrophil cytoplasmic antibodies; C3, complement factor 3; C4, complement factor 4; Ig, immunoglobulin; EM, electron microscopy; FN, fibrinoid necrosis; GBM, glomerular basement membrane; GN, glomerulonephritis; GS, globally sclerotic glomeruli; IFTA, interstitial fibrosis and tubular atrophy; MN, membranous nephropathy; PLA2R, M-type phospholipase A2 receptor; NA, not available; TBM, tubular basement membrane; TMA, thrombotic microangiopathy; TRIs, tubuloreticular inclusions.
presented with severe kidney dysfunction (eGFR ≤30 ml/min per 1.73 m²), 4 of whom required dialysis (2 with anti-GBM and 2 with MPO). Twelve patients received immunosuppression, 2 did not (1 had end-stage renal disease [ESRD]), and the other had a single fibrous crescent on biopsy); treatment data were not available for 1 patient. The most common drugs used were corticosteroids (n = 11) and cyclophosphamide (n = 10), followed by mycophenolate mofetil (MMF) (n = 4), azathioprine (n = 1), and rituximab (n = 1). Plasmapheresis was performed in 3 patients: 2 with anti-GBM and 1 with myeloperoxidase (MPO) antibodies and hemoptysis. Follow-up data were available for 13 patients, with a median follow-up of 38 months (4–98 months). Of these 13 patients, 5 reached ESRD (3 MPO, 2 anti-GBM), of whom 3 received a kidney transplant. Of the patients who reached ESRD, 2 had >50% crescents on biopsy, and 1 patient had >90% interstitial fibrosis and tubular atrophy (IFTA); the other 2 patients had up to 25% crescents and 25% to 35% IFTA (Table 2). Five patients developed chronic kidney disease, 2 died (both had solid organ malignancies), and only 3 (20%) had eGFR >60 ml/min 1.73 m² (all of these patients had only focal crescents and mild IFTA on biopsy). Conversely, renal survival in MN without crescents is estimated to be between 70% and 90%.6

Overall, our series findings are similar to those recently reported by Nikolopoulou et al., with approximately 40% of patients reaching ESRD. We had a greater number of anti-PLA2R-ppositive cases (26% vs. 13%), whereas they had a greater number of anti-GBM−positive patients (33% vs. 13%). Interestingly, however, outcomes were similar, which may be due to the fact that the prognosis of anti-GBM disease tends to be better in cases with associated MN,7 with close to 40% of patients recovering renal function in contrast to only 15% in pure anti-GBM disease.51 Potential explanations for that could be overall lower levels of anti-GBM antibodies in patients with concomitant MN as well as a narrower antigen reactivity spectrum of the anti-GBM antibodies present.7

In contrast to MN without crescents, in which case >90% of patients have normal renal function at presentation, and hematuria is generally microscopic and low-grade,52 most of our patients had significant hematuria, and approximately 75% presented with severe kidney dysfunction. In addition, although approximately 80% of cases of MN without crescents are considered primary, in our series only 26% of cases were PLA2R positive, and 40% were IgG4 dominant/co-dominant. Therefore, it appears that crescents occur more often in cases of secondary MN.

In conclusion, MN with crescents is a rare and heterogeneous entity that can be associated with ANCA, anti-GBM, PLA2R, and potentially other auto-antibodies. It presents more often with significant hematuria and renal dysfunction than MN without crescents and progresses more often to ESRD. Whether these cases represent a coincidental occurrence of 2 separate disease entities or whether they are pathogenically related remains to be determined,8 although the latter is conceivable. For example, subepithelial deposits may facilitate GBM damage, leading to anti-GBM antibody production. Conversely, GBM damage caused by anti-GBM (or other) antibodies could expose epitopes that lead to immune-complex deposition along the subepithelial aspect of the GBM.

DISCLOSURE
All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL
Supplementary File (Word)
Supplementary References.

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