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Membranous Nephropathy With Crescents

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Received 14 December 2019; revised 14 January 2020; accepted 20 January 2020; published online 30 January 2020

Kidney Int Rep (2020) **5,** 537–541; https://doi.org/10.1016/j.ekir.2020.01.010

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

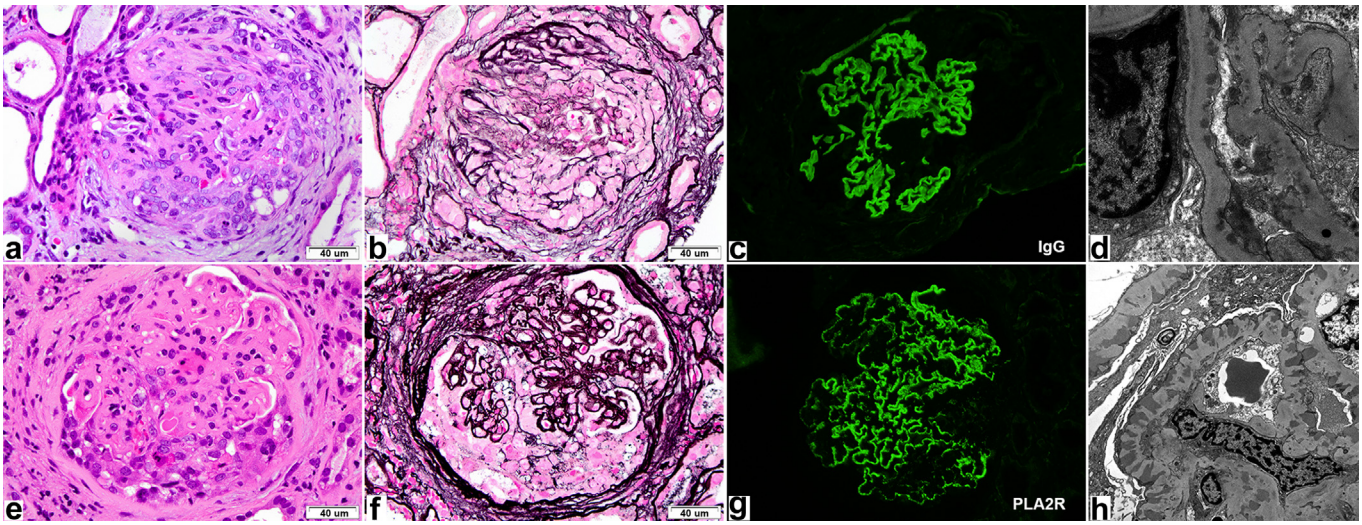

Figure 1. Top row (a–d): a case of anti–glomerular basement membrane (GBM) disease (case 12) with segmental membranous nephropathy (MN). (a) Glomerulus with a cellular crescent (hematoxylin and eosin [H&E] stain, original magnification ×400). (b) Silver stain shows a compressed glomerular tuft with no obvious spikes or lucencies along the GBM (original magnification ×4000). (c) Linear IgG staining (immunofluorescence, original magnification ×400). (d) Electron microscopic image showing segmental subepithelial deposits. Bottom row (e−h): a case of PLA2R-positive MN with concomitant p-ANCA (case 8). (e) Glomerulus with a cellular crescent (H&E stain, original magnification ×400). (f) Silver stain highlights capillary wall irregularities (fine lucencies and spikes) in the same glomerulus that contains a cellular crescent (original magnification ×400). (g) An anti-PLA2R antibody shows diffuse granular positivity along the GBM (immunofluorescence, original magnification ×400). (h) Electron microscopy confirms diffuse subepithelial deposits.

Table 1. Clinical characteristics

Case	Sex	Age (yr)	Ethnicity	Baseline Cr (mg/dl)	Cr at biopsy (mg/dl)	GFR at diagnosis (ml/min per 1.73 m^2)	Hematuria	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 m^2)	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 complicated by aspergillus pneumonia	Yes	Yes	NA	NA	NA
2	F	21	White	NA	15	3	Anuric	Anuric	ESRD	NA	NA	DAH, acute respiratory failure	NA	Anti-GBM	NA	PLEX, prednisone, and cyclophosphamide	Yes	No	ESRD	ESRD	47
3	M	65	White	0.9	2.2	30	>100 RBCs/HPF	2.89g/24h	ESRD	3.7	No	Hemoptysis	Raynaud syndrome	pANCA, MPO	ANA 1:80	prednisone, MMF switched to cyclophosphamide, PLEX, then azathioprine and prednisone	Yes	Yes	ESRD (5.38) after transplant nephrectomy	ESRD	98
4	F	64	AA	2	2.5	24	Moderate, 20–29 RBCs/HPF	1.6 g/24h	1.1 g UPC	2.2	Yes	Hemoptysis, DAH	Diabetes, hep C cirrhosis, HCC	pANCA, MPO, PR3	ANA 1:320, +anticardiolipin IgM, c3 77, c4 14	Prednisone and cyclophosphamide then MMF	No	None	4.33 Deceased	12	13
5	F	62	Asian	NA	1.09	51	NA	16.9g/24h	NA	0.6	Yes	NA	Liver dysfunction	NA	NA	None	NA	NA	1.14	49	79
6	F	61	AA	0.8	9	5	Few RBCs	8 g UPC	1.6 g/ 24 h	1.4	Yes	Pulmonary nodule	HTN, CKD, heavy smoker	NA	NA	Prednisone and cyclophosphamide	No	No	1.32	49	10
7	F	66	AA	1.3	2.9	20	NA	3.5 g UPC	NA	NA	NA	NA	Bladder cancer, MGUS	pANCA	NA	NA	NA	NA	NA	NA	NA
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	Minute IgG K	Prednisone and cyclophosphamide	No	No	1.99 Deceased	33	14
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
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
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 MRSA skin culture	MPO	Positive ANA and anti-SSB	Prednisone, MMF	NA	NA	0.8	>60	41 mo
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	None	PLEX, steroids, cyclophosphamide	Yes	Yes	2.01	39	38 mo

(Continued on next page)

Table 1. (Continued) Clinical characteristics

Case	Sex	Age (yr)	Ethnicity	Baseline Cr (mg/dl)	Cr at biopsy (mg/dl)	GFR at diagnosis (ml/min per 1.73 m^2)	Hematuria	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 m^2)	Follow-up duration (mo)
13	M	34	AA	1.03	1.18	93	45 RBCs/HPF	1.8 g UPC	1.2 g UPC	3.8	NA	NA	HTN, obesity	pANCA, MPO	ANA 1:40	Prednisone, rituximab	No	No	0.98	113	28 mo
14	M	41	White	1.8	10.9	5	Large	9.5 g UPC	ESRD	2.5	None	NA	Prior infection-related GN, i.v. drug use (including cocaine), hep C, endocarditis, seizure	pANCA, MPO	Positive anticardiolipin and anti-SSB	None	Yes	No	ESRD (10.2)	ESRD	4 mo
15	F	20	AA	0.83	3	24	3–5 RBCs/HPF	24.8 g/24 h	3.4 g UPC	1.4	Yes	SOB	Schizophrenia, bipolar disorder, Bell palsy, obesity	Anti-PLA2R antibody	Low C4 (17), normal C3	Prednisone, cyclophosphamide	No	No	1.51	52	17 mo

AA, African American; ANA, anti–nuclear antibodies; ANCA, anti–neutrophil cytoplasmic antibodies; Cr, creatinine; C3, complement factor 3; C4, complement factor 4; CKD, chronic kidney disease; DAH, diffuse alveolar hemorrhage; DM, diabetes mellitus; ESRD, end-stage renal disease; F, female; GBM, glomerular basement membrane; GFR, glomerular filtration rate; GN, glomerulonephritis; HCC, hepatocellular carcinoma; hep C, hepatitis C; HPF, high-power field; HTN, hypertension; labs, laboratory investigations; M, male; MGUS, monoclonal gammopathy of undetermined significance; MMF, mycophenolate mofetil; MN, membranous nephropathy; MPO, myeloperoxidase; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not available; NSAIDs, nonsteroidal anti-inflammatory drugs; PLA2R, M-type phospholipase A2 receptor; PLEX, plasma exchange; PR3, proteinase 3; RBCs, red blood cells; SOB, shortness of breath; SSB, anti-Sjögren's syndrome type B; UPC, urine protein-to-creatinine ratio.

toxins, and is most commonly IgG1 dominant.[1,2] The occurrence of crescents in MN is extremely rare, with a prevalence estimated between 0.39%[3] and 0.26%.[4] Crescents can be seen in both primary and secondary MN[3–5] 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 ANCAs or anti-GBM antibodies,[3] or in association with ANCAs.[5] In light of the recently published series of MN with crescents from the United Kingdom,[4] 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 ANCAs (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 gammopathy of undetermined significance, and 5 patients had positive autoantibodies (4 anti–nuclear antibodies, 2 anticardiolipin, and 2 anti-SSB). 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 m^2. Eleven patients

Table 2. Pathological characteristics

Case	Final diagnosis	Total glomeruli	Crescents/ FN	GS	% Active lesions[a]	IFTA%	Immunofluorescence[b]	IgG1	IgG2	IgG3	IgG4	PLA2R	EM stage	Mesangial deposits	TRIs	Extraglomerular deposits
1	ANCA-associated crescentic and necrotizing GN; membranous GN	16	4	8	25	25	IgG, 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 and lambda; linear TBM IgG (focal)	2.5 Linear	1.5 Linear	0	3 Linear	Negative	1	0	0	0
3	Focal crescentic GN with MN	30	1	10	3	35	IgG, IgA, C3, kappa, lambda GBM and mesangial; IgG, kappa, lambda TBM	1.5	1	0	0.5	Negative	1 to 2	1	0	TBM deposits by IF
4	MN with fibrous crescents; underlying diabetic glomerulosclerosis	24	4 (Fibrous)	10	0	60-70	IgG, IgM, C1q, C3, kappa and lambda GBM, IgG TBM (focal)	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, C1q, C3, Kappa and 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, 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	1 to 4	0	0	0
9	ANCA-associated necrotizing and crescentic GN with MN and TBM deposits	5	1	0	20	35	IgG, kappa, lambda GBM; 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 segmental 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	2 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 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

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.

[a]Active lesions include cellular or fibrous–cellular crescents and areas of glomerular segmental fibrinoid necrosis.

[b]Deposits are granular unless otherwise specified.

presented with severe kidney dysfunction (eGFR ≤30 ml/min per 1.73 m^2), 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 m^2 (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.*,[4] with approximately 40% of patients reaching ESRD. We had a greater number of anti-PLA2R−positive 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[8] in contrast to only 15% in pure anti-GBM disease.[S1] 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[1] and hematuria is generally microscopic and low-grade,[S2] 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 autoantibodies. 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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