CLINICAL RESEARCH

Membranous Glomerulonephritis With Crescents

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Introduction: Membranous glomerulonephritis (MGN) is rarely associated with necrotizing and crescentic glomerulonephritis (NCGN).

Methods: We report the clinical and pathologic findings in 15 patients with MGN and NCGN associated with anti-neutrophil cytoplasm antibodies (ANCAs), anti–glomerular basement membrane (GBM), or anti–phospholipase A2 receptor (PLA2R) antibodies.

Results: The cohort consisted of 15 patients: 7 males and 8 females with a median age of 63 years (range: 18–79). In 12 of 15 patients, MGN and NCGN were diagnosed at the time of the biopsy, and in 3 cases, MGN predated the NCGN. ANCA was positive in 7 cases (6 MPO myeloperoxidase (MPO)-ANCA and 1 PR3–ANCA), anti-GBM antibodies were detected in 5 cases, and anti-PLA2R antibodies were found in 2 cases. One case was negative for all antibodies. Microscopic hematuria was present in all but one patient who was anuric, and median urinary protein-to-creatinine ratio was 819.5 mg/mmol (range: 88–5600). Pathologic evaluation revealed MGN and NCGN with crescents involving 28% of glomeruli (median; range: 5%–100%). Follow-up was available for all 15 patients; all were treated with steroids; 10 with cyclophosphamide, and 6 also received rituximab. At a median follow-up of 72 months, 9 had stabilization or improvement of renal function, 6 had progressed to end-stage renal disease, and 4 died during the follow-up period.

Conclusion: MGN with crescents associated with ANCAs or anti-GBM antibodies is a rare dual glomerulopathy. Patients present with heavy proteinuria, microscopic hematuria, and acute kidney injury and should be treated for a rapidly progressive glomerulonephritis. Prognosis is variable, and 40% of patients progress to end-stage renal disease.

MGN is a common cause of nephrotic syndrome in adults. It is now recognized as an antibody-mediated glomerular disease, with antibodies against PLA2R found in over 70% of cases of primary MGN.[1] It is characterized by the presence of subepithelial immune complexes, basement membrane damage, and proteinuria. MGN is described as primary if there is no underlying cause, or as secondary if it presents in association with systemic lupus erythematosus (SLE), neoplasms, drugs, or infections.[2] The coexistence of MGN with NCGN is rare, and in the absence of SLE it is usually associated with circulating ANCAs or anti-GBM antibodies. Unlike MGN that typically presents with proteinuria and edema, patients with NCGN usually have a rapidly progressive form of glomerulonephritis that can be life-threatening. MGN with NCGN has also been described in the absence of circulating ANCAs or anti-GBM antibodies[3] and leads to rapidly progressive glomerulonephritis. Although a few case series and reports[3–9] describe the pathologic features and clinical outcomes of MGN with crescentic glomerulonephritis in the context of anti-GBM antibodies or ANCAs, little is known about the role of anti-PLA2R Ab in this setting.[10] Here, we present the clinical, pathologic, and outcome data of 15 patients with this rare form of combined MGN and NCGN, including patients with or without circulating ANCAs, anti-GBM antibodies, or anti-PLA2R antibodies.

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METHODS

A total of 5679 native biopsies were performed in our center from January 2004 to January 2018. Fifteen patients with renal biopsy findings of MGN with cellular or fibrocellular crescents were identified including 2 cases predating 2004. Patients with SLE were excluded because of the potential presence of crescentic and membranous changes in lupus nephritis.

All renal biopsies were processed according to standard techniques for light microscopy (LM), immunoperoxidase (IP), immunofluorescence (IF), and electron microscopy (EM). For each patient, glass slides were prepared and stained with hematoxylin and eosin, periodic acid-Schiff (PAS), trichrome, and Jones methenamine silver (JMS). IP was performed on 4-μm paraffin embedded sections for IgG and C3. IF was performed on 4-μm cryostat sections using polyclonal fluorescein isothiocyanate conjugated antibodies to IgG, IgM, IgA, C3, C1q, kappa, and lambda. IF was scored by the pathologist on a scale of 0 to 3+. Electron microscopy was performed as per clinical routine.

ANCAs were detected by indirect immunofluorescence (Inova Diagnostics, San Diego, CA) or antigen-specific assay (enzyme-linked immunosorbent assay or luminex-based assay) (2004–2013: FIDIS Multiplex, Theradiag, Marne-la-Vallee, France; 2013–2018: Immunocap250 CMIA, ThermoFisher Scientific, Waltham, MA). Anti-GBM antibody testing was performed by antigen-specific assay (2004–2013: FIDIS Multiplex, Theradiag, Marne-la-Vallee, France; 2013–2018: Immunocap250 CMIA, ThermoFisher Scientific, Waltham, MA) and confirmed by immunoblot.

PLA2R was tested by immunofluorescence on proteinase-digested paraffin embedded renal biopsies using an anti-PLA2R1 primary antibody (Sigma-Aldrich, St. Louis, MO) and an FITC conjugated IgG (Life Technologies, Carlsbad, CA) secondary. Biopsies were stained for thrombospondin type 1 domain containing 7A (THSD7A) by immunohistochemistry after standard heat antigen retrieval method (pH 9; 95 °C) with anti-THSD7A antibody (Atlas, Bromma, Sweden), and staining was visualized using a DAKO EnVision kit (DAKO, Glostrup, Denmark) as per manufacturer instructions.

Patients' medical records were reviewed for demographics, clinical findings of systemic vasculitis, treatment, and clinical outcomes. Laboratory results were reviewed for ANCAs, anti-GBM and anti-PLA2R antibodies, and parameters of renal function.

Patients with a diagnosis of SLE based on clinical features, serologic positivity for SLE such as positive anti-nuclear antibody (ANA), double-stranded DNA (ds-DNA), hypocomplementemia, and histopathologic findings of lupus nephritis on kidney biopsy were excluded.

Statistical analysis was performed using GraphPad PRISM (San Diego, CA). Continuous variables are reported as median with range. Analysis was performed using nonparametric tests including the Fisher exact test.

RESULTS

Clinical and Laboratory Features

The cohort consisted of 15 patients—7 males and 8 females with a median age of 63 years (range: 18–79 years). Seven patients were white, 6 Asian, and 2 black African. In 3 of 15 patients, biopsy-proven MGN was diagnosed prior to the development of NCGN: case number 1 had a diagnosis of MGN 8 months prior to presenting with crescentic MGN and anti-GBM disease; case number 13 had been diagnosed with anti-PLA2R-positive MGN 9 years prior to presentation with NCGN and had received treatment with tacrolimus; case number 14 had a diagnosis of anti-PLA2R-positive MGN in the context of hepatitis B (HBV) viremia 16 months prior to the development of NCGN. Despite treatment of HBV, anti-PLA2R antibody titres remained positive and the patient was started on treatment with tacrolimus. Both these patients with anti-PLA2R-positive NCGN were black African, and no ANCA or anti-GBM antibody was detected in the serum at the time of the development of NCGN.

In the remaining 12 patients, MGN and NCGN were diagnosed at the time of the biopsy. One patient (case 7) had a 2-year history of MPO–ANCA vasculitis; re-biopsy during a relapse showed new spikes on the GBM on silver staining and new subepithelial electron-dense deposits consistent with a diagnosis of MGN.

ANCA testing was positive in 7 of 15 cases; specifically, this was further identified as MPO-ANCA in 6 cases and as PR3 –ANCA in one. Anti-GBM antibodies were detected in 5 of 15 cases. One case was negative for anti-PLA2R antibodies, ANCAs, and anti-GBM antibodies.

None of the patients had a history of SLE. ANA was negative in all but one patient (case 6) who had a positive ANA at a dilution of 1:160 and subsequently had a negative ds-DNA. Rheumatoid factor was positive in one case (case 5) and negative in the remaining 14 patients. Complement C3 and C4 levels were normal in all but one case. In this case (case 12), C4 was transiently low at presentation at 0.07g/l, but this normalized 6 days later; notably, the rheumatoid factor and cryoglobulins were negative in this case. Anti-C1q antibodies, cryoglobulins, and 24-hour urine collection for proteinuria were not routinely tested in this cohort.

Hepatitis B and C and HIV were negative in all but one patient (case 14) who received treatment for HBV with entecavir and at the time of NCGN had undetectable viral load. This patient had normal complement level and

negative rheumatoid factor; cryoglobulins were not available.

None of the patients had diabetes or diabetic nephropathy, and none were taking thyrostatics or levamisole-adulterated cocaine to our knowledge.

At presentation with NCGN, microscopic hematuria was present in all but one patient who was anuric. Proteinuria was present in 14 of 15 patients with a median urinary protein-to-creatinine ratio of 819.5 mg/mmol (range: 88–5600), and one was anuric at presentation. A 24-hour proteinuria was recorded in 3 cases: one with anti-GBM and MN (case 4: 11.2 g), and 2 with MPO (case 7: 4.3 g; case 9: 2.1 g).

Median serum albumin was 24.5 g/l (range: 16–40). Four patients required dialysis at presentation, and only one recovered renal function after treatment but was re-established on dialysis 2 years later; 3 of these patients died during the follow-up period and the other received a kidney transplant.

The clinical presentation, treatment, and outcomes of patients with MGN and NCGN are summarized in Table 1.

Pathologic Features

Light microscopy sampling showed a median of 18 glomeruli per biopsy (range: 9–45). A total of 25% of all glomeruli were globally sclerosed, with median 7 (range: 1–12) per biopsy. All biopsies showed features of MGN and NCGN (Table 2). Crescents were seen in all biopsies (median 5 per biopsy; range: 1–22), and 30% of the total glomeruli examined showed crescents that were cellular, fibrous, or mixed fibrocellular. Silver staining showed "spikes" and "holes" in 7 cases. Interstitial fibrosis and tubular atrophy were noted in all cases, with a median of 20% (range: 10%–75%).

Immunostaining (immunofluorescence or immunoperoxidase) revealed granular or linear, segmental to global glomerular capillary wall IgG positivity in all patients, with a circulating anti-GBM or anti-PLA2R antibody, suggesting an immune complex–mediated GN. Linear IgG positivity was observed in 3 of 5 patients with anti-GBM disease, and in the remaining 2 of 5, IgG staining was more granular. The ANCA-associated rapidly progressive GN cases demonstrated a pauci-immune picture with faint capillary wall IgG positivity observed in 3 of 7 cases (Table 2). C3 was positive in 13 cases with tissue available for staining.

Electron microscopy was performed in all patients, and this showed features of MGN with subepithelial electron-dense deposits. A total of 53% of cases showed stage II MN, and 46% showed stage III alone or in combination with stages I or IV. Few or rare mesangial deposits were noticed in 3 cases with ANCA-associated GN and in the one case where no circulating antibody was detected (Table 2).

Immunofluorescence for PLA2R was performed in 12 cases with available tissue and was positive in 2 cases with pre-existing anti-PLA2R–positive MGN that demonstrated crescentic transformation. THSD7A immunoperoxidase staining was negative in 11 cases with available tissue that were also PLA2R negative. The renal biopsy findings are detailed in Table 2, and a selection of cases is illustrated in Figure 1.

Clinical Follow-up and Treatment

Follow-up data were available for all 15 patients for a median of 72 months (range: 10–216 months; Table 1). Patients were treated with steroids combined with either cyclophosphamide and/or rituximab with or without plasma exchange or mycophenolate mofetil. All 15 patients received prednisolone, 10 with cyclophosphamide and plasma exchange, and 6 in combination with rituximab. Three patients were treated with mycophenolate mofetil and steroids without cyclophosphamide or rituximab, owing to frailty or patient choice. Four patients required dialysis at presentation; 1 had a circulating MPO-ANCA and 3 had a detectable anti-GBM antibody. One of the MGN and anti-GBM patients (case 5) recovered renal function after the initial episode and remained off dialysis for 2 years before restarting dialysis. Two patients with anti-GBM and MGN who required dialysis at presentation were transplanted (cases 3 and 5) with good graft function at 3 and 17 years with no recurrence of MGN in the graft.

Anti-PLA2R antibodies were detected in 2 patients with preexisting MGN prior to transformation to NCGN; both were treated with rituximab and cyclophosphamide with or without high-dose steroids, and both had a significant improvement in renal function. During the follow-up period, 4 patients died—3 with MPO-ANCAs and 1 with anti-GBM disease.

DISCUSSION

Membranous glomerulonephritis with crescents is a rare clinical entity that can be found in association with circulating ANCAs, anti-GBM, or anti-PLA2R antibodies. Historically, the first case of MGN with anti-GBM disease was described by Klassen et al.[11] in 1974, and since then, more than 40 cases have been reported.[8,12,13] Anti-GBM disease can develop on preexisting MGN, suggesting a transformation into crescentic glomerulonephritis. In our cohort, 5 cases were associated with anti-GBM glomerulonephritis; only one had confirmed MGN on biopsy 8 months prior to presenting with anti-GBM GN and fulminant renal failure. The cause of this transformation is not clear. A number of factors such as solvent exposure and cigarette smoking have been associated with the development of anti-GBM disease,[14] although this was not the

Table 1. Demographics, clinical and laboratory data at presentation, and follow-up

Case	Age, yr	Race	Sex	Ab (titer u/ml)	Prior MGN	Hematuria	Extrarenal manifestations	Urine PCR mg/mmol	At presentation			Treatment	At follow-up			
									Alb, g/l	Creatinine, μmol/l	CRP, mg/l		F/U, mo	eGFR, ml/min per 1.73 m²	Creatinine, μmol/l	UPCR, mg/mmol
1	79	Caucasian	M	GBM (64)	Yes	Yes	Fatigue	5600	15	ESRD (1084)	321	Pred	93	ESRD—deceased	ESRD	ESRD
2	62	Caucasian	F	GBM (51)	No	Yes	Fatigue, breathlessness	2064	19	277	6.2	CYC, Pred	37	58	85	0
3	59	Asian	F	GBM (13)	No	Yes	Malaise	2107	26	ESRD (810)	16	Pred	84	45	106 (tx)	tx
4	18	Caucasian	M	GBM (61)	No	Yes	Fatigue	260	40	102	2	CYC, Pred	134	>90	72	114
5	58	Caucasian	F	GBM (38)	No	Anuric	Fatigue	Anuric	23	ESRD (1125)	121	CYC, Pred, PEX	216	32 (tx)	139 (tx)	tx
6	70	Asian	M	MPO (>134)	No	Yes	Hemoptysis	379	16	ESRD (877)	200	CYC, Pred	10	ESRD—deceased	ESRD	ESRD
7	73	Caucasia	M	MPO (86)	No	Yes	Malaise	4280		349	8	CYC, Pred, PEX	89	ESRD—deceased	ESRD	ESRD
8	66	Asian	M	MPO (>134)	No	Yes	Fatigue, weight loss	88	31	560	61	RTX, CYC, Pred	39	24	224	10
9	34	Caucasian	F	MPO (19)	No	Yes	Fatigue	2114	36	86	40	MMF, Pred	72	88	80	98
10	74	Asian	F	MPO (78)	No	Yes	Fatigue, pulmonary hypertension, protein C deficiency	1053	22	217	38	RTX, CYC, Pred	10	51—deceased	94	101
11	73	Asian	F	MPO (74)	No	Yes	Arthralgia	559	31	178	1.3	Pred, MMF	13	27	165	50
12	64	Caucasian	M	PR3 (544)	No	Yes	Pulmonary hemorrhage	113	35	263	411	CYC, Pred, RTX	81	80	83	62.5
13	63	Black	F	PLA2R (61)	Yes	Yes	No	2086	20	483	2	RTX, CYC, Pred	10	44	108	40
14	44	Black	F	PLA2R (85)	Yes	No	Fatigue	586	23	171	1.3	RTX, CYC	18	68	76	0
15	63	Asian	M	Neg	No	Yes	Arthralgia	311	38	165	1.7	RTX, MMF, Pred	84	33	192	0

Ab, antibody; ANCA, anti-neutrophil cytoplasm antibodies; creat, creatinine; CRP, C-reactive protein; CyC, cyclophosphamide; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; F, female; F/U, follow-up; GBM, glomerular basement membrane; M, male; MGN, membranous glomerulonephritis; MMF, mycophenolate mofetil; MPO, myeloperoxidase–ANCA; PCR, protein-creatinine ratio; PEX, plasma exhange; PLA2R, phospholipase A2 receptor; PR3, anti-proteinase 3 ANCA; pred, prednisolone; RTX, rituximab; tx, transplant; UPCR, urine protein-to-creatinine ratio.

Table 2. Biopsy findings

Case no.	Antibody (serum)	Total no glomeruli	Globally sclerotic/ obsolete	Crescents	Light microscopy	Silver stain	IFTA	IF/IP	Mesangial IC	EDD stage	PLA2R staining
1	GBM	12	0	12	MGN, crescents	Spikes	None	Granular capillary wall IgG, C1q, C3, C4 Linear capillary wall IgA and IgM	Not seen	III-IV	No tissue
2	GBM	22	3	7	MGN, focal segmental necrotizing GN with crescents	NA	10%	Granular capillary wall IgG IF no glomeruli	Not seen	II-III	Neg
3	GBM	15	9	3	Membranoproliferative GN, MGN	NA	30%	Granular capillary wall IgM, C3, C1q, linear capillary wall IgG, scanty granular mesangial IgM, C3	Not seen	I-II	Neg
4	GBM	30	3	11	Focal segmental proliferative GN, MGN	NA	15%	Linear capillary wall IgG, IgA, C3	Not seen	II	Neg
5	GBM	22	0	22	Crescentic GN, arteritis, MGN	Spikes		Granular capillary wall C3, linear capillary wall IgG, IgA, IgM, C1q, C4,	Not seen	II	No tissue
6	MPO	12	8	3	MGN, focal necrotizing GN with crescents	NA	50%	No glomeruli	Few peripheral	III-IV	Neg
7	MPO	45	9	3	MGN, focal segmental GN with crescents	Spikes	50%	Capillary wall granular IgG, IgM, C3 Segmental scars IgM, C1q, C3	Few	II-III	No tissue
8	MPO	18	7	5	Focal segmental necrotizing GN, MGN	NA	75%	Granular capillary wall C3 Mesangial IgM κ, λ positive	Not seen	I-II	Neg
9	MPO	12	4	1	Focal segmental glomerulosclerosis, MGN	NA	20%	Capillary wall segmental IgM, C3 Segmental mesangial IgG, IgM, C3	Not seen	I-II	Neg
10	MPO	21	8	6	MGN, focal segmental proliferative and necrotizing GN	Holes	20%	Faint granular capillary wall IgG, IgM, C3	Not seen	III	Neg
11	MPO	18	8	1	MGN, atrophy, small fibrocellular crescent	Segmental irregularities	50%	Granular capillary wall IgG+, C3+, κ, λ positive	Rare	II-III	Neg
12	PR3	9	1	3	Focal necrotizing GN with cellular crescents, MGN	Holes	10%	IF no glomeruli Mesangial, C3, C1q κ, λ positive	Not seen	II	Neg
13	PLA2R	11	1	7	MGN, crescentic GN, fibrous and cellular crescents	Spikes	15%	Granular capillary wall IgG, C3 κ, λ positive	Not seen	II-III	Pos
14	PLA2R	27	3	6	MGN, thickened capillary walls, cellular crescents	Spikes	20%	Granular capillary wall IgG+, IgM, κ, λ positive C3 negative	Not seen	I-IV	Pos
15	Neg	25	12	2	MGN with mesangial IgA and crescents	Spikes, holes	25%	Granular capillary wall IgG, mesangial IgA and IgM, κ, λ positive	Present	I-IV	Neg

EDD, electron dense deposits; GBM, glomerular basement membrane; GN, glomerulonephritis; IC, immune complexes; IF, immunofluorescence; IFTA, interstitial fibrosis tubular atrophy; IP, immunoperoxidase; MGN, membranous glomerulonephritis; NA, not available; neg, negative; pos, positive; PLA2R, phospholipase A2 receptor.

case in our patients. Approximately half of concomitant MGN and anti-GBM glomerulonephritis are diagnosed together at presentation,[12,15] making it difficult to determine whether MGN pre-dated the development of anti-GBM GN. It is known that the presence of HLA DRB1 and HLA DQ1 are strongly associated with susceptibility to anti-GBM disease,[16,17] and MGN,[18] respectively, and it is possible that the coexistence of these alleles leads to an increased risk for developing dual glomerulopathy.

In our series of MGN and anti-GBM glomerulonephritis, one patient was anuric at presentation, and the rest had microscopic hematuria and significant proteinuria as evidenced by a median urinary protein-to-creatinine ratio of 2085 mg/mmol (range: 260–5600). Three of these patients required dialysis at presentation, and one recovered renal function following treatment

with plasmapheresis, cyclophosphamide, and steroids. Treatment of MGN with anti-GBM glomerulonephritis should probably be focused on the anti-GBM element of the condition. Rituximab is a successful treatment for MGN[19–22] and has been suggested as an alternative treatment for refractory MGN and anti-GBM disease.[23] Interestingly, none of the patients with combined MGN and anti-GBM disease had alveolar hemorrhage, suggesting a renal limited variant of the disease. Primary MGN is associated with endogenous podocyte antigens such as the PLA2 receptor,[24] or less commonly with the THSD7A antigen.[25] In anti-GBM disease, the antibodies are primarily targeting the noncollagenous domain 1 of the a3 chain of type IV collagen. Jia *et al.*[4] showed that in cases of combined MGN and anti-GBM disease, these antibodies do not react with all 5 of the a chains of type IV collagen, and that serum from patients with MGN has

no reactivity against any of the 5 a chains, suggesting a different pattern of disease. The renal biopsies in our anti-GBM and anti-PLA2R antibody positive cases demonstrated a combination of linear and granular IgG staining, suggesting an immune complex–mediated pathology. However, capillary wall IgG positivity was either faint or absent in the ANCA cases, pointing to a pauci-immune process. C3 was positive in 4 cases in both granular and linear deposition, suggesting subepithelial deposits as well as continuous immunoglobulin and C3 deposition along the capillary walls.

One of the first cases of a crescentic MGN associated with ANCAs was described in 1993 by Gaber *et al.*[9] This was a C-ANCA positive case with multiple extrarenal manifestations (pulmonary capillaritis, otitis, and recurrent sinusitis) treated with prednisolone and cyclophosphamide.[9] In our series, 7 patients had a detectable circulating ANCAs that was further identified as MPO-ANCA in all but one case that had a circulating PR3-ANCA. PLA2R antibodies were not found in this subgroup, and this coexistence appears to be extremely rare, with just 3 cases described so far.[10,26] The presence of ANCAs was associated with significant renal disease, with 2 patients requiring

dialysis at presentation. The patient with PR3-ANCA had significant systemic disease and presented with alveolar haemorrhage. Nephrotic range proteinuria (>300 mg/mmol) was present in 5 of 7 of these patients, and all had microscopic hematuria. All these patients with crescentic MGN with ANCAs received induction therapy with prednisolone; 5 also received cyclophosphamide, in 3 cases in combination with rituximab. Plasmapheresis combined with prednisolone and cyclophosphamide was performed on one patient, and one received prednisolone with mycophenolate mofetil. Three of the patients in this subgroup died during the follow-up period, but the remaining 4 had a glomerular filtration rate of >24 ml/min per 1.73 m^2 at follow-up. In one case, the crescentic GN pre-dated the development of MGN; however, the dual glomerulopathy was diagnosed simultaneously on biopsy in all other cases at the time of presentation. In our series, all patients with MGN and ANCA-associated crescentic GN had extra renal manifestations, ranging from fatigue and malaise to arthralgia and hemoptysis, but none had ENT symptoms.

Two patients were PLA2R positive only and had a diagnosis of MGN 1 and 8 years prior to the crescentic
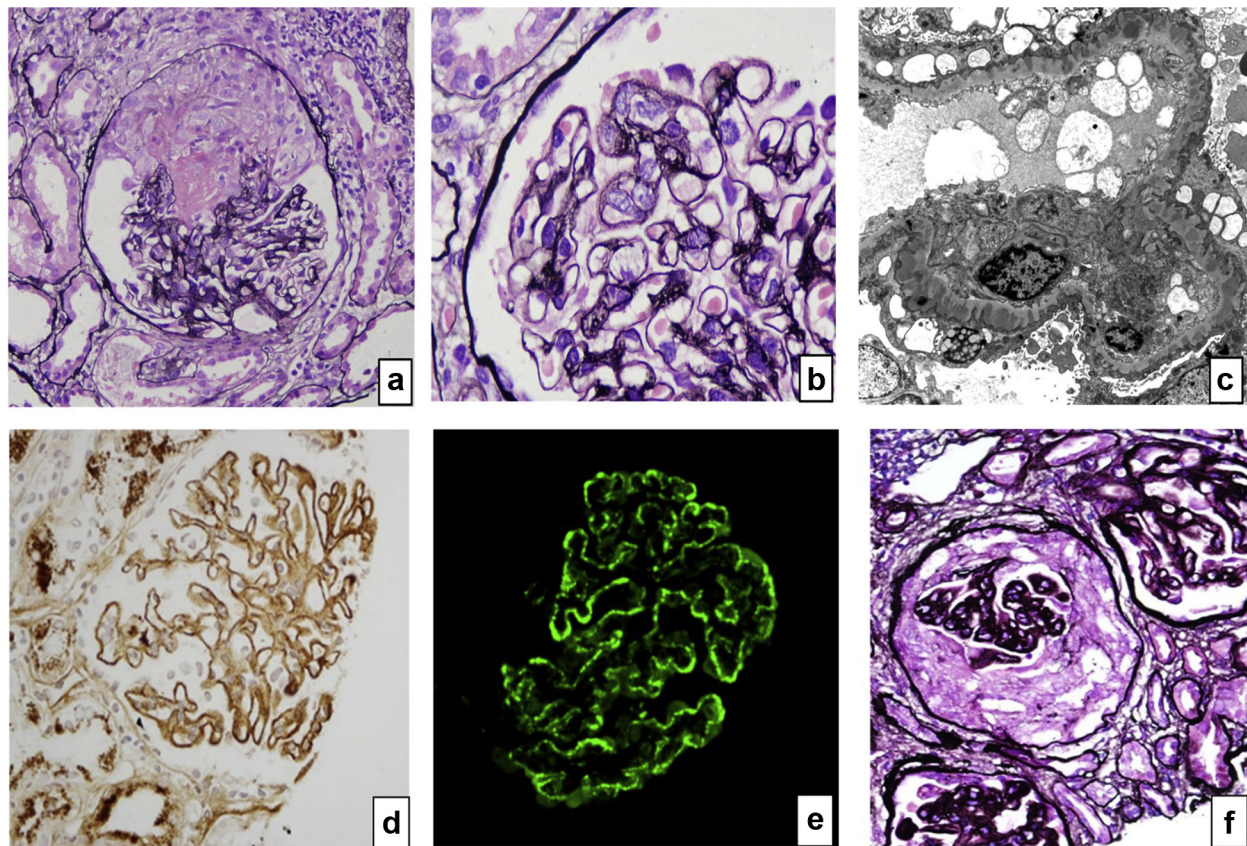

Figure 1. Microscopy findings of cases. Case 2: Glomerular tuft with a cellular crescent filling Bowman's space (a); glomerulus showing thickened capillary wall with spikes (b). Electron microscopy shows subepithelial electron dense deposits and extensive foot process effacement (c). Case 14: IgG staining revealed granular staining along the capillary walls (d). Immunofluorescence for PLA2R staining revealed strong granular staining along the capillary walls (e). Fibrocellular crescent engulfing the glomerulus is shown (f).

transformation. Both these patients were already on treatment for MGN with tacrolimus and underwent a repeat biopsy to investigate rising serum creatinine. Rodriguez *et al.*[3] describe a series of 19 cases with crescentic MGN without ANCAs or anti-GBM antibodies, 6 of which were PLA2R positive on biopsy; all had hematuria and proteinuria at presentation. Fourteen of these patients were treated with immunosuppressive therapy, and 4 progressed to end-stage renal disease. In our series, both patients with PLA2R-positive MGN and NCGN were treated with rituximab and cyclophosphamide, with a significant improvement in renal function and resolution of proteinuria. One of these patients had significantly less proteinuria at the time of the crescentic transformation and was also on treatment for hepatitis B with entecavir. The viral load at the time of crescentic GN was undetectable; however, it is possible that the previous immunologic response to the hepatitis B virus triggered the exposure and possibly the conformational change of podocyte antigens leading to antibody production and the development of PLA2R-positive MGN. PLA2R-positive MGN in hepatitis B–infected patients has been described and appears to affect approximately two thirds of patients with hepatitis B virus and MGN.[27] The one case in our series with MGN and NCGN on biopsy, with no detectable circulating antibody, presented with acute kidney injury, proteinuria, and arthralgia. Treatment with steroids, rituximab, and mycophenolate mofetil resulted in stabilization of renal function and resolution of proteinuria.

In summary, the cases in our series represent the distinct and rare entity of MGN with NCGN. The renal function at presentation in association with the presence of antibodies seems to be influencing the clinical outcome. MGN associated with anti-GBM and ANCA NCGN should be treated initially as for anti-GBM disease and ANCA-associated vasculitis, respectively. A repeat renal biopsy should be considered in patients with MGN and an acute deterioration in renal function, as this could suggest a superimposed crescentic pathology. Crescentic transformation in MGN in the presence of anti-PLA2R antibodies should also be treated as a rapidly progressive GN. In the patients that received a renal allograft, there was no recurrence of MGN or NCGN. Further studies of this rare glomerulopathy are needed to understand the mechanisms underlying the development of crescentic lesions in MGN.

DISCLOSURE

All the authors declared no competing interests.

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