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The Characteristics of Concurrent Anti-Glomerular Basement Membrane Nephritis and Membranous Nephropathy

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INTRODUCTION

Concurrent anti-glomerular basementmembrane (GBM) nephritis and membranous nephropathy (MN) is rare and previously addressed only in case reports or small series (≤12 patients).[1-3] The target antigen(s) in MN associated with anti-GBM nephritis are unknown. We report the clinicopathologic characteristics and outcome of 28 patients with this dual glomerulopathy, which were among 449 (6.2%) anti-GBM nephritis and 5183 (0.5%) nonlupus MN cases diagnosed at a large nephropathology laboratory over a 23-year period (Supplementary Methods). A pathologic diagnosis of anti-GBM nephritis was defined by the intense linear GBM staining for IgG by immunofluorescence, in the absence of (or much weaker) albumin staining, and concurrent MN was defined by the presence of segmental or global subepithelial deposits by electron microscopy.

RESULTS

The patients were 57% male and of a median age of 54 years (range 15–82) at diagnosis (Table 1). Most (96%) patients presented with acute kidney injury with a median serum creatinine at biopsy of 7.8 mg/dl (range 1.2–24.0), proteinuria (median 3.5 g/d, range 0.4–11) and hematuria. Four (22%) patients had preexisting chronic kidney disease; 3 (13%) patients had hemoptysis. Fourteen (54%) had new-onset or long-standing hypertension and 10 (35%) were current or former smokers. Coexistent medical conditions included diabetes ($n = 4$), Nonsteroidal anti-inflammatory drugs use ($n = 3$), malignancy ($n = 2$), liver transplant ($n = 1$), and lung sarcoidosis ($n = 1$).

Of 22 patients with information on therapy, 1 received symptomatic treatment alone and 21 received immunosuppressive therapy, most commonly (55%) cyclophosphamide and steroids. Twelve (55%) received plasmapheresis. Follow-up data were available for 26 patients. After a median follow-up of 17 months (range 0.3–248), 3 (11%) had complete remission, 7 (27%) had persistent kidney dysfunction, and 16 (62%) progressed to end-stage kidney disease (ESKD). Of the 15 patients who were on dialysis at presentation, only 1 (7%) recovered kidney function. The 3 patients who recovered kidney function were 2 with atypical anti-GBM nephritis (treated conservatively with losartan and hydrochlorothiazide in 1 and with prednisone and mycophenolate mofetil in 1) and 1 patient with classic anti-GBM nephritis treated with steroids, cyclophosphamide, and plasmapheresis. Median final serum creatinine in patients not reaching ESKD was 3.2 mg/dl (range 1.7–6.8). One patient with ESKD received a kidney transplant with a stable serum creatinine at 1.06 mg/dl 12 years after initial diagnosis.

Table 1. Clinical characteristics at diagnosis and outcome of patients with concurrent anti-GBM glomerulonephritis and membranous nephropathy

Characteristics	N = 28 patients
Male/female	16/12
Age, yrs	54 (15–82)
White race	24/25 (96%)
Hypertension	14/26 (54%)
Longstanding, new onset, unspecified	11, 2, 1
Pre-existing chronic kidney disease	4 (22%)
Presentation	
Acute kidney injury	27/28 (96%)
Nephrotic syndrome	1/28 (4%)
Pulmonary involvement (hemorrhage, hemoptysis)	3/24 (13%)
Dialysis requirement at diagnosis	15/25 (60%)
Serum creatinine, mg/dl	7.8 (1.2–24.0)
Hematuria: microscopic; macroscopic	25/25 (100%); 16/26 (62%)
Proteinuria, g/24h or g/g	3.5 (0.4–11.0)[a]
Nephrotic syndrome	5/19 (26%)
Positive anti-GBM antibody	18/25 (72%)
Positive ANA	2/17 (12%)[b]
Positive ANCA	4/23 (17%)[c]
Hypocomplementemia	2/23 (9%)[d]
Positive SPEP/SIF or UPEP/UIF	0/13 (0%)
Associated medical conditions	
Diabetes mellitus	4/27 (15%)
History of lupus, Sjogren syndrome, or rheumatoid arthritis	0/27 (0%)
Malignancy	2/27 (7%)[e]
Hepatitis B or C virus	0/23 (0%)
Drugs known to cause membranous nephropathy	3/27 (11%)[f]
Others	2 (11%)[g]
First line therapy	
Symptomatic measures alone	1/22 (5%)
Steroids alone	7/22 (32%)
Cyclophosphamide + steroids	12/22 (55%)
Mycophenolate + steroids	1/22 (5%)
Rituximab + cyclophosphamide + steroids	1/22 (5%)
Plasmapheresis	12/22 (55%)
Follow-up available	26/28 (93%)
Duration of follow-up, months	17 (0.3–248)
Kidney outcome	
Complete response	3/26 (11%)
Partial response	0/26 (0%)
Persistent kidney dysfunction	7/26 (27%)
ESKD	16/26 (62%)
Death	10/26 (38%)

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ESKD, end-stage kidney disease; GBM, glomerular basement membrane; h, hour; SPEP/SIF, serum protein electrophoresis/immunofixation; UPEP/UIF, urine protein electrophoresis/immunofixation; yrs, years.
[a]24-hour urine protein quantitation or urine protein-to-creatinine ratio available in 17 patients.
[b]ANA positive at a titer of 1:80 in 1 and 1:160 in 1; Complement levels normal in both patients and no clinical features of lupus.
[c]All p-ANCA and 1 also with positive c-ANCA. The 4 patients with + ANCA did not have clinical features of extra renal involvement by vasculitis (the 3 patients in the study with pulmonary involvement by anti-GBM disease all had negative ANCA).
[d]Low C3 in 1 with recent cellulitis treated with antibiotics and low C4 in 1.
[e]Uterine and breast cancer in 1 and hairy cell leukemia in remission in 1.
[f]Nonsteroidal anti-inflammatory drugs in all 3 patients.
[g]Liver transplant in 1 and lung sarcoidosis in 1.
Values are in n (%) or median (range) unless otherwise indicated.

Kidney biopsy (Table 2, Supplementary Figures S1 and S2) showed 26 (93%) classic anti-GBM nephritis with cellular or fibrocellular crescents involving a median of 77% (range 29%–100%) glomeruli and fibrinoid necrosis involving a median of 67% (range 0%–100%) glomeruli. The remaining 2 (7%) showed atypical anti-GBM nephritis without crescents (endocapillary proliferative glomerulonephritis with 5% fibrinoid necrosis in 1 and membranoproliferative glomerulonephritis in 1). "Spikes" or "holes" along GBM were present in 8 cases. The degree of tubular atrophy and interstitial fibrosis was none to mild in most (82%) patients, and almost all (96%) cases exhibited acute tubular injury (diffuse 68%) and interstitial inflammation (diffuse 35%). Necrotizing arteritis was present in 1 case with positive p-antineutrophil cytoplasmic antibody and anti-GBM antibodies. Concurrent diabetic nephropathy and IgA nephropathy each was present in 1 patient.

On electron microscopy, all cases showed subepithelial electron dense deposits, segmentally involving less than 50% of the total GBM in 11 (39%) and globally in 17 (61%). The MN was mostly (82%) stage I to II. Mesangial deposits were present in 4 (14%) cases whereas no subendothelial deposits were seen. Podocyte foot process effacement was segmental in 9 (32%) cases and global in 19 cases (68%).

On immunofluorescence, all cases showed global polytypic bright linear GBM staining for IgG (mean intensity 2.6 ± 0.6 on a scale of 0–3+). Fine or coarse granular GBM staining for IgG was observed in 14 (50%) cases, 6 segmental and 8 global. GBM linear segmental staining for IgA, IgM, C3, kappa, and lambda were present in 18% (1.5+), 18% (1.1+), 74% (2+), 100% (2.4+), and 100% (2.4+), respectively. No cases showed GBM staining for C1q or full house staining pattern. Linear GBM staining for ≥1 IgG subclass was observed in all 14 cases tested, most commonly IgG1-(co)dominant in 6 (43%). Granular GBM staining for ≥1 subclass was observed in 8 cases, IgG4-dominant in 4 (50%). Of note, the dominant IgG subclass of granular staining was different from that of linear staining in all 8 cases, a feature facilitating the recognition of granular staining and thus the diagnosis of concurrent MN, particularly when electron microscopy is unavailable.

Immunostains for phospholipase A2 receptor (n = 18), THSD7A (n = 8), neural epidermal growth factor-like 1 (NELL-1) (n = 8) and EXT2 (n = 8, including 1 with positive antinuclear antibody) were negative. Proteomic analysis of glomeruli, performed on additional 8 cases, including 2 with malignancy and 1 with nonsteroidal anti-inflammatory drugs use, did not detect any of the known MN antigens, including phospholipase A2 receptor, THSD7A, EXT1/2, NELL1, serine protease

Table 2. Pathologic characteristics (28 patients)

Kidney biopsy	Findings
Light microscopy	
Number of glomeruli	18 (4–42)
% Global glomerulosclerosis	12 (0–33)
Variant of anti-GBM nephritis	
Classic (i.e., CGN):	26 (93%)
% of glomeruli with cellular and fibrocellular crescents	77 (29–100)
% of glomeruli with fibrinoid necrosis	67 (0–100)
Atypical	2 (7%): MPGN in 1 and EPGN in 1
Spikes or pinholes along GBM	8 (28%)
TA/IF – none, mild, moderate, severe	9 (32%), 14 (50%), 4 (14%), 1 (4%)
Acute tubular injury – none, focal, diffuse	1 (4%), 8 (28%), 19 (68%)
Interstitial inflammation – none, focal, diffuse	1 (4%), 17 (61%), 10 (35%)
Interstitial edema – none, focal, diffuse	6 (21%), 15 (54%), 7 (25%)
Arteriosclerosis – absent, mild, mild to moderate, moderate, severe	11 (39%), 6 (21%), 3 (11%), 7 (25%), 1 (4%)
Immunofluorescence findings	
Linear GBM staining for IgG – 3+, 2–3+, 2+, 1–2+, 1+	19 (68%), 1 (4%), 6 (20%), 1 (4%)[a], 1 (4%)[a]
Granular GBM staining for IgG	14 (50%), 6 segmental and 8 global
Linear TBM staining for IgG	4 (14%)
Dominant or codominant IgG subclass linear GBM staining (n = 14): IgG1, IgG2, IgG3, IgG4, codominant IgG1/2	4 (30%), 2 (14%), 3 (21%), 3 (21%), 2 (14%)
Dominant or co-dominant IgG subclass granular GBM staining (n = 8): IgG1, IgG2, IgG3, IgG4, co-dominant IgG1/4	2 (25%), 1 (13%), 1 (13%), 3 (36%), 1 (13%)[b]
Electron microscopy findings	
Subepithelial deposits–segmental, global	11 (39%), 17 (61%)
Stage of subepithelial deposits–stage I, I-II, II, II-III, III	9 (32%), 7 (25%), 7 (25%), 4 (14%), 1 (4%)
Podocyte foot process effacement–segmental, global	9 (32%), 19 (68%)
Target antigens of membranous nephropathy	
PLA2R (IF on frozen n = 13; IF on paraffin n = 5; MS n = 8)	0/21 (0%)
Mass spectrometry	0/8 (0%)
THSD7A (IF on paraffin n = 8; MS n = 8)	0/16 (0%)
NELL1 (IHC n = 8; MS n = 8)	0/16 (0%)
EXT1/2 (IHC n = 8; MS n = 8)	0/15 (0%)
Other known target[c] or putative[d] antigens (MS n = 8)	0/8 (0%)
Novel target antigens (MS n = 8)	0/8 (0%)

CGN, crescentic glomerulonephritis; EPGN, endocapillary proliferative glomerulonephritis; EXT1/2, exostosin 1/2; GBM, glomerular basement membrane; IF, immunofluorescence; MPGN, membranoproliferative glomerulonephritis; MS, mass spectrometry; NELL1, neural epidermal growth factor-like 1; PLA2R, m-type phospholipase A2 receptor; TA/IF, tubular atrophy and interstitial fibrosis; TBM, tubular basement membrane; THSD7A, thrombospondin type 1 domain containing 7A.

[a]No glomeruli were sampled in the frozen tissue in these 2 cases; therefore, the immunofluorescence staining was performed on pronase-digested paraffin tissue, which shows weaker staining for IgG than fresh tissue in cases of anti-GBM nephritis. Both cases showed diffuse crescentic GN on light microscopy. Serum anti-GBM antibody, available in 1 of these 2 patients, was strongly positive.

[b]No granular GBM staining was observed in 6 of 14 cases tested.

[c]Serine protease HTRA1 (HTRA1), semaphorin 3B, protocadherin 7A (PCDH7A), PCDH FAT1, netrin G1,13 contactin 1 (CNTN1), neural cell adhesion molecule-1 (NCAM1), transforming growth factor beta receptor 3 (TGFBR3), neural-derived neurotropic factor, and proprotein convertase subtilisin/kexin type 6).

[d]FCN3, CD206, EEA1, SEZ6L2, NPR3, MST1, VASN, CRIM1, FLRT3, IDE, RECK, NLGN3, PGLYRP1, VEGFA, SULF1, EFEMP2, and FRAS1.

Values are in n (%) or median (range) unless otherwise indicated. N = 28 unless otherwise specified.

HTRA1, semaphorin 3B, protocadherin 7 (PCDH7), protocadherin FAT1, netrin G1, NCAM1, TGFBR3, NDNF, and PCSK6. In addition, none of the recently identified putative antigens (FCN3, CD206, EEA1, SEZ6L2, NPR3, MST1, VASN, CRIM1, FLRT3, IDE, RECK, NLGN3, PGLYRP1, VEGFA, SULF1, EFEMP2, and FRAS1)[4] of MN were present at a significant level. Moreover, no unique novel target antigens were detected in these cases.

DISCUSSION

To date, this series is the largest of patients with concurrent anti-GBM nephritis and MN. Similar to previous reports, our patients with classic anti-GBM nephritis and MN were predominantly male who presented with severe acute kidney injury, proteinuria, and hematuria.[1-3,5-9,S1–S13] Prognosis was generally poor despite aggressive immunosuppression and plasmapheresis with 1-year rates of patient survival and renal survival of 79% (19/24) and 42% (8/19), respectively. We found the prognosis to be particularly dismal in patients who required dialysis at presentation with a 93% rate of progression to ESKD. Of our 26 patients with classic anti-GBM nephritis, 5 had negative serum anti-GBM antibodies. Although these 5 patients presented with mildly or moderately elevated serum creatinine (median of 3.3 mg/dl; range 2.1–3.9), 4 patients progressed to ESKD, in concordance with the reported cases of seronegative anti-GBM nephritis.[S14] In contrast, the 2 patients with atypical anti-GBM nephritis and MN presented with nephrotic syndrome in 1 and mild acute kidney injury and proteinuria in 1, and both recovered kidney function, in line with the milder clinical phenotype and better prognosis of atypical anti-GBM nephritis compared with classic anti-GBM nephritis.[S15]

Most reported cases of combined anti-GBM nephritis and MN were phospholipase A2 receptor-negative,[2,3,S9–S13,S16] and similarly all 21 patients tested in our cohort were phospholipase A2 receptor-negative. We found that MN concurrent with anti-GBM nephritis is not associated with any of the known antigens most often associated with primary MN (THSD7A, NELL1, semaphorin 3B, PCDH7, netrin G1, and HTRA1) or secondary MN (EX1/2, NCAM1, TGFBR3, CNTN1, protocadherin FAT1, NDNF, and PCSK6).[S17,S18] Furthermore, we did not detect a unique novel target antigen in these 8 patients (using the same mass spectrometry platform that allowed for discovery of several novel MN antigens recently).[S17] Our negative findings suggest that the target antigen is likely a structural component of glomeruli, which is difficult to detect by our methodology. However, the small number of cases (n = 8) analyzed by mass spectrometry is a limitation of this

study. Further studies using more sensitive techniques are needed to determine the target antigen(s) and pathogenetic mechanisms of concurrent anti-GBM nephritis and MN.

DISCLOSURE

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Figure S1. Kidney biopsy findings.

Figure S2. IgG subclass staining.

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