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CASE REPORT

Combined membranous nephropathy and crescentic glomerulonephritis with concurrent anti-glomerular basement membrane antibody and myeloperoxidase-specific anti-neutrophil cytoplasmic antibody

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Abstract We report a case of a 71-year-old man with rapidly progressive nephritic syndrome and dual positivity for anti-glomerular basement membrane antibody and myeloperoxidase-specific anti-neutrophil cytoplasmic antibody. Renal biopsy revealed crescentic, mainly cellular, glomerulonephritis with granulomatous lesions, and advanced membranous changes. Membranous nephropathy had apparently existed for an extended period before the development of crescentic glomerulonephritis. In some studies reporting the simultaneous occurrence of both diseases, membranous nephropathy might be followed by crescentic glomerulonephritis, presumably from a histological point of view. Although we cannot prove a causal relationship between the two diseases, we caution that precise observations, especially histological, are necessary in similar cases.

Keywords Membranous nephropathy · Crescentic glomerulonephritis · Anti-glomerular basement membrane antibody · Myeloperoxidase-specific anti-neutrophil cytoplasmic antibody

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Introduction

Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults, and may occur concurrently with other glomerular diseases. Combined MN and crescentic glomerulonephritis (GN) is rare; however, several cases of this combination have been reported. Two types of combined MN and crescentic GN are recognized: anti-glomerular basement membrane (anti-GBM) antibody and anti-neutrophil cytoplasmic antibody (ANCA) [1]. We present a case of MN with both anti-GBM antibody and myeloperoxidase-specific (MPO)-ANCA.

Case history

A 71-year-old male was referred to our hospital because of a 1-month history of appetite loss, fatigue, headache, and dyspnea. The results of testing at least 9 years before admission reported no proteinuria or hematuria. He was not taking medications and had no known allergies. On examination, his blood pressure was 200/96 mmHg, pulse was 100 beats/min, and temperature was 37.3 °C. He was anemic, but not icteric. Mild wheezing was heard on auscultation of the lungs and bilateral pretibial edema was present. Skin lesions such as palpable purpura and urticaria were not noted. The remainder of the physical examination was normal. Soon after admission, the patient became oliguric and, soon after, almost totally anuric.

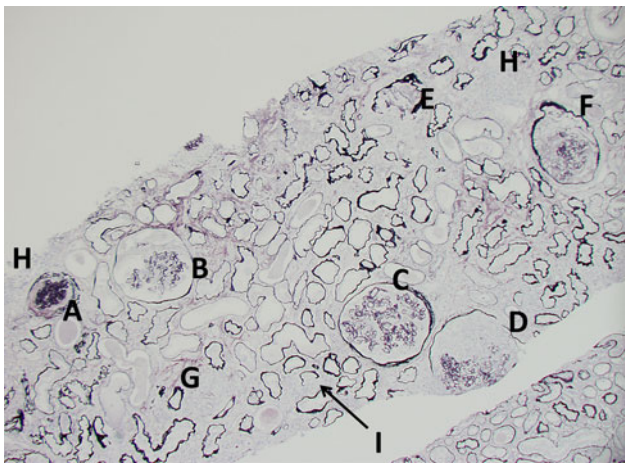

Fig. 1 Six glomeruli are shown in this area: one (*A*) is obsolete, three (*B*, *C*, *D*) have cellular crescents of various sizes, and two (*E*, *F*) have fibrocellular crescents. Many tubuli with thickened tubular basement membrane (TBM) are slightly to moderately atrophic. Mild and focally marked (*H*) cellular infiltrations in widened interstitium are seen (periodic acid-methenamine silver, original magnification ×25)

His laboratory findings were as follows: urinary protein, 478 mg/dl; protein/creatinine ratio in a spot urine specimen, 9.0 g/g; urinary sediment revealed >100 erythrocytes and 5–9 leukocytes per high-power field. The hematocrit was 24.8 %; hemoglobin concentration, 8.8 g/dl; platelet count, 248,000/mm^3; leukocyte count, 7,630/mm^3; serum urea nitrogen level, 87.1 mg/dl; creatinine, 14.53 mg/dl; uric acid, 9.2 mg/dl; cholesterol, 172 mg/dl; total protein, 5.2 g/dl; albumin, 3.6 g/dl; C-reactive protein, 4.84 mg/dl; immunoglobulin (Ig) G, 1,162 mg/dl; IgA, 303 mg/dl; IgM, 40 mg/dl; and ferritin, 494 ng/ml. Serum complement was normal and circulating immune complexes were negative. MPO-ANCA was positive (68.6 U/ml), but proteinase 3 (PR-3)-specific ANCA was negative and anti-GBM antibody was positive (148 EU). Rheumatoid factor, antistreptolysin O, hepatitis B virus surface antigen, hepatitis C virus antibody, human immunodeficiency virus antibody, antinuclear antibody, and cryoglobulin were negative during the entire observation period. Renal ultrasound and computed tomography showed normal-sized kidneys.

Owing to congestive heart failure and uremia, the patient was started on dialysis on the 2nd hospital day and continued on dialysis three times per week. After improving congestive heart failure, chest radiography and computed tomographic scans showed no findings suggestive of pulmonary hemorrhage or interstitial change. He was treated with pulse intravenous methylprednisolone at a dose of 1.0 g for 3 days during the early phase of the disease, followed by oral prednisolone (PSL) (40 mg/day). On the 10th hospital day, renal biopsy was performed to investigate the cause of acute renal failure. Under light microscopy, eight glomeruli were found; one was obsolete and the remaining seven had crescents, five cellular and two fibrocellular, with collapsed tufts and advanced membranous transformed and ruptured GBM (Figs. 1 and 2a). In almost all areas, tubuli were mildly to moderately atrophic with thickened tubular basement membrane (TBM) and occasional ruptured TBM (Fig. 1I). The widened interstitium showed mild cellular infiltration, mainly with mononuclear cells, and occasional focal marked cellular infiltration, mainly with lymphoid cells (Fig. 1H). There were also a small number of granulomatous lesions in the glomerular crescent and interstitium (Figs. 1G and 2b–d). Using an immunofluorescent assay, prominent fine granular IgG deposits and coarse granular IgA, IgM, and C3 deposits were found along the capillary walls. IgG subclass analysis revealed positive IgG1 (+), weakly positive IgG2 (±) and IgG4 (±), and negative IgG3. One glomerulus with a cellular crescent was assessed using electron microscopy. The crescent compressed the tufts, where a thickened GBM with electron-dense deposits was found, but detailed fine structures were not clear (Fig. 3a). Detailed structures of the GBM were observed in only small portions; dense deposits were found mainly intramembranously, leading to an interpretation of stage III membranous transformation (Fig. 3b). Secondary causes of MN were investigated using immunofluorescent assay and electron microscopy, but there was no evidence of additional disease, such as vasculitis, malignancy (negative results with thoracoabdominal computed tomography, endoscopy, and colonoscopy), or drug therapy usually associated with MN. In spite of methylprednisolone pulse therapy and oral prednisolone treatments, anuria continued and there was no significant improvement in renal function. Prednisolone was slowly tapered to 5 mg/day, and MPO-ANCA and anti-GBM antibody remained below the lower limit of detection. The patient underwent maintenance hemodialysis satisfactorily for approximately 2 years until death occurred, owing to unexpected congestive heart failure, possibly due to insufficient attention to an appropriate diet.

Discussion

Concurrent MN and crescentic GN is unusual, and there is evidence for at least two pathogenic mechanisms for the crescents seen in patients with MN [1]. The first mechanism is associated with anti-GBM antibodies. The coexistence of MN and anti-GBM GN was first reported by Klassen et al. [2], and, since then, at least 28 cases have been described [3]. The second mechanism occurs in the absence of anti-GBM antibodies, and most cases are associated with ANCA.

In some cases of combined MN and crescentic GN, as in our case, acute exacerbation of renal function warrants a

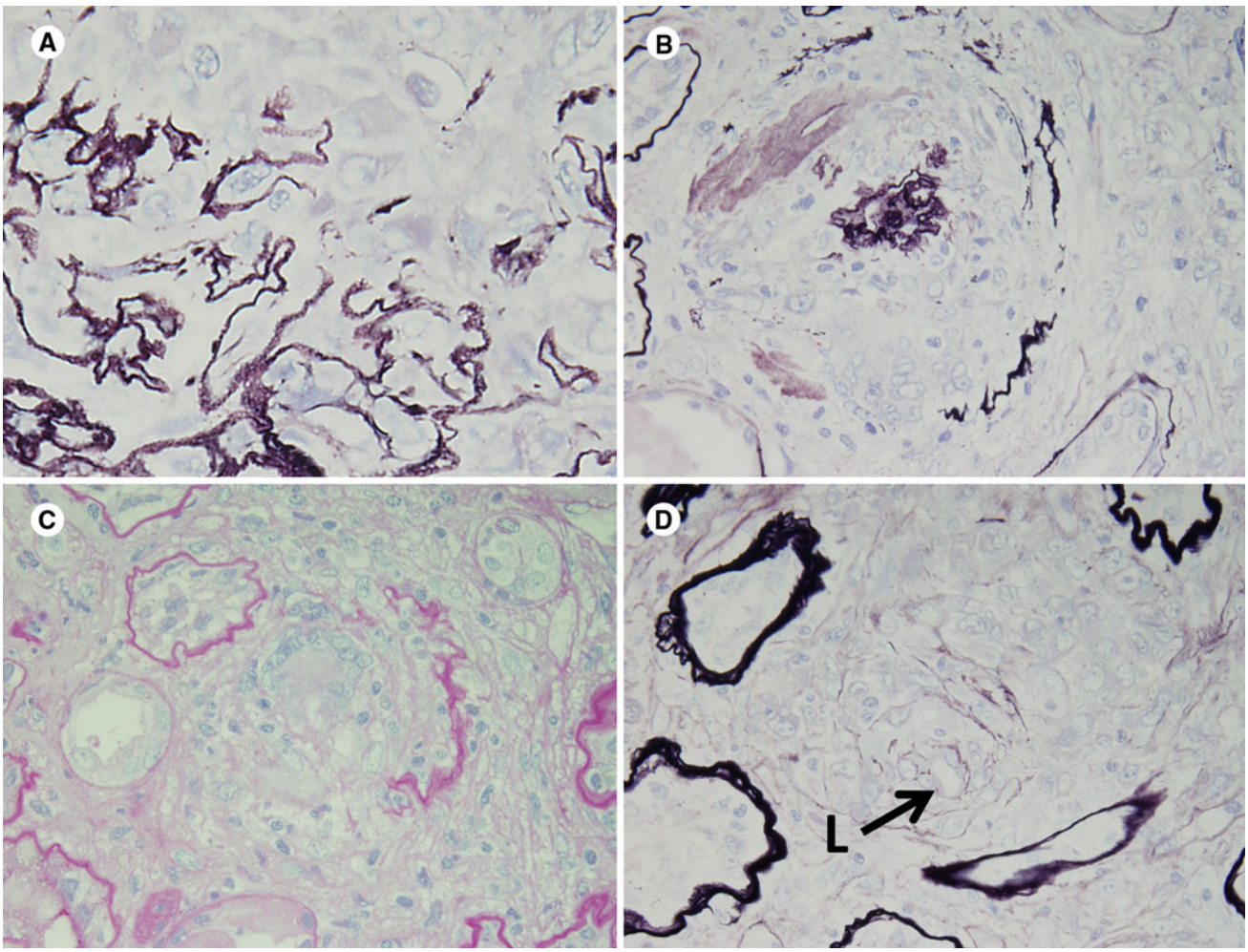

Fig. 2 **a** Magnified glomerulus marked *D* in Fig. 1. Cellular crescents and compressed glomerular tufts are seen and glomerular basement membranes (GBMs) are thickened and disrupted with advanced membranous transformation (periodic acid-methenamine silver, original magnification ×400). **b** A glomerulus with cellular granulomatous crescent with disrupted Bowman's capsule (periodic acid-methenamine silver, original magnification ×200). **c** A multinucleated giant cell found in the same glomerulus seen in **b** (periodic acid-Schiff, original magnification ×200). **d** An interstitial granulomatous lesion surrounding an apparent small vessel with small lumen (*L*), in *G* in Fig. 1 (periodic acid-methenamine silver, original magnification ×200)

renal biopsy; however, even if coexistence of the two diseases is confirmed, it is difficult to determine the exact onset of each disease and causal relationships. In cases showing fresh cellular crescent and distinct membranous changes, especially advanced membranous changes, as in our case, MN is apparently followed by crescentic GN, since early changes in MN may not be obvious under light microscopy. In such cases, it is suggested that MN damages the GBM and releases hidden antigens that incite anti-GBM antibodies [2]. However, cases of simultaneous occurrence [4] or of initial anti-GBM crescentic GN with subsequent MN [5] are reported.

In our patient, instead of positive anti-GBM antibody, immunofluorescent assay revealed prominent fine granular IgG deposits along the capillary walls. Klassen et al. [2] considered that it was possible, in combined MN and anti-GBM-positive crescentic GN, that linear staining of anti-GBM antibody was masked by the granular pattern of the MN, but in several other cases, both linear and dot-like IgG deposits were seen [4].

Nasr et al. [6] reported 14 cases of MN with ANCA-associated GN, and, in only one biopsy, proved that MN preceded the development of ANCA-associated GN on repeat biopsy 7 months later. However, in another 13 patients, both diseases were diagnosed at the time of renal biopsy. Granulomatous lesions found in our case were considered to be related to ANCA. Rutgers et al. [7] reported 10 cases of crescentic GN with concurrent positive anti-GBM antibody and MPO-ANCA, and found that patients with anti-GBM GN and granulomas were always MPO-ANCA positive.

Recently, MPO has been detected in MN-like deposits in patients with ANCA-associated GN [8], and the authors

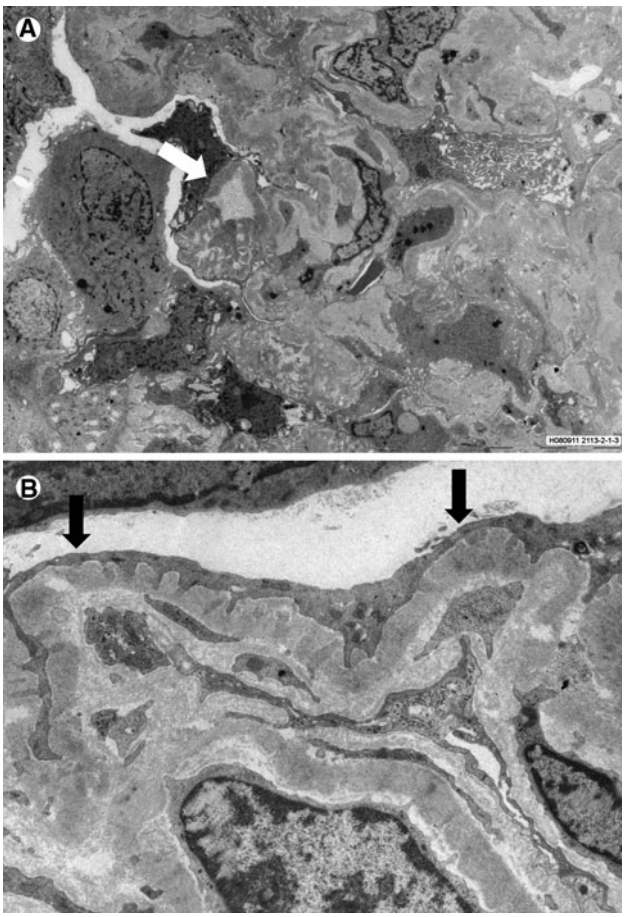

Fig. 3 **a** Thickened glomerular basement membrane (GBM) with electron-dense deposits (*arrows*) are seen in the compressed and degenerated tufts, but detailed structures are not clear (electron microscopy, original magnification ×1,000). **b** Detailed advanced GBM membranous transformation (stage III) is confirmed in only small portions (between the two *arrows*). Dense deposits are found mainly intramembranously (electron microscopy, original magnification ×2,500)

suggested that it might play a role in the formation of subepithelial deposits. This does not fit well in our case because the granulomatous lesions were relatively fresh, occurring at almost the same time as crescent formation; therefore, membranous changes might precede MPO-ANCA-related GN. Another possibility is that highly cationic-free MPO released from damaged leukocytes sticks to the GBM or preformed immune deposits. Further studies are necessary in order to determine the correct interpretation.

ANCA-related GN has been reported to occur superimposed on other renal diseases, including IgA nephropathy [9], lupus nephritis [10], and anti-phospholipase A2 receptor antibody-positive MN [11]. Rutgers et al. [7] reported that 43 % of patients with anti-GBM GN were positive for MPO-ANCA. ANCA-related GN triggers have been identified and are closely associated with drugs [12] and bacterial infections [13].

There are at least two reported cases which have dual positivity for anti-GBM antibody and ANCA with MN [14, 15]. One case [14] had both perinuclear and cytoplasmic ANCAs, and the other [15] had antibodies to both human lysosomal membrane protein 2 (anti-hLAMP-2) and MPO-ANCA. The significance of the dual positivity of perinuclear and cytoplasmic ANCA or MPO-ANCA and anti-hLAMP-2 antibody is unclear. At the present time, combinations of various renal diseases, including MN and ANCA-related GN, are likely to be incidental.

In conclusion, we report a case with combined MN and crescentic GN with concurrent anti-GBM antibody and ANCA. Although renal biopsy was obtained only once, we believe that MN preceded crescentic GN from a histological point of view. For the same reason, we propose that, in some cases reported as simultaneous occurrences of both diseases, initial MN might be followed by crescentic GN. Although we have no direct evidence, in such cases, Klassen et al.'s assumption may be plausible. At this time, we can suggest no reasons for a causal relationship between MN and ANCA-related GN and no plausible assumptions have been found in the literature.

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Conflict of interest None declared.

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