



Coexistence of antineutrophil cytoplasmic antibody-associated vasculitis and membranous nephropathy: a case report

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Abstract: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and membranous nephropathy (MN) are two types of diseases that can both involve kidneys. In recent years, there are some reports about the concurrence of these two diseases. However, the precise mechanism, clinical course, and optimal treatment of patients with this unusual combination of renal diseases are little known. Previously reported cases of MN combined with AAV presented characteristics of both MN and crescentic glomerulonephritis, manifesting rapid disease progression and poor prognosis. Diagnosis and treatment are essential and challenging. Here, we report a case of AAV and MN in a 62 years old man, who was admitted to hospital due to edema, low-grade fever, and cough. The patient showed a different pathological feature from previous cases, with no crescent formation. By analyzing the diagnoses and potential pathogenesis, we considered MN was secondary to the present AAV and suspected the existence of other alternative mechanisms. Also, we applied a new therapy, glucocorticoid with mizoribine. After one-year follow-up, this treatment is feasible, safe, and leads to a clinical improvement for AAV combined with MN. In this case, two diseases overlapped, and the laboratory analysis and pathology are both required to ensure diagnostic accuracy. The principal aim of this case report is to highlight the diagnostic challenge and distinct treatment in the simultaneous occurrence of AAV combined with MN.

Keywords: Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV); membranous nephropathy (MN); immunosuppressant; case report

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Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterized by focal necrotizing lesions, which can affect various vessels and organs; in the kidney, pauci-immune necrotizing crescentic glomerulonephritis (NCGN) may cause hematuria, proteinuria, and red cell casts, and there can be a rapid deterioration in renal function (1). Membranous nephropathy (MN), a common cause of the nephrotic syndrome in adults, is characterized by subepithelial immune deposits and glomerular basement membrane (GBM) thickening. MN is classified into idiopathic and secondary. About 75% of all MN is idiopathic, and the remainder is secondary to infections,

lupus nephritis, cancers, and drugs (2). The occurrence of AAV and MN has been documented. Pathology showed features of MN in addition to NCGN; crescents and stage I or II membranous changes occurred in the majority of cases. MN complicated by AAV appears to have a more aggressive clinical course compared to MN alone; however, the pathogenesis is unclear (3-5). Here, we report a case of AAV with secondary MN in a 62-year-old man whose renal biopsy revealed rare pathological features showing no crescents creation. We reviewed literatures to conclude possible pathogenesis and analyze the importance of testing antibodies and pathology. Besides, we provided a new treatment for this combined disease. After one-year follow-up, this treatment is feasible, safe, and leads to a clinically

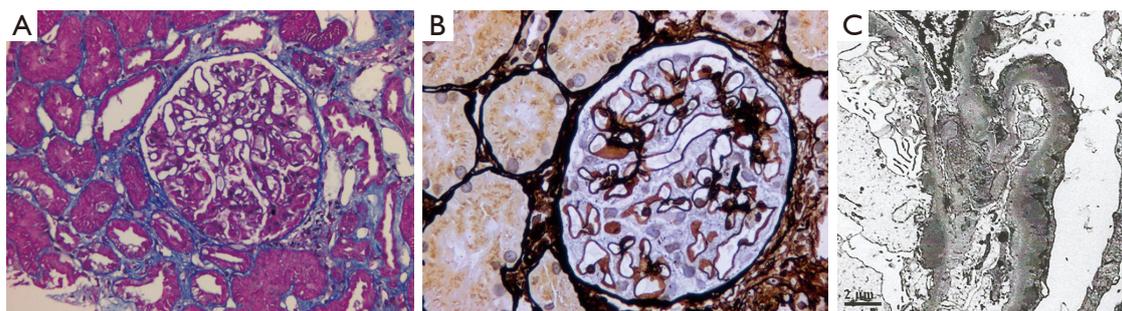


Figure 1 Pathological findings in the renal biopsy. (A,B) Thickened GBM and plasma cell infiltrates in the renal interstitium (A: MASSON $\times 400$, B: PASM $\times 400$). (C) Subepithelial electron-dense sediment deposition by electron microscopy (bar =2 μm). GBM, glomerular basement membrane.

improvement for AAV combined with MN. We present the following article in accordance with the CARE reporting checklist (available at <http://dx.doi.org/10.21037/apm-20-1323>).

Case presentation

A 62-year-old man presented intermittent puffiness of the face and edema of the lower extremities for one month. The patient persisted fatigue, low-grade fever ($<38.5\text{ }^{\circ}\text{C}$), cough, and weight-loss ($>2\text{ kg}$), with denying dyspnea, symptoms of serositis, oral ulcers, and rash. He was noted hematuria and proteinuria in a local hospital and treated with penicillin. However, the treatment was not curative. Therefore, he was referred to our hospital. He had no known personal or family history of renal dysfunction. On admission, the temperature was normal ($36.5\text{ }^{\circ}\text{C}$), blood pressure 124/70 mmHg, pulse rate 78/min. The physical examination revealed abnormal pulmonary sounds and bilateral pleural effusion.

Laboratory values are as follows: hemoglobin, 98 g/L; white blood cell (WBC) count, $11.19 \times 10^9/\text{L}$. The results of urinalysis were: glucose negative, protein 3+, and occult blood 3+. Examination of the urinary sediment showed 33.1 erythrocytes per high-power field. Urinalysis revealed hematuria with dysmorphic red blood cells. There was 7.09 g of protein on a 24-h urine collection. Biochemical data were as follows: albumin, 18.9 g/L; blood urea, 8.03 mmol/L; creatinine, 75.6 $\mu\text{mol/L}$; total cholesterol, 8.89 mmol/L; total triglyceride, 1.14 mmol/L. The erythrocyte sedimentation rate (ESR) was 99 mm/1 h, and the C-reactive protein (CRP) level was 32.9 mg/L. Levels of antibody-immunoglobulin (Ig) and complements were normal. Serologic studies were notable for the presence

of circulating perinuclear anti-ANCA (p-ANCA); a test for the myeloperoxidase (MPO) antibodies significantly elevated (253.96 U/mL), while a test for circulating anti-PR3 antibodies was negative. The anti-GBM antibody and serum anti-phospholipase A2 receptor (PLA2R) were negative. Serology tests, including tests for hepatitis B surface antigen, hepatitis C virus, and HIV were negative. Computed tomography (CT) of his chest showed pneumonia, bilateral pleural effusions, secondary pulmonary tuberculosis.

Owing to the presence of MPO-ANCA and large amounts of urinary proteins, there was a high suspicion of ANCA-associated glomerulonephritis (ANCA-GN) combined with other glomerular diseases; thus, a renal biopsy was performed. Light microscopy observations (*Figure 1A*) showed mild thickening of basement membranes. Crescents and prominent inflammatory cell infiltration were not observed in glomeruli. The tubules showed casts, focal interstitial inflammation, and mild tubule interstitial fibrosis. Arteriolar vessels found evidence of slight sclerosis. Immunofluorescence examination (*Figure 1B*) documented granular deposits IgG of 4+ and C3 of 2+ along the capillary wall. Electron microscopy (*Figure 1C*) revealed electron-dense deposits in the subepithelial area and segmental thickening of basement membranes with spike formation. The renal biopsy suggested MN in the stage of I or II. All findings suggested a diagnosis of AAV with secondary MN. Meanwhile, he had pneumonia, secondary pulmonary tuberculosis, and anemia.

There was a concern for the risk of adverse effects, particularly pulmonary infection with using immunosuppressants. Therefore, we prescribe a treatment different from previous cases. Pulse therapy with methylprednisolone (50 mg for three days) followed

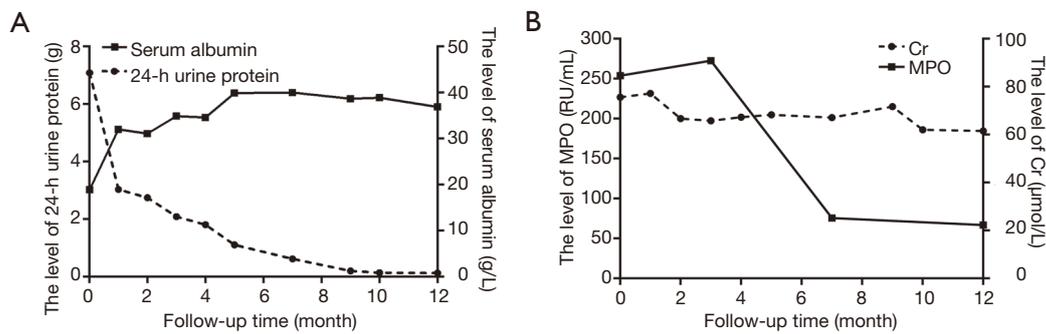


Figure 2 24-h urine protein, serum albumin, Cr, and MPO trend with follow-up. MPO, myeloperoxidase.

Table 1 Clinical course with follow-up

Parameter	Admission	1M	3M	5M	7M	10M	12M
Hb (g/L)	98	158	146	155	150	138	134
eGFR (mL/min)	97.05	94.62	114.78	109.72	112.10	101.07	101.41
UA (μmol/L)	507	452	322	309	337	360	342
Chol (mmol/L)	8.89	11.36	8.93	6.90	7.96	4.89	7.01
Glu (mmol/L)	4.30	5.37	5.38	5.12	5.42	5.63	7.18
urine RBC count (/HPF)	33.1	2.7	0.8	2.0	2.7	2.7	1.7
p-ANCA	1:32		1:10		1:10		1:32
c-ANCA	<1:10		<1:10		<1:10		<1:10

eGFR, estimated glomerular filtration rate; UA, uric acid; Chol, cholesterol; Glu, glucose; M, month.

by oral prednisolone (60 mg daily). He was also started on oral mizoribine (MRZ) 150 mg daily. Three months following treatment, the serum data results of the patient had improved. The results were as follows: albumin, 40 g/L; hemoglobin, 146 g/L. The 24-h urine protein was 2.09 g, and the MPO-ANCA concentration was 272.61 U/mL. Complete remission of proteinuria occurred within ten months (*Figure 2*). On clinical follow-up at one year (*Table 1*), albumin and hemoglobin were normal, MPO-ANCA concentration was 66.75 AU/mL, and hematuria disappeared. There were no manifestations of active systemic vasculitis. Pulmonary infection was also improved. The patient's renal function remained stable (creatinine ranged from 61.5 to 77.2 μmol/L, eGFR ranged from 94.62 to 114.78 mL/min). The patient showed good adherence with no adverse effects and unanticipated events occurred. Overall, he tolerated these therapies well, and his kidney lesion improved considerably. The major diagnosis, treatment and follow-up procedures of this patient were drawn as a timeline in *Figure 3*.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

Discussion

In this case, the patient presented with proteinuria, hematuria, fever, weight-loss, pulmonary lesions, and positive MPO-ANCA. Birmingham Vasculitis Activity Score (BVAS) was 17 (6). In combination, these results indicated an active AAV, and there was a high suspicion of ANCA-GN. Although proteinuria is generally in ANCA-GN, massive proteinuria ranging up to nephrotic levels is rare (1). Thus, the presence of significant proteinuria suggested that the patient may have another underlying disease. Surprisingly, the final histological diagnosis was different from expectation, revealing the characteristics of MN with subepithelial deposits. There was no evidence

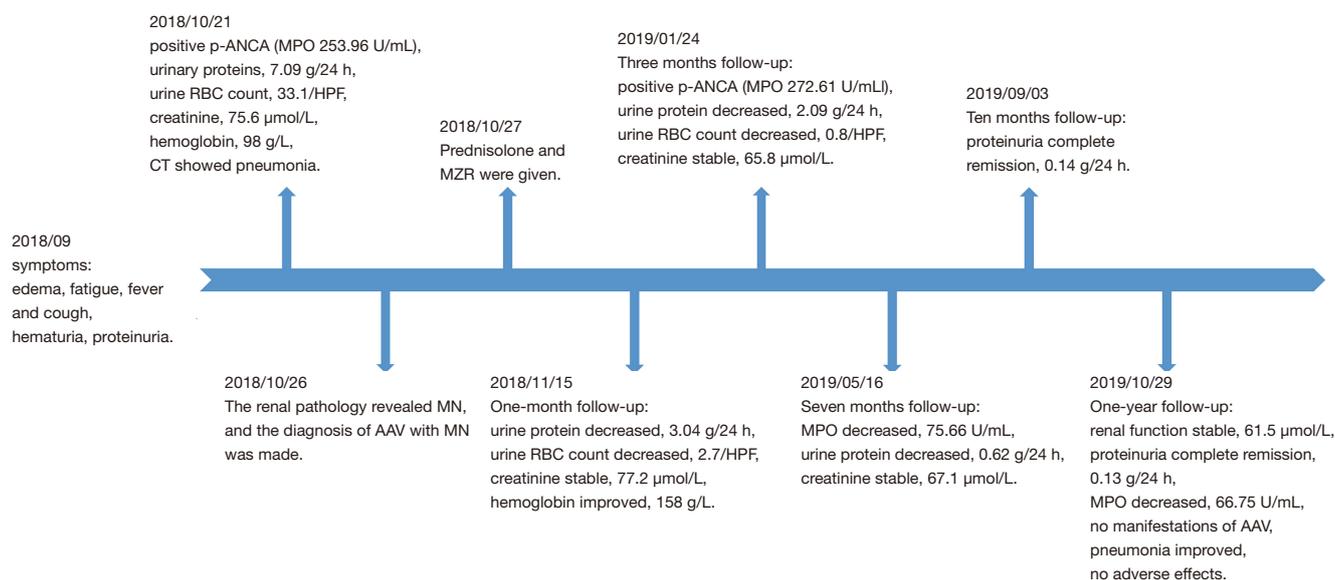


Figure 3 The timeline of the major diagnosis, treatment and follow-up procedures. AAV, associated vasculitis; MN, membranous nephropathy; MPO, myeloperoxidase.

for the existence of ANCA-GN, as no crescent was found. Considering that PLA2R is useful for differentiating between idiopathic and secondary MN (7), a diagnosis of secondary MN was made. As all possibilities, including cancer, drugs, and infection associated MN, have been ruled out, we speculate the pathogenesis of MN is associated with AAV.

Although the coexistence of AAV with MN has been reported, the precise mechanism of these two etiologies is not clear. The classical renal involvement of AAV is pauci-immune necrotizing and crescentic formation. However, recent studies reveal that the deposition of immune complex in ANCA-GN is not rare. When present, these changes suggest two diagnostic possibilities. First, the presence of immune deposits depends on the stage of development of the lesion, and leucocytes may not yet have degraded the immune deposits in newly developing injury (8). However, the role of renal immune complex deposition in the development of AAV needs further investigation. Besides, the concurrent of ANCA-GN and other glomerular diseases, such as MN and IgA, can also present immune complex deposition. The relationship between MN and AAV is mostly unknown. In an initial report, Surindran *et al.* (9) found that dual glomerulopathy was a result of the coincidental occurrence of two separate disease processes. On the other hand, a recent report has challenged this idea, and it is reported that the present

MPO-AAV probably caused MN. MPO could bind to GBM or endothelial cells, and play a part as a planted antigen, leading to cryptic podocyte neoepitopes that can lead to coexisting MN (10,11). Simultaneously, there is a hypothesis that concerns the role of PLA2R in this mechanism. Tominaga *et al.* (12) speculated that persistent stimulation by MPO and MPO-ANCA induced podocyte PLA2R expression, resulting in the development of MN-lesions. But some searchers hold the opposite opinion that MN lesions are not associated with anti-PLA2R, considering the less prevalence of circulating PLA2R antibodies and glomerular PLA2R deposits in patients with combined ANCA-GN and MN (5).

PLA2R antibody in the serum has high sensitivity and specificity for distinguishing idiopathic MN from secondary MN. Moreover, the staining for the positive PLA2R (7) and IgG subclass predominance also have been revealed to contribute to differential diagnosis between idiopathic and secondary MN. Idiopathic MN is characterized by the predominantly deposition of IgG4 subclass, along the epithelial surface of the GBM. However, the secondary forms are often positive for multi IgG subclasses, including IgG1 and IgG3, and some electron-dense immune could deposit in the mesangial region (13). In this case, the PLA2R antibody was negative, and this case was probably considered as secondary MN. However, this patient didn't has any particular diseases, such as cancer, drugs, and

infection, which cause secondary MN. For these reasons, it is reasonable to suspect the MN caused by AAV. The current case is a rare report of isolated MN occurring in a patient with active AAV without crescents formation. It has been proposed that MPO and MPO-ANCA antibodies are pathogenic in forming MN. Crescents were not identified in membranous within this case, possibly suggesting the existence of an alternative mechanism. Patients combined AAV and MN without crescents are rare. Apart from unique pathogenesis, for MN patients, ANCA was not routinely tested, and this is related to underestimate numbers. Therefore, we shouldn't ignore the test of ANCA, even though patients did not have many red blood cells in urinary analysis or elevated serum creatinine.

Little is known about the clinical course and optimal treatment of patients with this unusual combination of nephritis. We referred to the therapy of similar cases (3-5). Previous primary therapy was glucocorticoid and cyclophosphamide (CTX). Although the renal function was steady and no acute histological change found in admission, a rapid exacerbation is possible (14). For this reason, early treatment is of paramount importance for these patients. Thus, considering active AAV and large amounts of proteinuria, a combination of glucocorticoid and immunosuppressant was applied, despite no crescent formation and normal renal function. Based on the history of pulmonary infection and multiple severe adverse effects induced by CTX, he was treated with MRZ, a new type immunosuppressant, which was initially demonstrated in renal transplant recipients and recently was shown to be safe and effective against AAV, lupus nephritis and nephrotic syndrome (15,16). However, there was no report about using MZR in the patients combined with AAV and MN. Thereby, when using this special treatment, we strengthened follow-up (Table 1, Figure 2). One year after starting treatment, complete remission of proteinuria occurred, biochemical data was improved, and MPO titers also decreased. Although at the last follow-up, he showed persistent serological positivity for MPO, there was no active vasculitis. And we will continue to notice MPO titers. A report has described a patient with persistent positive MPO was effective in treating ANCA-GN histopathologically (17). Besides, the improvement of pulmonary lesions after treatment revealed some risk of infection doesn't increase, and the lesions may be characteristics of AAV involving lungs. Hence, this treatment is feasible, safe, and leads to a clinical improvement for AAV combined with MN.

A lack of testing PLA2R, MPO, and IgG subclass in

immune deposits is a limitation in our case, and then the analysis of the precise mechanism of the combination of these two etiologies is not clear. Moreover, it is well recognized that patients with crescentic glomerulonephritis have severe and often rapidly deteriorating failure (3). In this case, the patient's renal lesion is not grave, and it is in doubt whether the therapy is useful for the patients with crescent formation.

In conclusion, we report a case of AAV combined with secondary MN without crescents, and we provide safe and effective therapy. Meanwhile, we stress the importance of testing ANCA and analyzing immune deposits for diagnosis.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <http://dx.doi.org/10.21037/apm-20-1323>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/apm-20-1323>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for publication of this study and any accompanying images. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this study and any accompanying images.

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