Plasma exchange and rituximab treatments in primary membranous nephropathy combined with crescentic glomerulonephritis

A case report

Hui Lu, MBab,c,d, Zhao Cui, MDab,c,d, Xu-je Zhou, PhDab,c,d, Qi-zhuang Jin, MDab,c,d, Xiao-juan Yu, MDab,c,d, Su-xia Wang, MD, Yu Wang, MDab,c,d, Fu-de Zhou, MDab,c,d, Ming-hui Zhao, MD, PhDab,c,d,f

Abstract

Rationale: Crescent formation is rare in primary membranous nephropathy (MN). Anti-phospholipase A2 receptor (PLA2R) antibodies are detectable in these patients. The mechanism and treatments are unknown.

Patient concerns: A 72-year-old female patient who presented with nephrotic syndrome, hematuria, and rapidly progressive kidney dysfunction.

Diagnoses: Kidney biopsy was performed and the diagnosis was MN in combination with crescentic glomerulonephritis. Circulating anti-PLA2R IgG3 and IgG4 were detected of high level.

Interventions: The patient received plasma exchange and rituximab besides corticosteroids.

Outcomes: The patient achieved complete remission of proteinuria and recovery of kidney function after the clearance of anti-PLA2R antibodies.

Lesson: This case suggests a pathogenic role of anti-PLA2R antibodies in the mechanism of crescent formation in MN, which may need intensive therapy to eliminate the antibodies quickly.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ANCA = antineutrophil cytoplasmic antibody, ARB = angiotensin receptor blocker, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, GBM = glomerular basement membrane, MN = membranous nephropathy, PET-CT = positron emission tomography-computed tomography, PLA2R = phospholipase A2 receptor.

Keywords: anti-phospholipase A2 receptor antibodies, crescentic glomerulonephritis, IgG3, membranous nephropathy, plasma exchange

1. Introduction

Primary membranous nephropathy (MN) is a major cause of nephrotic syndrome in adults.[1,2] Kidney histomorphology shows thickened glomerular basement membrane (GBM), granular staining of IgG and complement along periphery of glomerular capillary loops, and electron-dense subepithelial deposits.[3] Phospholipase A2 receptor (PLA2R) on podocytes is the major autoantigen.[4,5] Studies have identified that the titer of anti-PLA2R antibodies is correlated with urinary protein excretion and disease activity. The antibody may disappear during a spontaneous or treatment-induced remission and reoccur at relapse. The high level of antibodies is associated with lower chance of remission and higher risk of renal function deterioration.[4,6–9]

Crescentic glomerulonephritis usually occurs in the presence of anti-GBM antibodies, antineutrophil cytoplasmic antibodies (ANCA), lupus nephritis, or IgA nephropathy.[10] The combination of MN and crescentic glomerulonephritis is rare. Most of the cases have been reported with the presence of anti-GBM antibodies or ANCA.[11,12] However, there are patients of MN and crescent formation without any signs of vasculitis, lupus, or anti-GBM disease.[13] Although the percentage of crescents in glomeruli was low of 5% (2%–17%),[14] these patients with crescents showed unfavorable therapeutic response and tended to have worse renal outcomes. Anti-PLA2R antibody was detectable in 79.7% of
the OD value of anti-PLA2R IgG1 was 0.283 (cut-off value 0.18), anti-PLA2R IgG2 was 0.216 (< 0.23), anti-PLA2R IgG3 was 2.237 (< 0.21), and anti-PLA2R IgG4 was 2.581 (< 0.17) (Fig. 1). Anti-thrombospondin type-1 domain-containing 7A antibody was negative. ANCA, anti-GBM antibody, antinuclear antibody, and anti-mCRP antibody were all negative. IgG was 17.4 (7.2–16.8) g/L, IgA was 4.2 (0.7–3.8) g/L, and IgM was 1.6 (0.6–2.8) g/L. Complement C3 was 1.0 (0.6–1.5) g/L and C4 was 0.26 (0.12–0.36) g/L. Her immunofixation electrophoresis of blood and urine was negative, and cryoglobulin was negative as well. Positron emission tomography-computed tomography (PET-CT) was performed for cancer screening with negative finding. Hepatitis B, hepatitis C, syphilis, and HIV screening were negative.

Kidney biopsy (Fig. 2) contained 18 glomeruli, 2 of them were global sclerosis, 13 of them had crescent formation, including 5 cellular crescents and 8 fibrocellular crescents, and the other 3 glomeruli showed GBM thickening. Some glomeruli showed rupture of Bowman capsule. Renal tubules presented with epithelial cells vacuolation and diffusive atrophy with many protein casts. The interstitium was infiltrated with multifocal lymphocytes, mononuclear cells, and plasma cells. Immunofluorescence showed granular deposits of IgG + and C3 + and PL2AR + along capillary walls. Immunohistochemical staining showed IgG1 –, IgG2 –, IgG3 +, and IgG4 ++ along capillary walls. Electron microscopy showed massive electron dense deposits in subepithelial area and diffuse podocyte foot-process effacement. The diagnosis was MN combined with crescentic glomerulonephritis.

She was treated with plasma exchange, 3 L per time every other day for 7 times, combined with prednisolone 40 mg per day (Fig. 3). After anti-PLA2R antibodies turned into negative, rituximab was given 375 mg/m² per week for 4 weeks. Two months later, the patient got complete remission of proteinuria and renal function recovery. Glucocorticoids were gradually reduced and stopped 7 months later. Her urinary protein excretion was 0.02 g/24h and serum creatinine was 108 (44–133) μmol/L.

3. Discussion

To our knowledge, this is the first case report of PLA2R associated MN combined with crescentic glomerulonephritis, which was successfully treated by plasma exchange and rituximab. ANCA associated vasculitis, anti-GBM disease, lupus, and IgA nephropathy were all excluded as the potential reasons for crescent formation. High level of anti-PLA2R IgG3 was detected in the circulation and IgG3 deposit was revealed in the glomeruli. The clearance of anti-PLA2R antibodies by plasma exchange was followed by the complete remission of proteinuria and kidney function recovery. This clinical course implies a pathogenic role of anti-PLA2R IgG3 in the crescent formation of MN and a favorable response by quick clearance of these antibodies.

It is known that anti-PLA2R antibodies are IgG4 subclass predominance and the titers of IgG4 significantly correlate with proteinuria and the occurrence of spontaneous remission. However, different subclasses of anti-PLA2R IgG were detectable above the normal threshold in 54% (IgG1), 34% (IgG2), 67% (IgG3), and 74% (IgG4) of all patients of primary MN.[7] In the comparison among different stages of MN, Huang et al.[13] revealed that in early stage (stage 1) of primary MN, IgG1 was the dominant IgG subclass (64% of cases); in all later stages IgG4 dominated. It indicates that there may be an IgG subclass switch in the antibody response to PLA2R. Actually, IgG3 appears earliest in IgG subclasses switching process. Subsequently, higher affinity IgG1 and IgG2 are produced. Finally, if antigen persists, high affinity IgG4 is produced. However, the less amount of IgG3 (7%) and its limited half-life (7 days)[16,17] make IgG3 hard to detect. There is 1 patient[18] with recurrent MN 13 days after kidney transplantation whose graft biopsy specimen showed granular staining for C3, C5b-9, C1q, and IgG3k. Retrospective evaluation of the native kidney biopsy sample revealed a similar pattern. The patient had IgG3k-restricted circulating anti-PLA2R antibodies. Treatment with rituximab stabilized both proteinuria and serum creatinine, and circulating anti-PLA2R became undetectable. This case suggests that circulating anti-PLA2R IgG3k caused the disease and the recurrence, by binding with PLA2R on the patient and donor podocyte and activating complement through the classic pathway. Of the 4 IgG subclasses, IgG3 has the greatest flexibility at the hinge region,
the highest capability of complement activation, and the highest binding affinity to FcR on phagocytes.\textsuperscript{[16,17]} These biological features make it intrinsically “nephritogenic.”\textsuperscript{[18]} In the current case, we found high titer of anti-PLA2R IgG3 and IgG4, and high percentage of crescents on MN. The kidney dysfunction achieved complete recovery by the clearance of antibodies after plasma exchange. It is plausible to propose that the pathogenicity of anti-PLA2R antibodies may play a crucial role in the crescent formation of MN.

There is no recommendation or guideline for the treatments to MN with crescents. In the case series of MN with crescents reported by Rodriguez et al.\textsuperscript{[13]} 14 of 19 patients received immunosuppressive therapy and 2 only angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) therapy (3 unknown). Four (21%) patients progressed to end-stage renal disease (ESRD) at 0 to 9 months postbiopsy, and the mean estimated glomerular filtration rate (eGFR) level of those without ESRD was 53.3 (range, 16–103) mL/min/1.73 m\(^2\). In our previous study\textsuperscript{[14]} on 28 MN patients with crescents less than 50% of glomeruli, who received the same treatments as those without crescent, fewer patients achieved remission (68% vs 87%). Crescent formation was a risk factor to no remission (OR = 3.1) and renal dysfunction (RR = 10.2). In the current case, considering the high percentage of crescents in glomeruli and the high level of anti-PLA2R IgG3, we performed plasma exchange to clean the circulating antibodies in 2 weeks, corticosteroids to reduce the inflammation in the kidneys, and rituximab to maintain antibody disappearance, restore Treg and Breg cells, and play direct actions on the podocytes.\textsuperscript{[19]} During follow-up, the patient achieved complete remission of proteinuria and kidney function recovery. This course suggests a beneficial effect of plasma exchange accompanied by corticosteroids and rituximab for MN patients with crescentic glomerulonephritis. Plasma exchange in combination with rituximab has been

\textbf{Figure 2.} Kidney biopsy examinations. Immunofluorescence study showed granular deposit of IgG (A), C3 (B), and immunohistochemical staining showed IgG3 (C) and IgG4 (D) along capillary walls. Cellular crescents (E) were shown on light microscopy. Electron microscopy showed massive electron dense deposits in subepithelial area and diffusive podocyte foot-process effacement (F).

Figure 2: Kidney biopsy examinations. Immunofluorescence study showed granular deposit of IgG (A), C3 (B), and immunohistochemical staining showed IgG3 (C) and IgG4 (D) along capillary walls. Cellular crescents (E) were shown on light microscopy. Electron microscopy showed massive electron dense deposits in subepithelial area and diffusive podocyte foot-process effacement (F).
documented as a successful treatment option for otherwise therapy refractory MN cases.\cite{20,21} This is the first and successful application of this therapy on the patients with crescentic MN. The wide spreading of this therapy needs further evidence from other patients of such conditions.

In conclusion, this case provides an argument that anti-PLA2R IgG3 may be pathogenic and lead to crescent formation in MN. Plasma exchange and rituximab therapy could be considered in such serious conditions of MN.

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Author contributions

Data curation: Hui Lu.

Resources: Xiao-juan Yu.

Supervision: Zhao Cui, Xu-jie Zhou, Qi-zhuang Jin, Xiao-juan Yu, Su-xia Wang, Yu Wang, Fu-de Zhou, Ming-hui Zhao.

Writing – original draft: Hui Lu.

Writing – review & editing: Zhao Cui, Su-xia Wang, Yu Wang, Fu-de Zhou.

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