Clinical Case Report

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A case report of remission of refractory membranous nephropathy progressing to stage 4 chronic kidney disease using low-dose rituximab

A long-term follow-up

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Abstract

Rationale: As suggested by the 2012 KDIGO guidelines, persistent elevation of serum creatinine >3.5 mg/dl (>309 μmol/l) (or an estimated glomerular filtration rate <30 ml/min per 1.73 m^2 is one of contradictions for the use of immunosuppressive therapy in membranous nephropathy.

Patient concerns: A 45-year-old man with membranous nephropathy negative for serum anti-phospholipase-A2-receptor antibody, showed no response to corticosteroids and cyclophosphamide. He progressed to chronic kidney disease stage 4 (CKD4) under tacrolimus and relapsed after withdrawal.

Diagnoses: The patient received repeated renal biopsy, comfirming the diagnosis of membranous nephropathy with progressive glomerular and tubulointerstitial scarring.

Interventions: He was treated with successfully four times with lose-dose (180 mg/m^2 every 2-3 months) rituximab (RTX) depending on his B cell counts, aiming to remain at 0-5 cells/μl.

Outcomes: The patient was followed-up for almost 6 years. He achieved a partial remission at 11 months and a complete remission of the nephritic range of proteinuria at 34 months following infusion of RTX. RTX was well tolerated and the patient's renal function improved. He had no edema and his dosage of corticosteroids could be discontinued.

Lessons: This case strongly suggested that rituximab has promising therapeutic significance, even in patients progressing to CKD4.

Abbreviations: CKD4 = chronic kidney disease stage 4, CNI = calcineurin inhibitor, CR = complete remission, CTX = cyclophosphamide, eGFR = estimated glomerular filtration rate, GBM = glomerular basement membrane, IMN = idiopathic membranous nephropathy, IVIG = intravenous immunoglobulin, KDIGO = Kidney Disease Improving Global Outcomes, NS = nephrotic syndrome, PLA2R = M-type phospholipase A2 receptor, PR = partial remission, RTX = rituximab, SAEs = serious adverse events, Tac = tacrolimus.

Keywords: CKD4, membranous nephropathy, refractory, rituximab

1. Introduction

Membranous nephropathy (MN) is a common cause of nephrotic syndrome (NS) in adults. Although several diseases such as viral infections, autoimmune diseases, certain drugs, and malignancies may cause secondary MN, most cases of MN are idiopathic MN (IMN).[1] M-type phospholipase A2 receptor (PLA2R) was identified as the major autoantigen for primary MN in adults.[2,3] The treatment of IMN is heavily debated.[4] Although one-third of the patients can develop a spontaneous remission during the first year of follow-up, about one-third will progress to end-stage renal disease.

Conventional therapies, consisting of corticosteroids and immunosuppressive agents, might induce significant adverse side-effects and are not effective in all patients. The current Kidney Disease Improving Global Outcomes (KDIGO) guideline favors treatment to be restricted to high-risk patients with use of alkylating agents or calcineurin inhibitors as an alternative therapy.[4] It did not suggest using immunosuppressive therapy in patients with a serum creatinine (SCr) persistently >3.5 mg/dL (>309 μmol/L) (or an estimated glomerular filtration rate [eGFR] <30 mL/min per 1.73 m^2) or those with concomitant severe or potentially life threatening infections.[4] It was reported that rituximab (RTX) administered at a dose of two 1 g infusions 2 weeks apart, or 4 once-weekly infusions of 375 mg/m^2, could achieve complete remission (CR) or partial remission (PR) of proteinuria in 50% and 80% of patients at 1 year and at 2 years, respectively.[5–12] Indeed, it has been suggested that RTX might replace steroids plus cyclical cyclophosphamide (CTX) as the first-line immunosuppressive therapy or as a rescue therapy.

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The study was approved by the medical ethics committee of Peking University. The patient provided informed consent. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

The data that support the findings of this study are available from the corresponding author (FDZ) upon reasonable request.

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However, there is still a lack of data on the efficacy of RTX in patients with chronic kidney disease stage 4 (CKD4) (or an eGFR <30 mL/min per 1.73 m^2).

We present a case of MN negative for serum anti-PLA2R, who previously showed no response to corticosteroids and CTX, and who progressed to CKD4 under tacrolimus (Tac) and relapsed after withdrawal. However, the patient was treated successfully with 4 low doses of RTX therapy. RTX induced prolonged remission and enabled discontinuation of other immunosuppressive agents without substantially increasing the risk of infections and other serious adverse events (SAEs). Importantly, we observed that infusions of low-dose RTX with "the B-cell-driven protocol" were effective in inducing remission without increasing the risk of SAEs. This case and data from literature support the idea that RTX could be used as a first-line therapy for patients at risk of progression because of persistent NS caused by IMN.

Written informed consent was obtained from the patient for the administration of RTX and for the publication of this report.

2. Case report

A 45-year-old man was admitted to another hospital because of newly developed peripheral edema 5 years ago. A urinalysis showed proteinuria with the excretion of 7.86 g/d, and laboratory tests revealed hypoalbuminemia with albumin levels of 22 g/L (day 0). The patient was diagnosed with NS. The patient's renal function was normal (serum creatinine 79.3 μmol/L, eGFR 103 mL/min per 1.73 m^2). Immediately after hospitalization a percutaneous renal biopsy was performed, which disclosed features of stage II MN under light and immunofluorescence microscopy. Initially, the patient was treated with an angiotensin II receptor blocker (valsartan), anticoagulant, prednisone (Pre; 60 mg/day), and intravenous CTX (0.6 g biweekly with a cumulative dose 1.2 g). CTX was stopped because of severe gastrointestinal discomfort and Tac (4 mg/d, 0.05 mg/kg*d) was subsequently started. Four weeks later (2nd month), his clinical condition had not improved. In 2012, he was admitted to our hospital for further investigation.

On admission to our hospital, the patient had a blood pressure of 130/90 mm Hg and a body weight of 95 kg. A physical examination was nonspecific, except for edema of the lower extremities. A urinalysis showed proteinuria with the excretion of 8.25 g/d and 2 to 5 urinary red blood cells per high power field. The laboratory tests revealed a normal serum creatinine concentration of 102 μmol/L (eGFR 76 mL/min per 1.73 m^2), and a serum albumin concentration of 18.1 g/L. Anti-PLA2R antibodies were not detected. The plasma trough concentration of Tac was 4.1 ng/mL. The routine blood tests were normal and immune indices were negative. Markers and imaging tests for tumors were negative. Serum and urine immunoelectrophoresis showed no monoclonal bands. The serum complement titers were within the normal limits. Hepatitis B surface antigen was negative. Antihepatitis B surface, antihepatitis B core, and antihepatitis B antibodies were positive and hepatitis B virus DNA was detected at <100 copies/mL. The dosage of Tac was adjusted to obtain a trough concentration in the range of 3.7 to 7.7 ng/mL. After 4 months of treatment with Tac and prednisone, the clinical condition of the patient had not improved. He received a second percutaneous renal biopsy (5th month) (Fig. 1A–C). Light microscopy showed 25 nonsclerotic glomeruli, and Jones silver staining showed that the glomerular basement membrane (GBM) was thickened with spikes. Tubular atrophy and interstitial fibrosis were moderate, with patchy infiltration of mononuclear cells. Immunofluorescence staining revealed fine granular staining of IgG, and C3 in the capillary walls. Staining

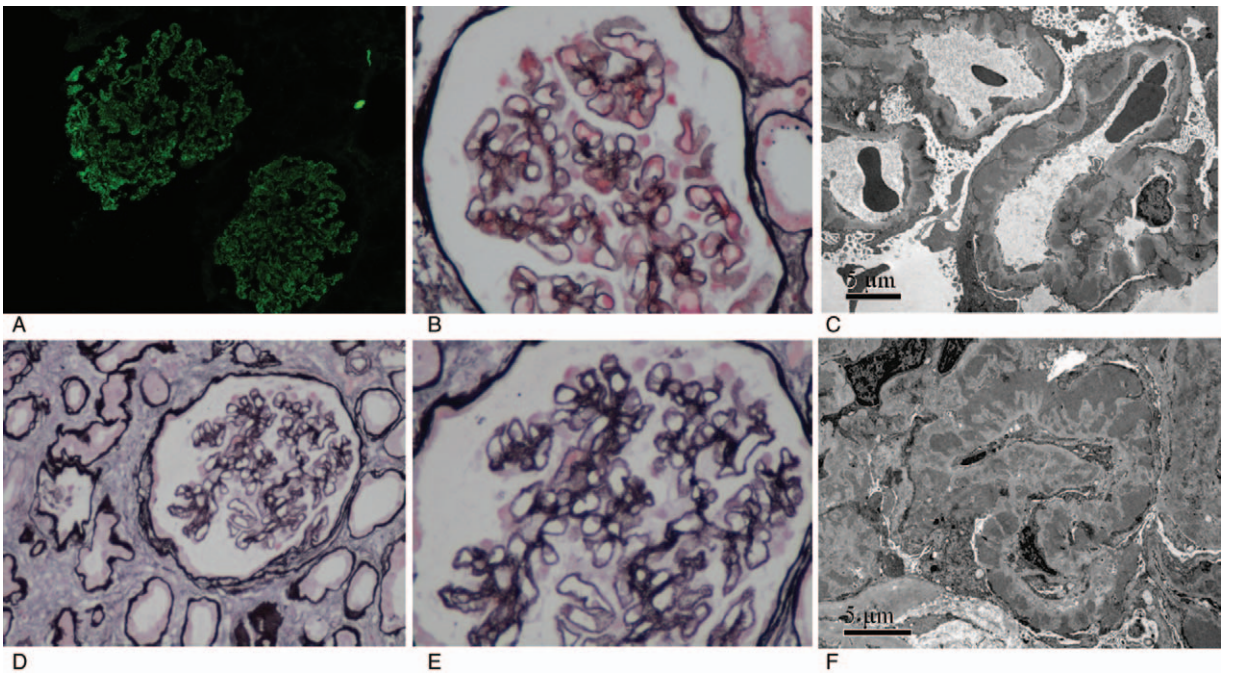

Figure 1. Renal biopsy samples showing membranous nephropathy in the patient. (A–C) In the second biopsy, using light microscopy, 25 glomeruli were observed. Thickening of the glomerular basement membrane was observed. Endocapillary hypercellularity, and extracapillary proliferation were not observed except for mild mesangial proliferation. Tubular atrophy and interstitial fibrosis were moderate with patchy infiltration of mononuclear cells. (D–F) The third biopsy, in contrast to the second biopsy, indicated that glomerular as well as tubulointerstitial scarring had progressed, with increased filtrates of eosinophils. Under light microscopy, 20 glomeruli were observed, including 4 fibrous crescents with sclerosis, 2 cellular crescents, 1 fibrocellular crescent, and 1 segmental sclerosis.

for IgG subclasses showed intense IgG1 and IgG4 staining, and trace amounts of IgG2 and IgG3. By electron microscopy, subepithelial electron dense deposits with diffusely effaced foot processes of podocytes were observed. Therefore, continuation of Tac was prescribed, with a trough concentration in the range of 2.1 to 8 ng/mL. PR was achieved at 6 months, with a serum albumin concentration that increased to 36.9 g/L (9th month). Urinary protein excretion was significantly decreased to 0.66 g/d (15th month). However, the serum creatinine levels began to increase (132 μmol/L, 15th month) without infection or novel medications. Despite tapering the Tac dose to achieve a trough concentration of 2.1 to 2.5 ng/mL, his serum creatinine increased to 202 μmol/L and proteinuria increased to 5.71 g/d. Repeated markers and imaging tests including 18F-fluorodeoxyglucose positron emission tomography-computed tomography for tumors were negative. Thus, Tac was stopped and the patient was switched to oral CTX (50 mg/d, 0.5 mg/kg*d). Although no further increase in serum creatinine was observed (stable for 6 months), NS relapsed with proteinuria increasing to 15.1 g/d and serum albumin decreasing to 29.4 g/L (25th month). In addition, he had an episode of herpes zoster (26th month), and CTX was stopped with cumulative dose of about 9 g. The treatment was then complemented by intermittent intravenous immunoglobulin (IVIG) with 3 pulses of 0.4 g/kg for 3 consecutive, repeated every month for a 3-month period. However, his serum creatinine then increased to 413 μmol/L (30th month), with 30 to 40 urinary red blood cells per high power field. Repeated serological workup for the hepatitis B surface antigen, hepatitis C antibody, antinuclear antibody, antineutrophil cytoplasmic antibody, anti-GBM antibody, and rheumatoid factor were all negative. To exclude crescentic nephritis or IVIG induced "sucrose nephropathy", a third percutaneous renal biopsy was performed (30th month) (Fig. 1D–F). In contrast to the second biopsy, the third biopsy indicated that glomerular, as well as tubulointerstitial scarring had progressed, with increased filtrates of eosinophils. Under light microscopy, 20 glomeruli were observed, including 4 fibrous crescents with sclerosis, 2 cellular crescents, 1 fibrocellular crescent, and 1 segmental sclerosis. Thus prednisone was increase from 5 to 30 mg/d (30th month), but without improvement. His serum creatinine increased to 504 μmol/L, and proteinuria increased to 20.9 g/d. Anti-PLA2R antibodies was still negative. Therefore, he was administered RTX at 180 mg/m^2, half of the suggested dose of 375 mg/m^2 in the standard protocol, considering his previous long-term use of immunosuppressive regimens and deteriorated renal function. The infusion was well tolerated. Circulating B cells decreased from 95 to 1 cell/μL. One month later, his serum creatinine decreased to 360 μmol/L and stabilized. Prednisone was gradually tapered and stopped. He received 3 subsequent administrations (every 2–3 months) of RTX with the same dose depending on his B-cell counts, aiming to remain 0 to 5 cells/μL. At 11 months after the RTX treatment, the patient achieved PR with a 24-h urinary protein output of 2.48 g/d and serum albumin in normal range. The patient then approached CR of nephritic syndrome with an albumin-to-creatinine ratio of 214 mg/g at the last visit (67th month), which was 35 months after the therapy. His serum creatinine was 297 μmol/L, with an eGFR of 20 mL/min per 1.73 m^2. In the recent 3-year follow-up after RTX, NS was not observed; anti-PLA2R antibodies were negative; the serum creatinine levels (range 300–340 μmol/L), blood pressure (108–138/72–88 mm Hg), hemoglobin (117–132 g/L), and body weight (75–80 kg) remained stable. The RTX treatment brought a remarkable improvement in the refractory MN of our patient (Fig. 2).

3. Discussion

We reported a case of refractory IMN progressing to CKD4 that was successfully treated with RTX. In the course of IMN, when the risks of immunosuppressive drugs become unacceptable and futile, there is still no agreed definition of the "no return point."[2,4] However, as suggested by the 2012 KDIGO guidelines, those likely indicators included the presence of severe tubular interstitial fibrosis, tubular atrophy, and glomerular obsolescence on biopsy, persistent elevation of SCr >3.5 mg/dL

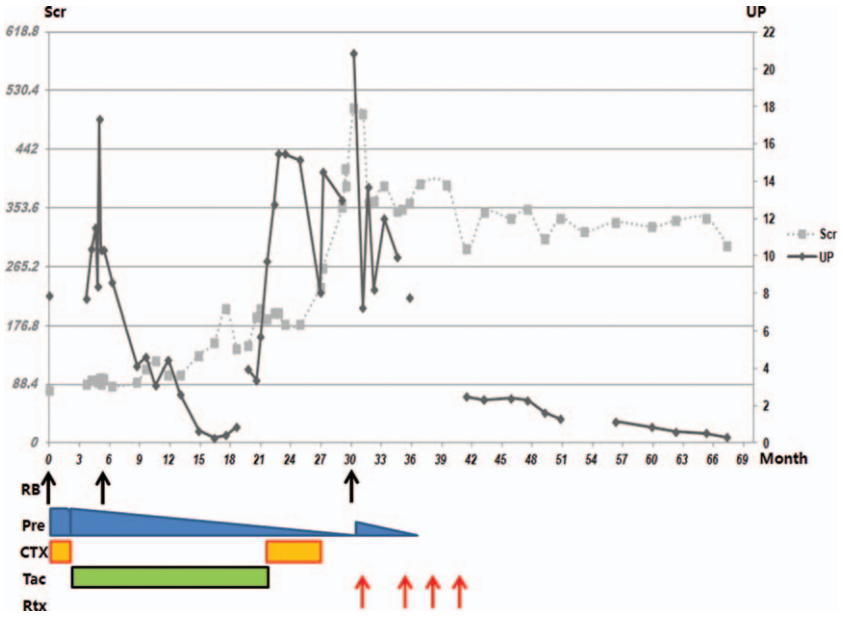

Figure 2. The clinical course of the current case. CTX = cyclophosphamide, Pre = prednisone, RB = renal biopsy, RTX = rituximab, SCr = serum creatinine, Tac = tacrolimus, UP = urine protein. The Y-axes show serum creatinine on the left and urine protein on the right. The X-axis shows the follow-up month.

(>309 μmol/L) (or eGFR <30 mL/min per 1.73 m^2), and reduction in kidney size on ultrasound. RTX-induced remission of proteinuria and stabilization of renal function in this refractory IMN patient with high risk of renal progression.[13] This case strongly suggested that RTX would have promising therapeutic effects, even in patients progressing to CKD4.

The optimal dosage of RTX may vary when it is used to treat different diseases. The appropriate dose, the number of doses, and the appropriate treatment period for MN remain unclear.[2,4,6–12,14–20] In the current case, previous long-term immunosuppression and deteriorated renal function prompted us to be cautious when administering of RTX, using only half of the standard four 375 mg/m^2 doses, and adjusting the treatment period according to the patient's B-cell count (in the B-cell-driven protocol, patients receive a second infusion of RTX only if they had more than 5 B cells per mm^3 of peripheral blood). Several observational studies support the view that low-dose RTX can be effective to treat NS, at a lower cost and with fewer SEAs. However, there are also data suggesting that low-dose RTX obtains remission in <50% of IMN patients. It was suggested that patients with normal renal function, lower proteinuria, lower anti-PLA2R antibodies, and those who responded to previous treatments were the most likely to achieve a response with low-dose RTX (375 mg/m^2 once or twice).[20] However, the follow-up time was limited and the duration of B-cell suppression was not checked. The remarkable reduction in treatment costs, means that the B-cell-driven protocol should facilitate access to RTX even in resource-limited settings.[10–12]

The patient was followed-up regularly for a long period (almost 6 years). The remission of NS was unlikely to have been spontaneous and RTX showed a favorable therapeutic effect. The patient achieved PR at 11 months and CR at 34 months following the infusion of RTX. Although the patient achieved a transient CR when he was treated with combination of Tac and low-dose steroid, it was observed a very short time. In addition, his renal function deteriorated even at a comparatively low plasma trough concentration of Tac after 1 year. The likely reason may be because of glomerular as well as tubulointerstitial scarring. The progression of tubulointerstitial damage may produce poor outcomes. However, the third renal biopsy showed evidence of crescents formation. Renal function was maintained by the administration of CTX; however, a more favorable prognosis of NS was not associated with CTX after a 1-year follow-up interval. In addition, considering the side-effects of infection (herpes zoster), continuation of CTX was another concern; however, the patient's the renal function progressively deteriorated. The condition was unchanged until RTX was adopted as the second-line therapy. RTX was well tolerated and the patient's renal function and NS improved. He had no edema and his dosage of corticosteroids could be discontinued. After a 5-year follow-up, his renal function is stable, and even slightly increased.

In summary, we presented patient with IMN that progressed to CKD4, which was refractory to alkylating agents and calcineurin inhibitors. The patient achieved CR with low-dose RTX, which suggested RTX as an economical and effective treatment for IMN.

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Author contributions

XJZ and FDZ were involved in the acquisition and analysis of data; wrote the manuscript; XJZ, SXW, MHZ, and FDZ revised the manuscript critically for important intellectual content; FDZ supervised the whole research group and has given the final approval of the version to be published.
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