Primary membranous nephropathy (PMN) is an antibody-mediated autoimmune glomerular disease. The incidence of PMN is 10/million populations/year and mostly adult patients present with nephrotic syndrome (NS). Moreover, the patients with persistent NS progressed to end-stage renal disease in 5–15 years.

A number of studies proved the efficiency of immunosuppressant. Combinations of corticosteroid with alkylating agents or calcineurin inhibitor (CNI) have been proved to be effective to induce remission of PMN with persistent heavy proteinuria. However, there are still 30% PMN patients refractory or dependent to immunosuppressant. A few studies showed rituximab (RTX) may be effective to treat refractory PMN with the protocol varies. The doses of 375 mg/m² every week for 4 weeks and 1 g fixed dose with a repeat dose in 2 weeks were commonly used. Nonetheless, some studies about anti-neutrophil cytoplasmic antibody-associated vasculitis, rheumatoid arthritis (RA), autoimmune cytopenias, focal segmental glomerulosclerosis, and so on showed a low-dose or single-dose RTX can be effective on proteinuria remission and peripheral blood B-cells elimination. Hereon, we present a 51-year-old refractory PMN patient who was induced complete remission by a low-dose RTX.

A 51-year-old Chinese man was admitted to our hospital complaining persistent edema of lower extremities for 2 years. He was diagnosed as NS and received renal biopsy in another hospital 2 years ago. Pathologic study showed membranous nephropathy [Figure 1]. A full dose of ACE inhibitors, prednisolone in combination with cyclophosphamide (“Ponticelli Regimen”) for 6 months failed to induce remission. Diltiazem were added to increase tacrolimus trough concentration to the range of 5.5–9.8 ng/mL. After 7-month treatment, the patient had not improved and was admitted to our inpatient department.

Physical examination was nonspecific except edema of lower extremities. The urine protein was 6.5 g/d, urine protein-to-creatinine (Cr) ratio was 0.663 g/mmol Cr, serum Cr was 13.8 mg/L, and serum albumin was 28 g/L. The blood lipid levels suggested hyperlipidemia. The plasma trough concentration of tacrolimus was 8.7 ng/mL. The CD19CD5 B-cells was 314 cell/μl (12.20%). The blood routine tests were normal and immune indices were negative. Markers and imaging tests for tumor were normal. Hepatitis B surface antigen was negative. Anti-hepatitis B core, anti-hepatitis B e antibody were positive and hepatitis B virus-DNA <10³ copies/mL. After informed consent was written from this patient, RTX 100 mg intravenous infusion was added to the former immunosuppressive protocol. To minimize the infusion reactions, dexamethasone 5 mg was injected intravenously before RTX. Serum Cr, serum albumin, urine protein-to-Cr, and other clinical parameters were measured every 2 weeks during the first 2 months, and 2–4 weeks thereafter.

One week after RTX treatment, there was a rapid clearing of circulating CD19CD5 B-cells from 314 to 1 cell/μl (from...
12.20% to 0.10%) and remained 1–8 cell/μl so far. Six weeks later, the urine protein was 3.06 g/d, the urine protein-to-Cr ratio reduced to 0.34 g/mmol Cr along with increasing serum albumin and decreased serum cholesterol. The adverse events were not observed in the 1st month. In the 2nd month, the patient experienced a community-acquired pneumonia (CAP) and recovered soon. At 6 months after the RTX treatment, the patient achieved partial remission with a urine protein-to-Cr ratio of 0.310 g/mmol Cr and the serum albumin, serum Cr were in normal rang. Then the patient achieved complete remission with a urine protein-to-Cr ratio of 0.025 g/mmol Cr and 24 h urinary protein of 0.23 g/d at the last visit of 13 months after the therapy. The RTX treatment brought a remarkable improvement in refractory MN of our patient [Figure 2].

RTX is a B-cell depleting monoclonal antibody targets at CD20, a transmembrane protein expressed on virtually all B-cells except when B-cells differentiate into antibody secreting plasma cells. RTX binding to CD20 initiates B-cells apoptosis, complement dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. RTX was first used to treat non-Hodgkin lymphoma in 1997 and be confirmed to be effective in RA, idiopathic thrombocytopenic purpura, pemphigus, and so on.

RTX was also gradually used in a wide variety of glomerular diseases including lupus nephritis, IgA nephropathy, minimal change disease and focal segmental glomerulosclerosis, fibrillary glomerulonephritis, and membranous nephropathy. Recently, a systematic review[1] which searched the available data on RTX therapy for MN from inception to August 1, 2008, recruited 21 case reports or case series and 85 patients without control. Among the 21 reports, the patients were given RTX at a high dose of 375 mg/m² once weekly for 4 weeks or 1 g RTX on days 1 and 15. RTX treatment can be repeated if the circulating B-cells and proteinuria not reach the remission rang (>3.5 g/d or <50% reduction in proteinuria). The results showed RTX has the similar remission rate and less adverse events compared with conventional therapy. The adverse effects were mostly due to infusion reactions. Ruggenenti et al.[2] observed 100 consecutive idiopathic membranous nephropathy patients for at least 6 months after RTX therapy, 65% remission was achieved over a median of 7.1 months and eGFR was significantly increased. The mild and transient adverse events such as allergy, bronchial wheezing, cutaneous rash, and hypotension were observed in 28 patients who were recovered with heteropathy. It was worth noting that 18 patients had a relapse in a median time of 42 months (range from 7 to 116 months) and 11 got remission after a second course of RTX therapy. It also reported that the longer follow-up time, the more remission we may observe.

Optimal dosage of RTX may vary when it is used to treat different diseases. Current protocol of RTX was mainly derived from lymphoma and so on. Lymphoma is a lymphoproliferative disease with tumor burden. Renal and rheumatologic diseases are not lymphoproliferative disorders. Therefore, it seems reasonable to use lower dose RTX to treat nonlymphoproliferative diseases with less adverse effects. In fact, it was shown that lower dosage RTX can also deplete B-cell significantly. There were few studies demonstrating effects of lower dose and shorter course of RTX. A systematic review and meta-analysis showed that low-dose RTX has similar effectiveness and met noninferiority criteria for most primary outcomes in RA. The 2 × 500 mg rather than 2 × 1000 mg should be the standard RTX regimen for RA.[3] Kurosu et al.[4] presented

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**Figure 1:** Pathology of renal biopsy. (a) electron microscopy: Subepithelial deposits of immunocomplex, thickening of glomerular basement membrane, effacement of podocyte foot. (b) Light microscopy: Inflammatory cells infiltration and part of the renal tubular atrophy. (c) Immunofluorescence: granular capillary wall deposition pattern of IgG (+++), IgA (++), C3 (+++) and C1q (+).

**Figure 2:** Time line of clinical response to rituximab. Before the therapy, the patient’s urine protein-to-creatinine ratio was always >0.6 g/mmol Cr. 100 mg rituximab was given to him combining with the former immunosuppressive protocol at 7 months. Six weeks later, the urine protein-to-creatinine ratio reduced to 0.34 g/mmol creatinine along with increasing serum albumin. At 13 months and 20 months the patient achieved partial remission and complete remission, respectively. PCR: Urine protein-to-creatinine ratio. TP: Total serum protein. Alb: Serum albumin.
a 23-year-old man with steroid-resistant NS due to minimal change disease. A single dose RTX of 375 mg/m² depleted CD19/20 positive B-cells rapidly to an undetectable level and the patient got a complete remission. Six months later, a second dose was given to the patients when there was a recovery of B-cell counts and the patient maintained a remission in the 1 year follow-up. Cho et al.\cite{5} treated a recurrent focal segmental glomerulosclerosis patient with once 100 mg of RTX and resulted in B-cell reducing to 0% 15 d later and full remission of proteinuria during the following 18 months. These cases suggest that low-dose RTX can be equally effective to treat NS with less cost and fewer adverse side effects. However, there was little study about low-dose RTX therapy for MN.

The major clinical manifestation of the patient in our study was NS proteinuria. The renal function was normal. The tests for antinuclear antibody, double-stranded DNA, infections (hepatitis B and hepatitis C), malignancies were in normal range. Renal biopsy revealed electron dense deposits in the subepithelial space with an electron microscopy. The patient was diagnosed with PMN and presented persistent NS refractory to the “Ponticelli regimen” and CNI. A single dose of 100 mg of RTX resulted in a rapidly decline of CD19CD5 B-cells 1 week later and a gradual reduction in proteinuria. The patient reached the complete remission at the last visit (13 months after RTX treatment). This is the first case about adult PMN treated by low-dose RTX. This case confirms the effects of RTX on PMN and suggests economical and effective treatment to PMN although more evidences are needed to confirm the effect of low-dose RTX in PMN. Nevertheless, attention should be paid on the adverse events of low-dose RTX for our patient got a CAP after the RTX treatment.

In summary, we presented a PMN patient refractory to alkylating agent and CNI achieved complete remission with low-dose RTX, which suggests economical and effective treatment to PMN.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Bomback AS, Derebail VK, McGregor JG, Kshirsagar AV, Falk RJ, Nachman PH. Rituximab therapy for membranous nephropathy: A systematic review. Clin J Am Soc Nephrol 2009;4:734-44. doi: 10.2215/CJN.05231008.
2. Ruggenenti P, Cravedi P, Chianca A, Perna A, Ruggiero B, Gaspari F, et al. Rituximab in idiopathic membranous nephropathy. J Am Soc Nephrol 2012;23:1416-25. doi: 10.1681/ASN.2012020181.
3. Bredemeier M, de Oliveira FK, Rocha CM. Low-versus high-dose rituximab for rheumatoid arthritis: A systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2014;66:228-35. doi: 10.1002/acr.22116/abstract.
4. Karuso N, Sugiura H, Iwasaki C, Asamiya Y, Kojima C, Moriyama T, et al. Successful use of single-dose rituximab for the maintenance of remission in a patient with steroid-resistant nephrotic syndrome. Intern Med 2009;48:1901-4. doi: 10.2169/internalmedicine.48.2435.
5. Cho JH, Lee JH, Park GY, Lim JH, Kim JS, Kang YJ, et al. Successful treatment of recurrent focal segmental glomerulosclerosis with a low dose rituximab in a kidney transplant recipient. Ren Fail 2014;36:623-6. doi: 10.3109/0886022X.2014.882238.