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【 CASE REPORT 】

Long-term Successful Treatment of Rituximab for Steroid-resistant Minimal Change Nephrotic Syndrome and Idiopathic Thrombocytopenic Purpura

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Abstract:
A 22-year-old woman had been diagnosed with idiopathic thrombocytopenic purpura (ITP) 5 years earlier. After undergoing splenectomy, she relapsed frequently following prednisolone tapering. She was complicated with minimal change nephrotic syndrome (MCNS) while taking 20 mg of prednisolone. Despite treatment with prednisolone, cyclosporin and low-density lipoprotein-apheresis, MCNS and ITP did not improve. We added rituximab in 4 weekly infusions of 375 mg/m^2. MCNS and ITP were in complete remission. After administering rituximab once, all medicines were discontinued. No relapse had occurred by 50 months following the first rituximab administration. Rituximab affects steroid-resistant MCNS and ITP for a long time without complications.

Key words: minimal change nephrotic syndrome, idiopathic thrombocytopenic purpura, rituximab, regulatory T cell

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Introduction

Rituximab (RTX) is a monoclonal antibody for CD20, which is a surface molecule specific to B cells, excluding plasma cells (1). The effectiveness of RTX has been reported in cases of idiopathic thrombocytopenic purpura (ITP) (2) and childhood-onset steroid-dependent or frequently relapsing nephrotic syndrome (3). However, the effects of RTX on steroid-resistant minimal change nephrotic syndrome (MCNS) in adults are controversial (4).

We herein report a case of the long-term efficacy of RTX for MCNS and ITP that were resistant to treatments including steroids.

Case Report

The patient was a 22-year-old woman. She suffered from menorrhagia, and her platelet count had been in the 10,000/μL range when she was 17 years old. There were no abnormalities in the morphology of her blood cells or myelogram, so she was diagnosed with ITP. After treatment was started with 55 mg (1 mg/kg) prednisolone (PSL), her platelet count improved to over 150,000/μL. However, ITP recurred when the PSL dose was reduced to 8 mg. Serum anti-*Helicobacter pylori* antibody was negative. Despite undergoing splenectomy, ITP recurred upon administering 9 mg PSL and 25 mg PSL following PSL tapering after the dose of PSL had been increased. Eltrombopag (12.5 mg) was added in addition to 25 mg of PSL. Her PSL dose was reduced to 20 mg one month later. After another month had passed, she developed vomiting and a slight fever and showed sudden leg edema. She had no remarkable medical history or allergies. As for her family history, her elder sister suffered from Graves' disease.

On admission, her body temperature was 37.4℃, blood pressure was 126/76 mmHg, pulse was 86 bpm, and SpO_2 was 94% (room air). A physical examination showed diffuse pitting edema. We did not confirm any subcutaneous bleeding or submucosal hemorrhaging. Her urinary protein level

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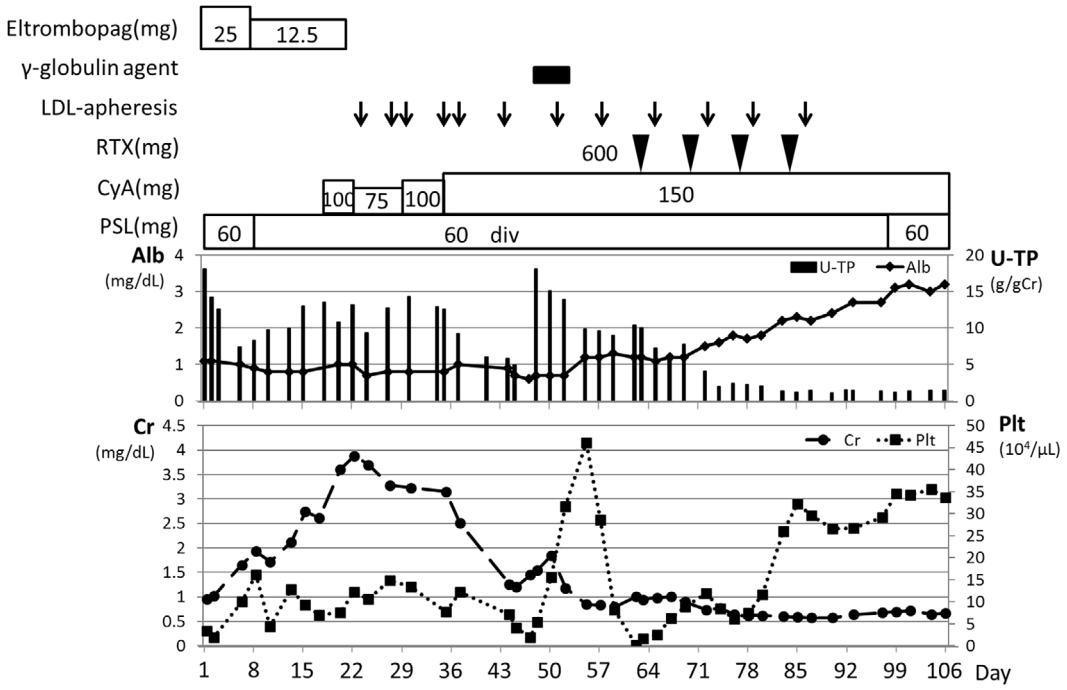

Figure 1. **Clinical course of the patient. Alb: albumin, Cr: creatinine, CyA: cyclosporin, div: intravenous drip, LDL-apheresis: low-density lipoprotein-apheresis, Plt: platelet count, PSL: prednisolone, RTX: rituximab, U-TP: urinary protein**

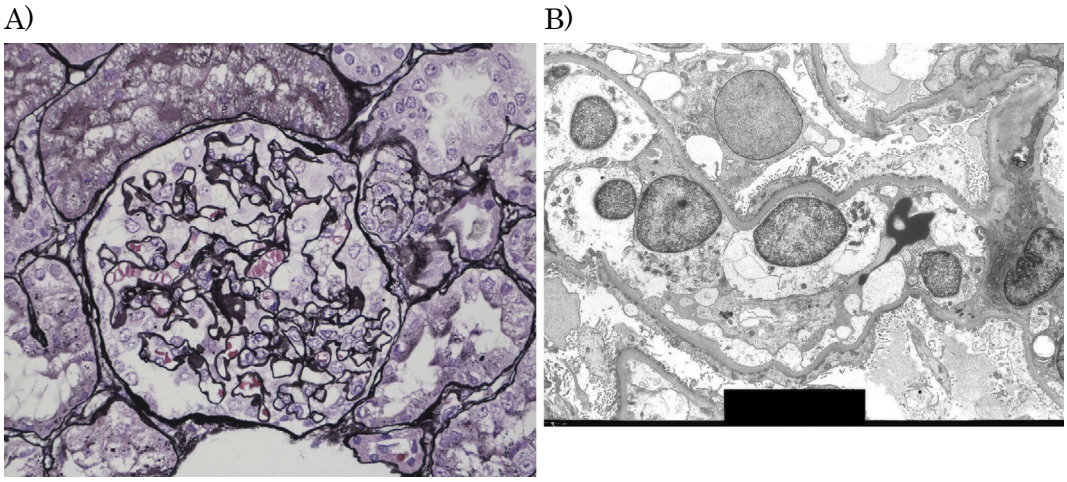

Figure 2. **Renal biopsy findings. A: Light microscopy shows minor glomerular abnormalities. (×400, periodic acidmethenamine-silver stain). B: Electro-micrograpy shows foot process effacement (×4,000).**

was 18.04 g/gCr, her selectivity index was 0.09, and she showed hematuria at 1-4 red blood cells per high-power field. We also confirmed epithelial casts at 10-19 per whole field. Her serum platelet count was 34,000/μL, albumin 1.1 g/dL, creatinine 0.96 mg/dL, urea nitrogen 24 mg/dL, total protein 3.7 g/dL, and total cholesterol 286 mg/dL. Anti-platelet antibody was present at 195 ng/10^7 cells. Her anti-nuclear antibody was 320-fold, and her anti-SSA antibody was 125 INDEX. However, she did not suffer from dry eye or dry mouth symptoms, so a diagnosis of Sjögren's syndrome was not made.

We initiated PSL 60 mg (1 mg/kg) from the second day, after which her urinary protein levels decreased to approximately 8 g/gCr (Fig. 1). A renal biopsy was performed on the 16th day (Fig. 2). Light microscopy revealed that all 12 glomeruli had minor glomerular abnormalities. In the immunofluorescence studies, IgA, IgG, IgM, C3, C1q, and fibrinogen were all negative. Electron micrography showed foot process effacement. The pathological diagnosis was MCNS.

We added cyclosporin (CyA) 100 mg (1.5 mg/kg) from the 18th day. Her blood concentration of CyA measured 2 hours after administration was 1,322 ng/mL. We therefore adjusted the dosage of CyA so that the blood concentration

of CyA was 600-900 ng/mL. We also added low-density lipoprotein-apheresis, but her urinary protein levels remained approximately 10 g/gCr, and her serum albumin was 1.0 g/dL. As for her platelet count, it increased temporarily after the administration of a γ-globulin agent but once again decreased to approximately 5,000/μL. From the 63rd day, RTX at 600 mg (375 mg/m^2) was administered once a week, for a total of 4 times. Her urinary protein level was <3.5 g/gCr on the 74th day, and her platelet count was 260,000/μL on the 83rd day. The serum albumin value was >3.0 g/dL on the 99 th day. Her urine protein level remained ≥1.0 g/gCr, so we continued PSL at 60 mg. She was discharged from the hospital with a reduced PSL dose of 40 mg on the 107th day.

Even after her discharge, we continued reducing the PSL and CyA dosages. Her urinary protein level was <0.3 g/gCr at 6 months after the first administration of RTX. Four months later, her CD19 level had increased to over 1%, and her platelet count decreased to 130,000/μL, so we administered RTX once at the same dosage. Eight months later, her CD19 level had increased again to over 1%, but there was no exacerbation of her platelet count or urinary protein. We were able to discontinue all medicines 14 months later. Neither MCNS nor ITP have recurred as of 50 months after the first administration of RTX.

Discussion

The patient followed a benign course in the long term after RTX successfully treated MCNS and ITP that were resistant to treatment, including PSL. There has only been one case report of an improvement in both ITP and nephrotic syndrome following the administration of RTX, for which the underlying disease of nephrotic syndrome was steroid-dependent focal segmental glomerular sclerosis (5). The mechanism and long-term effects of RTX for steroid-resistant nephrotic syndrome (SRNS) in adults and steroid-resistant ITP have not yet been established. The data of a randomized controlled trial did not support the administration of RTX to children with idiopathic nephrotic syndrome resistant to PSL and calcineurin inhibitors (6). Adult patients with ITP who relapse frequently despite receiving appropriate treatments, including splenectomy, account for <10% of all cases (7). These patients in whom the platelet count improved from <30,000/μL to >150,000/μL after the administration of RTX account for only 26% of the total population (7). Our patient, in whom both ITP and SRNS improved after the administration of RTX, is thus a useful case for studying which patient groups respond well to the effects of RTX.

While the combination of MCNS and ITP is rare, there are diseases that combine both conditions, such as immune dysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome (IPEX syndrome) (8, 9). In IPEX syndrome, various autoimmune diseases are caused by a lack of functional regulatory T cells (Tregs) due to a Foxp3 genetic mutation (9). Our patient developed MCNS when controlling ITP became difficult, so the presence of a common cause can be assumed. Furthermore, given the presence of autoantibodies, such as anti-SSA antibody, and her family medical history of Graves' disease, we suspected the possibility of dysfunction of Tregs.

In cases of MCNS (10) and ITP (11), RTX reportedly improves the function of Tregs and the condition of the disease. In the present case, we did not confirm a clear decrease in the Tregs ratio using flow cytometry performed 22 months after the first RTX administration. It is possible that the ratio did not decrease because remission had already been reached. However, there has also been a report indicating that the percentage of Tregs is similar between healthy controls and MCNS patients despite a decrease in the function of Tregs in patients with MCNS in relapse (12). We therefore believe it necessary to measure not only the percentage but also the function. The involvement of Epstein-Barr virus as a common cause of nephrotic syndrome (13) and thrombocytopenia (14) has also been reported. However, IgG antibody, IgM antibody, and Epstein-Barr nuclear antigen as well as virus DNA were all negative when she developed MCNS. Regarding the effects of RTX on MCNS and ITP separately, it has been reported that when RTX is used for MCNS, the drug suppresses urinary protein by directly acting on sphingomyelin phosphodiesterase acid-like 3b of podocytes (15) or resets autoimmunity by depleting B cells with RTX and then reconstructing them (16). As for its action on ITP, RTX influences the control of the immune response, improving the elevation of the Th1/Th2 ratio due to ITP (17). However, in the present case, we noted significant improvement in both MCNS and ITP after administering RTX, so we considered that RTX had exerted an effect on a common cause of the two diseases, such as improving the Treg function.

In the present study, the effect of RTX on MCNS and ITP lasted for a relatively long term of 50 months. In a report in which SRNS patients were administered 375 mg/kg of RTX once a week for a total of 4 times, including MCNS patients, who accounted for 51.5% of that study's population, the proportion in whom the urinary protein level became < 0.2 g/gCr by 6 months was 27.2%, and the proportion in whom the urinary protein level became <0.2 g/gCr by 21.5± 11.5 months was 21.2% (18). CD19 is reported to be useful for monitoring the effect of RTX administration (19). However, whether or not relapse will occur following an increase in CD19 remains controversial. In pediatric patients with steroid-dependent nephrotic syndrome who experienced efficacy of RTX in the long term, the switched memory B cells were reconstructed slowly after existing memory B cells had been eliminated by RTX (20), or the B cells were reconstructed slowly after the administration of RTX (21). Other reports have suggested that long-term remission can be obtained by the expansion of Tregs and regulatory B cells (22). Regarding the long-term prognosis of ITP after administering RTX, in a report on 72 adult ITP patients with a response to RTX in 4 weekly infusions of 375 mg/m^2

for 1 year, 21% of the total population maintained a treatment-free response for 5 years (2). The factors influencing a long-lasting effect were a long duration of decreased B cells and the responder achieving a platelet count increase to over 150,000/μL after receiving RTX (2). A previous report showed that adult patients with ITP who continued to experience efficacy of RTX for a median of 57 (39-69) months tended to be younger or have a shorter duration between their diagnosis and the start of RTX (23). However, it is possible that only the natural history of ITP was observed. No definitive factors exist for predicting the long-term prognosis.

Among ITP patients who were administered RTX, the ratio of severe or fatal side effects was 3.7%, and the ratio of death was 2.9% (24). There are some risks associated with the administration of RTX. Among patients with idiopathic membranous nephropathy, the evaluation of Tregs may be useful for predicting an early response to RTX (25). SRNS and ITP are heterogeneous diseases. Therefore, the continued accumulation of cases with both SRNS and ITP is desired in order to understand which patients are expected to respond best to the effect of RTX.

The authors state that they have no Conflict of Interest (COI).

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References

1. Grillo-López AJ, Hedrick E, Rashford M, Benyunes M. Rituximab: ongoing and future clinical development. Semin Oncol **29**: 105-112, 2002.
2. Patel VL, Mahévas M, Lee SY, et al. Outcomes 5 years after response to rituximab therapy in children and adults with immune thrombocytopenia. Blood **119**: 5989-5995, 2012.
3. Iijima K, Sako M, Nozu K, et al. Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet **384**: 1273-1281, 2014.
4. Sinha A, Bagga A. Rituximab therapy in nephrotic syndrome: implications for patients' management. Nat Rev Nephrol **9**: 154-169, 2013.
5. Benz K, Dötsch J, Rascher W, Stachel D. Change of the course of steroid-dependent nephrotic syndrome after rituximab therapy. Pediatr Nephrol **19**: 794-797, 2004.
6. Magnasco A, Ravani P, Edefonti A, et al. Rituximab in children with resistant idiopathic nephrotic syndrome. J Am Soc Nephrol **23**: 1117-1124, 2012.
7. Kojouri K, George JN. Recent advances in the treatment of chronic refractory immune thrombocytopenic purpura. Int J Hematol **81**: 119-125, 2005.
8. Hashimura Y, Nozu K, Kanegane H, et al. Minimal change nephrotic syndrome associated with immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome. Pediatr Nephrol **24**: 1181-1186, 2009.
9. Wildin RS, Smyk-Pearson S, Filipovich AH. Clinical and molecular features of the immunodysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome. J Med Genet **39**: 537-545, 2002.
10. Kimata T, Tsuji S, Kino J, Kitao T, Yamanouchi S, Kaneko K. Close association between proteinuria and regulatory T cells in patients with idiopathic nephrotic syndrome. Pediatr Nephrol **28**: 667-669, 2013.
11. Stasi R, Cooper N, Del Poeta G, et al. Analysis of regulatory T-cell changes in patients with idiopathic thrombocytopenic purpura receiving B cell-depleting therapy with rituximab. Blood **112**: 1147-1150, 2008.
12. Araya C, Diaz L, Wasserfall C, et al. T regulatory cell function in idiopathic minimal lesion nephrotic syndrome. Pediatr Nephrol **24**: 1691-1698, 2009.
13. Dossier C, Jamin A, Deschênes G. Idiopathic nephrotic syndrome: the EBV hypothesis. Pediatr Res **81**: 233-239, 2017.
14. Tanaka M, Kamijo T, Koike K, et al. Specific autoantibodies to platelet glycoproteins in Epstein-Barr virus-associated immune thrombocytopenia. Int J Hematol **78**: 168-170, 2003.
15. Fornoni A, Sageshima J, Wei C, et al. Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis. Sci Transl Med **3**: 85ra46, 2011.
16. Tanaka Y. Treatment of inflammatory immunologic disease 4. B cell targeting therapy using the anti-CD20 antibody rituximab in inflammatory autoimmune diseases. Intern Med **46**: 1313-1315, 2007.
17. Stasi R, Del Poeta G, Stipa E, et al. Response to B-cell depleting therapy with rituximab reverts the abnormalities of T-cell subsets in patients with idiopathic thrombocytopenic purpura. Blood **110**: 2924-2930, 2007.
18. Gulati A, Sinha A, Jordan SC, et al. Efficacy and safety of treatment with rituximab for difficult steroid-resistant and -dependent nephrotic syndrome: multicentric report. Clin J Am Soc Nephrol **5**: 2207-2212, 2010.
19. Jones JD, Hamilton BJ, Rigby WF. Rituximab mediates loss of CD19 on B cells in the absence of cell death. Arthritis Rheum **64**: 3111-3118, 2012.
20. Colucci M, Carsetti R, Cascioli S, et al. B cell reconstitution after rituximab treatment in idiopathic nephrotic syndrome. J Am Soc Nephrol **27**: 1811-1822, 2016.
21. Hogan J, Dossier C, Kwon T, et al. Effect of different rituximab regimens on B cell depletion and time to relapse in children with steroid-dependent nephrotic syndrome. Pediatr Nephrol **34**: 253-259, 2019.
22. Hu CY, Rodriguez-Pinto D, Du W, et al. Treatment with CD20-specific antibody prevents and reverses autoimmune diabetes in mice. J Clin Invest **117**: 3857-3867, 2007.
23. Medeot M, Zaja F, Vianelli N, et al. Rituximab therapy in adult patients with relapsed or refractory immune thrombocytopenic purpura: long-term follow-up results. Eur J Haematol **81**: 165-169, 2008.
24. Arnold DM, Dentali F, Crowther MA, et al. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. Ann Intern Med **146**: 25-33, 2007.
25. Rosenzwajg M, Languille E, Debiec H, et al. B- and T-cell subpopulations in patients with severe idiopathic membranous nephropathy may predict an early response to rituximab. Kidney Int **92**: 227-237, 2017.