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【 CASE REPORT 】

Successful Pregnancies in a Patient with Childhood-onset Steroid-dependent Nephrotic Syndrome during Rituximab Maintenance Therapy

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Abstract:
There are an increasing number of reports on the safe use of rituximab (RTX), a chimeric anti-CD20 monoclonal antibody, in pregnant women with hematological malignancies or refractory autoimmune diseases. In 2014, the use of RTX for patients with complicated steroid-dependent nephrotic syndrome (SDNS) was approved in Japan. We herein report a woman with childhood-onset complicated SDNS due to focal and segmental glomerulosclerosis, who had two successful pregnancies while receiving RTX maintenance therapy. No adverse complications were observed during the pregnancies, and she delivered healthy newborns. This case suggested that RTX may be used safely in pregnant women complicated with SDNS.

Key words: childhood-onset steroid-dependent nephrotic syndrome, focal segmental glomerulosclerosis, pregnancy, rituximab, safety use

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Introduction

Nephrotic syndrome (NS) is a condition resulting from massive glomerular proteinuria, and it is associated with hypoalbuminemia, hypercholesterolemia, and edema. Focal segmental glomerulosclerosis (FSGS) accounts for approximately 20% of childhood NS cases in the United States (1) and approximately 10% of NS cases in Japan (2), and it is a common glomerular disorder leading to end-stage renal failure (1, 3). Therapy for FSGS should be individualized based on factors particular to the patient, such as age and comorbidities (4). The commonly used agents for children with refractory FSGS are prednisolone (PSL), cyclosporine A (CyA), and mizoribine (MZR) (4, 5). A systemic review by Kronbichler et al. (6) suggested that rituximab (RTX) is effective in reducing the number of relapses and sparing immunosuppression in frequently relapsing and steroid-dependent nephrotic syndrome (SDNS) due to minimal change in disease and FSGS. Based on the results of a multicenter trial (7), the use of RTX for the treatment of complicated SDNS was approved in Japan in 2014 (8).

Women with childhood-onset complicated SDNS may face pregnancy problems. In the present report, we describe two pregnancies that occurred during RTX maintenance therapy in such a case.

Case Report

A Japanese girl developed NS at 9 years of age. The diagnosis of FSGS was made based on renal biopsy findings. Light microscopy showed global sclerosis in 14 of 36 glomeruli. Glomerulomegaly and adhesions were observed in some of the 22 remaining glomeruli; 2 glomeruli showed segmental areas of sclerosis and hyalinosis in the perihilar segment (Fig. 1). Mesangial hypercellularity or podocyte hypertrophy was not observed. There was mild tubular atrophy and interstitial fibrosis around the sclerotic glomeruli. Immunofluorescence microscopy showed granular IgM staining in the mesangial areas and along the glomerular capillary

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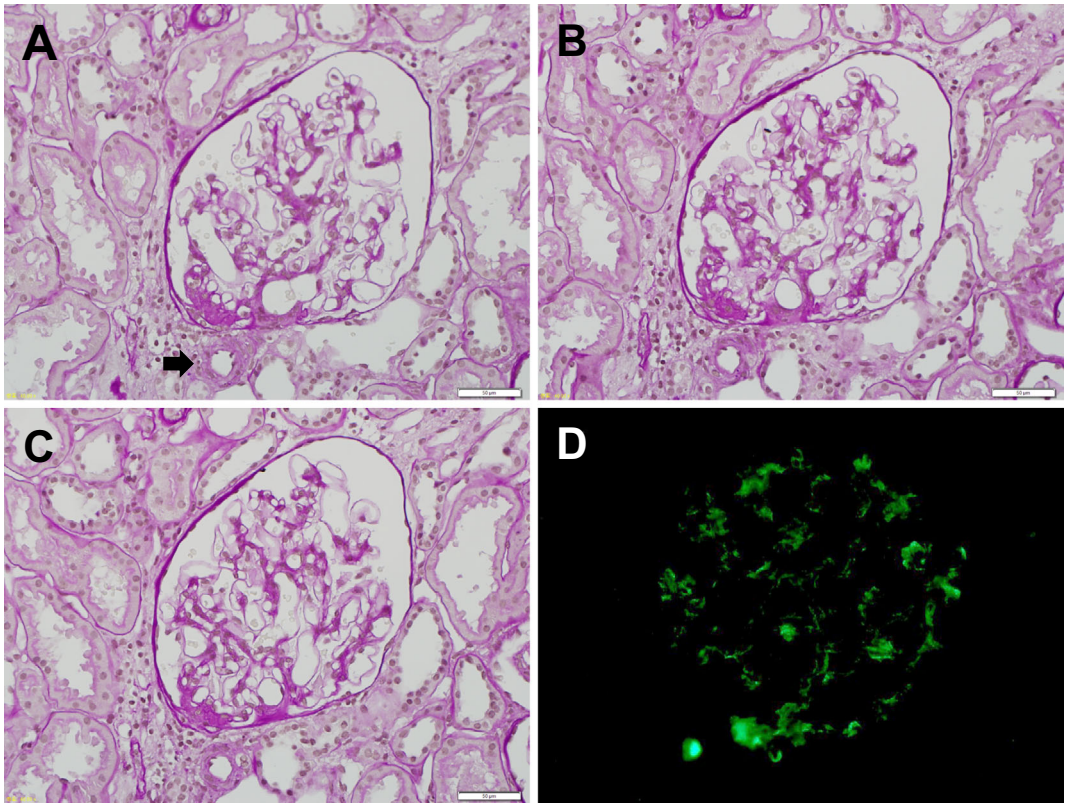

Figure 1. **Renal biopsy findings. A-C: Light microscopy of serial sections of a glomerulus, showing segmental areas of sclerosis and hyalinosis in the perihilar segment (periodic acid-Schiff staining, original magnification ×400). The arrow indicates an arteriole. The scale bars represent 50 μm. D: Immunofluorescence microscopy of a glomerulus, showing IgM deposits (original magnification ×400).**

walls (Fig. 1). These findings were consistent with those of a FSGS perihilar variant in the Columbia classification that had been proposed after renal biopsy of this patient (9). She was treated with oral PSL (60 mg/day) and CyA. Thereafter, remission was achieved. However, discontinuing PSL resulted in relapses at the ages of 12 and 16 years, requiring long-term therapy with oral PSL, CyA, and MZR. After 22 years of age, she was treated only with CyA. At 24 years of age, monotherapy with CyA resulted in a relapse, requiring high to middle doses of oral PSL. She also developed steroid-induced psychosis. At that time, her blood pressure was 116/73 mmHg. A physical examination showed pitting edema in the legs. The results of laboratory tests are shown in Table 1.

As shown in Fig. 2, RTX therapy (375 mg/m^2 weekly for 4 weeks) was introduced, in addition to treatment with PSL, CyA, and MZR. A significant improvement in NS was seen after introducing RTX therapy with a low dose of oral PSL. During maintenance therapy, single-dose infusions of RTX (375 mg/m^2) were administered at intervals of about 6 months with reference to the previously reported protocol for adult patients with SDNS (10), except after such patients became pregnant. The course of the peripheral blood CD19$^+$ B-cell counts and serum levels of IgG are shown in Table 2.

At 25 years of age, she got married and desired to have children. Because she did not wish to receive immunosuppressive therapy with CyA and MZR, these agents were discontinued. Based on evidence concerning RTX therapy before and during pregnancy (11), the potential risks and benefits of the RTX therapy (safety, steroid-sparing effect, and recurrence prevention) were discussed with the patient. At 26 years of age, she had a miscarriage at 9 weeks, 3 months after the RTX maintenance administration. A chromosomal analysis showed monosomy X. This abnormality seemed not to be related to RTX treatment, because rates of miscarriage and congenital malformation in 153 RTX-exposed pregnancies were similar to expected rates in the general population (11). Four months after RTX maintenance administration, she was found to be 5 weeks pregnant. She decided to continue the pregnancy. No complications were observed during the pregnancy, and recurrence of NS did not occur without maintenance RTX administration. She delivered a healthy baby girl (Apgar score 9/9, birth weight 2,932 g) at 38 weeks. After confirming that there was nothing wrong with her at the one-month postpartum check-up, RTX maintenance therapy was restarted. The following year, 1 month after the start of RTX maintenance administration, she was found to be 9 weeks pregnant. She again decided to continue the pregnancy. No complications were observed during the pregnancy, and recurrence of NS did not occur without maintenance RTX administration. She delivered a healthy baby boy (Apgar score 8/9, birth weight 3,117 g) at 39

Table 1. Laboratory Data at the Time of Initiation of Rituximab Therapy.

Urinalysis		Blood chemistry	
Protein	4+	Aspartate aminotransferase	24 IU/L
	9.1 g/g creatinine	Alanine aminotransferase	11 IU/L
Occult blood	±	Lactate dehydrogenase	209 IU/L
Red blood cells	1-4/high power field	γ-glutamyltransferase	16 IU/L
β2-microglobulin	65 μg/L	Total protein	5.5 g/dL
NAG	5.3 IU/L	Albumin	2.6 g/dL
Blood count		Blood urea nitrogen	9.1 mg/dL
White blood cells	7,300 /μL	Creatinine	0.58 mg/dL
Neutrophils	87.1 %	Total cholesterol	390 mg/dL
Eosinophils	0.1 %	Triglyceride	256 mg/dL
Basophils	0.4 %	LDL-cholesterol	164 mg/dL
Monocytes	1.5 %	HDL-cholesterol	131 mg/dL
Lymphocytes	10.9 %	Serology	
Red blood cells	396×10^4 /μL	Antinuclear antibody	-
Hemoglobin	12.7 g/dL	IgG	472 mg/dL
Hematocrit	36.8 %	IgA	192 mg/dL
Platelets	27.9×10^4 /μL	IgM	173 mg/dL
Coagulation test		CH50	27.6 IU/mL
APTT	23.2 s	C3	129 mg/dL
Prothrombin time-INR	0.93	C4	33 mg/dL

APTT: activated partial thromboplastin time, HDL: high-density lipoprotein, INR: international normalized ratio, LDL: low-density lipoprotein, NAG: N-acetyl-β-D-glucosaminidase

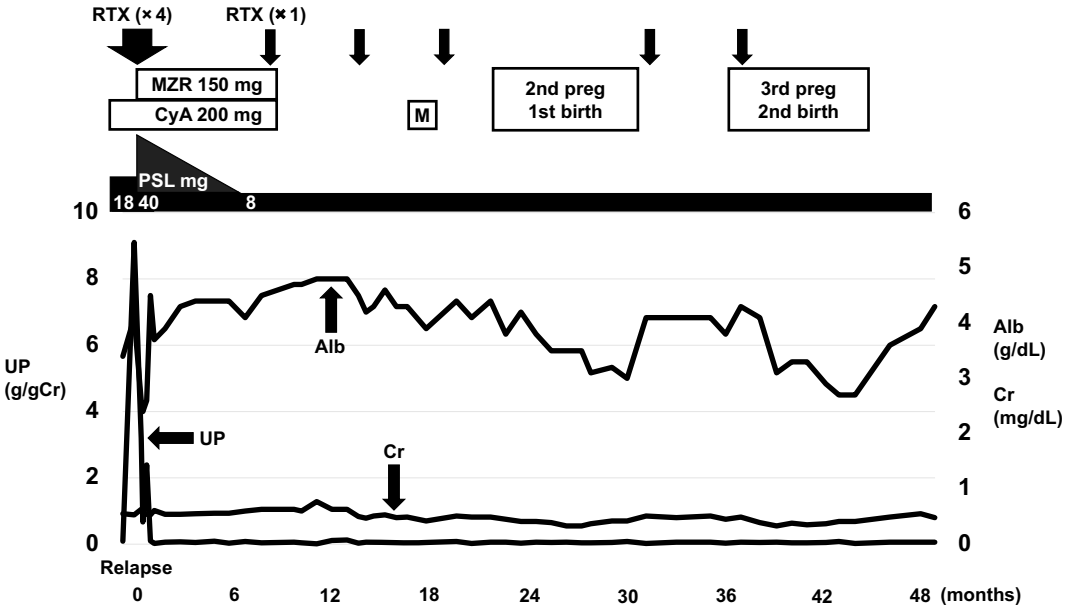

Figure 2. Clinical course. Alb: albumin, Cr: creatinine, CyA: cyclosporine A, M: miscarriage, MZR: mizoribine, PSL: prednisolone, RTX: rituximab, UP: urinary protein

weeks. Both babies were breastfed. The first child (1.5 years of age) and the second child (3 months of age) were developing normally with no history of any serious infection.

Discussion

Our patient with childhood-onset complicated SDNS (8) due to FSGS achieved a sustained remission with a low dose of oral PSL after introducing RTX therapy. During RTX maintenance therapy, the patient had two successful pregnancies. RTX was administered 3 months before the second pregnancy and during the first trimester of the third pregnancy. There is a case report on the safe use of RTX during pregnancy in a patient with primary membranous nephropathy and circulating autoantibodies to M-type phospholipase A_2 receptor (PLA_2R) (12). In this case, RTX was administered during the first trimester of pregnancy. To the best of our knowledge, our case is only the second reported

case of a successful pregnancy in a patient with primary glomerular disease treated with RTX.

The use of RTX for the treatment of relapsed/refractory non-Hodgkin's lymphoma was registered by the Food and Drug Administration in the United States in 1997. Thereafter, RTX has been used in the treatment of numerous other B-cell malignancies, as well as autoimmune conditions (13). Thus, the number of women of childbearing age receiving RTX therapy is increasing. Placental transfer of RTX containing IgG1κ occurs from the second trimester onwards; therefore, exposure during organogenesis in the first trimester is likely to be limited (14). Although the safety of RTX in pregnancy is not very well established, the existing evidence suggests that RTX is possibly safe for use during early pregnancy (11, 14). A recent retrospective cohort study of 74 pregnancies among 55 women treated with RTX for multiple sclerosis also showed the safety of RTX in pregnancy (15). Regarding maternal treatment and breastfeeding, the American College of Rheumatology considers RTX to be acceptable for use during breastfeeding (16). Krysko et al. (17) determined minimal transfer of RTX into mature breast milk in patients with multiple sclerosis, and suggested that low oral bioavailability may also limit the absorption of RTX by a newborn.

Table 2. Levels of Peripheral Blood CD19⁺ B-cells and Serum IgG over Time.

Months after 1st RTX therapy	CD19⁺ B-cells/ total lymphocytes (%)	Serum IgG (mg/dL)
0	27.2	472
6	0	-
12	0	-
24	0	-
30	0	-
36	0	-
42	0	493
48	1.3	743

RTX: rituximab

Table 3 summarizes the clinical findings in 9 reported cases of successful pregnancies in patients receiving RTX therapy during the first trimester of pregnancy, in which clinical information is available (12, 18-25), and in our case. The mean age of the patients was 31 years old (22 − 41 years). The indications for RTX therapy included non-Hodgkin's lymphoma, severe autoimmune hemolytic anemia, recalcitrant atopic dermatitis, active rheumatoid arthritis, PLA_2R-associated active membranous nephropathy, anti-glomerular basement membrane disease, and childhood-onset complicated SDNS. These underlying diseases were controlled by RTX therapy in these cases. No complications were observed during pregnancy, except for 2 patients with premature delivery or premature delivery episode at 35 weeks. In 4 cases, cesarean section was performed at 34-38 weeks. All newborns were healthy at birth and after follow-up, except for 1 child with transient low granulocyte levels and 1 child with suspected mild infection at 1-4 days. The levels of peripheral blood CD19⁺ B-cells were examined in 2 newborns. B-cell counts at 2-16 days were low in the case of Kimby et al. (18), whereas the count at 1 week was normal in the case of Sprenger-Mähr et al. (23).

In summary, the above-mentioned growing evi-

Table 3. Successful Pregnancies in Patients Receiving Rituximab Therapy during the First Trimester of Pregnancy.

Reference	Age, year	Indication	Complications during pregnancy	Pregnancy outcome	Newborn conditions	Child follow-up
18	37	Non-Hodgkin's lymphoma	No	40 weeks, V delivery	3,610 g	Low granulocyte count (0-5 weeks), low CD19⁺ B-cell count (2-16 days), normal immunity at 18 months
19	41	Severe AIHA	No	38 weeks, V delivery	Apgar 10/10, 3,060 g	Suspected mild infection (1-4 days), normal growth at 6 months
20	30	Recalcitrant atopic dermatitis	No	36 weeks, C section	Healthy identical twins	Normal growth and normal levels of B cells at 8 months (each twin)
21	22	Non-Hodgkin's lymphoma	No	34 weeks, V delivery	Apgar 9/9	Normal growth after 1 year
22	25	Active rheumatoid arthritis	Premature delivery episode at 35 weeks	37 weeks, C section	Apgar 10/10, 3,110 g	Doing well after 4.5 years
12	39	Active MN with anti-PLA_2R Ab	No	38 weeks, C section	Healthy	No proteinuria (0-6 weeks)
23	30	Anti-GBM disease	No	38 weeks, C section	Apgar 10/10, 2,280 g	Normal CD19⁺B-cell count (1 week)
24	28	Non-Hodgkin's lymphoma	No	Two times	Healthy (each newborn)	Neither child showed abnormalities of the immune system after >10 years
25	31	Non-Hodgkin's lymphoma	Preterm delivery at 35 weeks	35 weeks, V delivery	Apgar 8, 1,664 g No malformation	Not described
Present case	27	Complicated SDNS	No	39 weeks, V delivery	Apgar 9/9, 3,117 g	Normal growth after 2 months

Ab: antibodies, AIHA: autoimmune hemolytic anemia, C: cesarean, GBM: glomerular basement membrane, MN: membranous nephropathy, PLA_2R: phospholipase A_2 receptor, SDNS: steroid-dependent nephrotic syndrome, TTP: thrombotic thrombocytopenic purpura, V: vaginal

dence (11, 14, 15) and the reported cases summarized in Table 3 (12, 18-25) suggest the safety of RTX during early pregnancy. In the field of nephrology, the number of RTX-treated young women with childhood-onset complicated SDNS is increasing. Pregnancy may be planned in such patients during RTX maintenance therapy after balancing the potential risks and benefits.

Author's disclosure of potential Conflicts of Interest (COI).
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