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...
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/m² 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/m²) 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 weeks.

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 x400). The arrow indicates an arteriole. The scale bars represent 50 μm. D: Immunofluorescence microscopy of a glomerulus, showing IgM deposits (original magnification x400).
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 A2 receptor (PLA2R) (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 successful pregnancy during RTX maintenance in SDNS.

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

| Urinalysis                      | Blood chemistry                           |
|---------------------------------|-------------------------------------------|
| Protein                         | Aspartate aminotransferase 24 IU/L        |
| 4+                              | 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                | 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     | Creatine 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 396×10⁴ /μL     | Antinuclear antibody -                   |
| Hemoglobin 12.7 g/dL            | IgG 472 mg/dL                            |
| Hematocrit 36.8 %               | IgA 192 mg/dL                            |
| Platelets 27.9×10⁴ /μL          | IgM 173 mg/dL                            |
| Coagulation test                | CH50 27.6 IU/mL                          |
| APTT 23.2 sec                   | C3 129 mg/dL                             |
| Prothrombin time-INR 0.93       | C4 33 mg/dL                              |

APTPT: activated partial thromboplastin time, HDL: high-density lipoprotein, INR: international normalized ratio, LDL: low-density lipoprotein, NAG: N-acetyl-β-D-glucosaminidase
RTX therapy is increasing. Placental transfer of RTX con-
glomerular disease treated with RTX.

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 con-
taining IgG1x 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 evi-
dence 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 preg-
nancy (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 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,
PLA2R-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 nor-
mal in the case of Sprenger-Mähr et al. (23).

In summary, the above-mentioned growing evi-

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

| Reference year, Age, year | Indication                              | Complications during pregnancy | Pregnancy outcome | Newborn conditions | Child follow-up |
|---------------------------|-----------------------------------------|---------------------------------|-------------------|--------------------|----------------|
| 18, 2004                  | 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, 2006                  | 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, 2010                  | 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, 2012                  | Non-Hodgkin’s lymphoma                  | No                              | 34 weeks, V delivery | Apgar 9/9          | Normal growth after 1 year |
| 22, 2013                  | 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, 2016                  | Active MN with anti-PLA2R Ab            | No                              | 38 weeks, C section | Healthy           | No proteinuria (0-6 weeks) |
| 23, 2019                  | Anti-GBM disease                        | No                              | 38 weeks, C section | Apgar 10/10, 2,280 g | Normal CD19+ B-cell count (1 week) |
| 24, 2019                  | Non-Hodgkin’s lymphoma                  | No                              | Two times          | Healthy (each newborn) | Neither child showed abnormalities of the immune system after 10 years |
| 25, 2019                  | Non-Hodgkin’s lymphoma                  | Preterm delivery at 35 weeks   | 35 weeks, V delivery | Apgar 8, 1,664 g    | Not described |
| Present case              | 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, PLA2R: phospholipase A2 receptor, SDNS: steroid-dependent nephrotic syndrome, TTP: thrombotic thrombocytopenic purpura, V: vaginal
idence (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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