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**Rituximab treatment for post transplant lymphoproliferative disorder (PTLD)
induces complete remission of recurrent nephrotic syndrome.**

**Kandai Nozu, M.D., Ph.D.¹⁾, Kazumoto Iijima, M.D., Ph.D.²⁾,
Masato Fujisawa, M.D., Ph.D.³⁾, Atsuko Nakagawa, M.D., Ph.D.⁴⁾,
Norishige Yoshikawa, M.D., Ph.D.⁵⁾, and Masafumi Matsuo, M.D., Ph.D.¹⁾**

¹⁾ Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe,

**²⁾ Department of Nephrology, National Center for Child Health and Development,
Tokyo,**

³⁾ Department of Urology, Kobe University Graduate School of Medicine, Kobe,

⁴⁾ Department of Pathology, Aichi Medical University School, Nagoya,

⁵⁾ Department of Pediatrics, Wakayama Medical University, Wakayama,

Address for correspondence:

Kandai Nozu, M.D.

Assistant Professor

Department of Pediatrics

Kobe University Graduate School of Medicine

Kobe 650-0017, Japan

Fax: +81-78-382-6099

Phone: +81-78-382-6090

E-mail: nozu@med.kobe-u.ac.jp

Abstract.

A 12-year-old Japanese boy who underwent kidney transplantation with a kidney from his mother developed severe proteinuria immediately after the operation. Because his original disease was nephrotic syndrome (focal segmental glomerulosclerosis or FSGS) and electron microscopic examination of the renal biopsy showed foot process fusion, we diagnosed this as a recurrence of nephrotic syndrome to the transplanted kidney. Four months after the transplantation, post-transplant lymphoproliferative disorder (PTLD) developed which was pathologically diagnosed as diffuse large B cell lymphoma. Treatment consisting of a reduction in immunosuppression resulted in improvement in PTLD a month after start of the treatment. However, relapse occurred 2 months after the first onset of PTLD, which we treated with rituximab (CD-20 monoclonal antibody 375 mg/m²) once weekly for a total of four doses. The PTLD resolved immediately after the rituximab treatment was started and, interestingly, urinary protein levels also improved at the same time. Three years later, there is no sign of PTLD and no proteinuria has been detected. These findings suggest that rituximab may be an effective treatment for recurrence of nephrotic syndrome after transplantation and that activated B cells may play a pivotal role in the recurrence of nephrosis after renal transplantation.

Key words: post-transplant lymphoproliferative disorder (PTLD), Epstein-Barr virus, rituximab, pediatric patient, post renal transplantation, recurrence of FSGS

Introduction

Recurrence of nephrotic syndrome after renal transplantation in patients with focal segmental glomerulosclerosis (FSGS) is a major issue in renal transplantation. The recurrence rate is reported to be about 20% for transplanted FSGS patients [1,2]. The prognosis for recurrent FSGS is poor, as approximately one-third of the patients progress to end-stage renal failure within 5 years [3-7]. Although there have been case reports and case series of certain effective treatments for FSGS recurrence such as oral cyclophosphamide therapy, high-dose cyclosporine therapy, treatment with ACE inhibitors or/and angiotensin receptor antagonist, plasma exchange, or immunoabsorption [3, 4, 8, 9]. Recently reported that about 70% of recurrent FSGS respond to the high-dose cyclosporine A or combination of high-dose cyclosporine A and therapeutic plasma exchange, but about 20% of those patients didn't respond to the therapy and lost their grafts because of recurrent FSGS [8]. So it still remains as an important issue.

Several reports have suggested that T cells are pathogenetically involved in the development of nephrotic syndrome [10], but the role of B cells remains unclear. Some investigators have suggested that B cells may be involved in the pathogenesis of nephrotic syndrome [11, 12, 13, 14], while Benz et al. recently reported that rituximab (anti CD20 monoclonal antibody) treatment for steroid-dependent nephrotic syndrome with idiopathic thrombocytopenic purpura (ITP) induced a long-term remission in both nephrotic syndrome and ITP [15]. These findings suggest that activated B cells may play a pivotal role in nephrotic syndrome.

Post-transplant lymphoproliferative disorder (PTLD) is a severe complication in organ transplantation, and the use of strong immunosuppressants has increased the incidence of PTLD, which is reportedly high mortality [16]. Recent reports have indicated that rituximab is effective for PTLD [17-22].

This report concerns a 12-year-old boy who suffered PTLD and recurrent nephrotic syndrome after renal transplantation and was treated with rituximab.

Case Report

A 12-year-old boy who was serologically EBV-negative underwent kidney transplantation from his EBV-seropositive mother for end-stage renal failure due to sporadic FSGS. He was treated with tacrolimus (target trough level was 15-20 ng/ml in the first 2 weeks and reduced to 10 ng/ml in the next 6 months), methylpredonisolone and mizoribin after transplantation but severe proteinuria was detected immediately after the transplantation. The renal biopsy specimen obtained 2 months after the transplantation showed minor glomerular abnormalities under light microscopy (Fig. 1A), but electron microscopy indicated 60% foot process fusion (Fig. 1B). We therefore diagnosed this case as recurrence of FSGS, but the urinary protein level decreased gradually without specific treatment for the recurrent disease. Four months after the transplantation, the patient developed a post-transplant lymphoproliferative disorder (PTLD). The adenoids were swollen and much bloody stool was detected because of multiple colon ulcers. The presence of the adenoid tumors and colon ulcers led to a diagnosis of diffuse large B cell lymphoma and in situ hybridization showed that those tumor cells were EBER-1 positive. In addition, real-time PCR detected 1.5×10^4 EBV genomes/ μ g DNA in the peripheral white blood cells (normal level is $<1.0 \times 10^3$ EBV genomes/ μ g DNA) and it was significantly higher than usual. Changing the immunosuppressant from tacrolimus to low dose cyclosporine (target cyclosporine level was 40-60 ng/ml) resulted in remission of PTLD. However, 2 months after the first onset of PTLD, adenoid swelling was observed again, which adenoid biopsy showed to be a recurrence of PTLD. As the tumor cells were CD20 positive, we started treatment with 375 mg/m^2 of rituximab once weekly for a total of four doses.

Fig. 2 shows the clinical course in terms of peripheral B cell counts, serum IgG levels and the ratio of urinary protein to urinary creatinine (U-P/U-Cr). Immediately after the rituximab treatment was started, the adenoid tumors rapidly disappeared, B cells vanished from the peripheral blood and the serum IgG level gradually decreased. Severe proteinuria (U-P/U-Cr was up to 8 mg/mg) was detected on the first day of transplantation (day 0 after the renal transplantation) and the serum albumin level was down to 2.6 mg/dl, but U-P/U-Cr gradually decreased to less than 1.0 mg/mg within 3 months of the transplantation and serum albumin increased to 4.4 mg/dl. However,

U-P/U-Cr rapidly increased to 2-3 mg/mg after the first onset of PTLT (around day 120) and serum albumin decreased to 2.9 mg/dl again. Diminishing proteinuria to a U-P/U-Cr level of nearly 1.0mg/mg after the first remission of PTLT was achieved by reducing immunosuppression and kept the level for about 2 weeks, but the level increased again after the relapse of PTLT. Of special interest is that U-P/U-Cr decreased immediately after the rituximab administration and serum albumin returned to normal, while the proteinuria disappeared completely 7 months after the treatment although the peripheral B cell count went up again. After the rituximab treatment, EB viral DNA in the peripheral blood cells became undetectable. Three years after the rituximab treatment, no proteinuria has been detected and the graft has been functioning well. The electron microscopic picture of the renal biopsy 3 years after transplantation in Fig. 1C shows no foot process fusion. Blood pressure has been effectively controlled and serum creatinine level fortunately remained below 1.0mg/dl throughout the entire clinical course.

We performed genetic analysis of podocin after obtaining the parents' informed consent, but no mutation was detected.

Discussion

Recurrence of nephrotic syndrome in patients with FSGS remains a major post renal transplantation problem. In the case presented here, proteinuria was detected on the first day of transplantation because of the recurrence of nephrotic syndrome in the transplanted kidney. However, U-P/U-Cr decreased gradually without any specific treatment for the recurrent disease. The reason for the spontaneous reduction in urinary protein was estimated to be the effect of the immunosuppressants used to prevent rejection. However, U-P/U-Cr rapidly increased to 2 mg/mg after the development of PTLD, before reducing the immunosuppressants. During this clinical course, PTLD, through unknown mechanisms, may have contributed to the proteinuria increase associated with the recurrent disease. Interestingly, after the rituximab administration, urinary protein as well as peripheral B cells disappeared, suggesting that the activation of B cells may play a pathogenetic role in the recurrence of proteinuria or nephrotic syndrome after renal transplantation in FSGS patients.

The molecular link between the immune system and primary nephrotic syndrome remains unclear. It has been reported that T cell hybridomas from nephrotic patients synthesize a factor or factors that produce transient proteinuria when injected into rats, suggesting that T cell cytokines may induce the development of nephrotic syndrome [10]. Savin et al. reported the presence of circulating factor(s) with increased glomerular permeability to albumin in recurrent focal segmental glomerulosclerosis although the factor or factors themselves have not been identified [23]. Since the glomerular permeability factor can be removed by immunoabsorption to a protein A column [11] and a non-protein A anti-IgG affinity column (sheep anti-human antibody column) [12], immunoglobulins or immunoglobulin-like substances may be involved in the recurrence of proteinuria or nephrotic syndrome after renal transplantation in FSGS patients. Kakumitsu et al. reported a case of nephrotic syndrome with intravascular B cell lymphomatosis, which they concluded might play an important role in the pathogenesis of nephrotic syndrome as the latter went into remission after the treatment of lymphomatosis [13]. Kemper et al. observed T cell and B cell activation in childhood steroid sensitive nephrotic syndrome and analyzed this activation by measuring the soluble IL-2 and low-affinity IgE receptors. They found that both T and B cell activities

were elevated and suggested that steroid sensitive nephrotic syndrome is not only a T-cell but also a B-cell dysfunction [14]. Recently, Benz et al. found that anti-CD20 monoclonal antibody (rituximab) treatment for steroid-dependent nephrotic syndrome with idiopathic thrombocytopenic purpura (ITP) induced a long-term remission in both nephrotic syndrome and ITP [15]. Finally, in our case, urinary protein was elevated from the onset of diffuse large B cell lymphoma and decreased immediately after the B cells had disappeared, which suggests an important role for B cells in the pathogenesis of recurrent proteinuria or nephrotic syndrome after renal transplantation in FSGS patients.

Recently, strong immunosuppressants have increased the success rate of organ transplantation. However, such drugs may also increase the rate of PTLN, especially in pediatric EB virus seronegative recipients of organ transplantation. High mortality has been reported for PTLN, and treatment has been limited to the reduction of immunosuppression, and the use of chemotherapy, surgical resection, anti-viral therapy and radiation [16]. Several investigators have reported that 20% to 50% of patients can be expected to recover as a result of reduction of immunosuppression [24, 25]. However, poor prognosis has been reported for cases with no response to such reduction of immunosuppression [24]. Recently, rituximab treatment has been shown to be effective for the treatment of PTLN in adult patients [17, 18, 19] and pediatric patients [20, 21, 22]. Most common adverse reactions of rituximab are infusion-related fever, chills, or hives but no side effects were seen in our patient. When reduction of immunosuppression is not effective, rituximab treatment is a rational alternative because most PTLN is induced by EB virus-transformed CD 20 positive B-cells. Recent reports have stated that rituximab is also effective for idiopathic membranous nephropathy and lupus nephritis [26, 27]. Moreover, it is possible that rituximab treatment is effective for the treatment of recurrence of proteinuria or nephrotic syndrome after renal transplantation in FSGS patients. However, Weiss SF et al. reported that rituximab was ineffective in three children with FSGS (2 with recurrence in an allograft) [28]. Further studies are required to evaluate the role of rituximab in recurrent FSGS.

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Figure legends

Figure 1. Renal biopsy A & B: Two months after transplantation. **C:** Three years after transplantation. **A.** PAS staining shows minor glomerular abnormalities. **B.** Electron microscopy indicates 60 % foot process fusion. **C.** No foot process fusion is detectable.

Figure 2. Clinical course in terms of peripheral B cell counts, serum IgG levels and the ratio of urinary protein to urinary creatinine (U-P/U-Cr). **A.** Peripheral B cells disappeared immediately after the rituximab treatment, while serum IgG levels decreased gradually. **B.** Urinary protein decreased immediately after the rituximab administration.



