Different effects of rituximab on a native kidney and a post-transplant kidney with recurrence of focal segmental glomerulosclerosis

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Abstract

We present the case of a 29-year-old woman with focal segmental glomerulosclerosis (FSGS) who was treated with rituximab administration under different conditions for refractory nephrotic syndrome and posttransplant FSGS recurrence. At the age of 13 years, she developed FSGS, which followed a refractory clinical course, and eventually necessitated her to undergo plasmapheresis and receive rituximab at the age of 25 years. However, both therapies were ineffective, and she subsequently had progressive renal failure, for which dialysis was initiated at the age of 26 years. At the age of 28 years, she received a renal transplant from a living donor. However, nearly 1 year after the transplantation, nephrotic-range proteinuria was observed and FSGS recurrence was confirmed via biopsy of the transplanted kidney. Plasmapheresis resulted in complete remission, which was maintained by rituximab administration, and the patient followed a favorable course. To date, there have been no reports on the effect of rituximab on both the native kidney and post-transplant FSGS recurrence in the same patient. Interestingly, this case showed different responses to rituximab administration.

Keywords Kidney transplantation · Recurrent focal segmental glomerulosclerosis · Plasmapheresis · Rituximab

Introduction

Focal segmental glomerulosclerosis (FSGS) often follows a steroid-resistant clinical course and precipitates refractory nephrotic syndrome that may ultimately result in end-stage renal disease. Primary FSGS has been reported to recur in 20–30% of transplanted kidneys [1], and the 5-year survival rate in post-transplant cases was worse for recurrent FSGS than for nonrecurrent cases (57% versus 82%) [2]. Established protocols for the treatment of FSGS are inadequate, and strategies that can prevent end-stage renal disease are required. In Japan, the treatment of primary FSGS consists of steroids as first-line therapy, with the concomitant use of immunosuppressant agents, such as cyclosporine (CsA), and adjuvant therapies, such as angiotensin receptor blockers, statins, and antiplatelet agents. For refractory cases, concomitant low-density lipoprotein (LDL) apheresis and plasmapheresis may be performed. In August 2014, the

national health insurance coverage added rituximab, which is a monoclonal antibody against CD20, for the treatment of refractory nephrotic syndrome.

The mechanism of action of rituximab during FSGS treatment has not yet been elucidated. However, hypotheses include the suppression of the immune system dysfunction involved in nephrotic syndrome through its stimulatory effects on both T and B cells and its suppression of the production of the protein-inducing factors from B cells [3]. In addition, a recent report indicated that rituximab could bind to glomerular epithelial cells to exert protective effects on the cellular cytoskeleton [4].

Rituximab has demonstrated efficacy in steroid-dependent and frequently relapsing nephrotic syndrome [5]; however, its efficacy for steroid-resistant nephrotic syndrome (SRNS) has not been established by a consensus. Gulati et al. reported that, out of 33 cases with SRNS who received rituximab, 16 cases (48.5%) went into remission, including partial remission (PR) [6]. Studies that focused on SRNS due to FSGS alone showed a 31–37.5% rate of remission, including PR, with rituximab administration [6, 7]. These results suggested that the efficacy of rituximab decreased further when its use was limited to steroid-resistant FSGS

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cases. However, in a randomized comparative trial on pediatric SRNS cases, rituximab was found to be ineffective [8].

No treatment for post-transplant recurrent FSGS has been established, despite the use of several treatment modalities, including plasmapheresis, CsA, and cyclophosphamide. In 2005, Nozu et al. reported the resolution of proteinuria after rituximab administration in some patients with post-transplant FSGS recurrence complicated by post-transplant lymphoproliferative disease [9]. After the publication of that study, rituximab has been used in post-transplant recurrent FSGS cases. A systematic review of previous reports in 2011 [10] examined 18 case reports of 39 subjects with post-transplant FSGS recurrence and found that rituximab administration led to a decrease in proteinuria in 25 cases (64%).

These results indicated that rituximab is more favorable in post-transplant FSGS recurrence than in steroid-resistant FSGS in a native kidney. Although the efficacy of rituximab has been reported by separate retrospective studies on native kidney FSGS and post-transplant FSGS recurrence, to date, to the best of our knowledge, there have been no reports on both effects in the same patient. Here we describe a patient with FSGS who responded to rituximab in different ways before and after kidney transplantation.

Case report

A 29-year-old woman was diagnosed with nephrotic syndrome at another institution at the age of 13 years. She temporarily achieved complete remission (CR) after prednisolone (PSL) therapy, but immediately relapsed and developed SRNS thereafter. At the age of 15 years, she was diagnosed via renal biopsy with a collapsing variant of FSGS. The administration of various immunosuppressant agents, such as mizoribine (MZB) and CsA, was ineffective. Following a combination treatment with PSL 60 mg/day and LDL apheresis, proteinuria improved to 1 g/day and further decreased to ≤ 1 g/day after the addition of an angiotensin-converting enzyme inhibitor. However, at the age of 18 years, she was found to have nephrotic-range

proteinuria; her creatinine (Cr) level increased to 1.0 mg/dL at the age of 24 years and reached 1.3 mg/dL a year later. Renal biopsy showed global sclerosis in 66% of the glomeruli (Fig. 1). After three courses of plasmapheresis, rituximab was administered at a dose of 500 mg, which induced the suppression of CD19 and CD20 levels below 0.1%, but proteinuria of 5–6 g/day persisted. At the age of 26 years, the renal failure progressed and maintenance dialysis was initiated.

At the age of 28 years and 5 months, the patient underwent an ABO-mismatched living donor renal transplant (from O+ to B+) of a kidney donated by her mother after two sessions of plasmapheresis and rituximab administration (200 mg). The postoperative immunosuppressive therapy included tacrolimus (TAC), mycophenolate mofetil, and methylprednisolone (mPSL); however, on postoperative day (POD) 3, the patient exhibited increased resistive index, elevated Cr, and decreased urine output. Based on a diagnosis of acute rejection, she was placed on mPSL pulse therapy and received antithymocyte globulin. Subsequently, her Cr decreased to 1.0 mg/dL. On POD 30, proteinuria persisted at 2+ to 3+ and hematuria with dysmorphic red blood cells (RBCs) was observed. A repeat renal biopsy showed no signs of rejection, but only few glomeruli were observed and tissue assessment for the presence of glomerulonephritis was difficult. With a suspicion of recurrent FSGS, mPSL pulse therapy and plasmapheresis were administered, which improved the proteinuria.

At the age of 29 years and 3 months (i.e., 10 months after renal transplantation), proteinuria recurred at 3.4 g/g Cr, and her Cr was elevated at 1.3 mg/dL. Renal biopsy led to a final pathological diagnosis of FSGS, based on findings of global sclerosis in 5 of 30 glomeruli and segmental glomerulosclerosis in two glomeruli. Interestingly, one glomerulus showed collapse of the glomerular capillary area, with podocyte hyperplasia. There were mild tubular atrophy and interstitial fibrosis, but there was no evidence of rejection. Electron microscopic examination revealed segmental collapse of the glomerular capillaries and diffuse effacement of the foot processes (Fig. 2). Thereafter, she was referred to our hospital.

Fig. 1 Photomicrograph shows **a** global sclerosis in almost 60% of the glomeruli, with severe renal tubular atrophy and interstitial fibrosis (periodic acid-Schiff staining, $\times 100$) and **b** segmental sclerosis, with collapsing glomerular capillary areas in the glomeruli (periodic acid-Schiff staining, $\times 400$)

Fig. 2 Photomicrograph shows **a** normal glomeruli and no tubulointerstitial changes (periodic acid-Schiff staining, $\times 100$) and **b** biopsy specimen of the transplanted kidney shows collapsed glomerular capillaries and hyperplasia of the glomerular visceral epithelial cells

Upon the referral, laboratory data showed proteinuria of 3.5 g/g Cr, 3+ occult hematuria, 5–9 RBCs/high-power field, albumin of 3.8 g/dL, and Cr of 1.17 mg/dL. To induce CR, plasmapheresis using 30 units of fresh frozen plasma in total was administered in six sessions over 2 weeks, at three sessions per week. The proteinuria rapidly decreased after the initiation of plasmapheresis and resolved after completion of the fifth session. In order to maintain CR, the patient was started on steroid semipulse therapy (mPSL, 500 mg $\times$ 3 days) after completion of the sixth plasmapheresis session and was given rituximab 500 mg on day 19 after the final plasmapheresis session; at this time, proteinuria was observed at 0.39 g/day and gradually increased to 1.02 g/day on day 28. Due to the potential for further increase, we performed three additional sessions of plasmapheresis; the proteinuria resolved after completion of the second session, and the patient maintained CR.

However, at the age of 30 years, proteinuria recurred at 4 g/g Cr. After rituximab administration, CD19 and CD20

were suppressed from 1.4% and 2% to 0.1% and 0.1%, respectively. Two weeks before the recurrence, CD19 and CD20 were 0.1% and 0.5%, respectively, but, at the time of the recurrence, CD19 and CD20 had increased to 0.3% and 0.8%, respectively. Three additional plasmapheresis sessions were performed, and the patient achieved CR, which was maintained by rituximab administration (500 mg). Her follow-up treatment strategy included rituximab once every 6 months and an additional two doses of rituximab 500 mg during follow-up. Despite being able to maintain CR, the patient developed neutropenia, which required granulocyte-colony-stimulating factor treatment, *Campylobacter* enterocolitis, and cystitis during the course of the disease. Therefore, she was given additional rituximab 200 mg when her CD20 levels increased during CD20 monitoring. Thereafter, at 3 years after FSGS recurrence on the transplanted kidney, CR is maintained, renal function is preserved, and no adverse events have been reported (Fig. 3).

Fig. 3 Clinical course of focal segmental glomerulosclerosis recurrence after renal transplantation. *PE* plasma exchange, *mPSL* methylprednisolone, *TAC* tacrolimus, *MZB* mizoribine, *S-Alb* serum albumin (g/dL), *U-prot* urinary proteinuria (g/day), *TP* total protein (g/dL), *Cr* creatinine (mg/dL)

Discussion

In this case, plasmapheresis and rituximab administration were not effective for the native kidney but were effective in inducing and maintaining remission of post-transplant recurrence. An open-series prospective report indicated that rituximab for FSGS failed in 57% of the cases but was effective when administered at the time of remission [11]. For our patient, CR was induced by plasmapheresis and maintained by rituximab administration; notably, plasmapheresis was given concomitantly with rituximab. Although rituximab alone was not effective in inducing remission, we hypothesized that it would be effective in maintaining remission because the recurrence in our patient was associated with elevated CD19 and CD20 levels at approximately 6 months after the induction of remission.

Some kind of humoral factors may be involved in the mechanism of pathogenesis of FSGS owing to the occurrence of FSGS recurrence just after kidney transplantation and in the efficacy of plasmapheresis [12]. Studies are ongoing on such factors, but at this point, there is no sufficient understanding. There are many etiologies for FSGS, and it is possible that some cases of FSGS are caused by diseases for which rituximab is ineffective. In this study, we administered rituximab before and after the transplantation to the same subject under different conditions and noted differences in its efficacy. Thus, we examined the cause for such difference in the efficacy of rituximab. Clear differences were observed in proteinuria (7.3 g/day versus 0.4 g/day), serum albumin (2.0 g/dl versus 4.1 g/dl), Cr (1.4 mg/dl versus 1.1 mg/dl), percentage of global sclerosis glomeruli (66% versus 16.6%), and immunosuppressive therapy (20 mg PSL versus mPSL 4 mg + TAC + MZB) (Table 1).

There have been reports on the efficacy of rituximab on FSGS, and steroid resistance was noted as a factor in rituximab resistance in FSGS of native kidney. In addition, there is a report on renal failure and the impact of the ratio of global sclerosis [13]. On the other hand, a literature review by Sakai et al. on patients with post-transplant FSGS recurrence showed that the time between recurrence and rituximab administration was significantly shorter in those with favorable rituximab effects than in those without favorable rituximab effects (100.5 ± 95.4 days versus 468.1 ± 379.8 days; $P=0.003$) [14]. In a systematic review that examined the efficacy of rituximab on post-transplant FSGS in pediatric patients, a comparison of clinical data for rituximab responders and non-responders showed that the serum Alb was higher in the responders at the time of recurrence (point estimate 4.82, 95% CI 1.54–15.02, $P=0.007$) and young age (point estimate 0.89, 95% CI 0.82–0.96, $P=0.003$) was an independent factor. However, the period from recurrence to rituximab administration was not significant in a multivariate analysis [8]. As for proteinuria at the time of rituximab administration, some studies report that rituximab was effective even with a large amount of proteinuria [15], whereas other studies argue that its efficacy is weakened [11]. As such, at the present time, whether it is a native kidney or a transplanted kidney, there is no factor that accurately predicts the efficacy of rituximab on FSGS. We speculated that in the clinical background of the present case before and after the transplantation, markedly low ratio of global sclerosis was a clinical factor to predict the efficacy of rituximab. At the same time, when rituximab was administered before the transplantation with global sclerosis of 66%, it might have already been at the stage where immunological mechanism was no longer involved because plasmapheresis prior to rituximab administration was ineffective and rituximab was invalid despite CD19 and CD20 suppression. Further accumulation of cases and examinations are necessary.

Table 1 Comparison of clinical and histologic parameters at the first and the second rituximab administrations

	Native kidney	Post-transplant kidney with recurrence
Age at rituximab administration (years)	25	29
Interval from onset (or recurrence) to rituximab administration (months)	136	11
Proteinuria (g/day)	7.3	0.4
Serum creatinine (mg/dl)	1.4	1.1
Serum albumin (g/dl)	2.0	4.1
Immunosuppressive therapy	PSL 20 mg	mPSL 4 mg + TAC + MZB
FSGS variants	Collapsing	Collapsing
Global glomerulosclerosis (%)	66	16.6

Conclusion

In this case, plasmapheresis and rituximab administration were ineffective on advanced stage of FSGS in the native kidney, but the same treatment was effective in achieving remission and maintenance on the recurrent FSGS in the transplanted kidney.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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