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LETTER TO THE EDITOR

Successful treatment of recurrent focal segmental glomerulosclerosis after renal transplantation by lymphocytapheresis and rituximab

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Recurrence of focal segmental glomerulosclerosis (FSGS) in the transplanted kidney is a potentially detrimental condition associated with graft loss [1]. Although new immunosuppressive agents have improved the survival rates of kidney allograft, the development and progression of recurrent FSGS have not been influenced by the use of these agents [2]. Thus, the treatment of patients with recurrent FSGS after renal transplantation remains a significant clinical challenge. Permeability factors are speculated to have a crucial role in the proteinuria of nephrotic syndrome (NS) [3,4]. Circulating glomerular albumin permeability factors were detected in patients with primary FSGS as well as in patients with recurrent FSGS after renal transplantation [4]. Plasma protein adsorption, anti-human immunoglobulin affinity immunoadsorption, plasma exchange, low-density lipoprotein apheresis (LDL-A) and lymphocytapheresis (LCAP) have been reported to be effective in removing such factors or pathogenic lymphocytes in patients with NS [5]. Rituximab is a chimeric antibody that binds to the B-cell surface antigen CD20. Several recent reports have noted successful use of rituximab in primary and recurrent steroid-resistant NS [6]. In this report, we describe a case of sustained remission of recurrent NS after living-related donor renal transplantation using LCAP and rituximab.

The patient is a 20-year-old woman who developed NS at the age of six. Renal biopsy revealed FSGS. The patient progressed to end-stage renal failure 7 years later, despite treatment with immunosuppressive agents using LDL-A. After 16 months of peritoneal dialysis, the patient received a kidney from her father. Her immunosuppressive regimen consisted of tacrolimus, mycophenolate mofetil, methylprednisolone and basiliximab. Sixteen months after renal transplantation, massive proteinuria (6.2 g/day) appeared. Renal biopsy revealed focal and segmental sclerosis of some glomeruli and no signs of transplant rejection. Electron microscopic examination revealed evidences of early recurrence of FSGS with diffuse foot process effacement. The patient was treated four times with LCAP (Cellsorba; Asahi Medical Co., Osaka, Japan) with three doses of steroid pulse therapy (methylprednisolone 500 mg/day, 3 days). Each time, 3000 ml of whole blood were processed at a blood flow rate of 50 ml/min with one session lasting for 60 min. After these treatments, proteinuria decreased to 1–2 g/day. However, proteinuria gradually increased, and massive proteinuria (5 g/day) appeared within 16 months after LCAP therapy. To suppress massive proteinuria, the patient had been treated with monthly steroid pulse therapy; however, proteinuria became refractory to these treatments. Consequently, we decided to use LCAP and rituximab to achieve further immunomodulation. The patient was treated four times with LCAP, with one dose of steroid pulse therapy (500 mg/day, 3 days) and two doses of rituximab (375 mg/m^2) (Fig. 1). After treatment, proteinuria decreased continuously, and complete remission was achieved. Twenty-five months after treatment, graft function is good, and the serum creatinine level is 1.0 mg/dl. The patient has no significant proteinuria. She had no infectious episodes during this period.

After LCAP, the total number of peripheral blood WBCs did not change (Table 1). The total number of lymphocytes, T cells, B cells and human leukocyte antigen (HLA)-DR-positive activated T cells decreased (Table 1). After treatment with rituximab, the total number of WBCs, B cells and HLA-DR-positive T cells decreased (Table 1).

Lymphocytapheresis can remove pathogenic immune cells and is effective in the treatment of autoimmune diseases and lymphocyte abnormalities such as rheumatoid arthritis, ulcerative colitis and Crohn's disease [7]. LCAP is also effective in the treatment of kidney diseases including NS, antineutrophil cytoplasmic antibodies associated vasculitis and IgA nephropathy [5,8]. We had previously reported the beneficial effects of LCAP for the treatment of NS [8]. In the response group after LCAP, the total number of lymphocytes, T cells, B cells and HLA-DR-positive activated T cells decreased significantly. On the other hand, in the nonresponse group after LCAP, there was no alteration of lymphocyte subsets. The mechanism of LCAP in reducing proteinuria is still unknown; however, it may be different from the mechanisms of plasma

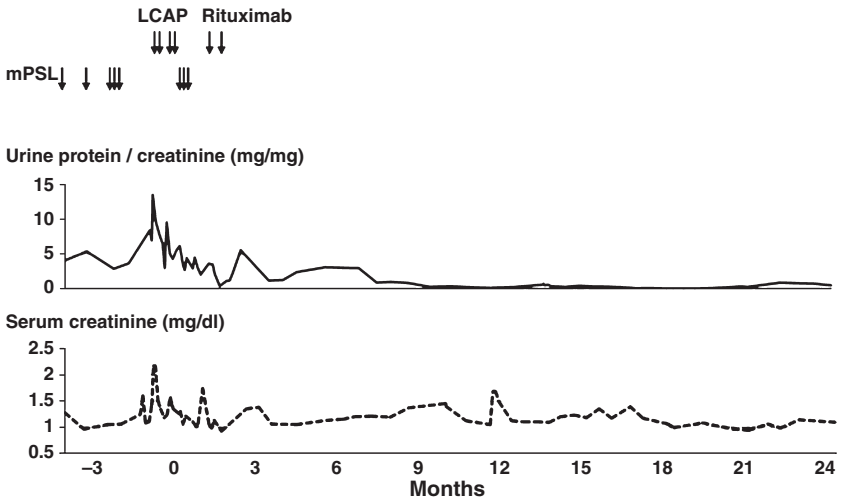

Figure 1 Clinical course in terms of ratio of urinary protein to creatinine (solid line) and serum creatinine (dashed line) after lymphocytapheresis (LCAP) and rituximab.

Table 1. Alteration of peripheral blood markers by lymphocytapheresis and rituximab.

	LCAP (first)		LCAP (second)		Rituximab	
	Before	After	Before	After	Before	After
White blood cells/μl	8500	8400	9930	8540	14 870	6060
Lymphocytes/μl	1020	336	2880	512	892	909
T cells/μl	704	222	2246	307	607	800
B cells/μl	133	24	345	20	125	0
Activated T cells/μl	71	16	58	26	89	36

LCAP, lymphocytapheresis.

protein adsorption, anti-human immunoglobulin affinity immunoadsorption, plasma exchange and LDL-A because the serum levels of immunoglobulins, complements and lipids show very little change during LCAP.

In this case, proteinuria significantly decreased after LCAP. The total number of lymphocytes, T cells, B cells and HLA-DR-positive activated T cells decreased significantly after LCAP similar to the response group. We believe LCAP is also effective in recurrent FSGS after renal transplantation. However, to achieve long-term remission, further immunomodulation was necessary. When rituximab was added, long-term remission was achieved. Interestingly, the number of activated T cells as well as B cells decreased after rituximab was added. These findings indicate that rituximab not only depletes B cells but also influences the interaction between T and B cells. The mechanism of reducing T-cell activation is still unknown. One possibility is the reduced presentation of antigens by B cells that also reduce T-cell activation.

Recent reports showed that rituximab with plasma pheresis or immunoabsorbtion or steroid therapy contributed to remission of proteinuria in patients with recurrent FSGS [9–11]. In our case, rituximab therapy in combination with LCAP was very effective, however, further studies are needed to evaluate which procedure is most effective. Furthermore, independent effects of each procedure should be properly evaluated too.

No acute adverse events related to use of LCAP and rituximab and no serious infectious events were observed in the patient. However, recent concerns regarding the role of rituximab are the development of progressive multifocal leucoencephalopathy and the risk of severe bacterial and fungal infections [12]. The complete side-effect profile of rituximab in FSGS and postrenal transplantation is not completely understood, and progressive multifocal leukoencephalopathy and severe bacterial and fungal infections are areas for future trials. Regular monitoring for these infections and precise evaluation of the pathogenesis are necessary to determine the optimal use of rituximab. Additional clinical investigation is necessary to establish a rationale for the use of rituximab in patients with recurrent FSGS.

In conclusion, this case suggests that LCAP and rituximab could be effective in treating recurrent FSGS after

renal transplantation and in inducing remission in proteinuria. Prospective randomized trials are required to validate the efficiency of LCAP and rituximab in this disorder and to understand the pathophysiological mechanisms.

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