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Successful Kidney Transplantation After Stepwise Desensitization Using Rituximab and Bortezomib in a Highly HLA-Sensitized and ABO Incompatible High Titer Patient

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Highly sensitized patients receive fewer kidney transplants and have a high risk for severe rejection, with increased rates of graft loss. We encountered a highly HLA-sensitized and ABO-incompatible patient with an extremely high antiblood group titer who underwent kidney transplantation successfully after a 2-year-long challenging desensitization therapy.

CASE DESCRIPTION

The patient was a 41-year-old woman with end-stage renal disease due to IgA nephropathy. She received her first kidney transplant from her father in 1985. The kidney transplant failed due to chronic rejection in 2007. She was diagnosed with hepatitis C infection in the same year. She hoped for a second kidney transplantation. Before the second kidney transplantation, the patient received treatment with pegylated interferon α and ribavirin for chronic hepatitis C, and she achieved a sustained virological response in 2010. Transplant nephrectomy was performed in the same year because of a long-term indwelling ureteral stent, which increases the risk of urinary tract infection. The patient was scheduled to receive a second living-donor kidney transplantation from her sister. A test with flow-PRA showed a baseline panel-reactive antibody level of 83.5% in class 1 and 50.8% in class 2. B cell complement–dependent cytotoxicity and T cell flow cytometric crossmatch tests showed positive reactions. A flow cytometric single-antigen test revealed the presence of HLA antibodies. The patient had donor-specific antibodies (DSAs)—namely, A33 and B44—with a molecules of equivalent soluble fluorochrome (MESF) of 20 341 and 4658 (Table 1). The donor's blood type was A+, which was incompatible with that of the recipient (B+). The antiblood type A IgG titer was extremely high at 1:524 288. Triple-drug immunosuppression regimen consisting of cyclosporine (CyA), mycophenolate mofetil (MMF), and methylprednisolone (MP) was initiated 6 weeks before kidney transplantation, and 100 mg of rituximab was administered 3 weeks before the scheduled date. Five sessions of plasmapheresis were performed to remove anti-HLA and blood type antibodies. The transplant operation was postponed because the antiblood type A IgG titer remaining high at 1: 262 144 after the last plasmapheresis session. However, 10 days after the final plasmapheresis (3 weeks after rituximab administration), the anti-A IgG titer dropped to 1:64. Therefore, the transplant operation was rescheduled. The patient underwent a second desensitization treatment with plasmapheresis and low-dose (100 mg/kg) intravenous γ globulin infusion. However, the transplantation was postponed again because the MESF of the DSAs increased. The triple-drug (CyA [100 mg/d], MMF [500 mg/d], and MP [4 mg/d]) immunosuppression therapy was continued.

Four months later, DSA levels remained high at MESF 62 842 (A33) and 23 762 (B44). Hence, a single course of bortezomib (1.3 mg/m^2 × 4 doses) was administered. Three months later, the MESF was still high at 53 236 (A33) and 14 975 (B44). Seven months after bortezomib administration, the A33 and B44 MESFs decreased to 4808 and 4945, respectively. T cell flow cytometric crossmatch turned to negative. Ten months later, the transplantation was rescheduled. The anti-A antibody titer was low at 1:4. However, DSAs were still detected (A33, 1177; B44, 680). The triple-drug therapy (CyA, MMF, and MP) was reinitiated 4 weeks before transplantation, and 2 doses of rituximab (100 mg/body) were administered at 21 days and 1 day before transplantation. A single session of double filtrated plasmapheresis was performed 4 days before transplantation. She underwent

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TABLE 1.

HLA typing and HLA antibodies at baseline

HLA	Donor A(+)		Recipient B(+)	
A	2	33	2	2
B	35	44	35	40
DR	13	15	11	15
		Antibodies		
Class 1	B45, A33[a], A31, B76, A66, B44[a], Cw1, Cw14, A34, A25, A69, A66, Cw12, Cw6, Cw8, Cw16, Cw18, A30, Cw15, A32, B8, Cw5, B49, Cw4, A3, B52, B59, A11, B54, A29, B51, A74, B82			
Class 2	DR12, DR9, DR7, DR52, DR14, DR2, DR11, DR51, DP17			

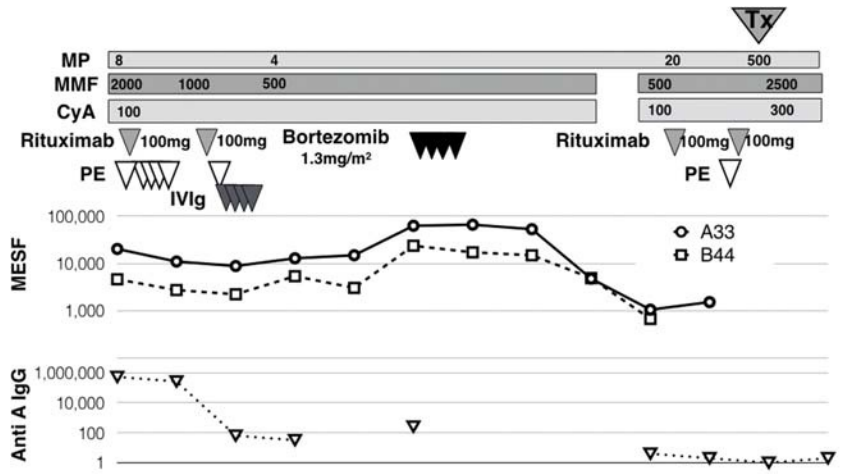
[a] Donor specific antibody.

living-donor kidney transplantation successfully. The result of the 1-hour biopsy showed no evidence of hyperacute rejection. All DSAs were undetectable on the day of the transplantation. The patient's postoperative course was uneventful, and she was discharged on postoperative day 28. Clinical course of the patient is shown (Figure 1). Through the entire observation period, the patient experienced no episode of severe infection. The results of protocol biopsies performed 6 and 30 months after the transplantation showed no evidence of rejection, and DSAs remained undetectable.

DISCUSSION

Highly sensitized patients have the highest risk of acute antibody-mediated rejection (AMR) and graft loss. In the present case, we encountered 2 problems; 1 is extremely high anti-ABO blood group titer and the other is high DSA titer.

High baseline anti A/B titer is a risk factor for post-transplant AMR. Recent reports from Korea[1] showed patients with a higher baseline anti A/B titer (≥1: 512 or 256) have a higher tendency of antibody rebound and AMR risk. On the other hand, there are some case reports[2,3] of successful transplantation in patients with high baseline anti-A/B titers (≥1: 512). In our case, anti-A titer was extremely high at 1: 524 288. This is the highest ever reported. Plasmapheresis could not decrease the anti-A/B antibody titer to the target level. Although it took 3 weeks, rituximab decreased the anti-A/B antibody titer successfully. Rituximab effectively eliminated sensitized B cells and IgM-producing cells, which are key in producing anti-A/B antibodies. Moreover, maintenance immunosuppression drugs, including calcineurin inhibitor and MMF, are thought to have contributed to the inhibition of antibody production. However, the anti-HLA antibody titer was unchanged. Additional intravenous immunoglobulin infusion was insufficient for inhibition of antibody production. Some antibody-producing memory cells demonstrate resistance to the conventional desensitization protocols based on intravenous immunoglobulin infusion, anti-CD20 antibody therapy, and plasmapheresis. Bortezomib, a selective inhibitor of the 26S proteasome, is widely used in the treatment of multiple myeloma. An in vitro study[4] showed that bortezomib led to bone marrow–derived plasma cell apoptosis and blocked anti-HLA IgG secretion. With regard to kidney transplantation, bortezomib is used for desensitization of HLA-sensitized patients. Bortezomib plus steroid therapy effectively decreases anti-HLA antibody titers in sensitized kidney transplant recipients.[5] Idica et al[6] reported the effects of bortezomib in 13 highly sensitized patients. They found elimination of DSAs in 10 patients and reduced mean fluorescence intensity in the remaining 3. Trivedi et al[7] reported a decrease in anti–mean fluorescence intensity of HLA antibodies in 9 of 11 patients treated with a combination of bortezomib and plasmapheresis. Ide et al[8] proposed a sequential desensitization protocol, with rituximab followed by bortezomib for highly HLA-sensitized patients. They determined the time to administration of bortezomib based on the results of peripheral blood B cell subset analysis and other immune monitoring methods to avoid drug toxicity and over immunosuppression. The interval between rituximab administration and bortezomib initiation was 9 to 20 months. We did not perform B cell subset analysis; however, regular B cell subset analysis would be necessary to perform desensitization therapy safely. A single course of



	-25M	-24M	-23M	-22M	-20M	-17M pre	-17M postBT	-14M	-11M	-1M	-7d	Tx	4M
A33	20341	11038	8882	12909	15014	62842	66290	53236	4808	1065	1538	0	0
B44	4658	2756	2250	5405	3069	23762	17279	14975	4945	680	0	0	0
anti-A	524288	262144	64	32		256				4	2	1	2
TFXM	+			+			-		-	-	-	-	-
BFXM	+			+			+		+	-	-	-	-

FIGURE 1. Clinical course.

bortezomib administered 8 months after rituximab treatment effectively inhibited antibody production without any adverse event. Molecules of equivalent soluble fluorochrome of DSAs significantly decreased 6 months later and became undetectable finally 16 months later and class 1 non-DSA with low MESF was detectable, DSAs remained undetectable 30 months after kidney transplantation. The patient experienced no episode of infection. In conclusion, the present case suggests that stepwise desensitization with rituximab and bortezomib is a safe and effective protocol in highly HLA and ABO-incompatible patients.

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