# Successful treatment of early acute antibody-mediated rejection in an human leukocyte antigen-incompatible and ABO-incompatible living-donor kidney transplant patient

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For successful human leukocyte antigen-incompatible (HLAi) or ABO-incompatible (ABOi) living-donor kidney transplantations (LDKTs), pretransplant desensitization is essential; however, early antibody-mediated rejection (ABMR) remains the most important complication after HLAi or ABOi transplantation. Here, we report a case of early acute ABMR in simultaneous HLAi and ABOi LDKT with preformed donor-specific antibody (DSA), despite desensitization. Dialysis-dependent, severe ABMR occurred with a rebound of pre-existing DSA and appearance of de novo DSA after initial normalization of renal function, 8 days postoperatively. However, a low anti-ABO antibody titer (1:8) was maintained after transplantation. Combination therapy of plasmapheresis, high-dose intravenous immunoglobulin, and bortezomib improved both ABMR and renal functions. Thus, an appropriate preventive and therapeutic management for early ABMR is important among high-risk LDKT patients. Furthermore, early AMBR can occur despite pretransplant desensitization as seen in this case, and close monitoring of the patient and prompt management are considered vital for better therapeutic outcomes.

Keywords: Desensitization; Human leukocyte antigen; Kidney transplantation; Living donor; Rejection

## INTRODUCTION

Donor shortage is responsible for the increase in the number of human leukocyte antigen-incompatible (HLAi) and ABO-incompatible (ABOi) living-donor kidney transplantation (LDKT) cases in Korea. For successful HLAi or ABOi LDKT, it is necessary to perform pretransplant desensitization; however, early antibody-mediated rejection (ABMR) is still the most important complication following HLAi or ABOi transplantation. ABMR is an immune response of alloantibodies against the transplanted organ, more specifically against mismatched classical HLA antigens of a donor, nonclassical major histocompatibility complex class I-related chain-A antibodies, non-HLA endothelial antigens, or mismatched ABO antigens [1-3]. Acute ABMR is a major cause for graft loss in kidney transplantation [1]. Here, we described a case of early acute ABMR after HLAi and ABOi LDKT, treated by a combination therapy of plasmapheresis, high-dose intravenous immunoglobulin (IV-Ig), and bortezomib.

## CASE REPORT

### Case

A 42-year-old female patient with blood group A approached us for LDKT. She was diagnosed with diabetes mellitus 4 years ago and had been on hemodialysis since 2018. She planned to receive ABOi LDKT from her hus-

band with blood group B. Both complement-dependent cytotoxic crossmatch and T cell-flow cytometric crossmatch test results were negative; however, the B cell-flow cytometric crossmatch result was weakly positive with a mean channel shift value of 250. Her calculated panel reactive antibody (cPRA) was 7% (class II) and her donor-specific antibody (DSA) results tested positive for DR7 (mean fluorescence intensity [MFI], 5,421). The anti-B antibody titers for immunoglobulin-M (IgM) and immunoglobulin-G (IgG) were 1:8 and 1:16, respectively (Table 1).

For achieving desensitization during simultaneous HLAi and ABOi LDKT, 500 mg rituximab was administered to the patient. One week after undergoing rituximab therapy, she underwent 10 sessions of plasmapheresis with low-dose IV-Ig (0.1 g/kg/session) and two doses of bortezomib (0.3 mg/m$^2$/dose). Additionally, maintenance immunosuppression with prednisolone (20 mg, once a day), tacrolimus (4 mg, twice a day), and mycophenolate mofetil (500 mg, twice a day) were initiated on the fourth day of plasmapheresis. After five plasmapheresis sessions, cPRA increased to 48% but the reduction in anti-DR7 DSA titer was unremarkable (MFI, 5,801), whereas anti-B antibody titers for both IgM and IgG decreased to 1:1. After five more plasmapheresis sessions, cPRA reached 0% and MFI of anti-DR7 DSA reduced to 935. At that time, the B cell-flow cytometric crossmatch results were negative. Proportion and number of CD19+ B cells were 10.3% and 133.5/μL before the rituximab treatment, and remained low until 9 months after transplantation (5.3% and 30.1/μL).

Two days after the tenth plasmapheresis session, the patient underwent LDKT and administration of anti-thy-
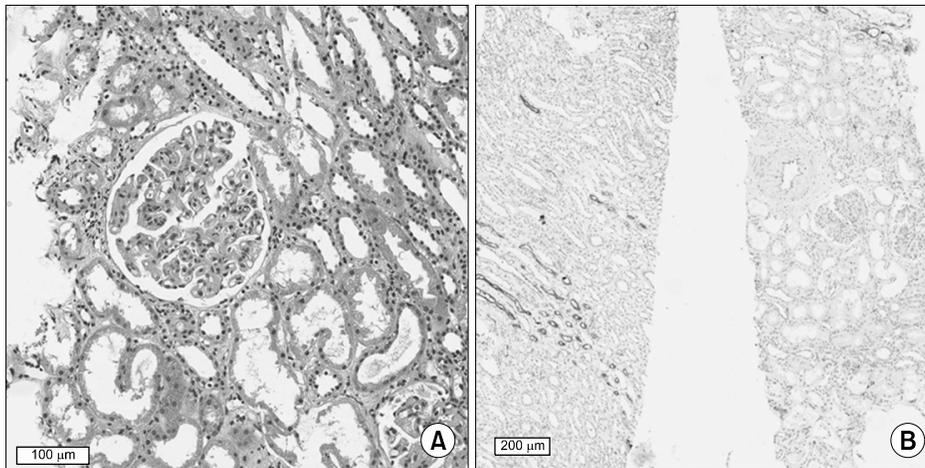


Fig. 1. Pathology of kidney biopsy on postoperative day 28 (POD28). Kidney biopsy on POD28 showed antibody-mediated rejection (ABMR) grade-II as per Banff classification 2017 (t0, i0, iIFTA0, g1, ptc1, v1, ci0, ct0, cg3, mm1, cv1, ah0, aah0, c4d2). According to Banff 2013 classification of acute ABMR in renal allografts, three criteria have to be met for diagnosing ABMR. For tissue injury compatible with ABMR, conditions include microvascular injury, intimal or transmural arteritis, acute thrombotic microangiopathy without other cause, and acute tubular injury without any other cause. Presence of donor-specific antibody (e.g., human leukocyte antigen-incompatible or other antigens) is needed for confirming ABMR. Evidence of their interaction with the vascular endothelium is needed, which include linear C4d staining of peritubular capillaries, at least moderate microvascular injury, and molecular markers [4]. (A) H&E, ×400. (B) Immunohistochemistry staining with peroxidase yielding a brown reaction product for C4d, ×100.

mocyte globulin (5 mg/kg/day) for the first 3 days as an induction therapy. Hyperacute rejection was absent. On postoperative day 7 (POD7), the serum blood urea nitrogen (BUN) and creatinine (Cr) levels decreased to 22 mg/dL and 0.86 mg/dL, respectively, and the urine output increased to 100–200 mL/hr. However, on POD8, the serum BUN and Cr levels rose abruptly and urine output decreased, and on POD10, the serum BUN and Cr levels reached up to 131 mg/dL and 4.01 mg/dL, respectively. On POD8, the cPRA for class I and II became 99% and 90%, respectively. Rebound pre–existing DSA (DR7; MFI, 17,648) and de novo DSAs against A3 (MFI, 3,008), B35 (MFI, 2,776), B51 (MFI, 11,877), DR4 (MFI, 10,879), and DR53 (MFI, 1,989) were observed. Kidney Doppler ultrasound examination showed an increase in the resistance index (0.81–0.89) without significant vascular or urinary tract abnormality.

Ten plasmapheresis sessions with low–dose IV–Ig (0.2 g/kg/session) replacement from POD9 to POD24, steroid pulse therapy, and three doses of bortezomib (1.3 mg/m$^2$/day) were empirically administered to treat suspected ABMR with rapidly developing dialysis–dependent renal dysfunction. Hemodialysis was performed from POD10 to POD22. The renal function initially improved (BUN, 57 mg/dL; Cr, 1.84 mg/dL), but the improvement soon reached a plateau. Kidney biopsy performed on POD28 revealed ABMR grade–II based on the Banff classification 2017 (t0, i0, iIFTA0, g1, ptc1, v1, ci0, ct0, cg3, mm1, cv1, ah0, aah0, c4d2) (Fig. 1) [5]. On POD28, despite a slight reduction, DSA persisted at high levels (anti–B51 [MFI, 575], DR4 [MFI, 868], DR7 [MFI, 16,614], DR53 [MFI, 721], DQ4 [MFI, 2,400], and DQ9 [MFI, 2,654]). Therefore, four more plasmapheresis sessions were performed, followed by high–dose IV–Ig (2 g/kg) administration from POD33 to POD38 to treat persistent ABMR. After the second therapy, the serum BUN and Cr levels decreased to 35 mg/dL and 1.56 mg/dL, respectively, along with marked reduction in DSA levels against DR4 (MFI, 787), DR7 (MFI, 3,782), DR53 (MFI, 752), DQ4 (MFI, 1,500), and DQ9 (MFI,
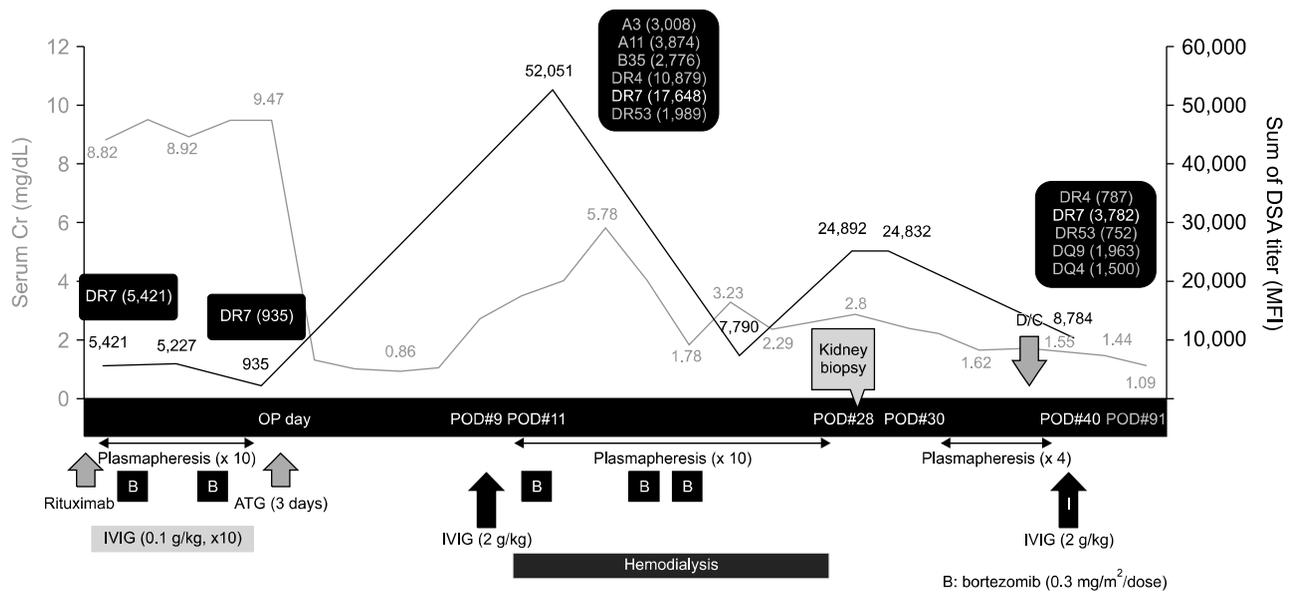


Fig. 2. Laboratory results and treatment over time. This figure shows treatments and changes in serum creatinine (Cr) level (mg/dL) and sum of donor-specific antibody (DSA; mean fluorescence intensity [MFI]) over a certain period. Immediately after transplantation, the serum Cr level decreased to near normal levels but increased on postoperative day 8 (POD8). DSA level was measured to evaluate such changes. The sum of serum DSA level increased and several de novo DSAs were newly discovered. After a combination of 14 therapeutic plasmapheresis sessions, steroid pulse therapy, high-dose intravenous immunoglobulin, and bortezomib administration, the sum of DSA and serum Cr level decreased. Decreased renal function was supported by hemodialysis. Kidney Doppler ultrasound examination showed an increase in resistance index (0.81–0.89). Antibody-mediated rejection (ABMR) was confirmed with biopsy on POD28. OP, operation; ATG, antithymocyte globulin; IVIG, intravenous immunoglobulin.

1,963) on POD40. During the outpatient visit on POD98, the patient's renal functions were stable (BUN, 45 mg/dL; Cr, 1.44 mg/dL). During the course of ABMR, the anti-B antibody titers for IgG and IgM remained low (1:1).

Despite repeated plasmapheresis sessions, the coagulation factors replenished well with each plasmapheresis session and replacement of fresh frozen plasma and albumin, with no transfusion-requiring bleeding episode. Pancytopenia appeared immediately after transplantation and antithymocyte globulin induction, which gradually improved, except for persistent mild anemia. Cytomegalovirus viremia developed approximately 1 month after transplantation, which improved without development of cytomegalovirus disease around 7 weeks after transplantation (Fig. 2).

## DISCUSSION

More than 300 ABOi LDKTs have been performed annually in the recent years since its introduction in 2007 and account for approximately 25% of the total LDKTs in Korea [6]. Short-term ABOi LDKT and ABO-compatible LDKT outcomes are comparable. In Korea, HLAi LDKT has been successfully implemented since 2002, and its frequency was approximately equal to one-third of that of ABOi LDKT [7]. HLAi LDKT indicates LDKT after desensitization in recipients with significant DSA levels showing positive or negative crossmatching results. HLAi LDKT showed better patient survival as compared to HLA-compatible (HLAc) deceased-donor kidney transplantation [8], but exhibited lower graft survival as compared to HLAc LDKT in USA because of high ABMR risk despite appropriate desensitization [9].

**Table 1.** HLA types of recipient and donor

| HLA type | Class I Ag | Class II Ag |
|---|---|---|
| Recipient | A26, A30, B13, B62 | DR13 (*13:01 g), DR14 (*14:06 g) DQ6(*06:03 g), DQ7 (*03:01 g) |
| Donor | A3, A11, B35, B51 | DR4 (*04:05 g), DR7 (*07:01 g) DQ4 (*04:01 g), DQ9 (*03:03 g) |

HLA, human-leukocyte antigen; Ag, antigen.

Acute ABMR occurs in approximately 5% HLAc LDKT patients, but its incidence can increase to 50% in HLAi LDKT patients [10]. Acute ABMR can cause 1-year graft loss in 15%-20% patients and exhibits worse prognosis than that of acute T cell-mediated rejection. It occurs in the first few days per weeks after transplantation and is less responsive to anti-rejection therapy; therefore, it could easily cause chronic allograft dysfunction and graft loss. The 5-year graft survival rate was 60% and 92.5% among patients with and without ABMR, respectively. For long-term survival of the graft, its prevention and treatment is important [1,11], and it is also a major hurdle to overcome in LDKT. Similar to this case, early ABMR usually occurs within the first few days/weeks after HLAi or ABOi LDKT in sensitized patients [12]. Memory B-cells stimulated by alloantigen rapidly increase the preformed DSA levels, and the incidence of early ABMR is closely linked to the DSA level at that time. The incidence is as high as 40% in patients with high DSA levels, whereas it is <10% in those with low DSA levels [13]. Anti-ABO antibody titer higher than 1:32 is associated with a higher ABMR rate in ABOi KT. We need to reduce the preformed DSA and anti-ABO antibody levels before HLAi or ABOi LDKT and maintain them at low levels after LDKT. Anti-ABO antibodies cannot induce overt ABMR when they are maintained at low levels during the initial 3-4 weeks, especially after ABOi LDKT, and this phenomenon is called accommodation. It explains the better prognosis of ABOi KT than that of HLAi KT, and emphasizes the importance of controlling the DSA levels rather than anti-ABO antibodies during simultaneous HLAi and ABOi LDKT.

ABMR diagnosis is based on kidney biopsy and DSA test results. Diagnosis of biopsy-proven ABMR is based on the Banff criteria [11,14]. Here, both DSA titer and spectrum increased, probably owing to the boosting effects exerted by alloantigen stimulation, while the kidney biopsy demonstrated microvascular inflammation and vasculitis along with C4d deposition, confirming the ABMR diagnosis.

Optimal regimens of ABMR prevention and treatment have not yet been established due to the lack of random-

ized controlled trials. However, the current care standard comprises of therapeutic plasmapheresis and IV-Ig with rituximab or bortezomib. Recently, complement inhibitors, including eculizumab, have also been introduced [1]. Despite desensitization in this case, our patient exhibited DSA levels higher than those before transplantation and developed severe, dialysis-dependent, early ABMR. Combination of 14 therapeutic plasmapheresis sessions, steroid pulse therapy, high-dose IV-Ig and bortezomib improved this severe ABMR. We used two doses of bortezomib in desensitization because our center had often experienced cases of side effects, such as gastrointestinal troubles, with three to four doses of bortezomib. Interestingly, the anti-ABO antibody levels in this patient had not substantially increased after transplantation and did not seem to contribute to ABMR. These results suggested that DSA is a more important risk factor than anti-ABO antibody for ABMR in simultaneous HLAi and ABOi LDKT, and timely treatment can rescue even dialysis-dependent, severe ABMR.

This extreme but rare case of early severe ABMR following simultaneous HLAi and ABOi LDKT emphasizes the focus on rebound DSA and risk of early ABMR, despite a successful initial posttransplant clinical course after desensitization. DSA rebound in this case could be attributed to the booster immune response of memory B-cells that were not completely depleted in the lymph nodes by rituximab treatment or the long-lived plasma cells in the bone marrow that were resistant to bortezomib or were replenished by humoral compensation [4,13]. Humoral compensation indicates that increased germinal center B-cells and follicular helper T-cells under B-cell activating factor (BAFF) can replenish plasma cells again after initial depletion [1,4]. Therefore, combination of bortezomib with BAFF inhibitors or belatacept that interferes with B-T interaction could be used to overcome humoral compensation for refractory DSA [15]. Due to this limitation of the current regimens, it is essential to monitor DSA and anti-ABO levels in HLAi or ABOi LDKT during the initial 3-4 weeks after desensitization.

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