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Successful Third Kidney Transplant After Desensitization for Combined Human Leucocyte Antigen (HLA) and ABO Incompatibility: A Case Report and Review of Literature

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 30
Final Diagnosis: 3rd kidney transplantation with HLA and ABO incompatibility
Symptoms: Renal failure
Medication: —
Clinical Procedure: Desensitisation
Specialty: Nephrology

Objective: Unusual or unexpected effect of treatment

Background: In the present era, kidney transplantation across immunological barriers (ABO incompatibility and human leucocyte antigen (HLA) incompatibility) is a successful strategy to provide transplantation to immunologically high-risk patients. The safety and outcome of crossing both ABO and HLA barriers simultaneously in a retransplantation scenario is rarely reported from the developing world.

Case Report: A 30-year-old female underwent a third living donor kidney transplantation. Her previous 2 transplants being lost to chronic allograft nephropathy. The transplantation was done across a simultaneous blood group as well as HLA incompatibility. The donor was the mother who was blood group B, with the recipient being blood group O. The complement dependent cytotoxicity crossmatch of the pair was negative but the flow cross match for T as well as B lymphocytes was positive. The mean fluorescence intensity value for class I antigens was 6951 and that for class 2 antigens was 7534. The patient underwent a desensitization procedure including rituximab, plasmapheresis and intravenous immunoglobulin pre-transplantation. The pre-transplantation isohemaglutunin titer was <1: 8 and the donor specific antibody against class 1 antigens was <2200 and <770 against class 2 antigens. Induction was done with anti-thymocyte globulin in the dose of 3 mg/kg in 2 divided doses. The patient is maintained on triple immunosuppression with tacrolimus, prednisolone and mycophenolate mofetil. After a follow-up period of 5 months, she maintains a good graft function with serum creatinine of 1.01 mg/dL.

Conclusions: With the advances in the desensitizing procedures in the developing world, kidney transplantation across a combined HLA and ABO incompatible barrier can be offered to these highly sensitized patients, even in case of retransplantation.

MeSH Keywords: ABO Blood-Group System • Antibody Specificity • Immunosuppression • Kidney Transplantation

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/913690

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Background

Kidney transplantation remains the choice of treatment for end stage renal disease (ESRD) and has significant survival benefit over long-term dialysis [1]. Even a third or fourth retransplantation is thought to exert survival benefit and as such more and more patients are considered for retransplantation [2,3].

Short-term graft survival has significantly improved while long-term graft survival remains static, hence a large number of patients are relisted as potential transplant recipients and received retransplantation after failed transplants [4,5].

Kidney transplantation is severely limited by ABO incompatibility and histo-incompatibility. In the twenty-first century, it has become possible to perform organ transplantation across antibody incompatible donors and there is a survival benefit of transplantation instead of remaining on the transplant waiting list or receiving a deceased donor transplant organ [6,7].

To overcome both blood group as well as human leucocyte antigen (HLA) incompatibility in the event of a third kidney transplant is a challenging situation. We hereby report the case of a patient who underwent a successful third kidney transplantation despite combined blood group and HLA incompatibility.

Case Report

A 30-year-old non- diabetic, normotensive female patient came to our hospital for third kidney transplantation. She was diagnosed to have ESRD in 1999 (native disease not known) and had undergone 2 previous kidney transplantations. She underwent the first living donor kidney transplantation in June 2002 by an altruistic donor. The first graft was lost due to chronic allograft nephropathy after 6 years. She underwent a second kidney transplantation in 2009 by an altruistic donor. After 8 years, the second graft was also lost to chronic allograft nephropathy.

The only available donor for the third kidney transplantation was her mother who was blood group incompatible. The mother's blood group was "B" and her daughter's was "O". The pair had 3/6 HLA mismatch and the anti- B antibody titer was 256 (IgG). Though the complement dependent cytotoxicity (CDC) crossmatch was negative, the flow cytometry crossmatch (FCM) was positive for both T and B lymphocytes. Donor specific antibody (DSA) by Luminex against both HLA class I and II were strongly positive, with mean fluorescence index (MFI) of 6951 and 7534 respectively.

Single antigen bead (SAB) assay revealed that the DSA against non-matching HLA alleles B*40: 01 and B*40: 02 (class 1) and DRB1*15: 01: 02: 03 (class II) of the donor present in the recipient serum in much higher MFI than permissible for a successful transplantation, in other words; 6806, 4828, and 7534, 5988, 3812 respectively.

After risk explanation, the pair agreed to the transplantation. The recipient patient was commenced on a de-sensitization protocol which comprised of rituximab, plasmapheresis, and intravenous immunoglobulin (IVIG). Rituximab was given in the dose of 500 mg, 2-weeks prior to the transplantation procedure. She was commenced on triple immunosuppressants, tacrolimus 3 mg twice daily (0.15 mg/kg), mycophenolate sodium 360 mg 3 times daily, and prednisolone 20 mg/day 2 weeks prior to transplantation. Absolute CD-20 count was 93 cells/µL before giving rituximab. She was given 10 sessions of plasmapheresis (PP) followed by 5 gm IVIG after each session. Fresh frozen plasma of B blood group was used as replacement fluid in addition to 0.9% normal saline and Ringers lactate. After desensitization the anti-B antibody titer came down to 1: 8 and DSA (class I) came down to 2200 and class II was 770. The absolute CD-20 count was 5 cells/µL (<1%) at the time of transplantation. Induction comprised of 2 doses of methylprednisolone of 500 mg each and rabbit anti-thymocyte globulin (rATG) 3.0 mg/kg of bodyweight.

She was given piperacillin-tazobactam as the antibiotic cover during and in the post-transplantation period. The third kidney allograft was placed intraperitoneally through a midline vertical incision. The renal bed was prepared by opening the peritoneum. The ascending colon, caecum, and terminal parts of small bowel were mobilized medially by dividing the retroperitoneum along the line of Toldt. There was a single renal artery and vein and single ureter. The reconstructed single stump of renal artery was anastomosed end to side to right common iliac artery. The renal vein was anastomosed to the common iliac vein. Ureter anastomosed to dome of bladder via by Lich-Gregoir technique. On declamping the kidney revascularized immediately and urine output started within 5 minutes. Total cold ischemia time was 30 minutes whereas warm ischemia time was 5 minutes. Anti-B antibody titers were monitored daily and stabilized at 1: 8 post-transplantation (Figure 1 shows the course of anti-B antibody titers).

She was discharged 2 weeks post-transplantation with tacrolimus at 4.0 mg twice daily, MMF 360 mg thrice daily, prednisolone 20 mg once daily. On discharge the serum creatinine level was 1.04 mg/dL and the tacrolimus level was 8.12 ng/mL. Figure 2 shows the graft function in the post-transplantation period. She was given cytomegalovirus prophylaxis with valganciclovir 450 mg once daily and trimethoprim/sulfamethaxazole (80/400 mg) once daily. She is being followed regularly in the transplant clinic. Her serum creatinine at 5-month post-transplantation was 1.01 mg% and anti B antibody titer was 1: 16.

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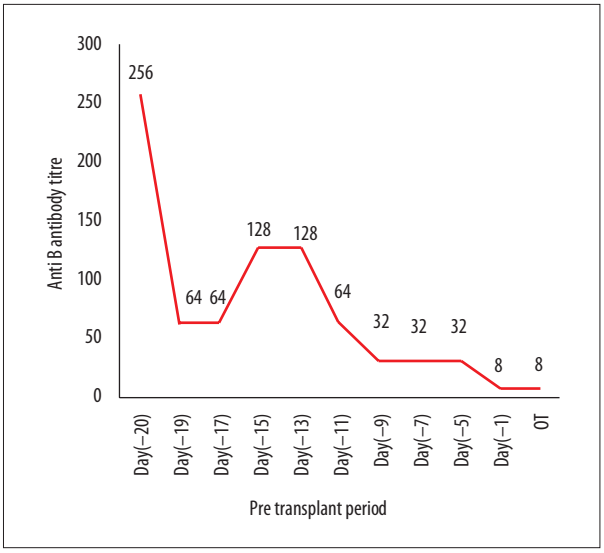

Figure 1. Anti-B antibody titers.

Discussion

There has been a significant improvement in the graft survival over the past 3 decades due to the advances in transplantation immunology. Despite this, the half-life of primary kidney transplants is 8.8 years for deceased donors and 11.9 years for living donor transplants [8,9].

After graft failure, the rates of retransplantation are increasing as even retransplantation offers a survival advantage and better quality of life over dialysis [10,11].

Blood group as well as HLA incompatibility are the major reasons of rejection of otherwise healthy donors. In the present era, kidney transplantation across ABO incompatibility generally produces excellent outcomes which are comparable to those of ABO compatible transplantation [12–14]. More than 30% of potential kidney transplant recipients have pre-existent anti-HLA antibodies. HLA sensitized patients present vexing problems as they express multiple alloantibodies and result in cross-match positivity. Patients transplanted across these barriers without adequate desensitization are at high risk of graft loss due to acute and/or chronic antibody mediated rejection [15,16]. Sensitized patients on dialysis have a death rate twice the rate of sensitized patients who receive transplantation after desensitization [17]. Montgomery et al. reported a survival benefit of HLA sensitized patients who underwent desensitization with low complication rates [6]. Desensitization is an important tool to overcome these immunological barriers. Desensitization protocols combining rituximab, IVIG, and plasmapheresis along with better risk stratification of immunological risk using sensitive DSA screening have been developed to improve the patient and graft survival in these patients [6,18,19]. Antimicrobial resistance and inferior graft outcomes remain the 2 most important obstacles to successful kidney transplantation in HLA and ABO incompatible kidney transplantations [16].

Living donor antibody incompatible retransplantation is both immunologically and surgically challenging. Several studies have shown increased blood loss and ureteric and vascular complications because of significant fibrosis and scarring [21–25].

In a National Registry Analysis of incompatible transplants from the UK there were 521 HLAi and 357 ABOi kidney transplant recipients: 55 of them were combined HLA and ABO incompatible and were included in the HLAi group. Whereas, 47% of the HLAi group were re-transplants and 10% in the ABOi group were retransplants. The 5-year transplantation survival rate were 71% for the HLAi group and 83% for the ABOi group compared with 88% for standard living donor group and 78% for standard deceased donor transplant group [26].

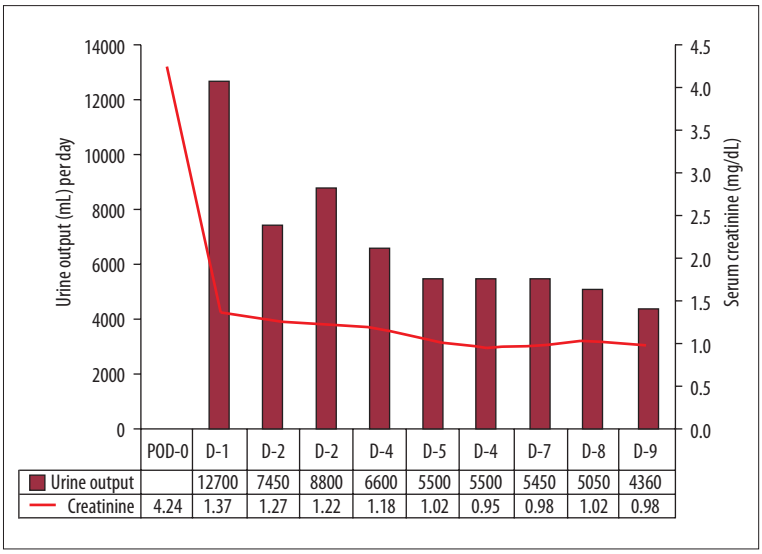

Figure 2. Urine output and serum creatinine levels.

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Table 1. Studies of kidney transplantation cases in ABO and HLA incompatible patients.

Author and time frame	Study type	Number of patients	No. of transplant and patients		Age (Yrs) mean ±SD	Graft survival	Patient survival	Follow up period
Pankhurst L. et al. [26] 2001–2012	Comparative Cohort Study UK National Registry	Total 879 ABOi 357 HLAi 522 ABOi+HLAi 55 *Included in HLAi group for analysis*	1 2+ 1 2+	322 35 275 247	46±14 45±12	83% 71%		5 years
Maheshwar K.A. et al. [20] 2007–2012	Single Center Prospective	Total 124 ABOi 39 HLAi 85 ABOi+HLAi 3 *Included in ABOi group for analysis*	1 2/2+	99 25	43 (15–83)	96%	98%	23 mths (1–53 mths)
Ko E.J. et al. [27] 2009–2012	Cohort study Comparative	Total 1964 ABOi 144 HLAi 248 ABOi+HLAi 31	2/2+ 2/2+ 2/2+	16 19 6	44.2±12 45.8±11 47.1±9	98.7% 100% 100%	97.5% 98.6% 96.7%	26.2+9.7 mths
Sharif A. et al. [28] 1998–2010	Single Center Prospective Database Analysis	Total 317 ABOi 68 HLAi 221 ABOi+HLAi 28	2/2+	16		79% 87% 82%	85% 88% 93%	36.2 mths
Barnes J.C.H. et al. [29] 2003–2011	Retrospective	Total 66 HLAi 66	1 2 2+	22 22 22	43.5±1.6 42.1±2 41.4±1.4	83.1% 85.6% 95%	82.5%	

In a study of 124 incompatible recipients, 85 recipients were HLAi and 39 recipients were ABOi. Three patients were both HLA and ABO incompatible. There were 20% of patients who were re-transplants. After a median follow-up of 23 months, patient survival was 98% and death censored graft survival was 96% [20].

In a nationwide cohort study done in Korea, there were 31 kidney transplant recipients who were both ABO and HLA incompatible. The patient survival rate was lower than the control group and desensitization was found to be an independent risk factor for mortality. 19.4% of patients in this group were re-transplants. The follow-up period was 26.2±9.7 months. The incidence of biopsy-proven acute rejection in the combined ABOi and HLA I group was higher than the control group, but the allograft survival remained same, the rejections were mainly late rejections. HLA incompatibility, irrespective of ABO incompatibility was found to be a significant risk factor for biopsy-proven acute rejection [27].

One study looked at outcomes of kidney transplant recipients transplanted across simultaneous ABO and HLA incompatibility (n=28) compared to recipients with ABO incompatibility (n=68) or HLA incompatibility (n=221) alone [28]. In the combined ABO and HLA incompatibility group, 57% of the recipients were re-transplants out of which less than half had received 2 or more transplants. In the study, 8% were CDC positive, 61% were flow cross match positive, and 31% were Luminex positive. Concomitant anti-human globulin (AHG) isohemagglutinin titer was 256 (21%), 128 (11%), 64 (25%), 32 (18%), 16 (14%), and 8 or under (11%). Patient and death censored graft survival at 1-year was 96% and 93% respectively. After a median follow-up of 1088 days, patient and death censored graft survival was 92% and 82% respectively. In the HLA incompatible group, the patient and death censored graft survival was 88% and 87% whilst in the ABO incompatible group the patient and death censored graft survival was 85% and 79% [28].

In a comparative study where the outcomes of recipients of third and fourth kidney transplantation were compared with first and second transplantations, no significant difference was found in graft and patient survival over 5 years of follow-up. The 5-year allograft survival was 83.6% for the first transplantation, 85.6% for the second transplantation, and 95% in the third and fourth transplantation. The 5-year recipient survival was 82.5% for first, 100% for second, and 95% for third and

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fourth kidney transplantation. On comparing the living donor HLA incompatible versus the deceased donor compatible third and fourth transplantations, no statistical difference was seen in the allograft survival or estimated glomerular filtration rate at any time between the 2 groups [29]. All the aforementioned studies are summarized in Table 1.

Our patient who underwent a third kidney transplantation after desensitization for simultaneous blood group and HLA incompatibility had a good graft function at least in the short-term. Even with limited resources the results are at par with the developed world.

Conclusions

With the advent of various desensitizing protocols, it has become possible to offer kidney transplantation as a modality of treatment to patients with ESRD who are highly sensitized with combined blood group and HLA incompatibility, even in the case of repeat transplantation.

References:

1. Wolfe RA, Ashby VB, Milford EL et al: Comparison of mortality in all patients on dialysis awaiting transplant and recipient of first cadaveric transplant. N Engl J Med, 1999; 341: 1725–30
2. Rao PS, Scharbel DC, Wei G, Fenton SS: Evaluating the survival benefit of kidney retransplantation. Transplantation, 2006; 82: 669–74
3. Park SC, Moon IS, Kof YB: Second and third kidney transplant. Transpl Proc, 2006; 38: 1995–97
4. Magec JC, Barr ML, Basadonna GP et al: Repeat organ transplant in the US (1996–2005). Am J Transplant, 2007; 7(S 2): 1424
5. Rao PS, Ojo A: Organ retransplantation in US: Trends and implications. Clin Transplant, 2008; 57–67
6. Montgomery RA, Lonze BE, King KE et al: Desensitisation in HLAiKTR and survival. N Engl J Med, 2011; 365(4): 318–26
7. Orandi BJ, Luo X, Massie AB et al: Survival benefit from HLAi live donors. N Engl J Med, 2016; 374: 940–50
8. Meier-Kriesche HU, Schold JD, Kaplan B: Long term renal allograft survival: have we made significant progress or is it time to rethink our analytic and therapeutic strategies? Am J Transplant, 2004; 4: 1289–95
9. Lamb KE, Lodhi S, Meier-Kriesche HU: Long term renal allograft survival in the United States: A critical reappraisal. Am J Transplant, 2011; 11: 450–62
10. Izquierdo L, Peri L, Piqeras M et al: Third and fourth kidney transplant: Still a reasonable option. Transplant Proc, 2010; 42: 2498–502
11. Redfield RR, Gupta M, Rodriguez E et al: Graft and patient survival outcomes of a third kidney transplant. Transplantation, 2015; 99: 416–23
12. Tanabe K, Ishida H, Inui M et al: ABOiKT: Long term outcomes. Clin Transplant, 2013; 307: 312
13. Takahashi K, Saito K, Takahasa S et al: Excellent long-term outcome of ABOi LKDT in Japan. Am J Transplant, 2004; 4: 1089–96
14. Montgomery JR, Berger J, Warren D et al: Outcomes of ABO-incompatible kidney transplantation in the United States. Transplantation, 2012; 93: 603–9
15. Loupy A, Hill GS, Jordan SC: The impact of DSA anti-HLA antibodies on late kidney allograft failure. Nat Rev Nephrol, 2012; 8(6): 348–57
16. Vo AA, Sinha A, Haas M et al: Factors predicting risk for AMR and graft loss in highly sensitized patients transplanted after desensitization. Transplantation, 2015; 99(7): 1423–30
17. Matas AJ, Smith JM, Skeans MA et al: OPTN/SRTR 2012 annual data report. Am J Transplant, 2014; Suppl. 1: 11–44
18. Vo AA, Choi J, Cisneres K et al: Rituximab and IVIG for desensitization during renal transplantation. N Engl J Med, 2008; 359(3): 242–51
19. Jordan SC, Vo A, Bunnapradist S et al: IVIG inhibits cross match positivity and allows for successful transplant in incompatible organs in living donor and cadaver recipients. Transplantation, 2003; 76: 631–36
20. Maheshwar KA, Pall A, Chaballout A et al: Outcomes of desensitisation in HLA and ABO incompatible living donor kidney transplantation – A single center experience of more than 100 patients. Transplant Proc, 2013; 45(4): 1423–26
21. Kienzl-Wagner K, Mark W, Maglione M et al: Single center experience with third and fourth kidney transplants. Tranplant Int, 2011; 24: 780–86
22. Halawa A: The third and fourth renal transplant: Technically challenging but still a valid option. Ann Transplant, 2012; 17: 125–32
23. Mazzuchi E, Danilovic A, Antonopoulos IM et al: Surgical aspects of third and subsequent renal transplants performed by extraperitoneal access. Transplantation, 2006; 81: 840–44
24. Nourbala MH, Ghaheri H, Kardavani B: Our experience with third renal transplantation: results, surgical techniques and complications. Int J Urol, 2007; 14: 1057–59
25. Ooms LS, Roodnat JI, Dor FJ et al: Kidney retransplantation in the ipsilateral iliac fossa: A surgical challenge. Am J Transplant, 2015; 15: 2947–54
26. Pankhurst L, Hudson A, Mumford L et al: The UK National registry of ABO and HLA antibody incompatible renal transplantation: Pre-transplant factors associated with outcomes in 879 transplants. Transplant Direct, 2017; 3(7): e181
27. Ko EJ, Yu JH, Yang CW, Chung BH, Korean Organ Transplantation Registry Study Group: Clinical outcome of Abo and HlAiKT: A nationwide cohort study. Transplant Int, 2017; 30(12): 1215–25
28. Sharif A, Alachakar N, Kraus E et al: Kidney transplant across simultaneous ABO/HLA incompatible barriers is similar to either ABO or HLA incompatible transplant for safety and efficacy. Transplantation, 2012; 10S: 178
29. Barnes JCH, Goodyear SJ, Imray CEA et al: Kidney retransplantation from HLA-incompatible living donors: A single center study of third and fourth transplants. Clin Transplant, 2017; 31: e13104

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