Austin Transplantation Sciences

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Case Report

HLA Incompatible Successful Renal Transplantation Across Bw4/Bw6 Alleles in Two Patients

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Received: December 12, 2017; **Accepted:** March 02, 2018; **Published:** March 09, 2018

Abstract

Two female patients with End–Stage Renal Disease (ESRD), who had Donor Specific Antibodies (DSA) against HLA- Bw4/ Bw6 and a positive flow cytometric B cell cross-match were successfully transplanted in Belfast from a pooled pair program after desensitization. Post-transplant; both patients developed deranged renal function which was corrected with plasmapheresis. Histopathological examination was confirmatory for antibody mediated rejection in first recipient but nonspecific in the second. Analysis of the antibody profile of the patients suggests that the cumulative Mean Fluorescence Intensity (MFI) rather than immune-dominant MFI needs to be considered particularly if there is reactivity on flow cross-match. This interesting case report is presented on account of its rarity in literature.

Keywords: HLA incompatible renal Transplant; Bw4/Bw6; Donor specific antibodies

Abbreviations

AMR: Antibody Mediated Rejection; BSHI: British Society for Histocompatibility and Immunogenetics; CDCXM: CDC Cross-Match; CREG: Cross Reactive Group; DSA: Donor Specific Antibody; FCXM: Flowcytometry Cross-Match; HLA: Human Leukocyte antigen; HLAi: HLA incompatible; IVIg: Intra Venous Immuno globulin; KSS: UK Living Donor Kidney Sharing Scheme; MFI: Mean Fluorescence Intensity; MMF: Mycophenolate Mofetil µ mol/L: Micromoles/litre; PRA: Panel Reactive Antibody; POD: Post Operative Day; SAB: Single Antigen Bead

Case Report

HLA Incompatible (HLAI) renal transplantation with desensitization is being increasingly performed in Northern Ireland because it results in better quality of life and improved survival compared to long term maintenance dialysis [1]. Risk stratification for potential recipients in the United Kingdom is performed according to British Society of Histocompatibility and Immunogenetics (BSHI) / British Transplant Society (BTS) guidelines, which involves comprehensive evaluation by a combination of Complement Dependent Cytotoxicity Cross-Match (CDCXM), Flowcytometry Cross-Match (FCXM) and Luminex Single Antigen Bead (SAB) assay, and correlation with sensitization history [2]. Transplanting successfully across a broad specificity such as HLA- Bw4 or Bw6 may prove more difficult, because non–DSA reacting with Bw4 or Bw6 epitopes could have an additive effect and hence greater overall reactivity even if reactivity against the donor mismatched allele is low. In this paper the workup leading to successful outcome of two HLAI transplants performed in Belfast City Hospital is presented. Maintenance immunosuppression was with the triple drug regimen of Prednisolone, Mycophenolate Mofetil (MMF) and Tacrolimus.

Case 1

Sixty-seven year old multiparous Caucasian woman developed ESRD due to antineutrophil cytoplasmic antibody positive vasculitis, for which peritoneal dialysis was commenced in June 2014. Both HLA -class I and II IgG antibodies including HLA- B35, B60, B71, B75, DPB11, DR103 and DR7 were as defined unacceptable on SAB assay. The T and B cell IgG Calculated Reaction Frequency (CRF) were 30% and 54% respectively. Her husband was considered suitable as a potential living donor but tested FCXM positive and she had high DSA against his mismatched antigens (Table 1). The recipient and her spouse were entered into the UK Living Donor Kidney Sharing Scheme (KSS). She received a kidney offer (1-1-1) match grade. All initial cross-matches (CDC and Flow) against the donor were negative except for weak historical B cell FCXM positive. Final FCXM was weakly positive against T cells and strongly against B cells which was attributed partially to non–specific reactivity due to transportation and ineffective pronase treatment, as DSA was negative on Luminex SAB. Further evaluation against another Bw4/ Bw6 volunteer whose freshly obtained cells gave a negative FCXM result. SAB assay showed peak MFI of 3466 against B35 (highest ranked Bw6) and MFI <50 against mismatched donor (B55–Bw6). She was administered Rituximab for induction in a dose of 375mg/ m2 and received the standard triple immunosuppressive regimen comprising of Prednisolone 20 mg once a day, Mycophenolate Mofetil 1000 mg twice a day and Tacrolimus 0.1 mg/Kg at the time of transplant. Post-transplant her graft function was excellent and she was discharged from the hospital. The patient developed graft pyelonephrtis which necessitated reduction in immune suppression and packed erythrocyte infusion following which she developed biopsy proven antibody mediated rejection six weeks after transplant. SAB assay showed MFI of 1026 against the immune dominant DSA, but her renal function improved rapidly with plasma exchange at no point of time. The cumulative DSA was higher than 1500 as seen in serial record of DSA until ten months post –transplant (Table 2). The patient had excellent renal function at one-year post transplant the serum creatinine and estimated GFR were176 µl/l and 26 respectively.

Citation: Mahendra NM, Miceal C, Aisling C and Jeanie M. HLA Incompatible Successful Renal Transplantation Across Bw4/Bw6 Alleles in Two Patients. Austin Transplant Sci. 2018; 3(1): 1007.

Table 1: HLA typing of recipients, spouse and donor and pre-transplant Donor specific antibodies.

	HLA- A	-B	- Cw	0	0	0	Cumulative MFI
Patient 1	2, -	27, 44	1, 5	1, 4	5, 7	4, -	
Spouse (1)	2,68	35, 44 (Bw6)	4, 16	103, 7	2, 5	4, 11	
MFI	432	3077		7261	6043	4266	21079
Donor 1	2, 25	44, 55 (Bw6)	5, 9	4, 14	5, 7	4,-	
MFI	668	869	0	786			2323
Patient 2	1, 2	7, 8	7, 7	103, 7	2, 5	1, 2	
Spouse(2)	3, -	15, 44 (Bw4)	5, 9	4, 15	6, 8	4, -	
MFI	0	1928	0				1928
Donor 2	2, 3	57 (Bw4), 60	6,10	7, 16	6, 8	Not done	1045
MFI	0	1045	0				

Table 2: Values of DSA for ten months in Recipient 1.

Date	A68	B55 (Bw6)	Cw9	DRB14	DRB3	**Total**
14.04.16	35	62	0	311	65	**473**
16.04.16	9	25	0	523	50	**607**
18.04.16	0	3	0	424	62	**489**
20.04.16	38	46	0	310	39	**433**
26.04.16	0	17	0	429	24	**470**
10.05.16	28	33	0	786	96	**943**
17.05.16	38	44	0	635	30	**747**
27.05.16	62	29	9	385	37	**522**
*14.06.16	120	87	66	346	407	**1026**
28.06.16	53	20	14	388	276	**751**
30.08.16	8	18	0	211	17	**254**
01.11.16	0	0	0	138	1	**139**
07.02.17	103	14	0	138	0	**255**

*Time of suspected Antibody mediated rejection

Case 2

A 68 years old Caucasian lady with history of three pregnancies developed insidious ESRD, presumed to be due to interstitial nephritis, and was entered in the UK KSS with her husband (to whom she had DSA and positive T and B cell FCXM). HLA typing results for the patient, her spouse and potential donor are shown in (Table 1). Luminex screen consistently showed pan HLA-class I reactivity, SAB assay demonstrated activity against some alleles of HLA-B12 CREG and B7 cross reactive groups with maximum reactivity (MFI 2226) against B44, to which she was exposed in pregnancy. Her CRF was 32% IgG. Reactivity against donor Bw4 associated B locus mismatched allele (HLA-B57) was relatively low with an MFI < 1500 on two occasions and reactivity against highest ranked Bw4 associated antigen (B44) was 2520. Except for borderline positive current B cell FCXM, all other evaluation including CDCXM, historical FCXM and current T cell FCXM were negative. Preemptive renal transplant was performed with Rituximab induction which was followed by standard triple drug therapy. She had allograft dysfunction on third postoperative day with a rise in serum creatinine, normal DSA and equivocal histopathological features on biopsy. Creatinine continued to rise despite high dose steroid therapy but fell once antibody removal with plasma exchange was initiated. At one year post –transplant the DSA MFI is 1312 with excellent renal function.

Discussion

In highly sensitized individuals living donor transplantation after desensitization is preferred treatment to waiting for a compatible organ [2]. Both patients in this study had a positive FCXM against their donor which could not be explained on the basis of reactivity against mismatched donor alleles even when the top-ranking allele with Bw4/Bw6 was evaluated. After extensive pre-transplant work up both patients proceeded to transplantation as they were willing to accept intermediate immunological risk. The first patient developed biopsy proven AMR without a large rise in antibody titre, and responded to enhanced immune suppression. The second patient had early graft dysfunction with clinical features consistent with antibody mediated rejection in spite of repeated low MFI (peak value 1928) against DSA, and responded to plasma exchange. A positive T and B cell cross-match against her husband cannot be explained on the basis of HLA DSA MFI values as usually MFI > 4000 is associated with positive flow cross-match [3]. In both recipients post -transplant improvement in renal function with plasmapheresis is suggestive of a diagnosis of AMR. This study is contradictory to that of Leffel et al, who observed that mismatching for Bw4 or Bw6 does not confer additional risk for sensitization or renal allograft failure [4].

Our findings suggest that cumulative MFI needs to be considered for risk stratification when DSA against a mismatched broad specificity is considered. In the first patient reactivity was also observed against many antigens of HLA-B7 CREG including HLA B27 (Bw6) with a cumulative MFI >70000. SAB assay is at best a semi-quantitative assay and MFI may not be directly proportional to reactivity. Therefore, there is a requirement for additional testing of samples in dilution for evaluation of true reactivity. Schintok et al regularly test samples with high PRA in 1:8 dilutions and suggest that the strength of an antibody directed against shared epitope would be diluted may not truly reflect its clinical significance [5].

Conclusion

The case report highlights that the cumulative reactivity against mismatched broad specificity may be considered when assessing patients with antibodies against a broad specificity for HLA incompatible transplantation especially if unexplained cross-match positivity is observed that can't be explained on the basis of Luminex SAB assay.

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