Transplant International

LETTER TO THE EDITORS

Transplant glomerulopathy and rapid allograft loss in the presence of HLA-Cw7 antibodies

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Dear Sirs,

Transplantation is the preferred modality of renal replacement therapy and as re-transplantation frequency increases, sensitized recipients require additional efforts to provide immunologically compatible grafts. Luminex® techniques can be utilized to monitor donor-specific antibodies (DSA) that may influence premature allograft loss. We report the unusual case of anti-HLA-Cw7 antibodies leading to rapid loss of a renal transplant.

The patient was a 21-year-old man (HLA-A3; B51,65; C*08:02,12:03; DRB1*01:01,13:02) with end-stage kidney disease because of congenital renal dysplasia. The first renal transplant from his mother (HLA-A3,24; B14[65],39; C*07:02,08:02; DRB1*13:02;15:01) failed after 5.5 years because of medication noncompliance. He made multiple DSA to his first transplanted kidney allograft (A24, C*07:02, DRB1*15:01). The first transplant was subsequently removed. As a consequence of his previous organ transplant and blood transfusion at the time of transplant nephrectomy, the patient was sensitized [complement-dependent cytotoxicity (CDC) panel reactive antibody peak 25%, confirmed by Luminex®]. The pre-transplant antibody specificities included HLA Class I anti C*07:01, C*07:02, A*23:02, A*24:02, A*24:03, B*54:01 HLA Class II anti-DR15 [mean fluorescence intensity (MFI) 2062]. The patient's father was a donor for the subsequent transplant (HLA-A2,3; B49,51; C*07:01,12:03; DRB1* 01:01,04:01). Because of ABO incompatibility (initial anti-A1 titre N/16 into O recipient) ABO desensitization was undertaken using an established protocol with a single dose of rituximab (375 mg/kg day −30), plasmapheresis (five complete 1.3 l plasma volume exchange) and immunoglobulin (0.5 g/kg day −1). HLA-C locus DSAs HLA-C*07:01 were noted in the pre-transplant serum (MFI 5206), but in the presence of a weak CDC B-cell crossmatch and negative T-cell crossmatch (pre-rituximab) desensitization for ABO incompatibility, with plasma exchange, was undertaken. At transplant, the recipient was CDC cross-match negative with an anti-A1 titre of 1:1 (tested by serial dilution against Dolichos Biflorus Lectin) with no evidence of DSA by enzyme-linked immunosorbent assay [1] or Luminex® single antigen (Table 1) [2]. Standard immunosuppression was utilized (basiliximab induction, prednisolone, tacrolimus and mycophenolate mofetil) in addition to three postoperative plasmapheresis treatments, with immediate graft function. Tacrolimus and mycophenolic acid levels were therapeutic throughout the post-transplant period; anti-A1 titres remained at 1:1. Graft function deteriorated acutely after 428 days; a biopsy demonstrated widespread transplant glomerulopathy and arteriolopathy that failed to respond to intravenous pulse methylprednisolone (1000 mg for three consecutive days), anti-thymocyte globulin (2.5 mg/kg for 7 days, Fresenius, Bad Homburg, Germany), plasmapheresis (6×1.3 plasma volume exchange for 2 weeks) and intravenous immunoglobulin (0.1 g/kg with each plasma exchange). Retrospective analysis of serum samples demonstrated a rise in HLA-Cw7 antibodies predating the deterioration in allograft function (Table 1).

This report is the first to identify HLA-Cw7 associated with rapid development of transplant glomerulopathy. HLA-C*07:01 and −C*07:02, the most common alleles of this locus, demonstrate significant homogeneity particularly at the α1 helix antigen recognition site [3]. Antibodies to both (DSA and non-DSA respectively) developed simultaneously post-transplantation and this phenomenon may be because of epitope sharing. In a recent publication by Duquesnoy and Marrari, 56 HLA class I eplets to define antibodies in relation to the HLA-C locus were described [4]. From this report, a review of the patients HLA antibody repertoire identified 13 eplets (9D, 12 AVR, 63REN, 69KRQ, 69RA, 73AS, 77VSN, 79VRN, 113YD, 147L, 151ARA, 193PL, 267QE) specific for C*07:01/07:02, which are not explicable by the presence of shared eplets from other HLA class I specificities. This case is consistent with Duquesnoy and Marrari's finding that HLA-C antibody producers were exposed to a median of 11 mismatched eplets resulting in increased detection of antibody by solid phase Luminex® testing [4]. Only one previous report has implicated anti-HLA-C antibodies as the cause of acute renal allograft rejection

Table 1. Antibody levels and renal biopsy findings post transplant.

Date (days post-transplant)	Serum creatinine (μmol/l)	Biopsy results	CDC cross-match/ELISA	DSA detected/ Luminex® MFI
14/11/2007	Dialysis dependent	–	Positive cross-match/ negative	C*07:01 – 5206 C*07:02 – 3914
21/7/2008 (day −2)	Dialysis dependent	–	Negative cross-match/ negative	C*07:01 – 0 C*07:02 – 0
23/7/2008 (day 0)	710 (pretransplant); 147 (12 h post-transplant)	Wedge biopsy – mild focal arteriolar hyalinosis, <2% interstitial fibrosis, no glomerular obsolescence, C4d negative	Negative cross-match/ negative	C*07:01 – 0 C*07:02 – 0
28/7/2008 (day +5)	97	Protocol biopsy – sparse inflammatory lymphocytic infiltrate, no rejection, C4d negative	–	N/A
1/9/2008 (day +40)	105	–	–	C*07:01 – 5114 C*07:02 – 4003 (retrospective analysis)
11/11/2008 (day +111)	136	Clinically indicated (rising serum creatinine) – no evidence of rejection, mild interstitial fibrosis (<10% cortical area), mild vascular sclerosis, C4d negative		C*07:01 – 5764 C*07:02 – 4237 (retrospective analysis)
20/4/2009 (day +271)	149	–	–	C*07:01 – 15076 C*07:02 – 15507 (retrospective analysis)
24/9/2009 (day +428)	203	Clinically indicated (acute graft dysfunction) – transplant arteriolopathy and glomerulopathy, superimposed acute cellular rejection, C4d positive	–	C*07:01 – 6996 C*07:02 – 7559 (performed at time of biopsy)
2/10/2009 (day +436)	260	Clinically indicated (8 days after commencing treatment) – continuing severe transplant arteriolopathy and glomerulopathy, diminished lymphocytic interstitial infiltrate, C4d positive	–	–
25/11/2009 (day +490)	361	–	–	C*07:01 – 11997 C*07:02 – 9781
23/12/2009 (day +518)	712 commenced dialysis	–	–	
9/6/2010	On haemodialysis	6 weeks post-transplant nephrectomy	–	C*07:01 – 9972 C*07:02 – 17213

CDC, complement-dependent cytotoxicity; DSA, donor-specific antibody; ELISA, enzyme-linked immunosorbent assay; MFI, mean fluorescence intensity.

[5]. The rapidity of allograft loss was faster than that seen with other DSA, which is usually >3 years [2,6,7], and transplant glomerulopathy is more likely to be associated with class II anti-HLA [6,8]. The HLA-C locus is not typically matched, although matching reduces acute rejection episodes in renal and liver transplants [9,10]. HLA-C cell surface expression is lower than other class I HLA. It is the major ligand for killer immunoglobulin-like receptors that regulate natural killer cell activity [11], and thus may play a role in long-term graft outcome. This report also raises the issue of DSA monitoring with few studies assessing post-transplant antibody levels. It is not known which DSA are deleterious and at what level, or how often they are involved in the pathogenesis of graft

failure. This report strengthens the case that HLA-C is relevant in organ transplantation.

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Conflict of interest

The authors declare no conflict of interest.

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