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Rapid Communication

Late antibody-mediated rejection by *de novo* donor HLA-DP-specific antibody after renal transplantation: A case report

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ABSTRACT

The role of donor HLA-DP-specific antibodies after renal transplantation is controversial, and only pre-formed HLA-DP-specific antibodies have been shown to mediate rejection. Here we present a case of late humoral rejection mediated by *de novo* donor HLA-DP-specific antibodies in a non-sensitized recipient. This unique case demonstrates the pathogenic role of *de novo* anti-DP antibodies and suggests that HLA-DP matching might be relevant for renal transplantation.

1. Introduction

Alloantibodies are involved in hyperacute, acute and chronic allograft rejection, but not all HLA alloantibodies are generally considered pathogenic [1,2]. Particularly, the role of HLA-DP mismatches and of anti-DP antibodies is controversial [3]. Several case reports demonstrated a role for donor HLA-DP-specific antibodies in antibody-mediated rejection (AMR) in sensitized recipients [4–6], and the presence of pre-transplant donor HLA-DP-specific antibodies correlated with the incidence of acute rejection episodes and with a reduced graft function [7–10]. However, the pathogenicity of *de novo* HLA-DP antibodies in previously non-sensitized recipients is unclear. Here, we report a case of *de novo* anti-HLA-DP mediated AMR following renal transplantation.

2. Case description

A 60-year-old Caucasian male with end-stage renal disease of unknown origin received a first kidney allograft from a deceased donor with a complete HLA class II match apart of a single mismatch in the HLA-DP locus (Table 1). Pre-transplant screening by Luminex single antigen beads was negative for anti-HLA class I & II antibodies. Donor and recipient were cytomegalovirus seronegative. The patient received induction therapy with basiliximab, followed by tacrolimus, mycophenolate mofetil and prednisone. The postoperative graft function was good with an eGFR of 76 ml/min (CKD-EPI) 1 month after transplantation. Graft biopsy 2 years after transplantation did not show any sign for rejection, and therefore prednisone was withdrawn. Three and a half years after transplantation proteinuria and a significant deterioration of graft function were registered (Fig. 1). Kidney biopsy demonstrated chronic active AMR with diffuse C4d positivity in peritubular capillaries, transplant glomerulopathy, transplant glomerulitis, peritubular capillaritis and calcineurin inhibitor – arteriolopathy (Fig. 2). Anti-HLA antibody screening by Luminex technology did not detect antibodies specific for HLA class I, and we did not find antibodies against MHC class I-related chain A and B (MICA/MICB) or angiotensin II Type 1 receptor. In contrast, anti-HLA class II turned positive. Further specification by Luminex single antigen bead analysis revealed a broad HLA-DP sensitization, with a donor-specific anti-HLA-DP10 antibody of a maximal MFI 1976 (Table 1). A retrospectively performed anti-C1q luminex assay was negative, indicating that the *de novo* anti-DP antibody was not complement fixing. The patient was treated with intravenous methylprednisolone and 5 sessions of plasma exchange. Transplant biopsy one month after initial evaluation showed persisting chronic active AMR with focal positivity for C4d in peritubular capillaries, transplant glomerulopathy and transplant glomerulitis. Donor-specific

Abbreviations: AMR, antibody-mediated-rejection; eGFR, estimated glomerular filtration rate; MFI, mean fluorescence intensity.

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Table 1
Recipient and donor HLA-typing are reported on the left side, single-antigen anti-HLA antibodies detected 3 years and 8 month after transplantation on the right side. Donor specific anti-HLA-DP10 is indicated in bold.

HLA-typing		Anti-HLA
Recipient	Donor	3 years and 8 months post-tpl
A2, A29	A2, A24(9)	Negative
B44(12), B18	B62(15), B60(40)	Negative
DR1, DR15(2)	DR1, DR15(2)	Negative
DQB1*05, DQB1*06	DQB1*05, DQB1*06	Negative
DPA1*01:03, DPB1*02:01 = DP2	**DPA1*02:01, DPB1*10:01 = DP10**	DPA1*02:01, DPB1*09:01 = DP9 (MFI 3033)
DPA1*01:03, DPB1*04:01 = DP4	DPA1*01:03, DPB1*04:01 = DP4	DPA1*02:01, DPB1*14:01 = DP14 (MFI 2436)
		DPA1*02:01, DPB1*01:01 = DP1 (MFI 2329)
		DPA1*02:01, DPB1*10:01 = DP10 (MFI 1976)
		DPA1*01:05, DPB1*11:01 = DP11 (MFI 1741)
		DPA1*02:01, DPB1*06:01 = DP6 (MFI 1741)
		DPA1*02:01, DPB1*03:01 = DP3 (MFI 1642)
		DPA1*02:01, DPB1*17:01 = DP17 (MFI 1617)
		DPA1*01:03, DPB1*03:01 = DP3 (MFI 1421)
		DPA1*01:03, DPB1*01:01 = DP1 (MFI 1416)
		DPA1*01:05, DPB1*03:01 = DP3 (MFI 1236)
		DPA1*01:03, DPB1*11:01 = DP11 (MFI 1082)
		DPA1*02:01, DPB1*05:01 = DP5 (MFI 986)
		DPA1*02:01, DPB1*18:01 = DP18 (MFI 802)
		DPA1*02:01, DPB1*13:01 = DP13 (MFI 510)

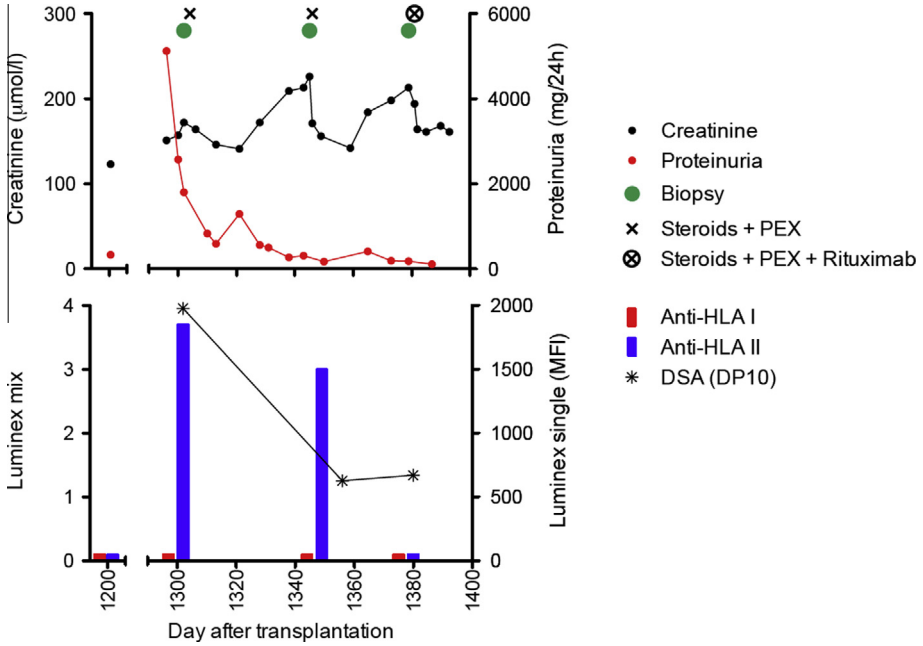

Fig. 1. Summary of the patient's clinical history and concomitant HLA antibody determinations: (upper panel) graft function is indicated by serum creatinine concentration, protenuria was determined by protein–creatinine ratio from morning spot urine. PEX: plasma exchange. DSA: donor specific antibody. (lower panel) Anti-HLA antibody screening is indicated by ratio of patient sample versus negative control serum (Luminex mix, left *x*-axis), donor-specific anti-HLA DP10 antibody (DSA) is indicated by mean fluorescence intensity values (Luminex single antigen bead assay; MFI; right *x*-axis).

anti-HLA-DP10 antibodies were markedly reduced (MFI 628). The patient was treated with two additional cycles of high-dose methylprednisolone, rituximab and 6 sessions of plasma exchange. Allograft function slowly improved and remained stable with an eGFR of 35 ml/min in the following months. A repeat biopsy 6 months later showed transplant glomerulopathy and transplant glomerulitis without C4d reactivity in peritubular capillaries (Fig. 3). Donor-specific antibodies now turned negative. One year after first diagnosis of AMR the patient developed several infectious complications including atypical mycobacteriosis (*Mycobacterium kansasii*/*Mycobacterium gastri*), which required withdrawal from immunosuppression and eventually transplant nephrectomy. No anti-donor-HLA antibody other than the DP antibody was detected throughout the posttransplant period.

3. Methods

Recipient and donor HLA-typing was done by serology and polymerase chain reaction with sequence-specific primers (PCR-SSP).

Anti-HLA antibody screening assay was performed with LABScreen mixed assay (LSM12, OneLambda, Canoga Park, CA). This assay contains a panel of color-coded microbeads coated with multiple HLA antigens to identify class I or II anti-HLA IgG antibodies and was performed according to the manufacturer's instructions. Single-antigen bead assay was performed using a high-definition LABScreen single antigen assay (OneLambda). Serum was added