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The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

CLINICAL DILEMMA

Successful lung transplantation in the presence of pre-existing donor-specific cytotoxic HLA Class II antibodies

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KEYWORDS:
lung transplantation;
HLA antibody;
donor-specific antibody;
rejection;
LSA

Pre-existing HLA antibodies are a well-established causal factor for rejection and graft dysfunction after solid-organ transplantation. In lung transplant recipients, the significance of HLA antibodies has not been fully established. Although rare, several cases of hyperacute rejection of the lung allograft due to pre-existing donor-specific HLA antibodies have been described. In contrast, we describe successful lung transplantation in a patient with pre-existing donor-specific HLA antibodies. Routine screening prior to lung transplantation revealed cytotoxic HLA Class II antibodies, directed against the alpha chain of HLA-DQ, induced by a previous liver transplant. Due to clinical deterioration, it was decided to accept a lung offer without virtual crossmatching for DQ compatibility. Cytotoxic antibodies against the lung donor were confirmed retrospectively, resulting in strong positive B-cell crossmatches. Interestingly, the patient showed no clinical or histologic signs of rejection. This case demonstrates that the presence of high levels of pre-existing donor-specific HLA antibodies does not necessarily lead to rejection and graft failure. Although screening for antibodies prior to transplantation remains crucial, this study shows that we are thus far not able to predict the effect of pre-existing HLA Class II antibodies on allograft survival in individual patients.

J Heart Lung Transplant 2012; 31: 1301–6

Lung transplantation is the final treatment option for patients with end-stage lung disease. Despite a stringent immunosuppressive regimen, complications due to rejection often occur after lung transplantation, severely influencing the long-term survival of lung transplant patients.[1] Donor-specific HLA antibodies, induced by pregnancy, transfusion or transplantation, are a well-established causal factor for hyperacute, acute and chronic rejection after solid-organ transplantation, such as kidney[2,3] and heart.[4] However, in lung transplantation the significance of pre-existing HLA-specific antibodies has not been fully established, which may be partly due to the low incidence of humoral sensitization in the lung transplant population.[5,6] Several cases of severe graft failure due to hyperacute rejection caused by pre-existing donor-specific anti-HLA antibodies have been reported,[7–12] but hyperacute rejection is a rare event after lung transplantation. The degree of humoral sensitization of a patient is determined by measuring

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1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2012.09.015

Table 1 HLA Type of Patient, Liver Donor and Lung Donor

	HLA type	DQA1 type
Patient	A2; B35, 62; Cw3, 4; DR13, 14; DR52; DQ5, 6	DQA1*01, *01
Liver donor	A2, **31**; **B44**, **38**; Cw4; **DR7**, 13; DR52; **DR53**; **DQ2**, 6	DQA1*01, ***02**
Lung donor	**A1**, **68**; **B8**, **B44**; **Cw7**; **DR1**, **3**; DR52; **DQ2**, 5	DQA1*01, ***05**

Mismatches with the patient are shown in bold.

antibody-mediated reactivity toward a defined panel of HLA antigens (panel-reactive antibody, or PRA). Although some studies could not identify differences in graft failure between sensitized and unsensitized patients,[6,13] most have shown that antibodies against HLA are associated with early graft dysfunction and decreased survival in lung transplant recipients.[5,14,15] However, these studies did not discriminate between donor-specific and non–donor-directed HLA antibodies. The effect of PRA on the allograft might therefore be due to donor-specific anti-HLA antibodies, but the concordant existence of antibodies toward non-HLA antigens or a general increased immune responsiveness could also play a role.[16]

In kidney transplantation, prospective crossmatching with donor lymphocytes and recipient serum is mandatory for sensitized patients. In lung transplantation, performing a pre-transplant crossmatch is difficult, as limitations in lung preservation prohibit prolonged ischemia times. Therefore, evaluation of the existence and specificity of HLA-specific antibodies, definition of unacceptable mismatches, and virtual crossmatching are used to prevent (hyperacute) rejection by pre-existing HLA antibodies.[17]

Herein we report a patient with 80% PRA after liver transplantation, who received a bilateral lung transplant without (virtual) crossmatching. The patient showed no signs of rejection, despite retrospective demonstration of donor-specific pre-existing HLA Class II antibodies and positive B-cell crossmatches. To our knowledge, this is the first report of a successful lung transplant in a patient with pre-existing donor-specific cytotoxic HLA antibodies.

Case report

Immunology

A 22-year-old Caucasian woman, blood group O^+, diagnosed with cystic fibrosis, was admitted for bilateral lung transplantation. She had received a liver transplant about 8 years before, because of liver cirrhosis with portal hypertension and hepatopulmonary syndrome. The patient's HLA type is listed in Table 1. The liver donor was mismatched for A31, B44, B38, DR7, DR53 and DQ2 (Table 1).

The patient was negative for HLA Class I and II antibodies before and directly after liver transplantation (Table 2). Before entry on the waiting list for lung transplantation the patient was routinely screened for panel-reactive HLA antibodies (PRA) with the complement-dependent cytotoxicity (CDC) technique. The CDC assay revealed cytotoxicity against HLA-DQ2, -DQ3 and -DQ4 (80% PRA), and also after treatment with dithiothreitol (DTT), indicating the presence of IgG antibodies. Presence of anti-HLA Class II IgG antibodies was also confirmed by enzyme-linked immunoassay (ELISA) (Table 2). A Life-codes Single Antigen assay (LSA; Lifecodes/Gen-Probe, San Diego, CA) demonstrated Class II antibodies to DRB1*07, a mismatch of the liver donor, and to DQA1*02, *03, *04, *05, *06 (Table 3). Subsequent typing for DQA1 revealed the patient to be DQA1*01, *01, but the liver donor was DQA1*01, *02 (Table 1). Analysis of polymorphic amino acid residues[18] showed that DQA1*02 shares epitopes with DQA1*03, *04, *05, *06, which are absent on DQA1*01 (Table 3). As the DQA1 chain is in strong linkage disequilibrium with the DQB1 chain, the identification of antibodies to a shared epitope on DQA1*02 to *06 explains the panel-reactive cytotoxicity to DQ2, DQ3 and DQ4. This case illustrates that antibodies most likely specific for a single epitope on the DQA1 chain can lead to a broad HLA Class II antibody pattern.

Due to strong anti-DQ cytotoxicity, transplantation with a DQ1-compatible lung was advised. However, clinical deterioration necessitated immediate transplantation and, for unknown reasons, this coincided with a decreased CDC

Table 2 Patient's HLA-specific Antibody Status (Determined by CDC, LSA and ELISA) and Retrospective CDC B-cell Crossmatching with the Lung Donor

	HLA Class II antibodies (specificity)			
Time-point of serum	CDC	LSA	ELISA	Retrospective B-cell crossmatch
Screening before liver Tx	−	−	−	−
After liver Tx	−	+ (DQA1*02, *06, DR4)	−	−
Screening before long Tx (2 y)	++ (DQ2, 3, 4)	++ (DQA1*02, *03, *04, *05, *06, DR7)	++	+++
Screening before long Tx (4 mo)	+	++ (DQA1*02, *03, *04, *05, *06, DR7)	++	+
Lung Tx (day of Tx)	++ (DQ2, 3, 4)	++ (DQA1*02, *03, *04, *05, *06, DR7)	++	+
After lung Tx (Day 1)	++ (DQ2, 3, 4)	+++ (DQA1*02, *03, *04, *05, *06, DR7)	ND	+++
After lung Tx (Day 15)	++ (DQ2, 3, 4)	+++ (DQA1*02, *03, *04, *05, *06, DR7)	ND	+++
After lung Tx (Day 77)	++ (DQ2, 3, 4)	+++ (DQA1*02, *03, *04, *05, *06, DR7)	++	+++

−, negative; +, weakly positive; ++, positive; +++, strongly positive; CDC, complement-dependent cytotoxicity; ELISA, enzyme-linked immunoassay; LSA, Life-codes Single Antigen assay; ND, not determined; Tx, transplantation.