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E. von Willebrand
M. Sandberg
K. Salmela
H. Isoniemi
P. Häyry

Expression of ICAM-1 and HLA class II in acute cellular and vascular rejection of human kidney allografts

E. von Willebrand (✉)
Transplantation Laboratory,
Helsinki University of Helsinki,
Haartmaninkatu 3,
SF-00290 Helsinki, Finland

M. Sandberg · K. Salmela
H. Isoniemi · P. Häyry
Fourth Department of Surgery,
University of Helsinki, Finland

Abstract We studied the relationship between ICAM-1 and class II expression on graft tubular cells and the relationship with graft inflammation in 50 kidney transplants monitored with serial aspiration biopsies after transplantation. Of the 50 grafts, 26 had an acute rejection 17 ± 10 days after transplantation, 5 also had acute vascular rejection (AVR) and 24 had no rejection. The initial post-transplant ICAM-1 and class II expression was low in all grafts. All 21 grafts with acute cellular rejection (ACR) displayed ICAM-1 induction, with a peak at the beginning of acute blastogenic rejection and declining over 20 days to prerejection levels. Class II expression reached a peak later and also declined later to prerejection levels. In the grafts with irreversible AVR both ICAM-1 and class II expression remained elevated. The 24 grafts with no rejection displayed no ICAM-1 or class II induction on tubular cells during the follow-up. The differences between ICAM-1 and classs II expression in biopsies with rejection and with no rejection were statistically significant. The results demonstrate that ICAM-1 was induced early during ACR on the graft tubular cells and that it disappeared rapidly in reversible rejections. The induction of class II antigens was slightly slower but quantitatively greater. In the irreversible rejections with a combination of ACR and AVR both ICAM-1 and class II expression remained elevated.

Key words ICAM-1 · HLA class II Acute rejection / Kidney allograft

Introduction

The cellular interactions involved in T-cell activation require adhesion receptors as well as the T-cell receptor for initiating the process. The expression of intercellular adhesion molecule-1 (ICAM-1), which is a ligand for lymphocyte function-associated antigen (LFA-1), is regulated by several cytokines, IL-1, TNF and IFN-gamma, which are produced early during lymphoid and monocytic activation [1–3]. In normal kidneys ICAM-1 is expressed on endothelial cells of capillaries, larger vessels and in the glomeruli, but not on tubular cells [4]. Induction of ICAM-1 on tubular cells has been demonstrated in vitro [5] and also in acute cellular rejection (ACR) of human kidney allografts [4, 6, 7]. The expression of ICAM-1 in acute vascular rejection (AVR) has not previously been studied. The induction of class II antigens on tubular cells is well established in ACR [8–10] and also in the majority of AVR of human kidney transplants [11]. In this study we analysed the expression of

Table 1 ICAM-1 and class II expression in acute cellular and vascular rejection. Values are percent of ICAM-1 and class II-positive tubular cells ±SEM in the aspiration biopsy specimens during the course of ACR and AVR and in normal grafts

	ACR		AVR		Normal		
	ICAM-1	Class II	ICAM-1	Class II		ICAM-1	Class II
Day −5	7±6	5±4	7±5	3±4	Day 5	3±3	5±3
Day 0	21±16**	34±11**	28±14**	48±12**	Day 10	3±4	4±5
Day 2	16±16**	50±16**	19±13**	56±11**	Day 15	5±5	6±5
Day 5	9±9	32±12**	19±12**	47±9**	Day 20	3±4	4±6
Day 10–15	6±5	18±16	20±12**	48±19**			
Day 20–25	3±3	11±7	38±23**	40±15**			

** $P < 0.001$ comparing the normal grafts and the grafts with ACR and AVR

ICAM-1 and class II on graft tubular cells in 50 kidney transplant recipients monitored with serial aspiration biopsies after transplantation.

Materials and methods

A total of 318 aspiration biopsies were obtained from 50 kidney transplants during the first post-transplant month. Of 26 biopsies taken from consecutive transplants with acute rejections, 21 had reversible ACR and 5 also had histological findings of AVR. A group of 24 transplants with no rejections during the same period were studied as controls. Diagnosis of rejection was based on clinical findings, aspiration biopsy cytology and histological examination of biopsy specimens. The rejections occurred on days 7 to 27 post-transplant (mean, day 17).

The patients were monitored with FNABs at 1–3 day intervals during the first post-transplant month. Of the 318 aspiration biopsies performed, 175 were from grafts with ACR (mean, 8.3 per patient), 50 were from grafts with AVR and 93 were from grafts with no rejection (mean, 3.9 per patient).

Evaluation of ICAM-1 and class II expression was done by indirect immunoperoxidase staining using monoclonal antibodies. ICAM-1 was determined in 203 biopsies and class II in 259 biopsies.

Results

Table 1 shows the progression of ICAM-1 and class II expression in the grafts with ACR and AVR and in the normal grafts.

The initial post-transplant ICAM-1 and class II expression was low in all 50 grafts, with 3±4% and 5±3% positive tubular cells, respectively. All 21 grafts with ACR displayed ICAM-1 induction, with a peak of 21±7% positive tubular cells at the beginning of acute blastogenic rejection and declining over 20 days to the prerejection level of 3±3%. Class II expression reached a peak of 50±8% positive tubular cells later, on day 2–5 after onset of blastogenic inflammation, and declined later,in 10–15 days, to the prerejection level. In the grafts with irreversible AVR both ICAM-1 and class II expression remained elevated.

The 24 grafts with no rejection displayed no ICAM-1 or class II induction on tubular cells during the follow-up of 20 days. ICAM-1 expression was consistently low with 3–5% positive tubular cells, and tubular class II expression was also low, with 4–8% positivity. The differences between ICAM-1 and class II expression in biopsy specimens with rejection and in those with no rejection were statistically significant ($P < 0.001$ and $P < 0.001$, respectively).

Discussion

This study confirms the earlier observation that ICAM-1 is induced early during ACR on the graft tubular cells, and also that this induction disappears rapidly in reversible ACR. The induction and down regulation of class II antigens on tubular cells follows somewhat later. The study also demonstrates that in severe rejections with features of AVR ICAM-1 induction persists, as does the induction of tubular class II antigens.

All 21 grafts with ACR displayed ICAM-1 induction, which reached a peak at the very beginning of blastogenic rejection, with 21±7% positive tubular cells, declining thereafter rapidly to the prerejection level of 3±3%. Class II expression peaked somewhat later, on day 2–5 after the onset of blastogenic inflamation, and declined later in 10–15 days to the prerejection level, but it was quantitatively greater, with 50±8% positive tubular cells. In severe AVR the inflammation in the graft continued, as did the induction of ICAM-1 and class IIb antigens, remaining at a level of 30–40% positive tubular cells. The local release of IFN-gamma and other cytokines, especially Il-1 and TNF, by the activated lymphoid and monocytic cells in the rejection infiltrate, is

apparently the mechanism responsible for the induction of both ICAM-1 and class II expression. The progression of both ICAM-1 and class II induction would support this; they were closely related to the monocytic and lymphoid blast cell infiltration of the graft.

The finding that in the 24 grafts with no rejection no induction of ICAM-1 or class II on the tubular cells was found during the follow-up also supports this hypothesis, and neither did these grafts contain any cellular infiltrates.

Induction of ICAM-1 on tubular epithelial cells may augment the adhesion of LFA-1-positive graft infiltrating cells to the tubular cells and thus enhance the rejection process.

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