Hiroshima Journal of Medical Sciences
Vol. 33, No. 1, 1～9, March, 1984
HIJM 33-1

Renal Transplantation in HLA-Identical Sibling Pairs*)

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(Received October 26, 1983)

Key words: Renal transplantation, Histocompatibility antigen, HLA-identical sibling

ABSTRACT

The author experienced 8 cases of renal allograft in HLA-identical sibling pairs, out of which rejection was noted on 2 cases (25%), but 5 years' actuarial graft survival rate was 100%.

According to the records the first year's graft survival rate is rainged from 85% to 100%, and in many cases rejection have occorred at a frequency of 40% or over. Upon studies of these reports, an analysis revealed that there is a possibility of including rejections caused by mistypings and low-dose immunosuppressions.

INTRODUCTION

In the clinical renal transplantation it is widely known that there is a correlation between histocompatibility and graft survival rate upon renal transplantation. As the major histocompatibility angigen of human, HLA-antigen is well known, in human, except for identical twins, graft survival rates upon renal transplantation conducted in HLA-identical siblings corresponding with each other as close as possible in histocompatibility are extremely favorable compared with that of 1-haploidentical and nonidentical groups[6,26,30]. However, even in the well-matched renal allografts some rejections were noted[4,12,29,46,47], which leaves something to be clarified about correlations between the results of renal transplantation and histocompatibility.

The author up to April, 1983, experienced 8 cases of renal allograft in HLA-identical siblings, and noted 2 cases of rejection onset. The rejections occurred on HLA-identical sibling pairs are reported below together with some literal discussions.

MATERIAL AND METHODS

A total of 89 renal transplantations were conducted including 59 cases from September, 1971 to April, 1983 at the Second Depertment of Surgery, Hiroshima University School of Medicine, and 30 cases from December, 1977 to October, 1982 at the Municipal Uwajima Hospital; out of which 8 cases determined as HLA-identical siblings genetically by the histocompatibility test (combining with the family study) were used. One of these 8 cases was of the cadaver renal transplantation.

1) HLA typing:

HLA-A, B, or C typing was conducted by the lynphocytotoxicity test[16], while HLA-DR typing was carried in accordance with the cytotoxicity test using B-cells separated from peripheral blood by the Nylon-wool column method[13]. Detected antigens were A : 14, B : 35, C : 5 and DR : 15 respectively.

2) D typing (Mixed lymphocyte culture):

It was conducted in accordance with Fukuda's micromethod[17]. That is, 5×10^4 responding cells and 5×10^4 stimulating cells (^{60}Co (2000 rad)-treated), as 0.1 ml of the cell suspen-

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sion respectively, were mixed, cultured at 37°C in the presence of 5% CO_2 for 6 days by microculture plate (NUNC), and uptake of ^{3}H-TdR was indicated as the stimulation index (S. I.).

3) Cell mediated lympholysis (CML):

It was conducted in accordance with Ono's method[34] as reported previously. That is, MLC to induce effector cells was conducted with 1×10^6 cells/ml each of responding cells and stimulating cells in a culture tube (Falcon 3033) for 5 days. For target cells, the cells labelled with ^{51}Cr after 3 days' culture adding PHA-P (Difco) to lymphocytes of stimulating cell donor in MLC were used. As to cell-mediated lympholysis 1×10^6 effector cells were added to 1×10^4 target cells and cultured at 37°C in the presence of 5% CO_2 for 4 hours, and radioactivity of emitted ^{51}Cr was measured as experimental release. Spontaneous release was estimated by measuring ^{51}Cr emitted upon single culture of the same number of the target cells, while maximum release was estimated by measuring ^{51}Cr emitted upon suspending the same number of target cells in distilled water containing 1% triton (Nakarai Chemical). A % cytotoxicity was calculated from the following formula as CML:

$$\%\ \text{cytotoxicity} = \frac{\text{Experimental release} - \text{Spontaneous release}}{\text{Maximum release} - \text{Spontaneous release}} \times 100$$

4) Cytotoxicity test:

According to the Nylon-wool column method, T and B cells were separated from peripheral blood. For anti-T cell antibody and warm anti-B cell antibody, lymphocytes and serum were incubated at 37°C for 1 hour and upon addition of complement reacted for 2 hours. For cold anti-B cell antibody, B cells and serum were incubated for 1 hour at 4°C, and upon addition of complement reacted for 2 hours.

Table 1 shows two protocols of the immunosuppressive therapy (Table 1). LD 16, LD 36 and CD 2 were treated with the protocol (2), and the others with the protocol (1). Rejection was determined by clinical findings, immunological monitoring[18,33], and by histological findings to be firmly diagnosed whenever feasible to be biopsied.

Table 1.

Immunosuppression in Renal Transplantation (1)
(1978. 2～1980. 3)

1) ALG
10～20 mg/kg/day, for 2 weeks, daily
2) Azathioprine
−2, −1…2 mg/kg/day
0, +1, +2…5 mg/kg/day
tapering to maintenance dose of 2～3 mg/kg/day (WBC>6000/mm^3)
3) Methylprednisolone (Solu-Medrol®)
0, +1, +2…20 mg/kg/day (i. v.)
4) Methylprednisolone (Medrol®)
−1…100 mg/day (p. o.)
0…52 mg/day (p. o.)
+1～+4…120～80 mg/day (p. o.)
+5～+7…80～64 mg/day (p. o.)
+8～+14…64～36 mg/day (p. o.)
then tapering to maintenance dose of 0. 25 mg/kg /day
5) Local irradiation
150R local irradiation…3～4 times in early postoperative period

Immunosuppression in Renal Transplantation (2)
(1980. 5～1982. 12)

1) ALG
10～20 mg/kg/day, for 2 weeks, daily
2) Azathioprine
−2, −1…2 mg/kg/day
0, +1, +2…5 mg/kg/day
3) Bredinin
−2～…2～3 mg/kg/day
4) Methylprednisolone (Solu-Medrol®)
0, +1, +2…20 mg/kg/day
5) Methylprednisolone (Medrol®)
−1…100 mg/day (p. o.)
0…0 mg/day (p. o.)
+1～+4…120～80 mg/day (p. o.)
+5～+7…80～64 mg/day (p. o.)
+8～+14…64～36 mg/day (p. o.)
then tapering to maintenance dose of 0. 25 mg/kg /day
6) Local irradiation
150R local irradiation…3～4 times in early postoperative period

※ administration of Azathioprine and Bredinin in early postoperative period

PBL (/mm^3)	Azathioprine (mg/day)	Bredinin (mg/day)
<3,000	0	0
3,000≦4,000	25	50
4,000≦5,000	50	50
5,000≦6,500	75	50
6,500≦9,000	100	50
9,000<	125	50

Table 2. HLA Identical Sibling Cases in Renal Transplantation

Case	Sex	Age	Donor	Blood Transfusion (Preop.)	Graft Survival	S-Creat.
LD 13	Male	29	Brother (30)	+	8Y 1M	1.2 (mg/dl)
LD 16	Male	44	Sister (46)	−	6Y 8M	1.5
CD 2	Male	50	Sister (41)	−	4Y 4M	1.9
LD 36	Male	41	Sister (38)	−	2Y 5M	1.6
*LD 17	Male	32	Sister (34)	−	6Y 1M	7.0
*ULD 4	Male	27	Brother (35)	−	4Y 4M	1.8
ULD 11	Male	25	Brother (23)	−	2Y 9M	0.8
ULD 15	Male	49	Sister (42)	−	1Y11M	1.2

* Rejestion Case

Table 3. HLA & Typing in HLA Identical Siblings of Renal Transplant

Locus	HLA Phenotype					ABO
Case	A	B	C	DR	D (S.I)	
LD 13	9,11	W51,15		1,W9	0.9	O
LD 16	2,W31	W48,W39.1	W7,−	N J 3,−	1.0	C
CD 2	2,W31	W51,W35	W3		N.D	A
LD 36	9,W31	W51,W35	W3	W8,N J 2	1.8	O
*LD 17	2,W24	7,W46	X46,W3	W8,1,4	1.1	AB
*ULD 4	9,11	7,W60	W3	4	0.9	A
ULD 11	9,−	W6,W6			1.7	O
ULD 15	9,−	W48,8W57	W4		2.9	B

* Rejection Case

RESULRS

Table 2 shows HLA-identical sibling cases, and Table 3 shows HLA and ABO types in HLA-identical siblings (Tables 2 & 3). One out of 8 cases, CD 2, was of cadaver renal transplantation.

Prognosis of six cases, LD 13, LD 16, CD 2, LD 36, ULD 11 and ULD 15, were uneventful without experiencing rejection, and at present they are under graft survival of 8 years & 1 months, 6 years & 2 months, 4 years & 10 months, 2 years & 11 months, 3 years & 3 months and 2 years & 5 months respectively showing favorable renal functions with S-creatinine of 1.2, 1.5, 1.9, 1.6, 0.8 and 1.2 mg/dl respectively.

The author experienced two cases of rejection out of 8, namely, LD 17 and ULD 4. Fig. 1 shows the course of LD 17 (Fig. 1). One week after the operation the patient had a gastrointestinal bleeding and diagnosed as multiple duodenal ulcer by the endoscopical examination. Maintaining favorable renal function the patient was cured by the conservative

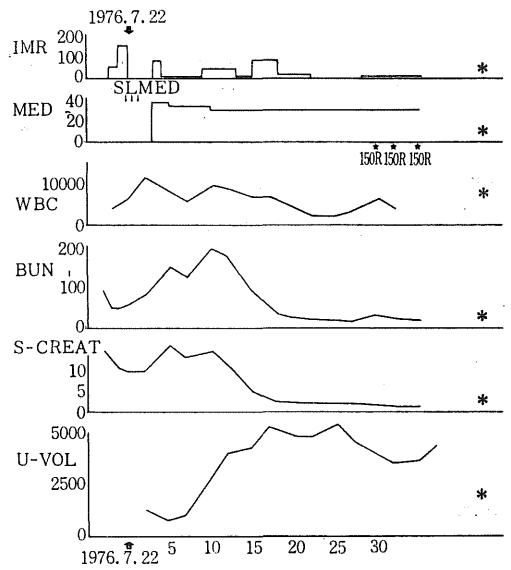

Fig. 1. LD 17

therapy as blood transfusion, ets. Scince about 1 month after the operation gradually renal hypofunction appeared, which was determined as rejection. Even after the pulse therapy with Solu-Medrol and local irradiation, renal hypofunction was not improved being gradually aggravated. For the time being, 6 years and 6 months after transplantation, BUN is 28 mg/dl, and S-creatinine is 6.5 mg/dl. In this case rejection was clinically determined and confirmed later by biopsy. Because renal hypofunction progressed extremely slow, hemodialysis has not been needed up to date. Before onset of renal hypofunction no complication with infectious diseases considered to be a precipitating cause of rejection was noted. Table 4 shows the red cell types of this case

Table 4. Red Cell Typing (LD 17)

	ABO	MN	Rh	P
Recipient	AB	MN	cDE	P(+)
Donor	A	MN	CcDEe	P(+)

(Table 4). MN and P of the donor and the recipient are corresponding with each other, while Rh is not. C and e are the brought-in antigens to the recipient. Irregular antigen in red cells was negative. Meanwhile, this is a transplantation of different red cell types from A to AB.

Table 5 shows the results of MLC and CML reactions on each case followed up for the purpose of detecting the cellular immunity. Including LD 17 with rejection, MLC reaction

Table 5. Cellular immunity of renal allograft recipients in HLA-identical siblings

	MLC (S. I)		CML	
	Pre. Tx.	Post. Tx.	Pre. Tx.	Post. Tx.
LD 13	0.9	0.9(1Y7M)		
LD 16	1.0	0.9(2M)		RDm-D −9.0% (2M)
				RDm-D −7.1% (3Y6M)
LD 17	1.1	1.1(3M)		R-D 0.2%(1Y9M)
		1.8(1Y8M)		RDm-D−6.5% (2Y)
LD 36	1.8	1.3(1M)	RDm-D 0.5%	RDm-D −3.0% (1W)
			Um-U 37.7%	RUm-U 83.8%
				RDm-D −4.5% (1M)
				RUm-U 42.5%

Table 6. Cytotoxic Antibody in Recipient Serum (LD 17)

		Tx ↓	1W	1M	2M	6M	1Y	1.5Y	2Y	2.5X	3Y	3.5Y	4Y	4.5Y	5Y	5.5Y
anti-panel	T	−	+	−	+	−	−	−	+	−	−	−	−	−	−	−
	WB	+	+	−	n.d	−	n.d	−	−	−	+	n.d	+	n.d	+	−
	CB	−	+	−	n.d	−	n.d	+	+	n.d	+	n.d	+	n.d	+	n.d
anti-donor	T	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	WB	−	−	−	−	−	−	−	−	−	−	+	+	+	−	−
	CB	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−
anti-recipient	T	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	WB	−	−	−	−	−	−	−	−	−	−	+	+	+	−	−
	CB	−	+	−	−	−	−	−	−	−	−	+	−	−	−	+

was, throughout the pre- and post-operative courses, always nagative. As to CML, only one case, LD 36, was detectable preoperatively, but including LD 17 all of them were negative to the donors.

Table 6 shows detection of cytotoxic antibody in the recipient serum of LD 17. That is, using lymphocytes of 20 healthy persons, the donors and recipients, anti-T cell antibody, warm anti-B-cell antibody and cold anti-B cell antibody in the recipient serem at every stage were detected. Warm anti-B cell antibody appeared for the panel cells, donor cells, and recipient cells during 3-5 years after transplantation. Furthermore, cold anti-B cell antibody for the panel cells was detected from 1.5 years after transplantation continuously. As to antibody for the donor cells, warm B cell antibody only was detected during 3.5-4.5 years after transplantation.

In case of ULD 14 on the 100th day after the operation, rejection was noted due to increase of weight and serum creatinine, derease of urine volume, which however was recovered being mild and easily reacted with anti-rejection therapy. After that no more rejection was experienced and now under the graft survival of 4 years and 4 months, favorable renal functions can be maintained with S-creatinine of 1.8 mg/dl.

DISCUSSION

Weil et al.[50] experienced 4 cases of identical twin renal isograft, either one of which was reported to be of favorably graft survival without immunosuppressive therapy. Thus, in the identical twin renal isograft corresponding with major and minor histocompatibility antigen, immunosuppression is not needed[51]. However, in case of HLA-identical siblings compatible with HLA antigen, which is an MHC of human, the minor antigen system cannot be said always compatible. Table 7 shows a summery of those reports on renal allograft in HLA-identical sibling pairs (Table 7).

According to the table, graft survival of renal allograft in the HLA-identical siblings is about 87-100% in one year, which is quite favorable compared with other HLA-mismatched groups. Furthermore, even after 2, 4, and 5 years it is maintaining high graft survival rates, which is characteristic. However, even in case with

Table 7. Renal Transplant in HLA Identical Sibling Pairs

Report	Case	Graft Survival	Rejection	Graft Loss		Typing	Immunosuppression (Steroid)
1971 Hors	25	1Y (100%), 5Y (100%)			A, B		
1973 Descamps	32	1Y (100%), 4Y (96%)	15/32		A, B,	D	decreased
1973 Kountz	15	7Y (100%)			A, B		
1974 Dausset	44	1Y (100%), 4Y (96%)			A, B,	D	
1974 Etheredge	11	1Y (100%)	1/9(1M)		A, B,	D (S I $<$3.0)	
1977 Cheigh	26	2Y (85%)		8/26	A, B,	D (13/26)	decreased
1977 Seigler	43	1Y (87%)	26/43		A, B,	D	decreased or off
1979 Ascher	100	2Y (88.5%), 8Y (79.7%)	18/100		A, B,	D (26/100, S I $<$5.0)	
1979 Montoliu	46		7/46(1M)	5	A, B,	(D)	
1981 First	24	1Y (91.7%)	*7/18		A, B,	D	off (1Y)
1981 Salvatiera	71	1Y (94%)	49% (3M)		?	D	
1982 Morimoto	12	1Y (92%)	7/12	1	A, B, C, DR, D		0-2mg/kg/day
1983 Dohi	8	1Y (100%)	2/8		A, B, C, DR, D		not change

* Steroid Off

these favorable HLA compatibilities it is reported that at a frequency higher than 50% rejection is occurred[30,46,48]. As reported, most of them are mild and easily treated with anti-rejection therapy, although some of them are reported to result in a graft loss[6,29,30].

However, in these cases there are two problems. One of them is a typing determined as HLA-identical, i. e., a possible mistyping. Another one is a possibility on onset frequency of rejection varying by immunosuppressive therapies. That is, being HLA-identical, if immunosuppression is reduced or ceased, rejection might possibly be occerred concerning with other transplantation antigen systems than HLA. To study this probhem, the HLA typing and the immunosuppressive therapy are indicated in Table 7.

That is, in the reports of Hors et al.[23] and Kountz[26], they have determined them as HLA-identical with HLA-A and B typing only. In addition MLC has conducted on nearly a half, 13 cases, out of 26 cases of Cheigh et al.[6] and on 26 cases only in 100 cases of Ascher et al.[4] It easily causes mistyping in determination of the correct genotype as well as makes HLA-A and B loci crossing cver D locus to determine that HLA-identical without carrying MLC.

Furthermore, from the report of Hors et al. in 1971[23] to that of First et al. in 1981[15], no DR typing has been conducted. Many reports state about importance of DR-typing on the same level as that of MLC typing[5,7,8,21,24,37,47], regarding influence on graft survivals. Lenhard et al.[27] state that DR better correlates with graft survival than A and B loci, while Albrechtsen et al.[2] state that regardless of preoperative blood transfusion, DR matching well correlates with graft survival. In cadaveric allograft, too, Deierhoi et al.[11] report that DR matching correlates with graft survival. Therefore, in case when either MLC (D) antigen or DR antigen is mismatched, even if HLA-A and B antigens are matched, there is a large possibility of causing rejection.

As to immunosuppression, Descamps et al.[12] Cheigh et al.[6] Seigler et al.[48] and First et al.[15] reduced or ceased administration of steroid due to the reason of being HLA-identical siblings. For example, Descamps et al.[12] reported that rejection noted on 15 cases out of 32, which however is under reduced administration with steroid. Cheigh et al.[6] reported on graft loss with 8 cases out of 26, in which however more than a half of them have not performed MLC

Seigler et al.[48] observed rejections at a high rate of 60%, with 26 cases out of 43, in which steroid is being reduced or suspended. First et al.[15] and Morimoto et al.[30] tried to reduce or suspend steroid administration on renal allograft recipients of HLA-identical sibling pairs, and reported on the results. First et al.[15] suspended doses of steroid with 18 cases 10-21 months after transplantation, and experienced rejections on 7 cases, although in either case it has mild and easily recoverable. Morimoto et al.[30] reduced the amount of steroid to 1/2 or lower than the initial dose with 6 cases out 12, and found onset of rejection on 5 cases.

Thus, the reports in the past on the fact that rejection was onset at a high rate of 40-60% on renal allografts of HLA-identical sibling corresponding with human MHC, i. e., HLA antigen, are considered to be possibly based on mistyping and reduction or suspension of immunosuppression.

The cases of Morimoto et al. can be of nearly the same as that of the author's referring to typing. Although the number of cases is few, a comparison within these cases shows a possibility of thus reduced or suspended immunosuppression that resulted in a higher onset frequency of rejection on the cases of Morimoto et al.

In the cases of the author's LD 17 had a rejection leaving renal hypofunction. The major cause is assemed to be that temporarily steroid had to be reduced in doses due to postoperative gastrointestinal bleeding. Furthermore in this case, being a transplantation in different blood types, from A to AB, there was no antigen newly brought into the recipient as to the ABO type. In Rh, C and e are the brought-in antigens to the recipient, which possibly are related to the cause of rejection. As to Rh, van Hoof et al.[22] reported that Rh compatibility does not give any influence on graft survival rate, while Murray et al.[31] and Opelz et al.[38] state that Rh positive patients show the better graft survival rates than the nagative patients. To make it sure, irregular antibody of red blood cell was detected in LD 17, which however resulted in a negative reac-

tion. There is a report stating that male Y-antigen, which is a minor antigen, is related to rejection[17,20,44], but from the case of LD 17 being a transplantation from female to male, no relation with Y-antigen can be considered.

According to the data of Ono, CML of renal allograft recipients in identical sibling pairs do not show any response as same as the autoreaction. Furthermore, as to acute rejection, CML shows a positive reaction[33], but in case of chronic rejection CML does not show any positive reaction at all including identical pairs. Referring to the author's case, too, including LD 17 with chronic rejection, all of them were negative for MLC and CML.

From the results of detecting cytotoxic antibodies, it is noted that cold B-cell antibody appears against panel cells about 1.5 years after transplantation, which does not appear against donor cells, which at the same time can be considered as autoantibody reacting also with the recipient cells. Thus, in serum of the recipient, specific antigen to the donor cells was not identified and from the detection of cytotoxic antibody no favorable results explaning rejection was obtained.

Rejection on renal allograft in HLA-identical sibling pairs are mild and easily treatable, but a few of them surely result in the graft loss. Morimoto et al.[30] noted a graft loss on one case with usual immunosuppression. As a cause of such rejection, an unknown antigen in HLA system or other major antigens can be considered. It is also possible to be ralated with minor antigens as H-Y antigen, Rh antigen, Lewis antigen, etc., and variety of the rejection is possibly due to qualitative and quantitative differences of the minor antigens. It must be clarified as to frequency of rejection and graft loss of renal allograft of HLA-identical siblings executed with immunosuppression similar to non-identical ones after correction of mistyping. The author experienced such a low onset frequency of rejection on our series of HLA-identical sibling pairs, which can be explained that because tissue typing was carefully executed including the family study on HLA-A, B, C, D and DR, and immunosuppression was performed as same as non-identical cases. For the time being there is no graft loss, which suggests a fact that in view of the present status no sufficient clarification being made on minor antigens, nearly 100% of the graft survival rate can be achieved in renal transplantation in the HLA-identical sibling pairs, if immunosuppression is conducted as usual.

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