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Combined liver–kidney transplantation and the effect of preformed lymphocytotoxic antibodies

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Abstract

Thirty-eight sequentially placed liver and kidney allografts were evaluated with respect to patient and graft survival, and the influence of preformed lymphocytotoxic antibodies was analysed. The results suggest that the survival rate of combined liver and kidney transplantation is similar to the survival rate of liver transplantation alone. Sequentially placed kidney allografts may be protected from hyperacute rejection in the presence of donor specific lymphocytotoxic antibodies, but not in all instances. Both patient and kidney allograft survival was lower in positive crossmatch patients (33% and 17% respectively) than in negative crossmatch patients (78% and 75%). High levels of panel reactive antibodies (>10%) also appeared to have a deleterious effect on survival, although the majority of the patients who failed also had a positive crossmatch. Although preformed lymphocytotoxic antibodies are not an absolute contraindication to combined liver–kidney transplantation, they do appear to have a deleterious effect on long-term graft survival. However, more correlation with clinical parameters is needed.

Introduction

It is becoming common for patients suffering from both hepatic and renal dysfunction to be referred for organ transplantation. Concomitant renal and hepatic failure may result from the same disease process (e.g. polycystic disease), or one coexisting disease may be a result of the other (e.g. postviral hepatic cirrhosis in a dialysis patient).¹ Patients with liver failure may also have an intrinsic renal defect (e.g. interstitial nephritis) or renal dysfunction resulting from liver failure (e.g. hepatorenal syndrome or nephrotoxicity of cyclosporine in patients requiring liver retransplantation). In any case, management of a liver transplant recipient is greatly complicated by the presence of renal dysfunction.² In those patients who have demonstrated irreversible and severe renal impairment, combined liver–kidney transplantation must be considered.

The effect of various immunological parameters on patient and graft survival in liver as well as in kidney transplantation has been reported. In renal transplantation, the degree of presensitization and the donor specific crossmatch can be clearly correlated with graft survival. More recently, a slight disadvantage has also been noted when liver grafts are placed into a presensitized recipient,^{3,4} although the effect is much less dramatic. Reports of successful combined liver–kidney transplants have been published,^{5–11} but the effect of preformed lymphocytotoxic antibodies on such transplants is unclear.

Objective

In this study we report our experience with 38 patients who received simultaneous liver–kidney transplants at the University of Pittsburgh. The patient and graft survival of these patients was correlated with immunological parameters, including donor specific crossmatch and the level of panel reactive antibodies (PRA) prior to transplant, in an attempt to determine the effect of preformed lymphocytotoxic antibodies on combined liver–kidney transplantation.

Materials and methods

During the seven year period from August 1983 to August 1992, 38 patients received combined liver–kidney transplants from single donors. Table 1 lists the clinical demographics for these patients. Twenty-five of the patients were male, while 13 were female. The age range was from five years to 69 years, with a median age of 44 years. Previous organ transplantation consisted of nine liver allografts into six recipients, and eight kidney allografts into six recipients. The timing of the prior transplants varied considerably between patients.

The causes of organ failure were varied. Seven patients had combined polycystic liver and kidney disease, and three had oxalosis which resulted in both liver and kidney failure. Seven patients had liver failure due to non-A non B-hepatitis, two had hepatitis B and five had hepatitis C. Three patients had Laennec's cirrhosis, 11 others had a variety of cholestatic cirrhosis or hepatocellular disease. The causes of kidney failure were as varied as the aetiologies of liver failure. The leading causes were polycystic kidney disease ($n = 7$) and diabetic nephropathy ($n = 6$). Other less common causes included oxalosis and cyclosporine nephrotoxicity among others.

The liver and kidney transplants were performed as previously described.⁴ Between August 1983 and August 1989, 18 liver–kidney combinations received a baseline immunosuppression regimen consisting of cyclosporine, steroids and azathioprine. After this period, the remaining patients received the investigational immunosuppressive agent FK506, in combination with low-dose steroids.

The percentage of panel reactive antibodies (PRA) was determined using the standard modified Amos technique at room temperature, against a panel of at least 50 HLA selected lymphocytes. In all but three cases, pretransplant sera were obtained within two days prior to surgery. Three patients (patients 5, 10 and 28) had their most recent serum drawn 18, 8 and 13 days prior to surgery, respectively. Historical sera were also analysed when available. All donor/recipient combinations were ABO identical, but HLA type played no role in donor selection.

Peripheral blood lymphocytes, lymph node cells and spleen cells were typed for HLA-A and -B antigens by either the Amos modified or standard NIH microlymphocytotoxicity technique with trypan blue dye exclusion. Serological typing for HLA-DR was done using either two colour fluorochromasia or microlymphocytotoxicity with B lymphocytes isolated from antibody coated magnetic beads. The donor lymphocytotoxic crossmatches were done using the standard modified Amos technique at room temperature against either unfractionated lymphocytes or T cells isolated from donor lymph nodes. The crossmatch was considered to be positive when more than 20% of the lymphocytes were killed.

Actuarial survivals were calculated using the Kaplan–Meier (product-limit) method. Differences between groups were compared using the log rank test. Statistical analysis was performed using the SPSS for MS Windows program.

Results

Overall patient and graft survival

Of the 38 patients undergoing combined liver–kidney transplantation, 26 (68%) are alive with follow-up times from 11 months to nine years, which is comparable to the overall survival of patients receiving liver transplants alone during this time period.¹² Figure 1 shows the actuarial patient survivals for the 38 cases. As is true for those patients receiving liver allografts alone, the majority of deaths and/or graft failures occurred during the first three months. Twenty-six of the 38 transplanted livers (68%) are still functioning. Six patients died with their combined transplants in place. Of the six patients who underwent retransplantation of the liver, five died within six weeks and one died 14 months later. Two kidney allografts have been lost (patients 7 and 14) without accompanying patient death, leaving an overall kidney graft survival of 60%.

Influence of crossmatch on patient and graft survival

Lymphocytotoxic crossmatches were negative in 32 patients at the time of transplantation and 25/32 (78%) are alive, all but one with functioning kidneys. Four of the six patients with a positive crossmatch have died (33% survival) and a fifth rejected his kidney. Actuarial patient and renal graft survival for these two groups of patients are shown in Figure 2. There is a statistically significant difference in both the patient survival ($p = 0.04$) and kidney allograft survival ($p = 0.001$) between the two groups.

Table 2 summarizes the clinical course of the six patients with a positive crossmatch. Patient 4 was previously reported as a case in which the liver transplant protected the kidney from hyperacute rejection.⁶ She had a relatively benign postoperative course and continues to do well over eight years post-transplant. Patient 6 was also reported in the same paper.⁶ He did well until nine days posttransplant, when he underwent rejection of both allografts, but both organs responded to OKT3 treatment. However, three months posttransplant he was diagnosed with *Pneumocystis carinii* infection and died two weeks later. Neither allograft showed signs of immunological damage at the time of his death.

Patient 7 has been described by Starzl *et al.*¹³ as a case in which the immediate nonfunction of the transplanted kidney warned of developing liver damage. The liver showed signs of severe dysfunction for two weeks posttransplant, but recovered and continues to function well. The transplanted kidney never functioned, but a subsequent crossmatch negative kidney transplant was successful 11 months later.

Patient 11 received a liver–kidney transplant after the failure of two livers transplanted within the prior three weeks. The patient suffered from graft-versus-host disease after the second liver (due to ABO nonidentity) and still had severe haemolysis at the time of the combined liver–kidney transplant. He died of multisystem failure and sepsis, with no evidence of immunological damage to the liver or kidney. It is not clear whether a residual effect of OKT3 last administered four days prior to the combined transplant resulted in a falsely positive crossmatch.⁶

In patient 22, the transplanted liver suffered from what appeared to be a severe persistent ischaemic injury. Biopsy of the kidney on day 14 revealed an active interstitial and vascular rejection with arterial deposition of IgG and C3. Eventually both grafts were removed on day 54, and both showed evidence of rejection at that time. He received a second liver but died of septic gangrene of the abdominal wall 35 days later.

Patient 28 had received two liver transplants one year prior, both with a positive crossmatch and both of which failed due to rejection. He had cytomegalovirus infection and sepsis at the time of the combined transplant. Initially his kidney functioned well, but deteriorated possibly

due to FK506. His third liver also functioned well initially, but he continued to have problems with sepsis and died 17 days post-transplant.

Influence of PRA on patient and graft survival

PRA levels were available for 35 patients prior to transplantation, as shown in Table 1, and the HLA defined private and/or public specificity of the preformed antibodies were identified where possible as previously described.¹⁴ Nineteen of 23 patients (83%) with PRA $\leq 10\%$ are still alive, and all but one has a functioning kidney, whereas only five of 12 patients (42%) with a high PRA ($>10\%$) have survived and one has lost his kidney allograft. The majority of the high PRA patients who suffered from death and/or organ failure (5/8) also had a positive crossmatch.

Of the 12 patients with a current PRA $>10\%$, HLA specificities could be determined in eight (Table 3). Three of the 12 received donor organs which carried the specific antigen, and all had positive crossmatches as expected. Two of the remaining three positive crossmatch patients had very high PRAs ($>90\%$) which made defining the antibody specificity impossible, and the third (patient 11) had a defined specificity which was not present on the donor but also had a large degree of additional reactivity which could account for the positive crossmatch.

Of the six patients with a current PRA $>10\%$ but a negative crossmatch, four (patients 9, 16, 35 and 38) had a defined specificity against an antigen which was not on the donor cells, and two (patients 13 and 15) had an undefined specificity with a relatively low PRA.

The clinical course of the six high PRA patients with a positive crossmatch has already been outlined in Table 2. The clinical course of the remaining high PRA patients is shown in Table 4. Only three of them failed (patients 9, 15 and 16). Patient 9 is the second so-called 'canary kidney' described by Starzl *et al.*¹³ The kidney never functioned and showed signs of humoral rejection. The patient also developed primary nonfunction of the liver and retransplantation was attempted on postoperative day three, but he succumbed to systemic sepsis.

Patient 15 suffered from a portal vein stricture almost three years posttransplant. He underwent a second liver transplant, but died 15 months later of sepsis. Patient 16 developed hepatitis B posttransplant and died of liver failure and sepsis without retransplantation. There was no evidence of rejection in either the kidney or liver.

Patient 24 is also shown in Table 5. He had 0% PRA at the time of transplant, but had a strong HLA-A2 specific antibody in an historical serum sample. The A2 antigen was present in the donor, and the historical crossmatch was positive. The liver functioned poorly and the patient was diagnosed with hepatic artery thrombosis two months posttransplantation. He died of liver failure and sepsis without retransplantation.

Five patients with PRA ≤ 10 and a negative crossmatch died posttransplant and one suffered from failure of his renal allograft (Table 5). Patient 12 suffered from a hepatic artery thrombosis and eventually succumbed to sepsis after a third liver was transplanted. The kidney showed no signs of rejection at autopsy.

Patient 14 resumed dialysis after failure of his kidney 35 months post-transplantation, and a biopsy that at that time showed evidence of chronic rejection. His liver continues to function well, as does a second kidney transplant received ten months after failure of the first. Patient 24 had a positive historical crossmatch and is described above. Patient 27 died from recurrence of his original disease (oxalosis). Patient 29 lost his liver due to severe ischaemic injury and sepsis and died of sepsis three days after retransplantation.

The final patient shown in Table 5 (patient 1) had a negative crossmatch but PRA was not determined. She died of sepsis and pancreatitis on postoperative day 16, with no evidence of rejection in either transplanted organ.

Effect of DTT treatment of the sera

Crossmatches on 19 patients (patients 20–38) were also performed using sera treated with dithiothreitol (DTT), which removes nonspecific IgM antibodies.¹⁵ Such treatment did not change the crossmatch results, even of the two patients with a positive crossmatch (patients 22 and 28). DTT treatment of serum resulted in slight decreases in PRA in some of the high PRA patients, but it did not affect the antibody specificities or the overall results.

Influence of other factors

HLA-A, -B and -DR typing was available on 30 donor and recipient pairs. Overall, the degree of matching was poor, as would be expected for random allocation of donor organs. The average number of mismatches was 4.4 (out of a possible six). There was no difference between the mismatches in the positive or negative crossmatch groups (4.6 vs 4.3).

The ability of the liver allograft to influence the antibody status of the recipient was also examined. All six of the patients who had a strongly positive crossmatch before the liver transplant had the crossmatch repeated with sera taken after liver transplantation but before the kidney was put in. Three patients (patients 4, 6 and 28) went from a strongly positive crossmatch to a negative crossmatch. In all three of these patients, the liver allografts were functioning during the immediate posttransplant period and there was no evidence of hyperacute rejection in any of the kidneys. In patient 7, the crossmatch remained strongly positive after transplantation and the kidney never functioned. In patient 22, the crossmatch went from strong positive to weakly positive. A kidney biopsy on day 14 showed evidence of humoral rejection. Interestingly, the liver allografts in both these patients functioned poorly from the start. The sixth patient (patient 11) had last received OKT3 four days prior to the combined transplant. The crossmatch went from strong to weakly positive, but he had good liver and kidney function in the immediate posttransplant period.

Previous organ transplantation appeared to have a deleterious effect on outcome. Of the 13 patients who had previously undergone organ transplantation prior to simultaneous liver–kidney transplantation, seven are still alive (54%), compared to 19 out of 25 (76%) of the patients who had no prior transplants. In addition, all six patients who required retransplantation of the liver after the combined transplant died.

Discussion

As the indications for transplantation of solid organs increases, the need for multiple organ transplantation will rise. There have been a number of published reports on the success of such transplants.^{3–9} The question of whether lymphocytotoxic antibodies are a contraindication to such transplants has been raised. We have attempted to correlate patient and graft survival with the immunological status of the recipients.

In general, renal transplantation across a positive crossmatch results in hyperacute rejection,¹⁶ but the liver is thought to be relatively resistant to antibody-mediated injury.^{17,18} In fact, we have previously reported two cases in which a liver transplant across a positive lymphocytotoxic crossmatch protected a subsequent kidney transplant from hyperacute rejection,^{6,7} but other studies have demonstrated that the liver does not always play a protective role.^{13,19} In addition, recent studies from this centre indicates that a positive crossmatch may have an adverse effect on liver allograft survival.^{3,4} Demetris *et al.*²⁰ reported that a series of

livers transplanted across a positive crossmatch did not show 'hyperacute' rejection, but numerous pathological changes including findings similar to preservation injury, cellular rejection, arterial vasospasm and focal large bile duct necrosis were seen.

The data presented here indicate that combined liver–kidney transplantation results in patient survival comparable to that seen in patients receiving liver allografts alone, and thus kidney failure should not be a contraindication for liver transplantation. Even in the presence of specific HLA antibodies, a liver transplant can protect a subsequent kidney transplant from hyperacute rejection as previously described^{6,7} but such protection is not absolute.

The effect of a positive crossmatch on long-term graft survival is less clear. Whereas 78% of the patients with a negative crossmatch are alive with both organs functioning, only two of six patients with a positive crossmatch are alive and one of these survivors lost his kidney graft. Two of the patients showed signs of kidney rejection and all three who died had sepsis. There is a statistically significant difference between the groups in spite of the low numbers of patients. High PRA levels may impact patient and graft survival in liver transplant patients by influencing other parameters such as blood usage.²¹ In this study, an adverse relation of patient survival with PRA exists, although most of the high PRA patients who failed also had a positive crossmatch.

It is interesting to speculate on what, if any, differences would be seen in the results if a more sensitive crossmatch technique such as antihuman globulin enhancement or flow cytometry had been used. It is possible that some of the high PRA patients with negative crossmatches may have had donor specific antibodies below the level of detection with the Amos modified crossmatch. This is especially true of patient 9, who showed evidence of antibody-mediated rejection in the kidney despite a negative crossmatch.¹³

There are numerous clinical parameters which can affect survival after liver and/or kidney transplantation, including status of the recipient prior to the transplant (UNOS score), condition of the donor organs, cold ischaemia times, donor and recipient age, and original disease of the recipient. None of these factors have been addressed in this study but will be analysed in a subsequent study to be published. The effect of prior transplants, including an analysis of their type and timing, is also a critical issue that will be addressed in more detail.

It has been demonstrated in animal models that transplantation of liver allografts protects other organs subsequently transplanted into sensitized recipients,^{22,23} with a decline of donor specific antibodies following liver transplantation.²³ Gugenheim *et al.*²⁴ showed that prolonged survival and decrease in antibodies was accompanied by deposition of immunoglobulin and C3 on hepatic nonparenchymal cells, supporting the hypothesis that the protective effect of liver transplantation and its resistance to hyperacute rejection might be due to absorption of lymphocytotoxic alloantibodies on nonparenchymal hepatic cells. Furuya *et al.*²⁵ noted a direct correlation between titre of lymphocytotoxic antibodies and graft survival, and IgG antibodies were shown to be more destructive than IgM. The variability we have seen in the ability of the liver to protect a subsequent kidney from immune attack is likely related to titre and class of antibody present. However, antibody titres were not routinely determined for these patients, and only two of the positive crossmatches were performed using DTT treated serum. Further studies are also needed to determine why only half of the positive crossmatches became negative after the liver was transplanted. Possible explanations include differences in antibody titre or differences in function of the transplanted liver.

The liver is a unique organ in the study of transplantation. Much of the lore of the immunobiology of liver transplantation can be translated into liver specific phenomena. The application of some of these findings into clinical settings may aid in expanding indications for transplantation. The experience of combined liver and kidney transplantation compares

favourably with liver transplantation alone. Also, like liver transplantation, prior organ transplantation and/or the need for subsequent retransplantation has a deleterious effect on patient survival. Preformed lymphocytotoxic antibodies are not an absolute contraindication to combined liver–kidney transplantation, but do appear to have a deleterious effect on long-term graft survival. Further studies with larger numbers and more correlation with clinical parameters are needed before a definite conclusion can be reached. It is possible that enhanced immunosuppression or the use of prophylactic treatment with prostaglandin may improve graft survival as it has in liver transplantation.²⁶

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Figure 1.
Actuarial patient survival of combined liver–kidney transplant recipients

Figure 2.

Actuarial patient (left) and kidney (right) allograft survival of combined liver–kidney transplant recipients in correlation with pretransplant donor specific lymphocytotoxic crossmatch results: (■), negative crossmatch, $n = 32$; (●), positive crossmatch, $n = 6$.

Table 1

Clinical profile of liver-kidney recipients

Patient number	Age (years)	Sex	Previous transplants	Time of previous transplant (months prior)	Current % PRA	Donor crossmatch
1	19	F	Liver	71	ND	Negative
2	42	F	No		ND	Negative
3	15	F	No		ND	Negative
4	43	F	No		94	Positive
5	36	M	No		0	Negative
6	65	M	No		20	Positive
7	12	M	No		91	Positive
8	15	M	Liver	35	5	Negative
9	61	M	No		20	Negative
10	48	M	No		0	Negative
11	63	M	Liver x2	0.6, 0.5	64	Positive
12	47	M	No		2	Negative
13	48	M	Kidney	~60	26	Negative
14	54	M	No		0	Negative
15	43	M	No		29	Negative
16	43	F	No		14	Negative
17	64	F	No		3	Negative
18	5	M	No		1	Negative
19	31	M	No		0	Negative
20	48	M	No		0	Negative
21	44	M	Kidney	85	10	Negative
22	29	M	Kidney x2	~144, ~132	98	Positive
23	50	M	No		6	Negative
24	40	M	Kidney x2	49, 23	0	Negative
25	50	F	No		0	Negative
26	19	M	Kidney	~84	0	Negative
27	14	M	Kidney	~72	2	Negative
28	20	M	Liver x2	12, 11	76	Positive

Patient number	Age (years)	Sex	Previous transplants	Time of previous transplant (months prior)	Current % PRA	Donor crossmatch
29	56	M	No		0	Negative
30	23	F	Liver	5	0	Negative
31	61	F	No		0	Negative
32	25	F	Liver ×2	17, 15	6	Negative
33	62	F	No		0	Negative
34	69	M	No		0	Negative
35	63	F	No		13	Negative
36	8	F	No		0	Negative
37	58	M	No		0	Negative
38	44	M	Kidney	81	28	Negative

ND, not determined.

Table 2

Clinical course of patients with positive crossmatch

Patient number	Patient survival (months)	Organ survival (months)		Cause of organ loss		Cause of patient loss
		Liver	Kidney	Liver	Kidney	
4	>78	>78	>78	–	–	Still alive
6	4	4	4	Death, no rejection	Death, no rejection	<i>Pneumocystis carinii</i>
7	>48	>48	0	–	Humoral and cellular rejection	Still alive
11	0.9	0.9	0.9	Death, no rejection	Death, no rejection	Pre-existing sepsis, CMV
22	3	2	2 ^a	Ischaemic injury	Humoral and cellular rejection	Retransplantation, wound sepsis
28	0.6	0.6	0.5	Death, no rejection	Drug toxicity	Pre-existing sepsis, CMV

^a Kidney never functioned, was removed at liver retransplantation.

CMV, cytomegalovirus.

Table 3

Histocompatibility profile and antibody specificity of high PRA recipients

Patient number	HLA recipient			Current crossmatch	Current PRA	Antibody specificity ^a	HLA donor		
	A	B	DR				A	B	DR
4	2, –	51, 57	2, –	Positive	94	Undefined	1, –	8, 35	3, 5
6	25, 32	18, 44	4, 6	Positive	20	Weak P02	1, 2	8, 51	3, 5
7	2, 24	7, 27	8, –	Positive	91	Undefined	1, 2	8, 57	3, 7
9	1, 2	35, –	4, 5	Negative	20	A10	1, –	7, –	7, –
11	24, –	44, –	5, 6	Positive	64	P02 + ?	1, 24	35, 57	6, 7
13	3, –	7, 35	2, –	Negative	26	Undefined	2, –	7, 51	2, 5
15	2, 29	7, 44	6, 7	Negative	29	Undefined	2, 28	14, 62	5, 6
16	26, 31	14, 35	1, –	Negative	14	B17	2, 11	7, 35	6, 8
22	2, 28	7, 62	2, 4	Positive	98	P81 + P71	3, –	7, 60	2, 6
24	32, –	18, 53	5, 7	Negative	0	A2 ^b	2, 29	7, 49	1, 6
28	24, 33	58, 60	ND	Positive	84	B12, B7, B22	2, 29	44, 50	4, 7
35	11, 32	35, 44	7, –	Negative	13	Weak A2	26, 36	53, 58	4, 7
38	30, 31	38, 51	7, –	Negative	28	A3	2, 31	60, –	4, 13

^aPrivate and public specificities were determined by panel cell analysis using a χ^2 tailed analysis as previously described.¹³ Public specificities are defined as follows: P02 = A2, A28; P81 = A9, A32, Bw4; P71 = A1, A3, A9, A10, A11.

^bSpecificity of historic serum, which was crossmatch positive. Current serum was crossmatch negative.

ND, not determined.

Underlined antigens indicate those included in the defined antibody specificities.

Table 4
Clinical course of negative crossmatch patients with panel reactive antibodies (PRA) >10%

Patient number	Patient survival (months)	Organ survival (months)		Cause of organ loss		Cause of patient loss
		Liver	Kidney	Liver	Kidney	
9	0.2	0.1	0	Primary nonfunction	Humoral rejection	Retransplantation, sepsis
13	>46	>46	>46	-	-	Still alive
15	50	35	50	Artery thrombosis	Death, no rejection	Sepsis
16	5	5	5	Hepatitis B	Death, no rejection	Retransplantation, pneumonia
35	>17	>17	>17	-	-	Still alive
38	>11	>11	>11	-	-	Still alive

Table 5

Causes of patient and graft loss in patients with low PRA and/or negative crossmatch

Patient number	Donor crossmatch	% PRA	Patient survival (months)	Organ survival (months)		Cause of organ loss		Cause of patient loss
				Liver	Kidney	Liver	Kidney	
1	Negative	ND	0.5	0.5	0.5	Death, no rejection	Death, no rejection	Pancreatitis, sepsis
12	Negative	2	1	0.3	1	Artery thrombosis	Death, no rejection	Retransplantation, sepsis
14	Negative	0	>45	>45	35	–	Cellular rejection	Still alive
24	Negative	0	2	2	2	Artery thrombosis	Death, no rejection	Liver failure, sepsis
27	Negative	2	8	8	0	Oxalosis	Oxalosis	Liver failure, sepsis
29	Negative	0	0.6	0.5	0.6	Infection, ischaemia	Death, no rejection	Sepsis

Patient 24 had prior antibody against A2 antigen carried by donor.

ND, not determined.