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Combined Liver-Kidney Transplantation: Analysis of Patients With Preformed Lymphocytotoxic Antibodies

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WITH THE INCREASING complexity of patients undergoing transplantation, the transplant services are called on to evaluate a variety of patients with concomitant metabolic derangements. Optimal function of an allograft and management of these patients in the posttransplant period may require consideration of multiorgan transplantation. The concept of multiorgan transplantation has become a reality. Combined pancreas-kidney transplantation was the first example of this. Thereafter, combined heart-kidney, heart-lungs, and heart-liver transplants have been reported. In each instance, the combined transplants have been performed in order to assure long-term allograft function by correcting coexisting dysfunction of other organ systems.

A number of liver transplant candidates will have preexisting renal dysfunction, either secondary to renal flow abnormalities, drug toxicity, or secondary to an intrinsic renal defect, eg, interstitial nephritis, glomerulonephritis, polycystic renal disease.[1,2] While correction of secondary renal dysfunction can be expected in the former group, the posttransplant management in the latter group is complicated by the necessity for adjustments in the immunosuppressive regimens.[3] Thus, if chronic renal disease can be documented before hepatic transplantation, combined liver-kidney transplantation should be considered. In this report, we address combined liver-kidney transplantation, with particular attention to the apparent phenomenon of protection of kidney allografts to antibody mediated destruction by liver allografts.

MATERIALS AND METHODS

During the period from July 1984 to August 1987, 12 patients received combined liver-kidney transplants from single donors. Table 1 lists the clinical data of these patients as well as the results of the initial lymphocytotoxic crossmatches. The donor specific crossmatches and panel reactive antibody levels (%PRA) were performed as previously outlined.[4] Detailed immunologic analysis of the four patients with strongly positive crossmatches are now presented.

Serum samples were collected from all four patients before, during, and following the combined liver-kidney transplant procedures. For purposes of this paper, pretransplant serum was designated, pre-OT/KT; the sample taken following liver revascularization, but before kidney transplantation is designated, pre-KT/post-OT; and those samples taken following completion of the combined transplant designated, post-OT/KT.

Demonstration of the nature of the lymphocytotoxic antibodies present in the sera of the strongly reactive, positive crossmatched patients was accomplished by solid phase immunoabsorptions, as previously described.[4] OKT3 levels were determined by enzyme linked immunoassay.[3]

RESULTS

Of the 12 patients undergoing combined liver-kidney transplantation, nine are alive during the follow-up period of 1 month to 36 months. Of the three deaths, two deaths occurred in retransplanted patients, one dying of fungemia, and the other of generalized sepsis within the first month following retransplantation. The other patient died 4 months following combined liver-kidney transplantation with good renal function until his death.

Of the remaining nine patients, one patient (no. 8), who had a positive crossmatch pretransplant, but had evidence of renal flow

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Table 1. Case Material

Patient No.	Age/Sex	Cause of Organ Dysfunctoin		Preoperative Evaluation		Crossmatch
		Liver	Kidney	Serum Cr	CrCl	
1	44/F	Polycystic	Polycystic	2	20	Negative
2	15/F	Polycystic	Polycystic	10*	0	Doubtful positive
3	43/F	PBC	GN	4	20	Strong positive
4	39/F	Rejection	Unknown	6	10	Negative
5	38/M	Cirrhosis	GN	4	10	Negative
6	34/M	Cirrhosis	GN	2.1	30	Doubtful positive
7	56/M	Etoh cirrhosis	GN	3.5	ND	Strong positive
8	12/M	Cysteamine toxicity	Cystinosis	6	5	Strong positive
9	15/M	Rejection	GN	2.5	28	Doubtful positive
10	61/M	Sclerosing cholangitis	Interstitial nephritis	4.2	ND	Negative
11	48/M	Etoh cirrhosis	Unknown	10.8	0*	Negative
12	33/M	Failed allograft	Unknown	3.3	ND	Strong positive

Abbreviation: GN, glomerulonephritis.

*On dialysis.

without function, eventually required dialysis and a second kidney transplant. In this patient, the kidney perfused well following the liver transplant, although urine function was reduced. Renal function remained depressed in this patient, although renal flow scans revealed fair blood flow to the allograft. Multiple biopsies of this allograft revealed tubular injury without evidence of humorally mediated injury. The remaining eight patients have shown good renal function in the posttransplant period.

As shown in Table 1, four patients (nos. 3, 7, 8, and 12) were found to have a positive crossmatch before the liver phase of the combined transplant (pre-OT/KT samples). These positive crossmatches were due entirely to anti-HLA class I antibodies, as demonstrated by their removal by immunoabsorption on pololed platelets. In three of these patients, post-OT/pre-KT samples showed a conversion to a negative crossmatch (in the fourth patient this was not done, no. 8). A kidney allograft, harvested from the same donor, was then placed into the recipient, and in patients no. 3, 7, and 12, good initial function was noted. In none of these patients was there evidence of hyperacute rejection. Post-OT/KT samples were collected in patients no. 3, 7, and 8, and then analyzed for the reappearance of donor specific lymphocytotoxic antibodies in the posttransplant period (data on patient no. 12 was not available at the time of preparation). Lymphocytotoxic antibodies with donor specificity could not be detected in any of the samples during the first week posttransplant.

In all three patients, no. 3, 7 and 8, allograft dysfunction due to rejection was treated with the mouse anti-human T cell monoclonal antibody, OKT3, during the second to fourth posttransplant week. During this time, when detectable levels of OKT3 could be demonstrated, a nonspecific lymphocytoxicity could be demonstrated. This nonspecificity was due to the nature of the administered monoclonal antibody, since OKT3 binds to human T cells and fixes complement leading to cytotoxicity. Absorptions of the administered OKT3 was done on solid-phase anti-mouse immunoglobulin beads. This led to removal of lymphocytotoxicity to background levels. Table 2 demonstrates an example in patient no. 3, where immunoabsorption of OKT3, found in quantitated levels in the serum, led to both negative crossmatches and a return of the %PRA to what would be expected.

The decrease in %PRA and conversion of a positive to negative crossmatch following liver transplantation was correlated to the HLA specificity of the antibody found in the pretransplant serum and the HLA type of the

Table 2. Patient No. 3 Crossmatch, % PRA, and OKT3 Levels

Serum Sample	Unabsorbed Values		Absorbed Values*		OKT3 Level (ng/mL)
	% PRA	Crossmatch	% PRA	Crossmatch	
Pre-OT/KT	94	+	94	+	0
Post-OT/pre-KT	48	–	46	–	0
Post-OT/KT					
Day 2	50	–	50	–	0
Day 3	48	–	48	–	0
Day 5	ND	–	ND	–	0
Day 6	50	–	50	–	0
Day 7	52	–	52	–	0
Day 9	76	+	52	–	100
Day 12	94	+	42	–	330
Day 13	96	+	46	–	330
Day 14	96	+	40	–	1,100
Day 15	96	+	44	–	1,700
Day 16	94	+	42	–	1,600
Day 19	92	+	38	–	2,200
Day 20	92	+	32	–	1,200
Day 22	56	–	38	–	0
Day 24	36	–	36	–	0
Polyvalent	100	+	100	+	0
OKT3 standard	100	+	0	–	2,500
Normal	0	–	0	–	0

*Absorbed on solid phase anti-mouse IgG immunoabsorbent.

transplanted organs. In the two instances where an HLA specificity could be determined by panel analysis, transplantation with donor organs bearing these HLA specificities led to a specific disappearance of these antibodies during the posttransplant phase.

DISCUSSION

In 1970, Simpson et al, first explored the notion of protection of renal allografts by using vascularized hepatic allografts from the same donor.[5] Other investigators have also implied a protective role of the donor liver in inducing a degree of protection toward other tissues.[6,7] While we cannot draw any conclusions regarding any protective effect of the liver allograft on the renal allograft in cell mediated rejection, we have presented evidence to suggest a role of the liver in removal of preformed lymphocytotoxic antibodies.

The procedure of combined liver-kidney transplantation appears to be safe, with two deaths occurring in patients being retransplanted for combined liver and kidney dysfunction, with historically poorer prognosis. In the remaining ten patients, the presence of a well functioning kidney allowed the transplant team to use therapeutic levels of cyclosporine A, without fear of further damage to compromised kidneys.

The mechanism of this apparent protective effect of the liver on preformed antibody states is not clear. The relative resistance of the liver allograft to antibody damage is well known.[8] Whether this is due to the unique anatomic architecture of the liver or whether it is able to "neutralize" the cytotoxic antibodies is not clear.

With the increasing use of anti-human T cell monoclonal antibodies in the treatment of rejection, the interpretation of crossmatch or %PRA in samples with potential levels of these antibodies, must be made cautiously. Confirmation of the nature of the lymphocytotoxic antibodies by specific immunoabsorptions must be done in order to avoid potentially conferring a label of a "positive crossmatch" on a transplant recipient awaiting another transplant.

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