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Successful Liver Transplantation From Crossmatch-Positive Donors

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We have published before that liver transplantation can be performed successfully in spite of positive anti-donor crossmatches detected with the standard cytotoxicity test.^{1,2} These so-called positive crossmatch cases were compiled before the classification of the responsible antibodies³ was possible.

In the present study, ten previously reported recipients whose sera contained anti-donor cytotoxic antibodies were reviewed. The quantity and type of antibodies in the recipient sera were determined from their reactions to a panel of lymphocyte donors. From the results, an educated guess became possible as to whether the previous positive crossmatches against the organ donors were caused by warm anti-T antibodies or by less dangerous varieties.

Finally, a fresh transplant was performed in a patient whose preoperative serum contained warm anti-T-lymphocyte antibodies that reacted with heavy killing against the liver donor.

Materials and Methods

In 11 of 179 cases of orthotopic liver transplantation in Denver, the patients received liver homografts from donors to whom the recipients' sera showed strong lymphocyte cytotoxic activity by standard cytotoxicity crossmatch tests. One of the 11 patients (OT 168) had proven strong anti-T- and anti-B-lymphocyte cytotoxicity against the donor. Clinical and pathologic observations of these 11 patients are listed in Table 1.

Pretransplant sera of these 11 patients were tested for anti-T- and anti-B-lymphocyte antibody under warm and cold temperatures against a random lymphocyte panel of 30-40 donors by a previously reported method.³ Sera from the first 10 patients had been stored at -80°C for long periods before testing against the lymphocyte panel. In the most recent case (OT 168), the cytotoxicity was tested with fresh sera against the organ donor lymphocytes as well as against a random lymphocyte panel. Immunologic observations in these 11 patients are summarized in Table 2.

Results

Immunologic Observation

Preoperative sera of all 11 patients had lymphocytotoxic antibodies against the specific donors by standard cytotoxic testing at the time of transplantation. In the most recent case

(OT 168), the pretransplant serum had strong anti-T- and anti-B-lymphocytotoxicity against the actual liver donor.

The results of retrospective anti-T- and anti-B-lymphocyte cytotoxicity against a random cell panel are shown in Table 2 for all 11 patients. Excluding the most recent case, OT 168, whose serum was tested against the specific donor cells, five (OT 63, OT 101, OT 114, OT 119, OT 122) of ten previously reported patients possessed strong and wide cytotoxic antibody against both T and B lymphocytes. Four more (OT 58, OT 71A, OT 138, OT 151) had narrow but definite antibody against T lymphocyte and wider antibody against B lymphocytes. One patient (OT 103B) did not have anti-T-lymphocyte antibody against the random cell panel, but she had anti-B-lymphocyte antibody.

None of the 11 patients had transplantation across an ABO blood group barrier.

Clinical and Pathologic Observation

Despite the probable presence of donor-specific anti-T-lymphocyte antibody in the pretransplant sera of at least half of the previous ten liver recipients and despite definite existence of such antibody in the most recent recipient (OT 168), hyperacute rejection such as seen in renal homografts was not observed in any case. Early graft dysfunction within 10 days after transplantation was observed only in two cases (OT 71A and OT 168). The liver pathology of the first case (OT 71 A) on the tenth posttransplant day revealed acute rejection of a cellular and humoral nature, and this could be interpreted at most as a modified type of hyperacute rejection in liver homograft. The second case (OT 168) had significant perioperative ischemic damage to the graft, but the graft produced bile on immediate posttransplant days. The liver biopsy obtained on the 15th posttransplant day did not show any rejection of either a cellular or humoral nature.

The remaining nine patients did not have early graft dysfunction, and one (OT 114) is still alive and well over 4 years after transplantation. Two (OT 58 and OT 103B) lived more than a year. The liver pathology of these nine patients did not show acute rejection (Table 1).

Discussion

The pathophysiology of hyperacute rejection has been well studied in recent years. Fixation of antibody to the graft is apparently the initial event followed by entrapment of clotting factors and formed blood elements in the microvasculature of the graft and consequent graft necrosis. The antibodies that are known to cause hyperacute rejection in kidney allografts are anti-A and -B red cell isoagglutinins⁴ and cytotoxins against T lymphocytes.^{3,5,6} Heterospecific antibody in the heterograft system can also have the same effect.⁷ Accumulated clinical and experimental evidence indicates that kidney grafts are unusually prone to the irreversible consequences of hyperacute rejection and that the liver graft, in contrast, is unusually resistant.^{1,2,7} The difference in microvascular structure between the kidney and the liver (capillary versus sinusoidal system) may be responsible.

We have previously reported ten patients who did not have hyperacute rejection of liver grafts in spite of the detection in their sera by standard cytotoxicity testing of antibody against the specific donor.^{1,2} With recent advances in transplantation serology, it is now known that anti-T-lymphocyte antibody is responsible for hyperacute rejection, but that anti-B-lymphocyte antibody is not responsible.^{3,6} As the donor lymphocytes were no longer available in the previous ten cases, the sera were tested for anti-T- and anti-B-lymphocyte toxicity against a random lymphocyte panel. In retrospect, five of the patients who did not possess warm anti-T antibodies were not at risk from hyperacute rejection. However, five

(OT 63, OT 101, OT 114, OT 119, and OT 122) of ten patients had strong and wide (greater than 75% of panel cells) anti-T-lymphocyte antibody.

It is reasonable to conclude from this information that at least some of these five patients had anti-T-lymphocyte antibody against the donor, but did not reject liver homografts hyperacutely. One (OT 114) of the five patients is still alive and well with normal liver function over 4 years after transplant. In the additional recent case (OT 168) such speculation is not necessary. The liver transplant was known to have been performed in the presence of strong cytotoxic antibody against the donor T lymphocytes. The liver homograft did not undergo hyperacute rejection and the biopsy on the 15th day did not show any sign of rejection, either of humoral or of cellular type.

Conclusion

The data presented above are consistent with previous reports that the liver is unusually resistant to hyperacute rejection and that a positive anti-T-lymphocyte crossmatch is not an absolute contraindication for liver homotransplantation. Further investigations are needed to explain the unusual resistance of the liver to hyperacute rejection.

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Table 1

Clinical Observation

OT No.	Age	Sex	Diagnosis	Survival (Days)	Main Cause of Death	Pathologic Changes in Liver
58	34	M	Chronic aggressive hepatitis	407	Refused medication; hepatic insufficiency	Resolution of previous obstructive changes at 8.5-month biopsy (no autopsy)
63	49	F	Primary biliary cirrhosis	26	Gastrointestinal hemorrhage	Normal liver
71A	2	M	Biliary atresia	(Homograft) Removal at 10 days		Acute rejection, cellular and humoral
101	28	F	Primary biliary cirrhosis	(Heterograft) 14 days after retransplantation	Pulmonary edema; bronchial hemorrhage	No evidence of cellular rejection; centrilobular cholestasis
114	27	F	Liver tumor of undetermined type	189	Hepatic insufficiency; renal and cardiac failure	Biopsy 5 days prior to death showed hepatocyte swelling, suggesting hepatitis; no rejection
119	23	M	Sclerosing cholangitis	Alive over 4 years	Alive	
122	28	F	Chronic aggressive hepatitis	33	Obstructed cholecystojejunostomy to choledochojejunostomy; subsequent rupture of mycotic hepatic artery aneurysm into jejunum	Biliary obstruction, intrahepatic sludge and cholangitis; no rejection
103B	21	F	Primary biliary cirrhosis	131	Pneumococcal meningitis; liver failure; liver abscesses	Chronic rejection
138	42	M	Sclerosing cholangitis	403	Cholecystojejunostomy to choledochojejunostomy; liver failure	Chronic rejection; massive liver necrosis
151	5	M	Biliary atresia	108	Leak of colonic anastomosis after emergency colectomy; liver and pulmonary failure; CMV infection	Chronic cholangitis; no rejection
168	33	F	Chronic aggressive hepatitis	72	Chicken pox; fresh portal vein thrombosis	Hepatitis group viruses seen by EM in necrotic tissue and in some of the adjacent cells
				23	Pulmonary sepsis	Biopsy on the 15th day showed no rejection

Table 2

Immunologic Profile

	Blood Type (Donor to Recipient)	HLA-A,B Mismatch Number	Donor-Specific Cytotoxic Antibody (Standard Crossmatch)	Nonspecific Cytotoxic Antibody Screening (% of Panel Cells)		
				T-Warm	B-Warm	B-Cold
OT 58	O to O	4	Pos. (1:2)	3	43	6
OT 63	O to O	3	Pos. (1:64)	76	100	0
OT 71 A	O to A	2	Pos. (1:16)	23	96	3
OT 101	O to O	4	Pos. (?)	84	100	0
OT 114	O to A	3	Pos. (?)	88	96	0
OT 119	O to O	4	Pos. (?)	92	100	0
OT 122	O to A	2	Pos. (?)	84	100	0
OT 103 B	O to A	3	Pos. (?)	0	3	0
OT 138	O to A	3	Pos. (1:4)	15	31	0
OT 151	A to A	4	Pos. (1:8)	3	43	3
OT 168	O to O	1	Pos. (1:64)*	100	100	0

* Positive T-warm and B-warm.