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THE ADVERSE IMPACT ON LIVER TRANSPLANTATION OF USING POSITIVE CYTOTOXIC CROSSMATCH DONORS^{1,2}

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Abstract

Because of the liver graft's ability to resist cytotoxic antibody-mediated rejection, it has become dogma that the conventional transplant crossmatch used to avoid hyperacute rejection of other organs is irrelevant to the liver. We examined this hypothesis in a consecutive series of adult primary liver recipients treated with FK506 and low-dose steroids.

Twenty-five of 231 (10.8%) patients received a liver from a cytotoxic-positive crossmatch donor (more than 50% of donor T lymphocytes were killed by dithiothreitol-pretreated recipient serum). The outcome was compared with that of 50 negative crossmatch patients who had their transplantations just before and after the crossmatch positive cases.

The one-year graft and patient survivals were 56% and 68%, for positive and 82% and 86% for negative crossmatch patients ($P=0.004$, $P=0.03$, respectively). The difference between patient and first graft survival was accounted for by retransplantation, which was 4 times more frequent in the positive-crossmatch cases. Histologically, failed allografts obtained at the time of retransplantation revealed a spectrum of pathologic findings related to vascular injury.

This study showed a higher difficulty of intraoperative blood product management, a degraded prognosis, and a poorer average quality of ultimate graft function when liver transplantation was performed against positive cytotoxic crossmatches. In such patients for whom crossmatch-negative donors may never be found because of the broad extent and intensity of sensitization, special therapeutic strategies perioperatively must be evolved if results are to improve.

The immune response to hepatic transplants has previously been described as a cellular rejection response (1). We have reported that human hepatic transplants are unusually resistant to antibody-mediated rejection, and can be successfully performed in the face of positive antidonor crossmatches, as detected by the standard complement-dependent cytotoxicity test (2–4).

It is true, however, that crossmatch-positive hepatic grafts have been lost repeatedly for inadequately explained reasons at our center and elsewhere (5–9). Experienced liver transplant surgeons speak of some patients as “liver-eaters” and there are case reports from several

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institutions describing hyperacute rejection of a liver allograft. This syndrome tends to be associated with a positive cytotoxic crossmatch, but not invariably (8).

There are many theoretical explanations for the liver graft's ability to resist cytotoxic antibody. These include: (a) release of soluble class I histocompatibility (HLA) antigens into the circulation, which presumably bind the preformed lymphocytotoxic antibodies, preventing their destructive effects; (b) Kupffer cell binding of preformed antibodies or immune complexes; (c) the unique sinusoidal microvasculature, and (d) a dual afferent blood supply that presumably protects the organ from ischemic damage (1,10–13).

In this study, we have reexamined the extent to which the liver is able to resist cytotoxic antibody-mediated rejection in a consecutive series of adult primary liver recipients treated with FK506 and low-dose steroid therapy. The sera were pre-treated with dithiothreitol before the T lymphocyte crossmatching and pretreatment panel screening for panel reactive antibodies.

MATERIALS AND METHODS

Between November 31, 1989 and September 9, 1990, 243 adult patients (16 years old or older) received their first orthotopic liver transplantation under FK506 and low-dose steroid therapy at the University Health Center of Pittsburgh.

In this period, 25 consecutive patients received a liver from a cytotoxic positive-crossmatch donor (more than 50% of donor lymphocytes were killed by dithiothreitol pretreated recipient serum). The crossmatch test was considered negative when less than 10% of cells were killed. When 11–50% of donor lymphocytes were killed by recipient serum, the crossmatch was interpreted as doubtfully or weakly positive.

None of the 243 patients received ABO blood group-incompatible grafts and 12 patients were excluded because they were not tested for lymphocytotoxic antibody against a specific donor with DTT treatment.

There was a generally high degree of illness in both the positive crossmatch group and their controls, as defined by the current United Network for Organ Sharing (UNOS) stratification: status 1—at home, functioning without nursing care; status 2—at home, not working and requiring professional nursing care; status 3—hospital-bound; status 4—ICU-bound; UNOS stat—ICU-bound on life support (14).

The outcome was compared between the crossmatch-positive grafts and that of 50 negative grafts with matched UNOS urgency score who had their transplantations just before and after the crossmatch-positive cases.

Crossmatch test

Pretransplant sera was drawn immediately before liver transplantation and used for the crossmatching. All sera were dithiothreitol-treated to inactivate IgM as described earlier (15). The donor T lymphocytes were isolated from lymph nodes using CD3-conjugated dynabeads (Dyna, Inc., Great Neck, NY).

The lymphocyte cytotoxicity test was performed according to NIH standards with one washing. Briefly, 1 μ l of 2×10^6 /ml T lymphocytes were added to 1 μ l of serum, which was 2-fold diluted up to 1:8 using RPMI1640 solution, for 1 hr at room temperature. After one washing, 5 μ l of rabbit complement was added for an additional 1 hr at room temperature and trypan blue was added to stain dead cells.

Immunosuppression

Intravenous doses of 0.1 mg/kg of FK506 were infused over 24 hr, starting in the operating room, and repeated every 24 hr until oral intake began. The conversion from intravenous to oral doses of 0.15 mg/kg every 12 hr was overlapped for one day.

In this period, 1 g intravenous methylprednisolone was given to 8 of 25 positive-crossmatch patients (32%) and 11 of 50 negative-crossmatch patients (22%) after reperfusion of the liver allograft. A daily dose of 20 mg methylprednisolone was started in all patients.

Rejection episodes that were unresponsive to increasing the maintenance doses of FK506 were treated with a single 1g bolus of methylprednisolone. If rejection persisted, the patient received an additional 5-day burst of methylprednisolone or a 3–5-day course of 5–10 mg/day of OKT3.

Organ preservation

All of the liver allografts in this study were preserved with the University of Wisconsin solution.

Graft survival, follow-up, and statistics

The survival rates were calculated by the method of Kaplan-Meier. The results were summarized as of April 30, 1991, with a median follow up of 12 months and a minimum follow up of 6 months.

Statistical comparisons were made by the generalized Wilcoxon method, by Student's *t* test and by chi-square analysis. The difference was considered statistically significant when $P < 0.05$. Data are shown as mean values $\pm$ SE.

RESULTS

The incidence of positive crossmatch

Of the 231 patients who had a donor lymphocytotoxic crossmatch test, it was positive against donor in 25 (10.8%) recipients, weakly or doubtfully positive in 10 (4.3%) recipients, and negative in 196 (84.8%) recipients.

Of the 25 cases with positive crossmatch recipients, 18 (72.0%) had panel-reactive antibodies of greater than 40%, which were pretreated by DTT. Seven patients had a PRA of less than 40%.

Table 1 shows the circumstances of 25 crossmatch-positive patients (positive-crossmatch group) and 50 crossmatch-negative patients (negative-crossmatch group).

The cold ischemic times of liver grafts in both groups were not statistically significantly different: 15.7 ± 0.9 hr (range 7.3–27.0 hr) in the positive-crossmatch group and 14.8 ± 0.7 hr (range 4.3–27.2 hr) in the negative-crossmatch group.

Survival

The graft survival of first hepatic allografts was compared in 25 positive crossmatch patients and 50 negative patients (Fig. 1). There was a statistically significant difference in the survival curves between the two groups ($P = 0.004$ by generalized Wilcoxon method). The one-year graft survival was 56% for positive-crossmatch patients and it was 82% for negative-crossmatch patients.

Eleven of 25 positive-crossmatch grafts (44%) failed for various reasons (Table 2). The median graft survival of those 11 failed grafts was 14 days (range: 1 day to 245 days).

Six crossmatch-positive patients (24%) were retransplanted at an interval of 1–125 days, and 3 of them are still alive. On the other hand, in the negative-crossmatch group, retransplantation of the liver was done in 3 of 50 patients (6%).

The patient survival was also significantly different in positive-crossmatch (68%) and negative-crossmatch patients (86%) ($P=0.03$). The difference between the first graft and patient survival were accounted for by the incidence of retransplantation, which was four times more frequent (24% versus 6%) in the positive-crossmatch cases than in the negative-crossmatch patients.

The cause of graft failure at the time of retransplantation

In the positive-crossmatch group, all of 6 failed grafts that required retransplantation had strong positive-crossmatch donors (more than 80% killing of donor lymphocytes) with more than 70% PRA. The pathological findings showed a widespread coagulative necrosis with intrahepatic venular thrombi in one graft, although the cold ischemic time was less than 8 hr. This graft failed on the operating room table and had to be immediately replaced. Two grafts had hepatic arterial thrombosis, in one case with severe acute cellular rejection with prominent neutrophilia. One graft had severe cholangitis with focal intrahepatic thrombi and infarcts. Another two grafts failed because of biliary tract problems accompanied by intrahepatic bile duct necrosis with intrahepatic arterial thrombi. Five of 6 failed grafts occurred when vascular problems were the cause of retransplantation.

In the negative-crossmatch group, three grafts required retransplantation for portal vein thrombosis, arterial graft thrombosis and acute cellular rejection (one case each).

Panel-reactive antibody (PRA)

The graft survival of crossmatch-positive allografts with high PRA titers (more than 40%) was 44.4%, while it was 85.7% when the PRA titers were less than 40%. There was no statistically significant difference ($P=0.07$) because the number of crossmatch-positive grafts was small. However, there was a tendency toward decreased graft survival when the PRA titer was higher than 40% (Fig. 3).

Intraoperative blood usage

Intraoperative blood product usage differed significantly in these two groups (Fig. 4). The packed red blood cell usage in crossmatch positive versus negative recipients was 35.6 units versus 15.1 units ($P<0.005$).

Platelet usage was 25.7 units versus 10.4 units, respectively ($P<0.005$). Fresh frozen plasma usage was 32.8 units in crossmatch-positive patients and 15.1 units in crossmatch-negative recipients ($P<0.005$).

Postoperative platelets usage was significantly higher in crossmatch-positive recipients than in crossmatch-negative patients—45.1 units/patient vs. 11.0 units/patient ($P<0.001$) during the first postoperative week.

Postoperative liver function

Postoperative liver function tests were done in these two groups. Seventeen crossmatch-positive patients and 47 negative patients who survived more than one month were studied. The preoperative total bilirubin in these two groups was not statistically significantly different.

During the first 3 weeks after liver transplantation, the total bilirubin in the positive-crossmatch patients was significantly higher than that of the negative crossmatch patients (Fig. 5). Even

at postoperative day 60, the total bilirubin of crossmatch-positive patients was still significantly higher than that of crossmatch-negative patients (2.32 ± 0.88 versus 0.98 ± 0.10 mg/dl, $P < 0.025$).

Alkaline phosphatase levels in positive-crossmatch patients tended to be higher postoperatively when compared with those of crossmatch-negative patients. But a significant difference ($P < 0.05$) was found only on postoperative day 90 (Fig. 6).

The postoperative platelet count in the crossmatch-positive patients was significantly lower than that of crossmatch-negative patients (Fig. 7), and the crossmatch-positive group required a significantly greater number of postoperative platelet transfusions (45.1 units vs. 11.0 units, $P < 0.001$).

OKT3 administration

OKT3 was administered to 11 of 25 positive-crossmatch patients. Four patients received this drug prophylactically, and 7 patients were treated for biopsy-proved rejection.

Three of 4 grafts in the prophylactic group failed, while rejection was successfully treated in 6 of 7 livers with biopsy-proved rejection (Fig. 8). One patient required retransplantation at 3 months for multiple intrahepatic biliary strictures.

DISCUSSION

Our previous study evaluating patients treated with cyclosporin and steroids demonstrated that antidonor lymphocytotoxic antibody (a positive crossmatch) adversely affected the survivals of primary hepatic allografts during the first 6 months after liver transplantation (16). The reason appears to be immunological, as the grafts were lost to rejection significantly more often in positive-crossmatch than in negative-crossmatch transplantations. One of the limitations of the previous report was that DTT pretreatment was not employed.

Since November 1989 we have adopted the antidonor T lymphocytotoxic antibody assay with DTT treatment of recipient sera. DTT dissects the disulfide bond and reduces the activities of IgM antibodies and is useful in distinguishing a false-positive crossmatch (from IgM antibodies) from true sensitization due to IgG antibody (15,17).

Hyperacute rejection of renal allografts is mediated by donor-specific lymphocytotoxic antibodies directed primarily against vascular endothelium (18). Within from minutes to hours of revascularization, complement activation by alloantibodies causes microvascular occlusion by platelet and fibrin aggregates, infiltration of neutrophils and mononuclear cells, and endothelial destruction (19–20).

In contrast to kidneys and hearts, the liver is relatively resistant to antibody-mediated rejection in experimental animals (21) and humans (4,22). While not invulnerable to humoral rejection, the liver's relative resistance to this process is not fully understood. The liver graft may neutralize existing antibodies by Kupffer cell action (23–24), by the secretion of soluble class I MHC antigens that neutralize or alter the antibodies (13,25–26) and/or by poor expression of class I antigens on hepatocytes (27–28). The dual blood supply is also advantageous as the microvascular thrombosis and intense vasoconstriction associated with humoral events only develop in the arterial tree. In addition, the enormous mass of the liver may offer protection against antibody-mediated graft destruction.

Classic hyperacute renal allograft rejection brings about the destruction of the graft within 24 hr. This type of biological event is extremely rare in liver transplantation, but antibody-mediated events can cause graft loss over days to weeks. Furthermore, sensitized patients may

have grave problems with both acute and chronic cellular rejection as we have previously reported (16).

The pathologic findings in biopsy specimens and failed allografts in this series of patients will be described in detail elsewhere.⁴ Immediately after reperfusion, crossmatch-positive grafts often contained platelet aggregates in the veins and sinusoids, although hemorrhagic congestion like that seen with ABO-incompatible grafts was not generally observed. Furthermore, patients with a positive crossmatch underwent liver biopsy more often, especially in the first 10 days, and demonstrated a higher incidence of cellular rejection and histopathologic changes of “preservation” in ischemic injury. This occurred despite no observable difference in the cold ischemic trial.

In summary, a range of pathologic findings were observed, but these had a common basis of presumed ischemic damage, with the differences being due to the severity and acuteness of ischemia. In this regard, recent experimental animal studies have shown that the timing, type, and eventual outcome of sensitized animals directly correlated with the titer anti-graft antibodies (Nakamura, Murase, Demetris et al., manuscript in preparation).

In view of the heterogeneous pathologic findings, it was not surprising that the causes of graft failure in the positive-crossmatch patients also were variable. The allograft of one patient who had a strong positive crossmatch with a 97% PRA had widespread coagulative necrosis with intrahepatic venular thrombi immediately after transplant and required immediate retransplantation. Three other failed grafts had hepatic arterial thrombosis. One of them was accompanied by severe, predominantly neutrophilic and lymphoblastic, portal infiltration. Two grafts failed due to biliary complications related to the hepatic arterial blood supply.

The indications for retransplantation were often related to vascular problems. These findings suggest ischemic insult to the hepatic lobule at the major arterial component—the arteriolar or sinusoidal levels. This feature was also seen in arteriograms of liver allograft recipients within days after liver transplantation. Presumably, the sinusoidal endothelium and the terminal hepatic vessels are the target for antibody- and complement-mediated injury of the allograft in positive-crossmatch recipients. This injury may lead to endothelial swelling with platelet and granulocyte trapping, and resultant hypoperfusion of the hepatic lobule and/or intrahepatic bile duct necrosis.

Intraoperative monitoring by thromboelastogram in the last five years has reduced blood infusion volume by 33% and has increased blood coagulation stability without adding blood products (30). Also, the appropriate use of epsilon-aminocaproic acid in patients undergoing liver transplantation is very effective in treating fibrinolysis and associated generalized oozing (29,30). Despite these advances, this study showed more difficulty in intraoperative blood product management in positive-crossmatch recipients.

The platelet counts prior to liver transplantation were not significantly different in the groups. The intraoperative platelet usage was significantly higher in positive-crossmatch patients during liver transplantation. Furthermore, postoperative platelet usage by positive-crossmatch patients was significantly higher than that of negative patients.

The fact that many of the crossmatch positive patients were highly sensitized may play a significant role in platelet transfusion requirements, as it is well known that platelets express class I antigens (31,32), and specific alloimmunization of these antigens is a major cause of

⁴Nakamura K, Yagihashi A, Iwaki Y, et al. A clinicopathologic study of human liver allograft recipients harboring preformed IgG lymphocytotoxic antibodies. (Submitted for publication.)

refractoriness in the thrombocytopenic patients to platelet transfusion (33,34). Furthermore, the liver plays a key role in removal of platelet aggregates and immune complexes (24). Recently, crossmatching with platelet targets in renal transplants has been reported and it may be helpful to avoid early primary nonfunction while minimizing false-positive reactions of lymphocytotoxic crossmatches (35).

Following the development of FK506 (9,36), the recent rate of early retransplantation has been reduced to 12.7% in adults (36). However, the retransplant rate in positive-crossmatch patients was observed to be extremely high (24%). Thus advances in immunosuppression added to improvements in surgical techniques, organ preservation, and perioperative care have allowed us to demonstrate the adverse impact on liver transplantation of the positive cytotoxic crossmatch state. How this information will affect management strategy is being studied.

We still advocate liver transplantation for desperately ill patients with high PRAs and do not discriminate against their selection on a serologic basis. We routinely obtain PRAs in all recipients prospectively in order to identify the high-risk recipient population. We now perform the crossmatch test whenever the donor lymphocyte preparations are ready so that the results are known before transplanting the liver. In case of a positive crossmatch, prophylactic high-dose steroids are begun in the operating room and continued for at least five days. OKT3 is started either prophylactically or subsequently at the slightest suspicion of rejection.

Conclusion

These data showed more difficulty in intraoperative blood product management, a degraded prognosis, and a poorer average quality of ultimate graft function when liver transplantation was performed against a positive cytotoxic crossmatch. In such patients, for whom crossmatch-negative donors may never be found because of the broad extent and intensity of sensitization, special therapeutic strategies perioperatively must be evolved if results are to improve.

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Figure 1. The actuarial graft survival rates in 25 adults positive-crossmatch patients and 50 negative-crossmatch patients.

Figure 2. The actuarial patient survival rates in 25 adult positive-crossmatch and 50 negative-crossmatch patients.

Figure 3. Actuarial graft survival rates for 18 patients whose PRA were $\geq 40\%$ and 7 patients whose PRA were $< 40\%$, with DTT treatment sera in positive-crossmatch patients.

Figure 4. Blood usage in positive- and negative-crossmatch patients. (PRBC) packed red blood cells; (FFP) fresh frozen plasma; (CRYO) cryoprecipitated plasma; (POST OP PLATELETS) postoperative usage of platelets. Mean $\pm$ SE is shown.

Figure 5. Serum total bilirubin levels after liver transplantation in positive- (n=17) and negative- (n=47) crossmatch patients who were followed for more than one month (mean $\pm$ SE). There was a significant elevation in total bilirubin levels in crossmatch-positive patients.

Figure 6. Serum alkaline-phosphatase levels after liver transplantation in positive- (n=17) and negative-crossmatch patients (n=47) who were followed for more than one month. Mean $\pm$ SE is shown.

Figure 7. The platelet count before and after liver transplantation in positive- (n=17) and negative-crossmatch patients (n=47) who were followed for more than one month. Mean $\pm$ SE is shown. The platelet counts in positive-crossmatch patients were significantly lower than those of crossmatch-negative patients.

Figure 8. Total bilirubin levels before and after OKT3 treatment in crossmatch-positive patients. The OKT3 was administered at the time of biopsy-proved rejection (n=7).

Table 1

Cases of positive and negative crossmatches

Crossmatch	Positive	Negative	P
Number of patients	25	50	
Age (mean + SE)	51.9 ± 1.7	45.4 ± 2.0	ns
Male/female	11/14	28/22	ns
UNOS score	3.7 ± 0.11	3.7 ± 0.08	ns
CIT (hr)	15.7 ± 0.9	14.8 ± 0.7	ns
PRA(%) (mean + SE)	69.4 ± 5.4	2.5 ± 1.6	<0.001
Original disease			
Nonalcoholic cirrhosis	11	17	ns
Alcoholic cirrhosis	7	18	ns
Cholestatic disease	7	9	ns
Hepatoma	0	3	ns
Fulminant hepatic failure	0	3	ns

^aUNOS: United Network for Organ Sharing; CIT: cold ischemic time; PRA: panel-reactive antibody.

Table 2

Outcome of 25 positive and 50 negative crossmatch patients

	Crossmatch test	
	Positive	Negative
Starting number of patients	25	50
Retransplantation	6	3
Death	8	7
Total graft loss	11	9
Clinical cause of graft loss:		
Primary nonfunction	1	1
Hepatic arterial thrombosis	3	1
Portal vein thrombosis	0	1
Biliary complication	2	0
Acute cellular rejection	0	1
Sepsis	2	3
Mycotic aneurysm	1	0
Recurrent hepatitis	0	1
Postoperative bleeding	1	0
GI bleeding ^a	1	0
Recurrence of malignancy	0	1

^aGI: gastrointestinal.