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Immunological Factors Influencing Liver Graft Survival

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Until recently, lack of sufficient case numbers and lack of time to perform prospective preoperative testing made it difficult to examine the importance of such immunological factors as ABO blood-group matching, preformed antidonor cytotoxic antibody, or HLA-antigen matching on graft outcome in liver transplantation. However, with the increased experience of the last several years it is now possible to begin to assess the significance of these factors.

ABO BLOOD GROUPS

The ABO isoagglutinins were the first preformed antibody system to be intensively studied. The ABO blood group substances expressed on red blood cells are also found in other tissues, including the kidney and the liver, and these organs do bind naturally occurring anti-A or anti-B isoagglutinins when transplanted into an ABO-incompatible recipient.[7-20]

Transplantation of a kidney from an ABO-incompatible donor results in hyperacute rejection of the allograft in most cases. Grossly, the organ turns dark and soft, usually within a few minutes of revascularization in the recipient. Angiography of such kidneys demonstrates diffuse closure of small vessels. Histopathologically, the arterioles and capillaries are clogged with blood elements, especially erythrocytes and platelets.

Alexandre and colleagues have demonstrated that ABO isoagglutinins can be successfully removed by plasmapheresis and drug therapy to allow

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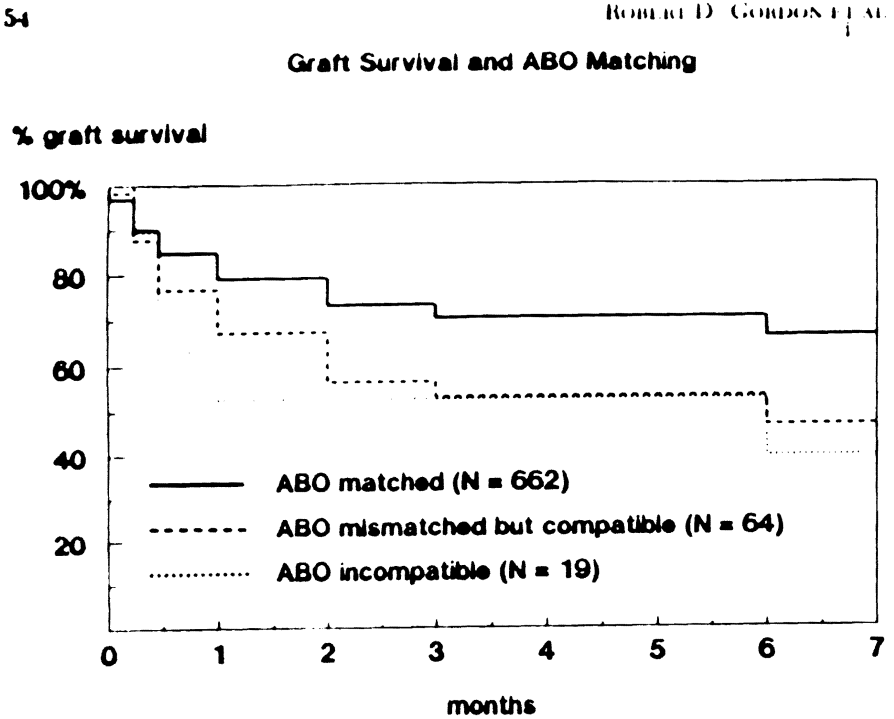

Figure 1. Actuarial survival of primary liver grafts based on donor-recipient ABO compatibility. Grafts between ABO identical donor-recipient pairs fare better than grafts between ABO-mismatched or -incompatible pairs. (Adapted from Gordon RD: Experience with ABO blood groups in liver transplantation. Transplant Proc [in press], with permission.)

the transplantation of ABO-incompatible kidneys.[1] It is not known whether ABO antigenic differences are, however, a late hazard to graft survival, but the studies of Rapaport and coworkers have demonstrated that products of the ABO system are histocompatibility antigens.[16]

It has been known for many years that transplantation of the liver across ABO blood groups does not result in hyperacute rejection.[17] However, we have found that there is a small but significant penalty for transplanting the liver across ABO blood groups. Survival of grafts between ABO-identical donor and recipient pairs is significantly higher than survival of ABO-mismatched but compatible or ABO-incompatible grafts.[3, 4]

Figure 1 presents primary graft survival data for 662 ABO-matched grafts 64 ABO-mismatched but compatible grafts, and 19 ABO-incompatible grafts, performed between January 1981 and December 1986. All patients were treated with cyclosporine and prednisone as has been previously described.[18] Preference in recipient selection was given to ABO matching except in cases of medical urgency or donor scarcity.

Thirty-day graft survival was 79.0 per cent, 67.2 per cent, and 52.6 per cent for ABO-matched, -mismatched but compatible, and -incompatible grafts, respectively, and 66.0 per cent, 46.5 per cent, and 39.5 per cent at 180 days, respectively. Survival of ABO-matched grafts is significantly better than mismatched or incompatible grafts ($p < 0.01$).

Survival of patients transplanted under urgent conditions including

active gastrointestinal bleeding, severe encephalopathy, or other conditions requiring intensive care were more common in the patients receiving mismatched or incompatible grafts. However, when the data were adjusted by analyzing only transplantation of stable patients, there was still a significant survival advantage for ABO-matched grafts ($p < 0.05$).[4]

With ABO-mismatched livers, it is common for a graft-versus-host (GVH) reaction to develop 10 to 21 days after transplantation.[15] In such cases, the production of anti-A or anti-B antibodies by donor B-lymphocytes transplanted with the graft results in a hemolytic anemia. The hemolysis is usually self-limited and mild, but in some cases may be so severe that retransplantation is required. The GVH reaction complicates the management of the patient and may, at least in part, be responsible for the poorer survival of ABO-mismatched grafts.

On the basis of these findings we limit use of ABO-mismatched or incompatible grafts to urgent cases or for cases where donor availability is severely limited, such as for small children. Although there clearly is a significant risk in using such grafts, this risk may be less than the risks of sepsis, coagulopathy, central nervous system damage, and metabolic derangement associated with liver failure.

PREFORMED LYMPHOCYTOTOXIC ANTIBODY

Transplantation of the kidney to a recipient with preformed circulating antibodies cytotoxic for donor lymphocytes is also associated with a hyperacute rejection phenomenon.[9, 14, 22] A neutrophilic infiltrate and glomerular immunofluorescent staining with immunoglobulin, usually IgG, are characteristic findings on examination of such kidneys.

Prior to transplantation, serum from the potential recipient is crossmatched with lymphocytes from the donor to test for the presence of donor-specific cytotoxic antibody. Although not all such antibodies are harmful, if a positive test is obtained, another recipient is selected or further testing is done to characterize the antibody.

In addition, renal transplant candidates are screened, usually on a monthly basis, to determine the extent of their reactivity to a randomly selected panel of lymphocytes from the population at large. A high level of reactivity against the panel (percentage panel reactive antibody or PRA) suggests a low probability of finding a crossmatch-negative donor. Furthermore, even if the donor-specific crossmatch is negative, transplantation of a kidney to a patient with a high PRA is associated with a decreased graft survival rate.[13]

In liver transplantation, the short cold storage times have not allowed routine prospective crossmatching in most cases, and therefore the liver has been transplanted in presence of cytotoxic antibody. Although antibody-mediated rejection is a well established component of rejection in experimental xenografting of the liver and has recently been demonstrated in an experimental rat allograft model,[10] it has been difficult to demonstrate antibody-mediated hyperacute rejection of the liver in the clinical setting.[6, 17]

We have reviewed our experience in clinical liver transplantation to determine whether either a positive donor-specific crossmatch or a high PRA is related to graft outcome.[3] The effects of PRA and antibody crossmatch on graft survival are shown in Figures 2A and *B* respectively. Neither has been found to have a statistically significant effect on graft survival.

Sequential liver-kidney transplants have been done successfully despite a strongly positive donor-specific antibody crossmatch. In such cases, when the liver is transplanted first, it is capable of clearing enough circulating preformed antibody to protect a kidney immediately transplanted from the same donor.[4]

Our conclusion is that antibody-mediated hyperacute rejection is a rare event that cannot be reliably predicted by the conventional antibody crossmatch. Further investigation is needed to better define the conditions under which antibody-mediated early rejection can occur, and how it can be predicted and thereby prevented.

HLA MATCHING

It is well established that the high grades of HLA matching produce superior graft survival in kidney transplantation.[21] Whether or not matching offers similar benefits in liver transplantation is not yet known. Since liver transplants are performed without prospective tissue typing, and in any single series the number of high-grade matches is relatively small, analysis of the effect of HLA antigens is difficult. Nevertheless, some interesting trends are suggested in our first analysis of this series.

We have found that grafts transplanted with no mismatch at the A locus have not done as well as grafts transplanted with a one or two HLA-A mismatches. Similar data for matching at HLA-DR approach statistical significance ($p = 0.06$). A longer followup of an even larger, multicenter series of patients is necessary to confirm these initial observations.

It has been suggested that this paradoxical effect of HLA matching might represent a dualistic effect of HLA antigens involving self-recognition (MHC-restricted processing of autoantigens) on the one hand and alloreactivity on the other.[11] Since many of the common causes of end stage liver disease (primary biliary cirrhosis, sclerosing cholangitis, and viral hepatitis) are thought to involve immune mechanisms, autoimmune responses might be facilitated by HLA matches. However, we have no direct evidence that disease recurrence facilitated by HLA matching is responsible for graft loss.

We emphasize caution in interpreting this analysis of HLA matching. It is quite likely that HLA compatibility will prove more important in liver transplantation just as it has in kidney transplantation, when larger multicenter series are available for analysis.

CONCLUSION

Liver transplantation is now the preferred treatment for many diseases leading to end stage liver disease, including antigen-negative chronic

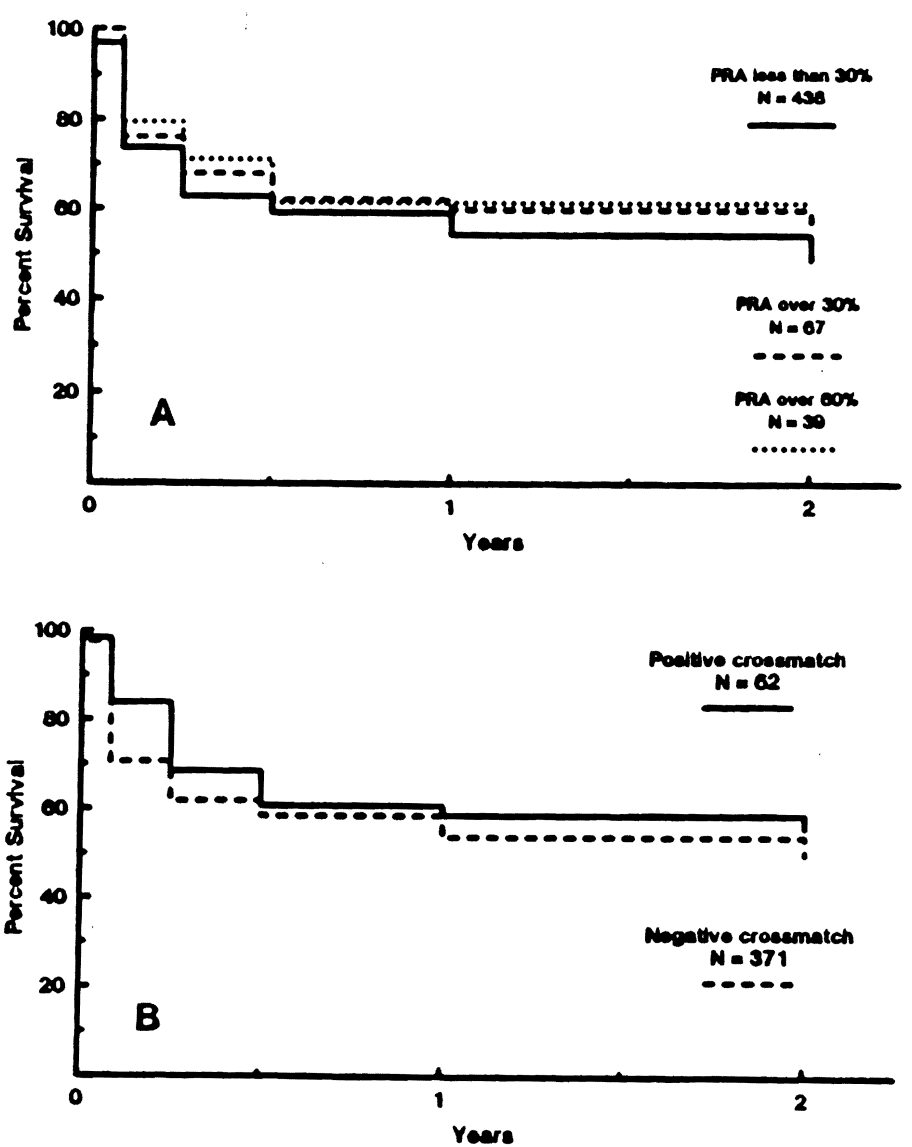

Figure 2. A. Actuarial survival of liver grafts based on recipient panel reactive antibody (PRA). *B*. Actuarial survival of liver grafts based on the donor-specific cytotoxic antibody crossmatch. (Adapted from Gordon RD, et al. Surgery 100:705–715, 1986, with permission.)

aggressive hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary atresia, congenital hepatic fibrosis, and inborn errors of metabolism based in the liver (Wilson's disease, tyrosinemia, glycogen storage disease).[6] The role of immunological factors in liver transplantation is not as well defined as for renal transplantation, and investigation so far suggests that ABO blood group differences, preformed cytotoxic antibody, and possibly HLA-matching have different effects on liver and renal allograft survival. This will be a fertile area of study for years to come.

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