Responsiveness to HL-A as Studied by Monitoring Blood Transfusions and Kidney Transplants

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Responsiveness to HL-A antigens as measured by the formation of lymphocytotoxic antibodies has been shown to have significant influence on the outcome of kidney transplants. Patients who have preformed cytotoxins before transplantation have a smaller chance for a successful graft than patients without cytotoxins (Terasaki et al, 1971; Opelz & Terasaki, 1972). Those who did not develop cytotoxins in spite of multiple blood transfusions were found to have exceptionally good graft survival (Opelz et al, 1972; Opelz et al, 1973a). In this communication we will report on some additional studies of the relationship between transfusions, transplants, and the occurrence of lymphocytotoxins.

METHODS

Dialysis and transplant patients from 11 Los Angeles hospitals were tested repeatedly for the presence of lymphocytotoxic antibodies in their serum by the standard micromethod (Mittal et al, 1968). All sera were tested against a panel of 90 random donors and reactivity against 5% or more of the panel was considered as cytotoxicity positive. Transfusion records of the patients showed that, with the exception of a few whole blood transfusions, all transfusions were given in the form of buffy coat poor blood. The rate at which cytotoxins occurred in transfused patients was calculated by actuarial methods.

RESULTS

Figure 1 shows the rate at which cytotoxins developed in haemodialysis patients with increasing numbers of blood transfusions. Most strikingly, even with 30 transfusions, about half of the patients had still not developed cytotoxic antibodies. Since all of these patients must have been repeatedly transfused with HL-A mismatched blood, the nonproduction of cytotoxins classifies these patients as nonresponders to HL-A.
The likelihood that a patient who has received more than six blood transfusions has never been challenged with HL-A2 is less than one in a hundred. Nevertheless, of 59 HL-A2 negative patients with more than six transfusions who were studied by us, only 15 (34%) had developed cytotoxins. Thus, unresponsiveness is rather common even to HL-A2, which has been thought to be the most immunogenic HL-A antigen.

The occurrence of cytotoxins was also studied in 144 patients after they had been transplanted with cadaver kidneys. As shown in Table I, cytotoxins were strongly associated with kidney graft failure. Of the four patients with antibodies in spite of functioning grafts, two had been found positive before transplantation (and of course received crossmatch-negative kidneys) and the other two had not been tested earlier.

Table I. Lymphocytotoxic antibodies in transplanted patients

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<tr>
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<th>Cytotoxicity positive</th>
<th>Cytotoxicity negative</th>
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<tr>
<td>Functioning graft</td>
<td>4 (9.5%)</td>
<td>38 (90.5%)</td>
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<tr>
<td>Graft failure</td>
<td>59 (57.8%)</td>
<td>43 (32.2%)</td>
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\[ p < 0.001 \]

Antibodies against the first and the second HL-A locus were found at about the same rate, suggesting that there is no significant difference in the immunogenicity of the two loci.
DISCUSSION

Our study confirms the close association of lymphocytotoxins with blood transfusions. Furthermore, the existence of unresponsiveness to HL-A antigens is clearly documented. Unresponsiveness to HL-A antigens in the form of transfused leucocytes has been shown to be paralleled by unresponsiveness to kidney transplants (Opelz et al., 1972; Opelz et al., 1973a). Preliminary evidence favours the idea of actively induced rather than primary unresponsiveness (Sengar et al., 1973a; Sengar et al., 1973b). Whether the recipient's tissue type and the specificity of mismatch are determining factors for the induction of unresponsiveness is currently being studied.

Lymphocytotoxins, when measured before (Terasaki et al., 1971) or after (Table I) transplantation, are clearly associated with transplant failure and this is further proof of the importance of HL-A antigens as transplantation antigens.

Rather than different grades of mismatches the state of responsiveness to HL-A in the recipient may be a better indicator for graft survival chances (Opelz et al., 1973b). Refined methods for the characterisation of a patient as responder or nonresponder are needed.

SUMMARY

The rate at which lymphocytotoxic antibodies developed in dialysis patients in relation to the number of blood transfusions was studied. Even with 30 transfusions only about half of the patients developed cytotoxins. Unresponsiveness to HL-A is believed to be the reason for this unexpected non-production of antibodies.

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REFERENCES

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OPEN DISCUSSION

R LUKE (Kentucky, USA): Have you any observations on the use of frozen red cells? If your hypothesis is correct frozen red cells may need their own type of white cells transfused to induce blocking antibody.

OPELZ: We have very little experience with frozen blood in Los Angeles, it was introduced only six months ago here. We do have some data on patients who have not been transfused although they have been transplanted and we found that they had a lower graft survival. This data is only based on 27 patients and one has to be very careful because in order to make a real statistical comparison you need to have more cases.

LUKE: We have been using lymphocyte poor blood in Lexington produced by centrifugation: about 95 per cent destruction of lymphocytes takes place. There is some evidence that the results are better with this than using total destruction of lymphocytes as in the frozen red cell technique.

OPELZ: This I think depends to a great extent on whether the patients make antibodies or not.

F BRUNNER (Basel): Is there any difference in whether you use Dextran washed erythrocytes or whole blood units for transfusion?

OPELZ: About 95 per cent of our transfusions were with packed cells. The remaining 5 per cent are whole blood transfusions. We have no knowledge about Dextran washed cells.