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Small Bowel Transplantation in Sensitized Recipients: Comparison with Heart, Kidney, and Liver Grafts

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SMALL BOWEL transplantation in humans, alone or in combination with other viscera, has been performed frequently using FK506 immunosuppression, and a large number of studies in cellular rejection have accumulated. However, the role of preformed lymphocytotoxic antibodies on small bowel transplantation is not yet defined clearly. We reported previously that Lewis rats sensitized with multiple ACI skin grafts produced a high titer of anti-ACI lymphocytotoxic antibodies (IgG > > IgM) and hyperacutely rejected ACI heart and liver grafts.[1] We also showed that the survival of either kind of graft in sensitized recipients inversely correlated to the lymphocytotoxic antibody titer and the length of time after the last skin grafting. When transplantation was delayed for 15 weeks or more after sensitization, heart and liver grafts were rejected in an antibody- and cell-mediated fashion, providing a clinically relevant animal model to study the role of preformed lymphocytotoxic antibodies on transplantation.[2]

In this study, using the same sensitization protocol, antibody-mediated small bowel allograft rejection was studied. Results were compared with those of other organ allografts in the same setting.

MATERIALS AND METHODS

Inbred Lewis (LEW, $RT1^l$) and ACI ($RT1^a$) rats were used as recipients and donors, respectively. LEW rats were sensitized with four successive ACI tail skin grafts at 14-day intervals.[1] The surgical procedure of small bowel transplantation with caval drainage has been described before.[3] To characterize the histopathological changes of antibody-mediated rejection seen in small bowel grafts, ACI intestine was transplanted into sensitized recipients either within 4 weeks (n = 2) or more than 15 weeks (n = 3) after the last skin grafting. Serial specimens were taken from the graft intestine and lymphoid tissues and processed for histopathological analysis.

In the following experiments, responses of small bowel graft to preformed antibodies were compared with those of other organ allografts. Sensitized recipients received either small bowel, heart, kidney, or liver graft from ACI rats more than 15 weeks after the last skin grafting. FK506 was given at a dose of 1.0 mg/kg/d for 7 days starting on the day of grafting to avoid acute cellular rejection.

RESULTS

Macroscopically, small bowel grafts transplanted into sensitized animals within 4 weeks after the last skin graft became dark in color and developed congestion within a few minutes after normal revascularization. During the next 60 minutes, grafts became completely hemorrhagic. A notable histopathological change seen in these specimens was congestion of capillaries in the lamina propria, submucosa, and inside the Peyer's patches, with diffuse hemorrhage and edema. The number of congested capillaries and area of hemorrhage increased and extended to the villi with time. These changes in the grafts were macroscopically and histopathologically less severe when transplantation was delayed for more than 15 weeks. The inflammatory infiltrates of neutrophils and lymphocytes appeared between 18 and 26 hours after grafting in the latter specimen.

When heart and kidney grafts were transplanted into sensitized recipients more than 15 weeks after skin grafting under FK506 treatment, median graft survivals were 4.5 (n = 4) and 3 days (n = 4), respectively. These survival times were much shorter than those seen in unsensitized recipients both with and without immunosuppression, suggesting that irreversible antibody-mediated damage occurred to these grafts. When liver grafts, which have been known to be resistant to antibody-mediated damage, were transplanted, three of five animals had a prolonged survival of more than 80 days and two survived for more than 100 days. After small bowel grafting in the same condition, three out of five animals died within 5 days; however, the other two survived for more than 100 days.

DISCUSSION

Although the development of acute cellular rejection following small bowel transplantation was demonstrated, antibody-mediated rejection in this transplantation is not clearly defined. Using a well-established animal model of antibody-mediated allograft rejection, humoral rejection of the small bowel graft was characterized in this study. Typical histopathological changes were capillary congestion and hemorrhage seen in lamina propria, submucosa, and inside the lymphoid tissues of Peyer's patches and mesenteric lymph nodes, and later in the villi. Similar findings were observed in one patient who received crossmatch positive isolated small bowel graft. Postperfusion biopsy of this patient showed capillary congestion and hemorrhage, which lasted for 2 weeks after transplantation.

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Delayed transplantation to primed animals (>15 weeks) under FK506 treatment was performed because of the relevance to the grafting to presensitized patients. In spite of sufficient FK506 treatment, survival times of heart and kidney grafts in sensitized recipients were reduced when compared to those in unsensitized recipients. Damage to heart and kidney grafts caused by preformed antibodies may be irreversible. On the other hand, 60% of liver grafts and 40% of small bowel grafts showed extended survival of more than 80 days in the same setting. The small bowel graft may be more resistant to antibody-mediated damage compared to heart and kidney grafts.

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