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Outcome of an ABO-incompatible renal transplant without splenectomy

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Sir,

The mechanism by which isohemagglutinins injure ABO-incompatible allografts is uncertain, and the need for splenectomy in ABO-incompatible transplantations remains controversial. In a previous study [6] we reported the rate of ABO titer elevation in a retrospective study of 101 ABO-incompatible renal transplantations accompanied by splenectomy. This rate was equivalent to the titer elevation in other reports of ABO-incompatible renal transplantations without splenectomy [7]. On the basis of these data the first ABO-incompatible transplantation without splenectomy was performed at our institution. In this study we investigated the immunological status of a recipient using a sequential flow-cytometry with anti-CD15s, CD19, CD3, CD4, and CD56 antibodies. CD15s, which is known to be a ligand for E- and L-selectin, is presented on activated T and B lymphocytes but not on rest cells. We found that CD15s is strongly expressed on peripheral lymphocytes at the time of acute rejection [5]. To examine the activated condition in each population of T, B, and natural killer cells three-color flow-cytometry was performed using anti-CD15s, anti-CD19, anti-CD3, anti-CD4, and anti-CD56 antibodies. We present a flow-cytometry analysis of immunological response in an ABO-incompatible renal transplant recipient without a splenectomy.

The patient was a 43-year-old man with type 0 blood. He received a renal transplant from his sister, who has type B blood. A previously described immunosuppressive regimen was performed [6]. Briefly, the patient received two sessions of double-filtration plasmapheresis before transplantation until the anti-B immunoglobulin G (IgG)/IgM titer had decreased to a level of 1:16 or below. The IgM anti-B level was determined using the saline and Bromerin agglutination technique, and the indirect Coomb's test was used to measure the IgG titer.

In the induction phase methylprednisolone, cyclosporine (CsA), azathioprine, and antilymphocyte globulin were administered [6, 8]. Methylprednisolone administration was started on the day of the transplantation at a dose of 250 mg/day and was reduced to a maintenance dose of 8 mg/day by the fourth month. The oral administration of CsA (8 mg/kg per day) was started 2 days before the operation, and a drip infusion of CsA (3 mg/kg) was given on the day of the transplantation. CsA administration was adjusted to maintain a CsA trough level in the whole blood of between 200 and 300 ng/ml for 1 or 2 months after the transplantation. Azathioprine administration was started at a dose of 2 mg/kg per day 2 days before the operation. Antilymphocyte globulin administration was begun at a dose of 20 mg/kg per day 2 days before the transplantation and continued for 14 days. Local irradiation of the graft was performed at a dose of 1.5 cGy on the first, third,

and fifth days after the transplantation. However, splenectomy was not performed at the time of operation. Informed consent from the patient and the donor was obtained, since the absence of a splenectomy was a violation of the protocol for AB0-incompatible transplants.

The patient's condition was stable, with sufficient urine volume and low titer of anti-B antibody until 4 days after the operation. The serum creatinine level also fell to 1.9 mg/dl. Five days after the operation the urine volume gradually decreased, and anuria accompanied by a sudden elevation in the anti-B antibody titer to 1:4096 was observed. The patient was maintained thereafter on chronic hemodialysis every second day. To remove the anti-B antibody titers in the serum during this period a total of three double-filtration plasmapheresis sessions were performed. Cyclophosphamide, deoxysperguarine, and muromonab (OKT3) were administered, but the graft was finally removed on the 20th postoperative day because the patient had a high, continuous fever, and an infected graft was strongly suspected. The pathological findings of the lost graft showed a severe humoral rejection, with large deposits of IgG and IgM (data not shown). The flow-cytometric analysis showed a small peak appearing on the slope of the main peak on the 4th postoperative day that became independent of the main peak on day 5. At this time the titer increased to 1:4096, and the patient became anuric. The cells in the separated peak stained positive for CD19 and CD56, while the cells in the main peak stained positive for CD4 (Fig. 1). The two peaks remained separate until the administration of OKT3. After the OKT3 treatment the two peaks combined into one peak on the 18th postoperative day. The number of cells returned to normal on the 20th postoperative day.

Splenectomy was viewed by Alexandre et al. [1, 2] as an essential

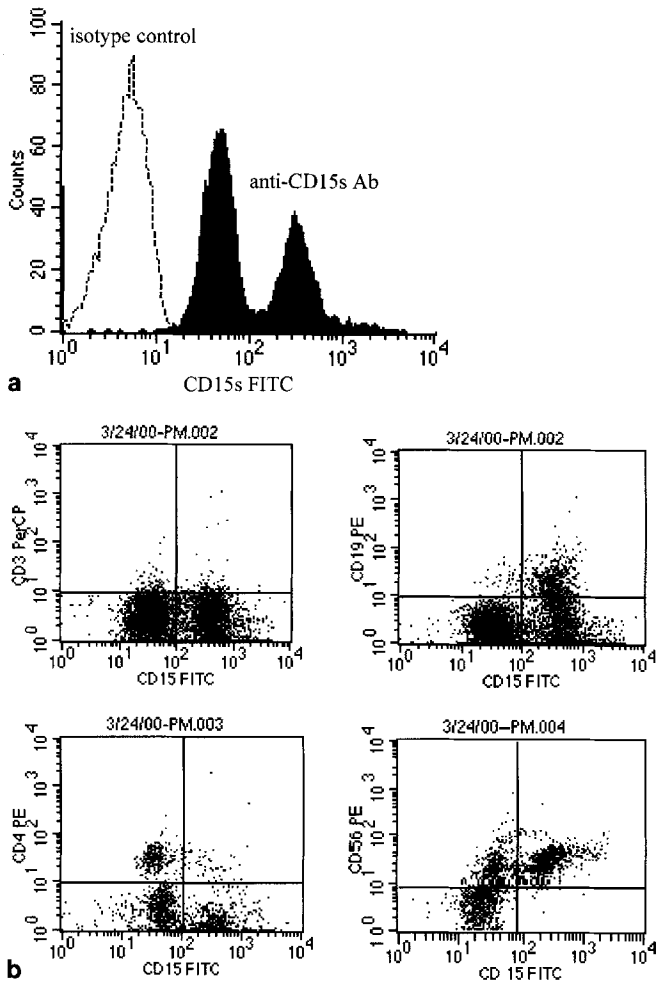

Fig. 1 **a** The flow-cytometric analysis showed a small peak appearing on the slope of the main peak on the 4th postoperative day that became independent of the main peak on day 5. **b** The cells in the separated peak stained positive for CD19 and CD56, while the cells in the main peak stained positive for CD4

procedure for successful allotransplantations across the AB0 blood group barriers. In the Alexandre et al. series none of the grafts in patients who had undergone splenectomy experienced rapid rejection. Carobbi et al. [4] reached a similar conclusion on the value of splenectomy in a cardiac xenograft model. On the other hand, some researchers have recently reported that a splenectomy is not always necessary in A20-incompatible renal transplantations [3]. In addition, we retrospectively investigated the rate of anti-AB0 titer elevation in 101 AB0-incompatible renal transplantations with splenectomy [6]. The rate of titer elevation was approximately 23%, which is similar to that of other reports on transplantations without a splenectomy [3]. On the basis of these findings the performance of splenectomies in conjunction with incompatible renal transplants seems reasonable. However, the possibility that splenectomies could be made less essential by new immunosuppressive regimens should be considered because of the infectious complications associated with splenectomies. Whether the risk of infection and malignancy is increased by a splenectomy remains unclear.

In this study an AB0 incompatible renal transplantation without

splenectomy was performed at our institution for the first time. We confirmed that in the ABO incompatible renal transplant without a splenectomy B cells were strongly activated to produce IgG and IgM antibodies, although none of the T cells were activated. The patients who routinely received a splenectomy did not exhibit any activated B cells in their flow-cytometry analysis (data not shown). These findings suggest that the spleen plays a role in producing or activating B cells in a T cell-independent manner. The activated B cells were not inhibited by the administration of OKT3 or any other treatment. We also found that the preoperative titer value is not a useful predictor for the outcome of ABO incompatible transplants, although a low anti-B titer was one of the factors that encouraged us to perform transplantation without splenectomy. The small preoperative level of anti-B antibody rapidly increased and produced a strong humoral rejection, similar to that frequently seen in xenotransplantations. CD15s proved to be an excellent antigen for identifying activated peripheral lymphocytes.

CD15s monitoring could be an easy, noninvasive, and useful clinical application. However, further research on a larger scale is needed. The discrepancy between our unfortunate experience in this study and that of the excellent outcomes reported elsewhere is remarkable [3]. In our previous report [6] no difference in the graft survival time was observed for different incompatibilities of blood types between donors and recipients. However, a more detailed analysis of blood type incompatibilities may be required in connection with the production of antibodies by the spleen. In conclusion, the spleen appears to play a critical role in the production of anti-ABO antibodies.

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