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LETTER TO THE EDITOR

Fatal impact of lymphocyte cross-matching upon humoral rejection after adult living related liver transplantation

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Although positive lymphocyte cross-match combinations of donor and recipient are rare, humoral rejection (HR) is still a serious problem after organ transplantation. The importance of lymphocyte cross-matching and human leukocyte antigen (HLA) histocompatibility have been reported for kidney and combined kidney-liver transplantation [1,2]. The role of anti-donor HLA antibodies in graft loss is also well-known [3]. However, it is generally believed that positive cross-match should not be considered a contraindication for liver transplantation (LT) [4]. We report a thought-provoking case of living donor liver transplantation (LDLT) with positive cross-match combination.

A 46-year-old female suffered from well-developed cirrhosis caused by hepatitis C virus. Because of her deteriorating condition, she was referred to our division for LDLT. On admission, she was found to have a low-grade fever; also, cell counts in ascites and pleural effusion were increased. Spontaneous bacterial peritonitis and pleuritis were managed by drainage and cefotaxime. Infections were well-controlled preoperatively.

Lymphocyte cross-match tests were performed using direct complement-dependent cytotoxicity and anti-human globulin assays [5,6]. Pretransplant results were positive. Recipient showed strong reactions against donor HLA Class I antigens, and the same immunoreactivity was confirmed by flow cytometry (FCM) (Fig. 1). We performed additional tests to assess antigen-specific immunoreactivity. Recipient's lymphocytes showed strong immunoreactivity against Class I loci including B 55. HLA typing revealed that donor had this HLA B locus. ABO blood group was compatible. As we were unable to find a more suitable donor, we performed LDLT accompanied by splenectomy. Graft recipient weight ratio was 0.91. We used tacrolimus, methylprednisolone and mycophenolate mofetil as immunosuppressants.

The postoperative course was uneventful until POD 3 when recipient experienced a sudden elevation of lactate dehydrogenase levels, a decrease in platelet count and severe fragmentation of red blood cells. Total bilirubin levels were increased after POD 3 leading to prolonged jaundice. On POD 4, X-ray showed acute respiratory distress syndrome-like condition. A diagnosis of HR was made, and other reasons were ruled out. Plasma exchange (PE) was performed daily after POD 4 and she received steroid pulse therapy from POD 5. Although immunoreactivity against Class I antigen was down-regulated during early postoperative period, it increased again from POD 6 (Fig. 1). On POD 8, peripheral blood examination showed evidence of hemolysis. Percutaneous micro-ecchymosis was noted and coagulation profiles were consistent with disseminated intravascular coagulation. Patient's condition worsened and she did not respond to further treatment, including daily PE. Histopathologic examination by liver needle biopsy clearly showed severe graft damage. The patient died on POD 9 despite intensive treatment.

Discussion

There is an obvious limitation of suitable donors in LDLT, and donor compatibility is still a serious problem. Because of the shortage of ideal candidates and the difficulties in treating HR successfully, perioperative strategies for cross-match positive LDLT are sorely needed.

There have been many contradictory reports regarding importance of cross-matching and HLA compatibility in LT [4,7–9]. Some studies have reported importance of appropriate cross-matching while others have concluded that positive cross-match has no bearing on LT outcome [4,7–9]. Therefore, significance of positive cross-match still remains a matter of debate within the LT field. Some investigators have suggested that HLA histocompatibility for Class I is crucial for graft survival after LT while others have speculated that there may be a dualistic effect of HLA histocompatibility in liver allografts. They suggest that although HLA histocompatibility reduced the incidence of rejection, it may also enhance other immunologic mechanisms which can lead to allograft dysfunction [4,7–9]. Thus, there is still no consensus on importance of cross-matching and HLA compatibility in the LT field.

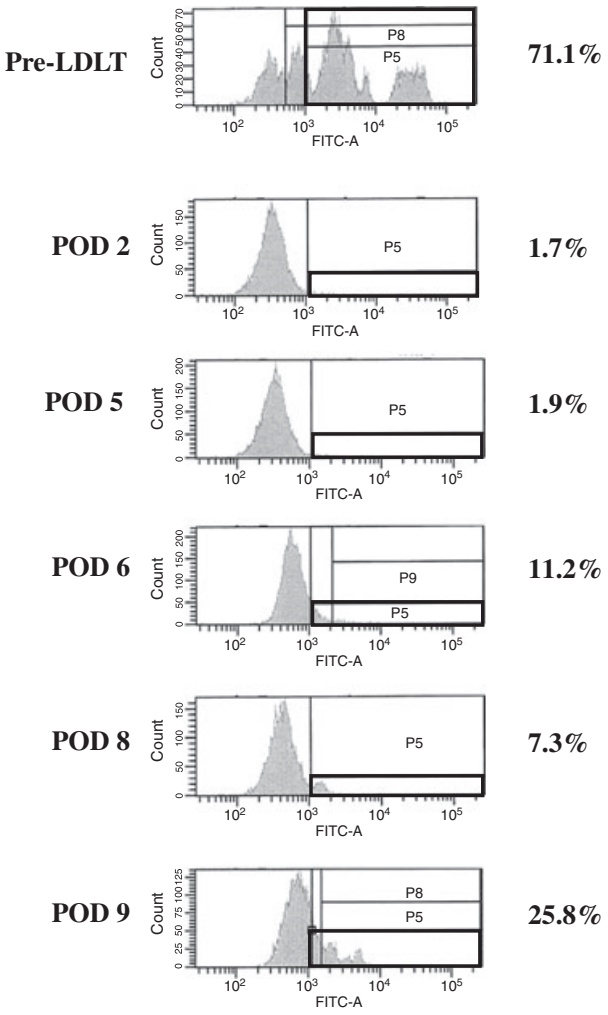

Figure 1 Temporal changes in the immunoreactivity to HLA Class I antigen as assessed by FCM. Recipient's pretransplant immunoreactivity against donor antigens as assessed by FCM, and recipient's lymphocytes clearly show reactivity against donor HLA Class I antigens. Immunoreactivity against Class I antigens is down-regulated immediately after LDLT. However, this increases again. The gated area represents immunoreactivity against Class I antigens, compared with the reactivity against the same antigen in a third party (other recipients). The percentages were calculated as the counts in gated area/the whole counts. Note that this immunoreactivity was down-regulated on POD 5 even though graft dysfunction began on POD 3 and that this immunoreactivity remained from POD 6 even after repeated PE. We diagnosed HR mediated by an antigen-specific immune response to the donor tissue based on the clinical, immunologic and histopathologic findings.

Previous reports have shown that cross-match can change from positive to negative after organ transplantation [1,2]. Perioperative monitoring by FCM is a method suitable for clinical use because it can be performed repetitively, noninvasively and in real-time. Based on our FCM results, it appears that lymphocytes reactive against Class I antigens can be controlled during early postoperative period but proliferate again after this initial period of down-regulation. It is worth noting that immunoreactivity against Class I antigens was down-regulated on POD 5 even though graft dysfunction was evident from POD 3, and that this immunoreactivity remained from POD 6 even after repeated PE. A possible explanation for the phenomenon seen on POD 5 is the immunoadsorption of anti-graft antibodies by PE [10]. This case suggests that PE can have positive effects on anti-graft immunoresponse in the initial period, but repeated PE has limited use as HR treatment. Some investigators have suggested that more aggressive immunosuppression is probably needed in immunologically high-risk recipients [11]. Basically, HLA antigens express more widely rather than ABO antigen [9], we therefore suggest that stronger immunosuppression is required in cross-match positive LDLT rather than in ABO incompatible cases [12]. In our case, trough level of tacrolimus was slightly low (8–10 ng/ml) because of consideration of the preoperative history. This case suggests that strong immunosuppression may be needed in positive cross-match cases in order to maintain negative cross-match after LDLT.

Many transplant centers skip HLA typing and crossmach tests before LT for reducing cost, because these influences are debatable. We routinely performed these examinations in 1399 LDLTs, and identical/compatible ABO but positive cross-match LDLT recipients showed poor prognosis in our institution [6]. We suggest that positive cross-match combination has fatal impacts on LDLT.

Plasma exchange (PE) and high-dose immunoglobulins are considered to be standard therapies for HR [13,14], and splenectomy is considered as a suitable intraoperative strategy to prevent HR [15]. In our case, splenectomy and intensive postoperative treatment were not successful. Therefore, we hypothesize that preoperative induction therapy to prevent HR is crucial in positive cross-match LDLT. Usefulness of anti-CD20 antibody (rituximab) is well reported in this respect. Rituximab is key in order to prevent HR after organ transplantation [12,13]. The use of a living donor may leave more time for immunologic testing and the induction of suitable preconditions for LT than the cadaver donor LT cases. Rituximab treatment alongside PE prior to LDLT is now under consideration in our institution, as preoperative conditioning for positive cross-match recipients.

We conclude that positive cross-match combinations without advanced immunologic strategies are contraindicated in LT.

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