Transpl Int (1998) 11 [Suppl 1]: S383–S384

T. Kiuchi
H. Harada
H. Matsukawa
M. Kasahara
Y. Inomata
S. Uemoto
K. Asonuma
H. Egawa
E. Maruya
H. Saji
K. Tanaka

One-way donor-recipient HLA-matching as a risk factor for graft-versus-host disease in living-related liver transplantation

T. Kiuchi (✉) · H. Harada · H. Matsukawa · M. Kasahara · Y. Inomata · S. Uemoto · K. Asonuma · H. Egawa · K. Tanaka
Department of Transplant Surgery, Kyoto University Faculty of Medicine, 54 Kawara-cho, Shogoin, Sakyo-ku, Kyoto 606-01, Japan

E. Maruya · H. Saji
Research Laboratory, Kyoto Red Cross Blood Center, Japan

Abstract Although one-way matching between an HLA-homozygous donor and a haploidentical recipient is a recognized risk factor in transfusion-associated graft-versus-host disease (GVHD), its impact in living-related liver transplantation (LRLT) has so far not been investigated. We present a case of fatal acute GVHD in our LRLT program that was attributed to one-way HLA matching between donor and recipient. Although the disappearance of donor cells in peripheral blood was suggested by genetic analysis, severe septicemia led to a fatal outcome. We further reviewed 280 LRLT cases and correlated one-way HLA matching with outcome. A total of 8 out of 280 donors (2.9%) and 11 out of 278 recipients (4.0%) were completely HLA homozygous in our LRLT program. Complete one-way HLA matching linked to GVHD was observed in four cases, including the present case. Although other contributing factors also need to be clarified, one-way HLA matching is a definite risk factor for GVHD in LRLT. We advocate caution before proceeding with one-way HLA donor-recipient combinations.

Key words One-way matching · Human leukocyte antigen · Graft-versus-host disease · Living donor · Liver transplantation

Introduction

Graft-versus-host disease (GVHD) is a rare complication in solid organ transplantation, despite the presence of significant numbers of passenger lymphocytes in the graft. On the other hand, one-way matching between an HLA-homozygous donor and a haploidentical recipient is a recognized risk factor for GVHD after transfusion of non-irradiated fresh whole blood [7]. The risk of one-way HLA matching is expected to increase in living-related donor transplantation, especially in living-related liver transplantation (LRLT).

Patients and methods

We present here a case of fatal acute GVHD that was clearly attributable to one-way HLA matching between donor and recipient. We have further reviewed 280 cases of LRLT performed in Kyoto, Japan, where preoperative serological HLA typing was available, and have correlated one-way HLA matching with outcome.

Results

An 8-month-old female infant with end-stage cirrhosis secondary to biliary atresia underwent an ABO-identical LRLT with a lateral-segment graft from her mother. The initial posttransplant course was excellent, but was complicated by pyrexia with endotoxemia by 2 weeks. A maculopapular skin rash was evident on day 2, and progressed until day 27, when a skin biopsy revealed GVHD. At this stage, the patient also developed a massive pleural effusion, respiratory distress, and severe watery diarrhea, associated with marked pancytopenia with total agranulocytosis (grade 4 GVHD of Glucksberg et al. [2]).

The recipient HLA was A2, 24; B52, 61; C10,–; DRB1*0802, 1502; DQB1*0302, 0601, and that of the mother was A24,–; B52,–; C–,–; DRB1*1502,–; DQB1*0601,–. Genetic analysis revealed complete chimerism of donor origin (30–50% by anti-HLA serum assay and microsatellite assay), which was homozygous for all loci. Although chimerism reduced over the next 7

days, as shown by the disappearance of donor cells in peripheral blood, with some recovery of granulocytes, severe septicemia led to multi-organ failure and a fatal outcome on day 43. Autopsy revealed a $CD8^+$ lymphocyte infiltration in the dermis and basal layer of the skin and in the submucosa of the intestine, as well as hypoplasia of the bone marrow with focal increase of myeloblasts. Bacterial pneumonia with hemorrhagic congestion and disseminated intravascular coagulation were evident as well as plasmacytosis in the spleen and lymph nodes. The liver revealed no inflammatory cellular infiltrate.

Serological analysis of 280 donor-recipient pairs in the LRLT program in Kyoto showed 23/280 donors (8.3%) and 30/278 recipients (10.8%) were homozygous in two or more loci of HLA-A, -B, and -DR (2.9% and 4.0% in three loci, respectively), thus 4.0% in three loci. One-way HLA matching in two or more loci prone to GVHD was 3.9% (1.4% in three loci), and one of four cases with complete one-way HLA matching died from GVHD (the present case). Two of the other three cases were adult recipients who received auxiliary grafts, and the remaining case, an 8-year-old recipient, received an ABO incompatible graft.

In contrast, one-way HLA matching due to homozygosity in two or three loci of the recipient is speculated to contribute to the host-versus-graft (HVG) reaction (rejection), which was observed in 8.2% (2.1% in three loci). Actually, one of 17 cases (5.9%) with one-way HLA matching in two loci linked to HVG and one of 6 cases (17%) with complete one-way HLA matching linked to HVG lost their graft from vanishing bile duct syndrome. The incidence of vanishing bile duct syndrome in our series is currently 1.3% (4/312).

It has been calculated that four kinds of combination of HLA-A, -B, and -DR accounts for up to 20% of the frequency in the Japanese population [1], and five more kinds in a further 10%. Actually, three of the four donors, including the present case, in complete one-way HLA matching linked to GVHD had that haplotype which is the most frequent (8.63%) in the Japanese population.

Discussion

So far at least 20 cases of clinically evident GVHD have been reported after liver transplantation [4]. However, the prognosis is generally poor. GVHD due to one-way HLA matching of donor and recipient has been established in only one case in North America [9]. Others have described clinically significant, but reversible, GVHD in approximately 5% of liver transplants which forms the background of the two-way paradigm between graft and recipient [5]. The current case of acute GVHD is classic, with skin, gastrointestinal, and bone marrow involvement, associated with complete one-way HLA matching. Although genetic analysis showed recovery of recipient native lymphocytes as well as granulocytes, overwhelming sepsis led to the demise of the patient.

The incidence of 9.5% (53/558) HLA homozygosity in two or more loci is a significant figure, though DNA-based typing may reduce it. Actually 5.3% of LRLT pairs had one-way HLA matching linked to GVHD, and 8.2% of pairs had that linked to HVG. Although other contributing factors for GVHD in the present case cannot be ruled out, the infant's immature immune system and the reduction of immunosuppression by the preceding sepsis may have also played a role. The fact that three other cases with one-way HLA matching did not develop overt GVHD may be explained by their adult age, coexistence of the native liver, and ABO incompatibility.

The present case clearly demonstrates that one-way HLA matching in LRLT is a definite risk factor for GVHD, and emphasizes the importance of pretransplant HLA typing. Although the Japanese population is more homogeneous in HLA than in Western populations, the estimated risk of one-way HLA matching is only two to three times higher in Japan [3, 6, 8]. From this experience, we would advocate caution before proceeding with one-way HLA donor-recipient combinations.

Acknowledgements This work was supported in part by the Scientific Research Fund of the Ministry of Education, Japan.

References

1. Akaza T, et al (1994) MHC & IRS (suppl) 1: 219
2. Glucksberg H, Storb R, Fefer A, et al (1974) Clinical manifestations of graft-versus-host disease in human recipients of marrow from HLA-matched sibling donors. Transplantation 18: 295–304
3. Grishaber JE, Birney SM, Strauss RG (1993) Potential for transfusion-associated graft-versus-host disease due to apheresis platelets matched for HLA class-I antigens. Transfusion 33: 910–914
4. Pirenne J, et al (1996) Transplantat Rev 10: 46
5. Starzl TE, Demetris AJ, Trucco M, et al (1993) Cell migration and chimerism after whole-organ transplantation: the basis of graft acceptance. Hepatology 17: 1127–1152
6. Takahashi K, Juji T, Miyazaki H (1991) Posttransfusion graft-versus-host disease occurring in nonimmunosuppressed patients in Japan. Transfus Sci 12: 281–289
7. Thaler M, Shamiss A, Orgad S, et al (1989) The role of blood from HLA-homozygous donors in fatal transfusion-associated graft-versus-host disease after open-heart surgery. N Engl J Med 321: 25–28
8. Wagner FF, Flegel WA (1995) Transfusion-associated graft-versus-host disease: risk due to homozygous HLA haplotypes. Transfusion 35: 284–291