Review Article
Ann Liver Transplant 2022;2(2):107-111
https://doi.org/10.52604/alt.22.0021

ALT
Annals of Liver Transplantation

pISSN 2765-5121
eISSN 2765-6098

Graft-versus-host disease after living donor liver transplantation: A collective review of Korean cases

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Received October 27, 2022
Revised November 7, 2022
Accepted November 8, 2022
Published online November 17, 2022

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Graft-versus-host disease (GVHD) occurs when donor lymphocytes recognize recipient cell surface antigens as foreign and react against them. Although GVHD is rare, it is a life-threatening complication. Following liver transplantation (LT), the incidence of GVHD is estimated to be 0.1% to 2%. However, more than 50% of affected patients have died. Living donor LT (LDLT) has a special risk of GVHD because implicating human leukocyte antigen (HLA) matching status between recipients and close-relative living donors. Therefore, we reviewed Korean GVHD cases following LDLT to identify LDLT-oriented characteristics of GVHD. This study included one case from each of three centers and three cases from one high-volume center. One-way donor-recipient HLA match was identified by HLA typing for donor and recipient. Of these six cases of LDLT diagnosed with GVHD, all patients died due to GVHD and its associated complications. In conclusion, post-LT GVHD is a fatal complication despite aggressive treatment approaches. Preventive measures, early diagnosis, early initiation of treatment protocols, prophylactic treatment, and appropriate palliative care are necessary to achieve success against GVHD. Further studies should be performed to reveal the mechanisms of GVHD and improve outcomes of patients who develop GVHD following LT.

Keywords: Graft-versus-host disease; Liver transplantation; Diarrhea; Skin rash; Human leukocyte antigen

INTRODUCTION

Graft-versus-host disease (GVHD) occurs when donor lymphocytes recognize recipient cell surface antigens as foreign and react against them. Although GVHD is rare, it is a life-threatening complication of bone marrow or solid organ transplantation such as liver transplantation (LT) [1–10]. Following LT, the incidence of GVHD is estimated to be 0.1% to 2%. However, more than 50% of affected patients have died [1,2]. Risk factors for post-LT GVHD include human leukocyte antigen (HLA) matching status, recipient age, donor age, age difference between donor and recipient, retransplantation, irradiated blood products transfusion, rejection before GVHD, and autoimmune hepatitis [2]. Because skin, gastrointestinal tract, and bone marrow are frequently involved, clinical manifestation of patients with GVHD includes rash, fever, diarrhea, and pancytopenia [2]. The diagnosis of GVHD is difficult because clinical presen-

tations of GVHD overlap with those of drug reactions and viral infection. Living donor LT (LDLT) has a special risk regarding GVHD because of unique HLA matching status between recipients and close-relative living donors. Therefore, we aimed to review Korean GVHD cases following LDLT to identify LDLT-oriented characteristics of GVHD.

KOREA-FIRST CASE REPORT OF GRAFT-VERSUS-HOST DISEASE FOLLOWING LIVING DONOR LIVER TRANSPLANTATION FROM SEOUL NATIONAL UNIVERSITY HOSPITAL

A 51-year-old male underwent LDLT for hepatitis B virus (HBV)-related liver cirrhosis and hepatocellular carcinoma. The donor was his 21-year-old son. The patient was discharged uneventfully. However, 56 days after LT, he was readmitted due to watery diarrhea, which was subsequently accompanied by a skin rash and leukopenia. Diagnosis was made by skin biopsy and by donor DNA chimerism testing in recipient tissue. A one-way donor-recipient HLA match was identified by HLA typing for both donor and recipient. The patient was treated by increasing immunosuppression. However, he died of septic shock. A pretransplant HLA typing of both donor and recipient should be taken. In cases of one-way donor-recipient HLA matching, LT should be avoided [11].

SINGLE-CENTER EXPERIENCE OF GRAFT-VERSUS-HOST DISEASE FOLLOWING LIVER TRANSPLANTATION FROM ASAN MEDICAL CENTER

Authors presented six cases of GVHD after LT. Among 4,294 LT recipients, authors identified 6 patients (0.14%) who were diagnosed with GVHD. Liver graft types included deceased donor whole liver graft (n=3) and right liver graft from son (n=3). Mean recipient and donor ages were 57.2±6.6 years and 32.7±10.8 years, respectively. Onset of GVHD symptoms occurred at 14 to 32 days after LT. Initial symptoms were skin rash (n=5) and fever (n=1). GVHD was pathologically confirmed by skin or rectal biopsy. Chimerism of donor lymphocytes was identified in all three patients who underwent a short tandem repeat (STR) polymerase chain reaction (PCR) assay. Attempts were made to treat the GVHD in all six patients by corticosteroids with or without low-dose calcineurin inhibitor. However, these agents were stop early or reduced due to aggravation of pancytopenia and septic complications. Ultimately, five patients died 6 to 106 days after the onset of GVHD. Only one patient recovered. All three LDLT recipients died. This surviving patient was diagnosed earlier and administered the recommended dosage of corticosteroid for a longer period with aggressive infection prophylaxis compared to other cases. Because of very poor outcomes of GVHD after LT, early diagnosis and vigorous treatment should be emphasized, although no effective treatment modality has been established yet. Authors strongly suggest performing aggressive infection prophylaxis during GVHD treatment [3].

CASE REPORT OF GRAFT-VERSUS-HOST DISEASE FOLLOWING LIVING DONOR LIVER TRANSPLANTATION FROM KOREA UNIVERSITY MEDICAL CENTER

Author experienced a fatal case of acute GVHD following adult-to-adult LDLT from a donor who was heterozygous at a single HLA locus. A 53-year-old female underwent LDLT for chronic hepatitis B and recurrent hepatocellular carcinoma. The donor was her 23-year-old son. The HLA phenotype of the donor was not homozygous (A24, -; B54, -; DR4, 9). It had a one-way donor-dominant HLA matching at two loci with the recipient (A2, 24; B48, 54; DR4, 12). On the 40th postoperative day (POD), the patient showed erythematous skin lesions. Skin biopsy revealed typical findings of GVHD. Donor-derived chimerism was demonstrated by performing fluorescent in situ hybridization using the recipient's skin tissue. As the clinical course deteriorated, etanercept was started in addition to broad-spectrum antibiotics. However, there was no improvement. As multi-organ failure progressed, the patient succumbed to death on the 54th POD, which was two weeks after onset of GVHD. Prevention of GVHD is important since results of treatment have been disappointing. Authors experienced a fatal case of acute GVHD following adult-to-adult LDLT from a HLA non-homozygous donor. HLA heterozygosity at a single locus does not preclude the possibility of developing GVHD following adult LDLT [12].

CASE REPORT OF GRAFT-VERSUS-HOST DISEASE AFTER ABO-INCOMPATIBLE LIVING DONOR LIVER TRANSPLANTATION FROM PUSAN NATIONAL UNIVERSITY YANGSAN HOSPITAL

The authors presented a unique case of GVHD fol-

https://doi.org/10.52604/alt.22.0021

lowing ABO-incompatible LDLT, for which cessation of immunosuppression could be responsible. A 50-year-old man (blood group O) with HBV infection–related cirrhosis underwent LDLT from his ABO-incompatible 20-year-old son (blood group B). HLA typing revealed donor-dominant one-way HLA type matching at two different loci. Preoperatively, rituximab and plasmapheresis were administered to deplete B-lymphocytes and isoagglutinin titers. Initial immunosuppressants consisted of tacrolimus, methylprednisolone, and mycophenolate. On POD 19, fever occurred and bacteremia was consequently identified, thus initial immunosuppressants were discontinued. On POD 26, skin rash developed presumably due to drug eruption for which methylprednisolone was administered again. On POD 39, diarrhea and vesicular skin rashes were identified. Stomach endoscopic biopsy revealed chronic gastritis with erosion, loss of most of gastric glands, and apoptosis of the epithelium, all of which were consistent with GVHD. Skin biopsy also showed histopathologic features of GVHD. At the same time, using 16 highly polymorphic STR markers, the presence of blood chimerism between the donor and recipient was investigated. Approximately, 62.4% of peripheral leukocytes in the recipient were leukocytes of donor origin, corroborating the diagnosis of GVHD. Upon identification of diarrhea and GVHD, tacrolimus was given to the patient for GVHD treatment. On POD 52, although diarrhea was ameliorated and skin rash did not become worse, there was no improvement in pancytopenia due to systemic infection. On POD 90, the patient's condition deteriorated progressively with septicemia, pancytopenia, and subsequently multi-organ failure, which resulted in death [13].

DISCUSSION

Since the first description of acute GVHD after LT in 1988 by Burdick and colleagues, more than 100 cases have been reported in the literature [2,14]. Its incidence was 0.14% in a Korean single-center series, which was comparable to the 0.1% reported by United Network for Organ Sharing (UNOS) data [3]. The mortality rate of acute GVHD following LT has been reported to be more than 75% [15]. In the present review for six cases of LDLT, all patients died due to GVHD and its associated complications.

There are two types of GVHD: The humoral type and the cellular type. The humoral type is characterized by hemolysis and fever. It occurs in patients transplanted with ABO blood group-incompatible or non-identical grafts. Humoral GVHD usually causes only a mild and self-limiting hemolytic anemia of little clinical importance [16]. The cellular type is directed against major histocompatibility complex. It often results in severe multisystem disease with a high mortality. After LT, 109 to 1,010 donor lymphocytes remain in portal tracts and the parenchyma of the donor liver graft after flushing the organ with cold preservative solution [17]. These donor lymphocytes become activated upon interaction with host antigen-presenting cells, triggering interleukin-2-dependent proliferation with predominantly T helper type 1 differentiation, which overwhelms the host's compromised immune system. Cytotoxic donor T lymphocytes target antigens expressed by host tissues, leading to cell death and tissue dysfunction. This sequence results in a vicious circle of stimulatory feedback, whereby destruction of the host's skin, bone marrow, and mucosal epithelium leads to additional immunocompromise. Cytokines released by targeted host cells further activate donor lymphocytes [6].

Clinical manifestations of GVHD after LT include fever, rash, diarrhea, and hematocytopenia [3]. The basic function of the transplanted liver graft is not affected. Initially, skin rash has maculopapular patterns on palms and soles. It may progress to bullae formation and whole-body desquamation. Diarrhea occurs secondary to the loss of absorptive function caused by destruction of the intestinal mucosa. However, these early symptoms are not specific. They are often misdiagnosed as infection, drug allergies, or rejection. Thus, clinical diagnosis of GVHD is difficult. Auxiliary diagnostic modalities such as histologic confirmation of skin rash or gastrointestinal tract, demonstration of chimerism by examining the presence of donor cells in the recipient's peripheral blood or various tissues, and detection of donor HLA types in peripheral blood, mucous membrane, or skin can help with the diagnosis. For this purpose, STR-PCR method is widely used [18].

A Japanese study has reported that donor-dominant one-way HLA matching at three loci of HLA-A, -B, and -DR represents an extremely high risk for GVHD, with mortality up to 50% [19]. Three of four GVHD cases included in a group comprised cases with donor-dominant one-way HLA matching at three loci of HLA-A, -B, and –DR [20,21]. Investigation of HLA matching status at HLA-C, -DQ, and -DP in these three cases with GVHD strongly suggested that they all had donor-dominant one-way HLA matching, indicating that they shared common HLA haplotypes. Donor-dominant one-way HLA matching at all HLA loci, where all donor HLA loci are homozygous, is an absolute risk for GVHD. There are three case reports describing the development of

GVHD with donor-dominant one-way HLA matching at only two loci of HLA-A, -B, and -DR, although analysis was only at the antigen level in two of these reports [12,22,23]. Some cases of transfusion-associated GVHD have also been reported [24]. These results suggest that LT between pairs with donor-dominant one-way HLA matching at three loci of HLA-A, -B, and -DR should be excluded to prevent GVHD. The impact of HLA-C, -DQ, and -DP on GVHD was not as strong as that of HLA-A, -B, and -DR. HLA genotypes should be determined at the allele level before LT [19].

Despite application of the most aggressive treatment protocols, mortality rates ranged from 33.3% to 100% in post-LT GVHD patients (mean: 81.7%, median: 83.3%) [22]. It is generally agreed that early diagnosis of GVHD and treatment options are not effective. Therefore, the most important step is to minimize or reduce T lymphocyte count to zero in the transplanted liver graft [23]. Although liver grafts are washed routinely, approximately some lymphocytes remained in the portal system or parenchyma of the graft and passed to the circulation of the recipient following graft implantation [17,23]. Therefore, perfusion should be performed carefully during the back table step. Complete removal of lymph nodes and channels located around the transplanted liver graft hilum might be used to reduce the number of lymphocytes that could pass to the recipient [23]. One of the most practical solutions is to evaluate HLA match between the donor and the recipient before LT. Planning a postoperative immunosuppressive regimen according to HLA match is also important.

In conclusion, post-LT GVHD is a fatal complication despite aggressive treatment approaches. Preventive measures, early diagnosis, early initiation of treatment protocols, prophylactic treatment, and appropriate palliative care are necessary to achieve success against GVHD disease. Further studies should be performed to reveal the mechanisms of GVHD and improve outcomes of patients who develop GVHD following LT.

FUNDING

There was no funding related to this study.

CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

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AUTHORS' CONTRIBUTIONS

Conceptualization: All. Data curation: All. Formal analysis: All. Supervision: JIP. Writing – original draft: All. Writing - review & editing: All.

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