Transplant International

Transplant International ISSN 0934-0874

CASE REPORT

Successful living donor liver transplantation for severe hepatic GVHD histologically resembling autoimmune hepatitis after bone marrow transplantation from the same sibling donor

Minako Mori,[1,5] Sumie Tabata,[1] Hisako Hashimoto,[5] Daichi Inoue,[1] Takaharu Kimura,[1] Sonoko Shimoji,[1] Yuya Nagai,[1] Katsuhiro Togami,[1] Kiminari Itoh,[5] Akiko Matsushita,[1] Kenichi Nagai,[1,5] Eiji Ikeda,[2] Naoya Kimoto,[2] Kenji Uryuhara,[3] Satoru Kaihara,[3] Yukihiro Imai,[4] Masafumi Itoh[6] and Takayuki Takahashi[1]

1 Department of Hematology and Clinical Immunology, Kobe City Medical Center General Hospital, Kobe, Japan
2 Department of Gastroenterology, Kobe City Medical Center General Hospital, Kobe, Japan
3 Department of Transplantation, Kobe City Medical Center General Hospital, Kobe, Japan
4 Department of Clinical Pathology, Kobe City Medical Center General Hospital, Kobe, Japan
5 Foundation for Biomedical Research and Innovation, Kobe, Japan
6 Division of Diagnostic Pathology, Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan

Keywords
autoimmune hepatitis, bone marrow transplantation, hepatic graft-versus-host-disease, living donor liver transplantation.

Correspondence
Takayuki Takahashi, Department of Hematology and Clinical Immunology, Kobe City Medical Center General Hospital, 4-6 Minatojima-Nakamachi, Chuo-ku, Kobe 650-0046, Japan. Tel.: 81-78-302-4321; fax: 81-78-302-7537; e-mail: sonata53@kcgh.gr.jp

Received: 5 August 2009
Revision requested: 22 August 2009
Accepted: 17 November 2009
Published online: 17 December 2009

doi:10.1111/j.1432-2277.2009.01028.x

Summary

A 30-year-old woman developed severe liver dysfunction 1 year after bone marrow transplantation (BMT) from an HLA-identical sibling donor for B lymphoblastic leukemia (B-ALL) during the tapering of cyclosporin A. The histologic picture resembled autoimmune hepatitis (AIH), although neither autoantibody nor hypergammaglobulinemia was detected. She entered hepatic coma, and underwent living donor liver transplantation from the same donor on day 421 after BMT. She is well 18 months after the procedure, showing normal liver function and hematopoiesis. AIH-like hepatic graft-versus-host disease (GVHD) has not been documented. This patient is the second case of living donor liver transplantation for hepatic GVHD from the same donor.

Introduction

Graft-versus-host disease (GVHD) is the most common complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT), which often affects the liver. Typical hepatic GVHD is characterized by jaundice and cholestatic liver biochemistry. The portal infiltration of cytotoxic T lymphocytes or NK cells and bile duct damage are characteristic histologic features of hepatic GVHD. Hepatic GVHD occasionally presents with acute liver damage exhibiting the marked elevation of blood aminotransferases without significant elevation of biliary tract enzymes. This type of hepatic GVHD histologically shows lobular hepatitis and mild bile duct injury. Such atypical form of hepatic GVHD has been described as hepatitic variant of GVHD [1]. We encountered a patient who developed severe liver dysfunction with marked elevation of serum aminotransferase levels 1 year after allo-HSCT from an HLA-matched sibling donor for B lymphoblastic leukemia (B-ALL). Histologic picture of a biopsy speci-

men of the liver showed portal and periportal inflammatory infiltrations with plasma cell predominance, while bile ducts were relatively preserved. We suppose this hepatitis was an hepatitic variant of GVHD AIH-like manifestation of hepatitic variant of GVHD.

There have been 10 patients in whom life-threatening hepatic GVHD after allo-HSCT was relieved after living donor (two patients) and orthotopic (eight patients) liver transplantation, reported in the literature [2–5]. In every case, the recurrence of hepatic GVHD has not been documented. We herein report successful living donor liver transplantation for hepatic insufficiency after allo-HSCT with the same sibling donor for both transplantations. In addition, only three patients have been reported in the literature, who underwent liver transplantation after allo-HSCT from the same donor [2,6,7], and the present patient is the second case of liver transplantation from the same living donor for severe hepatic GVHD [2]. Nevertheless, in these 10 liver-transplanted patients, hepatitic variant of GVHD as the cause of hepatic insufficiency, as seen in the present patient, has not been documented.

Case report

A 30-year-old woman with B-ALL was admitted in July 2006. She received induction chemotherapy consisting of daunorubicin, cyclophosphamide, vincristine, and L-asparaginase, and, subsequently, a complete remission was achieved. After two courses of consolidation chemotherapy, she underwent allogeneic bone marrow transplantation (BMT) from her HLA-identical brother who had no history of autoimmune disorders, during the first complete remission. The conditioning regimen consisted of total body irradiation (2 Gy twice a day for three consecutive days) and melphalan (60 mg/m^2 for three consecutive days), and nucleated marrow cells of 4.52×10^8/kg were transfused. Cyclosporin A (CyA) and short-term methotrexate were employed for the prophylaxis of GVHD. After successful engraftment, acute GVHD developed affecting the skin and intestine on days 22 and 41respectively. Skin GVHD but not that of the intestine was controlled with prednisolone (0.5 mg/kg/day). After increasing the dosage of prednisolone to 1 mg/kg in combination with budesonide (9 mg/day), intestinal GVHD improved. Then, prednisolone was tapered to 10 mg/day. She was discharged on day 110 after BMT. Budesonide and prednisolone were discontinued on days 195 and 240, respectively. We then began to taper CyA on day 258; however, on day 356, when the dosage of CyA was decreased to 40 mg/day, serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevated to 812 and 1980 IU/l respectively, while serum total bilirubin (T-Bil) and alkaline phosphatase (ALP) concentrations remained within the normal range (100–325 IU/l). She exhibited no sign of intestinal or skin GVHD. Serologic tests for hepatitis A, B, and C yielded negative results. Serum analysis of viral DNA for herpes simplex, varicella zoster, cytomegalovirus, and Epstein–Barr virus also resulted in negative results. All autoimmune markers available were negative. She was admitted in January 2008 (day 378) because of jaundice in addition to high levels of transaminases.

Physically, she showed no specific findings except for jaundice. Hematologic examination showed a white cell count of 7.0×10^9/l, a hemoglobin concentration of 11.9 g/dl, and a platelet count of 190×10^9/l. Tests for serum biochemistry revealed: AST 805 IU/l, ALT 848 IU/l, T-Bil 6.2 mg/ml, and ALP 491 IU/l. Activities of prothrombin and antithrombin III were decreased to 59.4% (normally 70–100%) and 24% (normally 79–121%) respectively. Abdominal ultrasonography (US) revealed that hepatic parenchyma was homogeneous and slightly enhanced. Also, US showed neither hepatomegaly nor atrophy of the liver. A small amount of ascites was observed on CT scanning. Liver biopsy was performed on day 2 after readmission. The histologic picture including immunostaining demonstrated predominant plasma cell and partial cytotoxic T lymphocyte infiltration in portal areas, and the mild destruction of bile ducts. The portal mononuclear cells invaded the limiting plates surrounding the portal triad and infiltrated the surrounding lobules, leading to interface hepatitis and piecemeal necrosis in both periportal and centrilobular areas. Inflammation of endothelial cells was modest. This picture was rather more consistent with that of autoimmune hepatitis (AIH) than hepatic GVHD (Fig. 1a and b). Although the bolus administration of methylprednisolone (500 mg/day) was started on day 6, she entered hepatic coma on day 9. Plasma exchange and hemodialysis resolved the coma. However, CT scanning showed liver atrophy and a focal necrotic portion in the liver and massive ascites on day 21. There was no improvement of her liver on CT scanning on day 36. A bone marrow aspirate showed no evidence for the relapse of ALL, and fluorescent *in situ* hybridization (FISH) analysis of marrow cells showed complete donor chimerism on day 37. She underwent living donor liver transplantation from the same donor on day 44 because there was no improvement of her liver function and the findings based on CT imaging of the liver. The donor left lobe graft weighed 490 g and the graft-to-recipient weight ratio was 0.8. The clinical course described as above is shown in Fig. 2.

Histopathologic examination of her explanted liver showed fulminant hepatitis with massive necrosis, the infiltration of plasma cells in portal areas, and extensive proliferation of bile duct. Postoperative immunosuppres-

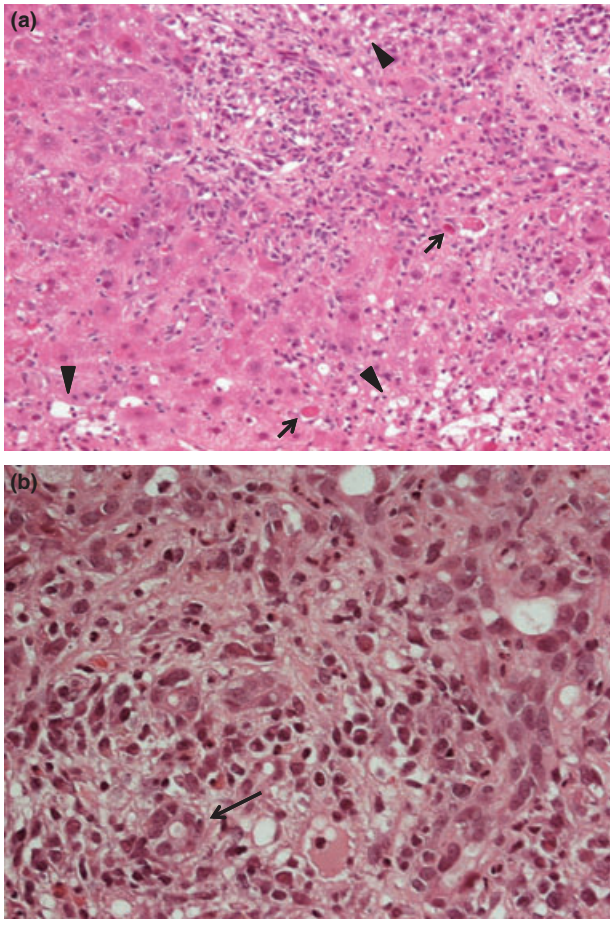

Figure 1 (a) Low power view of the liver biopsy on day 379 after allo-BMT (×100, HE staining). Interface of portal area (upper right) and surrounding parenchyma is obscured by inflammatory cell infiltration and loss of hepatocytes. Many eosinophilic apoptotic bodies (arrows) are observed. There are cell-scanty areas after hepatocellular loss (arrowheads) both in periportal and centrilobular areas. (b) High power view of the portal area. Most of cells infiltrating the portal area are plasma cells (×400, HE staining). Although interlobular bile ducts are involved in the inflammation, they are rather preserved (arrows).

sive treatment consisted of prednisolone and tacrolimus. She was discharged on postoperative day 36 with sufficient liver function. Prednisolone and tacrolimus were discontinued 4 and 17 months after the liver transplantation respectively. She is currently well (18 months after the procedure), showing normal liver function and complete donor chimerism of marrow cells.

Discussion

As for the cause of severe liver dysfunction in the present patient, drug- or virus-induced liver injury was unlikely because of absence of suspicious drug administration and negative laboratory results for viral infection. Histologically, biopsy specimen of the liver showed the features of AIH which usually exhibits inflammatory cell infiltration with plasma cell predominance in the portal area and occasionally in the lobes [8]. However, neither autoantibody nor hypergammaglobulinemia was detected, and the administration of bolus methylprednisolone could not improve the liver dysfunction. Therefore, it is unlikely that the liver dysfunction was caused by AIH.

Classical hepatic GVHD generally presents with cholestasis in association with increased serum levels of T-Bil or ALP, and is pathologically characterized by portal lymphocytic infiltration and epithelial injury of bile duct. Hepatitic variant of GVHD, unusual form of hepatic GVHD, is characterized by marked elevation of serum aminotransferase levels and histologic pictures of predominant lobular hepatitis and mild bile duct injury [1]. Hepatitic variant of GVHD sometimes occurs in the acute situation, but can also occur in chronic situation as observed in the present patient [9]. We suppose that the hepatitis in the present patient was an AIH-like manifestation of hepatitic variant of GVHD, although, hepatitic variant of GVHD with predominant plasma cell infiltration in portal areas has not been reported.

The clinical features of chronic GVHD (cGVHD) resemble those of autoimmune diseases and the epitope-specific autoimmune diseases such as thyroiditis, thrombocytopenia, and myasthenia gravis after allo-HSCT have been reported [10]. Recently, Teshima *et al.* have reported several potential mechanisms by which alloimmunity evolves into autoimmunity in animal models [11]. The mechanisms have been based on a long-standing hypothe-

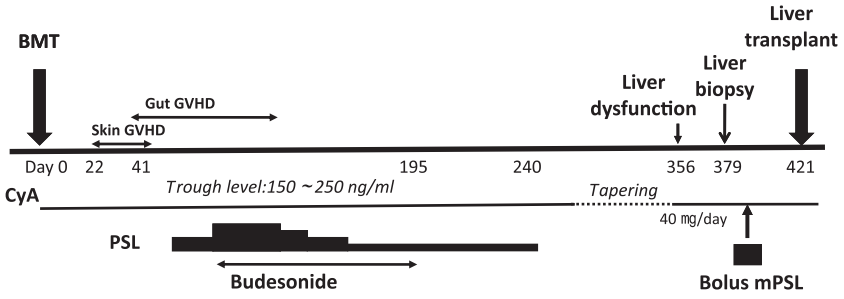

Figure 2 Clinical course of the present patient from bone marrow transplantation to living donor liver transplantation. CyA: cyclosporine A; mPSL: methylprednisolone.

sis that cGVHD results from pathogeneic effects mediated by 'autoimmune' T cells that recognize donor antigens or shared antigens of the donor and recipient rather than alloantigens of the recipient. In the present patient, alloantigens on the recipient hepatocytes might have been targeted by donor T cells, because the hepatic dysfunction as observed before the liver transplantation has not recurred after discontinuation of immunosuppressive agents. This alloreaction may have shared autoimmunity through the mechanism described as above, and shared autoimmunity might have led to the portal infiltration of plasma cells. However, it is still difficult to exactly explain the mechanisms which caused the feature of AIH-like hepatitic variant of GVHD.

In the present patient, liver transplantation was performed from same living donor and all immunosuppressive agents could be discontinued 17 months after the procedure without subsequent recurrence of the liver dysfunction. Successful discontinuation of immunosuppressive agents may be one of the advantages of donation of both marrow cells and the liver from a single donor because of low risk of allo-reaction against the liver. Discontinuation of immunosuppressive agents brings about not only immunologic recovery but also enhancement of graft-versus-leukemia effect. However, multiple organ donation should be carefully determined from the viewpoint of both donor's health and the moral issues involved.

Authorship

MM: wrote the paper and performed research. ST, HH, EI, NK, KU, SK, YI, MI: performed research. DI, TK, SS YN, KT, KI, AM, KN: analysed data. TT: designed research.

Acknowledgements

We are grateful to Dr Takanori Teshima at the Center for Cellular and Molelular Medicine, Kyushu University Hospital, Fukuoka, for helpful advices regarding hepatic GVHD. We are also grateful to Professor Tomoo Itoh at the Division of Diagnostic Pathology, Kobe University Graduate School of Medicine, Kobe, Japan, for pathological review of the biopsy preparation of the liver.

References

1. Akpek G, Boitnott JK, Lee LA, *et al.* Hepatitic variant of graft-versus-host disease after donor lymphocyte infusion. *Blood* 2002; **100**: 3903.
2. Shimizu T, Kasahara M, Tanaka K. Living-donor liver transplantation for chronic hepatic graft-versus-host disease. *N Engl J Med* 2006; **354**: 1536.
3. Yokoyama S, Kasahara M, Fukuda A, *et al.* Successful living-donor liver transplantation for chronic hepatic graft-versus-host disease after bone marrow transplantation for chronic granulomatous disease. *Transplantation* 2008; **86**: 367.
4. Barshes NR, Myers GD, Lee D, *et al.* Liver transplantation for severe hepatic graft-versus-host disease: an analysis of aggregate survival data. *Liver Transpl* 2005; **11**: 525.
5. Orlando G, Ferrant A, Schots R, *et al.* Liver transplantation for chronic graft-versus-host disease: case report with 10-year follow-up. *Transpl Int* 2005; **18**: 125.
6. Andreoni KA, Lin JI, Groben PA. Liver transplantation 27 years after bone marrow transplantation from the same living donor. *N Engl J Med* 2004; **350**: 2624.
7. Kadry Z, Mullhaupt B, Renner EL, *et al.* Living donor liver transplantation and tolerance: a potential strategy in cholangiocarcinoma. *Transplantation* 2003; **76**: 1003.
8. Vergani D, Mieli-Vergani G. Aetiopathogenesis of autoimmune hepatitis. *World J Gastroenterol* 2008; **14**: 3306.
9. Malik AH, Collins RH Jr, Saboorian MH, Lee WM. Chronic graft-versus-host disease after hematopoietic cell transplantation presenting as an acute hepatitis. *Am J Gastroenterol* 2001; **96**: 588.
10. Daikeler T, Tyndall A. Autoimmunity following haematopoietic stem-cell transplantation. *Best Pract Res Clin Haematol* 2007; **20**: 349.
11. Teshima T, Wynn TA, Soiffer RJ, Matsuoka K, Martin PJ. Chronic graft-versus-host disease: how can we release Prometheus? *Biol Blood Marrow Transplant* 2008; **14**: 142.

