Short Communication

The First Case of Deceased Donor Liver Transplantation for a Patient with End-Stage Liver Cirrhosis Due to Human Immunodeficiency Virus and Hepatitis C Virus Coinfection in Japan

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SUMMARY: We previously reported that progression of liver cirrhosis is quicker and survival is dismal in patients with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) coinfection, especially when acquired in childhood through contaminated blood products. Recently, we performed the first deceased donor liver transplantation (DDLT) for an HIV/HCV-coinfected hemophilic patient in Japan. A 40-year-old man was referred to our hospital for liver transplantation. Regular DDLT was performed using the piggyback technique with a full-sized liver graft. Cold ischemia time was 465 min, and the graft liver weighed 1,590 g. The antiretroviral therapy (ART) was switched from darunavir/ritonavir to raltegravir before the transplant for flexible usage of calcineurin inhibitors postoperatively; tenofovir was used as the baseline treatment. The postoperative course was uneventful, and the patient was discharged home on day 43. He started receiving anti-HCV treatment on day 110 with pegylated interferon, ribavirin, and simeprevir after the DDLT. Herein, we report the first case of DDLT in Japan. Meticulous management of ART and clotting factors could lead to the success of DDLT.

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection after the use of HIV/HCV-contaminated imported blood products for hemophilia patients in the 1980s has led to increased mortality rates due to end-stage liver disease resulting from chronic hepatitis C infection (1,2). In the meantime, the development of antiretroviral agents made it possible to nearly eliminate HIV-related morbidity and mortality (3). Therefore, an urgent need has developed to establish a system to salvage those patients with HIV/HCV coinfection. It is important to note that these patients usually develop end-stage liver cirrhosis at a young age, such as in their 30s and 40s. They may also develop hepatocellular carcinoma (4,5).

In Japan, the Tokyo University group has made an intense effort to salvage those patients undergoing living donor liver transplantation (LDLT) and to yield a good survival rate after LDLT (6). However, liver transplantation from a deceased donor has not been performed thus far. In the world literature, there have been some case series of deceased donor liver transplantation (DDLT) in patients with HIV infection (7); however, an optimal antiretroviral therapy (ART) regimen and anti-HCV treatment has not been clarified yet. Herein, we report the first case of DDLT for an HIV/HCV coinfected hemophilic patient, with special consideration for

antiretroviral conversion and immunosuppressive agent selection.

The patient was a 40-year-old man who was infected with HIV and HCV through imported contaminated blood products used for treating hemophilia when he was an infant. He received treatment with antiretroviral agents, and the HIV RNA levels remained under the detectable range. However, chronic hepatitis with HCV infection persisted, and he recently developed cirrhosis. Pegylated-IFN therapy combined with ribavirin was discontinued owing to mental depression, which was induced by the pegylated-IFN. He was also treated for esophageal varices with endoscopic variceal ligation. A computer tomography scan showed a relatively hypertrophic left lobe of the cirrhotic liver with ascites.

The inferior vena cava was completely surrounded by the enlarged caudate lobe of the liver. No tumor formation was noted inside or outside of the liver. The patient's Child-Pugh status was class C with 10 points and the Model for End-Stage Liver Disease score was 19 points. To HIV RNA level was below detection limits and his absolute CD4 number was around 150. However, the patient had a high HCV RNA titer. A clotting profile indicated that he had hemophilia A with a low factor VIII level, which necessitated administration of factor VIII 3 times per week. Finally, he was indicated for liver transplantation (LT) and waited 3 years with low points. However, over the 3 years his liver function progressively deteriorated. He obtained extra points on the waiting list because the mortality of HIV/HCV coinfected patients without LT is higher than that of HCV-mono-infected patients. Before LT, his ART was changed from darunavir/ritonavir to raltegravir in order to exercise flexible control of the calcineurin inhibitor. Tenofovir was used as the basic ART.

An ABO blood type-identical liver was finally offered and an orthotopic transplantation was performed. The cold ischemic time was 465 min and the graft weight was 1,590 g. The weight of the explanted liver was 836 g. The piggyback procedure was performed, with a blood loss of 16,500 ml. The duration of the operation was approximately 705 min, mainly because of disturbed clotting profile as well as difficulty obtaining complete hemostasis owing to the patient's hemophilic status. Splenectomy was also performed as a result of a low platelet count ($<50,000/\mu l$) and possible postoperative need for interferon or other anti-HCV drugs. Owing to the difficulty of achieving complete hemostasis, our strategy was to finally perform gauze packing and removal, on postoperative day (POD) 3. After the depacking, the postoperative course was rather uneventful and without any severe infectious complications.

Histological examination revealed marked variation in the size and shape of the hepatic nodules, known as mixed micro- and macro-nodular cirrhosis. Persistent active inflammation with lymphoid follicles and interface activity was observed in the portal tract and in the thick fibrous septa. There was no evidence of hepatocellular carcinoma. With regards to immunosuppression, we tried to avoid a steroid bolus in order to prevent infectious complications due to the nature of the HIV disease and HCV flares. Anti-CD25 antibody was adminis-

tered on POD 1 and 4, and tacrolimus was administered on POD 2, followed by aiming the trough level around POD 8 with steroid tapering (Fig. 1). On POD 7, ART was resumed and continued thereafter. The patient's CD4 count was preserved and even elevated owing to the splenectomy. The postoperative course of the patient was uneventful and he was discharged home on day 44 after the DDLT. He was administered the same dose and type of ART as before the DDLT. Anti-HCV treatment with combination of pegylated-interferon, ribavirin, and simeprevir was initiated on day 110 after the DDLT.

However, a sustained viral response was not achieved, and therefore, we initiated treatment with a new direct-acting antiviral agent anti-HCV drugs (DAA), sofosbuvir. The definitive outcomes of the antiviral treatment will be evaluated in the future.

We changed the ART from darunavir/ritonavir to raltegravir before LT for this purpose, which made it possible for us to use regular immunosuppressive agents (8). HIV RNA level has been undetectable throughout the observation period. Before the advent of raltegravir, most ART drugs, non-nucleoside reverse transcriptase inhibitors or protease inhibitors, interacted with immunosuppressive agents such as tacrolimus or cyclosporine because they are all metabolized by the same cytochrome P450 family (CYP3A4). Regarding the CD4
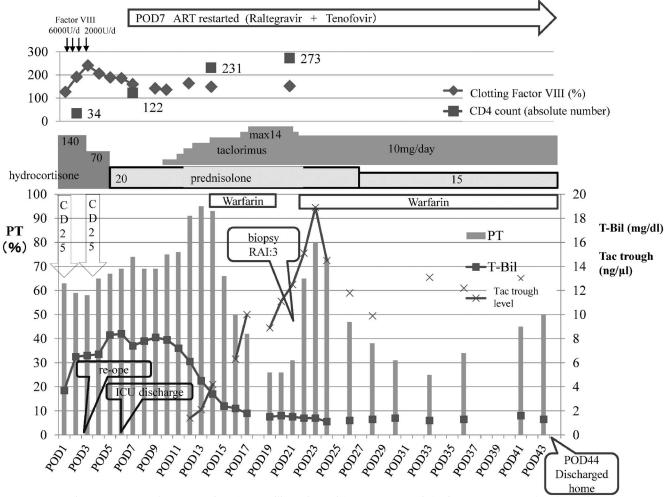

Fig. 1. Post-transplant course in a hemophilic patient with HIV/HCV co-infection. ART restarted (raltegravir, tenofovir) on day 7 and tacloriums on day 11 after the DDLT.

count, our indication for LT was a level above 100, owing to the hypersplenism due to severe portal hypertension. Immediately after the DDLT, the CD4 count dropped below 100, although it recovered spontaneously with the aid of a splenectomy, which was scheduled before the DDLT was performed (9). We believe that if the HIV titer is under control with ART, the absolute CD4 number for indication of LT could be lowered to 100, but not 200 because hypersplenism can mask the real immunological function of those patients with HIV/HCV coinfection. Also, splenectomy may increase the CD4 count and strengthen the immune function before or during LT. According to the article by Nomura et al., after splenectomy, the ratio of CD4 cells in peripheral blood decreases leading to a significant decrease in the CD4/CD8 ratio in patients with liver cirrhosis (10). Therefore, a splenectomy may not significantly increase the CD4 count before LT. However, Hashimoto et al. reported that the CD4 function, in terms of IFN-gamma production and CD4 proliferation, increased after splenectomy (11). Accordingly, it is still controversial whether splenectomy should be performed before LT for patients with HIV infection in order to increase the number or function of CD4 cells.

HCV infection control after DDLT is an important factor because the progression of fibrosis is quicker in patients with HIV/HCV coinfection than in patients with HCV infection only (12–14). In 2014, strong direct acting anti-HCV drugs were more commonly available, and currently in Japan, even HIV/HCV coinfected patients are administered DAAs such as sofosbuvir for better outcomes after DDLT (15). Accumulation of results regarding the use of DAAs in Japanese patients, first for HCV mono-infected patients, is necessary.

After implementation of additional points for HIV/HCV coinfected patients for eligibility for DDLT, it became possible to salvage those coinfected patients in whom the prognosis was definitely worse than that for HCV mono-infected patients, especially for those with platelet counts less than 10,000 cells/μl (5). In addition, because those patients were infected with HCV in their childhood, they developed cirrhosis in their 30s or 40s, sometimes with hepatocellular carcinoma. Although only a few patients with HIV/HCV coinfection should be indicated for DDLT, this first report offers special information for such cases.

In conclusion, this is the first report of DDLT performed for an HIV/HCV coinfected hemophilic patient. Meticulous management of ART and clotting factors could lead to the success of DDLT in such cases. Post-transplant anti-HCV therapy will be a key factor to preventing hepatitis recurrence and the progression of fibrosis.

REFERENCES

1. Smith CJ, Ryom L, Weber R, et al. for the D:A:D study group. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. Lancet. 2014; 384:241-8.
2. Limketkai BN, Mehta SH, Sutcliffe CG, et al. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfected with HIV/HCV. JAMA. 2012;308: 370-8.
3. Ioannou GN, Bryson CL, Weiss NS, et al. The prevalence of cirrhosis and hepatocellular carcinoma in patients with human immunodeficiency virus infection. Hepatology. 2013;57:249-57.
4. Di Benedetto F, Tarantino G, Ercolani G, et al. Multicenter italian experience in liver transplantation for hepatocellular carcinoma in HIV-infected patients. Oncologist. 2013;18:592-9.
5. Eguchi S, Takatsuki M, Soyama A, et al. Analysis of the hepatic functional reserve, portal hypertension, and prognosis of patients with human immunodeficiency virus/hepatitis C virus coinfection through contaminated blood products in Japan. Transplant Proc. 2014;46:736-8.
6. Tsukada K, Sugawara Y, Kaneko J, et al. Living donor liver transplantations in HIV- and hepatitis C virus-coinfected hemophiliacs: experience in a single center. Transplantation. 2011;91:1261-4.
7. Eguchi S, Takatsuki M, Kuroki T. Liver transplantation for patients with human immunodeficiency virus and hepatitis C virus co-infection: update in 2013. J Hepatobiliary Pancreat Sci. 2014;21:263-8.
8. Barau C, Braun J, Vincent C, et al., for the ANRS 148 study group. Pharmacokinetic study of raltegravir in HIV-infected patients with end-stage liver disease: the LIVERAL-ANRS148 study. Clin Infect Dis. 2014;59:1177-84.
9. Baccarani U, Scudeller L, Adani GL, et al. Is liver transplantation feasible in patients coinfected with human immunodeficiency virus and hepatitis C virus? Liver Transpl. 2012;18:744-5.
10. Nomura Y, Kage M, Ogata T, et al. Influence of splenectomy in patients with liver cirrhosis and hypersplenism. Hepatol Res. 2014;44:E100-9.
11. Hashimoto N, Shimoda S, Kawanaka H, et al. Modulation of CD4+ T cell responses following splenectomy in hepatitis C virus-related liver cirrhosis. Clin Exp Immunol. 2011;165:243-50.
12. Baccarani U, Righi E, Adani GL, et al. Pros and cons of liver transplantation in human immunodeficiency virus infected recipients. World J Gastroenterol. 2014;20:5353-62.
13. Eguchi S, Soyama A, Hidaka M, et al. Liver transplantation for patients with human immunodeficiency virus and hepatitis C virus coinfection with special reference to hemophiliac recipients in Japan. Surg Today. 2011;41:1325-31.
14. Fierer DS, Dieterich DT, Fiel MI, et al. Rapid progression to decompensated cirrhosis, liver transplant, and death in HIV-infected men after primary hepatitis C virus infection. Clin Infect Dis. 2013;56:1038-43.
15. Berenguer J, Alvarez-Pellicer J, Carrero A, et al., for the GESIDA HIV/HCV cohort study group. Clinical effects of viral relapse after interferon plus ribavirin in patients co-infected with human immunodeficiency virus and hepatitis C virus. J Hepatol. 2013;58:1104-12.