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Human T-cell leukemia virus type 1 infection worsens prognosis of hepatitis C virus-related living donor liver transplantation

Tatsuki Ichikawa,[1] Naota Taura,[1] Hisamitsu Miyaaki,[1] Toshihisa Matsuzaki,[1] Masashi Ohtani,[1] Susumu Eguchi,[2] Mitsuhisa Takatsuki,[2] Akihisa Soyama,[2] Masaaki Hidaka,[2] Sadayuki Okudaira,[2] Tetsuya Usui,[4] Sayaka Mori,[4] Shimeru Kamihira,[3,4] Takashi Kanematsu,[2] and Kazuhiko Nakao[1]

1 Department of Gastroenterology and Hepatology, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan
2 Department of Transplantation and Digestive Surgery, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan
3 Department of Laboratory Medicine, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan
4 Central Diagnostic laboratory of Nagasaki University Hospital, Nagasaki, Japan

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Correspondence
Tatsuki Ichikawa, Department of Gastroenterology and Hepatology, Graduate School of Biomedical Sciences, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan. Tel.: +81-95-819-7481; fax: +81-95-849-7482; e-mail: ichikawa@net.nagasaki-u.ac.jp

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Summary

Severe and life-threatening donor-transmitted human T-cell leukemia virus type 1 (HTLV-1) infections after solid organ transplantation have been reported. However, in HTLV-1-infected recipients, graft and patient survival were not fully evaluated. A total of 140 patients underwent living donor liver transplantation (LDLT). Of these, 47 of 126 adult recipients showed indications of hepatitis C virus (HCV)-related liver disease. The HTLV-1 prevalence rate was 10 of 140 recipients (7.14%) and three of 140 donors (0.02%). In HCV-related LDLT, graft and patient survival was worsened by HTLV-1 infection in recipients (seven cases). The 1-, 3-, and 5-year survival rates in the HCV/HTLV-1-co-infected group were 67%, 32%, and 15%, respectively, and the corresponding rates in the HCV-mono-infected group were 80%, 67%, and 67%, respectively. Only the 5-year survival rates were statistically significant ($P = 0.04$, log-rank method). HTLV-1 infection in recipients is also an important factor in predicting survival in HTLV-1 endemic areas.

Introduction

Human T-cell leukemia virus type 1 (HTLV-1) is highly endemic in the southwestern area of Japan, including Nagasaki as well as in Saharan Africa, South America, the Caribbean islands, and aboriginal Australia [1,2]. However, HTLV-1 infects approximately 15–25 million people worldwide [3] and is associated with adult T-cell leukemia/lymphoma (ATL), HTLV-1-associated myelopathy (HAM), uvetitis, sialadenitis-like Sjögren syndrome (SjS), and a wide variety lymphocyte-mediated disorders [2,4,5]. Severe and life-threatening donor-transmitted HTLV-1 infections after solid organ transplantation have been reported [6–8]. However, in HTLV-1-infected recipients, graft and patient survival has not been fully evaluated. The development of three ATL cases in eight HTLV-1 infected recipients after living donor liver transplantation (LDLT) was reported in Japan [9]. We also reported the development of HAM [10] and sialadenitis-like SjS [11] resulting from HTLV-1 in LDLT recipients. Previous reports state that HTLV-1 infection is associated with a nonresponse to interferon (IFN) monotherapy for chronic hepatitis C (CHC) [12] and flare-up of alanine aminotransferase in hepatitis C virus (HCV)-RNA carriers [13]. HTLV-1/HCV co-infection may affect the course of HCV-associated liver disease and liver cancer [14].

Additionally, HTLV-1 interferes with intracellular signaling by type 1 IFN and upregulates HCV replication [14–16]. However, the influence of HTLV-1 in recipients on the grafted liver has not been explored. The effect of HTLV-1/HCV co-infections in recipient compared with HCV mono-infections has similarly not been explored.

Between 1988 and 2000, 0.027% of donors reporting to the United Network for Organ Sharing (UNOS) were diagnosed with HTLV-1 infections [6]. However, the prevalence of anti-HTLV-1 antibodies in patients visiting Nagasaki University Hospital between 2000 and 2007 was 13.57% [2], indicating that HTLV-1 carriers are clustered in Nagasaki. To prevent vertical transmission of HTLV-1, the ATL Prevention Program, which is a prefecture-wide breastfeeding intervention study for HTLV-1 carrier mothers, was initiated in Nagasaki in 1987 [17]. As a result, age-specific rates of HTLV-1 among residents in Nagasaki have annually declined (Seropositive rate, 14.5% in 2000; 12.7% in 2007) [2]. The prevalence of anti-HCV antibody increased with age and was higher in populations in the southwestern area of Japan (including Nagasaki) [18]. In endemic areas of HTLV-1 infection, HTLV-1/HCV co-infected patients are frequently observed and increase the probability a person will have a liver transplantation.

The HTLV-1 infection rate is lower in Western countries; however, the influence of HTLV-1 on HCV infection after transplantation has not been examined. It is necessary to evaluate HTLV-1 infection rates in HTLV-1 endemic areas. We examined whether HTLV-1 infection influences patient and graft survival in cases of liver transplantation in endemic areas of HTLV-1 infection in Nagasaki.

Patients and methods

Patients

In total, 126 consecutive adult LDLT patients, 47 of who were HCV-infected, were enrolled in this study. This retrospective cohort study of LDLT recipients included a comparative analysis of HTLV-1-positive and HTLV-1-negative recipients to determine graft and patient survival. In particular, we evaluated whether HTLV-1 infection influenced HCV-related LDLT. Anti-HTLV-1 antibody was detected using an enzyme immunoassay (EIA). In addition, in HTLV-1-positive patients, we used polymerase chain reaction (PCR) analysis to evaluate HTLV-1 proviral DNA in the peripheral blood mononuclear cells. We diagnosed patients with the anti-HTLV-1 antibody and proviral DNA as being HTLV-1 positive. In our hospital, HTLV-1-positive grafts are not used for negative recipients, but are used for positive recipients. Recipient characteristics such as age, gender, body mass index, Child-Pugh score and medical model for end-stage liver disease (MELD) score at the time of transplantation, presence or absence diabetes mellitus (DM), and presence of hepatocellular carcinoma (HCC) were also analyzed. Surgical factors examined included blood type matching, bleeding volume, (ml), and surgery time (min). Donor age was categorized into those less than 50 years old and 50 years old and older. Additional donor characters, such as donor gender, donor BMI, and donor HTLV-1 status were analyzed. HCV factors included genotype (1b or non-1b), titer in 1b, core amino acid mutation in 1b, and IL28B SNP. The HCV-RNA high group (100 000 IU/ml or more in the serum) of patients was analyzed using real-time PCR.

Primary outcomes evaluated included recipient and graft survival. The cause of death was determined using various factors together with biopsy and necropsy. Liver biopsy was performed each year and at exacerbation of liver function.

Methods

The study design, which also included the collection of data from medical records from the associated hospitals mentioned above, was approved by the Ethics Review Board of our hospital.

In this study, 3 *IL28B* SNPs, i.e., rs8099917, rs12979860, and rs12980275, were examined (Nagasaki University Institutional Review Board approval number: 100511184). SNPs were detected using pyrosequence analysis. The sense, antisense, and pyrosequence primers were **B**-5′-TCCTCCTTTTGTTTTCCTTTCTG-3′, 5′-AAAAAG CCAGCTACCAAACTGT-3′, and 5′-TGGTTCCAATTT GGG-3′ for rs8099917, 5′-GTCGTGCCTGTCGTGTAC TGA-3′, 5′-**B**-GGAGCGCGGAGTGCAATT-3′, and 5′-GG AGCTCCCCGAAGG-3′ for rs12979860, and 5′-GCTG TATGATTCCCCCTACATG-3′, 5′-**B**-TACATTGTTCGG CAAGCAATCT-3′, and 5′-AGAAGTCAAATTCCTAG AAA-3′ for rs12980275, respectively. "**B**" in the primer sequences indicates that the primer is biotin-labeled.

Statistical analysis

Data were processed on a personal computer and analyzed using StatView 5.0 (SAS Institute, Inc., Cary, NC, USA).Graft and patient survival was determined using the Kaplan–Meier method and survival curves were compared using a log-rank test. A cox proportional hazard model was used to determine risk factors for graft and patient survival. Differences between each laboratory data were analyzed using the Mann–Whitney *U*-test and χ^2 test. P-values < 0.05 were considered statistically significant.

Results

We evaluated the impact of HTLV-1 on general graft and patient survival in HCV-infected patients. Of the 140 patients who had undergone LDLT at the Nagasaki University Hospital between 1997 and January 2011, 47 of 126 adult recipients showed indications of HCV-related liver disease. The HTLV-1 prevalence rate was 7.8% (11/140) in the recipients and 2% (3/140) in the donors. Fourteen of the 140 recipients were pediatric recipients. HCV-related LDLT was observed only in adults. All HTLV-1 infected recipients were adult cases. First, we evaluated impact of HTLV-1 for LDLT in adult cases. In HCV-related LDLTs (Fig. 1a), graft and patients survival was worsened by the presence of HTLV-1 infection of recipients. The 1-, 3-, and 5-year survival rates in the HCV/HTLV-1-co-infected group were 67%, 32%, and 15%, respectively, and the corresponding rates in the HCV-mono-infected group were 80%, 67%, and 67%, respectively. Only the 5-year survival rate was found to be statistically significant ($P = 0.04$, log-rank method). However, adult recipients without HCV infection did not develop graft loss and patient death (Fig. 1b). In HCV-related LDLTs, clinical and demographic characteristics in HTLV-1-positive and HTLV-1-negative recipients did not differ between groups, except for donor age (Table 1). We attempted to clarify the factors of graft and patient survival in HCV-infected recipients by univariate analysis. MELD score and donor age at transplantation in the HTLV-1-infected recipients were shown to be significant factors. However, according to multivariate analysis, only donor age was a factor in worsening prognosis ($P < 0.05$; Relative risk 1.048). Three types of IL28B SNPs were not associated with graft and patient survival in HCV infected recipients according to a log rank test and univariate analysis of a Cox proportion hazard test.

Second, we analyzed stratification by donor age. Clinical characteristics, shown in Table 1, in the recipients who tested positive and negative for HTLV-1 did not differ between groups. In HCV-related LDLT recipients from old age donor group (age, 50 years and more; co-infected, 3 cases; HCV mono-infected, 13 cases), graft and patient survival was not worsened by recipient HTLV-1 infection (log-rank test, not significant). However, in the young age donor group (age less than 50 years; co-infected, 4 cases; HCV mono-infected, 34 cases), graft and patient survival was significantly worsened by recipient HTLV-1 infection (log-rank test, $P < 0.05$). However, graft and patient survival in HCV/HTLV-1-co-infected patients did not differ between the old and young donors, and the outcomes of HCV-mono-infected patients differed between the old and young donors according to the log-rank test. On the basis of multivariate analysis using a Cox proportional hazard test, HTLV-1 infection in HCV-infected recipients who received the transplant from younger donors was the only factor contributing to a worsened prognosis ($P = 0.03$; relative risk, 0.207).

Finally, we present the profile of seven cases of HCV/HTLV-1 co-infected recipients (Table 2). In the HCV/HTLV-1 co-infected group, chronic rejection (CR) developed in 3 patients, cases 60, 80, and 117, during peg-interferon/ribavirin treatment. CR did not develop in HCV-mono-infected patients. However, the CR rate was not statistically significant between the HCV/HTLV-1-co-infected group and the HCV-mono-infected group. Patients with CR did not have a prior history of acute rejection and used cyclosporine as an immunosuppressant. HCV-RNA disappearance during peg-interferon combination treatment with ribavirin was not observed in 3 CR cases. The period of peg-interferon combination treatment with ribavirin is 47, 23, and 2 months for HTLV-1/HCV co-infected CR patients. The treatment regimen of the

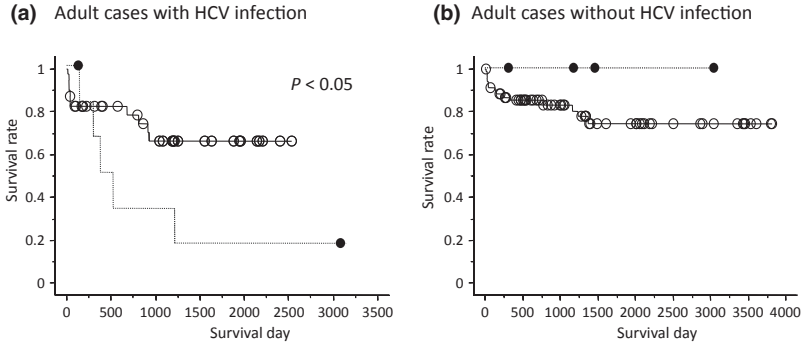

Figure 1 Kaplan–Meier curves for graft and recipient survival in adult transplant cases. A Kaplan–Meier curve revealed adult recipients with HCV infection (a) and without HCV infection (b). Black circle and dot line indicate HTLV-1 positive recipients and white circle and solid line indicate HTLV-1 negative recipients. In adult case with HCV-related LDLT, graft and patient survival of HTLV-1-infected recipients significantly decreased (a, $P < 0.05$).

Table 1. Clinical characteristics in patients with HCV infection.

	HTLV-1 positive	HTLV-1 negative	*P*-value
Number	7	40	
Age (years)	57.6 (7.16)	58.5 (6.48)	NS
Gender M/F	6/1	20/20	NS
BMI	25.6 (5.17)	25.0 (3.08)	NS
CP-score	10.6 (3.25)	9.85 (2.27)	NS
MELD	11.8 (8.38)	13.6 (8.16)	NS
DM +/-	2/5	20/20	NS
HCC +/-	4/3	27/13	NS
Donor age	48 (14.5)	37.6 (11.8)	0.04
Donor gender M/F	6/1	18/22	NS
Donor BMI	21.9 (2.42)	22.0 (2.62)	NS
Matching +/-	7/0	32/8	NS
Bleeding volume (ml)	5222 (3840)	14 182 (21 230)	NS
Surgery time (min)	902 (171)	934 (215)	NS
HCV GT1/non GT1	6/1	30/10	NS
HCV high titer in GT1	5	28	NS
IL28B SNP Major/Minor	1/2	24/6	NS
SVR rate	1/7	9/40	NS

Data are shown as means (standard deviation) and numbers, with statistical analysis assessed using a Mann–Whitney test for means and χ^2 test for numbers. Statistically significant difference between HTLV-1 positive and negative groups is $P < 0.05$. CP-score, Child–Pugh score; HCV GT, HCV genotype; Matching, Blood type matching; IL28B SNP Major, TT of rs8099917 in recipient and donor; Minor, TG or GG of rs8099917 in recipient and/or donor. BMI, body weight (kg)/height (m)/height (m). SVR, sustained viral response.

Table 2. Clinical characteristics in recipients with HCV and HTLV-1 co-infection.

Case number	20	59	60	80	112	117	132
Age (years)	58	50	68	65	48	54	58
Gender	M	M	M	F	M	M	M
Survival	+	+	–	–	–	–	–
Survival time (day)	3086	1210	528	378	139	301	132
Cause of death	–	HCC	CR	CR	Infect.	CR	–
IFN	+	–	+	+	–	+	–
Viral response	–	–	–	–		–	
IFN period (month)	48		47	23		2	
HCV GT1b	1b	1b	1b	1b	1b	N	1b
BMI	19.3	31.1	23.2	30.5	19.2	30.2	25.9
HCC	–	outside	Milan	Milan	–	Milan	–
MELD	8.1	8.5	4.4	7.3	29.3	15.2	9.9
DM	–	+	+	–	+	+	+
Donor	Sister	Brother	Child	Brother	Brother	Uncle	Child
Donor age	56	45	41	61	46	65	22
Donor HTLV-1	+	–	–	–	–	–	–

Viral response is the disappearance of HCV-RNA in patients under peg-IFN/ribavirin treatment. IFN period is treatment length (month) of peg-IFN/ribavirin treatment. Infect., infection; AIH, autoimmune hepatitis; BA, biliary atresia; LCN, cryptogenic cirrhosis; LCB, hepatitis B virus infected liver cirrhosis. Milan, HCC within Milan criteria, Outside, HCC without Milan criteria.

peg-interferon combination with ribavirin was performed under the rules of our hospital and was the same as was conducted for other HCV-related transplanted patients [19]. Hence, as an immunosuppressive therapy, tacrolimus was used for all HCV-infected patients as an induction therapy combined with steroid tapering; subsequently, tacrolimus treatment was intentionally replaced with cyclosporine treatment to facilitate interferon therapy [20,21] except in case 20. Case 20, which involved an HTLV-1 infected donor, suffered an onset of HAM and sialadenitis under the tacrolimus immunosuppressant regime [11]. Five cases of death occurred in the co-infected group. Causes of death in patients with HTLV-1/HCV co-infection included hepatoma recurrence, infection, and CR. ATL was not observed in this study. Progression of HCV and/or HTLV-1 infection was not always related to death. In particular, all CR cases developed during interferon treatment. Poor survival of HTLV-1/HCV-co-infected patients may have been caused by CR. HCV-RNA levels decreased in the CR cases when the length of peg-IFN/ribavirin treatment was less than 1 year.

Discussion

In this study, we clarified that HTLV-1 infection in HCV-infected recipients is an exacerbation factor involved in survival of both the graft and the patient. Particularly, young donors suffer detrimental effects caused by HTLV-1 infection. Survival of HCV-infected recipients is affected by donor age, MELD score, and HTLV-1 infection. Donor age is the most significant factor in graft and patient survival, and HTLV-1 infection in recipients is the second most important factor in survival in HTLV-1 endemic areas. Donors of advanced age and high MELD scores have been reported as complicating factors [22,23]. We report the impact of HTLV-1 infection on graft and patient survival for the first time.

The presence of HTLV-1 infection as a complicating factor in recipients was revealed after adjusting for age. As HCV/HTLV-1 co-infection occurred in three cases in older donors and four cases in younger donors, it was necessary to determine the role of donor age in HCV/HTLV-1-co-infected recipients. In the HTLV-1 infection-negative group, graft and patient survival was shorter in older donors than in younger donors, but in the HCV/HTLV-1-co-infected group, graft and patient survival did not differ between the old and young donors. Donor age is a complicating factor for graft and patient survival regardless of HTLV-1 infection [23]. The survival rate of the young donor group may initially be high, but survival rate decreases in the presence of HTLV-1 infection. HTLV-I possesses a unique and innate (or acquired) capacity to preserve cellular immunity, such as IL-2 and

IL-2-receptor induction [24]. HTLV-1 infection may lead to a stronger immune response in recipients when the donor is young than when the donor is old.

The relationship among IFN, HCV, and CR at post-liver transplantation has been previously studied. It is reported that peg-IFN/ribavirin treatment for HCV may trigger rapid CR in patients with therapeutic immunosuppressant trough levels, with or without first inducing acute cellular rejection [25]. Other reports state that the use of cyclosporine, ribavirin discontinuation, a peg-IFN treatment duration of over 1 year, and HCV infection elimination for IFN treatment appear to be associated with CR [26,27]. We suspect that HTLV-1-infected recipients under peg-IFN/ribavirin treatment may be associated with CR for young graft donors and have different immunological mechanisms than HTLV-1 negative recipients.

Recently, the relationship of IL28B SNP and HCV infection has been studied [28]. It has been reported that IL28B SNP is not only related to the effect of IFN treatment, but also to the natural course of HCV infection [29]. We conducted an analysis of IL28B SNP in only 33 pairs of donors and recipients who had obtained agreement in 47 cases of HCV-related liver transplantation. In this study, Il28B SNP was not related to graft and patient survival. However, upon analysis of three types of IL28B SNPs, the survival rate was the same for all three SNPs. Previous reports state that there are no statistical differences in overall graft survival according to recipient and donor IL28B SNPs [30,31].Since it is reported that IL28B SNPs in both recipients and donors is associated with IFN response [30–32], differences in long-term survival between IL28B SNP groups has been examined.

Due to the low prevalence HTLV-1 infection in western countries, the association of liver disease and HTLV-1 infection has not been evaluated. In this study, performed in an HTLV-1 endemic area, we determined that HTLV-1 increases mortality after HCV-related LDLT. Presently, to improve mortality rates, the presence of CR should be determined when HCV/HTLV-1 co-infected transplanted patients are treated using IFN/ribavirin. However, as CR treatment has not been fully evaluated, the mechanism of HTLV-1 infected T cells in HCV-infected graft liver patients under peg-IFN/ribavirin treatment should be determined. The follow-up period of the seven HCV/HTLV-1-co-infected patients was 132–3086 days. As our study population was small and follow-up periods were short, we will extend the follow-up period to validate our results.

Authorship

TI, NT, HM, TM, MO, SE, MT, AS, MH, SO, TU, SM: performed study. SK, TK and KN: designed the study. TI: wrote the manuscript.

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