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ORIGINAL ARTICLE

Spontaneous Clearance of Hepatitis C Virus After Liver Transplantation in Two Patients Coinfected with Hepatitis C Virus and Human Immunodeficiency Virus

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Spontaneous resolution of chronic hepatitis C virus (HCV) infection is exceedingly rare and poorly understood. As HCV and human immunodeficiency virus (HIV) have shared routes of transmission, HCV coinfection is estimated to affect 15%-30% of the HIV-positive population. We report 2 patients with HCV-HIV coinfection who underwent orthotopic liver transplantation at our center and had spontaneous clearance of their chronic HCV infection after transplantation without any anti-HCV treatment. Both patients showed no evidence of HCV recurrence for more than 3 years despite long-term immunosuppressant therapy. Spontaneous clearance of chronic HCV infection can occur in HIV-HCV–coinfected patients after liver transplantation. The mechanism of this phenomenon remains unclear. ***Liver Transpl 14:92-95, 2008.*** © **2007 AASLD.**

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The continuous improvements made in antiretroviral regimens have markedly increased the life expectancy of human immunodeficiency virus (HIV)–infected individuals. As hepatitis C virus (HCV) and HIV have shared routes of transmission, HCV coinfection is estimated to affect 15%-30% of the HIV-positive population.[1] Consequently, HCV-related liver disease has become a significant cause of morbidity and mortality among HIV patients. Orthotopic liver transplantation (OLT) is a complex yet increasingly acceptable consideration for these patients with end-stage liver disease. Between June 1, 1999 and August 2006, 17 HIV+ patients, 8 of whom were coinfected with HCV, underwent OLT at the University of Miami. We report 2 coinfected patients who underwent OLT and were subsequently found to have spontaneous HCV clearance.

CASE 1

A 43-year-old HIV-infected male on highly active antiretroviral therapy (HAART) was referred to our transplant center for end-stage liver disease secondary to coinfection with hepatitis B virus (HBV) and HCV. At the time of referral, the patient had a CD4 cell count of 240 cells/mm^3 and HIV viral load of 250 copies/mL with real-time polymerase chain reaction (PCR) assay (Abbott Molecular, Inc., Des Plaines, IL). The patient was started on pegylated interferon and ribavirin; however, this treatment was discontinued after 1 month because of intolerable side effects. Ten months prior to OLT, his HCV RNA level by PCR was 564,000 IU/mL with reverse-transcription PCR assay (Roche Molecular Systems, Inc., Branchburg, NJ). Five days prior to transplant, his HCV RNA level was 710 IU/mL and his HBV DNA level was 7,370,000 IU/mL with real-time nucleic acid amplification assay (RUO, Roche Molecular Systems). Throughout this period, he was treated with a combination of lamivudine/zidovudine and indinavir for his HIV infection. Posttransplant immunosuppression consisted of methylprednisolone and tacrolimus. All viral loads and CD4 counts were checked every week

Abbreviations: HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; OLT, orthotopic liver transplantation; PCR, polymerase chain reaction.

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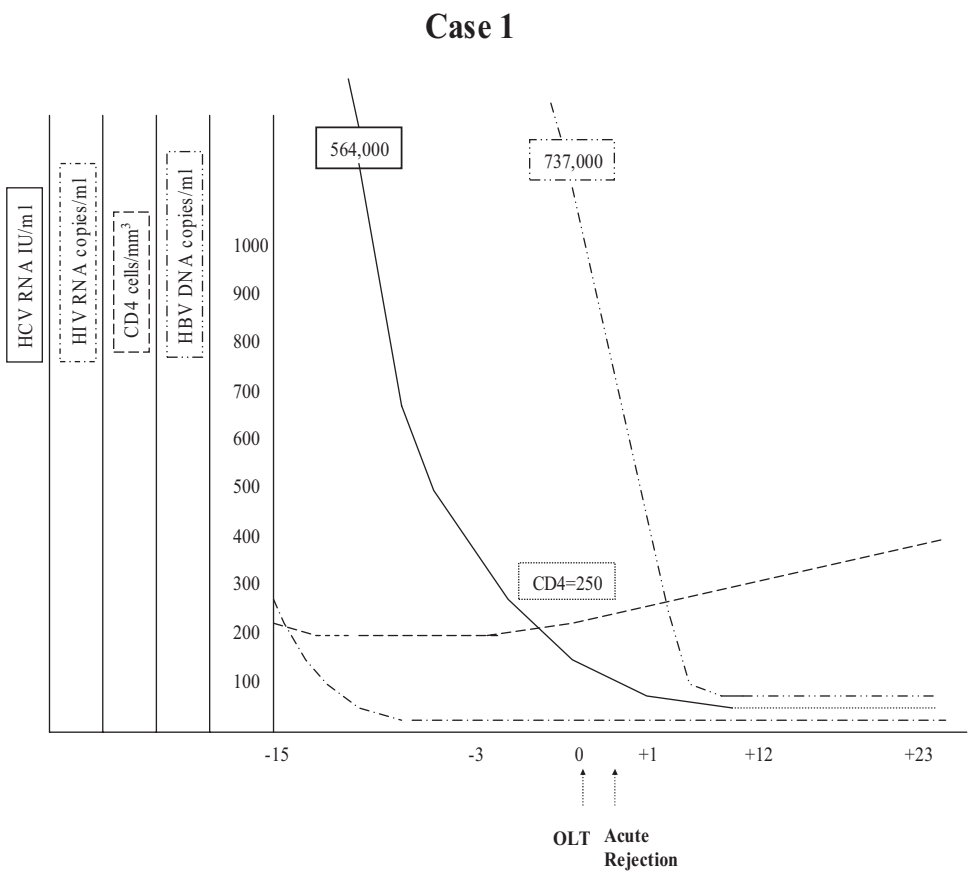

Figure 1. HIV, HCV, and HBV viral loads and CD4(+) counts before and after OLT.

for 1 month, every month for 3 months, and every 2-3 months after 3 months post-OLT in both patients. Two weeks following transplantation, the patient was diagnosed with mild acute rejection that was managed with an increase in the dose of methylprednisolone. One month after OLT, he was discharged on lamivudine, zidovudine, tenofovir, and efavirenz. Tacrolimus level were maintained at 10-15 ng/mL during the first month after transplant and at 6-9 ng/mL thereafter for 1 year post-OLT. Two months after OLT, mycophenolate mofetil was added to his regimen because of rising creatinine on tacrolimus, and steroids were tapered and subsequently discontinued. Three months following transplantation, HBV DNA became and ultimately remained undetectable. HCV RNA became undetectable a month after transplantation and remained undetectable (<10 IU/mL) on repeated blood tests after 4 years without anti-HCV treatment (Fig. 1).

CASE 2

A 44-year-old HIV-infected male on HAART was referred to our transplant center for end-stage liver disease secondary to chronic HCV infection. At the time of referral, his CD4 count was 244 cells/mm^3, HIV RNA was undetectable, and HCV RNA was 450,000 IU/mL. He was started on standard interferon alpha-2a and ribavirin for 6 months followed by pegylated interferon alpha-2b with ribavirin for 3 months. All HCV treatment was stopped 6 months prior to transplantation because of pancytopenia and hepatic decompensation. Two months prior to transplantation, his HCV RNA was 326,000 IU/mL and his CD4 count was 192 with an undetectable HIV viral load. Following OLT, immunosuppression was achieved with methylprednisolone and tacrolimus. All viral loads and CD4 counts were checked every week for 1 month, every month for 3 months, and every 2-3 months after 3 months post-OLT. Three days after OLT, a liver biopsy revealed hepatocellular necrosis suggestive of preservation injury, which was managed conservatively, with improvement in liver function tests observed within several days. A subsequent episode of acute rejection 2 weeks post-OLT was managed with the addition of muromonab-CD3. The CD4 count at that time was 574 cells/mm^3, but HCV RNA was not measured at the time of this episode. After 1 month of hospitalization, the patient was discharged on prednisone, tacrolimus, lamivudine, stavvdi, and efavirenz. Tacrolimus level was maintained at 10-15 ng/mL during the first month, 8-10 ng/mL for 1-3 months, and 6-9 ng/mL thereafter for 1 year post-OLT. After transplantation, his CD4 counts ranged from 180 to 574 cells/mm^3 with an undetectable HIV viral load. A blood test for HCV RNA by PCR 30 days post-OLT yielded undetectable HCV RNA. The HCV RNA

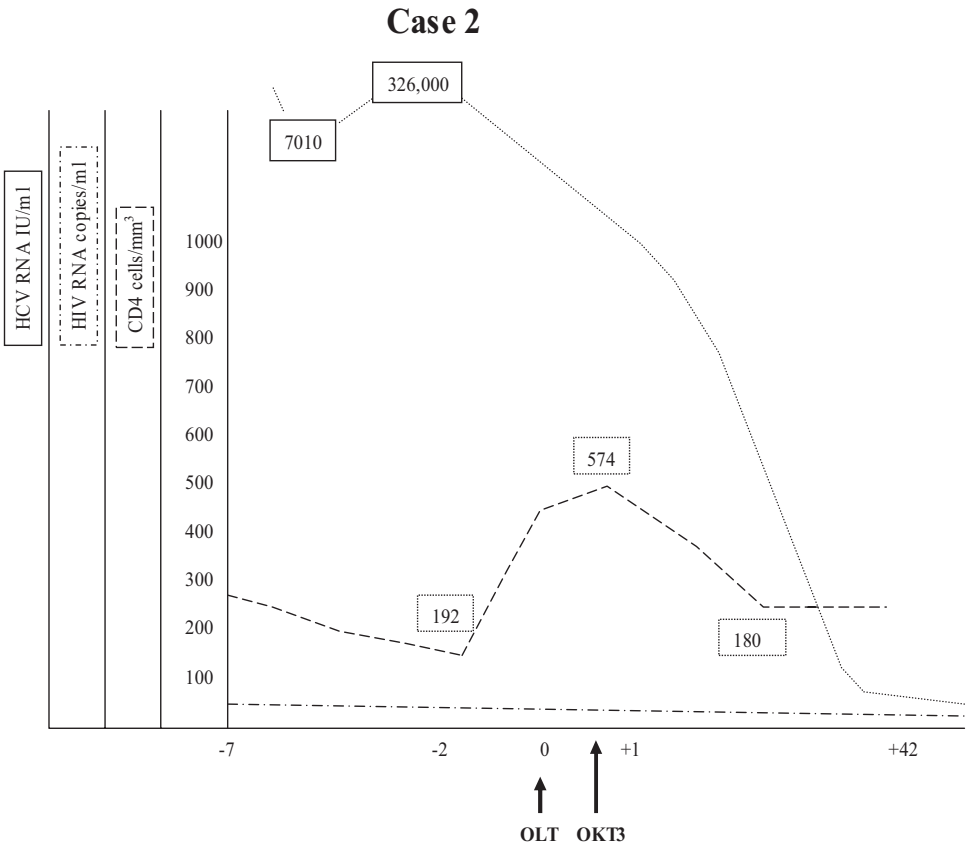

Figure 2. HIV and HCV viral loads and CD4(+) counts before and after OLT.

level remained undetectable (<10 IU/mL) on repeated blood tests 3 years following transplantation without anti-HCV treatment (Fig. 2).

DISCUSSION

Mortality among HIV-HCV–coinfected patients is significantly higher with respect to other patient populations awaiting liver transplantation. Thus, earlier transplantation has been suggested in this patient population.[2,3] Posttransplantation management of both infections with concomitant immunosuppressive therapy poses a complex challenge. Drug interactions may prevent physicians from optimizing both HAART and anti-HCV treatments.[4,5] Consequently, opportunistic infections, anemia, neutropenia, and thrombocytopenia are frequently encountered complications. To date, response rates to HCV treatment in the posttransplant HIV-HCV–coinfected population are lower than those seen in recipients solely infected with HCV.[6] In HIV-HCV–coinfected individuals, host genetic factors appear to play a role in both the development of fibrosis and the response to HCV therapy. Allelic variations in proteins critical to the inflammatory response found in these patients may alter hepatic response to HCV and thus alter the severity of infection.[7]

Spontaneous resolution of chronic HCV infection is exceedingly rare and poorly understood. Both host and viral factors that may influence HCV chronicity are not completely clear. Genetic variability of the virus allows it to evade the immune system, whereas host human leukocyte antigen (HLA) class II genotype plays an important role in host susceptibility. Both DQB1*0301 and DRB1*1101 HLA alleles are thought to be protective through more effective presentation of HCV epitopes to CD4(+) T lymphocytes. This leads to increased resistance to chronic HCV infection in patients who possess them.[8] Moreover, interleukin-10 haplotypes are possible predictors of spontaneous clearance of HCV infection.[9]

Here we report 2 HIV-HCV–coinfected patients who experienced spontaneous resolution of chronic HCV infection following OLT in the absence of anti-HCV treatment. This phenomenon, although reported among transplant recipients solely infected with HCV,[10-12] had never been described in HIV-HCV–coinfected patients until the 2006 annual meeting of the American Association for the Study of Liver Diseases.[13] Immune response measured by proliferative T-cell response and cytokine production (gamma-interferon and interleukin-10) after HCV-specific stimulation in cultured peripheral blood mononuclear cells despite immunosuppression may have contributed to HCV clearance.[9]

We propose that concomitant infection with hepatitis B in case 1 may have induced an immune response that

may have cross-cleared HCV, as has been described in some human models.[14,15] In addition, rejection episodes in both cases may have induced local production of T helper 1 cytokines in the liver, thus facilitating viral clearance.[10] Donor HLA genotypes may have also contributed to viral clearance. Hypergammaglobulinemia and possible immune modulation in HIV+ individuals may play a role in host response to HCV infection. There are reports on anti-HCV effects of immunosuppressive agents such as cyclosporine.[16,17] In addition, antiretroviral therapy used for HIV suppression may confer additional suppression of HCV, ultimately enabling HCV clearance.[18]

The mechanism for spontaneous clearance of chronic HCV infection observed in our coinfected patients post-OLT, however, remains unclear. As the population of coinfected individuals requiring OLT increases, our ability to prospectively analyze the interaction between host and viral factors influencing HCV clearance will improve. Further study in this complex population is needed to fully understand this phenomenon.

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