Spontaneous clearance of hepatitis C after liver and renal transplantation

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Spontaneous clearance of hepatitis C virus (HCV) is rare in immunocompromised patients, such as those who have undergone organ transplantation. It has been recognized that patients receiving liver transplantation for HCV-related disease have decreased graft and patient survival compared with those transplanted for other etiologies. There is a growing trend toward treating HCV recurrence aggressively after liver transplantation. For other organ transplant recipients with concurrent HCV, treatment is not often an option, given the high rates of graft rejection and loss secondary to interferon and its immunomodulatory effects. Although spontaneous clearance of HCV has been reported in recipients of solitary liver and renal transplants, a common factor arising in these cases has been previous exposure to interferon. To date, no reports of spontaneous clearance of HCV RNA have been reported in a multiorgan transplant recipient. A case of spontaneous clearance of HCV RNA in an immunocompromised patient, within five months of simultaneous liver and kidney retransplantation is described. Importantly, this patient had no previous exposure to interferon.

Key Words: Hepatitis C; Interferon; Liver transplantation; Spontaneous clearance

In 2004, she developed an abnormal liver profile and underwent liver biopsy that revealed cirrhosis with typical HCV pathological features. She did not undergo antiviral therapy with interferon given the risk to the renal allograft. In 2005, she developed progressive renal allograft failure and liver decompensation. She was listed for combined liver and renal retransplantation. At that time, she was documented to be genotype 1a with a high viral load (3.21×10^6 IU/mL).

In July 2006, she underwent a combined liver/renal retransplant. On the day of transplant, the recipient remained viremic (HCV RNA greater than 50 IU/mL). The donor was HCV antibody-negative. The recipient had a complicated postoperative course with multiple intra-abdominal abscesses requiring percutaneous drainage and a prolonged hospital stay. She ultimately recovered and was discharged home. Her immunosuppression consisted of basiliximab induction, followed by delayed tacrolimus, mycophenolate mofetil and tapering doses of prednisone. Cytomegalovirus (CMV) prophylaxis was provided for three months with oral valganciclovir.

At 11 weeks post-transplant, she developed a significant transaminitis. Her alanine aminotransferase and aspartate aminotransferase levels were 354 U/L and 303 U/L, respectively (normal range lower than 40 U/L), while her bilirubin and alkaline phosphatase levels remained normal. A liver
biopsy revealed portal tracts with mild lymphocytic infiltrates; however, no evidence of cellular rejection or fibrosis. At 14 weeks post-transplant, the levels of liver enzymes continued to rise. A second liver biopsy revealed moderate portal-based inflammation with predominant lymphocytic infiltration, without evidence of cellular rejection. Doppler imaging of the hepatic vessels was normal. Twenty weeks postoperatively, the liver enzymes continued to climb (alanine and aspartate aminotransferase 785 U/L and 1169 U/L, respectively). The bilirubin had risen to 29 µmol/L (normal less than 17 µmol/L) and alkaline phosphatase was normal at 81 U/L (normal range less than 113 U/L). A third liver biopsy revealed diffuse moderate lymphocytic infiltration expanding into the lobules with new features of hepatocyte necrosis consistent with severe hepatitis and bridging necrosis (Figure 1). There was no evidence of cellular or ductopenic rejection.

Given the worsening of transaminase levels and histology, the diagnosis was presumed to be recurrent HCV. After ample discussion of the risks and benefits associated with antiviral therapy, the patient consented to antiviral therapy. Pegylated interferon alpha-2a was initiated at 90 µg subcutaneously per day, with each article speculating on different causative factors for the viral clearance. Similar to the previous renal case, this was quite the contrary, given the immediate post-transplant period, our patient’s immunosuppression was actually enhanced with interleukin-2 induction, moderate doses of corticosteroids, tacrolimus and mycophenolate mofetil.

Somsouk et al (2) described the case of a young woman who developed progressive liver disease from HCV after primary renal transplantation. Eleven years after renal transplant, the patient developed allograft failure and immunosuppression was withdrawn. The patient was known to be genotype 1a, and the liver biopsy showed bridging fibrosis. She received one dose of interferon alpha-2b subcutaneously. The patient subsequently cleared the HCV RNA. The authors speculated that with the withdrawal of immunosuppression, the patient was able to mount a CD4 response and clear the HCV RNA. This patient also went on to have regression of hepatic fibrosis. In the present case, this was quite the contrary, given the immediate post-transplant period, our patient’s immunosuppression was actually enhanced with interleukin-2 induction, moderate doses of corticosteroids, tacrolimus and mycophenolate mofetil.

The liver transplant literature reports sporadic cases of spontaneous HCV RNA clearance in the post-transplant period, with each article speculating on different causative factors for the viral clearance. Similar to the previous renal case, Neumann and Neuhaus (3) presented a case of a patient retransplanted for hepatic artery thrombosis, who also had concomitant fibrosing cholestatic HCV and was known to have been viremic with genotype 1b. After retransplant, the patient required decreased immunosuppression secondary to renal failure. The patient subsequently cleared the HCV RNA. Before retransplant, this patient had received interferon monotherapy for three months, with no obvious response. Samonakis et al (4) reported two cases of spontaneous HCV RNA clearance in longer-term post-transplant liver recipients, who were genotype 1 and 4, respectively. Neither of these patients experienced immunosuppression withdrawal; however, both were known to be diabetic with proteinuria and some renal dysfunction. Both patients were converted to sirolimus due to...

**DISCUSSION**

Recurrence of HCV after liver transplantation is universal and leads to decreased graft and patient survival (7). Antiviral therapy is challenging in this population due to enhanced cytotoxicities, previous treatment failure and the ongoing need for immunosuppression. When a second organ graft is involved, antiviral therapy may be prohibited, given the threat of organ rejection and graft failure secondary to interferon and its immunomodulatory effects (8,9). Spontaneous clearance of HCV after transplant is rare; however, understanding this phenomenon may provide insight into future post-transplant HCV management strategies.

![Figure 1](image-url) Hematoxylin and eosin stain from the third liver biopsy, revealing severe hepatitis, with diffuse lymphocytic infiltration and bridging necrosis (original magnification ×40).

![Figure 2](image-url) Trend of hepatitis C RNA, aminotransaminase profile and immunosuppression from time of renal transplant until 16 months after combined liver and renal retransplant. ALT Alanine aminotransferase; AST Aspartate aminotransferase; Cya Cyclosporine; HCV Hepatitis C virus; LBx Liver biopsy; MMF Mycophenolate mofetil; Tac Tacrolimus.
renal dysfunction. One patient’s viral load was noted to be decreasing before the conversion and the patient had pretreatment exposure to interferon monotherapy. The other recipient had previous exposure to interferon and ribavirin, and was considered a treatment failure. The authors speculated that the HCV RNA clearance may be related to renal impairment and proteinuria. However, it is unclear as to whether the changes in immunosuppression such as decreased calcineurin inhibitor, conversion to sirolimus or the previous interferon exposure, may have contributed to the clearance of HCV RNA. In the present case, the patient had normal renal function after the transplant, no decrease or change in immunosuppression, or any exposure to interferon.

Bhagat et al (6) more recently reported two cases of spontaneous clearance of HCV RNA in liver transplant recipients who were coinfected with HIV before transplantation. One patient was multi-infected with hepatitis B (HBV), HCV and HIV, and had received one month of pegylated interferon and ribavirin therapy. However, it was discontinued due to poor tolerability. The HCV RNA level five days before the transplant was 710 IU/mL. One month after liver transplant, the HCV RNA was negative, and at three months the HBV DNA was also negative. The patient’s medication regimen consisted of corticosteroids, tacrolimus and eventually, mycophenolate mofetil in addition to lamivudine/zidovudine and indinavir. The second patient described had undetectable HCV RNA 30 days after transplant and also received six months of standard interferon and ribavirin therapy, followed by three months of pegylated interferon and ribavirin, with pegylated interferon and ribavirin being discontinued six months before transplant. This patient had detectable HCV RNA (3.26×10^5 IU/mL) two months before transplant. The post-transplant medication regimen included corticosteroids, tacrolimus, mycophenolate-CD3 for an acute rejection episode, as well as lamivudine, stavudine and efavirenz. Bhagat et al (6) speculate that the coexistent HBV infection in the first patient may have induced an immune response which led to clearance of the HCV RNA. Interestingly, both patients were receiving antiretroviral therapy which may have enabled clearance by an as yet undefined mechanism. As well, both patients had acute rejection episodes that may have affected immune modulation leading to clearance. Additionally, these individuals had significant interferon exposure. The present case did not include any of these factors to attribute to the clearance of HCV RNA.

The common factor noted in each previous report is that all patients had previous exposure, albeit sometimes brief, to interferon. Our patient had no previous exposure whatsoever to any interferon product. Her only exposure to an antiviral agent was valganciclovir for CMV prophylaxis during the initial retransplant period.

In the case presented, the patient had a brisk and significant elevation in transaminase levels, peaking at 30 times the upper limit of normal. There was no evidence of vascular abnormalities, exogenous substances or cellular rejection to account for the changes. There were no definite histological or immunological changes to suggest other viral etiologies (eg, CMV, Epstein-Barr virus or HBV) or de novo autoimmune hepatitis. As with previous authors, we can only speculate that the liver enzyme elevation likely represents a ‘clearance phase hepatitis’ perhaps caused by a host immune response or reconstitution, or an as yet undefined immunological phenomenon. The present case demonstrates that despite being significantly immunosuppressed, clearance of HCV RNA can occur spontaneously and is the first reported case of spontaneous clearance of HCV RNA in a multiorgan transplant recipient.

REFERENCES