

Case report

Sustained, spontaneous disappearance of serum HCV-RNA under immunosuppression after liver transplantation for HCV cirrhosis

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Immunosuppression is a main determinant for the increased Hepatitis C Virus (HCV) replication after liver transplantation and the accelerated course of recurrent HCV liver disease. We present two patients both with diabetes, renal dysfunction with proteinuria converted to sirolimus therapy, who cleared serum HCV RNA without antiviral treatment. This is a potentially important observation that should stimulate study into factors that may help viral clearance from blood.

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1. Introduction

Reinfection with HCV is nearly universal after liver transplantation (LT) for HCV cirrhosis with pre transplant viraemia. There is decreased graft and patient survival compared to other aetiologies. HCV reinfection occurs immediately after LT with a rapid increase in HCV-RNA peaking at 1–3 months, and acute lobular hepatitis develops in 60–80% at a median 4–6 months and cirrhosis develops in 20% at 5 years [1]. Spontaneous disappearance of HCV-RNA from serum is very unusual under immunosuppression, the latter a main determinant of accelerated HCV disease [2]. Following withdrawal of immunosuppression there has been only 1 report of spontaneous disappearance of serum HCV-RNA after liver transplantation [3]. We present two patients who had uninterrupted immunosuppression and spontaneously cleared serum HCV-RNA, several years after transplantation, without antiviral therapy.

2. Patients' presentation

The first patient was a forty-eight-year-old male Caucasian with HCV cirrhosis and alcohol abuse pretransplant. In 1998 he had a cadaveric whole liver graft—he had also history of insulin dependent diabetes mellitus (IDDM). The HCV PCR titre was 250,000 iu/ml, genotype was 1a, and he had failed interferon monotherapy. The donor was a 28-year-old male. Initial immunosuppression was tacrolimus 0.1 mg/kg, azathioprine (1 mg/kg) and prednisolone (20 mg tapered and stopped by 2 months). He received three 1 g boluses of methylprednisolone for acute rejection. Surveillance of CMV DNA by PCR was always negative. He had an acute rise in transaminase values at 7 months—confirmed histologically as acute hepatitis C. HCV-RNA titres were persistently between 1.5 and 12×10^6 iu/ml. Subsequent biopsies reconfirmed recurrent HCV infection; AST ranged from 85 to 137 and ALT from 108 to 151 u/L.

At 5 years he had histological features of developing cirrhosis, with an Ishak score: stage 5 and grade 3. Furthermore, the patient had resumed alcohol daily. Viral loads showed a rapid decline without any antiviral treatment for HCV: 60 months, 404,000 iu/ml; 69 months, 80,000 iu/ml; 72 months, 5000 iu/ml and then was undetectable at 75 and 78 months. At 6 years the histology was unchanged but liver function tests became completely

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normal and remained so. During this period increasingly abnormal renal dysfunction (creatinine clearance 36 ml/min, proteinuria 4.6 g/24 h) had developed attributable to tacrolimus toxicity; this was confirmed by renal histology. Sirolimus 2mg daily was started 72 months after transplant and tacrolimus and azathioprine discontinued. Up to the time of this report he had not yet been placed on dialysis.

The second patient was a fifty-five-year-old Egyptian male receiving a cadaveric whole graft for HCV cirrhosis from a 58-year-old female in 2001. His pre transplant viral load was 121,000 iu/ml; HCV genotype was 4, having failed interferon/ribavirin therapy. He had IDDM with diabetic retinopathy. Initial immunosuppression was the same as patient 1 with prednisolone tapered over 4 months. He had 3 rejection episodes (1 moderate, treated as for patient 1–2 mild not treated). At 2 months after LT he had an acute rise in transaminase values consistent with an acute flare of HCV. He developed significant renal impairment (creatinine clearance 40.5 ml/min- proteinuria, 3 g/24 h) due to diabetic glomerulosclerosis confirmed histologically. At 3 months the initial immunosuppression was substituted by sirolimus and mycophenolate mofetil (MMF). At this time AST was 112 u/L, ALT 165 u/L and HCV RNA was positive at 119,000 iu/ml, and then declined progressively becoming undetectable at 15 months. It remained continuously negative up to the current 38 months. He has not required renal dialysis to date. Liver function tests normalised and remained normal. He did not receive antiviral therapy for HCV. At 3 years he had mild fibrosis and mild chronic hepatitis compatible with chronic HCV infection (Ishak score: stage 3, grade 3).

3. Discussion

Although HCV infection always recurs after liver transplantation decreasing graft and patient survival, it is difficult to predict the outcome in individual patients [2]. Sustained spontaneous clearance of serum HCV-RNA by PCR, with normalisation of transaminase values under continued immunosuppression without antiviral treatment is a very rare event. Understanding of this phenomenon may lead to new strategies to ameliorate recurrent HCV disease.

Both our patients had uninterrupted immunosuppression and histologically proven recurrent disease with the most resistant genotypes (1 and 4). Interestingly, both had IDDM with significant proteinuria and renal dysfunction but to date neither have received renal dialysis. Dialysis per se has been related to lowering of HCV titres during the procedure, although rebound of viraemia described [4]. The disappearance of serum HCV RNA in both our patients occurred after substituting tacrolimus and azathioprine with sirolimus in patient 2 but HCV-RNA was already falling in patient 1. Although sirolimus has potent antifungal, antiproliferative and immunosuppressive effects, there are no reports of an

antiviral effect [5]. One patient remained on MMF, which some reports suggest may worsen HCV recurrence. On the other hand, withdrawal of immunosuppression is sometimes a feasible option in managing long term complications of immunosuppressive drugs. Obviously, such an approach could influence the course of the recurrent HCV infection as shown in the reports by Neumann and Somsouk [3,6].

The spontaneous clearance from the blood of HCV post transplant in the two patients described must have an immunological background. Liver damage due to HCV infection occurs in the context of an immune response, in which the host immune response plays a critical role in controlling HCV replication and liver damage [7]. Regulatory T cells consist of phenotypically and functionally distinct CD4⁺ and CD8⁺T cell subsets which are engaged in maintaining self tolerance and in preventing anti non self effector responses that may be harmful to the host; virus specific CD8⁺ in the livers of patients with chronic HCV infection play a cardinal role in antiviral immune defences [8]. After liver transplantation when immunosuppression modifies immune response, viral persistence and progression of recurrent infection may be related to an inappropriate helper T-cell response, whereas a vigorous T-cell response during early stages of re infection could be an important mechanism to limit the allograft injury. Weston et al. [9] recently reported that emergence of regulatory T cell responses (either spontaneously or after antiviral treatment) and their presence, correlated with mild histological recurrence and excellent clinical outcomes. Casanovas-Taltavull et al. [7] showed that patients transplanted for HCV cirrhosis, with sustained virological response after therapy as well as patients who spontaneously cleared HCV RNA post transplant, displayed an immune response despite immunosuppression, that might have contributed to the favourable outcome.

Another important characteristic of the hepatitis C virus is the highly heterogeneous nature of the viral population (complex mixture of related molecular species known as quasispecies), which has a role in the mechanisms of the transmission, persistence and pathogenesis of HCV infection. A recent study has shown that in liver transplant recipients, selection of viral sequences was markedly impaired especially early after transplantation; reduced sequence turnover correlated negatively with the outcome of graft infection [10].

The onset of severe renal dysfunction with proteinuria in the presence of diabetes, coupled with change in sirolimus could have favoured HCV clearance from serum of our patients. Although to date we have been unable to confirm the absence of HCV RNA in liver tissue, the sustained normalisation of transaminase values, with sustained clearance of serum HCV RNA, would be considered a cure in pre transplant patients. The case of these two patients represents one of the few reports of this “spontaneous” occurrence in liver transplantation, without antiviral therapy. The change in immune response which allowed

clearance from blood may be related to the renal dysfunction/proteinuria and a potential antiviral effect of sirolimus, both need further investigation in the context of appropriate trials.

The PCR assay that was originally used was: Amplicor HCV, Roche Diagnostic Systems Inc., Branchburg, NJ and later: Bayer TMA Component System, Berkeley, CA. The viral loads are expressed in iu/ml to maintain homogeneity.

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