Case Report

Undetected chronic hepatitis B virus infection of a vaccinated dialysis patient after liver transplantation

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Introduction

Organ recipients are at risk of chronic hepatitis B infection when organs harbouring the virus are transplanted. The ‘resolved’ hepatitis B virus (HBV) infections of organ donors (those HBsAg negative, anti-HBc positive, anti-HBs positive) are frequently reactivated in immunosuppressed liver transplant recipients [1].

In some cases, vaccination before transplantation does not protect the recipient against the reactivation of HBV received via the graft; in fact, it may set the stage for the emergence of HBsAg escape mutants years after transplantation [2]. The replication of these mutants often remains undetected, because of any one of the following: the clinical course in the majority of infected and immunosuppressed patients is silent, antibody response may be delayed, only a few commercially available HBsAg assays are able to detect vaccination- and immunoglobulin-induced variants [3] and techniques to detect nucleic acid are not routinely used for HBV screening.

Therefore, since renal replacement therapy is frequently needed in the management of liver transplantation, the potential exists to spread mutated HBV strains in the dialysis patient community—unless the high risk population of liver transplant recipients is screened with a nucleic acid technique (and due care is exercised in dialysis settings to prevent cross infection).

We report the case of a dialysis patient who received a liver graft and became infected with an HBV strain bearing a novel mutation from cysteine to tryptophane (sC137W) in the a- determinant of the surface antigen at the amino acid position 137. This mutant virus escapes vaccination-induced immunity and is not detected by a routine HBsAg screening test. Our patient never presented clinical signs of hepatitis, and her HBV infection was only diagnosed 46 months after transplantation.

Case

A 31-year-old woman received a highly urgent liver graft for Wilson’s disease. The post-transplant immunosuppressive protocol included corticoids and tacrolimus. She had high titers of anti-HBs, a result of an HBV vaccination with plasma-derived HBsAg more then 10 years earlier; and these antibodies (>100 IU/l) remained detectable after transplantation, suggesting immunity against HBV infection. She had tested negative for HBsAg and anti-HBc before transplantation.

The organ donor had been HBsAg negative and anti-HBc positive (oral communication); but HBeAg or nucleic acid detection assays had not been performed, and there was no stored serum available for later testing.

The patient had to have renal dialysis because of a hepatorenal syndrome already before transplantation. End stage renal disease finally resulted from acute renal failure with renal cortex necrosis, because of intraoperative cardiac arrest and reanimation. Her post-transplant course was unremarkable and liver function was appropriate.

We report the case of a dialysis patient who received a liver graft and became infected with an HBV strain bearing a novel mutation from cysteine to tryptophane (sC137W) in the a- determinant of the surface antigen at the amino acid position 137. This mutant virus escapes vaccination-induced immunity and is not detected by a routine HBsAg screening test. Our patient never presented clinical signs of hepatitis, and her HBV infection was only diagnosed 46 months after transplantation.

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assay was applied and not the nucleic acid technique. The assay was again negative. Thus, at 46 months after transplantation, alerted by a now-positive HBsAg report from an external laboratory that screened dialysis patients for HBV, we tested her serum and found it positive for HBV DNA, with a viral load of 140 000 copies/ml. (The course of the HBV infection is summarized in Table 1.) At that time no clinical or laboratory signs of hepatitis were observed.

Since the HBsAg was positive despite high anti-HBs titers, the HBV DNA in the blood sample from post-transplantation month 46 was sequenced. An amino acid exchange at position 137 from cysteine to tryptophane in the a-determinant of the HBsAg was verified. One of the HBsAg assays used routinely in our laboratory failed to detect this mutant; the other assay (used also by the external lab), was positive. Since anti-HBc antibodies were absent, the precore/core sequence was also analysed for mutations, but no noteworthy amino acid exchanges could be identified.

Retrospectively, the questionable positive HBV PCR result we had 16 months earlier (190 copies/ml) was already indicating the emergence of this mutant HBV strain. However, both HBsAg assays had been negative, the patient had had high anti-HBs titers, and contamination could not have been definitely ruled out. Later, this borderline result was confirmed by retesting a stored serum sample from post-transplantation month 4, when small amounts of HBV DNA were found—even years before the diagnosis of hepatitis B virus infection.

Because her viral load rose, antiviral therapy with lamivudine was started 3 months after the diagnosis of HBV infection, but the decline of the HBV load was slow. There was no mutation detectable in the polymerase YMDD motif, which would have indicated lamivudine resistance. However, lamivudine was substituted by adefovir after 16 months of therapy, and another 19 months later the HBV load dropped below its detection limit, and seroconversion to anti-HBe could be observed. The patient continues free of symptoms 88 months after transplantation.

**Discussion**

We report the occurrence of an undetected chronic hepatitis B virus infection in a dialysis patient after liver transplantation despite vaccination-induced immunity. The patient remained HBsAg negative for 46 months after transplantation although, retrospectively, her serum had detectable amounts of HBV DNA 4 months post-transplantation.

A recent study by Minuk et al. [4] found that 3.8% of haemodialysis patients have ‘occult’ HBV infections. These infections are characterized by low viral loads (10^3–10^4 copies/ml), the lack of HBsAg and, in minute’s study, by the high prevalence of the known immune escape mutant sG145R. Occult infections have been associated with HBV genotypes, with escape mutations of the HBsAg, which may display limited expression, but most likely have low viral replication rates [5]. Alterations in the HBsAg promotor genes may also influence expression of the surface protein [6].

We can confirm confined viral fitness in our case; in addition, the s137 mutation contributed to the late detection of this chronic HBV infection. Failures to detect mutated HBV strains by routine HBsAg assays are well known, because many of these assays capture antigenic sites, which are located in the immunodominant a-determinant. Alterations in this region do not affect the performance of those HBsAg assays that capture HBsAg outside of the a-determinant.

We believe the source of our patient’s infection to most likely be the liver donor. The risk of getting HBV infection from the organ of a donor with a history of HBV infection is well documented [1], and such infections have already been reported despite the vaccination of the recipients [7,8]. In contrast, HBV vaccination, but also immunoglobulins, are postulated

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### Table 1. Course of HBV infection

<table>
<thead>
<tr>
<th>Time</th>
<th>Before 6 days</th>
<th>4 months</th>
<th>30 months</th>
<th>40 months</th>
<th>46 months</th>
<th>47 months</th>
<th>48 months</th>
<th>51 months</th>
<th>57 months</th>
<th>63 months</th>
<th>70 months</th>
<th>82 months</th>
<th>84 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbsAg</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+(-)^b</td>
<td>(+)^b</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>–</td>
<td>–/+/c</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HBV load (Geqs/ml)</td>
<td>25b</td>
<td>190</td>
<td>140.000</td>
<td>910.000</td>
<td>2.4 x 10^6</td>
<td>86.000</td>
<td>43.000</td>
<td>190.000</td>
<td>25.000</td>
<td>460</td>
<td>Not detectable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbsAg mutation</td>
<td>–</td>
<td>a</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Pre-/core mutation</td>
<td>No</td>
<td>No</td>
<td>C137W</td>
<td>C137W</td>
<td>C137W</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>YMDD mutation</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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</tr>
</tbody>
</table>

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Empty data cells, assay not done.

a Fresh frozen plasma.
c One of two HBsAg assays did not detect the mutated HBsAg.
d Anti-HBe seroconversion.
to provide the immunological pressure for the outgrowth of viruses, that carry mutations in the surface antigen adding more variants to the list of already naturally occurring mutations [9]. Therefore, it should become common knowledge that dialysis patients who may have received liver grafts that could harbour HBV may develop chronic HBV infection, even if vaccinated before surgery. They therefore constitute a high risk population for the spread of mutated HBV strains.

The detection of de novo HBV infections after liver transplantation frequently is further complicated by the absence of clinical symptoms in the immunocompromised host. This is explained by the contribution of HBV-specific T cells to the damage of hepatic tissue. Thus the iatrogenic diminution of cellular immunity leads to the silent clinical courses of HBV infections after liver transplantation [10]. The contribution of HBV-reactive lymphocytes to the pathogenesis of HBV infection is further illustrated by the onset of hepatic symptoms in HBV-infected stem cell transplanted patients. By the time cellular immunity is restored, the patient develops clinical symptoms of hepatitis, though high HBV titers without hepatitis can be found even before that.

This case reveals the pitfalls of serologic HBV diagnosis in immunosuppressed patients. Combined HBeAg and HBsAg testing would have revealed the patient’s HBV infection early after transplantation. Besides, the precore region of HBV is prone to mutations; and the formation of antibodies against HBe limits the diagnostic value of HBeAg testing. Nucleic acid detection assays established for conserved HBV gene regions are, on the other hand, independent of protein expression levels or protein mutations, and deliver the most reliable measure of viral activity. Thus we consider the routine use of techniques of nucleic acid detection to be the best means for unveiling hidden HBV infections (which may not be detected by serologic screening procedures) to avoid the spread of new mutant viruses among the haemodialysis patient community.

Conflict of interest statement. None declared.

References

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