Permanent loss of anti-HBc after reactivation of hepatitis B virus infection in an anti-HBs and anti-HBc-positive patient after allogeneic stem cell transplantation

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Abstract

Background: Reactivation of a hepatitis B virus (HBV) infection after transplantation is associated with a high morbidity and mortality. HBV infections generally result in anti-HBc persisting lifelong.

Case report: A 44-year-old female presented 10 years after allogeneic stem cell transplantation with a chronic hepatitis B. The infection was reactivated from a resolved (anti-HBs and anti-HBc positive) HBV infection acquired some years prior to transplantation. Interestingly, she lost all antibodies to HBV including anti-HBc and is up to now anti-HBc negative. The sequence of the surface and the core gene did not reveal any escape mutations. Thus, the loss of anti-HBc might suggest an immunotolerance of the donor’s immune system against HBcAg.

Conclusion: This data illustrate that an HBV infection might be reactivated despite high anti-HBs levels prior to transplantation. Furthermore, this is the first patient in which a complete loss of anti-HBc could be documented. Moreover, since anti-HBc is often used as a screening marker for HBV it should be kept in mind that anti-HBc negative patients with high viremic HBV infection may occur.

Keywords: Immunosuppression; Bone marrow transplantation; Leukemia; Lamivudine; Adefovir; Tenofovir

1. Introduction

Hepatitis B virus (HBV) causes acute or chronic infections with highly variable disease activity ranging from almost normal liver function to fulminant hepatitis. The manifestations of the disease are mainly caused by the cytotoxic T cell response to HBV infected hepatocytes. In fact, a vigorous T cell response is necessary to resolve the infection either completely or to keep HBV replication at low levels in so-called healthy carriers of the hepatitis B surface antigen (HBsAg). Resolved HBV infection is characterized by the appearance of antibodies against HBsAg (anti-HBs) and disappearance of HBsAg. In contrast, antibodies against the core antigen of HBV (anti-HBc) are also present in the acute or chronic HBV infection. Thus, anti-HBc is a marker of previous or ongoing HBV infection (Kann and Gerlich, 1998). In spite of the clinical resolution of HBV infection and the appearance of anti-HBs antibodies, HBV may persist and replicate at low levels in the liver. Its activity is suppressed by HBV-specific cytotoxic T cells (Rehermann et al., 1996). Thus, anti-HBc and anti-HBs-positive patients
may develop HBV reactivation under conditions of T cell immunosuppression. Patients remain asymptomatic during immunosuppression but severe or even fatal hepatitis may occur after T cell function is reconstituted (Westhoff et al., 2003). Here, we report on an anti-HBc and anti-HBs positive patient who became an asymptomatic highly viremic HBV carrier after allogeneic stem cell transplantation. Importantly, the patient lost all antibodies against HBV, even anti-HBc despite complete immune reconstitution.

2. Case report

A 44-year-old Caucasian female with acute myeloid leukemia received an allogeneic stem cell transplant (June 1994) from an HLA-identical unrelated donor with a single HLA-DR B1 micromismatch. The donor had been negative for all HBV markers (last test 2004). Chimerism analysis revealed a complete donor profile after transplantation. Two years prior to receiving the transplant on multiple occasions the patient had serological markers of HBV compatible with a past infection. All samples were stored and restested using AxSym and Architect assay (Abbott, Wiesbaden, Germany). Prior to transplantation the patient was anti-HBc positive and had 500 IU/L anti-HBs antibodies; HBsAg, HBeAg, anti-Hbe and anti-HBc-IgM were negative, HBV-DNA was negative at a detection limit of 10 IU/mL corresponding to 50 genome equivalents/mL (ge/mL) (Jursch et al., 2002). Twelve weeks after transplantation HBV-DNA became low positive measured by two different in-house PCRs for the X gene (Jursch et al., 2002). The case has three important implications. First, it shows that high levels of anti-HBs antibodies in an HBV negative individual do not necessarily protect against reactivation of HBV. Recently, HBV reactivation has been reported in 2/228 HBsAg negative kidney transplant recipients (Berger et al., 2005). Similarly, HBV reactivation was observed in an anti-HBs and anti-HBc-positive lymphoma patient following Rituximab therapy (Westhoff et al., 2003). We have seen even HBV reactivation in an anti-HBs-positive, anti-HBc-negative lymphoma patient (Awerkiew et al., 2006). These cases point to the need to monitor HBsAg-negative patients with any HBV antibodies for HBV reactivation, after initiating immunosuppressive therapy using HBV-DNA as the

3. Discussion

The case has three important implications. First, it shows that high levels of anti-HBs antibodies in an HBV negative individual do not necessarily protect against reactivation of HBV. Recently, HBV reactivation has been reported in 2/228 HBsAg negative kidney transplant recipients (Berger et al., 2005). Similarly, HBV reactivation was observed in an anti-HBs and anti-HBc-positive lymphoma patient following Rituximab therapy (Westhoff et al., 2003). We have seen even HBV reactivation in an anti-HBs-positive, anti-HBc-negative lymphoma patient (Awerkiew et al., 2006). These cases point to the need to monitor HBsAg-negative patients with any HBV antibodies for HBV reactivation, after initiating immunosuppressive therapy using HBV-DNA as the...
earliest marker of reactivation (Kann and Gerlich, 1998). Early recognition of HBV reactivation is essential, since preemptive antiviral treatment with lamivudine is effective in alleviating or suppressing HBV replication and fulminant hepatitis (Lau et al., 2003; Shibole et al., 2002). Interestingly, reactivation of HBV is preventable by transplanting stem cells from vaccinated or immune donors (Ilan et al., 2000). HBV reactivation is a known problem in HBsAg positive carriers, but as we showed here, also in seemingly immune patients with past infections.

Second, this is the first report of a permanent loss of anti-HBc despite high viral replication after allogenic stem cell transplantation. HBV reactivation under allogenic stem cell transplantation is immunologically complex: the B and T lymphocytes of the recipient were completely depleted or rendered non-reactive following myeloablation. As a consequence the recipient’s B cell clones specific for anti-HBc were deleted. In all likelihood anti-HBc and anti-HBs detectable during the first month after transplantation resulted from antibodies produced before transplantation or from passively administrated antibodies in blood products. After transplantation, the HBV naïve donor immune system has resumed its function in the recipient, however, it did obviously not recognize the HBV antigens suggesting immunotolerance (although antibodies to other antigens such as herpes simplex virus Epstein-Barr virus a.s.o. have been detectable). Persistently infected HBV carriers without anti-HBc are very rare, but HBV-naïve patients may become persistently infected and may not develop anti-HBc antibodies, if they are infected with HBV while on chemotherapy (Repp et al., 1993) or occasionally after perinatal infection (Chan et al., 1994; Kagimoto et al., 1991; Lapercle et al., 2001; Lee et al., 1989; Ni et al., 1993). In fact, the reconstitution of the immune system after stem cell transplantation as shown here partially resembles the B cell ontogeny (Storck et al., 1993, 1995) and thus may resemble to perinatal infection.

Third, the role of anti-HBc antibodies as a screening parameter has to be questioned. Although there is no doubt, that anti-HBc is an important and excellent screening marker, that anti-HBc is an important and excellent screening marker, parameter has to be questioned. Although there is no doubt, that anti-HBc is an important and excellent screening marker, that anti-HBc is an important and excellent screening marker, it is not clear whether anti-HBc negative patients may become persistently infected and may not develop anti-HBc antibodies, if they are infected with HBV while on chemotherapy (Repp et al., 1993) or occasionally after perinatal infection (Chan et al., 1994; Kagimoto et al., 1991; Lapercle et al., 2001; Lee et al., 1989; Ni et al., 1993). In fact, the reconstitution of the immune system after stem cell transplantation as shown here partially resembles the B cell ontogeny (Storck et al., 1993, 1995) and thus may resemble to perinatal infection.

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