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CASE REPORT

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Successful pregnancy in a liver transplant recipient treated with lamivudine for de novo hepatitis B in the graft

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Abstract Pregnancy is often successful after liver transplantation, despite the potentially toxic effects of immunosuppressive drug therapy. Liver transplant recipients with recurrent hepatitis C or hepatitis B nonetheless appear to be at risk of a worse graft function in the event of pregnancy, and antiviral drugs are generally contraindicated in pregnancy because of their teratogenic effects. A 33-year-old woman had undergone liver transplantation for Caroli's disease 6 years previously. Two years later the patient experienced de novo HBV hepatitis. Lamivudine treatment (100 mg/day) was started and clearance of HBsAg was documented 1 year later. Four years after starting antiviral treatment the patient became pregnant, despite of the risk of teratogenic effects; lamivudine, cyclosporine and azathioprine were not discontinued for risk of break-through hepatitis and acute or chronic rejection. The course of gestation was uneventful and caesarean section was performed after 36 weeks. The newborn infant was a healthy male weighing 3,080 g and measuring 50 cm.

Keywords Pregnancy · Liver transplantation · HBV hepatitis · Lamivudine · Immunosuppressant drugs

Introduction

With increasing numbers of patients and improving survival rates, liver transplant centres are often confronted with the problem of pregnancy following liver transplantation. Nearly 100% of female patients of reproductive age with end-stage liver disease regain their reproductive function within a year of liver transplantation [1, 2]. As a consequence, an increasing number of these women would like to have children.

Pregnancy is often successful after liver transplantation and does not appear to induce major graft dysfunction, providing the transplanted organ's function is stable prior to pregnancy [3]. It must be regarded as high-risk, however, given the greater risk of hypertension and pre-eclampsia, retardation of intrauterine growth and prematurity, mainly due to the effects of immunosuppressive drugs on maternal and foetal health [4, 5, 6, 7, 8]. In the setting of recurrent liver disease, e.g. recurrent hepatitis B or hepatitis C, pregnancy may negatively influence graft function. Hepatitis B infection that develops in transplant patients with a previously negative HBV serology (de novo hepatitis B) is an emerging problem and a potential cause of liver dysfunction [9, 10]. Lamivudine, a nucleoside analogue, is a potent antiviral agent that is effective for de novo hep-

atitis B following liver transplantation [11, 12]. At present, little is known about its safety during pregnancy and its possible interactions with immunosuppressants.

This report describes a patient who underwent liver transplantation for Caroli's disease, developed de novo hepatitis B and had an uneventful pregnancy while on immunosuppression and lamivudine therapy.

Case report

The patient was a 33-year-old woman who had undergone orthotopic liver transplantation for Caroli's disease 6 years previously. She was anti-HBc negative at the time of transplantation. The donor's serum screening at the time of transplantation revealed that anti-HCV and anti-HIV antibodies were negative as well as HBsAg, whereas anti-HBcore and HBs antibodies were not available. Immediately after liver transplantation the immunosuppression was based on cyclosporine (675 mg/day), maintaining the serum range between 250 and 300 μg/l, and prednisone (20 mg/day).

Eight months after transplantation the cyclosporine dosage was reduced to 200 mg/day, maintaining the serum level between 100 μg/l and 150 μg/l because of the onset of mild renal insufficiency (urea 10.9 mmol/l, creatinine 123 μmol/l), and azathioprine (50 mg/day) was added.

A year after transplantation the patient was admitted to hospital for the routine follow-up, which unexpectedly revealed elevated aminotransferases (AST 353 U/l, ALT 521 U/l) (Fig. 1). Serological tests for viral hepatitis documented qualitative HBV DNA on in-house PCR testing positivity, HBsAg, qualitative anti-HBc IgM and anti-HBe positivity. Anti-HCV and HIV were negative. The patient informed the medical staff that her current partner was HBsAg positive but no more details on his virological status were available. Liver biopsy was performed and showed mild fibrosis, lymphocyte infiltration of the portal tract and activation of lobular Kuppfer cells. Immunohistochemistry for HBsAg and HBcAg on the liver specimen was negative.

At that time, the donor's stocked blood was analysed, confirming the HBsAg negativity, but anti-HBs and anti-HBc positivity. The donor's serum was HBsAg negative, anti-HBs positive and anti-HBc positive.

Two months later the liver enzymes had returned to normal and remained so at all subsequent check-ups performed every 2 months. HBV DNA was negative on in-house PCR testing, HBsAg was positive, and no antiviral treatment was given at that point.

Two years after transplantation the transaminases were mildly altered (AST 44 U/l, ALT 56 U/l), HBV DNA on molecular hybridization testing was present in the serum (10,330 pg/ml) and anti-HBc IgM was negative. Histological examination of the liver biopsy showed marked portal fibrosis with piecemeal necrosis; immunohistochemistry revealed the presence of HBsAg (focal type) and HBcAg in the nuclei (diffuse type) of the liver cytoplasm (Fig. 2).

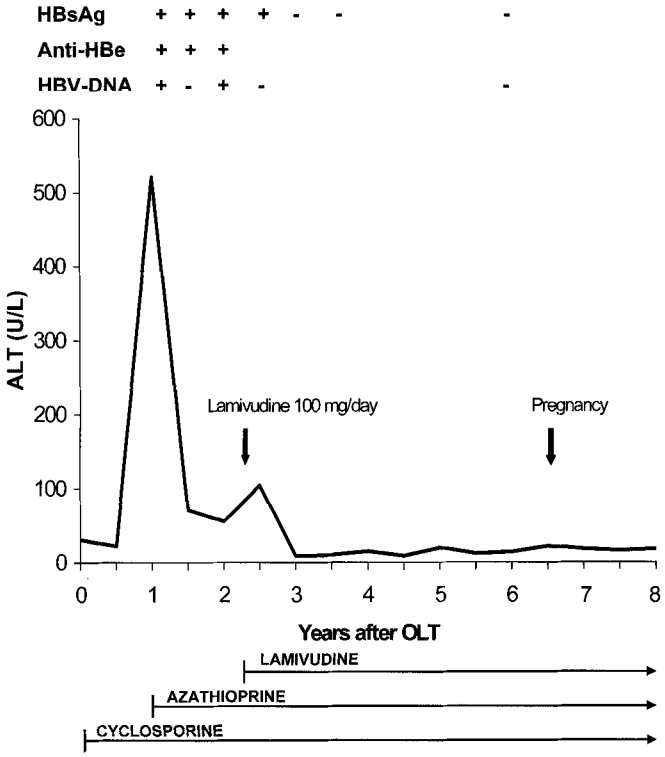

Fig. 1 ALT serum levels, HBV serology and immunosuppression regimen during the 8-year follow-up after liver transplantation

We started lamivudine therapy (100 mg/day), without changing the immunosuppressive regimen, maintaining a serum range between 100 μg/l and 150 μg/l (cyclosporine 175 mg/day and azathioprine 50 mg/day).

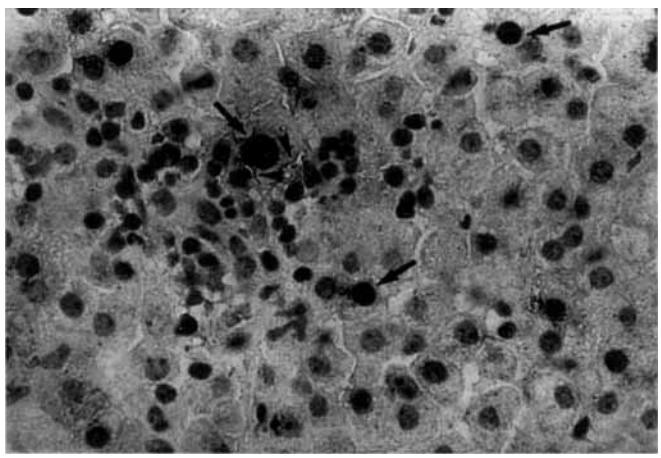

Fig. 2 HBcore immunostaining on liver biopsy. *Arrows* show hepatocytes positive for HBcAg expression

Three months later, HBsAg was still positive, but HBV DNA on in-house PCR testing was negative; anti-HBc IgG and anti-HBe were positive.

Three years after liver transplantation, sero-conversion from HBsAg to anti-HBs was observed (HBsAb titre 50 mU/ml), with normal liver function and mild renal insufficiency (urea 66 mg/dl; creatinine 1.37 mg/dl).

Four years after liver transplantation, the transaminases were still normal, HBsAg was negative, anti-HBs titre was < 10 mU/ml, anti-HBc was positive, anti-HBc IgM negative. Liver biopsy histology revealed mild portal inflammation and paucity of biliary ducts [13]. Immunohistochemistry for HBsAg and HBcAg on the liver specimen was negative.

The patient became pregnant in January 2002, approximately 6 years after liver transplantation. At the beginning of the pregnancy, serological screening was performed for toxoplasmosis, rubeola, cytomegalovirus, herpes simplex virus and hepatitis A, B and C; vaginal smears were also obtained. HBV DNA on in-house PCR testing and HBsAg were negative, and the anti-HBs titre was low (< 10 mU/ml).

The cyclosporine dosage was adjusted to maintain desired serum levels of between 50 μg/l and 100 μg/l (125 mg/day). Lamivudine and azathioprine were not discontinued. Liver and renal function tests were performed twice a month during the first 6 months and then weekly until the end of gestation. Obstetric ultrasound was performed at weeks 12, 21, 28 and 32 of gestation to monitor foetal growth. Caesarean section was performed, after 36 weeks of uncomplicated gestation, due to mild cholestasis and pruritus. The newborn infant was a healthy male weighing 3,080 g and measuring 50 cm; HBsAg and anti-HBs were negative. Immediately after the birth, he received i.v. passive anti-HBs immunoprophylaxis and then was vaccinated at 2 months of age. The mother was advised against breastfeeding because of the passage of cyclosporine, azathioprine and lamivudine in the milk. To date, at 24 months both the boy and the mother are well.

Discussion

De novo HBV infection has been recognized as an emerging problem and a possible cause of liver dysfunction [9, 10]. The potential sources of the infection include transfused blood products, occult donor-organ infection and occult pretransplant infection in the recipient. Blood products are occasionally able to transmit HBV despite negative serological testing [14] or past HBV infection [15, 16], with an estimated risk for the latter of 33%–78% [17, 18, 19, 20]. In the present case two possible sources of HBV infection were identified: sexual transmission from the HBsAg-positive partner or occult transmission from the HBcAb-positive liver donor.

De novo HBV hepatitis after liver transplantation was believed to follow a rather benign course compared to the aggressive evolution of recurrent HBV hepatitis. Liver transplant recipients rarely clear HBsAg, however, and viraemia persists at high levels, with potential graft damage [21].

In our patient, the liver disease took a relatively mild course, with transaminases returning to normal 2 months after the initial flare. When histology revealed marked portal fibrosis, piecemeal necrosis, cytoplasmic and nuclear HBV positivity, and HBV DNA was detected in the serum 2 years after transplantation, lamivudine therapy was started, since it has proved useful in preventing graft re-infection when administered before and/or after liver transplantation [11, 12].

At the time of the pregnancy, the patient's virological status was HBV DNA negative on in-house PCR testing with anti-HBs at a low titre. We considered an accelerated and intensive course of vaccination, to achieve protective titres of anti-HBs and safely suspend lamivudine for the first 6 months of the pregnancy, but there was concern that fatal hepatitis might develop after suspension of the lamivudine [22]. A case of HBV re-infection following lamivudine withdrawal has been reported in a patient with HBsAg loss after liver transplantation for HBV fulminant liver failure, suggesting that lamivudine prophylaxis should have been continued after HBsAg loss [23]. Moreover, HBV reactivation is frequently induced by medical treatments such as anti-rejection drugs and corticosteroids [24, 25].

In the last 4 weeks of pregnancy, lamivudine may improve the efficacy of passive–active vaccination to prevent perinatal transmission in highly viraemic women [24], but it has been demonstrated that it passes freely through the placenta [25]. No teratogenicity was recorded in rats and rabbits given 60-times the human dose, but such studies may be poor predictors of its embryo-lethal or teratogenic potential in humans. Some data are available on the teratogenic risk of lamivudine in combination with anti-retroviral drugs used for prophylaxis against mother–child HIV transmission and suggest that it is safe [26], but in a French study, eight cases of mitochondrial damage were diagnosed in children exposed to a zidovudine-plus-lamivudine treatment for HIV-positive mothers [27].

Immunosuppressants also cross the placenta. Cyclosporine is not associated with any increased risk of foetal malformations but carries a small-to-moderate risk of foetal growth retardation [28]. Azathioprine has demonstrated teratogenicity in animal studies, with a high incidence of embryonic resorption and/or foetal anomalies, but clinical data indicate that the teratogenic risk to a child born after in utero exposure to azathioprine is small [29]. Surveys and literature reviews show a 40%–

50% incidence of prematurity and an approximately 20% incidence of intrauterine growth retardation with azathioprine. A higher rate of low birth weights has been seen to coincide with cyclosporine-based regimens [30]. Lamivudine and immunosuppressants are excreted in breast milk, where they can reach much the same concentrations as in the maternal blood [26, 31]. The potential effect of such concentrations is not known at present, and the current tendency is to advise against breastfeeding until more clinical and epidemiological data are available. Some authors say, however, that the benefits of breastfeeding, e.g. protection against necrotizing enterocolitis, protection against infection, improved retinal function and cognitive performance, and lower risk of food allergies later in life, might outweigh any risks, especially in low birth-weight and pre-term infants [32, 33].

The long-term follow-up of infants exposed to immunosuppressants and lamivudine in utero is still limited, and more studies are needed to determine their possible interactions and long-term effects, but, from the present experience, it seems to be safe enough.

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