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CASE REPORT | LIVER

De novo Hepatitis B Virus Infection in a Post-transplant Patient Causing Stage 4 Cirrhosis Necessitating Retransplant

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ABSTRACT

Hepatitis B virus (HBV) is a common cause of liver cirrhosis worldwide, almost always as a result of HBV infection at birth or a very young age. HBV very rarely causes cirrhosis when contracted as an adult. Notably, the risk of HBV progression to cirrhosis is higher in immunocompromised patients, such as liver transplant patients, although it is still quite rare. We present a liver-transplant patient who acquired a de novo HBV infection and developed HBV-associated cirrhosis requiring retransplantation.

KEYWORDS: HBV cirrhosis; de novo HBV infection; liver retransplantation

INTRODUCTION

Hepatitis B virus (HBV) remains one of the most common causes of liver cirrhosis worldwide. With globally low HBV vaccination rates and globally high rates of vertical transmission, HBV-related cirrhosis typically occurs as a long-term sequela in patients who catch the disease at a very young age.[1] By contrast, in adult-aged immunocompetent patients who acquire a de novo HBV infection, the disease either clears or progresses to a state of chronic HBV infection but will very rarely progress to stage 4/4 cirrhosis.[2] In addition, even in liver transplant (LT) recipients who develop an HBV infection, the disease may advance rapidly to fulminant icteric HBV hepatitis and acute liver failure but will rarely lead to cirrhosis.[3] In the below case report, we present a patient who in the post-LT setting acquired a de novo HBV infection, which lead to biopsy-proven HBV-associated stage 4 cirrhosis, necessitating retransplantation.

CASE REPORT

The patient was originally transplanted 5 years before this current presentation, at which time both the donor and the recipient were HBV surface antigen, HBV surface antibody, HBV core antibody, and HBV DNA negative. The patient's post-transplant course was complicated by 4 separate instances of acute cellular rejection (RAI 4–5), all of which were treated with appropriate immunosuppressive agents with subsequent resolution. The patient's most recent immunosuppression regimen before this presentation was tacrolimus 2 mg twice daily (BID) and mycophenolate mofetil 500 mg BID. The patient endorsed 1 risky sexual encounter 6 months before his presentation and denied any other risk factors of HBV acquisition. Five years post-transplant, the patient presented with elevated liver enzymes (aspartate aminotransferase 1,089, alanine aminotransferase 549, total bilirubin 14.1, International Normalized Ratio, Rejection Activity Index 1.96) found on routine outpatient laboratory work and subsequently found to have new HBV viremia (genotype A) with 16 million copies. Liver biopsy interestingly showed stage 4/4 cirrhosis, with histopathology showing active HBV as the etiology of the cirrhosis (Figures 1 and 2). The patient then went on to develop esophageal variceal bleeding and hepatorenal syndrome, and was relisted for transplant at a Model for End-Stage Liver Disease 3.0 of 39. The patient was retransplanted approximately 2 weeks after presentation and was administered HBV immunoglobulin for 7 days post-transplant. The

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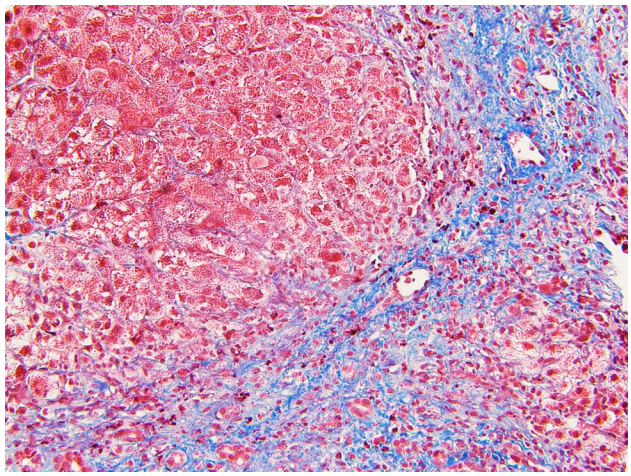

Figure 1. Trichrome stain liver biopsy showing regenerative hepatic nodules with broad band bridging fibrosis, grade 4/4 cirrhosis, 200×.

patient's post-retransplant HBV treatment regimen consisted of 6 months of dual-therapy with entecavir and tenofovir alafenamide, and the patient remains currently on entecavir monotherapy nearly 16 months post retransplant. The retransplant was successful and surveillance HBV studies, initially drawn weekly after transplant for 1 month and then approximately monthly thereafter, have shown dramatic reduction of HBV viral load.

DISCUSSION

HBV is a common cause of cirrhosis worldwide; however, almost all cases of HBV cirrhosis occur as a result of vertical transmission. As discussed above, even most immunocompromised patients who acquire de novo HBV do not progress to cirrhosis. In a recent large-scale retrospective German study, out of a population of 2,686 transplant patients, only 46 patients (1.7%) were found to have a de novo HBV infection.[4] These patients developed varying degrees of fibrosis with the vast majority of patients with only mild inflammation or stage 0–2 fibrosis, and just 2 cases of cirrhosis.[4] These patients were treated with varying combinations of nucleoside analogs, and 32 of 46 (70%) of them were able to clear the HBV DNA with survival rates comparable with the remainder of their non-HBV-infected LT recipient cohort.[4] Of the 14 of 46 patients (30%) who did not clear the HBV DNA, overall morbidity and mortality was worse, with 4 liver-associated deaths and 2 requiring retransplant.[4] One 1997 study of 570 post-transplant patients did find 4 patients to have HBV cirrhosis (0.7%), although in all of those patients either the donor or the recipient was HBV surface antigen positive or HBV DNA positive.[5] A more recent study of 159 post-transplant patients found 17 cases of de novo HBV infection, a minority of whom progressed to stage 2 fibrosis but none to stage 4/4 cirrhosis.[6] Elsewhere in the literature, there are smaller case reports or case-series of de novo HBV cirrhosis in LT patients, none of which show progression of de novo HBV post-transplant to HBV cirrhosis.[7–10] A common theme in these studies is that the presumed source of de novo HBV infection is from the donor liver itself or from exposure to known risk factors of HBV (or from a reactivation of the host HBV virus; however, this would not represent a de novo infection).[7–10] The natural history of HBV infection post-transplant in the above studies was most commonly a chronic HBV infection, a small minority of cases with some level of fibrosis, and only a handful of cases of cirrhosis.[4,7–10] Typically, factors associated with more severe HBV infection in the post-transplant setting include increased age of the recipient, level of active inflammation, and HBV core antigen expression in the native livers.[11] Our patient, a 43-year-old HBV core-negative man did, indeed, have severe inflammation at the time of presentation (AST 1,089, ALT 549), along with HBV genotype A infection, which in particular can lead to more severe complications compared with other genotypes.[12] We posit the above factors, in addition to his repeated bouts of acute cellular rejection with need for increased immunosuppression, predisposed him to more severe HBV infection. Patients with post-transplant HBV infection do generally have worse morbidity and mortality compared with the rest of their cohorts; however, with appropriate early treatment, this can largely be mitigated.[13,14] De novo HBV in the post-transplant setting is rare, but treatment consists of nucleoside analogs such as entecavir or tenofovir alafenamide, usually indefinitely, and with good results.[15] The addition of HBV immunoglobulin at the time of initial treatment did not affect mortality.[15] This case report represents a unique manifestation of de novo HBV-related cirrhosis in the post-transplant patient and a reminder of the importance of close follow-up for this population, including serial blood work monitoring and counseling patients against high-risk behaviors.

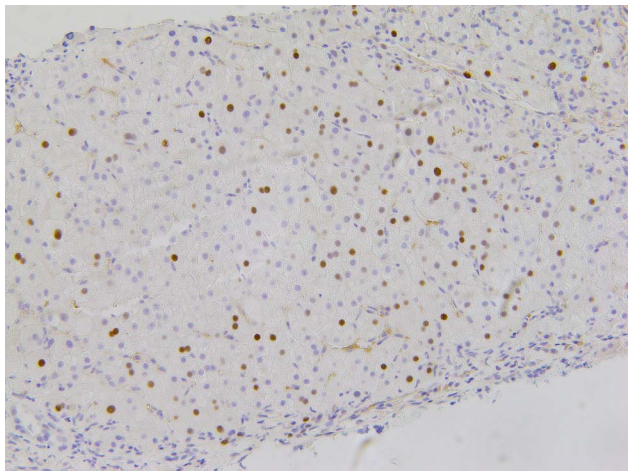

Figure 2. Immunohistochemical stain liver biopsy demonstrating the presence of hepatitis B core antigen in hepatocyte nuclei on liver biopsy, 200×.

DISCLOSURES

Author contributions: D. Halegoua-Demarzio is the article guarantor.

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