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Single Case

Severe de novo Hepatitis B Recovered from Late-Onset Liver Insufficiency with Prolonged Ascites and Hypoalbuminemia due to Hepatitis B Virus Genotype Bj with Precore Mutation

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Keywords
De novo hepatitis B · Reactivation · Precore mutant · Immunosuppression · Entecavir

Abstract
De novo hepatitis B is associated with a high risk of hepatic failure often resulting in fatal fulminant hepatitis even when nucleotide analogues are administered. A 77-year-old female developed de novo hepatitis B after R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) treatment for diffuse large B-cell lymphoma. Hepatitis B virus (HBV) isolated from the patient was of genotype Bj, with a precore mutation (G1896A) exhibiting an extremely high viral load at the onset of hepatitis. She showed markedly high levels of transaminase with mild jaundice on admission and rapid decrease of prothrombin activity

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after admission. Although acute liver failure was averted by the administration of entecavir and corticosteroid pulse therapy, liver volume decreased to 860 ml, and marked hypoalbuminemia accompanying massive ascites occurred 2 months after the onset of hepatitis and persisted for 3 months with high levels of HBV DNA and mild abnormal alanine aminotransferase levels. Frequent infusions of albumin solution, nutrition support, and alleviation therapy showed limited effect. However, overall improvement along with HBV DNA reduction was observed after increasing the dose of entecavir and completion of prednisolone that was administered with a minimum dose for adrenal insufficiency. An immediate and sufficient suppression of virus replication with potent antiviral therapy is critical, particularly in patients infected with HBV precore mutation (G1896A) and/or Bj genotype, which may have a high viral replication and direct hepatocellular damage.

Introduction

Reactivation of hepatitis B virus (HBV) replication is a well-recognized complication in patients with chronic HBV infection receiving cytotoxic or immunosuppressive therapy. It is characterized by the sudden increase or reappearance of HBV DNA in the serum of a patient with prior evidence of resolved or inactive HBV infection [1]. It is more frequent in patients with chronic HBV infection than in patients who have resolved the infection, as indicated by the presence of anti-HBc and/or anti-HBs, known as 'de novo hepatitis B' [2]. However, recently, the incidence of de novo hepatitis B is notably increasing with the introduction of molecular targeted drugs [3] and is of major concern because of its increasing morbidity and higher mortality rate [4, 5]. Although guidelines recommend the administration of a nucleos(t)ide analogue (NA) for the prophylaxis of HBV reactivation [6, 7], management after HBV reactivation is not well described because the clinical course varies. However, the prognosis of patients who develop hepatitis after chemotherapy including rituximab has shown to have high mortality, even when NA was administered [8]; recently, the fulminant outcome of HBV reactivation associated with genotype Bj with precore mutation (PCm) (G1896A) has been reported [9].

We describe a case of de novo hepatitis B caused by genotype Bj with PCm after R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (PSL)] treatment with late occurrence hepatic insufficiency showing prolonged ascites and hypoalbuminemia, and overall improvement along with reduction of HBV replication, suggesting the importance of immediate and sufficient viral suppression for the treatment of the disease.

Case Report

A 77-year-old female was treated with six courses of R-CHOP for stage 1a diffuse large B-cell lymphoma (DLBCL). Prior to chemotherapy, the patient had no history of blood transfusions or surgery, except for tonsillectomy due to DLBCL. The patient had hypertension and hyperlipidemia, which were treated with amlodipine besylate, candesartan cilexetil, hydrochlorothiazide, and pravastatin sodium. Before chemotherapy, her serum was negative for hepatitis B surface antigen (HBsAg) and she had a normal liver function test with a Fibrosis-4 score of 1.59, but anti-HBc and anti-HBs were not evaluated. Four weeks after the completion of R-CHOP, she presented to our hospital with general fatigue and a loss of appetite. The patient weighed 64.0 kg, and her height was 148 cm. Mild jaundice was noted on physical

examination, but an abdominal computed tomography (CT) revealed no abnormal findings in the hepatobiliary system. Laboratory examination revealed marked hepatocellular injury (table 1). HBsAg changed to positive and HBV DNA load exhibited ≥9.0 log copies/ml; therefore, the patient was diagnosed with de novo hepatitis B. The patient was immediately admitted, and entecavir (ETV) was administered at a dose of 1.0 mg on day 1 followed by 0.5 mg/day. On day 3, her serum transaminase levels appeared almost unchanged, total bilirubin slightly increased to 4.3 mg/dl, and prothrombin (PT) activity decreased from 80 to 71% in 1 day. Therefore, we commenced corticosteroid (CS) pulse therapy as follows: 1,000 mg/day of methylprednisolone (MPSL) was administered for 3 days and was reduced to half doses every 2 days. After the administration of 125 mg/day of MPSL for 2 days, 60 mg/day of PSL was administered for 4 days and then reduced by 5 mg every 5 days. PT activity recovered to >80% and alanine aminotransferase (ALT) levels decreased to 980 IU/l on day 5; however, serum albumin levels decreased to 2.8 g/dl (fig. 1). HBV DNA load amounted to 8.8 log copies/ml on day 7 and the decrease in load was very slow, amounting to 8.5 log copies/ml on day 14 and 7.9 log copies/ml on day 29. Hepatic volume measured by CT decreased from 1,360 ml on day 1, to 1,100 ml on day 18, and to 990 ml on day 41. On day 46, HBV DNA remained at 7.6 log copies/ml and serum albumin decreased to 2.5 g/dl, although the PT activity was 100%. We initiated the administration of branched chain amino acid (BCAA) granules (1.2 g/day), and 100 ml of 25% albumin solution was administered. However, the increase in serum albumin levels was only minor. On day 60, with ALT levels decreasing to <100 IU/l, PSL was reduced to 5 mg/day, but the patient complained of a sense of fullness. A CT of the abdomen revealed marked ascites and a decreased hepatic volume of 860 ml (fig. 2). Administration of BCAA was changed from granules to a BCAA-enriched nutrient mixture, containing 1.7 g of BCAA and 40.5 g of protein/day, and the administration of diuretics was started. However, the patient required frequent infusions of albumin solution to maintain serum albumin levels >2.5 g/dl. On day 68, PSL dosage was reduced to 2.5 mg/day, and the administration of ursodeoxycholic acid (UDCA) and intravenous glycyrrhizin was initiated. However, the patient complained of weakness and anorexia 3 days later. Her urine 17-ketogenic steroids showed markedly low levels (0.8 mg/day; standard value: 3.55–11.2 mg/day), indicating adrenal insufficiency. PSL dosage was increased to 15 mg/day, leading to a gradual alleviation of weakness and anorexia, and PSL was then reduced very slowly with a maintenance dosage of 5 mg/day since day 102. HBV DNA decreased to 5.4 log copies/ml on day 116, after which the decrease paused and the levels remained unchanged after 50 days, although ETV-resistant substitutions were not detected. However, serum albumin levels barely increased to 3.1 g/dl, hepatic volume recovered to 1,270 ml, ascites disappeared on day 114, and PSL was decreased gradually from 5 mg/day and discontinued after the administration of 2 mg/day during the last 2 weeks. Eight days after the cessation of PSL, ALT levels, having fluctuated within 55 IU/l for 60 days prior to this, now increased to 116 IU/l, and the serum albumin levels again decreased to 2.7 g/dl. We increased the dosage of ETV from 0.5 to 1.0 mg/day. ALT further increased to 260 IU/l, and the serum albumin levels decreased to 2.5 g/dl, resulting in pleural effusion. However, HBV DNA decreased from 5.5 to 4.5 log copies/ml, ALT decreased dramatically to 36 IU/l 2 weeks later, and serum albumin levels increased to 3.1 g/dl 3 weeks later. UDCA and glycyrrhizin were discontinued on day 186 with the stabilization of ALT levels <30 IU/l. Pleural effusion disappeared on day 214, and the patient was discharged.

Discussion

We present a patient with severe de novo hepatitis B recovered from liver insufficiency. This patient indicated the importance of immediate and sufficient suppression of virus replication of the disease, and suggested direct cytopathic effect of HBV under immune suppressive conditions.

De novo hepatitis B is associated with a high risk of hepatic failure, often resulting in a fatal fulminant hepatitis despite the administration of NA [5, 10]. According to a Japanese nationwide survey, all patients with acute liver failure associated with de novo hepatitis B had either a subacute type of fulminant hepatitis or late-onset hepatic failure [11], indicating that the clinical signs of liver failure may appear at a later stage after the onset of the disease. This patient developed neither marked coagulopathy nor encephalopathy; however, she showed a continuous decrease of hepatic volume and late occurrence of ascites, both of which are considered to be poor prognostic signs in patients with acute liver failure [12, 13]. Furthermore, a decline of the liver volume below 1,000 ml is reported to be less recoverable by medical management [14]. Although the patient did not develop acute liver failure, she suffered from prolonged ascites. The hepatic injury during acute and chronic hepatitis B has been considered to be caused by the host's immune response against infected hepatocytes [15]. Therefore, it is reasonable to treat severe hepatitis B with CS to suppress immune response [16]. Fujiwara et al. [17] reported that among patients with a severe acute exacerbation of chronic HBV, which is known to sometimes progress to hepatic failure, treated with CS in combination with NA, a decline of HBV DNA during the first 2 and 4 weeks was significant in recovered patients (mean: 2.0 and 3.0 log copies/ml, respectively). In this patient, a decrease in ALT was achieved by PSL with ETV therapy. However, the HBV DNA level before treatment was extremely high (≥9.0 log/ml) and the decline was slow, showing 7.9 log copies/ml on day 29, and had stopped at the level of >5.0 log copies/ml for 50 days although no drug resistance was detected. The ascites with lower serum albumin levels with mild ALT abnormality persisted until 5 months after the onset of the disease. These concurrently improved after the discontinuation of PSL and increasing ETV from 0.5 to 1.0 mg/day. Retrospectively, this change appeared essential due to a reduction in virus replication by immune restoration and by the dose increasing effect of ETV [18], and indicates the importance of sufficient suppression of virus replication.

At the same time, this clinical course suggests a direct cytopathic effect of HBV. Recently, several data supporting the cytopathic effect of HBV replication have been reported [19], and similar correlation between serum albumin levels and HBV DNA levels but not ALT levels was also reported [20]. Foo et al. [21] demonstrated accumulation of HBV large surface protein-induced hepatocyte apoptosis in cultured hepatoma cells, and Meuleman et al. [22] reported a direct cytopathic effect in hepatocytes that contained extremely high amounts of HBV genomes and proteins using severe combined immune deficient mice harboring human liver cells. Clinically, fibrosing cholestatic hepatitis (FCH), which is characterized by rapid and progressive liver dysfunction with increased viral replication and high intrahepatic expression of virus proteins, occurs in immunosuppressed patients and is considered to be a cytopathic form of the virus [23]. Although our patient was not cholestatic, functional failure with high viral replication and modest increase of transaminases is similar to the clinical features of FCH. Furthermore, HBV PCm has been reported to be associated with patients with FCH [24], and HBV Bj genotype with PCm, which was present in this patient and in the case of Sugauchi et al. [9], is reported to have a high viral replication and induces a direct cytopathic effect in immune suppressive conditions [25]. In this patient, ALT flare occurred

after discontinuation of PSL, indicating the recovery from immune suppression state. Thus, we considered that liver injury in acute phase would be mainly caused by enhanced immune response; however, in later stages it would be due to direct hepatocellular damage of the virus with high replication.

In conclusion, the immediate and sufficient suppression of virus replication with potent antiviral treatment as well as control of enhanced host immune response is important in severe de novo hepatitis B, particularly in patients infected with HBV PCm and/or Bj genotype, who may have associated high viral replication and direct hepatocellular damage.

Statement of Ethics

Informed consent was obtained from the patient prior to the publication of this study.

Disclosure Statement

The authors have no competing interest to declare.

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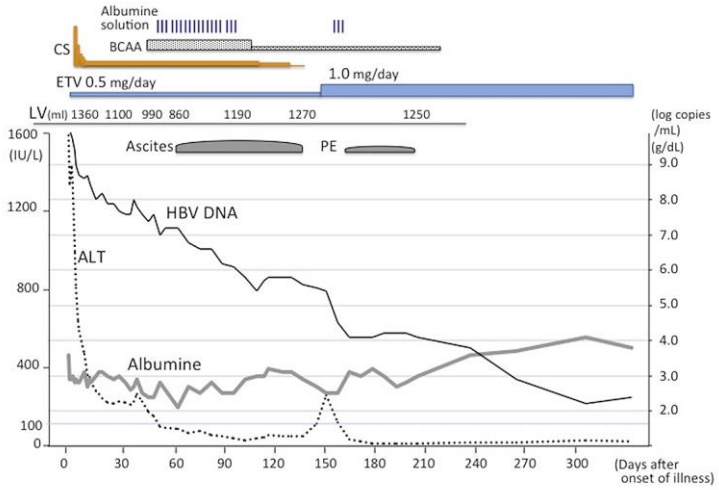

Fig. 1. Clinical course of the patient. BCAA = Branched chain amino acid; CS = corticosteroid; ETV = entecavir; LV = liver volume; ALT = alanine aminotransferase; PE = pleural effusion.

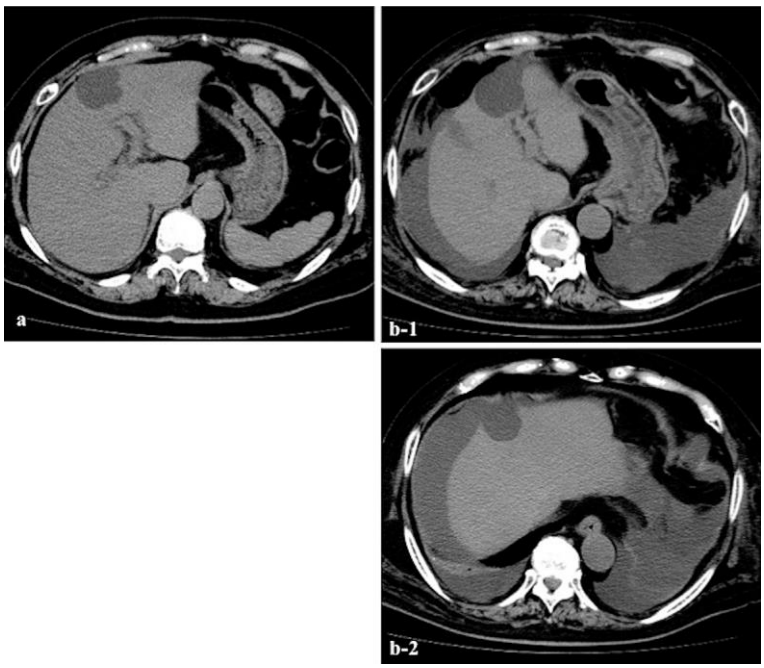

Fig. 2. Serial CT scans of the patient. **a** Initial CT scan obtained at disease onset showed neither ascites nor atrophy of the liver. **b** CT scan obtained on day 68 of the disease showed decrease in size of the liver (**b**-1), and massive ascites with moderate pleural effusion (**b**-2).

Table 1. Laboratory findings on admission

Item	Value	Item	Value	Item	Value
WBC	2,200/μl	γ-GTP	214 IU/l	Anti-HAV IgM	–
Hb	14.4 g/dl	TP	6.2 g/dl	HCV RNA	–
Hct	44.1%	Alb	3.6 g/dl	HBsAg	+ (>2,000) (S/CO)
Platelets	14.1 × 10^4/μl	TC	176 mg/dl	Anti-HBs	– (<×8) (PHA)
PT	79.0% [80.0, 71.0]	UA	4.4 mg/dl	Anti-HBc	+ (10.1) (S/CO)
PT-INR	1.11 [1.11, 1.18]	UN	13.4 mg/dl	Anti-HBc IgM	– (0.34) (S/CO)
T-BIL	3.9 mg/dl [3.3, 4.3]	Cre	0.88 mg/dl	HBeAg	– (0.47) (S/CO)
D-BIL	2.5 mg/dl [2.1, 2.9]	Glucose	93 mg/dl	Anti-HBe	– (19.6) (S/CO)
AST	2,771 IU/l	AFP	7.5 ng/ml	HBV DNA	≥9.0 log copies/ml
ALT	1,589 IU/l			HBV genotype	Bj
LDH	1,077 IU/l	ANA	–	Precore	Mutant 100%
ALP	566 IU/l			Core promotor	Wild

Values of days 2 and 3 are shown in square brackets. WBC = White blood cell count; Hb = hemoglobin; Hct = hematocrit; PT = prothrombin time; PT-INR = PT international normalized ratio; T-BIL = total bilirubin; D-BIL = direct bilirubin; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; ALP = alkaline phosphatase; γ-GTP = γ-glutamyltransferase; TP = total protein; Alb = albumin; TC = total cholesterol; UA = uric acid; UN = urea nitrogen; Cre = creatinine; AFP = α-fetoprotein; ANA = anti-nuclear antibody; HAV = hepatitis A virus; IgM = immunoglobulin M; HCV = hepatitis C virus; HBsAg = hepatitis B surface antigen; HBeAg = hepatitis B e antigen.