



CASE REPORT

Fatal liver failure caused by reactivation of lamivudine-resistant hepatitis B virus: A case report

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Abstract

We present a case of fatal liver failure caused by the activation of lamivudine-resistant hepatitis B virus (HBV) nine months after lamivudine treatment. A 57-year old man visited our hospital for the treatment of decompensated chronic hepatitis B. Lamivudine was started in December 2001. Subsequently, serum HBV was negative for HBV DNA with seroconversion from HBeAg to anti-HBe and improvement of liver function. However, HBV DNA and HBeAg were again detected in September 2002. He was complicated by breakthrough hepatitis and admitted to our hospital in November for severely impaired liver function. Vidarabine treatment was started and serum HBV DNA and alanine aminotransferase (ALT) decreased transiently. However, after the start of α -interferon treatment, HBV DNA level increased and liver function deteriorated. He died 1 mo after admission. An analysis of amino acid sequences in the polymerase region revealed that rtM204I/V with rtL80I/V occurred at the time of viral breakthrough. After the start of antiviral treatment, rtL180M was detected in addition to rtM204I/V and rtL80I/V, and became predominant in the terminal stage of the disease. HBV clone with a high replication capacity may be produced by antiviral treatment leading to the worsening of liver function. Antiviral therapy for patients with breakthrough hepatitis in advanced liver disease should be carefully performed.

INTRODUCTION

Lamivudine is a nucleoside analogue that interrupts the reverse transcription of hepatitis B viral (HBV) pregenomic RNA. Lamivudine is effective for controlling chronic hepatitis B and currently recommended as the first line of treatment for chronic active hepatitis B^[1,2]. Even for patients with decompensated liver cirrhosis, lamivudine improves liver function and extends transplantation free intervals^[3-10]. Since more than 10% of patients with chronic HBV infection are estimated to develop liver cirrhosis and may eventually suffer from decompensated liver cirrhosis or hepatocellular carcinoma, the role of lamivudine in the treatment of advanced liver disease caused by chronic HBV infection is large^[11-14].

The major problems concerning lamivudine treatment are the viral and biochemical breakthroughs caused by drug resistance. Amino acid mutation in the highly conserved tyrosine-methionine-aspartate-aspartate (YMDD) motif can occur six months after treatment and often increases alanine aminotransferase (ALT) level. Although the increase is usually mild, a marked increase in ALT level leading to fatal hepatic failure has been reported^[15-17]. Factors other than the YMDD motif mutation that are associated with the worsening of liver function remain to be clarified.

Here, we report a case of fatal hepatic failure caused by lamivudine-resistant HBV. A serial analysis of viral amino acid sequences indicated that the acquisition of mutations outside the YMDD motif might be related to the deterioration of the patient's condition.

CASE REPORT

A 57-year old man visited our hospital in September 2001

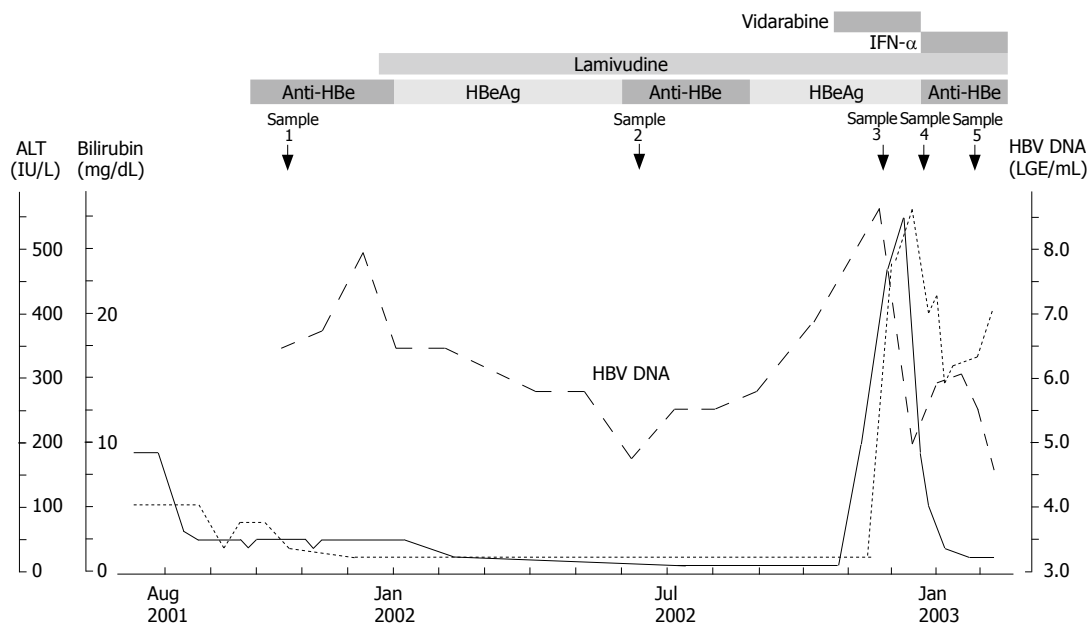


Figure 1 Clinical course of our patient. HBV DNA level was quantified by transcription-mediated amplification assay. The levels of HBV DNA started to increase 8 mo after treatment with reappearance of HBeAg. Breakthrough hepatitis developed 12 mo after treatment. The timing of serum sample analysis for mutations is shown by the arrowhead.

for the treatment of decompensated chronic hepatitis B. In 1978, He was found to be positive for serum HBs antigen (HBsAg). In July 2001, he was admitted to a nearby hospital for ascites where he was diagnosed as having decompensated cirrhosis with exacerbated chronic hepatitis B. The symptomatic control of his ascites improved his general condition. For further treatment, he was referred to our hospital.

On his first visit, he showed no symptoms or signs of worsening hepatic failure or encephalopathy. No ascites or leg edema was observed. His bulbar conjunctiva was slightly jaundiced. Dilated vasculature was observed in his neck and chest. His ALT, total bilirubin and albumin were 50 IU/L, 3.1 mg/dL and 3.7 g/dL, and his prothrombin time was 76%. He was diagnosed as having liver cirrhosis with a Child-Pugh score of 8. He was negative for HBe antigen (HBeAg) and his HBV DNA level measured by transcription-mediated amplification and hybridization protection assay^[18] was $10^{6.5}$ genome copies/mL.

In November 2001, he was found to be positive for HBeAg and showed an increase in HBV DNA level. Because he had a history of decompensated chronic hepatitis B, lamivudine treatment (100 mg/d) was started in December. Figure 1 shows the clinical course. The high serum levels of bilirubin and ALT decreased and normalized within 6 mo after lamivudine treatment was started. The patient became negative for HBV DNA and HBeAg.

However, in September 2002, he was found to be positive for HBeAg again and showed an increase in HBV DNA level. In November 2002, he observed jaundice of his bulbar conjunctiva and was admitted to our hospital. Although he was alert, his bulbar conjunctiva and skin were jaundiced. His ALT, total bilirubin, were 474 IU/L, 11.4 mg/dL and 4.3 g/dL. His HBV DNA level was $10^{8.6}$ genome copies/mL. He was diagnosed as having breakthrough hepatitis caused by lamivudine-resistant mutants of HBV. HBV with an amino acid substitution in the YMDD motif in the domain C of polymerase region

was detected.

Because interferon is not indicated in patients with decompensated cirrhosis, vidarabine, which is effective for the control of active HBV infection^[19-21], was administered together with lamivudine under informed consent. Liver function improved transiently with a decrease in HBV DNA within 2 wk. As prolonged vidarabine administration may induce several complications^[22], vidarabine was switched to interferon- α . After the start of interferon- α treatment, HBV DNA level increased and liver function worsened. He died of hepatic failure and rupture of esophageal varices 1 mo after his admission.

The histopathology of the patient's liver after necropsy showed cirrhosis with zonal necrosis. Hepatocyte regeneration was scarce (Figure 2).

To elucidate the viral factors affecting early viral breakthrough and fatal outcome, amino acid sequences of the upstream polymerase region (aa 1-250) of HBV DNA in serum were examined at 5 points as shown in Figure 1. The methods were as follows.

First, DNA was extracted from 100 μ L of a serum sample using the QIAamp DNA blood mini kit (Qiagen Inc., Valencia, CA). Three fragments spanning the upper polymerase region of HBV DNA were amplified by nested PCR with the primers shown in Table 1. The first stage of amplification was carried out using a thermal cycler for 40 cycles (94°C for 1 min, 55°C for 1 min, 72°C for 1 min) in 100 μ L of reaction mixture containing 200 mmol/L dNTPs, 1.0 mmol/L each of the primers and 1 \times PCR buffer [50 mmol/L KCl, 10 mmol/L Tris-HCl (pH 8.3), 1.5 mmol/L MgCl₂ and 0.001% (w/v) gelatin] and 2 units of Ampli-Taq polymerase gold (Perkin Elmer Cetus Corp., CT). Two microliters of the PCR products was subjected to the second stage of amplification under the same conditions as the first stage.

Second, PCR products were purified using Wizard PCR preps DNA purification resin (Promega, WI) and cloned into a plasmid vector using the TA cloning kit (PCR cloning kit Qiagen, CA). Four clones were selected from

Table 1 Primers used for amplification and sequencing of polymerase region of HBV

Region 1		
Outer sense	nt 2222-2241	CTTACTTTTGGGAAGAGAAAC
Outer antisense	nt 2490-2509	GGACAGTAGAAGAATAAAG
Inner sense	nt 2222-2241	CTTACTTTTGGGAAGAGAAAC
Inner antisense	nt 2478-2497	GAATAAAGCCCAGTAAAGTT
Region 2		
Outer sense	nt 2413-2434	GCGTCGCAGAAGATCTCAATC
Outer antisense	nt 2816-2835	GTTCCCAAGAATATGGTGAC
Inner sense	nt 2434-2452	CTCGGAATCTCAATGTTAG
Inner antisense	nt 2816-2835	GTTCCCAAGAATATGGTGAC
Region 3		
Outer sense	nt 2490-2509	CTTTATTCTTCTACTGTACC
Outer antisense	nt 3121-3143	CGATTGGTGGAGGCAGGAGGAGG
Inner sense	nt 2637-2656	ATGCTGCTAGGTTTTATCC
Inner antisense	nt 3121-3143	CGATTGGTGGAGGCAGGAGGAGG

each plate, from which recombinant plasmid DNA was purified using a commercially available kit (Plasmid midi kit, Qiagen, Valencia, CA). Nucleotide sequences were determined bidirectionally using the dye terminator cycle sequencing ready reaction kit (PE Applied Biosystems, CA) and the PCR primers. Sequencing was performed using an automated DNA sequencer (ABI 377: PE Applied Biosystems).

The determined amino acid sequences in the polymerase region are shown in Figure 3. No amino acid sequence changes were found at the start of lamivudine treatment. At the time of viral breakthrough, rtM204I with rtL80I became dominant. After the start of interferon treatment, rtM204I was replaced by rtM204V and rtL80I by rtL80V. At the final stage of the disease, mutation rtL180M appeared besides rtM204V and rtL80V.

DISCUSSION

Lamivudine monotherapy is effective in suppressing HBV replication and ameliorating liver disease in chronic hepatitis B patients regardless of HBeAg positivity. A one-year study of HBeAg-positive chronic hepatitis B patients showed that 16% of these patients become seroconverted to anti-HBe and 72% of these patients showed normalization of their ALT levels^[23]. Furthermore, treatment with lamivudine is associated with histologic improvement not only in terms of necroinflammatory score but also in terms of fibrosis score after long-term treatment^[24].

One advantage of lamivudine is that it can be used safely in patients with decompensated cirrhosis^[3-10]. In contrast to IFN- α , lamivudine is well tolerated without any significant side effects even in patients with decompensated cirrhosis. Furthermore, lamivudine can improve liver function and survival prognosis.

However, the emergence of a drug-resistant mutant is a big problem in lamivudine treatment. A large-scale Asian study showed that lamivudine resistant HBV infection occurred in 23% of patients in year one and 65% of patients in year five. Hepatitis flares, which occurred more commonly in patients with lamivudine resistant mutations, occurred in 10% of patients in year one, and in 18% to

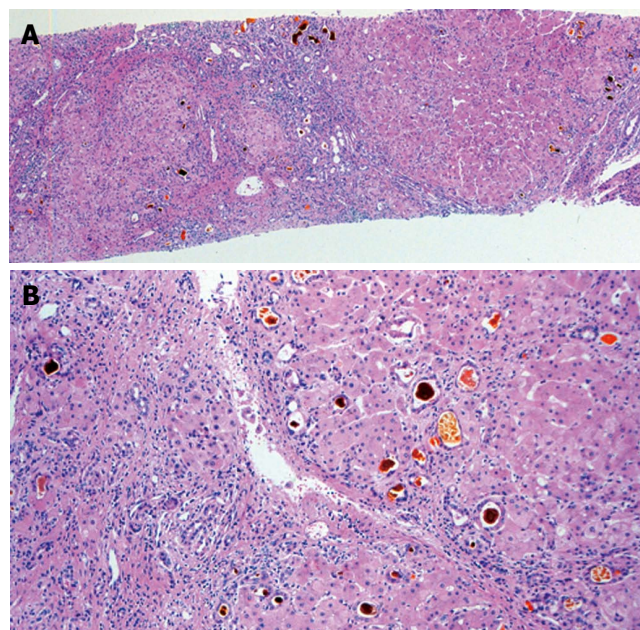


Figure 2 Histopathological findings of liver specimens showing irregularly-shaped parenchymal cells with massive necrosis (A) and scarce hepatocyte regeneration (B) surrounded by extensive fibrosis (A: HE \times 20; B: HE \times 80).

21% of patients in years two to five. Among patients with lamivudine resistant HBV infection, occurrence of hepatic decompensation increased significantly in patients with lamivudine resistant HBV infection for more than 4 years (from 0% to 6%)^[25]. In this large-scale Asian study, liver-disease-related death occurred in two patients.

The prognosis of patients with lamivudine-resistant HBV infection, particularly those with advanced liver disease, may be determined by the timing and severity of breakthrough hepatitis. However, the viral factors that may influence the severity of this hepatitis remain to be clarified. A recent study indicated that patients with a normal ALT level even after the emergence of a YMDD motif mutant are characterized by HBeAg negativity during pretreatment, HBeAg loss during therapy, a longer duration from the commencement of therapy until the emergence of YMDD mutant, and lack of mixed-type YMDD mutants^[26]. In contrast, patients with severely exacerbated hepatitis after the emergence of a YMDD mutant tend to have more substitutions in the reverse transcriptase (rt) region within the polymerase gene at the time of hepatitis exacerbation than those without hepatitis exacerbation^[26].

Our patient acquired amino acid mutations in the polymerase region one after the other. Amino acid changes in rtM204/I appeared at the time of viral breakthrough. After the initial treatment with vidarabine, rtM204/V substituted for rtM204/I in one of the four clones. During the interferon treatment, rtM204/V became predominant.

Another mutation observed in our patient was rtL80I/V. Ogata *et al*^[27] showed that rtL180M is accompanied with rtM204I in some patients with resistance to lamivudine. Because the mutation at aa position 80 was found at the same time as that at aa position 204 in our patient, it is not clear whether the mutation at aa position 80 affects the clinical course.

Figure 3 Comparison of amino acid sequences of HBV polymerase gene of isolates before lamivudine treatment (sample 1) and four sequential isolates (samples 2-5) during treatment. A HBV mutant with substitutions of isoleucine for leucine at residue 80 (rL80I) in combination with isoleucine for methionine at residue 204 (rM204I) was observed 12 mo after treatment (sample 3). After vidarabine treatment, another HBV mutant with substitutions of valine for leucine at residue 80 (rL80V) and valine for methionine at residue 204 (rM204V) was observed (sample 4). These mutants predominated in combination with methionine for leucine at residue 180 (rL180M) after interferon treatment (sample 5). The published HBV DNA sequence of hepatitis B virus variant (genotype C, AB033550, Okamoto *et al*) was used for comparison.

Vidarabine was replaced by interferon- α because adefovir dipivoxil was not available in 2002. Serum HBV DNA and bilirubin levels increased again, which led to a

In conclusion, antiviral therapy should be considered in the treatment of patients with hepatic failure after breakthrough hepatitis caused by HBV mutants to lamivudine. The serial acquisition of amino acid mutations outside the YMDD motif in the polymerase region may be associated with severe hepatitis.

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