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CASE REPORT

Surgical treatment of HCC in a patient with lamivudine-resistant hepatitis B cirrhosis with adefovir dipivoxil

Takashi Akima, Masaya Tamano, Hidetsugu Yamagishi, Keiichi Kubota, Takahiro Fujimori, Hideyuki Hiraishi

Takashi Akima, Hideyuki Hiraishi, Department of Gastroenterology, Dokkyo Medical University, Tochigi 321-0293, Japan
Masaya Tamano, Department of Gastroenterology, Dokkyo Medical University Koshigaya Hospital, Saitama 343-8555, Japan
Hidetsugu Yamagishi, Takahiro Fujimori, Department of Surgical and Molecular Pathology, Dokkyo Medical University, Tochigi 321-0293, Japan
Keiichi Kubota, Second Department of Surgery, Dokkyo Medical University, Tochigi 321-0293, Japan
Author contributions: Akima T and Tamano M did the research of this project and wrote the case report; Yamagishi H and Fujimori T did the pathological examinations; Kubota K did the hepatectomy; and Hiraishi H is the head of Department of Gastroenterology.
Correspondence to: Masaya Tamano, Professor, Department of Gastroenterology, Dokkyo Medical University Koshigaya Hospital, 2-1-50 Minami-Koshigaya, Koshigaya-Shi, Saitama 343-8555, Japan. mstamano@dokkyomed.ac.jp
Telephone: +81-48-965-1111 Fax: +81-48-965-1169
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Abstract

We describe a 77-year-old woman with chronic hepatitis B who became resistant to lamivudine. She was started on adefovir (10 mg daily) while still continuing lamivudine therapy. Four mo later her liver function improved and serum Hepatitis B virus (HBV)-DNA level became undetectable. Three years after the start of additional adefovir treatment, hepatocellular carcinoma (HCC) was detected and the patient underwent a successful hepatectomy. Our findings suggest that the addition of adefovir to ongoing lamivudine therapy cannot completely suppress hepatocarcinogenesis, but is useful for improving liver function in patients with lamivudine-resistant HBV-related cirrhosis, allowing HCC surgery.

Key words: Hepatitis B virus; Hepatocellular carcinoma; Hepatocarcinogenesis; Lamivudine; Adefovir dipivoxil

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most frequent malignant tumors worldwide and the third leading cause of cancer death, next to lung and stomach cancer. Hepatitis B virus (HBV) infection is one of the major causes of HCC, with interferon as one of several therapeutic options for chronic HBV infection. Recently, lamivudine, a nucleoside analogue, has been used to treat chronic HBV infection[1]. However, long-term lamivudine therapy may result in the emergence of genotypic resistance in the form of tyrosine-methionine- aspartate-aspartate (YMDD) mutations, which is occasionally associated with severe, or even fatal, breakthrough hepatitis[2,3]. Thus, there is a clear need for alternative or additional therapies. Adefovir dipivoxil (adefovir) is a nucleotide analogue that converts to an active metabolite, adefovir diphosphate[4,5]. In order to prevent breakthrough hepatitis induced by lamivudine-resistant HBV mutants, additional adefovir dipivoxil is recommended[6].

CASE REPORT

A 77-year-old Japanese female patient had been followed

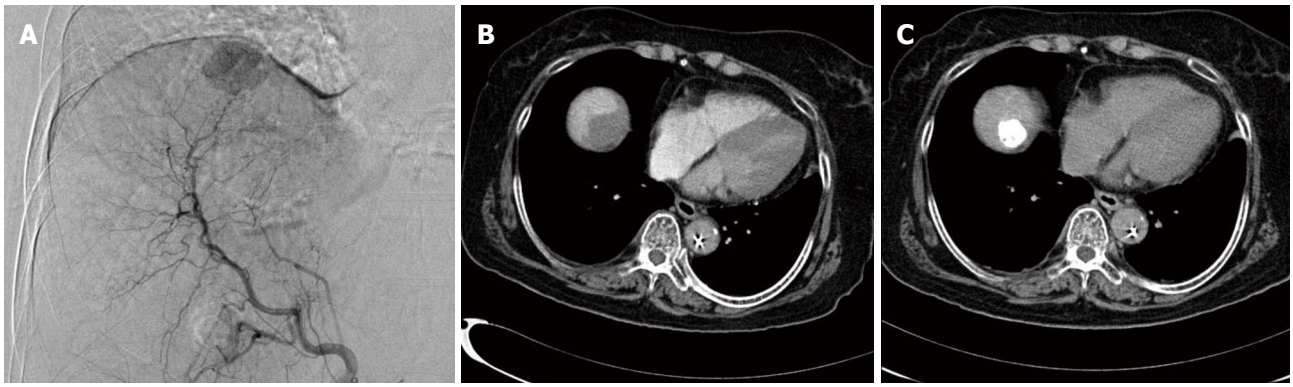

Figure 1 Digital subtraction angiography. A: Digital subtraction angiography showed tumor staining close against the diaphragm 20 mm in diameter; B: Computed tomography (CT) during arterial portography showed a perfusion defect in segment 8; C: CT during hepatic arteriography showed a hypervascularity lesion in the corresponding region.

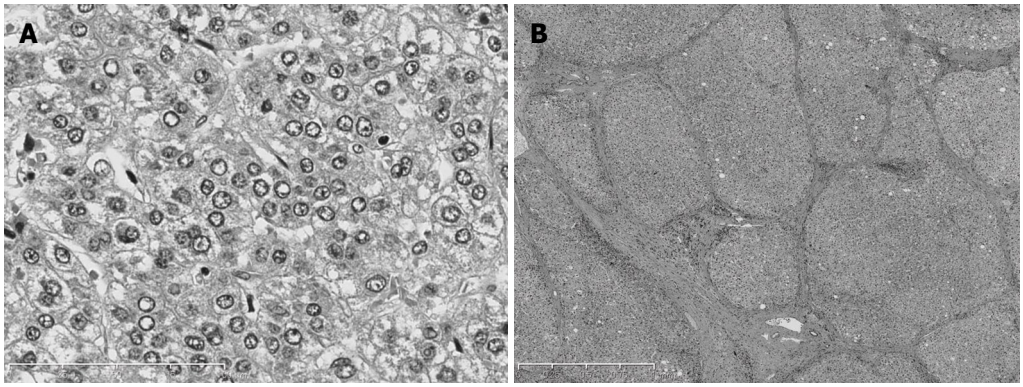

Figure 2 Histological findings of specimens obtained by subsegmentectomy. A: The tumor is a moderately differentiated hepatocellular carcinoma (H&E stain, × 100). B: The non-tumorous liver tissue around the tumor shows cirrhosis (H&E stain, × 40).

since 1977 for HBV-related chronic hepatitis. In 2002, her serum ALT level fluctuated between 100-400 IU/L (normal 4-40 IU/L), the HBV-DNA level was shown to be 6.2 log genome equivalent (LGE)/ml by transcription-mediated amplification, and alpha-fetoprotein (AFP) level was elevated to 537 ng/mL (normal upper limit 5 ng/mL). However, the desgamma carboxy prothrombin (DCP) level was within normal limits. Abdominal ultrasonography and dynamic computed tomography (CT) revealed no evidence of HCC. From December 2002, the patient started to receive lamivudine at a dose of 100 mg per day. The serum ALT and AFP levels decreased to the normal range, HBV-DNA decreased to undetectable levels. After 30 mo of lamivudine treatment, the serum HBV-DNA level increased rapidly to 5.1 LGE/mL with serum ALT elevation (127 IU/L). The lamivudine-resistant YVDD mutant strain of HBV was detected. The patient was then treated with adefovir at a dose of 10 mg daily in addition to lamivudine from July 2005.

Abdominal ultrasonography and dynamic CT were performed every 6 mo. In July 2008, dynamic CT showed a tumor in segment 8 of the liver measuring 10 mm in diameter. The patient was admitted for further examination in September 2008. Digital subtraction angiography showed a tumor staining 20 mm in diameter (Fi gure 1A), CT during arterial portography showed a perfusion defect in segment 8 (Figure 1B), and CT during hepatic arteriography showed a hypervascular lesion in the corresponding region (Figure 1C). The tumor was diagnosed typical stage I HCC. Laboratory data upon admission is shown in Table 1. The patient's Child-Pugh grade was A. Since the tumor was not detected by ultrasonography, percutaneous ethanol injection and radiofrequency ablation were not performed. After outlining the treatment plan, including surgery and transcatheter arterial chemoembolization (TACE), the patient opted to undergo surgery and subsegmentectomy was successfully performed in October 2008. The tumor was a nodular lesion measuring 16 mm × 13 mm. Microscopically, the tumor was a moderately differentiated HCC with a trabecular pattern (Figure 2A). The non-tumorous liver tissue showed cirrhosis (Figure 2B). HBs Ag and HBc Ag were not detected by immunohistological staining in either the tumorous or non-tumorous portions.

DISCUSSION

The epidemiological association of HBV with HCC is well established. In recent studies, it was revealed that HBsAg carriers have a 25-37 fold increased risk of developing HCC compared to non-infected people.

In 1998, lamivudine was approved as the first nucleotide analogue treatment of chronic hepatitis B[7]. However, drug-resistant mutants arise over the duration of lamivudine treatment, at 12.5% after 1 year, 43.8% after 3 years, and 62.5%-70.2% after 5 years[8,9]. For preventing breakthrough hepatitis induced by lamivudine-resistant HBV mutants, additional adefovir dipivoxil

Table 1 Laboratory data on admission

Blood chemistry	Value	Hematological analysis	Value	Viral markers	Value	Coagulation	Value	Tumor markers	Value
TP (g/dL)	7.8	WBC (× 103/L)	3.60	HBs Ag (IU/mL)	5.56	PT (%)	67	AFP (ng/dL)	< 5
Alb (g/dL)	4.1	RBC (× 106/L)	4.59	HBs Ab (mIU/mL)	1.20			PIVKA-Ⅱ (mAU/mL)	22
AST (IU/dL)	33.0	Hb (g/dL)	13.00	HBe Ag (S/CO)	0.30				
ALT (IU/dL)	28.0	Ht (%)	40.60	HBe Ab (%Inh)	89.60				
LDH (IU/dL)	168.0	Plt (× 103/L)	8.80	HBV-DNA	Undetectable				
ALP (IU/dL)	313.0								
GGT (IU/dL)	30.0								
T-bil (mg/dL)	0.6								
ZTT (KKU)	8.7								

TP: total protein; Alb: albumin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactic dehydrogenase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transpeptidase; T-bil: total bilirubin; ZTT: zinc turbidity test; WBC: while blood cells; RBC: red blood cells; Hb: hemoglobin; Ht: hematocrit; Plt: platelets; PT: prothrombin time; AFP: alpha-fetoprotein; PIVKA-Ⅱ: protein induced by vitamine K absence or antagonist-Ⅱ.

(10 mg daily) has been recommended[10] as it is more effective than switching to adefovir monotherapy and has fewer chances of developing drug-resistant mutants[11,12]. Lamivudine-resistant patients treated with lamivudine add-on adefovir can achieve both an excellent virological and biochemical response, but cannot completely suppress hepatocarcinogenesis[13,14]. It was reported that HCC development was observed in 7.3% of patients who received long-term adefovir add-on lamivudine over periods of up to 5 years. Serum ALT levels (≥ 70 IU/L), YMDD mutants, cirrhosis and age were independent factors for the development of HCC[15]. In the present case, serum ALT levels were within the normal range after receiving adefovir add-on lamivudine therapy, although the YMDD mutant was present. Furthermore, the patient was a senior citizen and her liver was cirrhotic at the start of lamivudine therapy. Therefore, this patient was at high hepatocarcinogenesis risk in the adefovir add-on lamivudine therapy group. HCC was detected about three years after starting additional adefovir treatment. The patient's clinical status and liver function were sufficiently improved when HCC was detected, allowing for successful surgical resection.

In conclusion, our experience suggests that adefovir add-on lamivudine therapy cannot completely suppress hepatocarcinogenesis, but is effective for reversing hepatic decompensation. The continuation of the combined lamivudine and adefovir treatment maintains stable liver function, permitting subsequent surgery for HCC.

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