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Hepatocellular Carcinoma 11 and a Half Years after the Resolution of Chronic Hepatitis C Virus Infection Successfully Treated with Interferon

Naoki Hotta Minoru Ayada Akihiko Okumura
Tetsuya Ishikawa Ken Sato Tomohiko Oohashi
Yasutaka Hijikata Shinichi Kakumu

Department of Internal Medicine, Division of Gastroenterology, Aichi Medical University School of Medicine, Aichi, Japan

Key Words
Hepatocellular carcinoma · Hepatitis C virus · Interferon

Abstract
A 41-year-old Japanese man had received successful interferon (IFN) therapy against chronic hepatitis C in 1994. Since then, serum hepatitis C virus (HCV) RNA had been negative, and aminotransferase levels had been continuously normal. He had abstained from alcohol. However, his serum aminotransferase levels showed slight elevation as his body weight increased gradually. He was diagnosed as having fatty liver and diabetes mellitus. In January 2006, 11 and a half years after the resolution of HCV infection, he was found to have a hepatic nodule 4.0 cm in diameter at liver S4/8 region by plain abdominal CT at an annual follow-up examination. He was diagnosed as having hepatocellular carcinoma (HCC) by angiography. The tumor was curatively resected and its histological diagnosis was moderately differentiated HCC. Noncancerous lesion of the liver revealed fibrosis of stage F2 and mild inflammation of grade A1 with mild steatosis. This case suggests that all patients with chronic HCV infection should be followed as long as possible for the potential development of HCC even after clearance of the virus.

Dr. Naoki Hotta
Department of Internal Medicine, Division of Gastroenterology
Aichi Medical University School of Medicine, 21 Karimata Yazako, Nagakute-cho
Aichi 480-1195 (Japan)
Tel. +81 561 62 3311 ext. 2382, Fax +81 561 63 0796, E-Mail naokiki@aichi-med-u.ac.jp

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Introduction

The incidence of hepatocellular carcinoma (HCC) is increasing in the United States, Europe, and worldwide, and has become a serious problem in many countries [1, 2]. Patients with chronic liver disease related to hepatitis B or C virus infection are at high risk for developing HCC [3], and the risk of HCC development becomes higher as fibrosis of the liver advances. Indeed, it is reported that the risk of HCC development in cirrhotic patients with hepatitis C virus (HCV) infection is as high as 7% per year in Japan [4]. Interferon (IFN) has a potent antiviral effect and has been widely used for the treatment of chronic HCV infection [5]. IFN therapy improves inflammation and fibrosis in the liver of the patients and reduces the risk of HCC development, particularly when it results in sustained virological response [6–8]. On the other hand, there are several reports that describe HCC development long after the clearance of HCV by successful IFN therapy [9–11]. Therefore, it is still uncertain how long the patients hold the risk of HCC development after the resolution of chronic HCV infection. In the current report, we describe a patient who developed HCC 11 and a half years after the clearance of HCV.

Case Report

A 41-year-old Japanese man was found to be seropositive for anti-HCV antibody (Dainabot, Tokyo, Japan) with abnormal liver function tests at a health check-up in 1994. He had no history of blood transfusion or drug abuse, but had been consuming approximately 25 g/day of alcohol for 20 years. He was introduced to Nagoya University Hospital (Nagoya, Japan). Serum HCV RNA detected by reverse transcription and nested PCR was positive. Serum hepatitis B surface antigen (HBsAg) and antibody to HBsAg (anti-HBs) were negative. A liver biopsy specimen was consistent with the feature of chronic hepatitis showing moderate fibrosis and mild necroinflammatory reaction, diagnosed later as F2/A1 according to the classification by Desmet et al. [12]. He was diagnosed to have chronic hepatitis C (CH-C) and received IFN monotherapy with natural IFN alpha (human lymphoblastoid IFN; Sumitomo Pharmaceutical Co., Osaka, Japan), 6 million units (MU), every day for the first 2 weeks and three times a week for the following 22 weeks. HCV RNA became negative during therapy, and the negativity of HCV RNA continued during 6 months of follow-up after discontinuation of therapy. Serum levels of aminotransaminases were also normal during the same period. He was judged to have achieved sustained virological response in HCV treatment.

He abstained from alcohol during and after the IFN therapy, but his body weight showed a gradual increase with slight elevation of serum aminotransferase levels. He was diagnosed to have fatty liver and diabetes mellitus, but treatment was not introduced. In January 2006, he was found to have a hepatic nodule 4.0 cm in diameter at liver S4/8 region by plain abdominal CT at an annual follow-up examination.

He was admitted to our hospital (Department of Gastroenterology, Aichi Medical University Hospital, Aichi, Japan) in February 2006. On admission, his height was 162 cm and his body weight 72 kg. Physical examination was unremarkable; the liver and spleen were not palpable, and jaundice, ascites, peripheral edema and other signs of chronic liver disease were not observed. Complete blood counts (CBC) were normal (white blood cell count 6,900/μl, hemoglobin 14.4 g/dl, and platelet count 253,000/μl). Liver function tests were normal; serum levels of transaminases and total bilirubin were within normal range (AST 22 IU/l, ALT 23 IU/l, and total bilirubin 0.9 mg/dl). Other laboratory tests, including liver fibrosis markers such as type IV collagen 7s, type III procollagen-N-peptide and hyaluronic acid, were also within normal range. However, fasting blood sugar (128 mg/dl) and HbA_1c (6.8%) were slightly elevated (**table 1**). Serum tumor makers of HCC were within normal range, prothrombin induced by vitamin K absence-II (PIVKA-II) level was 18 mAU/ml (normal range <40 mAU/ml), and α-fetoprotein level was 4.4 ng/ml (normal range <10 ng/ml). He was seropositive for anti-HCV by a second-generation enzyme immunoassay (Dainabot, Tokyo, Japan) and seronegative for HCV RNA by Amplicore HCV test (Roche Diagnostic Inc., Tokyo, Japan).

On dynamic CT, the nodule on liver S8 area revealed a tumor staining of 4.0 cm in diameter in the early arterial phase and modest washout density in the post-vascular phase (**fig. 1**a, b). On contrast-enhanced US scan, blood inflow into the same nodule was detected in the early arterial phase,

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and the nodule became hypoechoic compared to the liver parenchyma in the post-vascular phase. Celiac angiography revealed a hypervascular tumor with proliferation of fine tumor vessels (which also showed nodular and mosaic features) at the S4/8 region of the liver, just below the dome of right the diaphragm (fig. 2). The findings were compatible with HCC.

Percutaneous liver biopsy was performed at the noncancerous lesion, and the specimen showed fibrosis of stage F2 and mild inflammation of grade A1 with mild steatosis (fig. 3a, b). The tumor was curatively resected without any complication, and the histological study of the resected specimen revealed that the tumor was a moderately differentiated HCC (fig. 4).

Discussion

In the present study we describe a patient with HCC who developed HCC 11 and a half years after the eradication of HCV. There are many reports aimed to elucidate the risk factors for liver carcinogenesis, and some of them have tried to examine the incidence of HCC in patients with CH-C after IFN therapy [6–8]. Kasahara et al. examined the risk of HCC development in CH-C patients treated by IFN and showed that the cumulative incidence of HCC in relapsers (transient responders) to IFN therapy was almost equal to that in sustained responders, and that it was significantly higher in nonresponders than in sustained and transient responders [6]. The seventh-year cumulative incidence rates of HCC in sustained responders, relapsers, and nonresponders were estimated to be 4.3, 4.7, and 26.1%, respectively. They suggested that patients in the high-risk group of HCC after IFN therapy were those who showed no response, those who were older, or males. Sustained responders to IFN therapy usually show normal ALT levels continuously. In relapsers, ALT values usually become normal when HCV RNA becomes seronegative during therapy. Thus, the reduction in the necroinflammatory activity in the liver appears to be an important factor to prevent the development of HCC even when the eradication of HCV is not achieved.

Another report indicated that the group at high risk for developing HCC in sustained responders to IFN therapy were older, more often male, and had more advanced histological disease stages [13]. In addition, Kasahara et al. showed that the risk of death from liver-related diseases in sustained and nonsustained virological responders was significantly lower compared with that in untreated patients [14]. Furthermore, sustained and transient biochemical responders were shown to have a reduced risk of liver-related death compared to biochemical nonresponders. Thus, it is likely that IFN treatment prevents liver-related death and improves survival of CH-C patients with virological as well as biochemical response.

In the present case, the patient had mild fatty liver and diabetes mellitus without need for medication. The liver biopsy specimen at the time of operation (before operation) revealed liver damage of F2/A1. This finding was almost the same compared with that at the start of IFN therapy 12 years earlier. We considered the possibility that the presence of nonalcoholic fatty liver disease (NAFLD) might contribute, at least in part, to the development of HCC. NAFLD is a clinicopathological term that encompasses a disease spectrum ranging from simple triglyceride accumulation in hepatocyte (hepatic steatosis) to hepatic steatosis with inflammation (steatohepatitis), fibrosis, and cirrhosis [15]. Judging from the clinicopathological features in the current case, we could not exclude the influence of NAFLD for the development of HCC, while the pathological role of NAFLD might be limited.

Although it has been reported that HCC rarely develops long after eradication of HCV [9–11], all patients with chronic HCV infection should be followed as long as possible for

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the potential development of HCC, even sustained virological responders to IFN therapy. More careful follow-up is recommended, particularly when patients have complications such as NAFLD.

Table 1. Laboratory data on admission

Peripheral blood	
WBC	6,900/μl
RBC	436×10^4/μl
Hb	14.4 g/dl
Ht	40.2%
Plt	25.3×10^4/μl
Coagulation	
PT	102%
HPT	116%
Tumor marker	
AFP	4.0 ng/ml
AFP-L3	0%
PIVKA-2	18 AU/ml
Blood chemistry	
AST	22 IU/l
ALT	23 IU/l
LDH	246 IU/l
T-Bil	0.88 mg/dl
ALP	246 IU/l
γ-GTP	29 IU/l
T.P	7.4 g/dl
Alb	4.5 g/dl
T-Cho	159 mg/dl
BS	128 mg/dl
HbA1c	6.8%
Viral marker	
HBsAg	negative
HCVAb	positive
HCV-RNA	negative

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Fig. 1. On dynamic CT, the nodule on liver S8 area revealed a tumor staining of 4.0 cm in diameter in the early arterial phase (**a**) and modest washout density in the post-vascular phase (**b**).

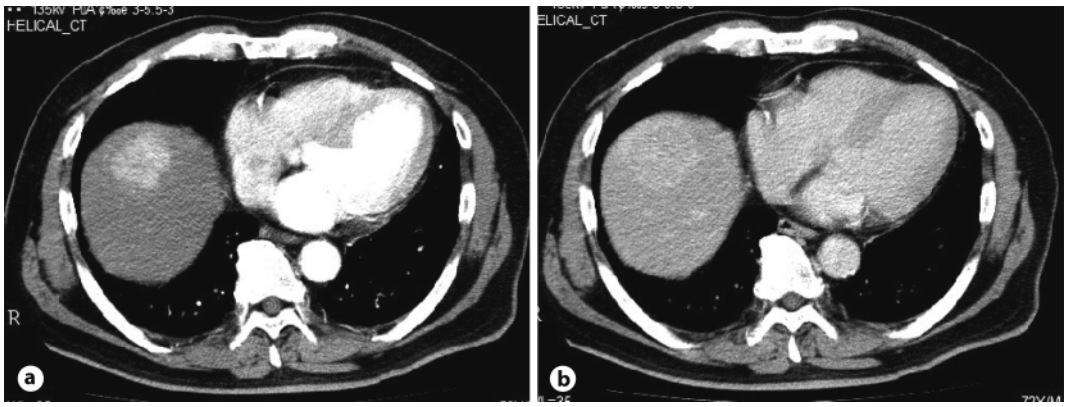

Fig. 2. Celiac angiography revealed a hypervascular tumor with proliferation of fine tumor vessels (which also showed nodular and mosaic features) at the S4/8 region of the liver, just below the dome of right diaphragm.

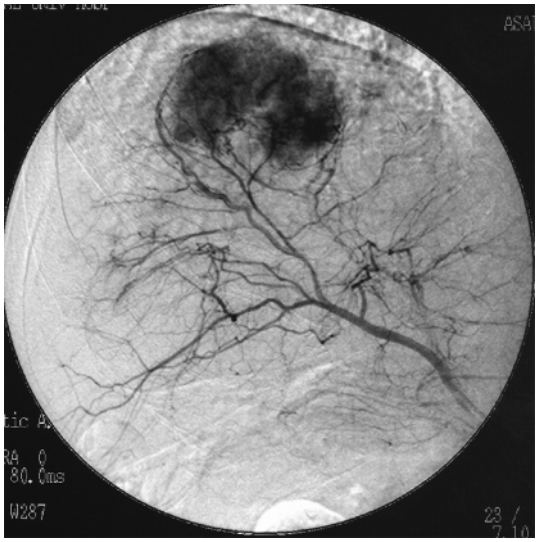

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Fig. 3. Percutaneous liver biopsy was performed at the noncancerous lesion, and the specimen showed mild inflammation of grade A1 (**a**, HE stain; original magnification ×200) and fibrosis of stage F2 (**b**, Azan stain; original magnification ×100), accompanied by mild steatosis.

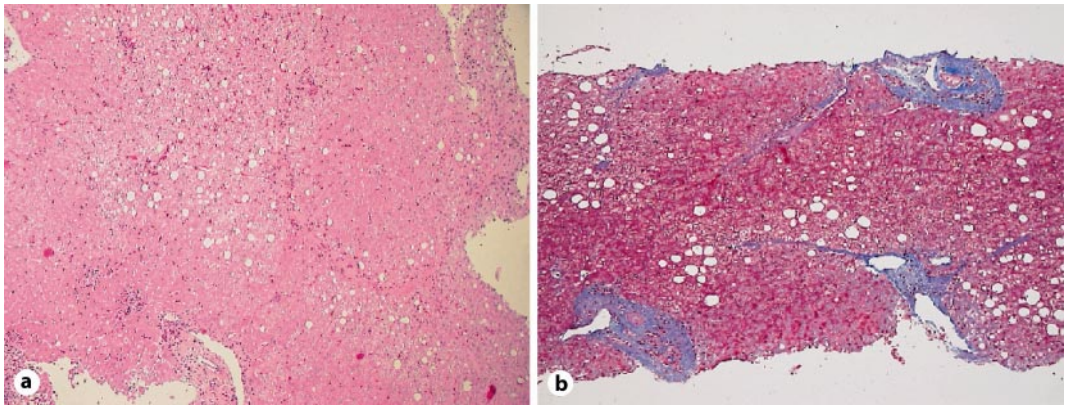
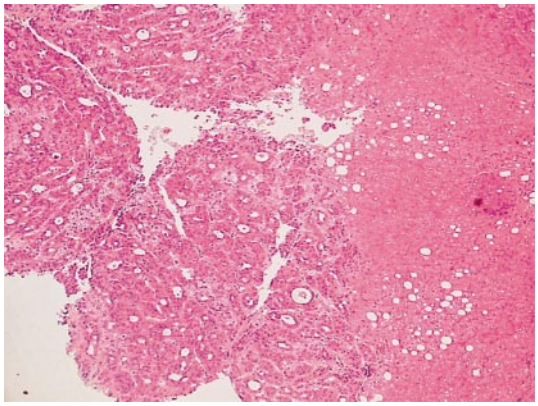


Fig. 4. Histological study of the resected specimen revealed that the tumor was a moderately differentiated HCC.



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