Two Cases of Hepatocellular Carcinoma Arising Over 20 Years after a Sustained Virologic Response Following Interferon Therapy for Chronic Hepatitis C

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Abstract:
The development of hepatocellular carcinoma (HCC) after a sustained virologic response (SVR) due to interferon (IFN) therapy for hepatitis C virus infection remains a serious problem. We herein report 2 cases of HCC that developed more than 20 years after SVR with IFN therapy for chronic hepatitis C. The patients were 89- and 72-year-old men with HCC that developed 24-25 years after an SVR with IFN therapy. These patients regularly underwent imaging examinations; therefore, the HCC was detected in the early stage, when it was still curable. Both cases suggest that long-term surveillance after an SVR is effective for the detection of HCC, and radical treatment is possible.

Key words: hepatocellular carcinoma, interferon therapy, sustained virologic response

(Intern Med 59: 1855-1860, 2020)
(DOI: 10.2169/internalmedicine.4479-20)

Introduction
Hepatitis C virus (HCV) is a major cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC) worldwide. Since 1992, patients with chronic hepatitis C (CHC) have been administered interferon (IFN) treatment. A sustained virologic response (SVR) during successful IFN therapy reduces the incidence of de novo HCC, although it is not completely suppressed (1-5). The incidence of HCC over 10 years and even more than 20 years after an SVR have been reported (6, 7). Therefore, long-term cancer surveillance is required after an SVR for early HCC detection at a curable stage; however, no consensus has been reached concerning how long such monitoring should continue.

Case 1
An 89-year-old man was referred to our hospital for the further investigation of a liver tumor. His medical history included type 2 diabetes mellitus treated with metformin and treatment with IFN-alpha 3 times a week for 24 weeks for CHC at a local hospital with achievement of an SVR at 65 years of age. After achieving an SVR, he had been followed up with regular ultrasonography (US) once every six months by his primary care physician. He had a history of alcohol intake of about 10 g per day for over 20 years.

He was asymptomatic, and the physical findings were normal. His body mass index (BMI) was 20.2 kg/m². Laboratory tests showed normal serum liver enzyme levels and an elevated glucose level suggesting known diabetes (glucose 142 mg/dL, HbA1c 7.4%). Tumor marker levels were

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Received: January 14, 2020; Accepted: March 10, 2020; Advance Publication by J-STAGE: April 30, 2020
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Abdominal US revealed a 20-mm lesion with low echogenicity in segment 5 of the liver that had not been present 6 months earlier (Fig. 1a); this nodule exhibited the characteristics of HCC on gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (EOB-MRI) (Fig. 1b, c). According to a needle biopsy specimen, the tumor was histologically confirmed to be well to moderately differentiated HCC arising from the liver without inflammation and fibrosis (Fig. 2a, b). In addition, HBV cccDNA was not detected in hepatocytes. Radiofrequency ablation was performed, which provided good results, and no recurrence has been observed on follow-up.

**Case 2**

A 72-year-old man was referred to our hospital for the further investigation of a liver tumor that was detected coincidentally by follow-up computing tomography (CT) after surgery for esophageal cancer. His medical history included treatment with IFN-alpha 3 times a week for 24 weeks for CHC resulting in an SVR at 47 years of age. After achieving an SVR, he had not received regular cancer surveillance, although he had been followed up with regular CT once every 6 months after subtotal esophagectomy for esophageal cancer at 70 years of age. He had a history of alcohol intake of about 100 g per day for over 30 years until esophageal cancer was diagnosed.

He was asymptomatic, and the physical findings were normal except for a chest operative scar. His BMI was 18.8 kg/m². Laboratory tests showed normal serum liver enzyme levels and elevated des-γ-carboxy prothrombin (DCP) level (84 mAU/mL). Serum HCV-RNA level was not detected (Table 1).

Contrast-enhanced CT and EOB-MRI revealed a 20-mm nodule with early-phase enhancement in segment 8 of the liver, suggesting an HCC diagnosis, that had not been present 6 months earlier (Fig. 3a). He underwent subsegmental resection of the liver. Upon a histological examination, the tumor was diagnosed as poorly differentiated HCC arising from the liver with severe fibrosis (Fig. 4a, b). The patient’s postoperative course was uneventful, and no recurrence has been observed on follow-up.

**Discussion**

The clinical courses of these patients provide two important clinical points. The first is that HCC can develop even more than 20 years after achieving an SVR. Previous studies have demonstrated how successful IFN treatment for CHC results in improvement of liver inflammation and hepatic fibrosis and decrease in the incidence of HCC (1-5). However, numerous patients have developed HCC after an SVR, and these cases should not be underestimated. The 5- and 10-year cumulative carcinogenic rates were 2.3-8.8% and 3.1-11.1%, respectively (7). However, the rate after more than 10 years is unclear, and there have been only a few reports of carcinogenesis after 20 years or more (Ta-

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Table 1. Laboratory Data after Development of Hepatocellular Carcinoma.

| Case 1 | Case 2 |
|--------|--------|
| White blood cell | 6,300 | 3,100 /μL |
| Red blood cell | 403 | 311 10³/μL |
| Hemoglobin | 12.8 | 10.8 g/dL |
| Platelets | 249 | 109 10³/μL |
| PT | 98 | 77 % |
| PT-INR | 1.01 | 1.12 |
| Albumin | 4.1 | 3.7 g/dL |
| Total bilirubin | 0.8 | 0.5 mg/dL |
| AST | 16 | 27 IU/L |
| ALT | 9 | 25 IU/L |
| GGTP | 25 | 50 IU/L |
| ALP | 254 | 216 IU/L |
| BUN | 16 | 11 mg/dL |
| Creatinine | 1.05 | 0.73 mg/dL |
| eGFR | 142 | 88 mg/dL |
| Glucose | 7.4 | 5.4 % |
| Insulin | 2.4 | ND μU/mL |
| HOMA-IR | 0.84 | ND |
| M2BpGi (1+) | 1.42 | (-) 0.68 COI |
| M2BpGi (1-) | 32.1 | 135.1 ng/mL |
| Type IV collagen 7S | 4.6 | 4.7 ng/mL |
| Infectious Makers | | |
| HCVAb | (+) 7.9 | ( +) 5.6 COI |
| HBsAg | not detected | not detected |
| HBsAb | (-) | (-) |
| HBcAb | (+) 0.014 | (-) COI |
| HBcrAg | <3,0 | ND LogU/mL |
| HBV-DNA | not detected | ND |
| Tumor Makers | | |
| AFP | 7.2 | 3.0 ng/mL |
| AFP-L3 | 12.8 | ND % |
| DCP | 15 | 56 mAU/mL |

AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyl transferase, ALP: alkaline phosphatase, BUN urea nitrogen, eGFR: estimated glomerular filtration rate, HOMA-IR: homeostasis model assessment of insulin resistance, M2BpGi: Mac-2 binding protein glycosylation isomer, HCVAb: hepatitis C virus antibody, HBsAg: hepatitis B surface antigen, HBsAb: hepatitis B surface antibody, HBcAb: hepatitis B core antibody, HBcrAg: hepatitis B core-related antigen, AFP: alphafetoprotein, DCP: des-γ-carboxy prothrombin, ND: no data.
the long-term SVR through successful IFN therapy might have improved the degree of hepatic fibrosis in this patient. In contrast, in Case 2, advanced hepatic fibrosis, possibly due to his alcohol consumption, was observed at the onset of HCC. In Case 1, the patient was diabetic, although there was no steatosis suggesting NASH. In addition, although latent HBV infection, which is associated with carcinogenesis after an SVR (15), was suspected, a test for HBV cccDNA in the liver tissue was negative; therefore, its association with the carcinogenesis of HCC is unlikely.

Some previously reported cases of carcinogenesis detected over 20 years after an SVR were detected in an advanced stage with a large HCC that might have first manifested several years earlier. However, in both of the present cases, HCC had not been noted on imaging examinations performed just six months before the HCC detection, suggesting de novo carcinogenesis over 20 years after achieving an SVR.

The second important clinical point suggested by the present findings is that long-term monitoring after achieving an SVR is crucial. In Case 1, the patient had been followed-up for a long time with regular imaging examinations, resulting in the detection of a large HCC. Thus, we conclude that long-term monitoring of patients with a history of HCC is necessary to prevent its development.
Figure 3. Image findings in case 2. (a, b) Early-phase computed tomography revealed hyperenhancement and a decrease to hypoenhancement in late-phase computed tomography. (c) The tumor (arrow) showed hypointensity in the hepatobiliary phase of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced MRI.

Figure 4. Histological findings of the resected liver specimen in case 2. (a) Macroscopically, the cut-surface reveals the mass lesion of the liver. (b) The specimen from the tumor nodule was confirmed to be poorly differentiated hepatocellular carcinoma [Hematoxylin and Eosin (H&E) staining, ×400]. (c) The specimen from the non-tumor area showed no steatosis and was classified as F3, A0, according to the New Inuyama Classification of hepatitis activity grading (H&E staining, ×40).
in curable treatment for early stage HCC. In contrast, Case 2 had not been followed up after achieving an SVR, although regular imaging examinations as follow-up for other diseases fortunately led to the detection of HCC at a curable clinical stage. Furthermore, in both cases, the expected time of carcinogenesis was revealed through regular imaging surveillance.

Successful IFN treatment is known to improve the prognosis of patients with CHC by suppressing the incidence of HCC and preventing the progression of liver fibrosis. In addition, preserving the liver function by achieving an SVR enables radical treatment for HCC to be performed, resulting in a favorable prognosis (16-18). Several studies have recently addressed the association between a lack of surveillance and a poor prognosis (19-21). However, there are currently no prospective studies on effective surveillance methods for early HCC detection after an SVR, including imaging intervals and discontinuation timing.

Recently, with the advent of direct-acting antiviral (DAA) treatment, the number of patients achieving SVR has increased dramatically. Whether or not SVR due to DAA treatment reduces the carcinogenicity of HCC development remains controversial; however, the importance of surveillance after an SVR is increasing (22, 23). Therefore, further studies are needed to evaluate the efficacy of future surveillance methods.

As HCC can develop over 20 years after achieving an SVR, long-term cancer surveillance is crucial for ensuring a favorable patient prognosis.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We are indebted to Dr. Yoshihiro Hamada and Prof. Kazuki Nabeshima, Department of Pathology at Fukuoka University Hospital, for providing histological information and Dr. Wako Yoshimitsu, Postgraduate Clinical Training Center at Fukuoka University Hospital, for the valuable support.

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Table 2. Previous Reports of Hepatocellular Carcinoma Occurrence 20 Years or More after an SVR Including Our Cases.

| Reference | Age | Intervals (years) | Sex | Ethanol (g/day) | DM | Steatosis | HBeAb | AFP (ng/mL) | Histology at HCC occurrence | BCLC stage | Size maximum (cm) | Treatment |
|-----------|-----|-------------------|-----|----------------|----|-----------|-------|-------------|---------------------------|------------|---------------------|-----------|
| 8         | 63  | 83                | 20  | M              | 0  | (-)       | (-)   | 4.5         | N/A                       | N/A        | 6.0                 | HR        |
| 9         | 46  | 66                | 20  | M              | 4-6| (-)       | N/A   | 3.0         | N/A                       | mode-poor  | 9.5                 | HR        |
| 10        | 15  | 55                | 20  | M              | 0  | (-)       | N/A   | 1.8         | N/A                       | A          | 2.0                 | TACE      |
| 11        | 66  | 86                | 20  | M              | 20 | (+)       | N/A   | 538         | N/A                       | C          | 2.0                 | TKI       |
| 12        | 43  | 63                | 20  | M              | 0  | (+)       | (+)   | 2.4         | 20                        | N/A        | 1.5                 | TACE+RFA  |
| 7         | 58  | 82                | 24  | M              | 100| (-)      | (+)    | 7,060       | N/A                       | N/A        | 8.0                 | TACE      |
| our case 1 | 65  | 89                | 24  | M              | 10 | (+)      | (-)   | 7,2         | 0.0                       | well-mode  | A                   | 2.0       | RFA      |
| our case 2 | 47  | 72                | 25  | M              | 100| (-)     | (-)   | 3.3         | 3.0                       | poor       | 1.7                 | HR        |

SVR: sustained virologic response, HCC: hepatocellular carcinoma, DM: diabetes mellitus, AFP: alphafetoprotein, HR: hepatic resection, TACE: transcatheater arterial chemoembolization, TKI: tyrosine kinase inhibitor, RFA: radiofrequency ablation, N/A: not applicable
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