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【 CASE REPORT 】

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

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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 Reports

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/m^2. 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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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	10^6/μL
Hemoglobin	12.8	10.8	g/dL
Platelets	249	109	10^3/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
GGT	25	50	IU/L
ALP	254	216	IU/L
BUN	16	11	mg/dL
Creatinine	1.05	0.73	mg/dL
eGFR	50.7	80.2	mL/min
Ferritin	280	ND	ng/mL
Glucose	142	88	mg/dL
HbA1c	7.4	5.4	%
Insulin	2.4	ND	μU/mL
HOMA-IR	0.84	ND	
M2BpGi	(1+) 1.42	(-) 0.68	COI
hyaluronic acid	32.1	135.1	ng/mL
Type IV collagen 7S	4.6	4.7	ng/mL
Infectious Makers			
HCVAb	(+) 7.9	(+) 5.6	COI
HCV-RNA	not detected	not detected	
HBsAg	(-)	(-)	
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

normal except for lens culinaris agglutinin-reactive fraction of alphafetoprotein (AFP-L3), (AFP, 7.2 ng/mL; AFP-L3, 12.8%, range <10%; des-γ-carboxy prothrombin, 15 mAU/mL). No fibrosis markers showed prominent elevation [Mac-2 binding protein glycosylation isomer (M2BPGi), 1.42 COI; hyaluronic acid, 32.1 ng/mL]. The serum HCV-RNA level was not detected. The hepatitis B core antibody test was positive; however, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core-related antigen, and hepatitis B virus (HBV) DNA were negative (Table 1).

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/m^2. 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-

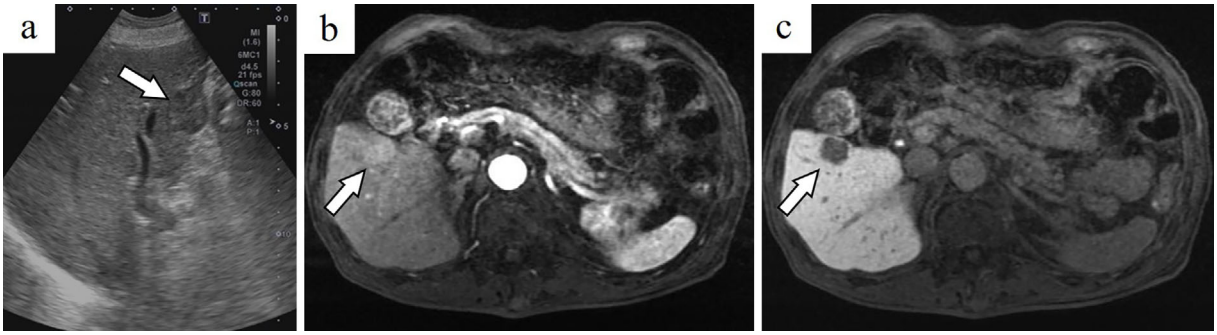

Figure 1. **Image findings in case 1. (a) Ultrasonography revealed that the tumor (segment 5) exhibited low echogenicity (arrow). (b, c) The tumor (arrow) showed hyperintensity in the early phase of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced MRI and clear hypointensity in the hepatobiliary phase.**

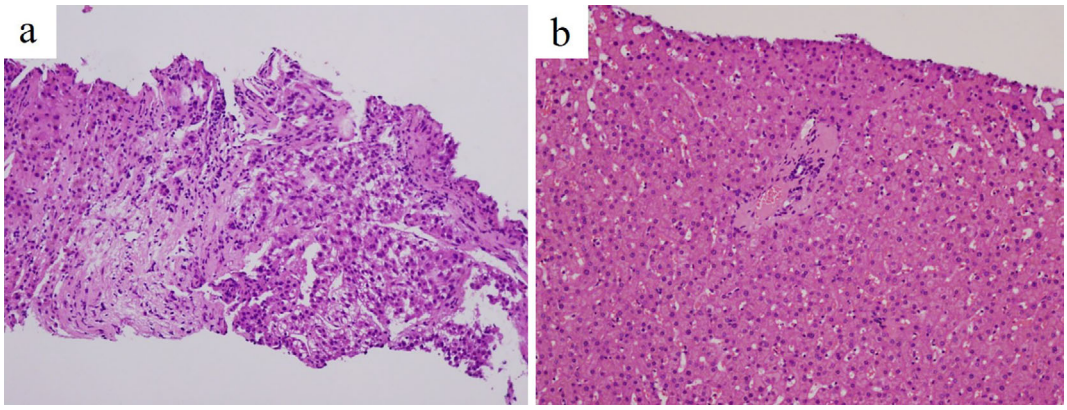

Figure 2. **Histological findings of the liver biopsy in Case 1. (a) The biopsy specimen from the tumor nodule was confirmed to be well to moderately differentiated hepatocellular carcinoma [Hematoxylin and Eosin (H&E) staining, ×100]. (b) The biopsy specimen from the non-tumor area showed no steatosis and was classified as F0, A0, according to the New Inuyama Classification of hepatitis activity grading (H&E staining, ×200).**

ble 2) (7-12).

Hepatocarcinogenesis after an SVR is associated with risk factors other than carcinogenicity due to HCV. Well-known major risk factors for developing HCC after an SVR are male sex, age exceeding 50 years old, and F3 or F4 fibrotic stage at the time of IFN introduction (13). However, these are risk factors for hepatocarcinogenesis occurring within 10 years after having an SVR. It is expected that the longer the time after an SVR, the greater the extent that carcinogenesis is influenced by aging and lifestyle-related factors, such as alcohol consumption, metabolic disorders such as diabetes and insulin resistance, liver steatosis, and nonalcoholic steatohepatitis (NASH) (7, 14).

Of the 9 reported cases of carcinogenesis occurring over 20 years after an SVR, including our own cases, all patients were men, and 6 of them (66.7%) were over 50 years old at the time of the IFN treatment. In Case 1, hepatic fibrosis was not observed at the onset of HCC. Although it was difficult to determine the status of liver fibrosis before IFN treatment due to the absence of any liver tissue specimens, the long-term SVR through successful IFN therapy might thus 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

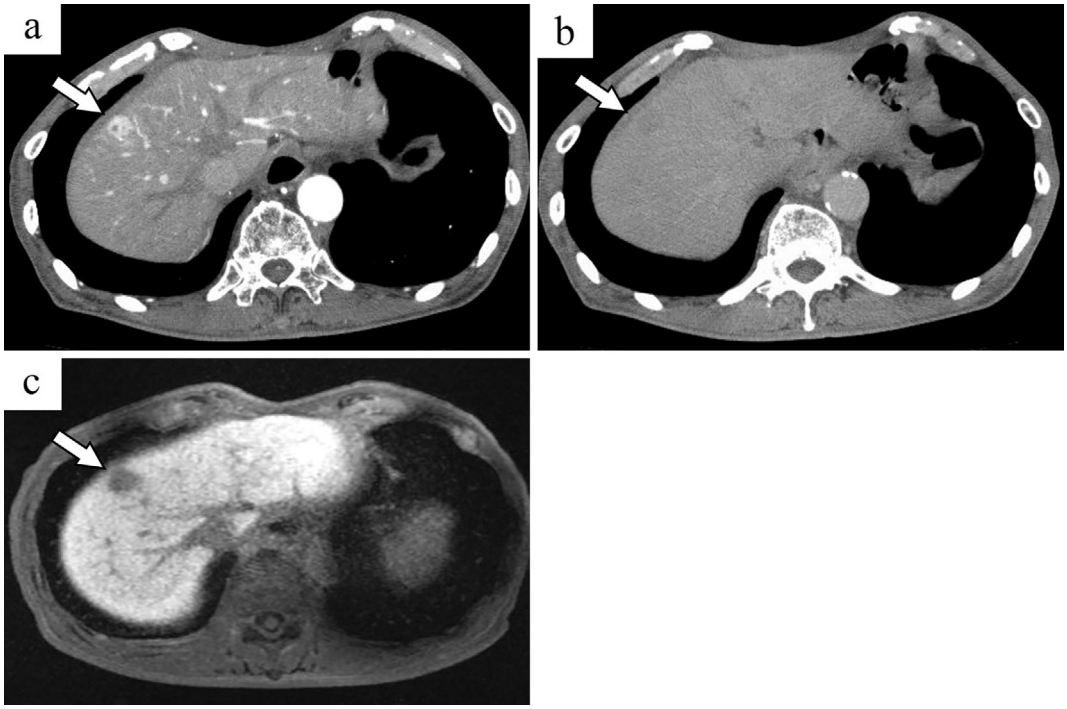

Figure 3. **Image findings in case 2. (a, b) Early-phase computed tomography revealed hyperenhancement and a decrease to hypoenhancement in late-phase computed tomography. (c) The tumor (arrow) showed hypointensity in the hepatobiliary phase of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced MRI.**

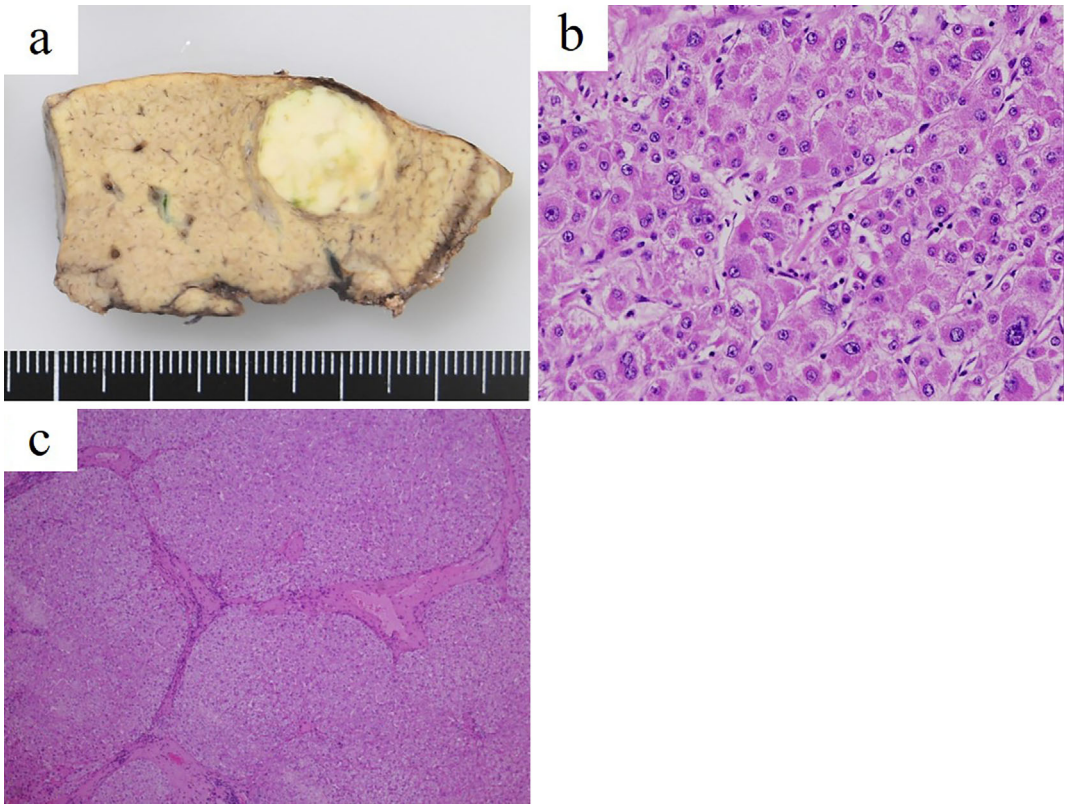

Figure 4. **Histological findings of the resected liver specimen in case 2. (a) Macroscopically, the cut-surface reveals the mass lesion of the liver. (b) The specimen from the tumor nodule was confirmed to be poorly differentiated hepatocellular carcinoma [Hematoxylin and Eosin (H&E) staining, ×400]. (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).**

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	HBcAb	AFP (ng/mL)	Histology at HCC occurrence	HCC			Treatment
	at SVR	at HCC occurrence								Non tumor (F/A)	Histology	BCLC stage	Size maximum (cm)	
8	63	83	20	M	0	(-)	(-)	(-)	4.5	N/A	N/A	N/A	6.0	HR
9	46	66	20	M	4-6	(-)	N/A	N/A	3.0	N/A	mode-poor	A	9.5	HR
9	61	82	20	M	0	(-)	N/A	N/A	1.8	N/A	N/A	A	2.0	TACE
10	55	75	20	M	0	(-)	N/A	N/A	538	N/A	N/A	C	2.0	TKI
11	66	86	20	M	20	(-)	N/A	(+)	2.4	2/0	N/A	A	1.5	TACE+ RFA
12	43	63	20	M	0	(-)	(+)	N/A	459.8	0/0	mode	C	6.4	HR
7	58	82	24	M	100	(-)	(-)	(+)	7,060	N/A	N/A	C	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	A	1.7	HR

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

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 after an SVR and more advanced HCC at detection, resulting in 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).

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