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CASE REPORT

Occurrence of hepatocellular carcinoma 24 years after successful interferon therapy in a patient with chronic hepatitis C: a case report

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Abstract

An 82-year-old man presented with hepatocellular carcinomas (HCCs) 24 years after achieving a sustained virological response (SVR) to an interferon for hepatitis C. His hepatic fibrosis stage was F1 when he was treated at 58 years. He was followed-up by annual blood tests and abdominal ultrasonography or computed tomography. After the IFN treatment, he had drunk approximately 100 g of ethanol. Serum aspartate aminotransferase and gamma-glutamyl transpeptidase levels had been elevated since 2012. To investigate the possible factors that affect hepatocarcinogenesis over 10 years after achieving an SVR, we reviewed the literature. Of 39 reported patients, 26, as well as ours, had one or more lifestyle-related factors, including body mass index ≥ 25 kg/m^2, diabetes mellitus, impaired glucose tolerance, hepatosteatosis, or alcohol consumption. In our patient, aging and daily alcohol consumption might have triggered the development of HCCs.

Keywords Alcohol consumption · Diabetes mellitus · Body mass index · Hepatosteatosis · Sustained virological response

Abbreviations

HCV	Hepatitis C virus
HCC	Hepatocellular carcinoma
IFNs	Interferons
SVR	Sustained virological response
DEB-TACE	Drug-eluting beads transcatheter arterial chemoembolization
CT	Computed tomography
BMI	Body mass index
HBsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
GGT	Gamma-glutamyl transpeptidase
AFP	Alpha-fetoprotein
BCLC	Barcelona clinic liver cancer
M2BPGi	Mac-2 binding protein glycosylation isomer
AUROC	Area under the receiver-operating characteristic curve
COI	Cut-off index

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Introduction

Hepatitis C virus (HCV) is a blood-borne single-strand RNA virus belonging to the *Flaviviridae* family. HCV is a major cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC) worldwide. To prevent liver-related complications, interferons (IFNs) have been used in the treatment of patients infected with the HCV. IFN-alpha and -beta, which are type I IFNs, trigger the host's immune response resulting in eradication of several viruses including HCV. Sustained virological response (SVR) is defined as aviremia 24 weeks after anti-HCV treatment and is considered to be an indication of virological cure. Achievement of SVR has been found to be associated with the inhibition of hepatocarcinogenesis [1]. However, several cases of HCC after SVR have been reported, especially in patients who are male, 65 years or older, and have severe hepatic fibrosis or a history of alcohol consumption [2–4]. Although most HCCs were detected within 10 years after SVR, the longest interval reported is 20 years [5–9].

We herein describe a male patient who developed HCCs 24 years after achieving an SVR at the age of 58 years. Although he was treated by drug-eluting beads transcatheter arterial chemoembolization (DEB-TACE), his HCCs developed aggressively resulting in his death at the age of 82 years.

Case report

In September 2016, an 82-year-old asymptomatic man visited Iwate Medical University hospital (a center for HCC treatment in northern Honshu, Japan) for assessment of liver tumors. He had hypertension and lumbar spinal canal stenosis, but did not have diabetes mellitus, dyslipidemia, a history of blood transfusion, or a family history of a liver disease. In 1992, at the age of 58 years, he was diagnosed with chronic hepatitis C. His hepatic stage was F1A1 according to the METAVIR score [10]. Thereafter, he was treated with IFN-alpha for 24 weeks at a local hospital. The HCV genotyping and viral load were unclear. He was free of HCV RNA after the IFN therapy and achieved an SVR in 1992. He was followed-up by annual blood tests and abdominal ultrasonography or computed tomography (CT). After the IFN treatment, he had drunk approximately 720–900 ml of Japanese sake daily, which includes 86–108 g of ethanol. In 2016, a new and irregular region over 8 cm in diameter was detected in segment 6 of his liver on abdominal CT. He was therefore admitted to Iwate Medical University hospital for further evaluation and treatment. Blood examination results on admission are presented in Table 1. His body mass index (BMI) was 22.5 kg/m^2, and his Child–Pugh grade was A. Throughout the clinical course, he remained negative for HCV RNA. He was negative for serum hepatitis B surface antigen (HBsAg) and hepatitis B viral DNA but positive for hepatitis B core antibody (HBcAb). Serum aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (GGT) levels had been elevated since 2012 (Fig. 1). In addition, serum albumin, total bilirubin, levels of total cholesterol, high-density lipoprotein cholesterol, triglyceride, hemoglobin A1c, and fasting glucose were within normal limits, but platelet counts were decreased. Tumor biomarkers including total alpha-fetoprotein (AFP), AFP-L3, and des-gamma-carboxy prothrombin were increased. AFP had not been elevated between 2000 and 2003. Abdominal gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging showed poor contrast enhancement of his right hepatic lobe in the hepatobiliary phase, and the maximum diameter of the tumors was 8 cm. CT arteriography showed enhancement of the entire tumors of hepatic segment 8, and massive lesions consisting of multiple tumors in segments 6 and 5 (Fig. 2). CT during arterial portography showed poor contrast enhancement of these tumors and invasion of P6. The tumors were therefore diagnosed as HCC stage C according to the Barcelona Clinic liver cancer (BCLC) criteria. Although the European guidelines recommended sorafenib for BCLC stage C HCCs, the patient refused it and underwent DEB-TACE twice. Eight months after the first DEB-TACE, he complained of abdominal distention and fatigue. Dynamic abdominal CT showed recurrence of HCCs, thrombosis of the portal and superior mesenteric veins, formation of an esophageal varix, cavernous transformation of the portal vein, ascites, and multiple lymph nodes metastases. He only received the best supportive care because of his deteriorating performance status and hepatorenal dysfunction. As a result, he died 9 months after the initial admission.

Table 1 Laboratory blood findings

White blood cell count (/μL)	7070
Red blood cell count (10^6/μL)	4.98
Hemoglobin (g/dL)	16.2
Platelet count (10^3/μL)	150
Prothrombin time (international normalized ratio)	1.11
Fibrinogen (mg/dL)	488
Total protein (g/dL)	7.6
Albumin (g/dL)	4.6
Aspartate aminotransferase (U/L)	33
Alanine aminotransferase (U/L)	22
Alkaline phosphatase (U/L)	445
Gamma-glutamyl transpeptidase (U/L)	110
Cholinesterase (U/L)	371
Lactate dehydrogenase (U/L)	214
Total bilirubin (mg/dL)	0.7
Ammonia (μg/dL)	34
Total cholesterol (mg/dL)	192
High-density lipoprotein cholesterol (mg/dL)	44
Triglyceride (mg/dL)	128
Fasting plasma glucose (mg/dL)	104
Hemoglobin A1c (%)	5.5
Urea nitrogen (mg/dL)	12.9
Creatinine (mg/dL)	103
HCV RNA (Log IU/mL)	ND
HBs antigen	Negative
HBs antibody (mIU/mL)	20.9
HBc antibody (S/CO)	6.2
Immunoglobulin A (mg/dL)	226
Immunoglobulin G (mg/dL)	1,340
Immunoglobulin M (mg/dL)	87
Ferritin (ng/mL)	642.3
Total alpha-fetoprotein (AFP) (ng/mL)	7,060
AFP L3 (%)	75.4
Des-gamma-carboxy prothrombin (AU/L)	2,900
Indocyanine green retention at 15 min (%)	16
Type IV collagen 7S (ng/mL)	7
M2BPGi (COI)	1.47

HCV hepatitis C virus, *HBs* hepatitis B virus surface, *HBc* hepatitis B virus core, *AFP* alpha-fetoprotein, *M2BPGi* Mac-2 binding protein glycosylation isomer, *ND* no detection

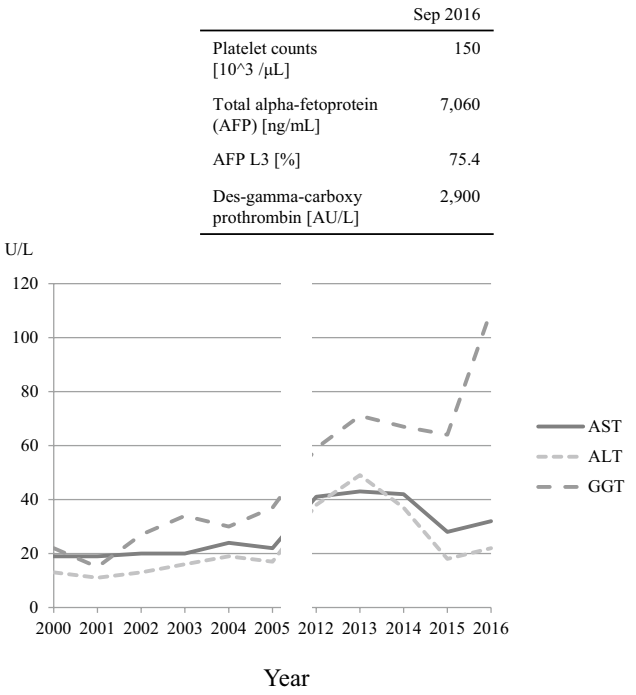

Fig. 1 Time courses of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GGT) levels from 2000 to 2016 (admission year). The data from 2006 to 2011 were unavailable

Because consent for liver biopsy or pathological autopsy was not obtained, histological examination could not be performed in 2016. Recently, it has been reported that the hepatic fibrosis stage of chronic liver disease associated with HCV can be predicted using markers or scoring models. It should be noted that these hepatic fibrosis markers and scores change before and after the achievement of SVR. To estimate the hepatic fibrosis stage, cut-off values, determined by clinical studies comparing the liver tissue with the results of these markers or models from patients achieving SVR are needed. Markers including type IV collagen 7S and *Wisteria floribunda* agglutinin-positive Mac-2 binding protein glycosylation isomer (M2BPGi), have been reported as good predictors of hepatic fibrosis [11]. Based on an area under the receiver-operating characteristic curve (AUROC) analysis, the cut-off value for diagnosis of severe hepatic fibrosis (F3–4) was reported as M2BPGi 1.42 cut-off index (COI) on the post-IFN treatment day (AUROC, 0.784: positive predictive value, 0.462: negative predictive value, 0.904) [12]. In our patient, the M2BPGi of 1.47 COI at the initial admission suggested severe hepatic fibrosis of F3–4. Progression from F1 at the time of the pre-IFN treatment in 1992 to F3–4 at admission in 2016 was presumed.

We searched the literature in the Medline and Igaku Chuo Zasshi databases, the Japanese largest medical literature database, to investigate the post-SVR factors associated with the occurrence of HCC over 10 years after an SVR achieved by IFNs. We identified a total of 38 patients from 24 studies reported from Italy and Japan [5–9, 13–31]. The clinical findings in these studies and our patient are shown in Table 2. None of the 39 patients (36 men, 2 women, and 1 without a reported sex) had a history of HCC before achieving SVR. They achieved an SVR between the ages of 41 and 69 years, and their HCC occurred between ages 54 and 86 years. Although only 5 patients were over 65 years at the time of achieving an SVR, 28 developed HCC at 65 years or older. The F stages were F0 in 0, F1 in 4, F2 in 9, F3 in 10, and F4 in 6 among 29 patients who underwent liver biopsy before IFN. Among 29 patients, 16 (55%) showed non-severe hepatic fibrosis (F0–2) and 13 patients (44%) showed severe hepatic fibrosis (F3–4). A total of 22 patients underwent pathological examination at the time of HCC occurrence, showing an F0 stage in 4, F1 in 8, F2 in 7, F3 in 2, and F4 in 1. The F stage of 18 patients was determined before IFN treatment and after occurrence of HCC, and showed improvement in 14 and no change in 4. Although HBsAg was negative in all reported patients, HBcAb was positive in 13 of 25 patients (52%). BMI, diabetes mellitus or impaired glucose tolerance, hepatosteatosis, and alcohol consumption were surveyed as lifestyle-related factors. The average BMI at HCC development was 24.0 kg/m^2 (17.5–28.1) and 13 of 29 patients (44%) had a BMI ≥ 25 kg/m^2. There were 8 patients with diabetes mellitus, and 3 with impaired glucose tolerance. Although the precise degree of hepatosteatosis was not fully described in all studies, 11 patients had a finding of "fatty liver" or steatosis which is more than 5%. A history of drinking alcohol at least once per week was found in 12 patients, 4 of whom had an intake of over 50 g/day of ethanol and 2 drank approximately 100 g/day of ethanol. One or more lifestyle-related factors were present in 26 of all 39 patients (66%), 12 of the 16 with F3–4 fibrosis before IFN treatment (75%) and 9 of the 13 with F0–2 (69%).

This study was approved by the Iwate Medical University ethics committee (H29-101). All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The need for informed consent was waived.

Discussion

Previous studies have demonstrated how successful IFN treatment for chronic hepatitis or compensated liver cirrhosis results in HCV eradication, amelioration of liver inflammation, improvement in hepatic fibrosis, and decrease in the incidence of HCC. Indeed, successful efforts to prevent and eradicate HCV have resulted in a decrease in the liver-related and all-cause mortality rates in patients with chronic HCV infection in Japan [1]. On the other hand, numerous

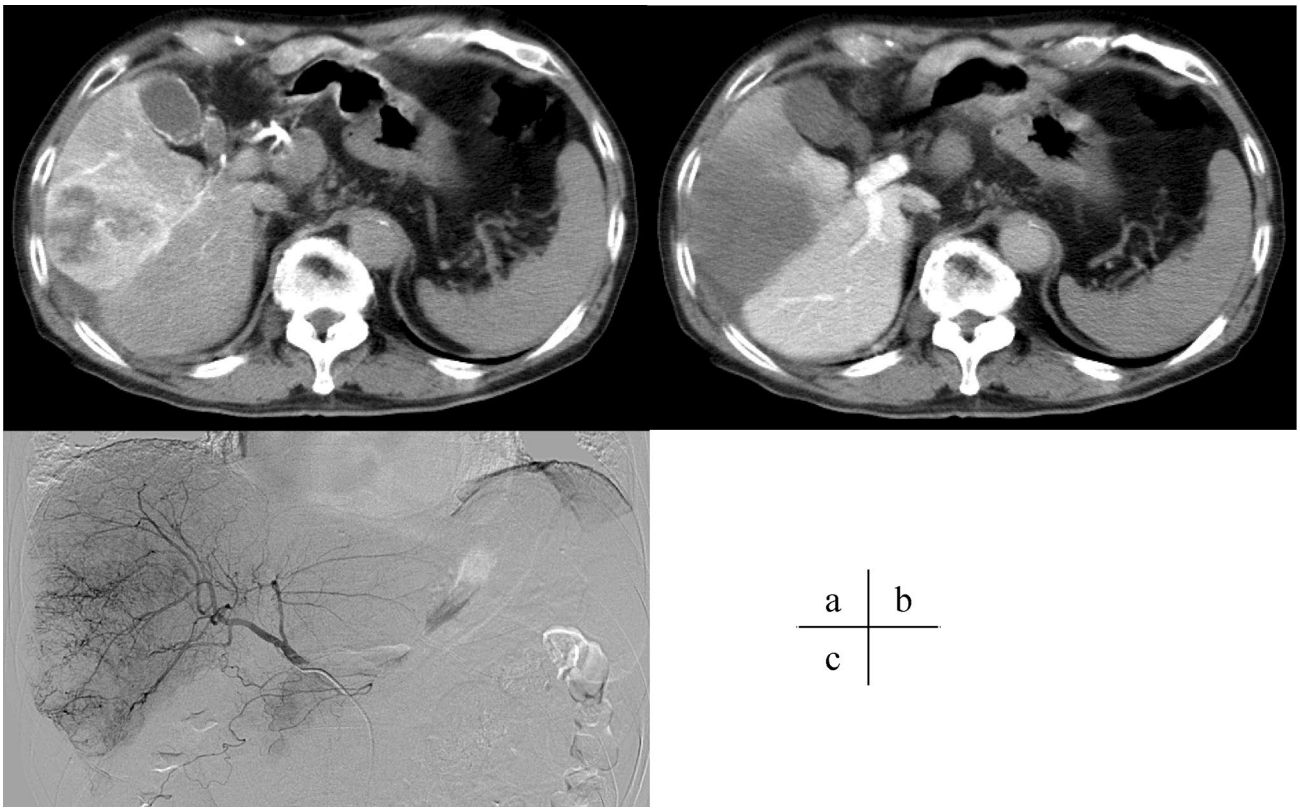

Fig. 2 Classical imaging findings of hepatocellular carcinoma were detected by computed tomography (CT) and angiography. CT hepatic arteriography showed enhancement of the entire tumor in hepatic segment 5 (**a**). CT during arterial portography showed poor contrast enhancement of this tumor (**b**). Hepatic arteriography showed massive multiple tumor lesions in the hepatic right lobe (**c**)

patients have developed HCC after successful IFN or direct acting antiviral (DAA) therapy, and they should not be ignored [32]. HCC development after eradication of HCV can be fatal for patients, and behoove a discussion of the medical economics of using costly DAAs. Some pre-SVR factors have been found to be associated with subsequent HCC, including sex (male), age (65 years or older), hepatic fibrosis (F3–4), and AFP [2, 3, 33]. The concurrent occurrence of these pre-SVR risk factors might correlate with hepatocarcinogenesis. However, in our patient, these risk factors do not fully explain the extremely long interval of 24 years from SVR to HCC occurrence. Although the patient was a man and developed HCCs at 82 years, he achieved SVR at the age of 58 years and his pre-SVR fibrosis stage was only F1. Patients in stages F1–2 comprised 44% of the reported patients who underwent liver biopsy before IFN treatment and developed an HCC 10 or more years after achieving an SVR (Table 2). This suggests that in addition to the pre-SVR risk factors including severe hepatic fibrosis, other factors that may develop or change after SVR might also have been involved in his hepatocarcinogenesis.

Several post-SVR factors are associated with increased incidence of HCC. Aging may be the most common, since 27 of the 34 reported patients developed HCC at 65 years or older. Metabolic disorders, including diabetes mellitus, hepatosteatosis, and hepatic iron deposition, may affect the development of HCC after achieving an SVR [3, 34, 35]. The presented patient, however, did not have diabetes mellitus, hepatosteatosis, or obesity. Hyperferritinemia indicates iron overload that might promote hepatic fibrosis and carcinogenesis, although serum ferritin levels are elevated in patients who consume alcohol, which is a risk factor for HCC after SVR [36]. Iwasaki et al. suggested that drinking 50 g of alcohol or more daily was associated with HCC after SVR [4]. Our patient had consumed approximately 100 g of ethanol per day and his blood examination on admission showed decreased platelet counts and elevated AST, GGT, type IV collagen 7S, and M2BPGi. According to these elevated hepatic fibrosis markers, his fibrosis stage on initial admission was predicted to be F3–4, which was higher than his pre-IFN fibrosis stage (F1). Of the 38 patients reported in the literature, 11 had a daily drinking habit. Long-term drinking after achieving an SVR might promote hepatic fibrosis and may be involved in the development of HCC 24 years after SVR in our patient.

Table 2 Previous reports of patients developing HCC 10 or more years after achieving SVR

References	Country	Age		Sex	Histology pre-SVR		Intervals[a] (years)	Histology post-SVR		BMI (Kg/m^2)	Alcohol consumption (1, ≥ once weekly; 0, none)	Ethanol (g/day)	DM or IGT	Hepatosteatosis (1, positive[b]; 0, negative)	HBcAb (1, positive; 0, negative)
		At SVR	At HCC occurrence		*F*	*A*		*F*	*A*						
[13]	Japan	58	68	M	N/A	N/A	10	2	1	26.8	1	43	0	N/A	N/A
[14]	Japan	53	63	M	2	1	10	1	0	27.8	1	64	0	1	1
[15]	Japan	68	78	M	1	1	10	N/A	N/A	N/A	N/A		N/A	N/A	N/A
[7]	Japan	61	72	M	4	2	10	2	1	26.2	0		IGT	1	1
[16]	Japan	60	70	F	N/A	N/A	10	N/A	N/A	27.7	0		DM	1	N/A
[15]	Japan	50	61	M	2	2	11	1	1	17.5	1	14–20	0	N/A	1
[17]	Japan	55	66	M	2	1	11	1	0	26.3	0		0	1	1
[18]	Japan	44	55	M	3	2	11	N/A	N/A	N/A	1	43.2	[c]	[d]	0
[7]	Japan	57	68	M	1	1	11	N/A	N/A	24.2	0		DM	0	1
[19]	Japan	42	54	M	4	1	12	3	1	N/A	1	100	N/A	N/A	N/A
[20]	Japan	52	65	M	3	2	12	0	0	N/A	N/A		0	N/A	N/A
[21]	Japan	N/A	N/A	M	N/A	N/A	12	1	1	20.3	N/A		N/A	N/A	N/A
[22]	Japan	N/A	N/A	N/A	N/A	N/A	12	N/A	N/A	N/A	N/A		N/A	N/A	N/A
[7]	Japan	54	67	M	3	N/A	12	N/A	N/A	25.8	0		0	0	0
[7]	Japan	66	79	M	3	N/A	12	N/A	N/A	27.7	0		0	1	0
[23]	Japan	43	56	M	2	2	13	1	1	22.4	1	21	DM	0	0
[21]	Japan	N/A	N/A	M	4	1	13	3	1	28.1	N/A		N/A	N/A	N/A
[21]	Japan	N/A	N/A	M	2	3	13	0	0	23.6	N/A		N/A	N/A	N/A
[24]	Japan	62	75	M	1	1	13	1	0	23.9	0		0	N/A	1
[25]	Japan	60	73	M	N/A	N/A	13	N/A	N/A	21.5	0		0	N/A	1
[26]	Italy	63	76	M	2	2	13	2	0	25.5	0		0	0	N/A
[7]	Japan	60	75	M	3	2	14	N/A	N/A	26.3	0		IGT	1	0
[18]	Japan	52	67	M	3	2	15	N/A	N/A	N/A	0		[c]	[d]	0
[18]	Japan	41	56	M	3	2	15	N/A	N/A	N/A	N/A		[c]	[d]	0
[27]	Japan	69	84	F	4	1	15	4	1	25.5	0		0	0	0
[28]	Japan	55	70	M	4	1	15	2	2	26.1	1	6	0	0	1
[29]	Japan	67	83	M	2	0	16	0	0	22.2	0		DM	N/A	1
[7]	Japan	52	69	M	3	N/A	17	N/A	N/A	25.5	1	≥ 65	IGT	1	1
[18]	Japan	62	80	M	2	2	18	2	0	N/A	0		[c]	[d]	0
[18]	Japan	59	77	M	2	2	18	1	0	N/A	1	43.2	[c]	1	0
[30]	Japan	49	67	M	3	2	18	2	1	20.8	0		0	1	1
[31]	Japan	55	74	M	N/A	N/A	19	1	1	24.2	0		0	0	0

Table 2 (continued)

References	Country	Age		Sex	Histology pre-SVR		Intervals[a] (years)	Histology post-SVR		BMI (Kg/m^2)	Alcohol consumption (1, ≥ once weekly; 0, none)	Ethanol (g/day)	DM or IGT	Hepatosteatosis (1, positive[b]; 0, negative)	HBcAb (1, positive; 0, negative)
		At SVR	At HCC occurrence		*F*	*A*		*F*	*A*						
[7]	Japan	63	83	M	3	N/A	20	N/A	N/A	22.9	0		0	0	0
[5]	Japan	46	66	M	N/A	N/A	20	N/A	N/A	20.9	1	4–6	0	N/A	N/A
[5]	Japan	61	82	M	N/A	N/A	20	N/A	N/A	19.9	0		0	N/A	N/A
[8]	Japan	55	75	M	N/A	N/A	20	N/A	N/A	22.8	0		0	N/A	N/A
[6]	Japan	66	86	M	4	1	20	2	0	21.4	1	20	0	N/A	1
[9]	Japan	43	63	M	N/A	N/A	20	0	0	N/A	0		DM	1	N/A
[e]	Japan	58	82	M	1	1	24	N/A	N/A	22.5	1	100	0	0	1

HCC hepatocellular carcinoma, *SVR* sustained virological response, *BMI* body mass index, *DM* diabetes mellitus, *IGT* impaired glucose tolerance, *HBcAb* hepatitis B core antibody, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* gamma-glutamyl transpeptidase, *N/A* not applicable

[a]Intervals between achieving SVR and HCC occurrence

[b]Defined as a finding of "fatty liver" or steatosis, which was present in 5%

[c]3 of 5 patients had DM

[d]1 of 4 patients had hepatosteatosis

[e]Our patient

The reason why HCC occurred in the patients without severe hepatic fibrosis over 10 years after SVR is unclear, since severe hepatic fibrosis was considered to be a risk factor for hepatocarcinogenesis within 5 years of SVR [2]. In an attempt to explain this long interval between SVR and development of HCCs, we developed the following hypotheses: first, within 5 years of SVR, HCC occurs mainly in high-risk patients who are older or have severe hepatic fibrosis on pre-SVR day. Second, the presence of lifestyle-related factors, including obesity, diabetes mellitus, hepatosteatosis, and/or habitual drinking, promote the development of HCC after SVR. Third, over 10 years after SVR, long-term accumulation of low-risk hepatocarcinogenesis factors, such as aging and lifestyle-related factors, may result in the occurrence of HCCs in the patients with relatively young and mild hepatic fibrosis. This concept remains speculative and should be verified in further studies comparing patients with and without occurrence of HCC.

The effect of latent HBV infection on hepatocarcinogenesis in patients with HCV-related liver disease has been reported [37]. Integration of the HBV gene into the host genome may affect hepatocarcinogenesis. The prevalence of concomitant HBsAg-negativity and HBcAb-positivity was 14 of 25 Japanese patients (56%), including our patient as shown in Table 2. This rate was higher compared with that reported on the general population of Japan surveyed from 2005 to 2006 (22%) [38]. However, it should be noted that the prevalence of HBcAb-positivity was 392 of 846 (46%) in Japanese HBsAg-negative patients with HCV-related chronic liver disease followed-up from 1995 to 2005 [37]. Prospective cohort studies comparing patients with and without occurrence of HCC are desirable to verify the effect of lifestyle-related factors or latent HBV infection on hepatocarcinogenesis. Considering prospective cohort studies are limited by the observation period or loss to follow-up, case–control studies based on a case report or a retrospective cohort study are important to assess the pertinent risk factors.

Although early diagnosis of HCC at a curable clinical stage is necessary for survival, an appropriate method and interval of surveillance of HCC in patients who have achieved an SVR have not been established. In our patient, annual laboratory and imaging studies were inadequate to discover the HCC before it progressed. The post-SVR factors, including aging and alcohol consumption, might have affected the long interval between SVR and HCC development. Therefore, stratification of HCC risk based on pre- and post-SVR factors may help optimize the monitoring procedure after SVR.

In conclusion, we identified a patient who had developed HCC 24 years after achieving an SVR. Although male sex plays an important role in the occurrence of HCC, aging post-SVR and lifestyle habits may be associated with hepatocarcinogenesis in patients without severe hepatic pre-IFN treatment.

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