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Case report

Recurrent hepatocellular carcinoma after spontaneous regression

Hyo-Suk Lee, June Sung Lee, Gwang Hoon Woo, Jung-Hwan Yoon, and Chung Yong Kim

Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Korea

Abstract: The prognosis of untreated hepatocellular carcinoma (HCC) is usually grave, although there have been a few case reports of spontaneous regression. Tumor recurrence after spontaneous regression has been rarely reported, and there have been no previous reports of recurrent hepatocellular carcinoma after spontaneous regression. Two cases of hepatocellular carcinoma that spontaneously regressed and subsequently recurred are presented. The patients' tumors spontaneously regressed, as reflected by the radiologically evidenced reduction in tumor size and markedly decreased alpha-fetoprotein levels. Subsequent tumor recurrences after regression were evidenced by radiologic findings of newly growing nodules and appreciably increased alpha-fetoprotein levels. To the authors' knowledge, these two patients represent the first reported cases of hepatocellular carcinoma recurrence after spontaneous regression. In both of these patients, new hepatocellular carcinomas recurred at different sites before the spontaneous regression of the original HCCs was complete. Although the precise causes of the regression and the subsequent recurrence remain to be further investigated, this phenomenon suggests that multicentric hepatocarcinogenicity and intratumoral events in each hepatocellular carcinoma nodule may be involved.

Key words: hepatocellular carcinoma, spontaneous regression, recurrence

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent human cancers worldwide, especially in Asia and Africa. Survival time after the onset of symptoms averages less than 6 months.[1] Factors which contribute to this dismal outcome are its biologically highly malignant nature as well as associated cirrhosis and a far-advanced stage when diagnosed.

Spontaneous regression of HCC is very rare, and 17 cases have been reported so far.[2–18] It is conceivable that spontaneous regression of HCC may be followed by subsequent recurrence because of the preneoplastic nature of the preexisting liver cirrhosis; however, spontaneous regression and subsequent recurrence of hepatocellular carcinoma has not previously been reported, although recurrence of other neoplasms after spontaneous regression has been, rarely, reported.[19–23] We report here two patients with HCCs which showed recurrence after spontaneous regression.

Report of cases

The clinical characteristics of the two patients are summarized in Table 1.

Patient 1

In May 1993, a 44-year-old man was referred to our hospital because of a liver mass detected by abdominal ultrasonography. He had been a social drinker, but during the 5 months prior to referral, had been drinking more than 80 g/day of alcohol every day.

Physical examination on admission revealed a hard nodular liver that extended for 5 cm below the right costal margin. He was positive for antibody to hepatitis C virus (HCV; anti-HCV) test. His serum alpha-fetoprotein (AFP) level was 12 200 ng/ml; serum albumin, 2.9 mg/dl (normal range, 3.3 to 5.2 mg/dl); and serum total bilirubin, 3.8 mg/dl (normal range, 0.2 to 1.2 mg/dl); his Child-Pugh score was 8. Abdominal enhanced computed tomography (CT) scanning (Fig. 1A)

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Reprint requests to: H.-S. Lee

Table 1. Clinical characteristics of two patients with hepatocellular carcinoma (HCC) which underwent spontaneous regression and subsequent recurrence

	Patient 1	Patient 2
Age (years)	44	63
Sex	Male	Male
Etiology	HCV	HBV
Diagnosis of HCC	5-cm Sized mass with portal vein thrombosis on CT scan, and high serum AFP level (12200 ng/ml)	Hypervascular mass (11 cm) on angiogram and high serum AFP level (1410 ng/ml)
Assessment of regression	Decreased tumor size (1 cm) on CT scan, and AFP level of 131 ng/ml	Decreased tumor size (3 cm) on CT scan, and serum AFP level of 5 ng/ml
Interval from initial diagnosis to regression (months)	5	7
Diagnosis of recurrence	New growth of another hypervascular tumor, as seen on CT scan and angiogram, and increase of serum AFP level to 47900 ng/ml	New growth of another hypervascular tumor, as seen on follow-up CT scan and angiogram, and compact Lipiodol[a] uptake after TACE
Interval from the initiation of regression to recurrence (months)	5	13
Survival (months)	13	37+ (Alive)

HCV, hepatitis C virus; HBV, hepatitis B virus; CT, computed tomography; AFP, alpha-fetoprotein; TACE, transarterial chemoembolization
[a] Lipiodol (iodized oil manufactured by Andre Guerbert, Aulnay-sous-Bois, France)

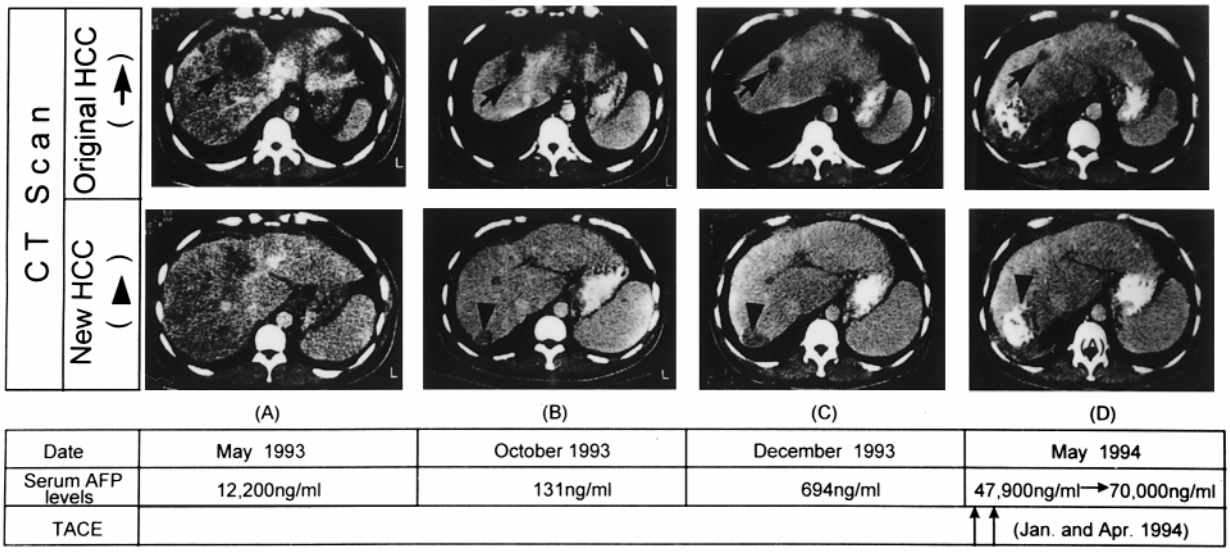

Fig. 1. Spontaneous regression and subsequent recurrence of hepatocellular carcinoma (*HCC*) in patient 1. The *upper and lower panels* of the enhanced computed tomography (*CT*) scans show the gradual spontaneous regression of the original HCC (*arrow*), and continuous new growth of the recurrent HCC (*arrowhead*), according to the time points shown in the *box beneath the panels*. Serial changes in serum alpha-fetoprotein (*AFP*) levels and the time points of transarterial chemoembolization (*TACE*) performance are indicated *in the box below the panels* (see the text for more details)

revealed a 5-cm-sized low attenuating mass, involving the left medial and right anterior superior segments (numbers 4 and 8, respectively) of the liver. Adjacent branches of the right and left portal veins were occluded. HCC was diagnosed, and as the patient was assessed as not treatable at that time, he was discharged with no medication and attended the outpatient clinic regularly.

Five months later (October 1993), the patient felt better than before. His serum AFP level had spontaneously decreased to 131 ng/ml, and enhanced CT scan-

ning showed a markedly smaller tumor, but a new tumor nodule had developed in the right posterior superior segment (number 7) (Fig. 1B). Two months later, in December 1993, enhanced CT scan showed that the previous tumor involving segments 4 and 8 had become even smaller, and was a 1-cm-sized mass; however, the new tumor in segment 7 had become larger, and was a 3-cm-sized mass (Fig. 1C) and the serum AFP level had increased to 694 ng/ml. In January and April 1994, respectively, he underwent two sessions of selective transarterial chemoembolization (TACE), as reported previously,[24] for the new tumor in segment 7, but the response was negative (Fig. 1D), as evidenced by continuous elevation of the serum AFP level (which reached 70000 ng/ml), and subsequent lung metastasis. He died of hepatic failure in July 1994.

Patient 2

In September 1994, a 63-year-old man was referred to our hospital for evaluation of hepatomegaly. Except for having suffered from chronic hepatitis B for the past 15 years, his medical history was unremarkable, and he had no history of excess alcohol ingestion.

Physical examination revealed non-tender rubbery-hard enlarged liver which was palpable 10 cm below the right costal margin in the midclavicular line. Liver function tests revealed normal levels of serum albumin and bilirubin, and his Child-Pugh score was 5. Serum AFP level was 1410 ng/ml. The arterial phase of abdominal spiral CT scan (Fig. 2A) revealed an enhancing mass, 11 cm in diameter, occupying almost the entire right lobe of the liver. Celiac angiography showed it to be highly vascular, and inferior vena cava (IVC) venography (Fig. 2B) indicated that a tumor had invaded the IVC. HCC was diagnosed and, as no treatment was considered worthwhile, the patient was sent home without medication, but was regularly followed-up at the outpatient clinic.

After discharge, his liver became progressively smaller. Three months after discharge, it was not palpable and his serum AFP level had decreased to below 5 ng/ml. Follow-up spiral CT scanning in April 1995 showed that the previous tumor had shrunk considerably and had become an about 5-cm-sized well marginated low-attenuating hypovascular mass (Fig. 2C). One year after presentation, he remained well, but on follow-up spiral CT scan in October 1995, a new 1.5-

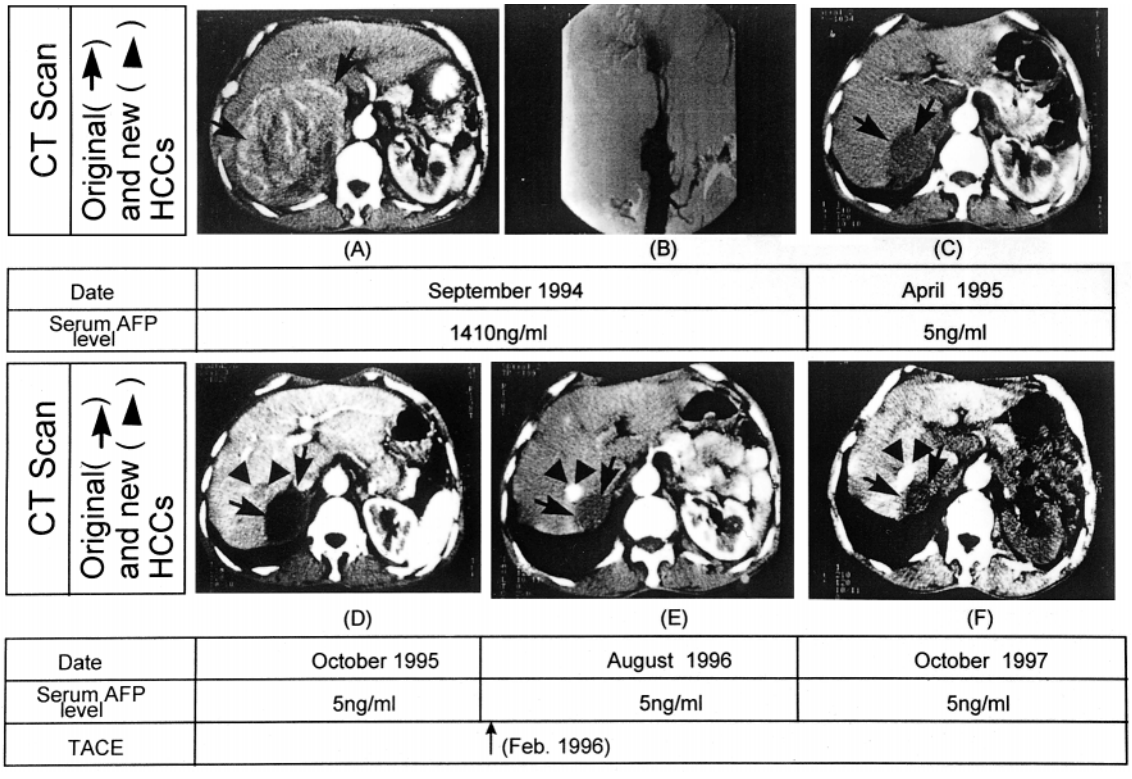

Fig. 2. Spontaneous regression and subsequent recurrence of HCC in patient 2. Spontaneous regression of the original tumor and subsequent recurrence of a new HCC nodule are indicated in *A* to *F* by *arrows* and in *D* to *F* by *arrowheads*, according to the time points shown in the *box beneath the panels*. Venogram in *B* shows near-complete obstruction of the inferior vena cava by the original HCC at first presentation

cm-sized low-attenuating nodule was detected in the right lobe, anterior to the previous shrunken low-attenuating mass (Fig. 2D). Three months later, in January 1996, liver ultrasonography (USG) showed that the previous shrunken tumor was still present, as a well marginated hypoechoic 5.3-cm-sized mass, and the previous compression of the IVC by the original tumor had disappeared, but the new nodule had become larger and was now a 2.8-cm hyperechoic nodule with a hypoechoic peripheral rim. His serum AFP level was still less than 5 ng/ml. He underwent TACE in February 1996 for the newly developed nodule, and a subsequent Lipiodol (Andre Guerbert, Aulnay-sous-Bois, France) CT scan revealed compact Lipiodol uptake by a 2.8-cm-sized nodule, which, 6 months later, had shrunk to 1.8 cm (Fig. 2E). Subsequent 3-monthly follow-up USG and laboratory tests showed no change in tumor size and in serum AFP level. On his last visit, in October 1997, the patient felt healthy and the results of liver function tests were normal. Spiral CT scan showed that the previous low-attenuating mass had become smaller, and was a 3-cm-sized mass, and the nodule with compact Lipiodol uptake was no larger (Fig. 2F).

Discussion

We have described two cases of HCC which showed spontaneous regression and subsequent recurrence, in one patient with HBV-related and one patient with HCV-related chronic liver disease. Our patients differ from previously reported cases involving spontaneous regression in that the HCCs recurred when the original HCC was regressing. The recurrence of other neoplasms after spontaneous regression is rarely reported,[19–23] and, to the best of our knowledge, the present report is the first to describe the recurrence of HCCs after spontaneous regression.

The limitation of the present study is that these cases were not histologically proven before spontaneous regression. A definitive diagnosis of HCC usually depends on the results of liver biopsy, although diagnosis on the basis of a combination of characteristic radiologic findings and highly elevated serum AFP levels is also possible.[25–29] Actually, in most patients, biopsy should not be used if the lesion has already been confidently characterized by imaging studies.[30] In the present patients, high serum AFP levels, in addition to the characteristic radiologic findings, were convincing in regard to the diagnosis of HCC (Table 1).

Clinical evidence of tumor regression in our patients was provided by radiologically visualized reduction in the neoplastic mass, as well as by markedly decreased AFP levels. The tumors were not treated, and the regression can therefore truly be described as spontaneous.[31] Subsequent tumor recurrences were demonstrated by radiologic findings and by appreciable increases in AFP levels (Table 1). The clinical, laboratory, and radiologic features seen at presentation and the subsequent clinical courses of these particular patients indicate that they were patients in whom HCC recurred after spontaneous regression.

The spontaneous regression of cancer is rare, with an estimated incidence of one per 60000 to 100000 patients.[32] The mechanism involved is still poorly understood, although various associated conditions have been proposed. According to previous reports, HCC regressed spontaneously after abstinence from alcohol,[2] persistent fever,[3,4] the withdrawal of androgen,[5] surgery involving blood transfusion,[6] upper gastrointestinal bleeding,[7,8] the use of herbal medicine,[9] spontaneous arterial thrombus,[10] or rapid tumor growth,[11,12] but cases for which no associated condition was found have also been reported.[13–18] In our patient 1, regression may have been related to abstinence from alcohol. Epidemiological data suggest an indirect role of ethanol in hepatocarcinogenesis,[33] but whether the regression of this patient's cancer was simply coincident with, or whether it was causally related to alcohol withdrawal, is a matter of speculation. In patient 2, the previous diagnostic angiography may have caused iatrogenic arterial thrombosis or intimal injury resulting in necrosis of the HCC, as in a previously reported patient;[34] however, neither intimal injury nor arterial thrombosis could be found on angiography and subsequent follow-up CTs in our patient and he did not present postembolization syndrome, which had been observed in the patient previously reported;[34] therefore, we think that patient 2 can be described as having had spontaneous regression.

In the patients we reported, the recurrent HCCs developed at different sites in the liver before the preexisting HCC had completely regressed (Figs. 1 and 2), suggesting that multicentric hepatocarcinogenicity, rather than intrahepatic metastasis, was more likely to have been involved in the recurrence. Furthermore, the findings that the recurrent HCC in patient 1 did not secrete AFP into the serum, while the original HCC showed a very high serum level of AFP before regression also support the multicentric origin of the recurrent HCC.

The interesting observation that the recurrent HCCs developed while the preexisting HCCs were regressing also suggests that, in tumor regression, an intratumoral event may be involved in addition to systemic events, although the precise nature of the intratumoral event remains to be investigated. To date, the precise nature of these events has not been clarified. Therefore the growth patterns of HCC, as presented in this study, should be the basis of future studies to elucidate these mechanisms.

References

1. Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment: study of 850 patients. Cancer 1985;56:918–28.
2. Gottfried EB, Steller R, Paronetto F, Lieber CS. Spontaneous regression of hepatocellular carcinoma. Gastroenterology 1982; 82:770–4.
3. Lam KC, Ho JCI, Yeung RTT. Spontaneous regression of hepatocellular carcinoma. A case study. Cancer 1982;50:332–6.
4. Markovic S, Ferlan-Marolt V, Hlebanja Z. Spontaneous regression of hepatocellular carcinoma. Am J Gastroenterol 1996;91: 392–3.
5. McCaughan GW, Bilous MJ, Gallagher ND. Long-term survival with tumor regression in androgen-induced liver tumors. Cancer 1985;56:2622–6.
6. Sato Y, Fujiwara K, Nakagawa S, Kanishima S, Ohta Y, Oka Y, et al. A case of spontaneous regression of hepatocellular carcinoma with bone metastasis. Cancer 1985;56:667–71.
7. Gaffey MJ, Joyce JP, Carlson GS, Esteban JM. Spontaneous regression of hepatocellular carcinoma. Cancer 1990;65:2779–83.
8. Tocci G, Conte A, Guarascio P, Visco G. Spontaneous regression of hepatocellular carcinoma after massive gastrointestinal haemorrhage. BMJ 1990;300:641–2.
9. Chien RN, Chen TJ, Liaw YF. Spontaneous regression of hepatocellular carcinoma. Am J Gastroenterol 1992;87:903–5.
10. Imaoka S, Sasaki Y, Masutani S, Ishikawa O, Furukawa H, Kabuto T, et al. Necrosis of hepatocellular carcinoma caused by spontaneously arising arterial thrombus. Hepatogastroenterology 1994;41:359–62.
11. Suzuki M, Okazaki N, Yoshino M, Yoshida T. Spontaneous regression of a hepatocellular carcinoma: a case report. Hepatogastroenterology 1989;36:160–3.
12. Iwasaki M, Furuse J, Yoshino M, Moriyama N, Kanemoto H, Okumura H. Spontaneous regression of hepatocellular carcinoma: a case report. Jpn J Clin Oncol 1997;27:278–81.
13. Ayres RCS, Robertson DAF, Dewbury KC, Millward-Sadler GH, Smith CL. Spontaneous regression of hepatocellular carcinoma. Gut 1990;31:722–4.
14. Grossman M, Hoermann R, Weiss M, Jauch KW, Oertel H, Staebler A, et al. Spontaneous regression of hepatocellular carcinoma. Am J Gastroenterol 1995;90:1500–3.
15. Ozeki Y, Matsubara N, Tateyama KI, Kokubo M, Shimoji H, Katayama M. Spontaneous complete necrosis of hepatocellular carcinoma. Am J Gastroenterol 1996;91:391–2.
16. van Halteren HK, Salemans JM, Peters H, Vreugdenhil G, Driessen WMM. Spontaneous regression of hepatocellular carcinoma. J Hepatol 1997;27:211–5.
17. Kaczynski J, Hansson G, Remotti H, Wallerstedt S. Spontaneous regression of hepatocellular carcinoma. Histopathology 1998;32: 147–50.
18. Gómez Sanz R, Moreno Gonzalez E, Colina Ruiz-Delgado F, Garcia-Muñoz H, Ochando Cerdan F, Gonzalez-Pinto I. Spontaneous regression of a recurrent hepatocellular carcinoma. Dig Dis Sci 1998;43:323–8.
19. Mayolo JA, Ahn YS, Temple D, Harrington WJ. Spontaneous remission of acute leukemia after the termination of pregnancy. Cancer 1989;63:1621–3.
20. Penchansky L, Wollman MR, Gartner C, Wenger SL. Spontaneous remission of infantile acute nonlymphocytic leukemia for 11 years in child with normal karyotype. Cancer 1993;71:1928–30.
21. Shimamoto Y, Kikuchi M, Funai N, Suga K, Matsuzaki M, Yamaguchi M. Spontaneous regression in adult T-cell leukemia/lymphoma. Cancer 1993;72:735–40.
22. Ide M, Jimbo M, Yamamoto M, Hagiwara S, Aiba M, Kubo O. Spontaneous regression of primary intracranial germinoma. A case report. Cancer 1997;79:558–63.
23. Marcus SG, Chiyke PL, Reiter R, Jaffe GS, Alexander RB, Linehan WM, et al. Regression of metastatic renal cell carcinoma after cytoreductive nephrectomy. J Urol 1993;150:463–6.
24. Lee H-S, Kim JS, Choi IJ, Chung JW, Park JH, Kim CY. Safety and efficacy of transcatheter arterial chemoembolization in patients with hepatocellular carcinoma and main portal vein obstruction. A prospective controlled study. Cancer 1997;79: 2087–94.
25. Okuda K, Obata H, Jinnouchi S. Angiographic assessment of gross anatomy of hepatocellular carcinoma: comparison of celiac angiograms and liver pathology in 100 cases. Radiology 1977; 123:21–9.
26. Honda H, Ochiai K, Adachi E, Yasumori K, Hayashi T, Kawashima A, et al. Hepatocellular carcinoma: correlation of CT, angiographic, and histopathologic findings. Radiology 1993;189: 857–62.
27. Choi BI, Han JK, Cho JM, Choi DS, Han MC, Lee H-S, et al. Characterization of focal hepatic tumors. Value of two-phase scanning with spiral computed tomography. Cancer 1995;76:2434–42.
28. Maringhini A, Cottone M, Sciarrino E, Marceno MP, Seta FL, Fusco G, et al. Ultrasonography and alpha-fetoprotein in diagnosis of hepatocellular carcinoma in cirrhosis. Dig Dis Sci 1988;33: 47–51.
29. Lee H-S, Chung YH, Kim CY. Specificities of serum alpha-fetoprotein in HBsAg(+) and HBsAg(−) patients in the diagnosis of hepatocellular carcinoma. Hepatology 1991;14:68–72.
30. Ros PR, Davis GL. The incidental focal liver lesion: photon, proton, or needle? Hepatology 1998;27:1183–90.
31. Everson TC, Cole WH. Spontaneous regression of cancer. Philadelphia: WB Saunders, 1966.
32. Cole WH. Efforts to explain spontaneous regression of cancer. J Surg Oncol 1981;17:201–9.
33. Bassendine MF. Alcohol—a major risk factor for hepatocellular carcinoma? J Hepatol 1986;2:513–9.
34. Takayasu K, Muramatsu Y, Shima Y, Moriyama N, Yamada T, Yoshida T, et al. Necrosis of hepatocellular carcinoma as a result of subintimal injury incurred by hepatic angiography: report of two cases. Am J Gastroenterol 1986;81:979–83.