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Spontaneous Regression of Hepatocellular Carcinoma: Report of a Case

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Abstract
A spontaneous regression of hepatocellular carcinoma is an extremely rare phenomenon. A 69-year-old Japanese man with hepatitis C virus-related chronic hepatitis presented with a liver tumor. We diagnosed the tumor to be hepatocellular carcinoma in the course of spontaneous regression, by imaging studies and changes in the tumor markers. Because the possible presence of viable cancer cells could not be ruled out, we recommended surgery. He refused all treatments at first, but finally agreed to undergo surgery about 10 months after presentation. A hepatectomy was performed. Histologically, no viable tumor cells were found. In our case, the vascularity of the tumor according to the imaging findings was followed up during the clinical course. The patient is now doing well and without any evidence of recurrence at 37 months after surgery.

Key words Spontaneous regression · Hepatocellular carcinoma · Hepatectomy · Vascularity

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers throughout the world, and it normally has a poor prognosis. Patients diagnosed at an early stage may achieve a 5-year survival rate about 50%, while those at an intermediate to advanced stage demonstrate a 20%–50% survival at 3 years, and those at a terminal stage die within 6 months.[1] A spontaneous regression of HCC is a rare phenomenon. To our knowledge, only 40 such cases have been reported so far in the medical literature in English. The exact mechanism of this phenomenon remains unknown. We herein report the case of a patient who underwent a hepatectomy after spontaneous regression of HCC, and discuss the clinical course and treatment of cases with a spontaneous regression of HCC.

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Case Report

A 69-year-old man with chronic hepatitis C, diagnosed in 2001 and a gastric ulcer, was treated as an outpatient at a hospital. A liver tumor was first detected by ultrasonography (US). Plain computed tomography (CT) showed an almost uniformly low-density area measuring 4.0 cm in diameter in Couinaud's segment 4 (S4) with several liver cysts. Contrast enhanced computed tomography (CECT) revealed the tumor to be encapsulated, enhanced for the most part, while it also had small, low-density areas suggesting necrosis (Fig. 1a). One month after the first US, the serum level of protein induced by vitamin K absence or antagonist-II (PIVKA II) was high, at 1773 mAU/ml (normal range, 0–39 mAU/ml) and that of α-fetoprotein (AFP) was 5 ng/ml (normal range, 0–20 ng/ml). His family history was unremarkable. He had no known history of a blood transfusion or medication such as anticoagulant drugs and vitamin K. He was, however, a heavy drinker.

He was referred to our hospital 2 months after the first US, and a new US showed a 5.1 × 5.0-cm liver tumor in S4. The tumor showed a mosaic pattern with a halo (Fig. 2). Doppler US demonstrated the tumor to be hypervascular. Dynamic CT performed 3 months after the first US showed the tumor, measuring 4.5 cm in diameter, to be slightly enhanced in the early phase while it also showed a low-density area in the late phase (Fig. 1b). There was a large nonenhanced region in the

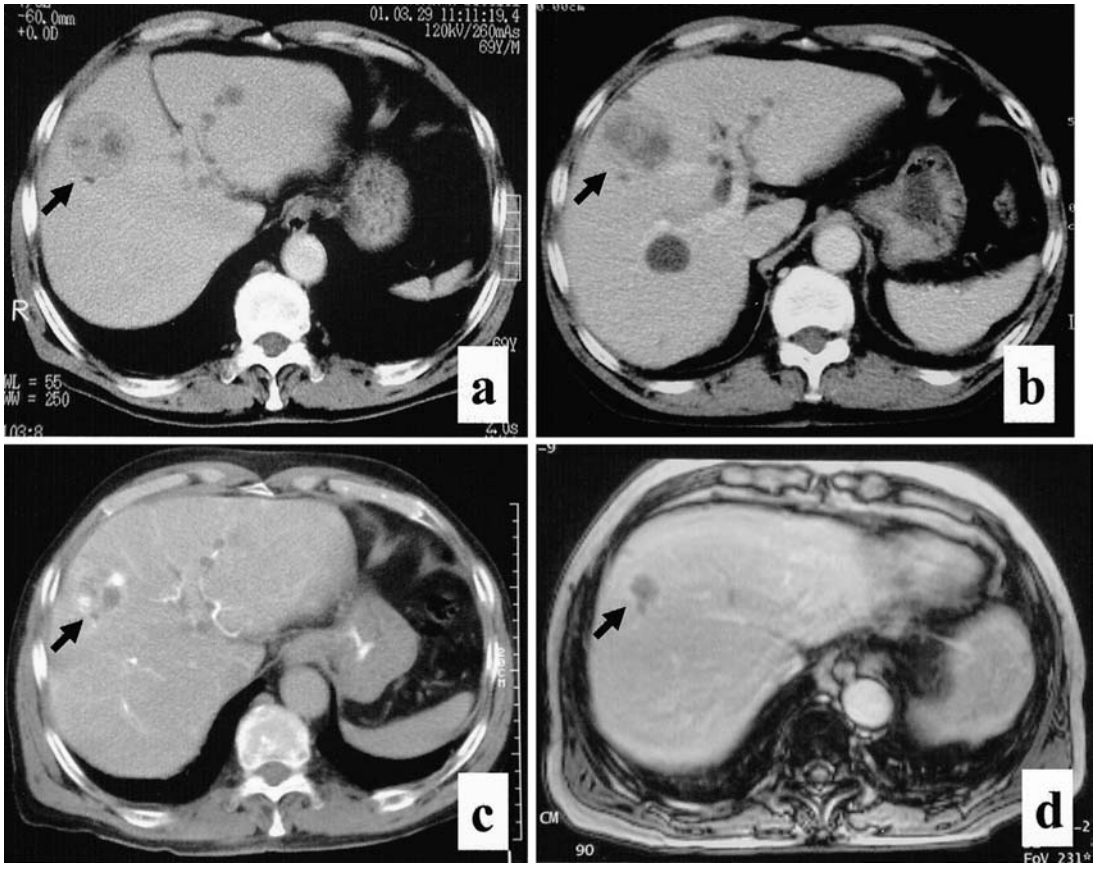

Fig. 1. a Contrast-enhanced computed tomography (CT) showed a low-density area measuring 4 cm in diameter in S4 (*arrow*) taken during the same period as the first ultrasonogram (US). **b** Dynamic CT in the late phase revealed a low-density tumor measuring 4.5 cm in diameter (*arrow*) 3 months after the first US. **c** Angiographic CT showed the tumor to have regressed to 3 cm in diameter with two hypervascular parts (*arrow*) 4 months after the first US. **d** Dynamic magnetic resonance imaging showed the tumor to have regressed again to 1.8 cm with ring enhancement (*arrow*) 10 months after the first US

tumor, thus suggesting that the necrosis had spread. The serum PIVKA II level decreased to 1180 mAU/ml 2 months after the first US. He was admitted to our hospital 3 months after the first US. A physical examination revealed no evidence of hepatomegaly, jaundice, or vascular spider. There were no ascites. Laboratory studies on admission disclosed leukocytes 6050/μl, hemoglobin 12.9 g/dl, hematocrit 40.4%, platelets 258×10^3/μl, serum total protein 7.9 g/dl, albumin 4.3 g/dl, total bilirubin 0.9 mg/dl, serum aspartate transaminase (AST) 76 IU/l, serum alanine transaminase (ALT) 66 IU/l, prothrombin time 11.0 s (control 10–15 s), indocyanine green clearance test at 15 min (0.5 mg/kg body weight) 20% (normal 0%–10%), AFP 4.3 ng/ml, AFP-L3 0.0%, and PIVKA II 79 mAU/ml. Hepatitis C virus antibody was positive and hepatitis B surface antigen was negative. A hepatic angiogram, which was performed 4 months after the first US, revealed a hypervascular tumor in S4. No subintimal vascular injury was observed. Lipiodol was not administered. Angiographic CT performed at the same time showed the tumor, measuring 3.0 cm in diameter, to consist of two hypervascular parts (Fig. 1c). The patient was therefore diagnosed to have HCC in the course of spontaneous regression. We recommended surgery, but he refused any further examinations and all treatments such as surgical or nonsurgical therapies. He was followed up in the outpatient clinic. For the time being, he rejected both blood examination and imaging studies. He had never received any anticancer treatment and had not taken herbal medicine. He later told us that, after he had been admitted, he sometimes consumed a small amount of alcohol when staying away from the hospital overnight. His serum PIVKA II level declined to 22 mAU/ml 9 months after the first US. Dynamic CT performed at the same time revealed the previous tumor in S4 to have decreased to 2.0 cm in diameter, but it was not enhanced. Because the possible presence of viable HCC in the tumor could not be ruled out, we again recommended that he undergo an operation. This time he agreed to our proposal.

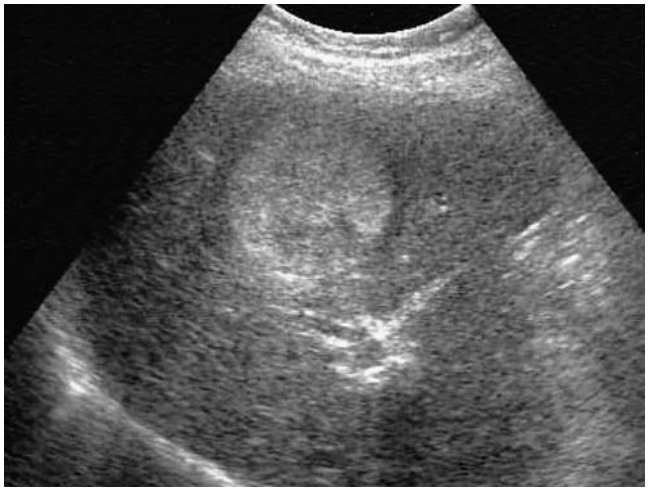

Fig. 2. The 5.1-cm tumor in S4 showed a mosaic pattern with a halo on ultrasonography

He was readmitted to our hospital 10 months after the first US. Dynamic MRI carried out at the same time demonstrated shrinkage of the tumor, now measuring 1.8 cm in diameter, with ring enhancement and without intratumoral enhancement (Fig. 1d). An S4a (caudal part of S4) subsegmentectomy of the liver was performed 11 months after the first US. A contracting scar due to a regression of the tumor was recognized on the surface of the liver in S4 over the tumor. Intraoperative ultrasonography showed the tumor to be fed by two feeding arteries of S4 and S5. The postoperative course was uneventful.

Macroscopically, the tumor on the cut surface of the specimen, measuring 1.9 × 1.7 cm, was whitish and partially yellowish with a fibrous capsule and septum-like structures (Fig. 3a). Microscopically the tumor was a completely necrotic nodule with inflammatory cell infiltration, and it was encapsulated by a fibrotic capsule. No viable malignant cells were noticed (Fig. 3b). The main histological feature of the background liver was active chronic hepatitis. Three years one month after surgery, he is doing well and has no signs of recurrence.

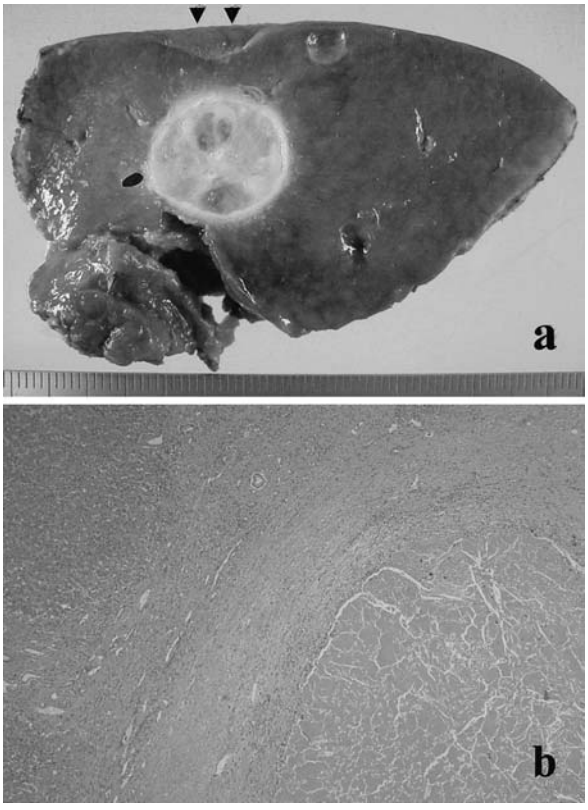

Fig. 3. **a** The cut surface of the tumor was whitish and partially yellowish with a fibrous capsule and septum-like structures. A contracting scar was seen on the liver surface, over the tumor (*arrowheads*). **b** A microscopic view of the tumor showed a completely necrotic nodule with inflammatory cell infiltration, and it was encapsulated by a fibrotic capsule. H&E, ×40

Discussion

In the 40 cases of spontaneous regression of HCC that have been reported in the medical literature in English (Table 1), the survival period ranges between 1 year and 20 years, and the prognosis is relatively good. The causative factors and mechanism leading to a spontaneous regression of HCC are not clearly known. Possible mechanisms proposed in the literature include abstinence from alcohol consumption, taking herbal medicine, gastrointestinal bleeding, high fever, immunological systems, a deficiency in the tumor blood supply, androgen therapy, subintimal vascular injury by angiographic procedures, and the tumor's rapid growth.

There was no histological evidence of HCC in our case, as in eight other cases (Table 1), although angiography and dynamic CT demonstrated almost typical patterns of HCC. Moreover, changes in the PIVKA II level in parallel with tumor growth also suggested HCC. We presented this case at the 38th Annual Meeting of Liver Cancer Study Group of Japan in June 2002, and the audience supported our diagnosis.

In the present case, the vascularity of the tumor was followed up. As the tumor decreased in size and changed from hypervascular to avascular, the PIVKA II level decreased from a high level to the normal range. No viable malignant cells existed in the tumor speciemen. In 12 of the 40 cases reviewed, accounts of vascularity in the tumor at regression were given.[2] In 11 cases,[3–6] no intratumoral staining was recognized at tumor regression. In 10 of them, all the tumors

Table 1. Clinical charactretistics of 40 cases of hepatocellular carcinoma with spontaneous regression

No.	First author[Ref.]	Year	Age (years)	Sex	Etiology	Liver	Tumor size (cm)	Vascularity at tumor regression	Radiological disappearance	Surgery	Necrosis
1	Johnson[13]	1972	2	f	Androgen	Normal	6	U	Complete		
2	Gottfried[14]	1982	65	m	Alcoholic	LC	2	(+ →) U	Complete		
3	Lam[15]	1982	50	m	B	NonLC	U	U	Complete		
4	Sato[5]	1985	78	m	U	CH	10, 6	(+ →) –	Complete		
5	McCaughan 1[16]	1985	28	m	Androgen	U	U	U	Complete		
6	McCaughan 2	1985	40	m	Androgen	Normal	U	U	Complete		
7	Takayasu 1[17]	1986	38	m	B	U	U	(+ →) 1/2-	No regression	+	1/2, Necrosis
8	Takayasu 2	1986	58	f	U	LC	3	(+ →) –	Partial	Autopsy	Complete
9	Suzuki[18]	1989	67	m	U	LC	3.2	(+ →) U	Complete		
10	Tocci[19]	1990	79	m	U	LC	5	U	Complete		
11	Gaffey[20]	1990	63	m	U	LC	10	U	Partial	Autopsy	Complete
12	Ayres[21]	1990	63	f	U	LC	U	U	Complete		
13	Mochizuki[4]	1991	61	m	U	LC	U	(+ →) –	Complete		
14	Chien[22]	1992	65	m	B	LC	12	(+ →) U	Complete		
15	Imaoka[8]	1994	65	m	C	CH	U	–	U	+	Almost
16	McDermott[23]	1994	23	f	U	U	U	U	Complete		
17	Grossmann[24]	1995	52	m	U	LC	4.5	U	Al.complete		
18	Ozeki[3]	1996	69	f	U	LC	5	–	Partial	+	Complete
19	Markovic[2]	1996	62	m	B	LC	13	+	Partial	+	Complete
20	van Halteren[25]	1997	72	f	U	U	8	U	Complete		
21	Iwasaki[6]	1997	72	f	C	LC	1st)3.9→2 2nd)3.8→1	–	Partial Partial		
22	Gomez[26]	1998	66	m	C	LC	8	U	Complete		
23	Kaczynski[27]	1998	73	m	U	NonLC	7	U	Complete		
24	Ohba[28]	1998	76	m	C	LC	U	U	Al.complete		
25	Magalotti 1[10]	1998	66	m	Alcoholic	LC	3	U	Complete		
26	Magalotti 2	1998	75	f	C	LC	4.5	U	Partial		
27	Stoelben 1[9]	1998	56	m	U	Normal	6	U	Partial	+	Mainly
28	Stoelben 2	1998	74	m	U	Normal	6	U	Partial	+	Totally
29	Toyoda[29]	1999	82	m	C	LC	1	U	Complete(lung)		
30	Misawa[30]	1999	62	m	B	LC	6	(+ →) U	Complete		
31	Izushi[7]	2000	50	m	C	CH	3.5	–	No regression	+	Complete
32	Takeda[11]	2000	68	m	C	LC	6.3	U	Complete		
33	Ikeda[31]	2001	75	m	C	U	?	U	Partial(lung)		
34	Lee 1[12]	2000	44	m	C	CH	5	U	Partial		
35	Lee 2	2000	63	m	B	CH	11	(+ →) –	Partial		
36	Jang[32]	2000	54	f	B	LC	7	U	Complete		
37	Uenishi[33]	2000	65	m	C	CH	12	–	Partial	+	Almost
38	Matsuo[34]	2001	72	m	C	CH	3.5	U	Partial	+	Complete
39	Nakai[35]	2001	76	m	C	LC	3	U	Complete		
40	Present case	2005	69	m	C	CH	4.5	(+ →) –	Partial	+	Complete

U, unknown; LC, liver cirrhosis; CH, chronic hepatitis; al., almost; Y, year; M, month; LN, lymph node; a, alive; d, dead; GI, gastrointestinal; A-P, arterioportal, AFP, α-fetoprotein
(1)*, existence of viable malignant cells; (2)*, histological evidence of HCC

either radiologically disappeared or were histologically necrotic. Six tumors of the spontaneous HCC that regressed may have lost their vascularity during the clinical course. In three cases,[6,7] the tumors were either hypovascular or avascular lesions with ring enhancement. In the present case, the blood supply on the central side may have been sufficient, because the tumor was fed by two feeding arteries of S4 and S5. Therefore the main mechanism of tumor regression in our case may be possibly related to a disturbance of the blood supply on the peripheral side, such as the formation of a thick capsule.[7] A thick capsule may prevent the nutrient blood supply from reaching the tumor through the feeding arteries. Judging from the changes in the tumor size during the clinical course, no rapid growth of the tumor was recognized. Changes in the immunological function, caused by abstinence from alcohol, may not be taken into consideration because the tumor had already regressed at the beginning of the patient's decrease in alcohol consumption.

Cases with a spontaneous regression of HCC have a relatively good prognosis. In our case, no viable malignant cells were seen. In 5 of 10 surgical cases, cancer cells remained in a part of the tumor in the resected speciemen.[8,9] Five of the 40 cases reviewed showed recurrence after spontaneous regression.[10–12] One case also revealed the same tumor to again relapse after spontaneous regression.[6] We therefore propose that HCC tumors that show spontaneous regression should be treated the same as in our case, if the tumor remains to some degree and the patient's liver function is acceptable.

Spontaneous tumor regression is an interesting phenomenon, but its mechanism remains unclear. We hope

(1)*	(2)*	Period to (almost) complete regression or surgery: Liver	Period to (almost) complete regression or surgery: Metastatic lesion	AFP (ng/ml)	PIVKA II (mAU/ml)	Distant metastasis	Proposed mechanism of regression	Prognosis
	+	1Y		Negative	U	No	Androgen withdrawal	1Y, d
	+	1Y		Normal	U	No	Abstinence from alcohol	4Y, a
	+	1Y	1Y	U	U	Lung	Infection, herbal medicine	14Y, a
	+	4Y10M	3M	26 200	U	Bone	GI bleeding	5Y2M, a
	+	6Y7M		Normal	U	No	Androgen withdrawal	10Y7M, a
	+	9Y2M		Normal	U	No	Androgen withdrawal	13Y2M, a
+	+	2M		16 950	U	No	Subintimal injury on angiography	4Y,a
+	+	Dead		Normal	U	No	Subintimal injury on angiography	2Y6M, d
	–	1Y5M		7 767	U	No	Rapid growth	5Y10M, a
	+	2.5Y		625	U	No	GI bleeding	4Y, a
–	+	2Y		2 690	U	No	GI bleeding, macrobiotic diet	2Y, d
	+	5M	5M	7 390	U	Lung	U	1Y, a
	+	1Y6M	U	221 000	U	Bone	Abscopal regression after radiation	1Y6M, d
	+	5M		>10 000	U	No	Herbal medicine	3Y1M, a
+	+	1M		6 609	U	No	Arterial thrombus	U
	+	5Y		U	U	No	U	20Y, a
	+	1Y1M		310	U	No	Abstinence from alcohol	1Y2M, d
–	–	U		1 050	U	No	U	1Y+α, a
U	+	3M		11	U	No	Inflammatory cytokines	8Y, a
	+	1Y8M		U	U	No	Infarction due to poor vascularity in LC	2Y4M, a
	+	1st)3M 2nd)2M		105 340	U	No	Tumor's rapid growth	1Y5M, a
	+		6M	4	U	LN	Immune mechanism	5Y+α, a
	+	1Y3M		U	U	No	U	15Y, d
	+	10M	1M	429 998	4 900	Bone	Abscopal regression after radiation	2Y5M, a
	+	1Y		2 500	U	No	U	6Y3M, d
	+	1M		37 500	U	No	U	2Y5M, d
+	+	2M		3.7	U	No	Biological effects triggered by infection	2Y, a
+	+	3M		3 850	U	No	Biological effects triggered by infection	3Y5M, a
	+	Size up	14M	50 000	U	Lung	U	1Y9M, d
	–	1Y		1 400	Normal	No	Biological effects by A-P shunt	1Y, a
–	–	2M		16.4	U	No	U	5Y, a
	+	4M		8 230	1 477	No	Herbal medicine	1Y3M, a
	–	Size up	4M	14 734	U	Lung	U	10M, a
	–	7M		12 200	U	No → lung	Abstinence from alcohol	1Y1M, d
	–	7M		1 410	U	No	Arterial thrombosis or intimal injury due to previous angiography	3Y1M, a
	+	4Y		4	U	No	U	4Y, a
+	+	3M		4 796	223	No	Abstinence from alcohol, A-P shunt	1Y4M, a
–	–	2M		1 000	2 000	No	Ischemia, immuno responses	1Y3M, a
	+	1Y		Normal	675	No	Immunological mechanism (NK cell)	3Y, a
–	–	11M		5.6	1 773	No	Ischemia	3Y1M, a

that in the future, further accumulation and discussion of such cases will help to elucidate the etiology and treatment of this phenomenon.

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