Case Report

A Case of Hepatocellular Carcinoma with Spontaneous Regression of Primary Tumor and Progression of Intrahepatic Metastasis

Minil KIM, Takayoshi ITO, Tatsuo OZAWA, Takashige TOMITA,
Hitoshi NISHIDA, Keiji MITAMURA and Michio IMAWARI

Abstract : A 71-year-old Japanese male with liver cirrhosis due to hepatitis C virus infection showed a markedly elevated serum α -fetoprotein (AFP) concentration. Computed tomography (CT) revealed a hypervascular tumor compatible with hepatocellular carcinoma (HCC) in Couinaud's segment 4 (S4) in the liver. One month later, the tumor was enlarged and five months later, the serum AFP level began to decrease without any therapy. The tumor in S4 subsequently regressed over two months. Tumor stains were not observed in the S4 area on digital subtraction angiography (DSA) and the serum AFP level had decreased to within normal range. On admission, another hypervascular tumor was visualized in S5 by CT and the lesion was treated with transarterial chemoembolization (TAE). After TAE treatment, there was no finding of HCC recurrence on CT for at least twenty months. This report describes a case of spontaneous regression of HCC with a second enlarged tumor, which was satisfactorily treated with TAE.

Key words : hepatocellular carcinoma, intrahepatic metastasis, spontaneous regression

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent carcinomas with a high mortality rate and increasing incidence. The spontaneous regression of malignant tumors in humans, particularly that of HCC is extremely rare. Recent advancements in diagnostic imaging make it possible to observe the natural course of HCC, and identify the spontaneous regression. In 1972, the first case report of HCC with spontaneous regression was published¹⁾, and many case reports have been published since that time. Most of these reports describe cases with solitary and large HCCs (30 mm in diameter), and only 5 cases in 4 reports were of patients with HCC and intrahepatic metastasis²⁻⁵⁾. The mechanisms of both spontaneous regression and intrahepatic metastasis remain unclear. Here, we report a case of small HCC (30 mm in diameter) with spontaneous regression and progression of intrahepatic metastasis as demonstrated by imaging studies.

Case Report

A 71-year-old Japanese male with liver cirrhosis due to hepatitis C virus infection had

Second Department of Internal Medicine, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan.

Fig. 1. Time course of hepatocellular carcinoma regressing in the patient on Computed Tomography(CT). An enhanced CT scan shows a well enhanced mass lesion in the segment 4 (S4) of the liver five months before admission (a), enlargement of tumor with irregular low density area in S4 two months before admission (b), regression of the tumor in S4 area on admission (c) and complete regression two months later (d).

undergone follow-up for three years. He had a past history of blood transfusion due to a traffic accident at 40 years of age, and has undergone a splenectomy due to a splenic malignant lymphoma (non-Hodgkin, B cell, diffuse type) at the age of 68 years. Six months before admission, a blood examination showed a high level of AFP (1,894 ng/ml). Five months before admission, computed tomography (CT) of the abdomen revealed an enhanced tumor of 15 mm in diameter in the arterial phase and an isodensity in the portal phase compatible with advanced HCC without capsule at Couinaud's segment 4 (S4) (Fig. 1a). The patient did not consent to admission at this time. One month before admission, the patient's serum AFP level had elevated to 11,710 ng/ml. The patient was admitted to our hospital in January 2001 for treatment of his liver tumor. Anticancer medication and herbal medication were not administered during this period.

A physical examination showed a chronically ill-appearing male with an abdominal operation scar. No lymph node was palpable. The liver was palpable 3 cm under the right costal margin. There was no ascites or edema. A laboratory evaluation (Table 2) classified his liver function as Child-Pugh grade A. The serum AFP level had decreased from 11,710 ng/ml to 51 ng/ml.

The HCC in S4 had enlarged to 30 mm in diameter without enhancement in the arterial phase on CT two months prior to admission, and showed a mosaic pattern with capsule

Table 1. Characteristics of spontaneous regression of HCC with intrahepatic metastasis

Authors	Years	Age	Sex	Cirrhosis	AFP (ng/ml)	Size (cm)	Etiology
Gottfried <i>et al</i>	1982	65	M	Yes	Normal	Multi focal	Alcoholic
Ayres <i>et al</i>	1990	63	F	Yes	8868	Multi focal	Unknown
Magalotti <i>et al</i>	1998	66	M	Yes	2500	Multi focal	Alcoholic
Magalotti <i>et al</i>	1998	75	F	Yes	37500	1.5 and 4.5	HCV
Uenishi <i>et al</i>	2000	65	M	No	4796	12	HCV

HCV ; hepatitis C virus, HBV ; hepatitis B virus, AFP ; ng/ml, Size ; cm

Table 2. Laboratory data on admission

Blood cell count			Biochemistry			Serology		
WBC	7700	/ μ l	T-P	7.7	g/dl	CRP	<0.2	mg/dl
RBC	452	$\times 10^4$ / μ l	Alb	4.5	g/dl	IgG	1327	mg/dl
Hb	15.6	g/dl	TTT	19.3	U/l	IgA	63	mg/dl
Hct	46.3	%	ZTT	8.8	U/l	IgM	134	mg/dl
Plt	20.2	$\times 10^4$ / μ l	T-Bil	0.7	mg/dl			
			GOT	33	IU/l			
Coagulation tests			GPT	20	IU/l	Virus markers		
PT	>100	%	γ -GTP	34	IU/l	HBs-Ag	<2.0	
HPT	>100	%	LDH	524	IU/l	HCV-Ab	90.4	
Fig	268	mg/dl	ALP	434	IU/l	Sero group	1	
			T-Cho	298	mg/dl	HCV-PCR	>850	copy/ml
			Glu	99	mg/dl	(amplicore)		
Urinalysis			BUN	14	mg/dl			
protein	(-)		Cre	1.3	mg/dl	Tumor markers		
sugar	(-)		Na	140.6	mEq/l	AFP	51	ng/ml
			K	4.7	mEq/l	PIVK-II	21	ng/ml
Stool			Cl	108.6	mEq/l			
Hb	(-)		CRP	<0.2	mq/l	ICGR15	18	%

(Fig. 1b). On admission, CT and ultrasonography (US) scans revealed another hypervascular tumor at S5. This S5 tumor was compatible with an intrahepatic metastasis from the primary HCC because the tumor was enhanced despite its small size (Fig. 2a). The new lesion at S5 was 10 mm in diameter on CT. Ultrasonography detected the tumor in S5 but not the tumor in S4 (Fig. 3). A needle biopsy of the S5 tumor was performed. Biopsy specimens from the non-tumor area showed liver cirrhosis. Specimens from the tumor revealed a moderately differentiated HCC (Fig 4). Digital subtraction angiography (DSA) showed an avascular area in S4 compatible with spontaneous regression (Fig. 5b), and a tumor stain in S5 (Fig. 5a). The HCC in S5 was selectively treated with transarterial embolization (TAE) using 40 mg of doxorubicin-lipodiol emulsion and gelatin sponge particles (gelform). The HCC in S4 had diminished one month following TAE treatment (Fig. 1c), and had completely regressed 2 months later (Fig. 1d). CT of the HCC in S5 three months following TAE treatment confirmed the patient was in remission (Fig. 2b).

Fig. 2. Dynamic study on CT scan shows the other lesion that was enhanced well at early phase on admission (a) and accumulation of lipiodiol after TAE in S5 area on a month after admission (b).

Fig. 3. The ultrasonography on admission shows high and mosaic pattern of a liver tumor, indicating an intrahepatic metastasis in S5 area.

Fig. 4. Histological findings of a biopsy liver specimen from the tumor in S5 reveals moderately differentiated hepatocellular carcinoma with liver cirrhosis. H.E staining (a: $\times 100$, b: $\times 40$)

Fig. 5. DSA of right hepatic artery shows a tumor stain in S5 area (a) and that of left hepatic artery reveals an avascular area in S4 area of the liver (b).

<Clinical course>

Fig. 6. Clinical course of the patient. Changing of tumor size in S4 and the serum AFP level was indicated.

The serum AFP level normalized, and normal levels were maintained 9 months after TAE. The patient is alive without any HCC recurrence 20 months after TAE. A follow-up CT showed no HCC recurrence for the same interval.

Discussion

Everson⁶⁾ and Cole⁷⁾ define the spontaneous regression of malignant tumors as the disappearance of malignant tumor without administration of anticancer drugs or surgical resection.

The spontaneous regression of malignant tumors occurs one in every 100,000 cases⁷⁾ with the spontaneous regression of HCC being extremely rare. Almost all of the cases involving spontaneous regression of HCC in the literature describe large and solitary HCCs (>30 mm) with capsule formation. Only 5 cases in 4 reports consist of multiple cases (Table 1)²⁻⁵⁾.

The causes of spontaneous regression of HCC are considered to involve both ischemic and humoral factors. Local ischemic factors include subintimal arterial damage during angiography, tumor biopsy, rapid tumor growth and arterial thrombosis in tumors^{5, 8-13)}. Gastrointestinal bleeding and shock are known systemic ischemic factors. Reported causes of spontaneous regression via humoral factors include blood transfusion, viral or bacterial infection, abstinence of alcohol and immunological mechanisms^{6, 8, 14, 15)}. Cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-12 may have potential antitumor activities in patients with these conditions.

Early, well-differentiated HCCs not greater than 20 mm in diameter are not enhanced in dynamic CT. At the early stage, both the hepatic artery and portal vein supply the HCC. As the HCC enlarges, the histological features change from well differentiated to moderately or poorly differentiated, and a capsule is formed. The histological change leads to intrahepatic metastasis. A well-differentiated carcinoma does not progress to intrahepatic metastasis.

The patient in this case report had two HCC lesions (S4 and S5). The HCC in S5 was histologically diagnosed by needle biopsy, and the HCC in S4 was diagnosed by CT and tumor size before regression. The primary HCC in S4 was 15 mm in diameter, and at an advanced stage without capsule formation. At the advanced stage, the blood supply to the tumor is mainly through the hepatic artery, a capsule has not formed and ischemic change does not easily occur. Furthermore, this tumor had metastasized to the S5 area. After metastasis formation, the primary HCC enlarged to 30 mm in diameter and formed a capsule. The regressed HCC had showed rapid growth and a remarkable increase in AFP during the 4-month interval. Local therapies such as TAE or PEIT were not performed before regression. In this patient, we hypothesize that the rapid tumor growth induced spontaneous regression due to a poor supply of blood flow to the tumor. The intrahepatic metastasis is thought to seed through the portal vein before capsule formation. When the metastatic tumor was visualized on CT, the original tumor in S4 had regressed.

Suzuki *et al* suggested that rapid growth triggers tumor necrosis due to a relative decrease in blood supply to the tumor. They also suggested that immunological mechanisms are important in spontaneous tumor regression¹²⁾. We could not rule out the possibility that an immunological response against the HCC in S4 had occurred, particularly because of the high levels of AFP in the lesion. Further analysis is required to elucidate the mechanism of spontaneous regression of HCCs.

References

- 1) Johnson FL, Lerner KG, Siegel M, Feagler JR, Majerus PW, Hartmann JR and Thomas ED: Association of androgenic-anabolic steroid therapy with development of hepatocellular carcinoma. *Lancet* 2 : 1273-1276 (1972)
- 2) Ayres RC, Robertson DA, Dewbury KC, Millward-Sadler GH and Smith CL: Spontaneous regression of hepatocellular carcinoma. *Gut* 31 : 722-724 (1990)
- 3) Gottfried EB, Steller R, Paronetto F and Lieber CS: Spontaneous regression of hepatocellular carcinoma. *Gastroenterology* 82 : 770-774 (1982)

- 4) Magalotti D, Gueli C and Zoli M: Transient spontaneous regression of hepatocellular carcinoma. *Hepatogastroenterology* **45** : 2369-2371 (1998)
- 5) Uenishi T, Hirohashi K, Tanaka H, Ikebe T and Kinoshita H: Spontaneous regression of a large hepatocellular carcinoma with portal vein tumor thrombi: report of a case. *Surg Today* **30** : 82-85 (2000)
- 6) Everson TC: Spontaneous regression of cancer. *Prog Clin Cancer* **3** : 79-95 (1967)
- 7) Cole WH: Efforts to explain spontaneous regression of cancer. *J Surg Oncol* **17** : 201-209 (1981)
- 8) Lee HS, Lee JS, Woo GW, Yoon JH and Kim CY: Recurrent hepatocellular carcinoma after spontaneous regression. *J Gastroenterol* **35** : 552-556 (2000)
- 9) Misawa K, Hata Y, Manabe K, Matsuoka S, Saito M, Takada J and Sano F: Spontaneous regression of hepatocellular carcinoma. *J Gastroenterol* **34** : 410-414 (1999)
- 10) van Halteren HK, Salemans JM, Peters H, Vreugdenhil G and Driessen WM: Spontaneous regression of hepatocellular carcinoma. *J Hepatol* **27** : 211-215 (1997)
- 11) Imaoka S, Sasaki Y, Masutani S, Ishikawa O, Furukawa H, Kabuto T, Kameyama M, Ishiguro S, Hasegawa Y, Koyama H and Iwanaga T: Necrosis of hepatocellular carcinoma caused by spontaneously arising arterial thrombus. *Hepatogastroenterology* **41** : 359-362 (1994)
- 12) Suzuki M, Okazaki N, Yoshino M and Yoshida T: Spontaneous regression of a hepatocellular carcinoma-a case report. *Hepatogastroenterology* **36** : 160-163 (1989)
- 13) Takayasu K, Muramatsu Y, Shima Y, Moriyama N, Yamada T, Yoshida T, Makuuchi M and Kishi K: Necrosis of hepatocellular carcinoma as a result of subintimal injury incurred by hepatic angiography: report of two cases. *Am J Gastroenterol* **81** : 979-983 (1986)
- 14) Sato Y, Fujiwara K, Nakagawa S, Kanishima S, Ohta Y, Oka Y, Hayashi S and Oka H: A case of spontaneous regression of hepatocellular carcinoma with bone metastasis. *Cancer* **56** : 667-671 (1985)
- 15) Lam KC, Ho JC and Yeung RT: Spontaneous regression of hepatocellular carcinoma: a case study. *Cancer* **50** : 332-336 (1982)

[Received January 13, 2004 : Accepted February 12, 2004]