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Single Case

Spontaneous Regression of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus

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Keywords
Hepatocellular carcinoma · Spontaneous regression · Portal vein tumor thrombus

Abstract
An 83-year-old man underwent transcatheter arterial chemoembolization (TACE) for a 20-mm hepatocellular carcinoma (HCC) in Couinaud's segment 4. Computed tomography (CT) 4 months after TACE showed tumor thrombus in the portal vein in addition to diffuse metastases and arterioportal shunts in the left lobe. Although we performed the best supportive care, the tumor thrombus in the portal vein and tumors in the left lobe had completely disappeared on CT 16 months after the TACE. Rapidly grown portal vein tumor thrombus and arterioportal shunt might be the causes of spontaneous regression of HCC, probably associated with tumor hypoxia.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and mostly develops in patients with chronic hepatitis B and C virus infections, although non-B, non-C HCC has been increasing in Japan [1, 2]. Many patients are still diagnosed at the advanced stage, and their prognosis is poor, even if appropriate treatments are performed. Portal vein tumor thrombus is one of the advanced findings of HCC, and treatment options are sometimes restricted [3].

Spontaneous regression has been reported in various kinds of malignancies, including HCC [4, 5]. Although several mechanisms of spontaneous regression of HCC have been proposed, it remains unclear. Here, we describe a rare case of spontaneous regression of HCC with massive main portal vein tumor thrombus that might be one of the causes of tumor regression.

Case Report

An 83-year-old man with hepatitis C virus infection was admitted to our hospital for the treatment of HCC. He had received a diagnosis of HCC and had been treated by radiofrequency ablation and transcatheter arterial chemoembolization (TACE) since the age of 74 years. He had a past medical history of hypertension, diabetes mellitus, and benign prostatic hyperplasia at 60 years of age and cerebral infarction at 72 years of age. He had no history of blood transfusion, alcohol consumption, or smoking and no family history of note. He had been receiving oral treatment with diuretics and a preparation of branched chain amino acid but not herbal medicine. Physical examination showed no symptoms suggesting severe liver damage, such as jaundice or hepatosplenomegaly. Blood tests on admission showed hemoglobin 11.9 g/dL, platelet count 100,000/m^3, albumin 3.2 g/dL, total bilirubin 0.57 mg/dL, aspartate aminotransferase and alanine aminotransferase 28 IU/L and 46 IU/L, respectively, and gamma glutamyl transpeptidase 67 IU/L. Serum alpha fetoprotein (AFP) and protein induced by vitamin K absence/antagonist-II (PIVKA-II) were 117 ng/mL and 21 mAU/mL, respectively. The Child-Pugh classification belonged to category B, score 7. Serum ammonium level was within the normal range (Table 1). A contrast-enhanced computed tomography (CT) scan, which was performed 2 months before TACE, showed a tumor of 20 mm in diameter in Couinaud's segment 4 (S4) with the typical imaging of HCC. Then, tumor invasion into the left branch of the portal vein was not detected (Fig. 1a, b). We performed conventional TACE with Miriplatin hydrate to the S4 HCC, but lipiodol accumulation in the left branch of the portal vein was observed on a CT scan that was taken 1 week after the TACE (Fig. 1c, d). Moreover, the tumor progressed in the main portal vein after 4 months. Lipiodol in the left branch of the portal vein was completely washed out. Diffuse metastasis in the left lobe, ascites, and arterioportal shunts were newly detected by CT scan (Fig. 1e, f). Tumor markers were remarkably elevated (AFP, 631 ng/mL; PIVKA-II, 501 mAU/mL; Fig. 2). He did not receive any interventional treatments because of his age and the advanced stage of HCC. We subsequently attentively followed up his general conditions. Contrary to our expectations, his general condition gradually improved. A CT scan 16 months after the last TACE revealed disappearance of the thrombus of the left branch of the portal vein and atrophic change of the left lobe (Fig. 3). The tumor thrombus in the main portal vein and the tumors in the left lobe also disappeared, so we diagnosed

spontaneous regression of HCC. There are no signs of recurrence on imaging findings or increase of tumor markers 2 years after the last TACE (Fig. 2).

Discussion

Spontaneous regression of a malignancy has been defined as a partial or complete disappearance of tumor without receiving any specific treatment [6] and is a well-established phenomenon in certain malignancies, including renal cell carcinoma, neuroblastoma, and choriocarcinoma [4]. It is a rare phenomenon with a frequency of occurrence estimated at between 1/60,000 and 1/100,000 malignant cases [4]. Among these malignancies, regression of HCC appears to be a rare event. Oquiñena et al. [5] collected data from 10 randomized controlled trials involving 1,640 HCC patients and estimated the value to be 0.4%.

Portal vein tumor thrombus is one of the advanced findings of HCC, and patients' prognosis is poor [3]. According to the Barcelona Clinic Liver Cancer (BCLC) staging system, which is used broadly worldwide, HCC with portal vein tumor thrombus belongs to "advanced stage," and the administration of sorafenib is recommended [7]. In Japan, a patient with HCC accompanied by a main portal vein tumor thrombus is recommended to be treated by hepatic arterial infusion chemotherapy or by the administration of sorafenib or regorafenib according to the Child-Pugh classification [8]. These treatments are sometimes effective but are harmful to the liver and accelerate the progression of pre-existing chronic liver injury. Thus, it is very difficult to survive for 2 years. In the present case, massive tumor thrombus in the main portal vein indicated a poor prognosis, but it may be one of the causes of the regression of HCC.

There are some hypotheses about the causes of spontaneous regression of HCC. Kato et al. [9] suggested that tumor hypoxia, systemic inflammatory response, and the use of herbal medicine might play an important role in the regression of HCC. Tumor hypoxia is induced by the disruption of the portal vein or feeding artery to the tumors, rapid tumor growth, large arterioportal shunt, and a shock due to massive gastrointestinal bleeding [10, 11]. Hemorrhagic shock may produce optimum conditions to regress neoplastic cells without damaging normal tissues. The neoplastic tissue is more sensitive than normal tissue to a sudden reduction of the blood and oxygen supply because of its high metabolic requirements [12]. A systemic inflammatory response includes cholangitis, sepsis, and trauma [13, 14]. Huz et al. [15] also suggested that the spontaneous regression of HCC is most commonly associated with tumor hypoxia or a systemic inflammatory response.

In the present case, the patient had not taken any herbal medicine or consumed any new drugs. There were no symptoms (e.g., fever up, abdominal pain) suggesting a systemic inflammatory response before regression of HCC. CT scan showed rapid tumor growth in the left branch to the main portal vein without formation of collateral vessels and occlusion of the artery (Fig. 1e, f). In addition, arterial blood flow and arterioportal shunt in the left lobe complementarily increased. Therefore, the massive main portal vein tumor thrombus decreased portal blood flow, and the arterioportal shunt decreased blood supply from the hepatic artery to the tumors. These disturbances of the blood circulation could have induced hypoxia of rapidly increased tumors and precipitated a tumor regression, although the hepatic artery itself was not disrupted. A delayed tumor effect of sustained release of platinum cannot be denied, but lipiodol in the left branch of the portal vein was completely washed out 4 months after the

TACE. It is also undeniable that some occult systemic inflammatory response to HCC also precipitates a tumor regression. This is because the almost 2 years of long relapse-free survival cannot be explained by tumor hypoxia alone.

The mechanism of spontaneous regression of HCC has been studied by imaging findings and the clinical course in addition to histological and immunological findings, but it remains unclear. The accumulation of cases of spontaneous regression of HCC will contribute to the understanding of the phenomenon and is expected to give us the possibility to improve the treatment strategy for HCC.

Statement of Ethics

Consent for publication has been obtained from the patient.

Disclosure Statement

The authors have no conflict of interest.

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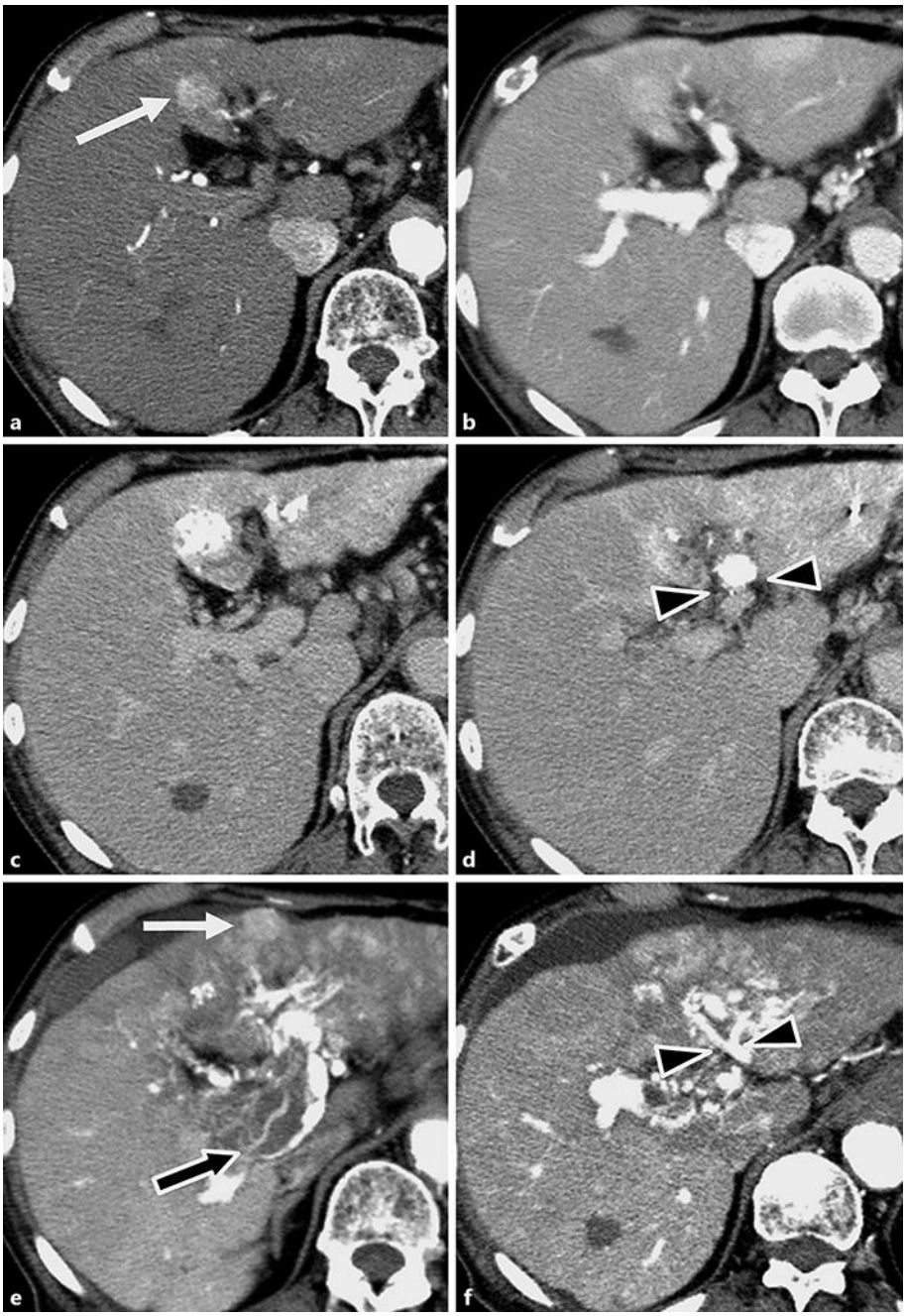

Fig. 1. Contrast-enhanced computed tomography (CT) scan performed 2 months before the transcatheter arterial chemoembolization (TACE) (**a**, **b**). A tumor 20 mm in size was observed in the S4 liver segment. The tumor was revealed as a high-density area in the arterial (**a**) (arrow) and portal (**b**) phase. Tumor invasion into the left branch of the portal vein was not detected. CT scan performed 1 week after conventional TACE showed lipiodol accumulations not only in the main tumor (**c**) but also in the left branch of the portal vein (**d**) (arrowheads). CT scan performed 4 months after conventional TACE showed an extensive tumor invasion into the main portal vein (**e**). Thread and streak sign caused by the portal vein tumor thrombus during the arterial phase was observed (**e**) (black arrow). Diffuse high-density area in the left lobe during the arterial phase (**e**) (white arrow), ascites, and arterioportal shunt were newly detected. Occlusion of the hepatic artery was not observed (**f**) (arrowheads). Lipiodol in the left branch of the portal vein was completely washed out.

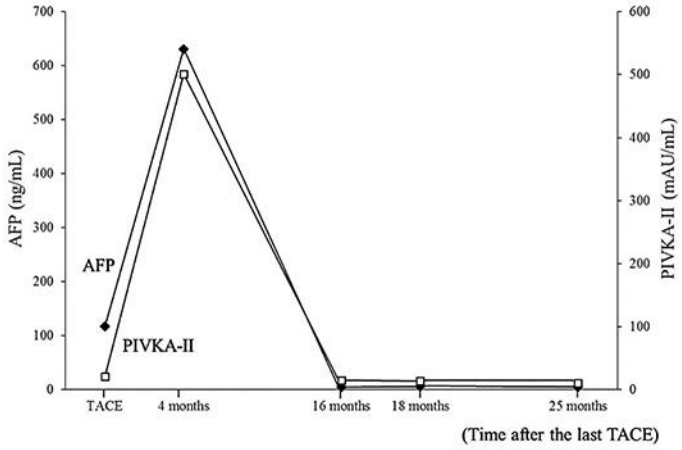

Fig. 2. Clinical course of the patient. AFP, alpha fetoprotein; PIVKA-II, protein induced by vitamin K absence/antagonist-II; TACE, transcatheter arterial chemoembolization.

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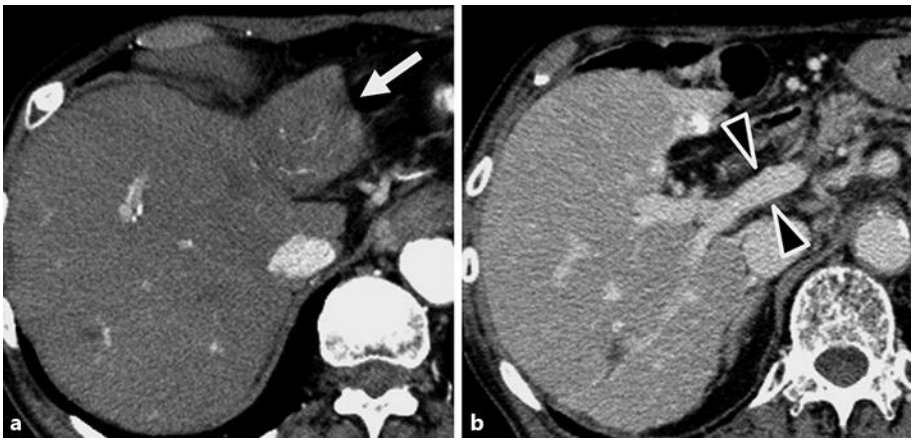

Fig. 3. Contrast-enhanced computed tomography scan performed 16 months after conventional transcatheter arterial chemoembolization showed disappearance of the diffuse high-density area in the left lobe during the arterial phase (**a**) (white arrow) as well as of the tumor thrombus in the main portal vein during the delayed phase (**b**) (arrowheads). Atrophy of the left lobe was observed.

Table 1. Laboratory findings on admission

Hematology			**Serology**		
WBC	5,000	/μL	CRP	0.09	mg/dL
RBC	378×10^4	/μL			
Hb	11.9	g/dL	**Coagulation**		
Ht	34.9	%	PT%	84.2	%
Plt	10×10^4	/μL	PT-INR	1.13	
			APTT	38	s
Biochemistry			**Virus markers**		
TP	6.1	g/dL	HBsAg	(–)	
Alb	3.2	g/dL	HBcAb	(–)	
T-bil	0.57	mg/dL	HCVAb	(+)	
AST	28	IU/L			
ALT	46	IU/L			
LDH	129	IU/L	**Tumor markers**		
ALP	327	IU/L	AFP	21	ng/mL
GGT	67	IU/L	PIVKA-II	117	mAU/mL
BUN	26.2	mg/dL			
Cre	0.85	mg/dL			
Na	137	mEq/L			
K	3.8	mEq/L			
FPG	118	mg/dL			
NH_3	34	μg/dL			

WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; Plt, platelet count; TP, total protein; Alb, albumin; T-bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; GGT, gamma glutamyl transpeptidase; BUN, blood urea nitrogen; Cre, creatinine; FPG, fasting plasma glucose; NH_3, ammonia; CRP, C-reactive protein; PT, prothrombin time; APTT, activated partial thromboplastin time; HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody; HCVAb, hepatitis C antibody; AFP, alpha fetoprotein; PIVKA-II, protein induced by vitamin K absence/antagonist-II.