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Case Report

Solitary Cardiac Metastasis of Hepatocellular Carcinoma

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Cardiac metastasis originating from hepatocellular carcinoma (HCC) is a rare condition with a poor prognosis. No therapeutic standards for cardiac metastasis originating from HCC have been established. At 19 months after a curative hepatectomy, a 64-year-old Japanese hepatitis B virus-positive male patient experienced solitary cardiac metastasis originating from HCC. The cardiac tumor was discovered in the right ventricle. The patient received three courses of radiotherapy and chemotherapy and survived >3 years after the initial diagnosis of cardiac metastasis. His case demonstrates that radiotherapy combined with chemotherapy can be an effective treatment for cardiac metastasis.

Key words: hepatocellular carcinoma, cardiac metastasis, radiotherapy, chemotherapy

Hepatocellular carcinoma (HCC) metastasizes mainly within the confines of the liver. Metastasis to the heart from other carcinoma sources is not infrequent, but a solitary cardiac metastasis originating from HCC is rare and has a poor prognosis, in part because of the lack of standardized therapies. At our hospital, one patient lived >3 years after his initial diagnosis of a solitary cardiac metastasis originating from HCC following the curative resection of the cancerous area of his liver. The patient received therapy comprised of three courses of combined radiotherapy and chemotherapy. He was able to live a nearly normal daily life until multiple lung metastases were discovered. We report the case in detail.

Case Report

A 64-year-old Japanese hepatitis B virus-positive male was admitted to our hospital for a S7 liver tumor discovered by abdominal ultrasonography. The patient underwent an S7 segmentectomy in September 2013. The preoperative ECG was normal. Microscopically, the tumor was moderately differentiated hepatocellular carcinoma, measuring 6.5 cm; s0, vp1, vv0, va0, b0, with a pathological stage of III, based on the general rules for clinical and pathological studies of primary liver cancer in Japan (Fig. 1). In June 2015, 19 months after the segmentectomy, a CT/PET-CT scan result revealed a 28×43-mm tumor in the right ventricle that was not recognized in testing prior to the hepatectomy. The tumor was clinically diagnosed as solitary recurrent HCC (Figs. 2, 3). An MRI exam was not performed due to the patient's extensive body tattoos. Echocardiography demonstrated a slightly protruding right ventricle tumor suggestive of endomyocardial metastasis (Fig. 4).

The patient's serum PIVKA-II was elevated at 16,500 mAU/ml, a figure that had normalized after the hepatectomy. The laboratory data at recurrence are shown in Table 1. Although no other metastases were found, resection of the cardiac tumor was not indi-

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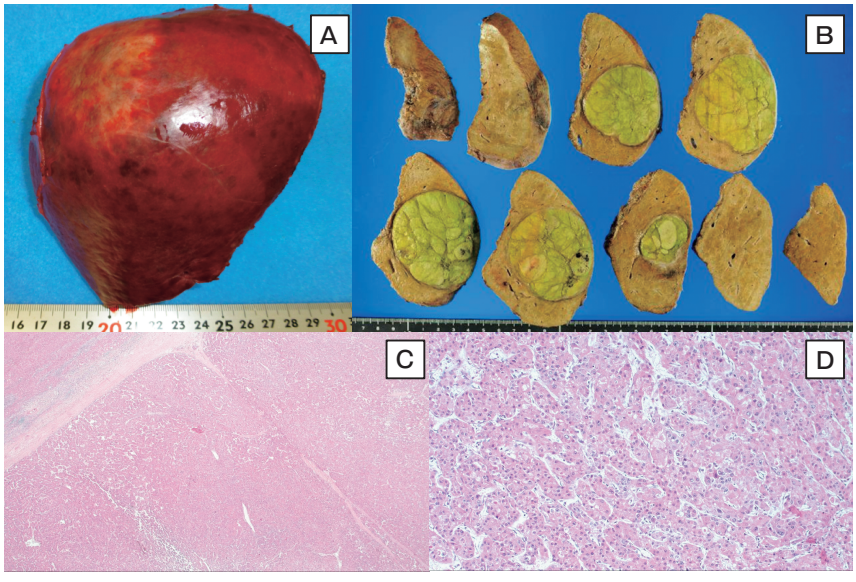

Fig. 1 Resected specimen. A, S7 liver 282 g; B, cross-sectional slices of the liver tumor; C and D, microscopic images of the tumor by HE stain.

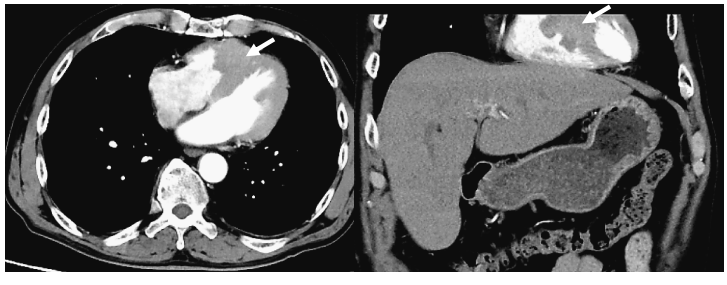

Fig. 2 Enhanced CT

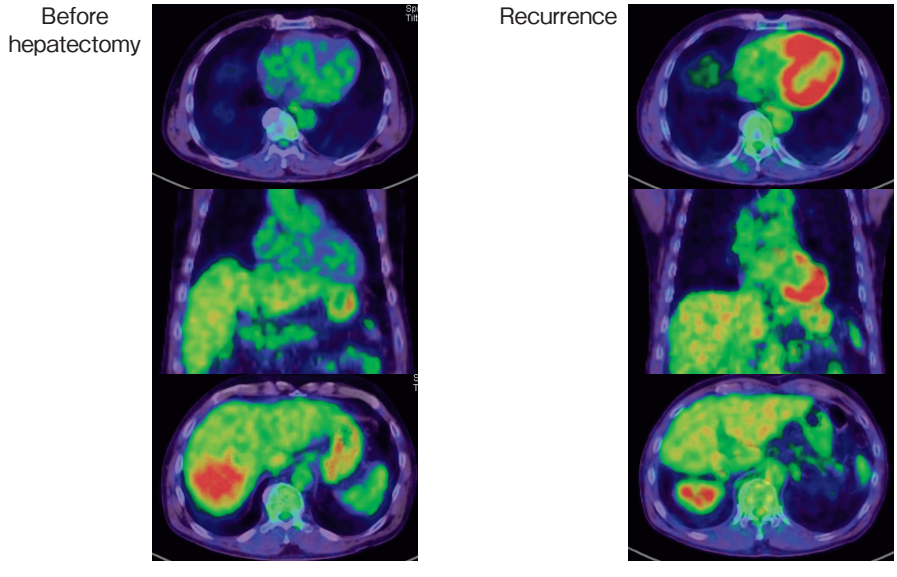

Fig. 3 PET-CT

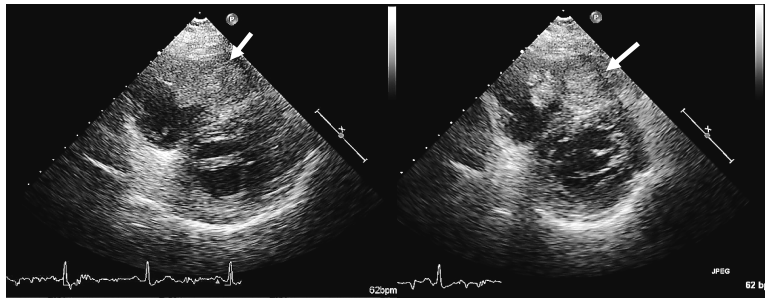

Fig. 4 Echocardiography

Table 1 Laboratory data at recurrence

WBC	7,300	/mm^3	PT-%	**46.4**	%	γ-GTP	31	IU/l
RBC	459 × 10^4	/mm^3	PT-INR	**1.57**		LDH	**346**	IU/l
Hb	17.1	g/dl	Alb	**3.7**	g/dl	BUN	**26.6**	mg/dl
Ht	**52.2**	%	CRP	0.09	mg/dl	Cr	**1.16**	mg/dl
Plt	**12.3 × 10^3**	/mm^3	T-Bil	**3.40**	mg/dl	AMY	96	IU/l
Neutrphil	41.9	%	D-Bil	**1.20**	mg/dl	HbA1c	5.4	%
Lymphocyte	**49.7**	%	AST	**55**	IU/l	AFP	2.5	ng/ml
Monocyte	**6.3**	%	ALT	**74**	IU/l	PIVKA Ⅱ	**16,500**	mAU/ml
Eosinophil	1.2	%	ALP	248	IU/l			
Basophil	0.9	%						

cated, because (1) a complete resection was projected to be exceedingly difficult, and (2) resection could have led to systemic spread of the tumor. Thereafter, because the patient had untreated hypertension, tegafur-uracil therapy was initiated at a daily dose of 600 mg. This therapy was halted after 4 months of use because the patient experienced nausea.

In November 2015, the patient was taken to the hospital with sudden palpitations and dyspnea. No murmurs or rales were audible. An ECG test in the emergency room showed inverted T waves and bi-phased P waves. The tumor was found to have enlarged to 41 × 59 mm, and it induced right ventricular outflow tract stenosis (which was thought to be the cause of the dyspnea). The right ventricular outflow tract flow was 3.8 m/sec, which was faster than before (1.7 m/sec when the cardiac metastasis was initially detected). The patient underwent 50 Gy of palliative radiotherapy. Ten MV X-ray wedge pair fields were given as the course of radiotherapy.

Within 1 month after the radiotherapy, the patient's dyspnea and appetite improved and in another 2 months, the tumor was slightly reduced in size (34 × 48 mm). Chemotherapy was reinitiated, but the tumor continued to increase in size and the patient's symptoms gradually grew more severe. Palliative radiotherapy was carried out in June 2016 (30 Gy) and August 2017 (20 Gy). After each radiotherapy session, the serum PIVKA-II level was decreased. Although pericardial effusion was detected afterward, pericardiocentesis was deemed too difficult to conduct from a technical perspective. Echocardiography did not indicate endocarditis or myocarditis as signs of adverse effects of radiotherapy. No other severe complications occurred.

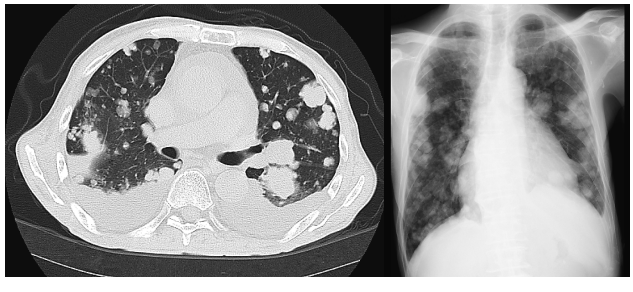

Fig. 5 Multiple lung metastases.

A CT scan in August 2018 revealed multiple lung metastases (Fig. 5), although no abnormal lesions had been revealed by a chest X-ray exam earlier in June. After the lung metastases were discovered, oral sorafenib therapy was initiated. The patient was later taken to our hospital in cardiopulmonary arrest and died in October 2018, 61 months after the initial hepa-

tectomy and 42 months after the diagnosis of cardiac metastasis. A decision was made to not perform an autopsy. The relationship between the patient's treatment and his serum PIVKA-II levels is indicated in Fig. 6 as a summary of the clinical course.

Discussion

Abdominal surgeons seldom encounter metastatic tumors in the heart. Hepatocellular carcinoma in the liver can metastasize into the right atrium through the inferior vena cava. Usually, however, such a situation is not considered to be distant or hematogenous cardiac metastasis.

The incidence of secondary metastatic tumors to the pericardium, myocardium, great vessels, or coronary arteries in the general population at autopsy is between 0.7% and 3.5% [1]. Among post-mortem patients who had died of the malignancy, however, that figure rises to 25% [2]. The most common site of cardiac metastasis is the pericardium (64-69%), followed by the epicardium (25-34%) and the myocardium (29-32%). Metastasis to the endocardium is rare (3-5%) [3]. The most common tumors with cardiac metastatic potential are carcinoma of the lung (36-39%) and breast (10-12%) and hematologic malignancies (10-21%) [1, 2].

Regarding the routes of metastatic spread to the heart, lymphatic spread tends to give rise to pericardial metastasis, and a hematogeneous spread preferentially gives rise to myocardial metastasis [2]. Cardiac metastases are ordinarily small and multiple. They usually therefore remain clinically silent [2]. Sometimes, however, cardiac metastasis cases are an oncological emergency, because some patients have an outflow tract obstruction due to lesions that occupy space in the heart, especially on the endocardium, as was seen in our patient's case. Pericardial involvement has the potential to cause pericardial effusion or pericarditis. Epicardial and myocardial involvement could cause dysrhythmias or decreased cardiac output.

MRI screening is generally thought to be the best diagnostic option, although this technology could not be used for our patient due to his extensive tattoos. Other assessment options include the use of multiple cardiac imaging planes, which allows a more complete description of the anatomic relationships involved [3]. Sato reported that careful attention to the heart using imaging evaluations including FDG-PET is valuable for the detection of the early stages of cardiac metastasis [4]. Echocardiography has been described as a noninvasive and informative tool. Transcatheter aspiration cytology could serve as a definitive diagnostic option [5], although the procedure is invasive. The scientific consensus [6] seems to be that an endomyocardial biopsy for a cardiac tumor is a reasonable procedure if a diagnosis cannot be established by noninvasive modalities. The main point of concern should be that any new cardiac symptom in a patient with a known malignancy

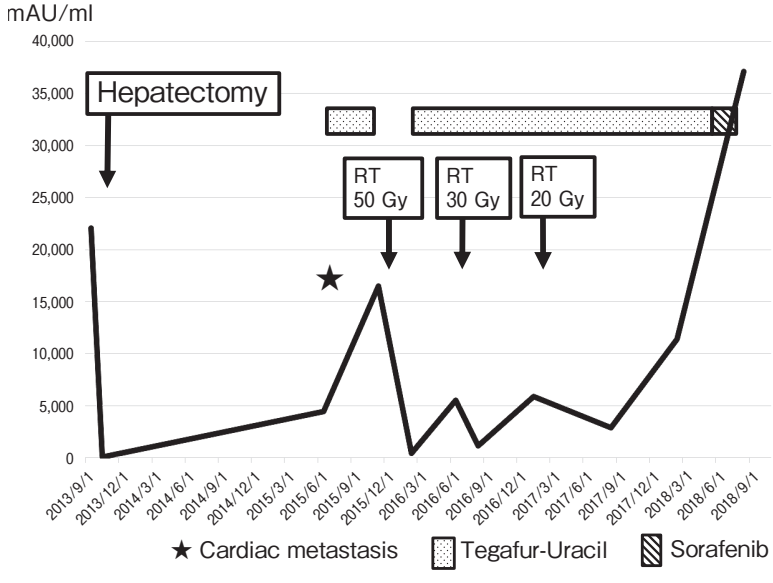

Fig. 6 Treatments, serum PIVKA-II.

might indicate the possibility of cardiac metastasis [3], such as that seen in the present case.

Cardiac metastatic tumor locations are right-side dominant. Kawakami collected and analyzed 17 cases of isolated HCC metastasis to the heart [7]; 13 of the 17 cases were right-side only, but 2 cases were left-side only, and 2 cases were of a bilateral nature. Tastekin *et al.* reported a rare case of left cardiac ventricular metastasis [8], and they speculated that the tumor cells had spread via a pulmonary vein from a tumor originating in the lung. Fukuoka also reported isolated HCC metastasis in the left atrium extending from lung metastasis through the left pulmonary vein [9]. From these reports, it would seem that left-sided cardiac metastasis usually occurs with lung metastasis.

With regard to chemotherapy, tegafur-uracil was the initial treatment of choice for our patient. One reason for this selection was the patient's untreated hypertension. Although he had been diagnosed with hypertension, he had never taken medication to treat the disorder. Sorafenib was found to be significantly effective for advanced HCC by SHARP test [10], but the effectiveness was modest, with the overall response rate only 2% and all of the responses partial. At the time of our patient's diagnosis, some reports of Japanese patients indicated the effectiveness of tegafur-uracil for inoperable HCC [11] or HCC with distant metastasis [12]. Tanabe collected 16 complete remission cases and 19 partial response cases treated by tegafur-uracil for locally advanced or distant metastatic HCC [12], and some reports indicate that sorafenib might cause severe cardiac events [13, 14]. For the treatment of cardiac metastasis therefore, close attention is warranted regarding the use of tyrosine kinase inhibitors.

Concerning the prognosis of patients with HCC and a solitary cardiac metastasis, Kawakami reported that excluding three patients without a detailed prognosis, 11 of 14 patients had died within 6 months of their diagnoses [6]. None of the patients in the Kawakami series had undergone radiotherapy. Only one patient alive at 21 months after treatment had undergone surgery, and the seven other patients who had undergone surgery succumbed within 6 months.

Lui analyzed 48 HCC patients with metastasis in the cardiac cavity [15]; only one of the patients was isolated and categorized as having discontinuous cardiac metastasis. The median and mean survival times from the time of diagnosis of cardiac metastasis were 102 days and 161 days, respectively. Takaya reported the case of a patient who had undergone the resection of a pedunculated right atrial metastasis [5]. The patient's primary lesions were treated by transcatheter arterial chemoembolization and radiofrequency ablation. Six months later, the patient developed lung metastasis. The patient underwent chemotherapy with sorafenib but succumbed 36 months after the diagnosis. If resection is being considered a treatment option for cardiac metastasis, its effectiveness should first be analyzed carefully.

There are several case reports demonstrating the effectiveness of external beam radiation for cardiac tumors. Dasgupta describes how radiotherapy can successfully palliate cardiac metastasis while preserving the patient's quality of life [16]. In the largest report of its kind published thus far, Ghiam *et al.* analyzed 10 cases including that of an HCC patient who was treated with palliative radiotherapy for cardiac metastasis from different origins [17]. They recommended that palliative RT should be considered early in the management of patients with cardiac metastasis. They also emphasized that a delay in palliative radiotherapy could potentially deprive such patients of an effective treatment that could potentially help manage symptoms.

In conclusion, a patient treated at our hospital developed a solitary cardiac metastasis of HCC after curative hepatectomy. He underwent 3 courses of combined radiotherapy and chemotherapy and survived >3 years after the initial diagnosis of cardiac metastasis. His case demonstrates that radiotherapy in combination with chemotherapy can be an effective treatment, and a palliative option, for cardiac metastasis.

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