

Isolated metastases of hepatocellular carcinoma in the right atrium: Case report and review of the literature

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Abstract. The aim of this study was to clarify the clinical features of patients with isolated HCC metastases to the heart. A 66-year-old female hospitalized with a hepatocellular carcinoma (HCC) ranging from the right to the left lobe and with a tumor thrombus in the main portal vein, was treated with intraarterial cisplatin, 5-fluorouracil, adriamycin and mitomycin. Computed tomography (CT) one month later revealed that the HCC had progressed with multiple lung metastases and moderate ascites. The patient had no symptoms. Magnetic resonance imaging (MRI) and echocardiography revealed a round, movable tumor with a diameter of 2 cm in the right atrium (RA). The patient succumbed to HCC five months later. An autopsy revealed HCC with portal tumor thrombi and metastases to the lungs, inferior vena cava (IVC) and RA. The metastases in the RA and IVC were not continuous with the intrahepatic tumor and were histologically attached to the endocardium and endothelium, respectively. An isolated metastasis of a HCC of the RA and IVC is extremely rare. In conclusion, although the majority of isolated metastases of HCC to the heart were diagnosed by echocardiography and were treated with mainly surgery, they had poor prognosis. The echocardiography should be performed for patients with advanced HCC. A novel treatment including molecular targeted drugs is required.

Introduction

Hepatocellular carcinomas (HCCs) frequently invade the vascular system at points such as the portal and hepatic veins. The results of autopsy studies indicate a 2.7-4.1% incidence of atrial metastases of HCC (1,2). A correct diagnosis is important in the clinical setting since cardiac metastases are able to induce sudden cardiac arrest. The majority of metastases develop as continuous extensions of a tumor thrombus in the hepatic vein. However, isolated cardiac metastases are extremely rare. The present study describes a 66-year-old female with an isolated right atrial metastasis of a HCC and reviews previous published studies, treatments and outcomes in similar patients. Written informed consent was obtained from the patients' family.

Case report

A 66-year-old female was diagnosed with chronic hepatitis type B and HCC in May 2004. The patient had no jaundice, vascular spiders, palmar erythema or cardiac murmurs. A hard mass was palpable from the right hypochondrium to the epigastrium. The laboratory results (normal ranges in parentheses) were as follows: total bilirubin, 0.9 mg/dl (0.2-1.2 mg/dl); aspartate aminotransferase, 115 IU/l (5-40 IU/l); alanine aminotransferase, 105 IU/l (5-47 IU/l); alkaline phosphatase 491 IU/l (111-295 IU/l); and lactate dehydrogenase, 199 IU/l (100-225 IU/l). The patient was positive for the hepatitis B surface antigen and e-antibodies. The serum α -fetoprotein and des- γ -carboxy prothrombin levels were elevated to 687,460 ng/ml (normal range, <13.2 ng/ml) and 1037 mAU/ml (normal range, <40 mAU/ml), respectively.

Abdominal sonography and computed tomography (CT) imaging revealed a large mass reaching from the right to the left lobe and a tumor thrombus in the main portal vein (Fig. 1A and B). Angiography revealed a hypervascular tumor in the right lobe exhibiting the thread and streak sign. No metastases were identified in the right atrium (RA) or inferior vena cava (IVC) prior to starting intraarterial chemotherapy with cisplatin, 5-fluorouracil, adriamycin and mitomycin.

An enhanced CT in July, 2004, showed that the HCC had progressed and that multiple lung metastases had developed with moderate ascites. Magnetic resonance imaging (MRI)

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Abbreviations: CT, computed tomography; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging

Key words: hepatocellular carcinoma, isolated atrial metastasis, prognosis

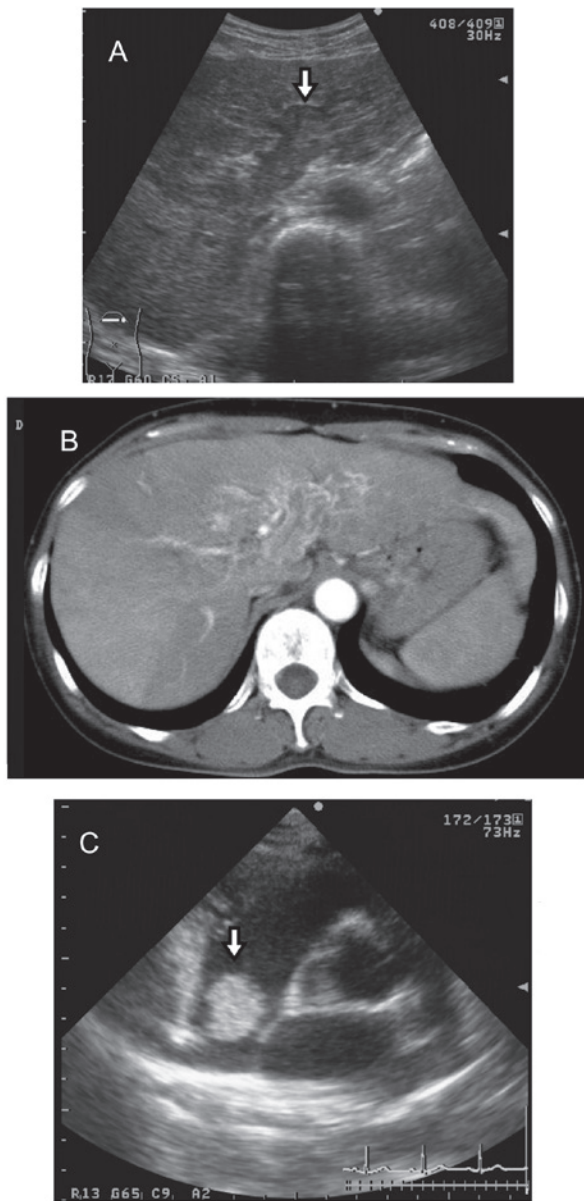


Figure 1. Imaging findings. (A) Abdominal sonographic image showing ill-defined large isoechoic mass with portal thrombus (arrow). (B) Computed tomography (CT) image showing ill-defined large heterogeneous mass occupying the bilateral liver lobes, and portal thrombus accompanying a cavernous transformation. (C) Transthoracic echocardiography image showing a round, movable tumor of a 2-cm diameter in the right atrium (RA; arrow).

and echocardiography revealed a round, movable tumor with a diameter of 2 cm in the RA (Fig. 1C), but no tumor thrombus in the IVC. The atrial tumor was not continuous with the intrahepatic HCC. Anticoagulation therapy with warfarin was administered, however the patient succumbed to hepatic failure five months later (Fig. 2).

An autopsy revealed diffuse-type HCC in the bilateral lobes of the liver that weighed 1,365 g, with a tumor thrombus in the main trunk of the portal vein, bilateral multiple lung metastases and tumor thrombi in the artery of the right upper lung. A yellowish irregular-surfaced mass with a diameter of 10 mm located in the RA, and a similar small independent mass in the IVC (Fig. 3), were discontinuous with the intrahepatic HCC. Histologically, the intrahepatic and right atrial

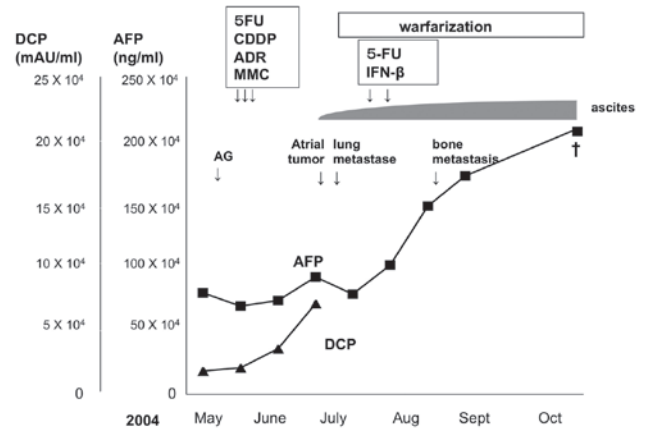


Figure 2. Clinical course of the patient. ADR, adriamycin; AFP, α -fetoprotein; AG, angiography; CDDP, cisplatin; DCP, des- γ -carboxy prothrombin; 5-FU, 5-fluouracil; IFN- β , interferon β ; MMC, mitomycin C.

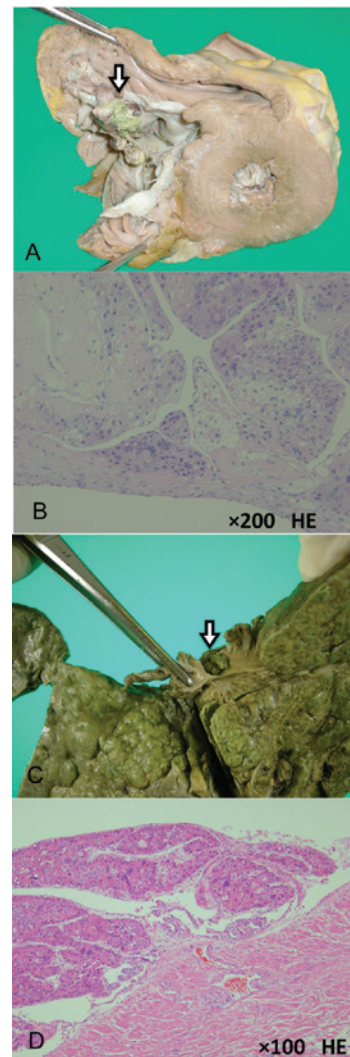


Figure 3. Appearance and diagnosis of autopsy specimen. (A) Yellowish tumor with irregular surface (arrow) located in the right atrium (RA) of the heart specimen at autopsy. (B) Right atrial tumor attached to the endocardium diagnosed as a moderately differentiated HCC of trabecular type (hematoxylin-eosin stain). (C) Greenish tumor with irregular surface (arrow) located in inferior vena cava (IVC), discontinuous with the intrahepatic HCC. (D) Tumor attached to the endothelium in the IVC, pathologically diagnosed as a moderately differentiated HCC of trabecular type (hematoxylin-eosin stain). HCC, hepatocellular carcinoma.

Table I. Patients with isolated HCC metastases to the heart.

| Case | Ref. | Age (years), gender | Diagnosis stage | Symptoms | Pretreatment for cardiac metastases | Pathology | Location of initial HCC | Treatment for cardiac metastase | Prognosis |
|------|---------------|---------------------|-----------------|------------------------------------|-------------------------------------|-----------|-------------------------|---------------------------------|----------------------------|
| 1 | 3 | 52M | Autopsy | Dyspnea, heart murmur | None | NS | RA, endocardium | Supportive care | Succumbed after 1 month |
| 2 | 4 | 55M | Autopsy | Dyspnea, cyanosis | None | Ed II-III | RA, LA, endocardium | Supportive care | Succumbed after 1 month |
| 3 | 5 | 67M | Autopsy | Fever, cough, chest discomfort | None | Ed III | LV, epicardium | Supportive care | Succumbed after 2 months |
| 4 | 6 | 73M | Autopsy | Heart murmur | None | Ed I-II | RA, RV | TAE | Succumbed after 1 month |
| 5 | 7 | 51M | CT | Dyspnea, palpitation | Hepatectomy | NS | RV, myocardium | Surgery | Succumbed |
| 6 | 7 | 29M | UCG | Dyspnea | Hepatectomy | Ed II | LA | Chemotherapy | Succumbed |
| 7 | 8 | 71M | Autopsy | Consciousness disorder | Chemotherapy | Ed II | RV, LV, myocardium | NS | Succumbed after 0.5 months |
| 8 | 9 | 76M | UCG | Dyspnea | Hepatectomy, MCT, chemotherapy | Ed I-II | RV, myocardium | Surgery | Succumbed after 6 months |
| 9 | 10 | 49F | UCG | Dyspnea, palpitation, heart murmur | Hepatectomy | Ed I-II | RV, myocardium | Surgery | Alive at 21 months |
| 10 | 11 | 67F | UCG | Dyspnea, heart murmur | Hepatectomy | Ed II | RV | TAE | Alive at 3 months |
| 11 | 12 | 43M | UCG, CT | Dyspnea, cough | Hepatectomy | Ed I-II | RV | Supportive care | Succumbed after 20 days |
| 12 | 13 | 45M | UCG, CT | Dyspnea, dizziness | Hepatectomy | NS | RV | Surgery | Alive at 3 months |
| 13 | 14 | 65F | CT | Dyspnea | Hepatectomy | NS | RV | Surgery | Succumbed after 3 months |
| 14 | 15 | 45F | UCG | Dyspnea, syncope | Hepatectomy, TAE | Ed II | RV | Surgery | Succumbed after 4 months |
| 15 | 16 | 63F | UGC | Dyspnea | TAE | Ed IV | RA | Surgery | NS |
| 16 | 17 | 74F | UCG | Dyspnea, syncope | TAE | NS | RV | Surgery | Succumbed after 4 months |
| 17 | Present study | 66F | UCG | None | Chemotherapy | Ed II | RA, endocardium | TAI | Succumbed after 5 months |

UCG, ultrasound cardiography; MCT, microwave coagulation therapy; TAE, transcatheter arterial embolization; Ed, Edmondson; NS, not stated; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; TAI, transcatheter arterial infusion chemotherapy; HCC, hepatocellular carcinoma.

tumors were moderately differentiated HCCs. The right atrial tumor was fixed to the atrial wall and arose from sites on the endocardium of the RA (Fig. 3A and B). The small tumor in the IVC was similarly fixed to the endothelium (Fig. 3C and D).

Discussion

The mechanism of cardiac metastases is as a contiguous extension from the intrahepatic HCC via a tumor thrombus to the IVC or by lymphatic or hematological spread. The majority of cardiac metastases are direct and contiguous extensions of the intrahepatic HCC. Isolated cardiac metastases that are discontinuous with an intrahepatic HCC are extremely rare. The literature was searched for descriptions of isolated cardiac metastases of HCC and 17 patients were identified (Table I) with a mean age of 58 ± 13 years. In total, 15 patients (88.2%) had symptoms, with 13 (76.5%) suffering dyspnea. Intermittent obstruction by tumors in the cardiac cavity led to

the symptoms of ball valve thrombus syndrome, which is able to induce sudden cardiac arrest (18). However, in the present study, the patient had no symptoms since the diameter of the tumor was 2 cm.

Extracorporeal echocardiography was useful for detecting the atrial tumor in the present case. Kanematsu *et al* (19) described a tumor thrombus of HCC in the IVC detected by CT and MRI. Yoshitomi *et al* (20) and Van Camp *et al* (21) found transesophageal echocardiography useful. In these studies, cardiac metastases were diagnosed by UCG and CT in 10 (58.8%) and 4 (23.5%) patients, respectively. Cardiac metastases were identified at autopsy in the early cases. The HCC was initially treated in 13 (76.5%) of the 17 patients [hepatectomy, n=9; transcatheter arterial embolization (TAE), n=3; chemotherapy, n=3] and then the cardiac metastases were identified.

In the present study, the tumors in the RA and IVC were not continuous growths from the intrahepatic HCC in

the patient. The two tumors were individually isolated and attached to the endocardium or endothelium, respectively. This metastatic pathway was considered to be comprised of two mechanisms. The first was the seeding of a blood flow onto the endocardium or endothelium from the intrahepatic HCC and the second was cancer embolisms of the small vessels under the endocardium and endothelium via arterial systemic spread. However, in the published cases, the mechanism associated with the metastases could not be clarified. Cardiac metastases were notably located in the right ventricle (RV), RA and left ventricle (LV) in 10 (58.8%), 5 (29.4%) and 2 (11.8%) patients, respectively. A greater number of metastases had invaded the RV than the RA. These findings indicate that the main mechanism is embolism via arterial systemic spread as massive myocardial involvement was described in 4 patients.

Surgical (22) or non-surgical approaches, including TAE (23), transcatheter arterial infusion chemotherapy (TAI) (24) and radiotherapy (25), have been undertaken to treat IVC/RA metastases. In the selected published cases, eight (47.1%) out of 17 patients underwent surgery to relieve symptoms. In the present study, the patient underwent TAI only, but succumbed to HCC progression five months later. Overall, all the patients had an extremely poor prognosis regardless of the treatment strategy. Chang *et al* (26) reported that thalidomide is a useful angiogenesis inhibitor for IVC/RA metastases and new molecular target drugs, such as Sorafenib, have since emerged (27). However, further studies involving a larger cohort of patients with IVC/RA tumor thrombi are required.

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