

# Isolated right ventricular metastasis of hepatocellular carcinoma induced by epithelial–mesenchymal transition: a case report

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## Background

Hepatocellular carcinoma (HCC) that metastasizes to the right ventricle has rarely been reported. An important link between epithelial–mesenchymal transition (EMT) and the invasion and metastasis of cancer cells has recently been demonstrated. However, there are few reports on the relationship between HCC metastasized to the heart and EMT.

## Case summary

We here report the case of a 74-year-old woman who had type C HCC referred to our hospital with general fatigue due to a right ventricular tumour diagnosed at a general hospital. Anticoagulation therapy was done, but the mass had rapidly grown. We performed surgical resection of the mass. Histopathological examination revealed that the tumour was diagnosed as a poorly differentiated HCC metastasis induced by EMT.

## Discussion

Isolated metastasis of HCC to the right ventricle is extremely rare. The HCC with EMT has a potentially high risk of metastasizing to the heart and other organs, and the prognosis is poor.

## Keywords

Metastasis • Cardiac tumour • Hepatocellular carcinoma • Epithelial–mesenchymal transition • Case report

## Learning points

- To be aware of potential risk of isolated right ventricular metastasis in hepatocellular carcinoma (HCC) patients.
- To understand the diagnosis, surgical indication, and prognosis of cardiac tumour.
- To recognize the HCC with epithelial–mesenchymal transition has a potentially high risk of metastasizing to the heart and other organs, and the prognosis is poor.

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## Introduction

Hepatocellular carcinoma (HCC) is the 6th most common cancer in the world.<sup>1</sup> HCC that metastasizes to the right atrium is found in fewer than 6% of autopsies,<sup>2</sup> but isolated right ventricular (RV) metastasis is extremely rare (1.2% of autopsies).<sup>3</sup> Epithelial–mesenchymal transition (EMT) has recently been reported to play a crucial role in the progression and metastasis of HCC.<sup>4</sup> EMT may alter the gene expression of epithelial cells due to the activation of EMT-inducing transcription factors such as zinc finger E-box binding homeobox (ZEB1/ZEB2) and the zinc-finger transcriptional repressor. EMT-inducing transcription factors are involved in metastasis of malignant cells.<sup>4</sup> However, there are few reports on the relationship between HCC metastasized to the heart and EMT. We report a case of HCC metastasis to the right ventricle that was induced by EMT.

## Timeline

Time	Events
Day 1	A 74-year-old woman who had a type C hepatocellular carcinoma (HCC) was referred to our hospital because a right ventricular (RV) tumour was diagnosed at a general hospital. Because the tumour was suspected to be a thrombus, anticoagulation therapy was performed.
Day 2	Magnetic resonance imaging revealed a large solid tumour (42 × 21 mm) involving the right ventricle and the root of the pulmonary trunk without infiltrating the inferior vena cava.
Day 10	Although anticoagulation therapy was carried out, the mass rapidly grew to a size of 50 × 25 mm, and the tricuspid regurgitation pressure gradient increased from 48 to 70 mmHg. We decided to surgically resect the mass in order to prevent collapse of RV outflow.
Day 18	We performed surgical resection of the tumour in order to prevent collapse of RV outflow. A large, soft and dark-red tumour was observed in the RV cavity. The tricuspid valve was replaced with a bioprosthetic valve.
Day 24	Histopathological examination revealed that the tumour was diagnosed as a poorly differentiated HCC metastasis induced by epithelial–mesenchymal transition.
Day 25	Echocardiography showed no residual or recurrent tumour in the right ventricle.
Day 47	The patient was discharged from our hospital to the previous referring hospital.
Day 53	Recurrence of the tumour in the right ventricle was confirmed (25 × 35 mm).
Day 67	Finally, the patient died due to HCC.

## Case presentation

A 74-year-old Japanese woman who had type C HCC (Child Pugh score: Class A) referred to our hospital due to a RV tumour diagnosed at a general hospital. The patient exhibited general fatigue with New York Heart Association functional class III. A systolic murmur (Levine grade 3/6) was heard at the left sternal border. There were no jugular vein distention and peripheral oedema. An electrocardiogram presented inverted T wave in leads V1–3. Echocardiography, computed tomography with contrast media, and gadolinium-enhanced magnetic resonance imaging revealed a large solid tumour (42 × 21 mm) involving the right ventricle and the root of the pulmonary trunk (*Figure 1A and B* and [Supplementary material online, Videos S1 and S2](#)). Primary tumours were found in the liver (*Figure 1C*), but the tumours did not infiltrate the inferior vena cava. At first, because the tumour was suspected to be a thrombus or a primary tumour, anticoagulation therapy was administered for 10 days. However, the mass rapidly grew to a size of 50 × 25 mm, and the tricuspid regurgitation pressure gradient increased from 48 to 70 mmHg. We decided to surgically resect the mass in order to prevent collapse of RV outflow.

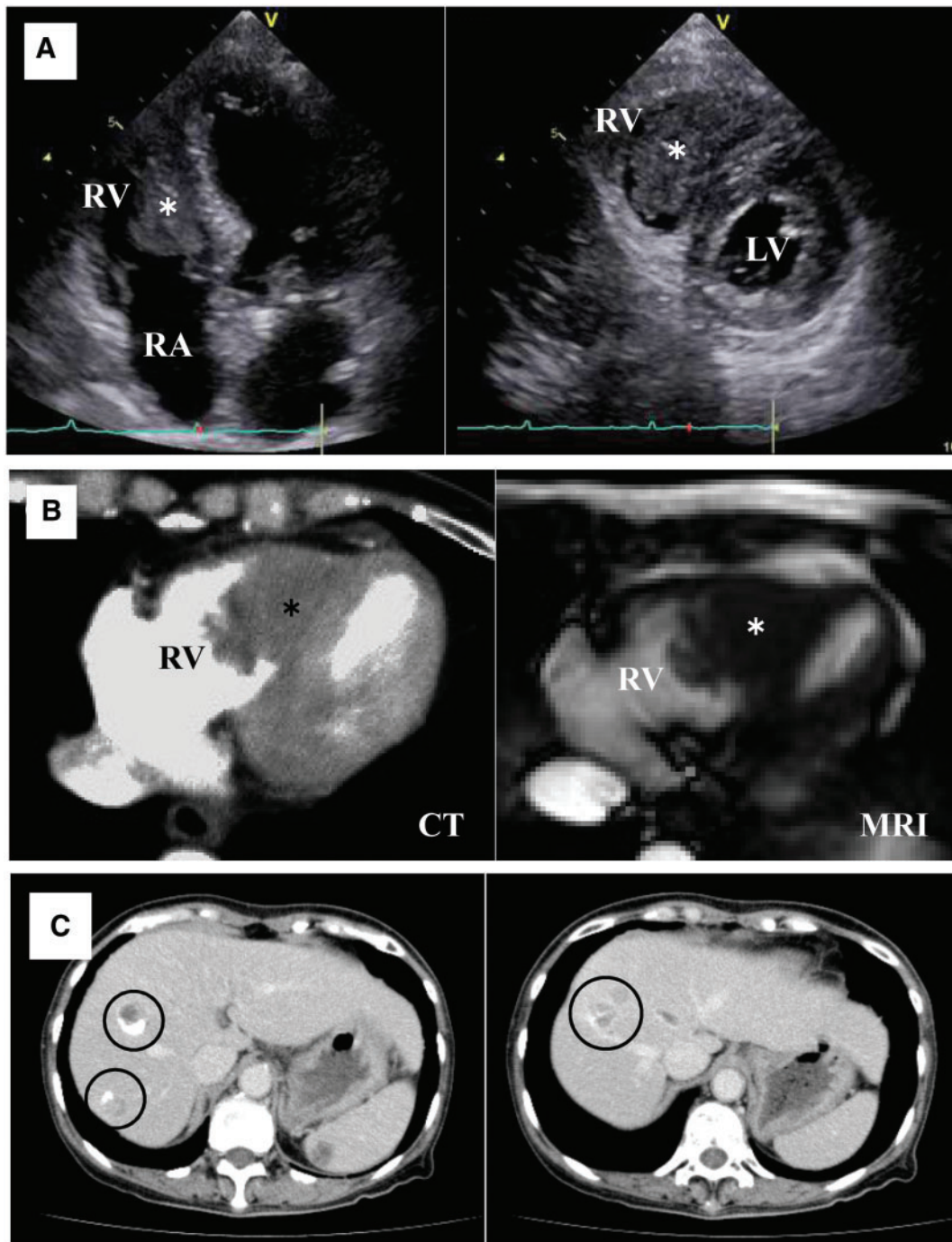
After a median sternotomy, cardiopulmonary bypass was established as usual with cannulation of the ascending aorta and the superior and inferior vena cava. When the incision was made in the right atrium, a large, soft, dark-red tumour was observed in the RV cavity. Because the tumour had invaded the RV free wall, papillary muscles, and tricuspid valve (*Figure 2A*), it was resected along with the RV free wall, chorda tendineae, and valve (*Figure 2B*). The tricuspid valve was replaced with a bioprosthetic valve (Mosaic valve, 27 mm; Medtronic, Dublin, Ireland), and cryoablation was performed at the site of tumour resection.

Haematoxylin and eosin staining showed nuclear enlargement, anisonucleosis, and a high nuclear/cytoplasmic ratio, which indicated that the tumour was malignant (*Figure 2C*). Immunohistochemistry stains revealed positivity of the ZEB1 (*Figure 2D*). Also, p53 gene staining revealed a mutation pattern (*Figure 2E*), and tests for K18 and K19 yielded positive results. The tumour was diagnosed as a poorly differentiated HCC metastasis induced by EMT.

On postoperative Day 7, echocardiography showed no residual or recurrent tumour in the right ventricle (*Figure 3* and [Supplementary material online, Video S3](#)). Chemotherapy could not be performed because liver failure progressed after the surgery. The patient was discharged from our hospital to the previous referring hospital on postoperative Day 47. However, 53 days after the surgery, recurrence of the tumour in the right ventricle (25 × 35 mm) was confirmed (*Figure 4* and [Supplementary material online, Video S4](#)). Finally, the patient died due to HCC on postoperative Day 67.

## Discussion

Secondary cardiac tumours are more common than primary cardiac tumours.<sup>5</sup> Generally, tumours that metastasize to the heart are bronchogenic and breast carcinomas, lymphomas, leukemias, and various sarcomas. The majority of such tumours metastasize directly and



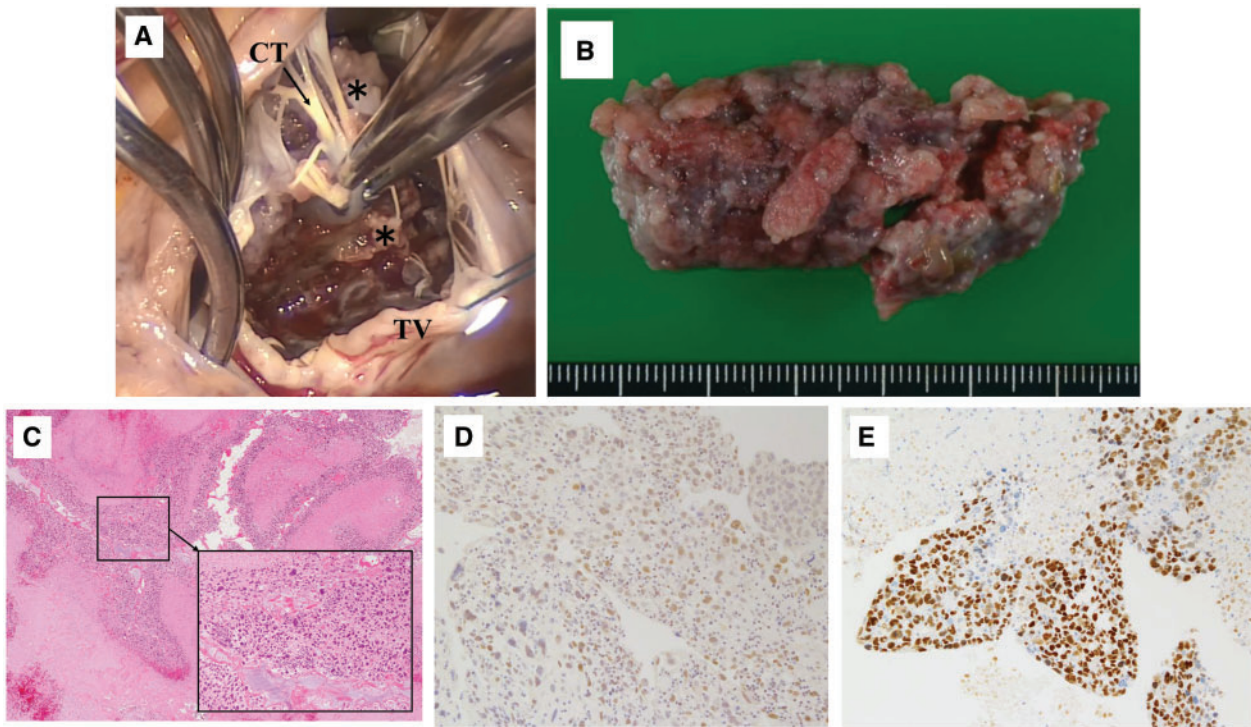
**Figure 1** Echocardiography showed a large solid tumour in the right ventricle. (A) Computed tomography and magnetic resonance imaging demonstrated a large tumour involving the right ventricle (B). Primary tumours were found in the liver (C). LV, left ventricle; RA, right atrium; RV, right ventricle. The asterisks or circles represent the tumour.

continuously to the right atrium via the inferior vena cava.<sup>2</sup> Isolated metastasis of HCC to the right ventricle, however, is extremely rare. In our patient, the mode of metastasis was thought to be haematogenous because the tumour did not infiltrate the inferior vena cava.

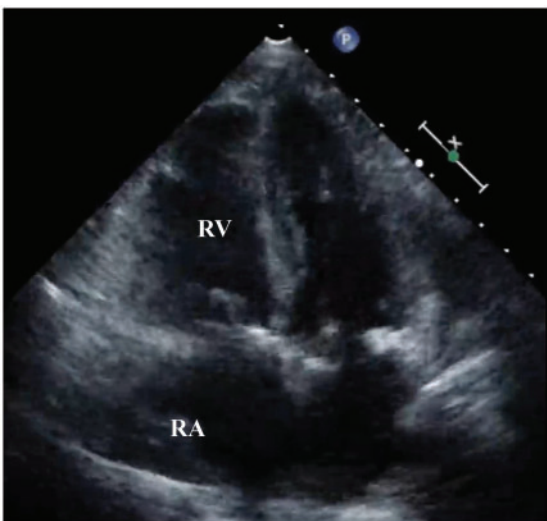
A few researchers have reported treatment strategies such as chemotherapy or surgical resection for isolated metastatic HCC in

the right ventricle.<sup>2,6</sup> However, all cases had poor outcomes. Surgical resection of the metastatic tumour is the only way to prevent collapse of the RV outflow, progressive right-sided heart failure, or sudden death.<sup>2</sup> Chieng *et al.*<sup>6</sup> surgically resected a metastatic HCC in the right ventricle, but the tumour recurred only 2 months after surgery, and the patient died 1 month later.





**Figure 2** (A) Intraoperative view of the cardiac mass. The tumour invaded the right ventricular free wall, tricuspid valve, chorda tendineae, and septal papillary muscle. (B) Macroscopic findings of the tumour. (C) Haematoxylin and eosin staining revealed nuclear enlargement, anisonucleosis, and a high nuclear/cytoplasmic ratio. (D) Immunohistochemistry findings; positivity of ZEB1 was established. (E) Immunohistochemistry findings; p53 gene staining was positive and revealed a mutation pattern. CT, chorda tendineae; TV, tricuspid valve. The asterisk indicates the tumour.

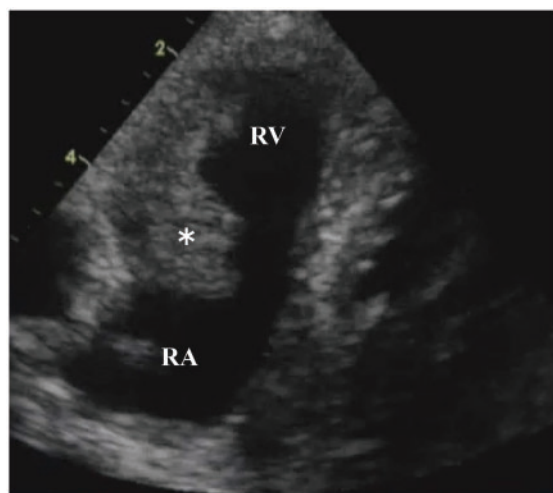


**Figure 3** Echocardiography showed no residual or recurrent tumour in the right ventricle at postoperative Day 7. RA, right atrium; RV, right ventricle.

The clinical EMT in HCC progression has been discussed in recent years. EMT is involved not only in metastasis and progression of HCC but also in cancer recurrence and resistance to conventional adjuvant therapies.<sup>4</sup> The expression of EMT indicates an unfavourable prognosis in patients with HCC.<sup>4</sup> ZEB family proteins are known pivotal factors in the process of EMT and are among the markers of EMT in immunohistochemistry studies.<sup>4</sup> The tumour suppressor gene p53 has recently been implicated in EMT and tumour metastasis by its regulation of microRNA expression.<sup>7</sup> In addition, K19 is a known marker of cancer stem cells in HCC.<sup>8</sup> Kim et al.<sup>8</sup> reported that K19-positive HCC exhibited significantly increased levels of EMT-related proteins, which suggests that K19-positive HCC metastasizes more often than does K19-negative HCC. In our patient, the development of metastasis was predictable, and the prognosis was poor.

## Conclusion

Isolated metastatic HCC in the right ventricle is extremely rare. Surgical resection for the cardiac metastasis is the only way to prevent collapse of RV outflow, progressive right-sided heart failure, or sudden death. However, the prognosis is unfavourable. Whether



**Figure 4** Echocardiography demonstrated a recurrence tumour involving the right ventricle after surgery. RA, right atrium; RV, right ventricle. The asterisk indicates the tumour.

EMT is directly involved in cardiac metastasis is unknown, but HCC with EMT has a potentially high risk of metastasizing to the heart and other organs.

## Lead author biography



Kosuke Saku was born in Cincinnati, USA in 1985. He received the MD degree from Kawasaki Medical University (Kurashiki city, Japan) in 2011. Since 2014, he has worked in the cardiovascular surgery department, Kurume University (Kurume city, Japan).

## Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

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**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

**Consent:** The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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