

## Hepatocellular carcinoma with tumor thrombus extends to the right atrium and portal vein: A case report

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### Abstract

#### BACKGROUND

Hepatocellular carcinoma (HCC) is the most important primary malignant liver disease. A large proportion of patients with advanced HCC have macrovascular invasion. HCC tends to infiltrate vascular structures, particularly the portal vein and its branches, and more rarely, the hepatic veins. The intravascular tumor thrombus can affect the inferior vena cava (IVC) or even the right atrium (RA), the latter having a poor prognosis.

#### CASE SUMMARY

HCC is one of the most aggressive malignant tumors. Tumor thrombus (TT) formation in advanced HCC stages is common and usually involves the hepatic or portal veins. Herein, we report a 69-year-old woman who presented with dyspnea to the emergency department. A ventilation/perfusion lung scan was performed, ruling out pulmonary embolism. Hepatopulmonary syndrome and portopulmonary hypertension were discarded with contrasted echocardiography, but a mass in the RA was detected and confirmed by cardiac magnetic resonance imaging. Abdominal computed tomography showed a liver mass with a dynamic enhancement pattern compatible with HCC and an intraluminal IVC mass extending from the hepatic vein into the RA. HCC with TT expansion to IVC and RA is rare and indicates poor prognosis.

#### CONCLUSION

HCC with TT expansion to IVC and RA is rare and indicates poor prognosis. There is no consensus about anticoagulation or other interventions in these patients.

**Key Words:** Hepatocellular carcinoma; Alpha-fetoprotein; Tumor thrombus; Right atrium;

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**Core Tip:** Hepatocellular carcinoma (HCC) with tumor thrombus (TT) in the right atrium (RA) is an unusual but critical condition. There is no standard treatment strategy or consensus. Alpha-fetoprotein is reportedly a new alternative biomarker to RECIST in order to detect tyrosine kinase inhibitors response in HCC, and our case supports this hypothesis. We report this HCC case due to the exceptionality of a TT extending into the RA in a patient with stable cirrhosis. We believe this case will warn professionals when facing similar cases, so systemic treatment can be started in a timely fashion and the treatment response can be evaluated with a serial blood test in patients suffering from advanced HCC.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignant liver disease and the fourth most common cause of cancer-related deaths, resulting in a global incidence of approximately 800000 cases per year<sup>[1]</sup>. Currently, liver cancer is the second most lethal tumor, after pancreatic cancer, with a 5-year survival rate of 18%<sup>[2]</sup>. The most common cause of HCC worldwide is hepatitis B virus chronic infection, but in Western countries, hepatitis C virus infection, chronic alcohol consumption and non-alcoholic steatohepatitis predominate.

HCC primarily develops in cirrhotic livers, which is the major cause of death in this population<sup>[3]</sup>. HCC also tends to infiltrate vascular structures, particularly the portal vein and its branches, and more rarely, the hepatic veins. Intravascular tumor thrombus (TT) can progress and extend to the inferior vena cava (IVC) or even to the right atrium (RA), the latter having a worse prognosis compared with patients with TT in the portal or hepatic vein<sup>[4,5]</sup>. IVC/RA tumor thrombus is an infrequent event of patients with HCC, with a reported incidence of 3% to 4%. Its diagnosis is challenging due to the lack of specific clinical signs<sup>[6-8]</sup>.

## CASE PRESENTATION

### Chief complaints

A 69-year-old woman complained about experiencing asthenia and dyspnea with dizziness and diaphoresis.

### History of present illness

A 69-year-old woman arrived at the emergency department with a 15-d history of progressive asthenia, dyspnea on moderate exertion and progressive worsening shortness of breath associated with dizziness and diaphoresis.

### History of past illness

The patient was diagnosed in 2005 with alcoholic cirrhosis, without any decompensation since 2011. She followed an adequate follow-up in the hepatology department of the hospital and she had been abstinent since the last decompensation. Her last abdominal Doppler-ultrasonography from May 2019 showed liver cirrhosis with signs of portal hypertension, mild ascites and cholelithiasis. Furthermore her last upper gastrointestinal endoscopy from June 2019 showed esophageal varices and portal gastropathy. She also received treatment with beta-blockers and diuretics with

good tolerance and adherence. Thereafter, she had a biological aortic valve replacement for severe aortic stenosis in December 2018, and since then, she remained asymptomatic.

### **Physical examination**

The vital signs were within range and the physical examination was fairly normal. She had no chest discomfort or palpitations, orthopnea or an increase in the perimeter of lower limbs. She also denied having fever, chills, cough or expectoration, abdominal distention or any weight loss. In addition, she had a regular cardiac rhythm without cardiac murmur or rub noted, and the jugular venous pressure was not elevated. Her lungs were clear on auscultation and the oxygen saturation was correct without oxygen therapy. Her abdomen was also soft, non-tender and had no hepatosplenomegaly or clear signs of ascites. Moreover, she had no leg swelling, bruising or petechiae. There was no clubbing or cyanosis of her feet or hands. Signs of liver cirrhosis were found on examination, such as spider angioma and mild palmar erythema.

### **Laboratory examinations**

The blood test at admission revealed an impaired renal function with a creatinine of 1.82 mg/dL and a glomerular filtration rate of 28 mL/min/1.73 m<sup>2</sup>, mild hyponatremia with sodium of 132.3 mmol/L, elevated pro-brain natriuretic peptide (923 pg/mL) and high D-dimer (917 ng/mL).

### **Imaging examinations**

Her chest X-ray showed pathological signs. Due to the high suspicion of pulmonary embolism (PE) in a patient allergic to iodine, a ventilation/perfusion lung scan was performed, which did not exhibit any signs of PE. Contrasted echocardiography was requested to rule out portopulmonary hypertension or hepatopulmonary syndrome as the cause of the dyspnea of the patient. The test did not reveal signs of pulmonary hypertension nor shunts and showed a preserved systolic function (left ventricular ejection fraction [LVEF]: 58%) and a normally functioning prosthetic aortic valve. Unexpectedly, a mass at the posterior wall of the RA of 32 by 20 mm suggestive of an intracavitary thrombus was detected.

### **Further diagnostic work-up**

Magnetic resonance imaging was performed to confirm this finding due to its higher sensitivity and specificity. The mass inside the RA coming from the liver through the IVC was noted. This image was suggestive of an infiltrating HCC tumor thrombus (TT) (Figure 1). With the previous premedication, an abdominal multiphase CT was finally performed, thereby confirming the presence of a lesion in segment VIII with extension to segments V and I, suggestive of hepatocarcinoma (Figure 2). Left suprahepatic vein thrombosis with extension to the IVC until the RA and thrombosis in the left portal vein was noted, suggestive of tumor infiltration (Figure 3). On further work-up, her alpha-fetoprotein level was 6856.1 ng/mL.

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## **MULTIDISCIPLINARY EXPERT CONSULTATION**

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A multidisciplinary committee was held to decide treatment and further work-up.

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## **FINAL DIAGNOSIS**

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The final diagnosis of the presented case is HCC with TT extended to the RA and portal vein.

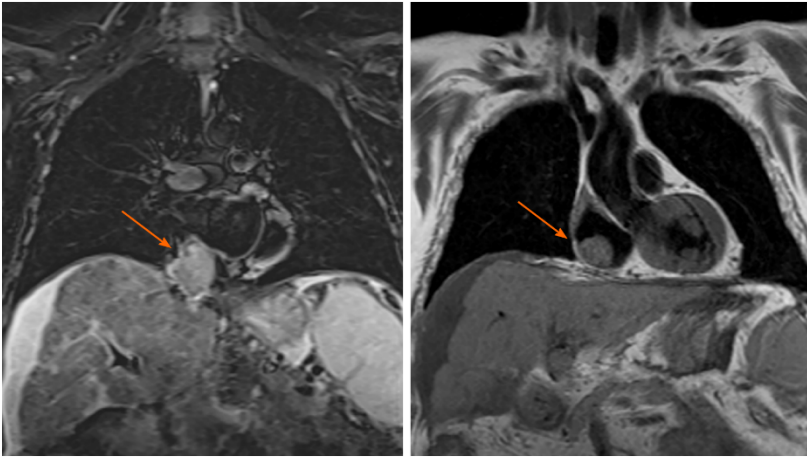
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## **TREATMENT**

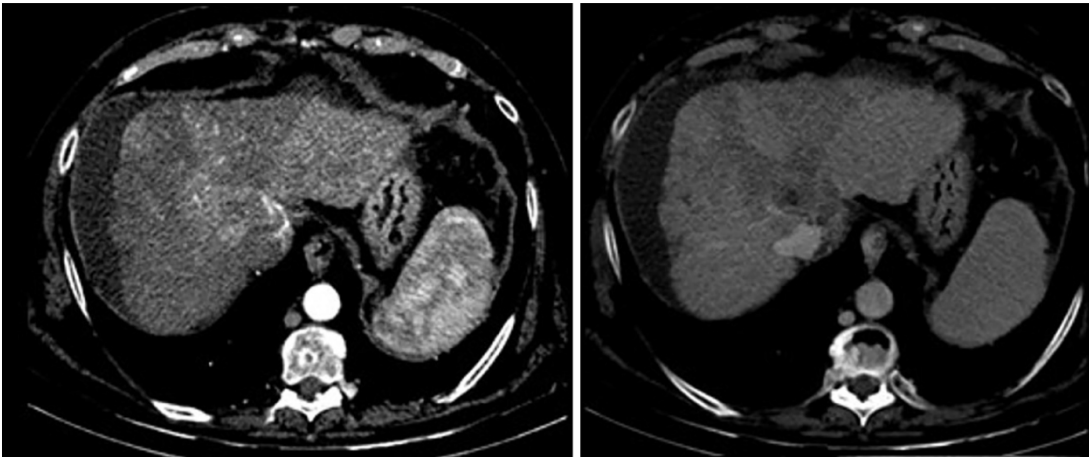
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A multidisciplinary committee evaluated the patient and determined that she was not a candidate for surgical or ablative therapies. Thus, systemic treatment with sorafenib was started at 400 mg every 12 h and required dose reduction for asthenia. Given that the patient presented an extended TT, anticoagulation was introduced with low





**Figure 1** Magnetic resonance imaging coronal view of a polylobulated mass of 59 mm × 51 mm × 52 mm inside the right atrium (right arrow), which extends from the liver through the inferior vena cava (left arrow) to the inside of the right atrium occupying its lower-posterior wall. These findings suggest as the first diagnostic possibility: A tumor thrombus of an advanced infiltrating hepatocellular carcinoma. Volumes and biventricular function within physiological parameters.



**Figure 2** Computed tomography scan axial view shows a poorly defined liver injury with margins of 55 mm × 90 mm located in segment VIII and with extension to segment V and segment I, enhanced in arterial phase with fast venous phase washing.

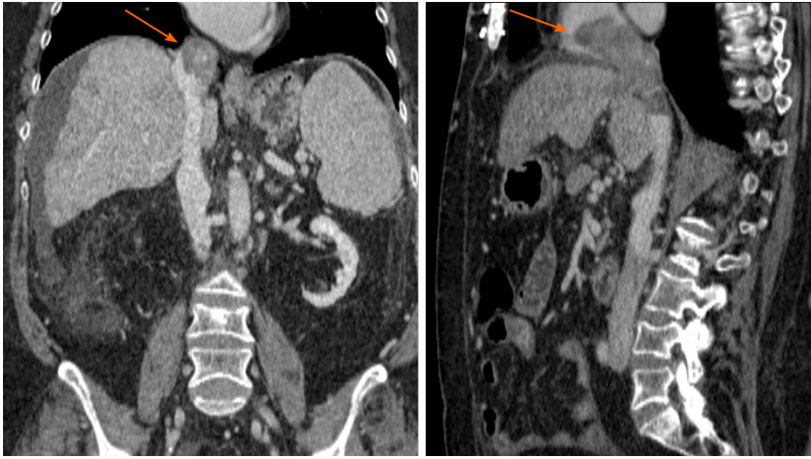
molecular weight heparin at a dose of 1 mg/kg every 12 h.

## OUTCOME AND FOLLOW-UP

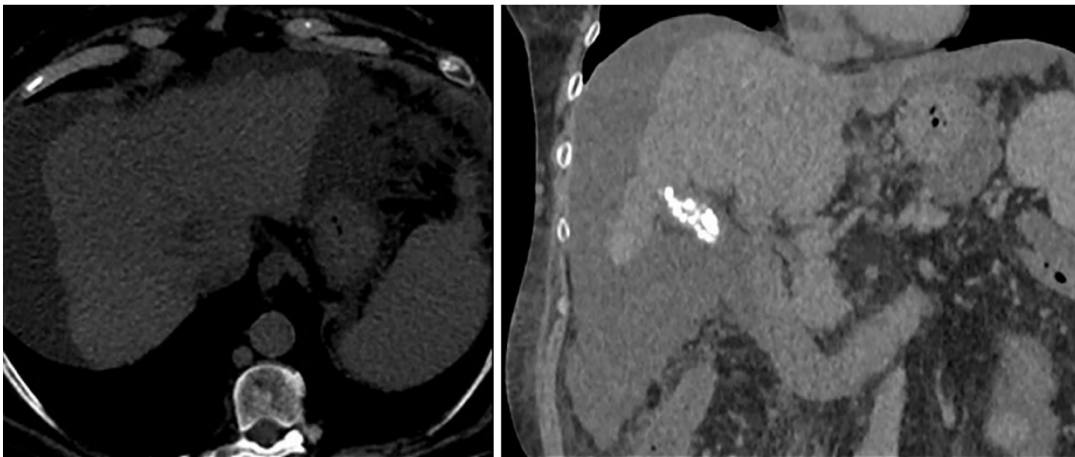
The patient was seen after 1 mo of being discharged, and she remained stable. She also showed an improved capacity for physical activities without any signs of embolism and diminished hepatomegaly in physical exploration. The dose of sorafenib was increased to a standard dose with positive tolerance. A non-contrast CT scan was completed 3 mo later (due to impaired kidney function). The limited evaluation presumed apparent stability of the tumoral mass (Figure 4). The alpha-fetoprotein level was 4156.1 ng/mL, thereby indicating a response to sorafenib. After 5 mo after receiving systemic therapy, the patient sought evaluation in the emergency department for being in a critical condition and was diagnosed with septic shock related to spontaneous bacterial peritonitis that ended fatally.

## DISCUSSION

HCC is the most common primary liver neoplasm. It is the fifth most frequently diagnosed cancer in men, and it is the ninth most commonly diagnosed cancer in



**Figure 3** Computed tomography scan coronal and sagittal views show a 55 mm × 90 mm mass in segment VIII with a tumor thrombus extending to the inferior vena cava (left arrow) and reaching up to right atrium (right arrow). Left intrahepatic portal thrombosis. Portal vein thrombosis with hypercaptation of the thrombus, suggestive of infiltrative tumor.



**Figure 4** Non-contrast computed tomography scan axial view showing persistence of the heterogeneous lesion in the segment VIII seen previously, not delimitable in the current study. Hypodensity persists in the inferior vena cava and right atrium suggestive of tumor extension, with apparent small reduction, although the intravascular tumor thrombus cannot be properly determined in a non-contrast computed tomography.

women worldwide<sup>[9]</sup>. The development of HCC is intently related to the presence of chronic liver diseases.

The diagnosis of HCC can be difficult and often requires the use of one or more imaging approaches. Ideally, tumors should be detected when they are  $\leq 2$  cm so that all treatment options can be offered. Vascular invasion and tumor thrombus formation are commonly seen in cases of advanced HCC due to the activation of hemostasis<sup>[10]</sup>. The incidence of vascular invasion increases with a larger tumor size, and it has been reported to be present in 82% of patients with serum AFP levels  $> 1000$   $\mu\text{g/L}$  and a tumor diameter of  $> 5$  cm<sup>[11]</sup>. IVC thrombosis is often asymptomatic, but symptoms related to portal hypertension can develop, for example, upper gastrointestinal bleeding, abdominal pain and ascites. Contrarily, the intra-atrial growth of HCC may not cause any symptoms per se but may lead to pulmonary thrombosis and pulmonary metastasis<sup>[12]</sup>. Advanced HCC with the invasion of the IVC and RA is exceptional, but it has been associated with poor prognosis and limited treatment options. In a retrospective study of 50 patients with advanced HCC with RA involvement, the median survival was only 2 mo with supportive care and only marginally improved to 4 mo with aggressive therapies<sup>[13]</sup>.

The European Association for the Study of the Liver (EASL) recommends patients with preserved liver function and minimally affected performance status (PS 0-2), stage C according to the Barcelona Clinic Liver Cancer Group (BCLC) and intermediate-stage (BCLC B) not eligible for locoregional therapies to undergo treatment with systemic therapy. Sorafenib, a multi-kinase inhibitor (TKI) was

introduced in the EASL guidelines in 2008. Sorafenib showed a survival benefit, documenting prolonged median survival and a nearly 3-mo extension of time to radiologic progression, which represented a breakthrough in the management of HCC<sup>[14]</sup>. Alpha-fetoprotein has been reported as a new alternative biomarker to RECIST to detect a sorafenib response in HCC, with the optimum cut-off points varying in published literature but suggesting that higher pre-treatment (AFP > 200 ng/mL) is associated with earlier recurrence and poorer overall survival<sup>[15,16]</sup>. Other experimental treatments were dismissed due to the age and medical history of the patient. Although sorafenib is the standard of care in these patients for more than a decade, further treatments and approaches have been undertaken in several reports as the resection of TT, the simultaneous resection of liver tumor and TT, external beam radiation therapy (EBRT), thalidomide treatment and transarterial chemoembolization (TACE). The postoperative survival period of patients with HCC and tumor thrombus in the RA varies from 18 d to 56 mo, with a mean survival of 20 mo<sup>[17]</sup>. In a retrospective cohort study of patients with HCC extending into the IVC/RA, treated with hepatectomy and thrombectomy, TACE and symptomatic treatment, the median survival was 19, 4.5 and 5 mo, respectively<sup>[17]</sup>. All these data indicate that removing the thrombus surgically combined with hepatectomy, or only TT extraction, might result in an improvement of survival in selected patients compared with other non-surgical procedures.

Radiofrequency ablation (commonly referred to as RFA) can result in long-term remission in small HCC. Nonetheless, performing RFA near the major vessels or diaphragm is difficult and challenging<sup>[18]</sup>. Several studies have validated that EBRT alone or combined with non-surgical treatment might achieve an excellent intrahepatic tumor control and a potential survival benefit of advanced HCC EBRT, presenting objective response rates ranging from 39% to 62% in patients with an associated macrovascular invasion<sup>[19]</sup>. The combination of TACE and RT has been beneficial compared with TACE alone for unresectable HCC in two meta-analyses<sup>[20,21]</sup>. Moreover, for major vessel invasion cases, combined TACE and RT had better OS and PFS than sorafenib, with a liver function not significantly worsened after treatment<sup>[22]</sup>. Further studies are crucial to accurately establish the incidence of adverse events and confirm these findings.

In our case, the patient was not a candidate for an invasive procedure; hence, systemic therapy with sorafenib was initiated. No predictive biomarkers of response to sorafenib or other TKI have been identified, and objective responses have been uncommon with the RECIST and modified RECIST criteria<sup>[23]</sup>. At a 3-mo follow-up, the patient improved symptoms with less dyspnea and asthenia, diminished hepatomegaly at physical exploration, a lower AFP levels and reached stable disease by CT scan.

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## CONCLUSION

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HCC is one of the most common and aggressive malignant tumors, being the TT formation in advanced stages a relatively common complication usually involving the portal vein, and less frequently, the hepatic veins. Hepatopulmonary syndrome and portopulmonary hypertension are the two main causes of dyspnea that must be discarded in a cirrhotic patient.

Non-invasive imaging is an essential part of HCC diagnosis and contributes to primary liver tumor staging. When dynamic explorations demonstrate a typical diagnostic pattern, no further diagnostic invasive procedures are necessary. HCC TT expansion to IVC and RA is rare and indicates poor prognosis. There is no consensus on anticoagulation or other interventions in these patients. Treatment response has formerly been evaluated using the RECIST criteria by CT scan, but alpha-fetoprotein may be employed to consider sorafenib or any other TKI's activity in HCC. Other treatment approaches could have been feasible as EBRT alone or combined with non-surgical treatment, but more data are essential to further establish the status of EBRT for the management of HCC.

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