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Case Report

Intra-atrial Thrombosis Complicating Hepatocellular Carcinoma with Positive Clinical Response to Sorafenib: A Case Report and Review of Literature

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Abstract

Introduction: Tumoral thrombus extension to inferior vena cava (IVC) and right atrium is an infrequent complication of hepatocellular carcinoma (HCC), with dismal prognosis and poorly codified treatment.

Presentation of case: We report the case of a 58-year-old man diagnosed with stage IV HCC in the right lobe of the liver, with intracavitary cardiac involvement. Under Sorafenib, the patient showed quick favourable clinical response, with decrease of the dyspnea and edema, but severe adverse effects led to early treatment discontinuation. We review the different therapeutic approaches to advanced HCC with cardiac extension.

Conclusion: Patients with intra-atrial thrombosis complicating hepatocellular carcinoma, when not eligible for surgery, might benefit from Sorafenib, to alleviate symptoms and prevent short-term cardio-vascular complications.

Keywords: Hepatobiliary cancer; chemotherapy

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Introduction

Incidence of hepatocellular carcinoma (HCC) is in constant increase in the United States and Europe, making it the third highest cause of cancer-related death globally [1]. The majority of these cancers are diagnosed at advanced, unresectable stages [2]. While vascular extension to the portal vein has been described in up to 65% of these cancers [3], involvement of the inferior vena cava and the right atrium is less frequent, and its management still debated.

Sorafenib, a mulikinase inhibitor, was the first tratement to show a favourable impact on the prognosis of patients with advanced or metastatic HCCs [4-5]. Its potential effect on inferior vena cava tumor thrombosis secondary to HCC has been seldom evaluated.

Case presentation

We report the case of a 58-year-old man of Caribbean origin who came to the emergency room presenting with severe asthenia, edema of the lower limbs and mild right-upper-quadrant abdominal pain which started 3 weeks earlier. His medical history included high blood pressure.

On physical examination, haemodynamics were preserved. A 38,4 ℃ fever, hepatomegaly, and abdominal tenderness without rebound tenderness were noted, as well as a heart murmur.

Initial blood tests showed moderate liver cytolysis (AST 8N, ALT 7,5N) and cholestasis (Total Bilirubin 41 µmol/L) with spontaneous Prothrombine Ratio and Factor V at 55% and 60 % respectively.

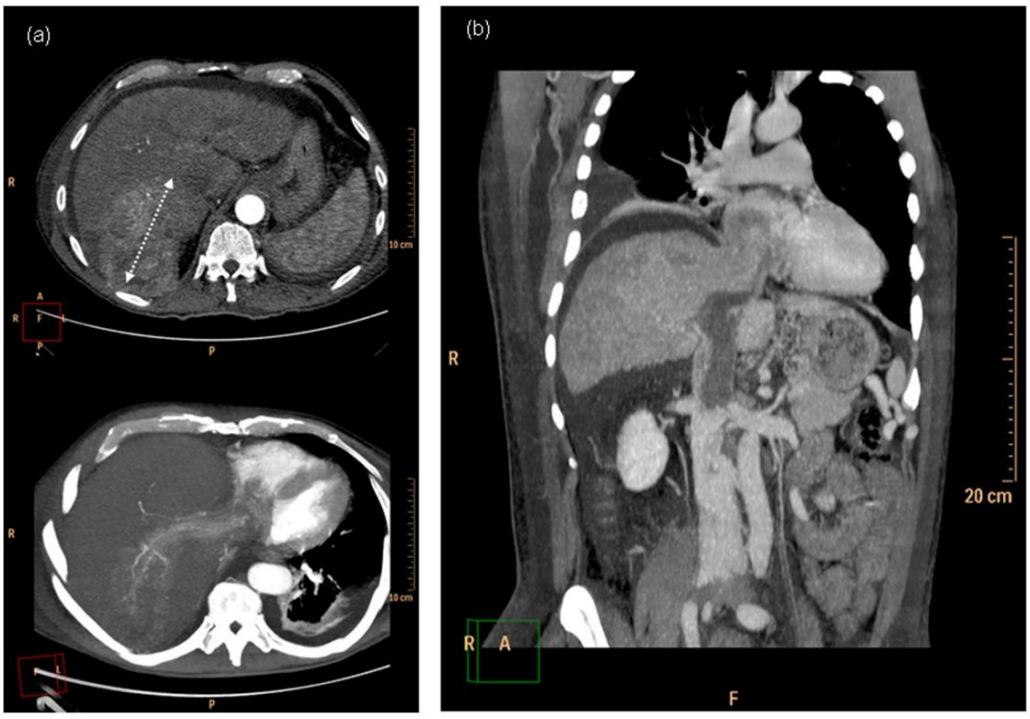

Figure 1 Computarized Tomography axial (a) and frontal (b) sections showing a highly-vasculared hepatic tumor on liver cirrhosis, compatible with Hepatocellular Carcinoma, complicated with ascites and tumoral thrombosis extension to the Inferior Vena Cava and right atrium.

Abdominal ultrasound described perihepatic ascites, an enlarged dysmorphic liver, associated with an 8-centimeter-large heterogeneous mass infiltrating the right liver and right-hepatic-vein thrombosis, extending to the inferior vena cava. Computerized tomography (CT) showed typical aspect of hepatocellular carcinoma on liver cirrhosis, complicated with extensive inferior vena cava and intra-atrial thrombosis (figure 1). Chest CT Scan showed bilateral distal pulmonary embolisms. Transthoracic echocardiography described a voluminous, mobile and highly-vasculared right-atrial tumor thrombosis, protruding through the tricuspid valve, associated with inferior vena cava stasis (figure 2).

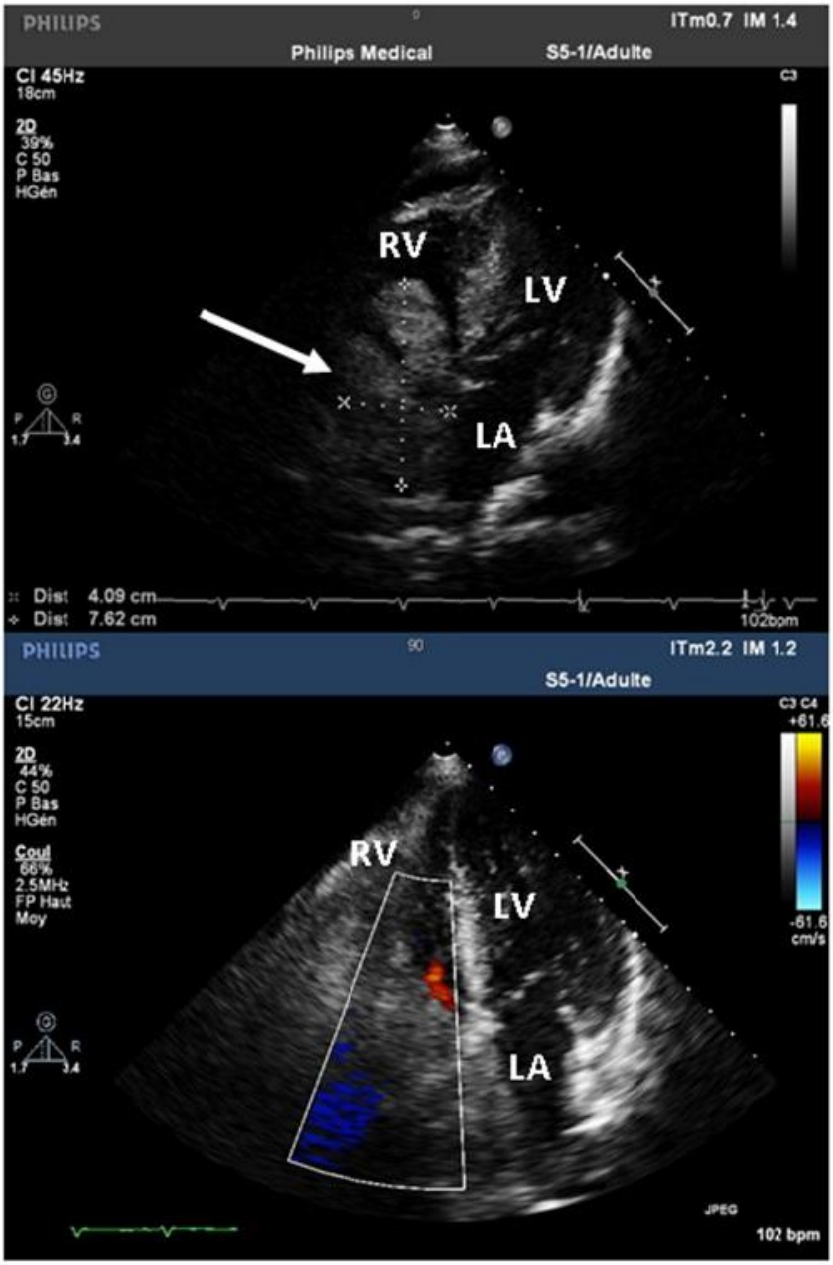

Figure 2 Transthoracic echocardiography showing a vasculared mass in the right atrium prolapsing through the tricuscpid valve inside the right ventricule. Arrow, Thrombus; RV, Right ventricule; LV, Left ventricule; LA, Left atrium.

Alpha-foeto-protein was measured at 21866 ng/ml. Evaluation of the liver function showed a Child-Pugh score of B7. The patient declared no alcohol abuse history, but was found positive for Hepatitis B, with a high viral load of 1320000 UI/ml, of which he was unaware until then.

Initial treatment included anticoagulation therapy and diuretics. Despite these measures, edema of the lower limbs worsened, associated with palpitations and fainting when standing-up. A new CT-Scan performed 2 weeks after anticoagulation was started showed a stability of the hepatic lesion, but an extension of the intra-atrial thrombus associated with the IVC thrombus.

After a multidisciplinary staff, with digestive and vascular surgeons, gastroenterologists and radiologists, the clinical state of the patient and the tumor massive extension were deemed unsuitable for a surgical procedure including hepatic resection and thrombectomy or intra-arterial chemoembolization.

Oral chemotherapy with Sorafenib was eventually decided. After a month on this therapy, at 800 mg/day, the clinical status of the patient had improved, with complete regression of lower-limb edema, and disappearance of palpitations, allowing the patient to stand and walk. Unfortunatly, the patient suffered from serious adverse effects from Sorafenib. Symptoms included severe diarrhea and fatigue, grade 2 and 4 on the NCI Common Terminology Criteria for Adverse Events scale respectively. Treatment discontinuation was decided after 6 weeks, with no prior dose reduction, at the patient's request, before response to treatment could be evaluated on a follow CT scan. The patient eventually died 4 months after the diagnosis.

Discussion

While 30 to 40 % of HCCs are discovered at early stages, with potential curative treatments (resection, hepatic transplantation or radiofrequency ablation) and 5-year survival rates higher than 50 %, the majority of these cancers are diagnosed at advanced stages, possibly involving extra-hepatic metastases, with dismal prognosis [2].

Lung, bone, brain and adrenal glands are the most common sites of metastasis. HCC is also a venotrophic tumor, with portal vein thrombosis involving 20 to 65 % of these tumours [3]. The natural history of HCC complicated with macroscopic vascular invasion portends a median survival time of only 9 to 10 weeks [6].

Infrequently, inferior vena cava (IVC) thrombosis, extending to the right atrium (RA) has been described in pre-mortem evaluations, but has been observed in up to 3,5% of patients with HCC, on post-mortem autopsies [7].

After initial assessment with abdominal ultrasonography, contrast-enhanced CT-scan and/or magnetic resonance imagery can efficiently point to the diagnosis of hepatic carcinoma and establish the space continuity between the lesion and the atrial thrombus.

Intra-atrial extension can be assessed by trans-thoracic echocardiography (TTE), but evaluation can be hampered by thorax conformation. Although limited by multiple contraindications, Trans-oesophageal echocardiography offers great sensibility in the detection of cardiac metastasis in HCC and must be considered before all surgical intervention in HCC [8].

Advanced HCC with IVC invasion or RA tumor thrombus is associated with an overall median survival of 3 months with a 6-month survival rate of 24% [9]. Potentially fatal complications of the RA thrombus include myocardial infarction, right ventricular outflow tract obstruction, pulmonary tumor embolism and "cannonball" lung metastases [10-13].

Among potential treatments, surgery currently offers the best prognosis. En bloc hepatectomy

and resection of the RA thrombus under cardiopulmonary bypass results in a lower incidence of heart failure deaths and allows a median survival of 11 months [14]. But this procedure requires skillfull techniques, with a high risk of per-operatory tumor emboli and does not prevent short-term recurrent malignancy, with most HCCs recurring within one year [15]. Moreover, surgery has shown a favourable impact in retrospective studies only, involving patients with good general condition, and stable cirrhosis, compatible with a surgical procedure. In our case, as in many situations, surgery may not be adequate.

Non surgical approaches include systemic chemotherapy, Trans-Arterial Chemoembolization (TACE) and chemoradiation.

When possible, chemoembolization may present potential benefits not only for the frequent Budd-Chiari syndrome due to the tumor thrombosis, but could also induce down-staging of advanced HCCs with extensive tumor thrombi, sometimes allowing secondary surgery [16-17]. But application of this procedure may be limited by the presence of extra-hepatic metastases or the severity of the underlying liver disease. Moreover, impact on survival rate remains controversial [14].

Among systemic chemotherapeutic agents, Sorafenib has proved to be beneficial for patients with advanced hepatocellular carcinoma, with a 3-month median survival benefit [4-5]. Sorafenib is a multikinase inhibitor of the platelet-derived growth factor receptor, the vascular growth factor receptors and serine-threonine kinases (Raf).

In the specific situation of HCC complicated with portal vein tumor thrombosis (PVTT), sorafenib has shown favourable impact. In a Chinese pospective study of 2009, single-agent sorafenib showed similar therapeutic benefits in patients with HCC, with or without PVTT [18]. Complete regression of the HCC with PVTT under sorafenib has been described in various case-reports [19-20].

As far as we know, the impact of Sorafenib in the context of advanced HCC complicated with IVC and RA thrombi has seldom been described [21]. In this american study, one month after Sorafenib therapy had been undertaken, a follow computarized tomography revealed a decrease in size of the hepatic mass and the IVC thrombus. Echocardiography showed a decrease in size of the right atrial mass.

In our case, despite significant clinical improvement, early treatment discontinuation due to severe adverse effects prevented imagery reevaluation. Yet, in this palliative setting, prolonged symptoms alleviation under Sorafenib may be an endpoint for treatment success as valid as improvement on imagery.

Conclusion

In patients with advanced HCC, complicated with inferior vena cava thrombosis extending to the right atrium, surgical intervention currently offers the best prognosis. Yet in many cases, poor general condition, extra-hepatic metastasis or altered liver function may prevent a surgical curative approach. Sorafenib could be an interesting alternative to limit tumor progression, alleviate patients' symptoms and prevent short-term cardio-vascular complications.

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