

# A Rare Presentation of Primary Multifocal Hepatocellular Carcinoma in Non-cirrhotic Liver

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## ABSTRACT

Hepatocellular carcinoma (HCC) is the most frequent type of primary liver malignancy. Most cases of HCC are secondary to either alcoholic cirrhosis or viral hepatitis. Liver cirrhosis due to any other causes is considered as a risk factor for the development of HCC. HCC in non-cirrhotic livers remains a rare condition. The present case report describes an 86-year-old man patient admitted to explore epigastric pain, with no evidence of pre-existing liver disease and in a good general condition. The computed tomography was very suggestive of multiple metastatic liver lesions. However, after a thorough diagnostic and anamnestic workup, no primitive tumor was found. Histopathological and imaging studies confirmed the presence of a Primary Multifocal HCC in a non-cirrhotic liver. HCC occurs more frequently on a cirrhotic liver; however, it can occur on a non-cirrhotic liver and remains an extremely rare case. In our case, the primary HCC in non-cirrhotic liver occurs with a multifocal pattern.

**Key words:** Hepatitis C virus hepatitis virus, hepatocellular carcinoma, liver, non-cirrhotic liver disease, sorafenib

## INTRODUCTION

Primary liver cancer is the sixth most common cancer worldwide<sup>[1]</sup> and the second leading cause of cancer-related deaths worldwide.<sup>[2]</sup> 90% of liver cancer are hepatocellular carcinoma (HCC).<sup>[3]</sup> Although most of the cases occur in developing countries,<sup>[4]</sup> its incidence in developed countries has increased recently.<sup>[5]</sup> HCC typically arises in a cirrhotic liver; however, approximately 20% of HCCs have been known to develop in a non-cirrhotic liver.<sup>[6]</sup> Fibrolamellar carcinoma, a rare variant of HCC also occurs without any background cirrhosis or hepatitis.<sup>[6]</sup> In our case, the histology shows a moderately differentiated HCC, alpha-fetoprotein negative, with the peculiarity of being multifocal in origin and whether it is developed in a non-cirrhotic liver.

gave no history of jaundice or gastrointestinal bleeding. He had a good general well-being. He suffers from hypertension, thalassemia minor, hypothyroidism, and type 2 diabetes mellitus. His therapy is Atenolol + Chlortalidon 100/25 mg; Metformin 500 mg; and Levothyroxine 0.1 mg.

On examination, the patient was not jaundiced. The abdominal examination revealed a distended abdomen, without evident masses or collateral circulation. There were scars due to a previous hernioplasty surgery. Bowel sounds present. The abdomen was treatable, with defense signs on the epigastric and right hypochondriac regions, without splenomegaly.

He had bilateral legs edema and a 4/6 systolic heart sound with carotid irradiation.

No other signs of hepatic stigmata. Examination of other systems was unremarkable.

A computed tomography (CT) [Figure 1] with minimum detectable change of the abdomen showed several solid

## CASE REPORT

An 86-year-old man without pathological antecedents presented with epigastric pain from the previous day. He

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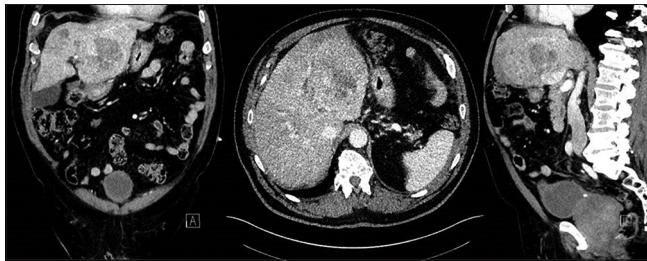
nodular lesions of the liver, the biggest of 11.5 × 9.5 cm at the III segment. It has a dishomogeneous structure due to the combination of hypo-, iso-, and hyper-dense areas.

The main left portal branches appear compressed, but pervaded. Biliary tract is not dilated. There is non-dilatation of the Wirsung, but there is perihepatic and perisplenic effusion, with a density compatible with blood. Coprostasis and diverticulosis of the colon has been found, with a pericardiophrenic lymph node of 15 x 10 mm. No more significant finds has been detected. Our first idea was of liver metastases [Figure 2]. We performed abdomen ultrasound and CT scan of the chest to find the primitive tumor and perform the staging of the disease.

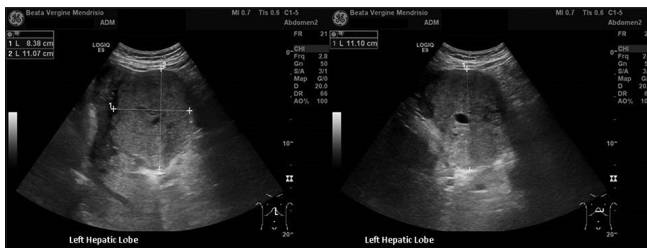
Even after these examinations, no reasonable primary tumor was found. No pathological findings, other than that already known to the CT of the abdomen.

At this point, we move our attention to a possible primary liver cancer with multifocal origin a pattern of non-cirrhotic liver.

The liver tests showed minimum pattern of cholestasis: Alkaline phosphatase: 63 UI/L (<129), gamma-glutamyl transpeptidase: 100 UI/L (<71), total bilirubin: 22.4 mg/L (<21), and direct bilirubin 15.2 mg/L (<5) and no increase in transaminases: Aspartate aminotransferase 28 UI/L (<50) and alanine aminotransferase: 29 UI/L (<50). Cell blood count revealed a Hb of 128 g/L (normochromic and microcytic),



**Figure 1:** Computed tomography of the abdomen in three planes reconstruction. Presence of numerous masses of neoplastic nature affecting the liver. Associated perihepatic and perisplenic effusion, denser than water and compatible with dripping

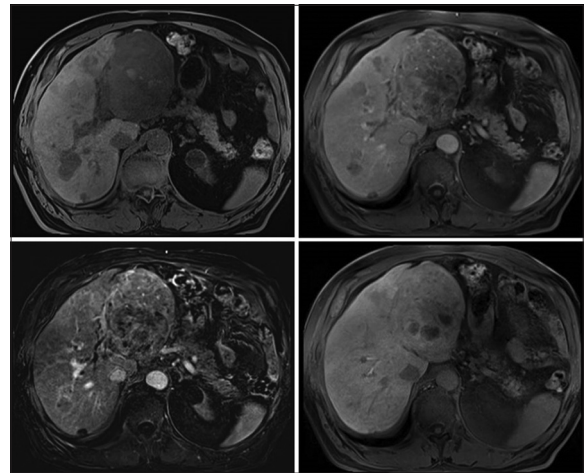


**Figure 2:** Ultrasound representative images of the abdomen. Multiple nodular liver lesions

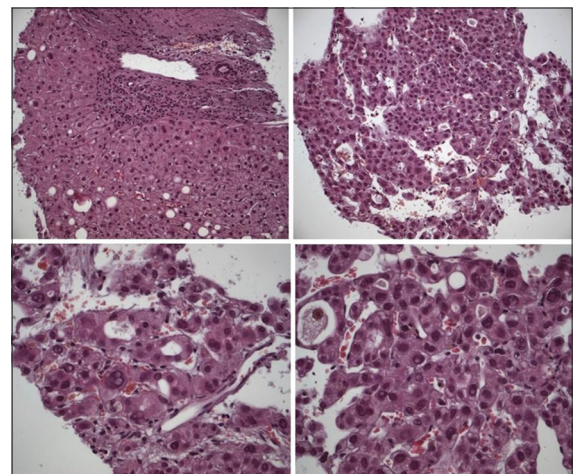
white blood cell of 8600/cmm, and platelets of 156,000/cm. The prothrombin level was 81%. Serology for viral hepatitis B including hepatitis B surface antigen, hepatitis B core antibody, and hepatitis B surface antibody was negative. Hepatitis C virus (HCV)-Ab and HCV immunoblot were positive.

At this point, we decided to discuss the case at the local hepatobiliary board. After the multidisciplinary discussion, we decided to perform a magnetic resonance imaging (MRI) of the abdomen in order to perform a biopsy of the liver lesions [Figure 3].

The MRI showed an enlarged liver, with irregular profiles and presence of multiple neoformations with diameter



**Figure 3:** Magnetic resonance imaging of the liver. Hepatic disease with a primitive appearance and prevalent involvement of the left hepatic lobe. Intraductal papillary mucinous neoplasia of the pancreas, without signs of malignant transformation



**Figure 4:** Histologic sample of the main lesion with perilesional tissue at different magnifications. Needle biopsy, 18G, of the right liver lobe: Moderately differentiated hepatocellular carcinoma; adjacent hepatic parenchyma with slight portal inflammation; and mild macrovascular steatosis (about 30%)

between a few millimeters and 12 × 9 mm on the left hepatic lobe. These lesions were in homogeneously hypervascular and with washout, referable to a primitive disease compatible with hepatocarcinoma or hepatocolangiocarcinoma.

The histology shows a moderately differentiated HCC, alpha-fetoprotein negative [Figure 4]. The adjacent hepatic parenchyma shows mild portal inflammation and mild macrovascular steatosis (about 30%).

We have concluded that, reasonably, the patient has come into contact with the virus in the past and there has been spontaneous healing (viremia 15 IU/ml).

The neoplasia is of empathic origin and multifocal and for this reason not susceptible to any locoregional intervention.

On the other hand, a medical treatment would have the sole objective of trying to slow down its development. Due to the good clinical conditions, despite the age, we have agreed to make a therapeutic attempt with the multikinase inhibitor Sorafenib 200 mg/die.

## DISCUSSION

HCC is the most common type of primary liver cancer. The world annual incidence is of 600,000 newly diagnosed patients.<sup>[7]</sup> HCC in non-cirrhotic liver is a relatively rare diagnosis: 14% in Schutte's cohort (664 cases of HCC),<sup>[8]</sup> 8.8% in Gomez-Rodriguez's cohort (469 cases of HCC),<sup>[9]</sup> 6.2% in Nunez-Martinez's cohort (469 cases of HCC),<sup>[10]</sup> and only 1.7% in Giannini's cohort including 3027 cases of HCC.<sup>[11]</sup> Non-cirrhotic HCC reveals a bimodal distribution, peaking at the 2<sup>nd</sup> and 7<sup>th</sup> decades. In the present case, the patient is a mean age of 86. Although liver cirrhosis is the main risk factor for HCC, this tumor may develop in patients with non-cirrhotic chronic liver disease such as chronic hepatitis B virus infection<sup>[12]</sup> and chronic HCV infection.<sup>[13]</sup> HCC can also develop in subjects without evidence of chronic liver disease. This condition remains exceptional and it represents only 0.32% in literature's largest cohort of HCC including 3027 cases. This is compatible with the presented case as the patient showed no evidence of pre-existing liver disease. The pathogenesis is still not well understood. Several pathogenic risk factors are discussed such as ionizing radiation, exposure to toxins,<sup>[14]</sup> and benign focal liver lesions, mainly the hepatocellular adenoma. Our patient had none of these risk factors (especially, the hepatocellular adenoma). HCC in non-cirrhotic patients may remain asymptomatic in more than half of the cases and is often diagnosed at an advanced and inoperable stage. This was the case in this presentation. There were only a spontaneous epigastric pain and right hypochondriac evocable pain at deep palpations, without any other associated symptoms. The patient had a good general condition. Alpha-fetoprotein can be high or

remain in the standards,<sup>[15]</sup> as in our patient. According to the guidelines, diagnosis is based on medical imaging and histology. HCC in non-cirrhotic patients shows similar CT and MRI patterns to those of HCC in cirrhotic patients.<sup>[16]</sup> Unfortunately, the abdominal CT performed in the presented case was very suggestive of a metastatic disease, due to the multifocal pattern. According to histological classification criteria of the World Health Organization, in our case, the histological study confirmed the diagnosis of a primary multifocal HCC in a non-cirrhotic liver and there were no characteristics of a fibrolamellar HCC. In the non-tumoral liver, there were no signs of cirrhosis. Patients with HCC diagnosed at an early stage are optimal candidates for resection, liver transplantation, or percutaneous ablation. Surgical resection is recommended for patients with single tumors, absence of clinically relevant portal hypertension, and normal bilirubin. Transplantation is indicated in patients with three nodules of <3 cm or with single tumors <5 cm with liver function impairment precluding resection. Transarterial chemoembolization is recommended in asymptomatic patients with multinodular tumors that have not invaded hepatic vessels nor been disseminated outside the liver. Sorafenib is indicated as the first line of treatment in patients who cannot benefit from the above therapeutic options and still have a preserved liver function.<sup>[17,18]</sup> In the case of our patient, the tumor was primary and multifocal in origin. The above mentioned and the age of the patient made the surgical resection impossible. According to the tumor stage and the liver's biological parameters, the patient was a candidate for chemotherapy by Sorafenib. Survival of patients with HCC in non-cirrhotic liver mainly depends on tumor-related factors such as tumor size, existence of satellite lesions, existence of a tumor capsule, vascular invasion, and grading. The altered condition, tobacco consumption, macroscopic vascular invasion, the large size of the tumor, and the non-surgical treatment were predictive factors of a bad prognosis of HCC on a healthy liver.<sup>[19]</sup> In the presented case, the tumor-related factors and the absence of treatment worsened the prognosis.

## CONCLUSION

HCC on a healthy liver remains an exceptional condition. The multifocal presentation of HCC is rare. The finding of a primary multifocal HCC in a non-cirrhotic liver is extremely rare and there are not yet statistic and epidemiology on it. The pathogenesis is still not well understood. It is characterized by a clinical latency explaining the delay in the diagnosis and, consequently, the poor prognosis at an advanced stage. The connection with the HCV virus is the probable etiological cause.

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