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An Uncommon Presentation of Hepatocellular Carcinoma

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Abstract **Case Report**

Hepatocellular carcinoma (HCC) is the most frequent type of primary liver cancer, with an important characteristic being the development on a background of cirrhosis. HCC in non-cirrhotic liver is rare. We report a case of an HCC on a non-cirrhotic liver in a 66-year-old patient who was admitted with a 3 months history of right hypochondriac pain and weight loss. He had a medical history of hypertension, type 2 diabetes, obesity, and no alcohol abuse. Abdominal computed tomography (CT) and hepatic magnetic resonance imaging (MRI) showed a 115x100x110mm mass in the segment V and VIII, hypodense with heterogeneous and early arterial enhancement, and clearing in portal and late phase. He underwent a liver biopsy that confirmed an HCC without underlying cirrhosis. Surgical treatment was not an option since our patient presented multiple risk factors of recurrence. The patient underwent two sessions of transarterial chemoembolization (TACE) but the follow-up showed signs of progression.

Keywords: Hepatocellular carcinoma, Noncirrhotic, Liver cancer.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most frequent type of primary liver cancer. It is the 6th most common cancer, and the second leading cause of cancer related deaths worldwide [1]. It is a hypervascular hepatocellular tumor, with the primary characteristic being the development in approximately 80% on a background of cirrhosis [2]. HCC in a non-cirrhotic liver is a distinct entity, not only in terms of epidemiology and clinical presentation, but also in terms of treatment and prognosis. In fact, it is often an optimal candidate for resection, and the prognosis is better compared to HCC arising in the context of cirrhosis.

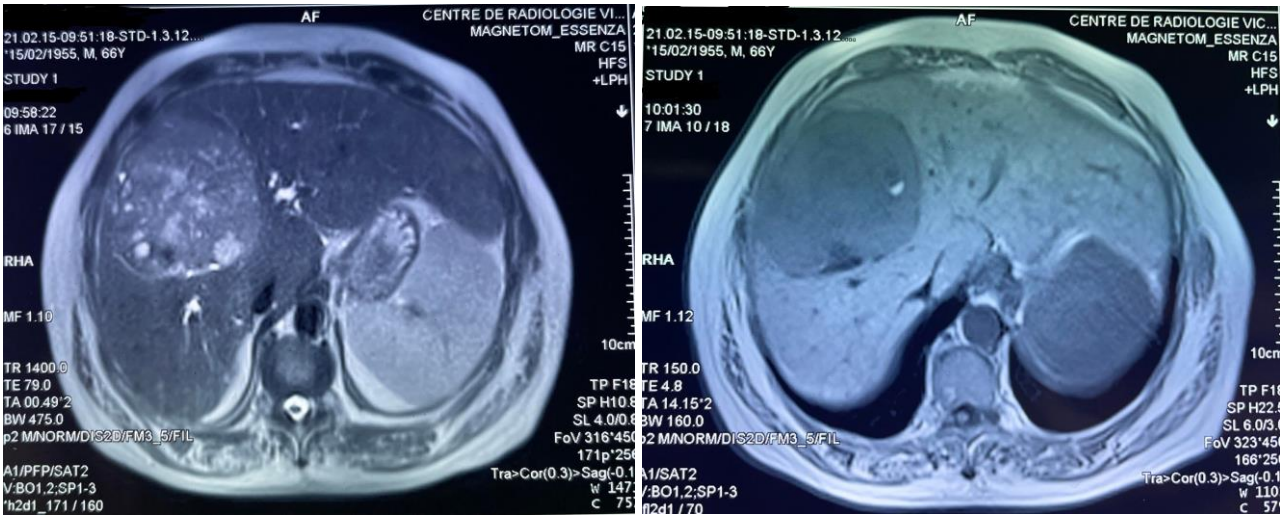
We report a case of an HCC on a non-cirrhotic liver in a 66-year-old patient.

CASE REPORT

A 66-year-old patient with a medical history of hypertension, type 2 diabetes, and obesity, with no alcohol abuse, was admitted with a 3 months history of right hypochondriac pain and weight loss. On examination, the patient had a good general condition. His body-mass index was 36Kg/m2. The abdominal examination revealed a firm and painful hepatomegaly. He did not exhibit signs of chronic liver disease or heart failure. The rest of physical examination was unremarkable. Abdominal computed tomography (CT) showed a 115x100x110mm mass in the segment V and VIII, hypodense with heterogeneous enhancement after contrast injection, arterial phase hyperenhancement avec wash out on portal venous and delayed phases.

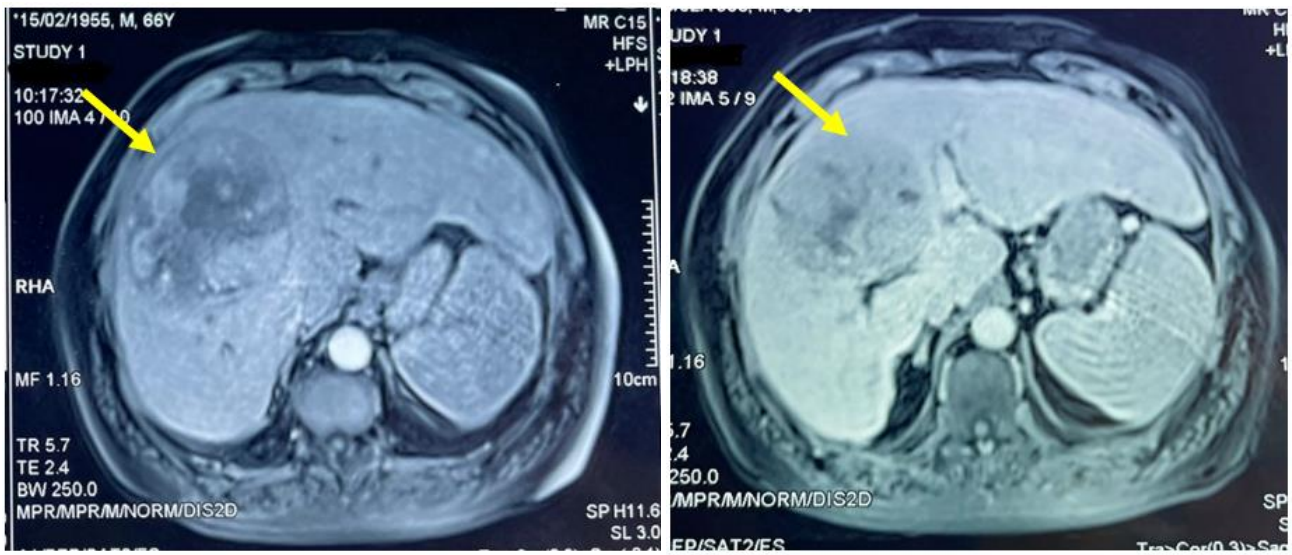
Magnetic resonance imaging (MRI) identified the same lesion in a non-cirrhotic liver (Figure 1a and 1b), with early arterial enhancement, and clearing in portal and late phase (Figure 2a, b and c). The tumor develops towards the right portal vein, but there were no signs of portal extension, portal hypertension or cirrhosis. Liver tests showed cholestasis: AP: 168UI/l (<105 UI/l), GGT: 296 UI/l (<42UI/l), total bilirubine: 14.9 µmol/l (<20 µmol/l) and a minimum increase in transaminases: ALAT: 65UI/l (<41 UI/l), ASAT: 66UI/l (<50 UI/l). The prothrombin level was 84%, the factor V level was 110%, and platelet count was 202000/mm^3. Serologies for viral hepatitis B and C were negative. Iron and copper tests were normal, and the immunological panel was also negative. Serum alpha-fetoprotein (AFP) concentration was 2.4 ng/mL (0–15 ng/mL). A liver biopsy was performed on both tumoral and non-tumoral liver tissue. Histological examination revealed a predominantly trabecular tumor proliferation, consistent with hepatocellular carcinoma. There were no large

eosinophilic hepatocytes or fibrolamellar bands that are characteristic of the fibrolamellar HCC. Immunohistochemistry showed a positive staining for glypican 3 (GPC3), glutamine synthetase and heat shock protein 70 (HSP70). The tumor was negative for CK7 and CK20. The liver tissue around the tumor exhibited moderate inflammation without fibrosis, steatosis, hepatocytes ballooning, iron or copper deposition. The final diagnosis was an HCC in a non-cirrhotic liver. Staging for distant metastasis did not reveal any secondary lesions. Given the patient's age, diabetes, hypertension, obesity and the significant tumor size, surgical treatment including liver resection and liver transplantation could not be options. Therefore, after multi-disciplinary consultation meeting (MCM), the patient underwent two sessions of transarterial chemoembolization (TACE) in order to reduce the tumor size. Unfortunately, the follow-up showed an increase in the size of the hepatic nodule, measuring 134x110x120mm versus 115x100x110mm. Also, four other lesions appeared in segments II and III. The largest one was a 22x20mm nodule. On MRI, they all showed early arterial enhancement, and clearing in portal and late phase. The patient's general condition had also significantly deteriorated. Palliative care was subsequently provided to our patient. Unfortunately, he died a few days later.

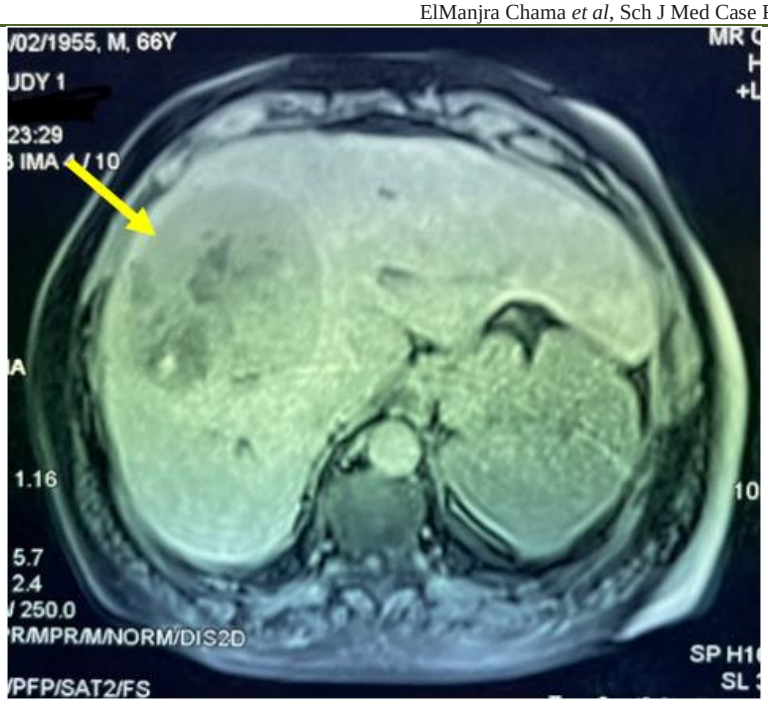


A **B**

Figure 1: Magnetic resonance imaging of liver acquisition shows a non-cirrhotic liver with a 115x110 mm heterogeneous mass in the segment V and VIII



A: Axial fat-saturated T2 weighted image **B: Axial T1 weighted image**



C:

Figure 2: Magnetic resonance imaging of liver acquisition shows the liver mass (yellow arrows) with early arterial enhancement (a), and clearing in portal phase (b) and late phase (c)

DISCUSSION

HCC is one of the deadliest cancers, causing over 700000 deaths worldwide annually [3]. It occurs in the setting of liver cirrhosis in 80% of cases [4]. The development in a non-cirrhotic liver represents only 10% to 20% of cases in most series [5]. It was first described in 1956 [6]. Peak incidence of HCC occurs near 20 years with a second peak in individuals aged 60-70 years, which was the case of our patient [7]. The primary risk factors for HCC in non-cirrhotic livers include non-alcoholic fatty liver disease, hepatitis B, less frequently hepatitis C, as well as ionizing radiation, exposure to toxins such as aflatoxin B1 (AFB1), the use of anabolic steroids, or even hepatic adenoma as a precancerous lesion [8] [9]. Our patient had none of these risk factors, and despite the presence of metabolic syndrome, there were no histological criteria to support non-alcoholic fatty liver disease. The clinical signs are variable, ranging from right hypochondriac pain to jaundice, often accompanied by asthenia, anorexia and weight loss. Paraneoplastic syndromes can also be present, such as hypercalcemia or hypoglycemia. Tumor rupture is rare but can be life-threatening. HCC in a non-cirrhotic liver can remain asymptomatic for a long period, explaining the frequent discovery of large tumors and subsequently a late-stage diagnosis, unlike HCC in cirrhotic livers. Indeed, since patients with cirrhosis are regularly monitored, HCC in cirrhotic-liver is typically discovered at an early stage. Diagnosis of HCC occurring in non-cirrhotic liver relies on imaging techniques and histology. It typically shows a large, solitary nodule with hypointensity on T1-weighted images, frequent hyperintensity on T2-weighted images, and intense arterial vascularization [10]. Imaging also allows for the assessment of tumor extension, which can result in metastases, particularly in the lungs and abdominal lymph nodes. Alpha-fetoprotein levels are not always elevated. Unlike HCC in cirrhotic livers, which can be diagnosed based on imaging alone, HCC in non-cirrhotic livers requires histological confirmation. The four most common histopathological presentations are microtrabecular, macrotrabecular, compact, and pseudoglandular forms. The trabecular form is the most common (41-76%) [11]. The liver parenchyma adjacent to the tumor can be entirely normal or show varying degrees of inflammation, fibrosis, steatosis, iron or copper accumulation [12]. On our patient, liver biopsy allowed to confirm predominantly trabecular HCC with no signs of underlying chronic liver disease. Immunohistochemistry can be necessary since the differential diagnosis with a secondary liver nodule can be difficult.

The treatment of choice for HCC in non-cirrhotic livers is surgery [13]. Since hepatic function is preserved, even extensive surgical resections are possible with lower morbidity and mortality rates. It can achieve a 5-year survival rate of 41% to 74% [14]. Preoperative evaluation is necessary. Poor prognostic factors after surgical resection include advanced age (>65 years), the presence of comorbidities such as diabetes, hypertension, dyslipidemia, obesity, heart failure, or respiratory insufficiency, and large tumor size [15]. Due to multiple risk factors in our patient, surgical treatment was no considered. Other therapeutic alternatives are possible for HCC in non-cirrhotic livers, such as radiofrequency ablation, or TACE, which can be used for tumor size reduction, as was the case with our

patient. Liver transplantation (LT) in the setting of HCC in non-cirrhotic livers is less well defined than for HCC in cirrhosis. The recommendation for LT is therefore fragile [16].

CONCLUSION

Hepatocellular carcinoma in a non-cirrhotic liver is rare, and its pathogenesis is still not fully understood. It is characterized by a clinical latency, often leading to diagnosis at an advanced stage. However, unlike HCC in cirrhotic livers, surgery remains the treatment of choice even for large tumors, with a relatively low morbidity and mortality rate. The prognosis is also better compared to HCC in cirrhotic-livers [9]. It is important to select high-risk patients and include them in a surveillance program to enable early diagnosis of HCC in non-cirrhotic livers.

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Authors' Contributions:

All authors participated in the conception, drafting the work, critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

Consent to Publication:

The patient has declared his consent freely and in an informed manner, in order to allow the production and publication of this manuscript.

Ethical Approval: Ethical approval is not required at our institution to publish an anonymous case report.

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