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Metabolic-Associated Fatty Liver Disease - A Silent or an Aggressive Killer? A Case-Report

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Abstract

The rising incidence of hepatocellular carcinoma (HCC) in non-cirrhotic patients in recent years implies the presence of other factors that could contribute to liver carcinogenesis. Metabolic-associated fatty liver disease (MAFLD) can progress to HCC, which poses a significant burden on the healthcare systems worldwide and has a high mortality rate. An aggressive non-invasive surveillance strategy is necessary in order to detect liver cancer in non-cirrhotic patients, especially in those with risk factors such as diabetes, obesity or older age. An acute clinical presentation is possible through complications, such as the development of hemoperitoneum due to the non-traumatic HCC rupture.

Keywords: Hemoperitoneum • Metabolic-associated fatty liver disease • Liver cirrhosis • Hepatocellular carcinoma covid-19 acute coronary syndrome • Thrombosis

Introduction

Hemoperitoneum arising as a consequence of spontaneously ruptured hepatocellular carcinoma (HCC) is associated with a significant mortality rate, reported between 25-75% [1]. Often, this serious complication may be the first clinical manifestation of the disease in a non-cirrhotic patient. HCC frequently occurs in the presence of liver cirrhosis, but it can also develop in the context of other diseases. Metabolic-associated fatty liver disease (MAFLD), previously known as non-alcoholic fatty liver disease (NAFLD), represents nowadays the most common cause of chronic liver disease [1,2]. With a global incidence ranging between 6% and 35%, MAFLD is more prevalent in the more developed Western countries [2,3]. The term MAFLD encompasses a broad spectrum of different stages of liver damage, ranging from steatosis and metabolic steatohepatitis (MeSH) to MAFLD-related cirrhosis and even hepatocellular carcinoma (HCC) [2,4].

In this paper, we describe the case of a patient with an acute clinical presentation of MAFLD-related HCC through hemoperitoneum, with a favorable post-operative outcome.

Case Presentation

An 85-year-old Caucasian female presented to our Gastroenterology outpatient clinic with acute onset upper abdominal pain, bloating and faintness, precipitated by an intense defecation effort. The patient had been found by her daughter lying down on the floor of her bathroom, conscious and with appropriate time and space orientation. The past medical history evidenced arterial hypertension, hepatic steatosis and grade 1 obesity for 25 years, type 2 diabetes for 4 years and an episode of SARS-COV 2 pneumonia one year previously.

Clinical examination revealed a BMI of 31 kg/m^2, skin pallor, tachycardia (100 bpm), but with a blood pressure within the normal range (120/80 mmHg), with a distended abdomen presenting diffuse tenderness. There were no signs of peritonitis and the digital rectal examination found an empty rectal ampulla, without any traces of blood. Laboratory blood tests showed moderate iron deficiency anemia (Hb=9 g/dL, iron=31 mcg/dL), inflammatory syndrome (CRP=4 mg/dL, WBC=15370/mm^3), mild hepatocytolisis syndrome (ALAT=60 UI/L, ASAT=60UI/L), hyperglycemia (193 mg/dL), elevated blood urea=114 mg/dL and serum creatinine=2.45 mg/dL, and a slight elevated alpha-fetoprotein level of 9.02 ng/mL. The abdominal ultrasound examination revealed an isoechoic hepatic nodule of approximately 50/60 mm located in the 2nd and 3rd segment of the liver, ascites in the pelvis and hepatorenal space.

At the time of the presentation, the patient refused admission in the hospital, therefore an abdominal computed tomography (CT) scan with IV contrast was recommended. The CT scan confirmed the presence of a mass in the left hepatic lobe, inhomogeneous, vascularized, with regions of necrosis and with two areas of disruption of the liver capsule adjacent to the nodule. At this level, an imprecisely delimited inhomogeneous fluid collection with mixed densities was described in the epigastric and mesogastric area. The CT scan also showed 55mm of fluid with hematic densities in the peritoneal cavity. These features were suggestive of a ruptured hepatocarcinoma and hemoperitoneum, with low flow bleeding (Figure 1).

Given the results of the CT scan, the patient was immediately admitted to our surgical department. Emergency laparotomy was performed, which revealed massive hemoperitoneum with active bleeding from the ruptured hepatic nodule. The resection of the hepatic segment containing the mass was performed, followed by peritoneal lavage and drainage (Figure 2).

The anatomopathological examination of the resected specimen found moderately differentiated hepatocarcinoma, with zonal infiltration of the hepatic capsule and adjacent hepatic parenchyma. It also revealed moderate non-specific porto-billiary inflammatory infiltrates and reduced porto-portal fibrosis

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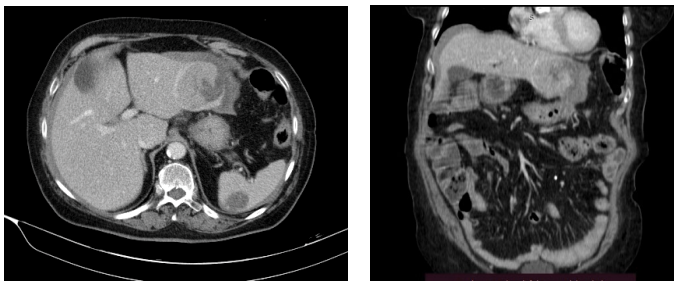
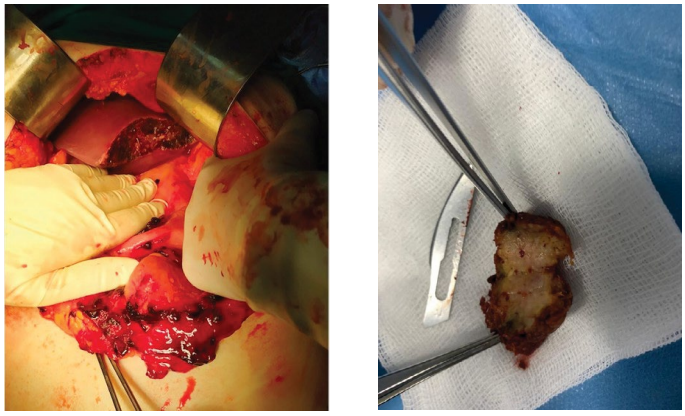


a) b)

Figure 1. CT aspects: **a)** Axial view and **b)** Sagittal view.



a) b)

Figure 2. a) Intraoperative view of non-cirrhotic liver and **b)** Resected specimen.

(Ishak F0). There were no signs of liver cirrhosis in the resected specimen or in the adjacent hepatic parenchyma. The post-operative evolution was favorable and the patient was discharged 3 days after surgery.

At 6 months, the patient's clinical examination, laboratory values and abdominal ultrasound were within the normal range. The examination by transient elastography (FibroScan®) showed stage F0 fibrosis and S3 grade steatosis.

Results and Discussion

MAFLD is currently the leading cause of chronic liver disease in the absence of liver cirrhosis. An Asian meta-analysis reported an incidence of 1.8 cases per 1000 MAFLD patients per year [5], while a global study showed a much higher incidence, of 5.29 per 1000 patients-year [6]. A broad range of risk factors are associated with the occurrence and progression of MAFLD [2]. Systemic metabolic dysregulation seems to represent the main factor contributing to the development of MAFLD [7]. Insulin resistance, obesity, a sedentary lifestyle, diabetes mellitus, arterial hypertension, dyslipidemia and chronic kidney disease are considered major risk factors with a great impact on liver inflammation and hepatocyte injury [2,5,8]. In terms of age and gender, there are two trends: MAFLD has been found to be more prevalent in older females (> 65 years) and in young males [2,9]. The explanation may be related to different sex hormone metabolism, body fat distribution and body composition [10]. MAFLD poses a significant burden on the medical system as one of the most resource-consuming clinical entities. Based on current trends, the MAFLD prevalence is expected to increase over time [2].

In the past few years, clinical data showed that MAFLD is a significant promoter of HCC, which can occur even in the absence of advanced liver fibrosis or cirrhosis [2,7]. Nowadays, MAFLD represents the third most common cause of HCC and MAFLD-related HCC is among the three main causes of death in the US [11-13]. Even if the overall liver damage is less significant in MAFLD-related HCC, the size of the tumors is generally larger in these patients compared to other liver diseases [2,7]. The lesions are, in generally, well-differentiated and characterized by increased inflammatory infiltration and decreased risk of extrahepatic metastases [12].

Hemoperitoneum is a possible complication of HCC and may be its first clinical manifestation. Spontaneously ruptured HCC occurs in 3-26% patients and is associated with high mortality rates [14]. The most frequent complaint of patients is usually abdominal pain with an acute onset, as the common underlying mechanisms are tumor necrosis, vascular erosion and hepatic vein occlusion [15]. The liver function is the most reliable parameter that predicts the therapeutic outcome. By now, there are no specific guidelines for managing ruptured HCC.

Uncertainty also exists regarding the mechanics underlying HCC's spontaneous rupture. HCC has a strong capacity for angiogenesis and vascular invasion [16,17]. A multicentric study revealed that HCC rupture is influenced by both patient and tumor characteristics, including advanced age, large tumor size (>5cm), the presence of portal hypertension and severe liver damage [18]. Acute hemoperitoneum is generally caused by the rupture of peripherally located HCC, just as in our clinical case. In patients with no previous history of liver disease, a breakdown of HCC is often found during exploratory surgery [19,20].

The review of Moris D, et al. showed that HCC spontaneous rupture occurred most frequently in men (77.9%), with a mean age of 55.6 years (± 6.64) [21]. The diagnosis might be challenging, especially in patients who are hemodynamically unstable and have no prior history of liver illness. Clinical signs and hemoglobin level at presentation must be used for a high suspicion of diagnosis [22]. In 66% of patients with a ruptured tumor, an ultrasonography may show a hyperechoic region around the tumor. CT scans continue to play an essential role in detecting the source of active bleeding and the evaluation of tumor size and location [15,22]. A big peripheral tumor, a tiny localized or intraperitoneal collection, and a "pseudoretraction sign" at the liver capsule beneath the fluid collection show a 100% sensitivity for a restricted HCC rupture [17,22].

Transarterial embolization or hepatic resection with arterial ligation, along with supportive treatment, are the main hemostatic procedures that can be applied in the case of a ruptured HCC in patients with no history of cirrhosis, with varying outcomes [14]. In hemodynamically unstable or advanced cirrhotic individuals, emergency liver resection can be necessary, with mortality rates ranging between 16.5% and 100% [16]. An Asian multicenter analysis showed that a much greater overall survival rate is provided by phased partial hepatectomy, such that staged hepatectomy should be considered in spontaneous rupture of HCC with resectable tumor and preserved liver function [23].

MAFLD provides the majority of new cases of HCC in patients without liver cirrhosis or severe fibrosis, although it is yet unknown how to monitor non-cirrhotic patients. Early HCC detection enables prompt treatment, and it may also reduce the likelihood of spontaneous HCC rupture [24].

The particularity of this case lies in the acute clinical onset of the disease, by the nontraumatic rupture of the HCC and consequent hemoperitoneum. Moreover, another noteworthy feature is the occurrence of HCC in the context of liver steatosis, without any significant inflammation or advanced fibrosis. In addition to that, it is important to note that in spite of the medically complex patient with significant comorbid conditions and advanced age, the post-operative outcome was not negatively impacted. In light of these features, it is essential to underline the importance of regular screening in patients with steatosis, especially in the presence of additional metabolic risk factors. Given the possibility of developing HCC even in the absence of liver cirrhosis, an optimal follow-up should be performed regularly in these patients.

Conclusion

The diagnosis of HCC in non-cirrhotic patients is still challenging. An accurate diagnosis based on advanced imaging techniques and laboratory testing and an optimal therapeutic management can improve patient outcomes.

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