Hepatocellular adenoma in the context of non-alcoholic steatohepatitis: a case report of an unusual presentation more and more frequent?

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Abstract: Hepatocellular adenoma (HA) is a rare benign tumor that usually occurs in the context of a young woman using oral contraception pills (OCPs), or rarely in certain inherited metabolic disorders like glycogen storage diseases, vascular hepatic disorders, and familial adenomatous polyposis. Other risk factors are not clearly established. In this unique case, we present a middle-aged man with history of non-alcoholic fatty liver disease (NAFLD), and metabolic syndrome who attend the Emergency Department for intense precordial pain, paresthesia in the left arm and diaphoresis. Ischemic heart disease was ruled out, however, during his evaluation the antecedent of a liver injury suggestive of malignancy was discovered, so it was decided to hospitalize the patient to complete his study. Laboratory data showed a slight elevation in transaminases and gamma glutamyl transpeptidase, without any other reported alteration. CT-scan reported a solid nodular lesion of 51 mm × 47 mm in segment IV LI-RAD 5 with no evidence of lymph node invasion or metastasis. A Barcelona Clinic Liver Cancer Classification Stage A hepatocellular carcinoma (HCC) was allegedly diagnosed, so it was decided to perform surgical resection. The postoperative histopathological study surprisingly showed an HA with steatohepatitis by a NAFLD Activity Score of 5 points and stage 2 periportal fibrosis. A couple of studies have reported similar findings in patients with metabolic comorbidities such as the one presented in this case. Due to the several metabolic disorders associated with NAFLD, it could represent an important risk factor for the development of HA. Studies that seek to clarify this association are necessary in the near future.

Keywords: Hepatocellular adenoma (HA); nonalcoholic steatohepatitis; case report

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Introduction

Hepatocellular adenoma (HA) is a rare benign tumor derived from the monoclonal proliferation of mature hepatocytes (1). Usual presentation of HA encompasses young women using oral contraception pills (OCPs) with an estimated incidence of 3/100,000 cases in this group (2). Other infrequent risk factors associated with the development of this tumor are glycogen storage diseases, vascular hepatic disorders, and familial adenomatous polyposis. The signs and symptoms

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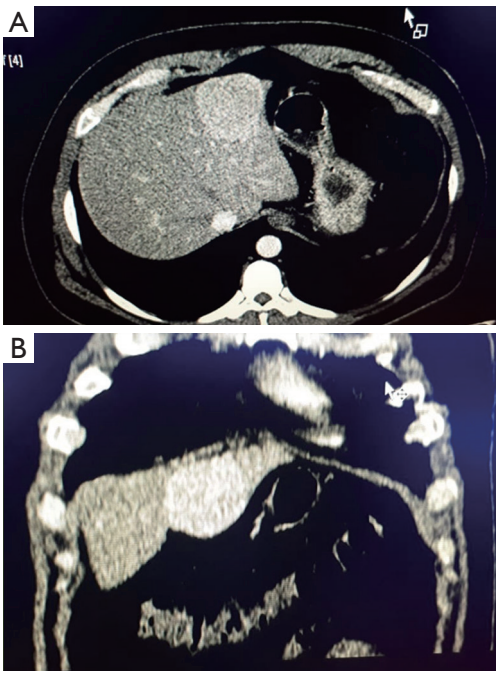

Figure 1 CT-scan. (A) Cross section study showing a solid nodular lesion in segment IV of the liver with enhancement to the intravenous contrast medium and measurements in an axial contour of 51×47 mm^2. (B) Coronal section of the lesion where no pulmonary infiltrates are identified.

are usually very nonspecific, so up to 10–20% of patients are detected until complications appear such as tumor bleeding or malignancy (1,2).

Interestingly, metabolic disorders could also be associated with the development of this tumor. However, regarding metabolic liver diseases such as non-alcoholic fatty liver disease (NAFLD), little information exists about it. Here we present a unique presentation of HA in a 41-year-old man with history of NAFLD and metabolic syndrome (MetS) of 7 years of diagnosis.

We present the following case in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/dmr-20-118).

Case presentation

A 41-year-old man with NAFLD and MetS of 7 years of diagnosis treated with ursodeoxycholic acid, diet, and exercise started presenting intermittent holocranial headache, accompanied with fatigue, asthenia, and pain in the right hypochondrium without nausea, vomiting, or weight loss performing abdominal ultrasound and detecting a liver injury suggestive of malignancy in June 2019. Two months later, he arrived to the Emergency Department of our hospital for presenting precordial pain with an intensity of 8/10 on the pain analogue scale with paresthesia in the left arm and diaphoresis. During the initial evaluation, ischemic heart disease was ruled out, however, it was decided to hospitalize the patient to complete the study of the liver injury. No significant family history of cancer was detected, and no relevant interventions had in the past.

Laboratory data were normal except for a slight elevation in transaminases and gamma glutamyl transpeptidase. Viral profile for hepatitis B and C were negative, and no significant changes in tumor markers were found (CA 19-9: 3.1 U/mL, alpha-fetoprotein: 1.16 ng/mL, and carcinoembryonic antigen: 0.75 ng/mL). For extension studies, it was decided to perform an MRI reporting hypervascular neoformation in liver segments III-IVB of 52×46×48 mm^3 LI-RADS 5 and a CT-scan reporting a solid nodular lesion of 51×47 mm^2 in segment IV with no evidence of lymph node invasion or metastasis (*Figure 1*).

Both clinic and extension studies pointed out to a probable hepatocellular carcinoma (HCC) initial stage A of the Barcelona Clinic Liver Cancer Classification. Based on this classification and in the liver function of the patient, it was decided to perform a left hepatic lobectomy with cholecystectomy and omentum resection without complications during and after the procedure.

The postoperative histopathological study surprisingly showed an HA of 55 mm in the major axis with tumor-free surgical margin and residual liver with steatohepatitis by a NAFLD Activity Score of 5 points and stage 2 periportal fibrosis (*Figure 2*). The patient evolved satisfactorily without complications, so his hospital discharge and his follow-up as an outpatient were decided. The patient was referred at two weeks for postoperative evaluation with liver function tests, and subsequently at 3 and 6 months with liver function tests and hepatic and bile ducts ultrasound. Hygienic-dietetic measures were continued for its metabolic control and management for NASH with vitamin E were started without presenting any adverse effects within follow-up.

All procedures described in this case were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

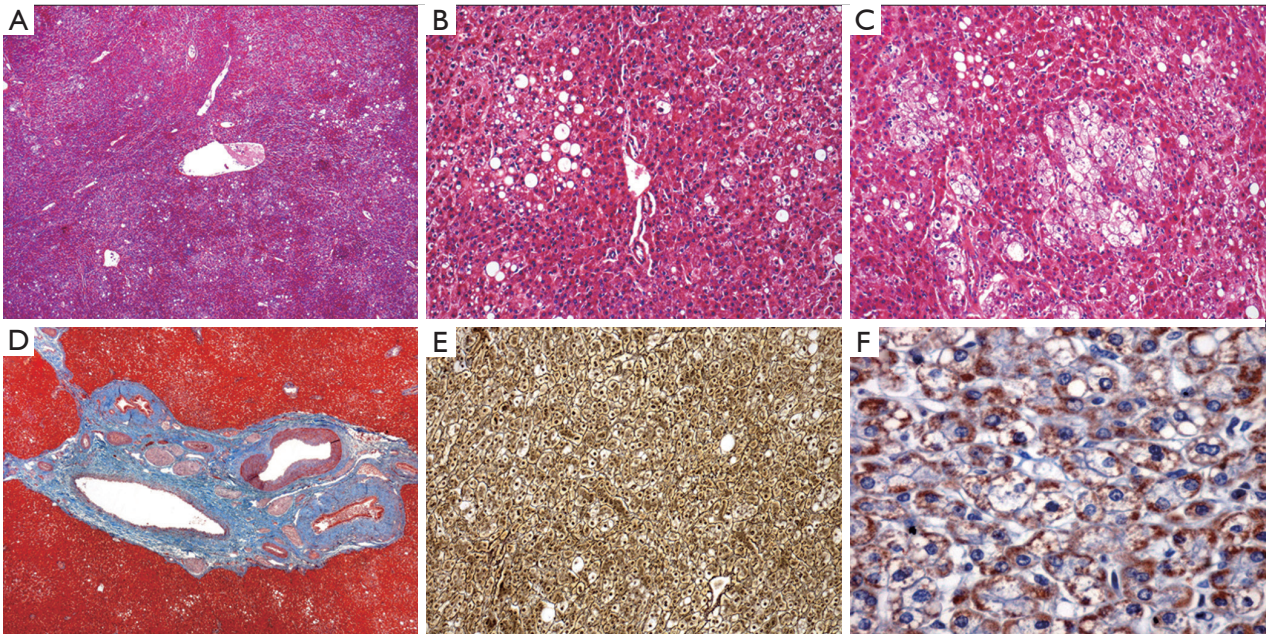

Figure 2 Histological aspect of liver tumor. (A) The tumor exhibits a solid pattern, with preserved central veins and very few bile ducts. (B) Hepatocytes are organized into thin trabeculae and show no significant atypia or mitotic activity. Some steatotic vacuoles can be seen in the tumor. (C) The surrounding parenchyma shows hepatocytes with regenerative changes, mild lobular inflammation, and foci of clear hepatocytes with ballooning degeneration. (D) Masson's trichrome shows periportal fibrosis, present in the residual liver parenchyma. (E) Reticulum staining corroborates intact trabecular thickness, which varies from one to two hepatocytes throughout the tumor. Necrotic areas were not observed. (F) Immunostaining with β-catenin demarcates individual cell membranes and shows granular cytoplasmic staining. Lack of nuclear staining is considered negative and suggests absence of β-catenin mutation. Hematoxylin and eosin stain, original magnification ×100 (A) and ×200 (B,C,D,E,F).

Discussion

In this unusual presentation of HA, there are some lessons to take home that we would like to address. First, it is interesting to see that if we go back to the 1970s, HA was a neoplasm almost exclusively of women who were under treatment with OCPs (3), but nowadays there is an increasing evidence of "unusual" presentations of HA (mainly the inflammatory subtype) in middle-age men with metabolic disorders. Could it be that HA is another problem associated with the growing pandemic of global overweight and obesity that we are experiencing today? The answer for this question should be yes.

Analyzing the molecular aspects of this neoplasm, the classic molecular subtypes of HA includes mutations in hepatocyte nuclear factor 1-A and β-catenin due to estrogen exposure in women. However, these and the two other molecular subtypes (inflammatory and sonic hedgehog) are presenting an interesting shift in their etiology and frequency as they are increasingly related to the body mass index and the metabolic aspects of the patient (2).

Fascinatingly, non-alcoholic steatohepatitis (NASH) by itself could be an independent risk factor for the development of HA by the results found in an elegant study in liver-specific growth hormone receptor knockout mice that develop MetS and NAFLD. In this model, the increased production of inflammatory cytokines, chemokines, and fibrosis were found to correlate with HA development with different degrees of malignancy (4). In this context, an increasing incidence of atypical large well-differentiated HCC that is also being observed in these days, could be the direct consequence of HA progression of patients with NASH (5).

However, today more than ever we should consider the distinctive characteristics between HA and HCC due to their apparent similarity in developing in the same risk populations. Although contrast-enhanced CT-scan findings are similar, HA characteristically demonstrates a peripheral enhancement during the arterial phase with subsequent centripetal flow during the portal venous phase in contrast

with the arterial enhancement and rapid "washout" during the portal venous phase of HCC lesions (6,7). In this case, we evidently let ourselves be guided by the imaging findings of the tumor rather than by frank clinical findings that will support our diagnosis of HCC. The absence of a cirrhotic liver, as well as the null increased levels of serum alpha-fetoprotein, must have made us rethink our initial diagnosis in search of other options that could better explain this clinical picture. Furthermore, our main limitation was not knowing the molecular subtype of this tumor since we only ruled out the β-catenin mutation subtype due to its high risk of malignant transformation.

For the authors of this work, the case presented represents a new perspective in the approach to these patients, which we hope can be shared by other physicians who daily face these complex scenarios.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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