

Multifocal Nodular Fatty Infiltration of the Liver: A Rare Benign Disorder That Mimics Metastatic Liver Disease

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ABSTRACT

Fatty liver disease is a frequent diagnosis. Rarely, it adopts a multifocal nodular pattern mimicking multiple liver metastases. Multifocal nodular fatty infiltration of the liver entails a challenging problem that must be included as a differential diagnosis when dealing with healthy patients with an incidental finding of multiple liver lesions, even in the absence of obesity or metabolic syndrome. A complete clinical examination and high-quality imaging, including magnetic resonance imaging, might help to confirm diagnosis and to avoid unnecessary liver biopsies.

INTRODUCTION

Nonalcoholic fatty liver disease is becoming the leading cause of liver disease worldwide, and its prevalence has increased in parallel to the pandemic of obesity.^{1,2} Its association with other systemic diseases such as metabolic syndrome, diabetes, and hemochromatosis has been described.^{3,4} Fatty infiltration of the liver usually has a diffuse pattern in the parenchyma. Occasionally, fatty infiltration may appear as multiple nodular areas separated by normal liver tissue producing a pseudotumor appearance, which has been described as multifocal nodular fatty infiltration of the liver (MNFIL).⁵ MNFIL poses a diagnostic dilemma as its imaging appearance mimics metastatic liver disease. Advanced liver imaging techniques and a complete clinical assessment are the key to the diagnosis of this rare entity.

CASE REPORT

A 47-year-old woman with a family history of hereditary hemochromatosis presented asymptotically with an incidental finding of multiple hepatic nodules on an abdominal ultrasound (Figure 1). She had a normal physical examination, body weight (body mass index = 24 kg/m²), and no malignancy history. She and her mother have hemochromatosis with a homozygous mutation of HFE gene H63D. Hemogram and liver function tests were within the normal range, and she was not receiving any treatment for hemochromatosis. Although the Homeostatic Model Assessment for Insulin Resistance was elevated at 3.2, serum glucose levels and glucose tolerance test were within normal limits and excluded the presence of diabetes mellitus.

Moreover, the serum ferritin was elevated at 309 ng/mL, transferrin serum concentration and saturation values were within normal limits. She underwent a thorough diagnostic workup with an upper endoscopy, a colonoscopy, and a gynecologic examination that were unrevealing. Tumor markers including carcinoembryonic antigen, carbohydrate antigen 19-9 (CA 19-9), and alpha-fetoprotein were normal. A contrast-enhanced computed tomography (CT) scan showed multiple focal hypodense liver nodules (Figure 2). After intravenous contrast medium administration, they showed similar enhancement to normal liver parenchyma. As CT scan was inconclusive, an abdominal contrast-enhanced MRI was performed and showed multiple pseudonodular images in both liver lobes. No displacement nor invasion of hepatic vascular structures, diffusion restriction, or enhancement after contrast injection was observed. Signal drop on out-of-phase sequence compared with in-phase sequence confirmed intracellular lipid content (Figure 3). Since the patient has hemochromatosis, a liver and myocardial MRI with T₂ relaxometry was performed to exclude iron overload. Measures of iron concentration in liver parenchyma and myocardium were within a normal range.

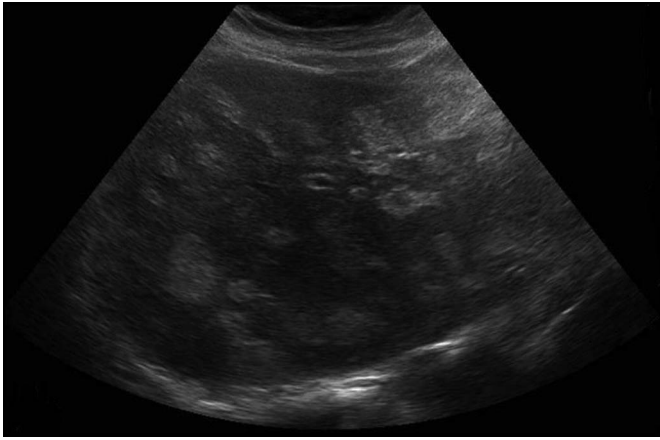


Figure 1. Abdominal ultrasound showing multiple hyperechoic liver lesions.

The patient was presented in our multidisciplinary tumor board, and a close clinical and imaging follow-up was decided. During surveillance, a contrast-enhanced MRI reinforced MNFIL diagnosis. After 3 years of clinical follow-up, the multifocal nodular fatty infiltration persists, but the patient remains symptom-free and nodules experienced a partial reduction in size and number.

DISCUSSION

Hepatic steatosis is a benign disorder characterized by the accumulation of excessive fat in the liver. This condition affects 10%–24% of the general population and up to 75% of obese individuals.¹ Despite being frequently idiopathic, associations with obesity, diabetes mellitus, alcohol intake, parenteral nutrition, and steroid therapy have been described.

MNFIL is an uncommon presentation of fatty liver disease, and its nodular pattern can be mistaken for a multifocal primary tumor or multiple hepatic metastasis. Differential diagnoses include lymphoma, abscesses, hemangiomas, biliary hamartomas, hepatic adenomas, and multiple hepatocellular carcinomas. Interestingly, MNFIL has been associated with other systemic diseases such as porphyria cutanea tarda and hemochromatosis.^{3,4} Hemochromatosis gene (HFE)

variants have been linked with nonalcoholic fatty liver disease and hepatocellular carcinoma risk. Iron overload might contribute to this association by acting as a fundamental regulation factor.⁶ Our patient had an H63D mutation, which usually does not cause significant iron overload, but may act as a cofactor for liver damage.

The physiopathology of focal hepatic steatosis is not fully understood. Tissue hypoxia, accumulation of toxins, or increased portal flow are possible mechanisms.⁷ Moreover, an alternative vascular supply to the liver could play a role. Veins that enter the liver directly, independently of the portal venous system, may contribute to focal metabolic changes. For instance, the parabiliary venous system that drains the head of the pancreas might induce focal steatosis changes by delivering high insulin concentrations.⁸ Most patients with fatty liver disease remain asymptomatic or have mild hepatomegaly or altered liver function tests.

MNFIL usually presents on CT as multiple hypodense non-enhancing lesions, similarly to metastatic disease.⁹ In these cases, a triple-phase contrast-enhanced MRI is probably the most useful diagnostic tool. MRI can detect areas of fatty infiltration as hyperintense lesions on T1- and T2-weighted images if fat content is high enough to alter signal intensity. Lack of invasion or displacement of vascular structures, similar enhancement to normal liver parenchyma, and stability over time supports MNFIL diagnosis. Moreover, MRI with signal drop on out-of-phase sequence compared with in-phase sequence is extremely helpful for confirming intracellular lipid content in these liver lesions.^{5,10} Similarly, contrast-enhanced ultrasound has also been described as a useful imaging method for differential diagnosis, but this intravenous contrast is not available in many countries of our region, including Argentina.^{11,12} Fortunately, our patient presented with each of the above-mentioned typical features in the abdominal MRI. Moreover, as our patient had hereditary hemochromatosis, a noninvasive assessment of the hepatic iron concentration using MRI with T₂ relaxometry helped differentiate iron overload from fat infiltration of the liver parenchyma. In our patient without signs of iron overload, the use of 2 contrast-enhanced abdominal imaging confirmed the presence of MNFIL. In the future, with a higher index of suspicion on part of the radiologist or treating physician at the

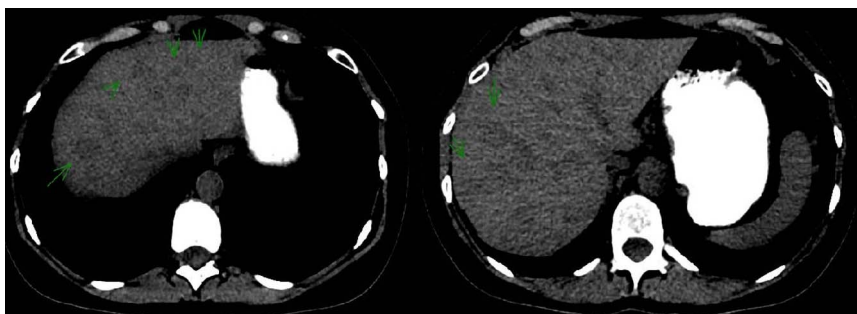


Figure 2. Abdominal contrast-enhanced computed tomography scan showing multiple liver hypodense lesions (green arrows).

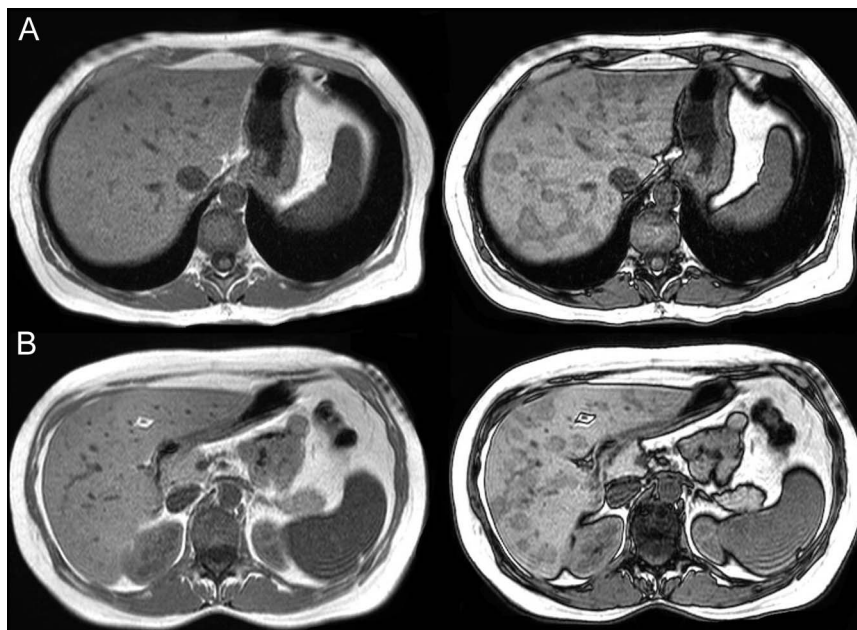


Figure 3. (A and B) Liver magnetic resonance imaging out-phase (left) and in-phase (right) image showing signal drop on the latter, indicating intracellular lipid content into hepatic lesions.

time of the initial ultrasound, a single triple-phase contrast-enhanced MRI might be considered as the next modality to avoid unnecessary workup and anxiety in these patients. However, it must be emphasized that a percutaneous or laparoscopic liver biopsy might be needed in patients with inconclusive imaging tests.

This case report demonstrates that MNFIL is a condition that could mimic multiple liver metastasis, even in a patient without metabolic syndrome and with a normal body mass index. MNFIL should be considered on the differential in patients with multiple liver lesions and no previous malignancy history. Moreover, potential association between hemochromatosis with HFE gene variations needs further investigation. A high index of suspicion at the time of initial radiologic findings is of utmost importance to avoid unnecessary workup and invasive procedures.

DISCLOSURES

Author contributions: All authors contributed equally to this manuscript. L. McCormack is the article guarantor.

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