

Magnetic Resonance Imaging of the Diffuse Hepatocellular Carcinoma. Two-Case Report

Imágenes por resonancia magnética en hepatocarcinoma difuso. Presentación de dos casos



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Key words (MeSH)

Carcinoma hepatocellular
Magnetic resonance imaging
Liver neoplasms



Palabras clave (DeCS)

Carcinoma hepatocelular
Imagen por resonancia magnética
Neoplasias hepáticas

Summary

Purpose: To describe the MRI findings in diffuse hepatocellular carcinoma and to review the clinical manifestations and laboratory test results. **Methods:** Abdominal MRI was performed in two patients with confirmed diagnosis of hepatocellular carcinoma. **Results:** The first case is a 71-year-old female who underwent MR imaging of the abdomen demonstrating diffuse hepatocellular carcinoma with invasion to the right hepatic vein, intrahepatic vena cava and extension into the right atrium. The second case is a 59-year-old female with chronic hepatic disease and portal hypertension. A diffuse hepatocellular carcinoma was diagnosed with invasion to the inferior vena cava, tumoral thrombus of the portal vein and involvement of the bile ducts. **Conclusion:** In order to make an early diagnosis and provide opportune treatment, radiologists must be familiarized with MRI findings of diffuse hepatocellular carcinoma such as those presented in our report.

Resumen

Propósito: Describir los hallazgos imagenológicos por resonancia magnética (RM) del hepatocarcinoma difuso, revisar las manifestaciones clínicas y los hallazgos en pruebas de laboratorio. **Metodología:** Se analizan los hallazgos imagenológicos de dos pacientes con diagnósticos de hepatocarcinoma difuso. **Resultados:** El primer caso es una paciente de 71 años de edad a quien se le realizó una RM de abdomen que evidenció un hepatocarcinoma difuso, con invasión de la vena hepática derecha y de la vena cava intrahepática, con extensión hasta la aurícula derecha. El segundo, se trata de una paciente de 59 años de edad, con hepatopatía crónica y signos de hipertensión portal. Se diagnosticó un carcinoma hepatocelular difuso con infiltración de la vena cava inferior, trombo tumoral en la vena porta e infiltración de la vía biliar. **Conclusión:** Es de gran importancia para el radiólogo familiarizarse con los hallazgos por RM del hepatocarcinoma difuso y, de este modo, realizar un diagnóstico y tratamiento oportunos.1.

1. Introduction

The primary cancer of the liver is the fifth malignant tumor in prevalence in the world and the second cause of cancer mortality, with approximately 800,000 cases diagnosed for 2012 (1). Hepatocellular carcinoma (HCC) is the most common histological type of primary hepatic tumor and corresponds to approximately 90% of this type of lesion (2).

HCC is a genetically heterogeneous tumor. Hepatocarcinogenesis is a complex process that requires genetic and epigenetic alterations and the compromise of signal translation pathways that include p53, MAPK, JAK / STAT and Wnt / B-catenin (3). Multiple predisposing causes have been described for this type of tumor: chronic liver disease, cirrhosis, infection with hepatitis B and C viruses, excessive alcohol consumption, obesity, meta-

bolic syndrome, non-alcoholic fatty liver disease, smoking, hemochromatosis, diabetes mellitus type 2, Wilson's disease, congenital biliary atresia and aflatoxins. These risk factors have a synergistic effect on the pathogenesis of the tumor and your coexistence has been associated with an increased incidence of the disease (4).

The incidence of HCC is not evenly distributed in the world. More than 80% of cases occur in sub-Saharan Africa and East Asia. It is said that China contributes 50% of all cases of HCC in the world. Comparatively, America and Europe have a relatively low incidence of this disease. This difference is attributed to specific risk factors in those regions (2).

For example, in Asia, the high incidence of this neoplasm is attributed to infection with the hepatitis B virus (HBV), especially in China, where vertical transmission

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from mother to child has traditionally been proposed as an influencing factor. Meanwhile, infection by the hepatitis C virus (HCV) predominates in Japan. Infection with this virus increased in this country especially after the Second World War, secondary to the use of intravenous drugs, as well as transfusions with contaminated blood (5).

In the United States, the incidence of HCC is lower than in other parts of the world and for 2012 this was 6.2 / 100,000 inhabitants (1). This figure is attributed to the lower HCV infection, largely supported by the great effort that has been put into HBV vaccination programs in this country (6).

According to the macroscopic growth pattern, hepatocellular carcinoma can be classified into three subtypes: nodular (multifocal), massive (focal) and infiltrative (diffuse) (7). Each of these can behave differently with respect to etiology, progression, diagnosis and treatment. The nodular form is commonly presented as a mass with arterial enhancement with well-defined margins, while diffuse HCC may be difficult to identify, as it manifests as an ill-defined mass that mixes with the cirrhotic liver parenchyma in the background. This is why, sometimes, this subtype is not diagnosed until advanced stages, when the therapeutic portfolio is limited (8). It is estimated that the diffuse subtype corresponds to approximately 7-13% of all HCC; however, it remains poorly characterized in the literature (9).

Next, two cases of diffuse hepatocarcinoma are exposed. A brief description of the clinical history, the findings by image and the conclusions drawn from these cases are made.

Case 1

A 71-year-old female patient with a personal history of Child A cryptogenic liver cirrhosis, who had a clinical picture of several days of evolution consisting of lower limb edema and increased abdominal perimeter, with jaundice and feeling of fullness. Paraclinical tests were performed, including total bilirubin: 1.4 mg / dL, direct bilirubin: 0.7 mg / dL, albumin: 3.2 g / dL, gamaglutamyl transpeptidase: 162 U / L, alkaline phosphatase: 156 U / L, aspartate aminotransferase: 105 U / L, alanine aminotransferase: 35 U / L, prothrombin time: 16s, ascitic fluid cytochemistry that rules out spontaneous bacterial peritonitis and alpha feto-protein: 25,631 ng / mL.

A magnetic resonance imaging (MRI) of the abdomen was performed, simple and with contrast medium, which showed liver of cirrhotic appearance with hypervascular, heterogeneous, irregular lesion that compromises segments VI and VII, measuring approximately 8 × 8 × 4.6 cm (AP × T × L). The lesion presented areas of washing of the contrast medium (Figure 1). In addition, invasion of the right hepatic vein, the intrahepatic vena cava, and extension to the right atrium with tumor thrombus inside were demonstrated (figure 1).

Additionally, a partial eccentric thrombus, with a subacute-chronic and non-tumoral appearance, was identified in the main portal vein, the superior mesenteric vein and the left branch of the portal vein (figures 2 and 3).

Due to the described findings, the diagnosis of diffuse hepatocellular carcinoma with metastatic compromise is made; Palliative management was proposed by the treating team.

Case 2

A 59-year-old female patient with a history of Child B alcoholic liver cirrhosis, who consulted for a picture consistent with hepatic en-

cephalopathy and liver and bile duct ultrasound that shows hepatomegaly and echogenic nodular image with a solid, rounded appearance, without evident calcifications and with peripheral vascular flow. A fetus-protein alpha value was found in 34.73 ng / mL.

On admission to the emergency department, it is confusing, icteric, with low blood pressure figures, jugular vein enlargement, distended abdomen with collateral circulation, ascitic wave, palpable liver below the costal margin, pain in the right hypochondrium and grade II edema in the lower extremities. It was decided to extend the study with paraclinical and abdominal MRI with contrast medium, to characterize the lesion found in the ultrasound.

Total bilirubin was found: 4.53 mg / dL, sodium: 136 mEq / L, carbohydrate antigen 19-9: 18 U / mL, hemoglobin: 14.4 g / dL, hematocrit: 44%, leukocyte count: 7.600 / mm³, prothrombin time: 13.6 sec, partial thromboplastin time: 31.9 sec, carcinoembryonic antigen: 2.05 ng / mL, platelets: 175.000 / mm³, erythrocyte sedimentation rate: 96 mm / h, alkaline phosphatase: 472 U / L, gamaglutamyl transpeptidase: 204 U / L and creatinine: 0.71mg / dL.

MRI of the abdomen showed stigmata of advanced chronic liver disease with redistribution of hepatic volume, and large infiltrating mass of low signal in sequences with T1 information and moderate signal with T2 information, with diffusion restriction, which compromised both hepatic lobes, demonstrating microscopic fat transformation and heterogeneous enhancement in the arterial phase to wash with "wash" in the late phase where they are defined internal hyperremolar septa with contrast enhancement (figures 4 and 5).

This poorly defined mass measured approximately 19 cm on its major axis. It infiltrated the most cranial region of the inferior vena cava, which was associated with to tumor thrombosis of the common portal vein and its intrahepatic branches (Figure 6), and compressed the common bile duct with consequent dilatation. The diagnosis of diffuse hepatocellular carcinoma was made and palliative management was considered given the advanced stage of the compromise.

Discussion

Diffuse hepatocarcinoma corresponds to approximately 7-13% of the cases of hepatocellular carcinoma, making it a rare diagnosis and scarcely reviewed in the literature (7). Recent data associate this type of tumor with infection with the hepatitis B virus, regardless of the age or time of evolution of the cirrhosis; Likewise, the incidence of infiltrative hepatocellular carcinoma is higher in patients with coinfection with hepatitis B virus and with hepatitis C virus.

The usefulness of alpha-fetus-protein (AFP) for diffuse hepatocellular carcinoma is a matter of debate. Most studies suggest that this parameter is highly specific, with high values of the protein (for example > 400 ng / ml), while a low sensitivity of around 54% is suggested. For this reason, a high alpha-feto-protein value should ignite the alarms for hepatocellular carcinoma and a low value does not exclude diagnosis (9).

Diffuse hepatocellular carcinoma is frequently associated with high levels of alpha fetus-protein given its infiltrating nature to the liver parenchyma. However, when gathering the evidence it is suggested that between one fifth and one third of the patients with diffuse hepatocellular carcinoma can have a completely normal alpha-fetus-protein and up to half of these, they will have a value lower than 400 ng / ml (10)

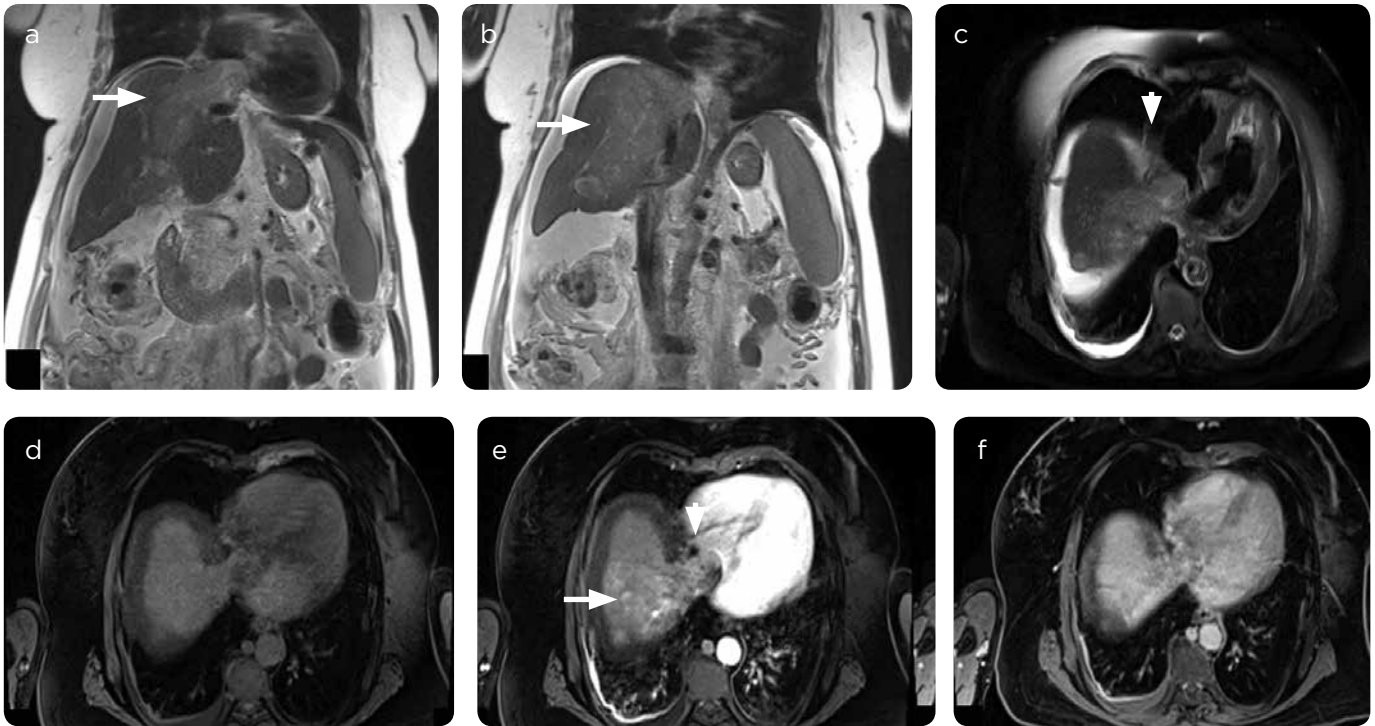


Figure 1. MRI of simple abdomen and with contrast medium. a and b) Coronal sequences with information T2, c) axial with information T2 and fat suppression, d) axial volumetric with information T1 and simple fat suppression, e) dynamic after administration of contrast medium, f) in equilibrium phase. Liver of cirrhotic appearance with large infiltrating mass (arrows) with moderate high signal with conventional T2 information and with fat suppression (a, b and c, respectively), e) hypervascular, heterogeneous and irregular, f) with contrast washout foci in the phase late, localized in the right hemi-liver, invading the right hepatic vein and the intrahepatic vena cava to extend to the right atrium by tumoral thrombi (arrow head) (a, c, d, e and f). Ascites and mild bilateral free pleural effusions, predominantly right (c). Smooth thickening and enhancement of the posterobasal visceral pleura on the right side (e and f).

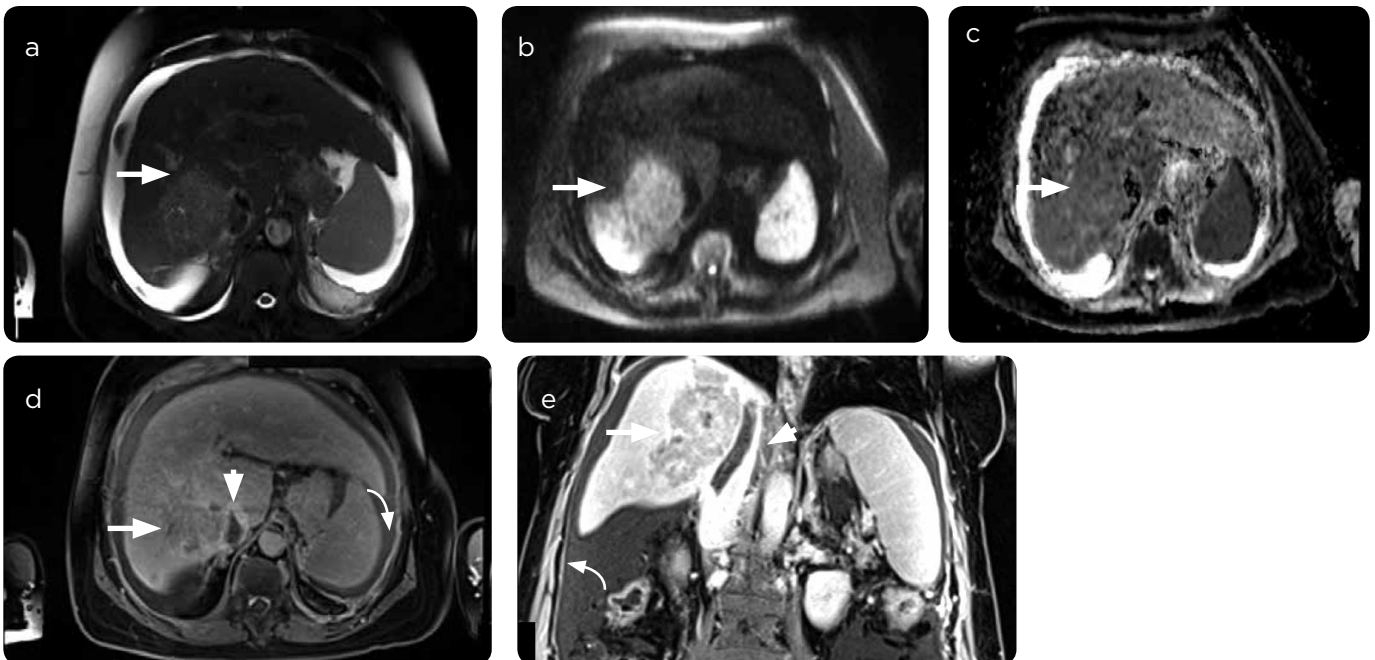


Figure 2. MRI of simple abdomen and with contrast medium. Axial sequences of the liver, a) with information T2 fat suppression, b) diffusion b 800, c) its respective map ADC, d) volumetric axial T1 dynamic fat suppression after contrast medium, e) coronal equilibrium phase. It is observed in (b and c) infiltrating hepatic mass (arrows) with slight restriction of diffusion; washing of the contrast medium in the late phase in (d and e); Partial thrombus in the intrahepatic vena cava (arrow head) is identified. Portal hypertension with ascites, splenomegaly and collateral circulation; there is also smooth thickening and diffuse enhancement of the parietal peritoneum (curved arrow).

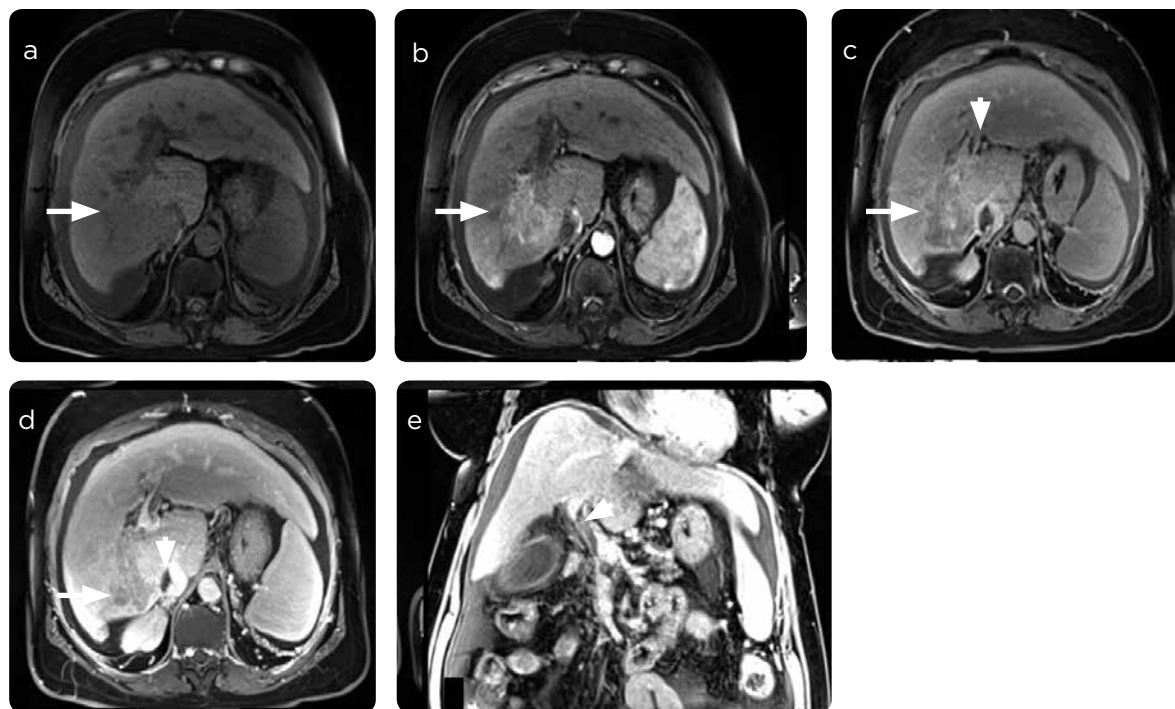


Figure 3. MRI of simple abdomen and with contrast medium. Axial sequences of the liver a) T1 simple, b) after the contrast medium in the arterial dominant phase, c) equilibrium, d and e) axial and coronal volumetric T1 and fat suppression, dynamic, after the contrast medium in the equilibrium phase. An infiltrating mass (arrows) with posterior enhancement to the moderate and heterogeneous contrast medium in the dominant arterial phase (b) is observed, denoting its hypervascular nature and with washing in the late phase where peripheral retention of the contrast is observed (c). Soft thrombi (arrowhead) in the vena cava and in the portal; in smaller proportion in the porto-mesenteric axis (a, b, c, d and e).

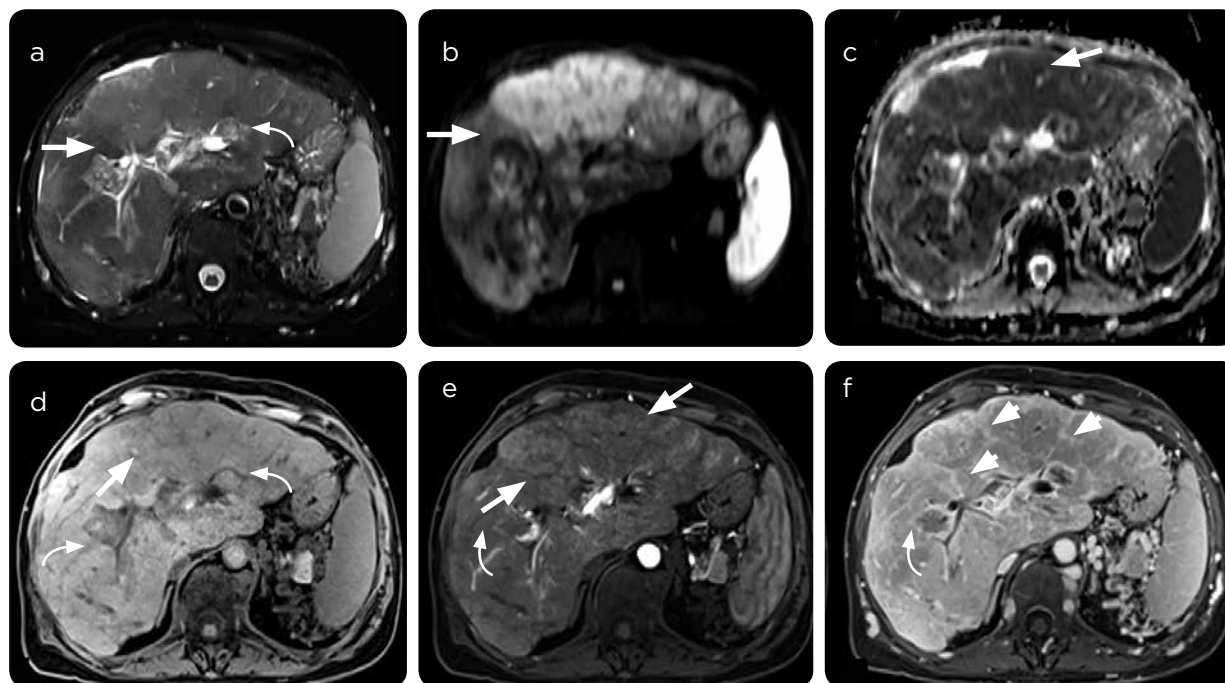


Figure 4. Simple and contrasted MRI of the abdomen. a) Axial sequences of liver with information T2 fat suppression, b) diffusion b 800, c) map ADC, d) volumetric with information T1 and simple fat suppression, e) volumetric with information T1 fat suppression dynamics post Gadolinium in arterial phases, f) equilibrium. Stigmas of advanced chronic liver disease with redistribution of hepatic volume and irregular contours (a and d). Large infiltrating mass (arrows) poorly defined, with slightly low signal in volumetric image T1 fat suppression (d) with subtly high signal in sequences with T2 information (a), with slight diffusion restriction (b and c), which compromises both hepatic lobes, with post-enhancement slight and heterogeneous contrast during the dominant arterial phase (e) to wash in the late phase where hyperreflective internal septa (arrowhead) are defined (f). There is a tumoral thrombus (curved arrow) in the intrahepatic branches of the portal vein (a, b, c, d, e and f).

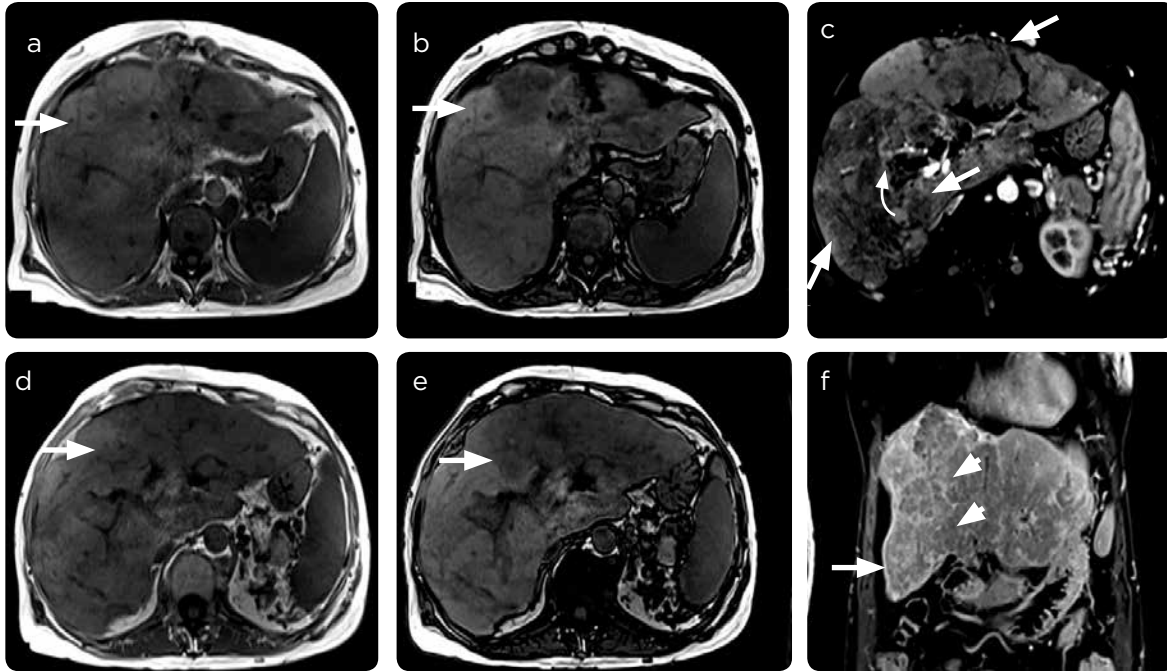


Figure 5. Simple and contrasted MRI of the abdomen. a and d) Axial slices of the volumetric liver T1 fat suppression-DIXON T1 in phase, b and e) T1 out of phase. c) Volumetric axial T1 dynamic fat suppression after the contrast medium in arterial phase with subtraction, f) coronal in equilibrium phase. Infiltrating and poorly defined hepatic mass (arrows), discretely hypointense in T1 (a and d) and with areas of microscopic fatty transformation (isointense zones with the rest of the parenchyma in T1 in phase, falling signal in T1 images out of phase: a and d in comparison with b and e, respectively). Tumor thrombus (curved arrow) in the branches of the portal vein, which are expanded by soft tissue that demonstrates posterior enhancement to both central and peripheral contrast media secondary to neovascularization; slight enhancement of the mass is also seen in the dominant arterial phase (c). Heterogeneous enhancement by washing the lesion in the late postcontrast phase where internal hyperrefining septa (arrowhead) are defined (f).

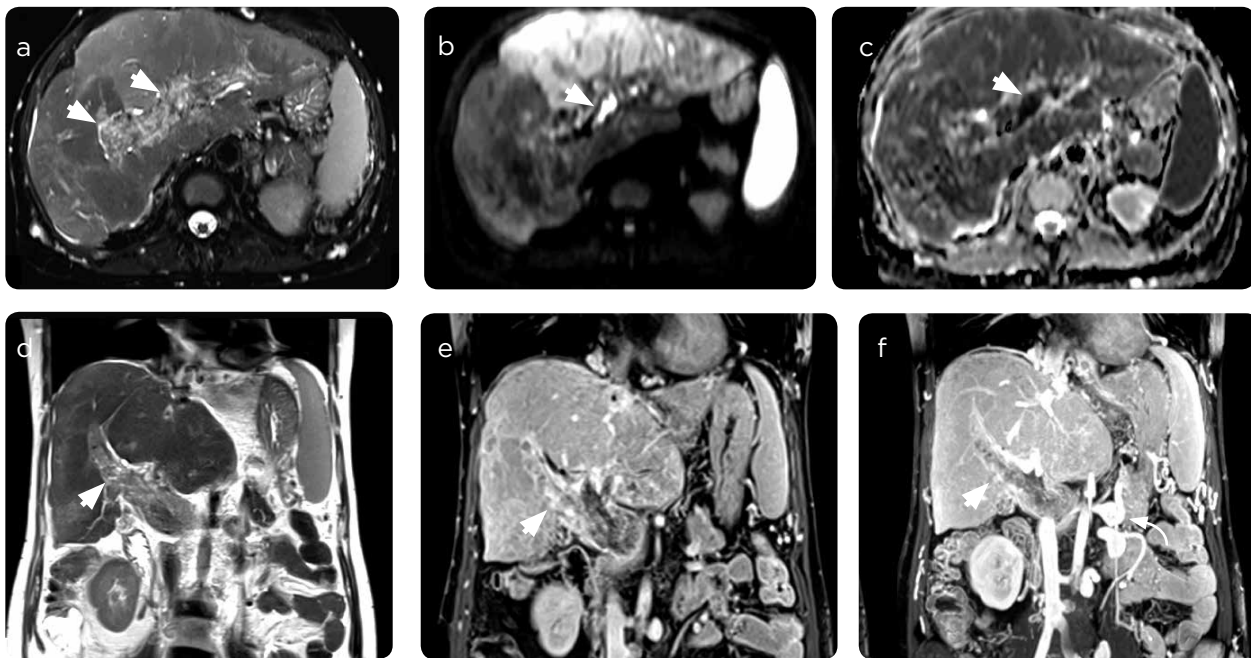


Figure 6. Simple and contrasted MRI of the abdomen. a) Axial slices of liver T2 fat suppression, b) diffusion b 800 and c) ADC map. d) Coronal images T2, e) volumetric T1 dynamic fat suppression after the contrast medium in equilibrium phase and f) corresponding maximum intensity projection. Large tumor thrombus (arrow head) in the common portal vein and in its intrahepatic branches (a, b, c, d, e and f), which are expanded by heterogeneous mass slightly hyperintense in T2 (a and d), with restriction of the diffusion (b and c) and non-uniform postcontrast enhancement (both central and peripheral secondary to neovascularization) (e and f). Important porto-systemic collateral circulation (e and f) (curved arrow).

Although hepatocellular carcinoma has a characteristic appearance, detection of the infiltrative subtype can be a diagnostic challenge.

The image characteristics of this tumor are poorly described in the literature and therefore radiologists may be unfamiliar with the findings associated with this variant.

Diffuse hepatocellular carcinoma has an infiltrating appearance, which makes it difficult to distinguish it from the diseased hepatic parenchyma. This fact has been histologically correlated, where the tumor looks similar to the regenerative nodules of chronic liver disease.

The tumor is observed as a poorly demarcated area within the liver, characterized by an alteration in the intensity of the signal, which may be homogeneous or heterogeneous in appearance.

Specifically, magnetic resonance imaging (MRI) appears as a predominantly low-signal lesion in the T1-weighted sequences; in sequences weighted in T2, a slight to moderately high signal is observed. After the intravenous administration of the contrast medium, a “miliar” pattern can be observed, which demonstrates the micronodule composition seen in the histological analysis of the lesion. This finding may be particularly striking in the context of portal vein thrombosis, which results in an increased blood supply by the hepatic artery.

In dynamic postcontrast sequences, most diffuse hepatocellular carcinomas show heterogeneous areas of enhancement in early phases and washing in later stages (11).

Due to the high cellular packing of these lesions, they are typically observed with high signal in the diffusion sequences and corresponding low signal in the ADC map (12).

A useful clue in the diagnosis to detect the diffuse subtype is the presence of portal vein thrombosis given the high prevalence of this finding in this group of patients. Although portal thrombosis is common in all varieties of hepatocellular carcinoma, the diffuse subtype has unique characteristics. Generally, the pattern of invasion of the portal vein is associated with marked distention of the vein and when the invasion is extensive it may compromise the peripheral portal branches creating the appearance of a “mold” in these vessels (9).

Additionally, the portal thrombus of infiltrative hepatocellular carcinoma commonly demonstrates neovascularization, which has also been termed “arterialization” of the thrombus. In fact, this may be the only detectable characteristic initially (8).

In the portal phase, the portal thrombus is observed as a filling defect, similar to a soft thrombus. Diffusion-weighted images have also been proposed as a method for the detection of the tumor thrombus and to differentiate it from the soft thrombus (12).

The prognosis of patients with diffuse hepatocellular carcinoma is poor, probably related to the late stage of presentation and diagnosis. The diffuse subtype is a contraindication for surgical resection or transplantation, which is why transcatheter chemoembolization may be the therapeutic option for some patients. However, the data in the literature are discordant with series that do not report the benefit of this behavior and others that support it for selected cases (11). Without a doubt, it is an area that in the future can be used for research.

Conclusion

Diffuse or infiltrative hepatocellular carcinoma is a diagnostic challenge. Its appearance can mimic that of the underlying cirrhotic liver and

is usually discovered in advanced stages of the disease, when the prognosis is bleak.

It is for these reasons that the radiologist must relate to the imaging findings of diffuse hepatocellular carcinoma, to achieve an opportune diagnosis and give adequate management.

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Received for evaluation: March 29, 2017

Accepted for publication: December 18, 2017