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Atypical Magnetic Resonance Imaging Findings in Hepatocellular Carcinoma

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Magnetic resonance imaging (MRI) is currently the modality of choice to evaluate liver lesions in patients with cirrhosis and hepatitis B and C. Hepatocellular carcinoma demonstrates typical imaging findings on contrast-enhanced MRI, which are usually diagnostic. Unfortunately, a subgroup of hepatocellular carcinoma presents with atypical imaging features, and awareness of these atypical presentations is important in ensuring early diagnosis and optimal patient outcomes. Herein, we review some of the more common atypical presentations with a focus on MRI.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancies globally, causing up to 1 million deaths worldwide annually, with a median postdiagnosis survival of 6-20 months.[1-5] Survival is highly dependent on stage, with a 5-year survival rate of 55% for stage I disease in contrast to only 15% for stage III disease.[6] Early diagnosis is therefore vital for maximizing patient survival. For patients at high risk of HCC, including those with hepatitis B or C, aflatoxin exposure, hemochromatosis, Wilson disease, or α1 antitrypsin deficiency, the American Association for the Study of Liver Disease recommends hepatic ultrasound surveillance be performed at 6-month intervals, with abnormal nodules larger than 1 cm to be further evaluated with computed tomography (CT) or magnetic resonance imaging (MRI).[7]

Both CT imaging and MRI can be diagnostic, without the need for biopsy in lesions exhibiting typical radiologic features of HCC.[7,8] CT is preferred as an initial study because of the higher cost of MRI. However, MRI has better sensitivity and specificity in cirrhotic patients in whom regenerative nodules can be difficult to distinguish from HCC and is better at differentiating dysplastic nodules from HCC.[9,10] MRI also provides better identification of focal fat and is superior for assessing vascular lesions such as hemangiomas. When typical features are present on imaging, HCC can be confidently diagnosed without tissue biopsy. However, HCC often has atypical imaging findings, making it difficult to distinguish from other, potentially benign, conditions. An understanding of these atypical presentations is important to ensure an early and accurate diagnosis. A high index of suspicion for malignancy should be maintained, as well as a low threshold for biopsy.

We review some of the atypical presentations of HCC on MRI with pertinent differential diagnoses. Each diagnosis was validated with a follow-up biopsy.

MRI Protocols

Liver imaging has improved significantly with advances in MRI technology. The advent of newer and faster sequences on higher magnetic fields allows for greater temporal and spatial resolution. Dynamic contrast-enhanced imaging of the liver plays a dominant role in lesion characterization. A typical MRI protocol for HCC involves both T1- and T2-weighted imaging with dynamic contrast-enhanced MRI in arterial, venous, and delayed phases. When using hepatobiliary (HPB) agents, far-delayed (from 20 minutes to 1 hour) phase can be obtained for hepatobiliary phase. T1-weighted in-phase and out-of-phase gradient-recall sequences may be obtained using a 2-point Dixon method.

Both gadolinium-based chelated agents (GBCAs) and non-GBCAs can be used for HCC diagnosis. GBCA can be divided into extracellular GBCA and hepatobiliary (HB) agents. The non-GBCAs include reticuloendothelial (RE) agents such as superparamagnetic iron oxide and Mangafodipir trisodium (Mn-DPDP). The GBCAs are paramagnetic, whereas the RE agents are superparamagnetic. Based on the biochemical distribution, extracellular GBCAs behave similar to iodinated contrast used in CT by distributing into the extracellular compartment. However, the HB agents are distributed in extracellular space in early phase and also accumulated in the hepatocytes and extracted in bile.[11] The RE agents are accumulated in the RE system (ie, Kupffer cells in the liver). HB

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agents (Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) or gadopentetate dimeglumine) can be used to obtain both dynamic imaging and hepatobiliary phase imaging and are now considered as standard contrast agents for liver MRI. With the combination with diffusion-weighted imaging (DWI), a superior diagnostic performance of HB agents for detecting HCC was reported, in comparison with extracellular gadolinium-based contrast agents.[12,13]

Typical MRI Appearances of HCC

HCCs may be classified according to growth patterns and macroscopic aspects with prognostic implications:

(1) Expansile, single nodular type, well-defined, encapsulated, and typically with a better prognosis, representing about 50% of HCCs.
(2) Infiltrating type, consisting of a lesion with irregular, poorly defined borders, without a definable capsule, and frequently presenting with vascular invasion. This subtype usually has a poorer prognosis.
(3) Multifocal with multiple nodules scattered in several hepatic segments. This subtype also has a poor prognosis.

Classic HCCs are hypointense on T1-weighted imaging, mildly hyperintense on T2-weighted imaging, and exhibit brisk arterial phase contrast enhancement with rapid washout in the portal venous and delayed phases.[14] Intense arterial phase enhancement is therefore characteristic of HCC, decreasing thereafter on subsequent phases. In larger lesions, a mosaic or heterogeneous pattern is seen on MRI because of the presence of fibrosis, hemorrhage, arteriovenous shunting, and intratumoral necrosis. Nodule-in-nodule appearance is another typical imaging feature of HCC. In hepatobiliary phase, most HCCs are hypointense compared with the hepatic parenchyma. However, paradoxical enhancement of HCC is also reported.[15]

Atypical MRI Appearances of HCC

Unusual Enhancement Patterns

HCC typically exhibits brisk arterial phase enhancement with rapid washout in the venous phase along with possible persistent rim enhancement in the delayed phase; however, there are variations in enhancement pattern. Enhancement patterns have been shown to be dependent on cellular differentiation.[16] A higher proportion of moderate and poorly differentiated, rather than well-differentiated, HCC lesions exhibit the typical pattern of arterial phase enhancement followed by portal venous phase washout.[17] Some HCCs however show lack of or poor arterial phase enhancement. Another mechanism that has been proposed is portal vein thrombosis secondary to HCC involvement, resulting in a compensatory increase in hepatic arterial supply to the liver parenchyma. This has been termed the “arterial steal” phenomenon, resulting in decreased blood supply to the tumor and increased enhancement of the hepatic parenchyma. The result is decreased relative enhancement of the HCC lesion.

These variations include lack of arterial phase enhancement with persistent enhancement in the venous and delayed phases (Fig 1). Other patterns include quite commonly, nodular enhancement and enhancement of septations, which may be mistaken for abscesses. Continuous rim enhancement can be seen in a subgroup of HCCs and may mimic a metastatic lesion, especially in the setting of previous or concurrent extrahepatic malignancy.

A fibrotic capsule is commonly seen in HCC, which may show persistent enhancement in the delayed phase. A subgroup of HCCs demonstrates a central enhancing scar, usually because of the presence of central necrosis and subsequent fibrosis. These lesions may mimic focal nodular hyperplasia (FNH) if a proper history is not sought, leading to misdiagnosis.

Another atypical finding is persistent enhancement of the HCC in the venous and delayed phases (Fig 2). This is usually seen in small HCCs, because of uncertain reasons. Larger HCC lesions are more likely to exhibit more typical enhancement kinetics. In contrast, small (subcentimeter) HCC lesions are seen to follow this pattern in only 24% of cases.[18-20] Rather than showing brisk arterial phase enhancement, small HCC lesions may frequently show isoattenuation during the arterial and portal venous phases making the diagnosis of these lesions difficult.[16]

A group of HCCs demonstrates a dominant hypervascular pattern with massive intratumoral vessels including large draining veins mimicking vascular tumors such as hepatic angiosarcoma.[21] The diagnosis can be made on the basis of serum alpha-fetoprotein (AFP) levels and history of chronic liver disease, as a biopsy may not be feasible because of extreme tumor hypervascularity (Fig 3).

HCC may also exhibit nodular peripheral enhancement, which can be mistaken for hemangioma. This nodular enhancement in HCC has been proposed to be because of variations in tumor differentiation.[14] A stepwise progression model for the development of HCC has been proposed, beginning with a regenerative nodule and progressing through dysplastic nodules of increasing grade, to dysplastic nodules with foci of HCC, and finally to small and large HCC.[14] In this model, the nodular enhancement pattern sometimes seen in HCC is actually because of the foci of HCC on a dysplastic background, resulting in a nodular appearance. This may be mistaken for a hemangioma, which also frequently presents with a nodular peripheral enhancing pattern. Fibrolamellar carcinomas is particular may show peripheral irregular pattern of enhancement with gradual centripetal fill-in on delayed images, which can lead to a misdiagnosis of hemangioma, especially in the setting of normal liver function and AFP.

DWI has been proposed as an aide for small lesions showing abnormal enhancement kinetics and may help identify HCC in cases where enhancement kinetics are equivocal.[22] These sequences are highly susceptible to motion artifact, which has limited their use for HCC imaging. Respiratory and, possibly, cardiac gating should be considered to minimize artifact.

In rare cases, HCC can mimic an abscess on imaging. The presence of a rim-enhancing lesion with or without internal septations can raise suspicion for an abscess. Biopsy is usually necessary in such cases for a diagnosis.[23] Imaging findings should be correlated with the patient’s clinical status to help differentiate HCC from abscess.

HCC With Atypical Signal From Intralesional Fat

HCCs, in particular the clear cell type, may contain intracytoplasmic fat in 17%-20% of cases, and in approximately 2% of cases, this fat is radiographically apparent.[18,24] The microscopic intravoxel fat can be seen as decreased signal in opposed-phased MRI (Fig 4). HCCs containing microscopic fat may be mistaken for hepatic adenoma, angiomyolipoma, or a fat-containing metastasis. Alternatively, in HCCs areas of macroscopic fat are apparent as a decrease in signal intensity in opposed-phase MR or fat-suppressed images or fat attenuation on CT imaging. These fatty areas may be mistaken for a hepatic lipoma, focal steatosis, fat-containing adenoma, angiomyolipoma, or even hepatic liposarcoma.[19,25] HCC with fatty metamorphoses tend to appear hyperintense on T1, with a concomitant loss of signal on out-of-phase, T1-weighted images. Presence of contrast washout during the