Portal Vein Thrombosis May Alter the Correct Evaluation of Hepatocellular Carcinoma With the Sonographic Contrast Pulse Sequence Technique

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Current developments in nonlinear imaging modes, combined with second-generation sonographic contrast agents, enable continuous, real-time imaging of blood flow in normal and pathologic tissues, allowing for the characterization of focal liver lesions similar to that of contrast-enhanced computed tomography (CT) and magnetic resonance imaging.[1–4] The contrast pulse sequence (CPS) imaging mode is a novel nonlinear imaging technique that is based on the processing of nonlinear signals in the fundamental frequency band, with improved sensitivity to contrast agent depiction. It is particularly useful for characterizing benign lesions, which show progressive enhancement in the arterial and portal venous phases, with contrast uptake/retention in the late phase similar to that of the adjacent liver.[1] Conversely, metastases show variable arterial enhancement followed by rapid wash-out in the portal venous phase and appear as filling defects in the late phase.

Hepatocellular carcinoma (HCC) is usually characterized by rapid contrast wash-in and wash-out during the arterial and portal phases, respectively, with less retention of contrast than the adjacent parenchyma in the late phase[1–4]; however, well-differentiated HCC may show considerable contrast uptake in the late phase, making the differentiation difficult between HCC and benign lesions, such as regenerating or dysplastic nodules. In this regard, the accurate diagnosis of HCC by using the CPS mode may be problematic, especially in the presence of altered hepatic perfusion attributable to portal thrombosis. In this report we describe the contrast-enhanced sonographic imaging of HCC in a cirrhotic patient with portal vein thrombosis. Computed tomographic and magnetic resonance images are also provided.

Abbreviations
CPS, contrast pulse sequence; CT, computed tomography; HCC, hepatocellular carcinoma; MI, mechanical index

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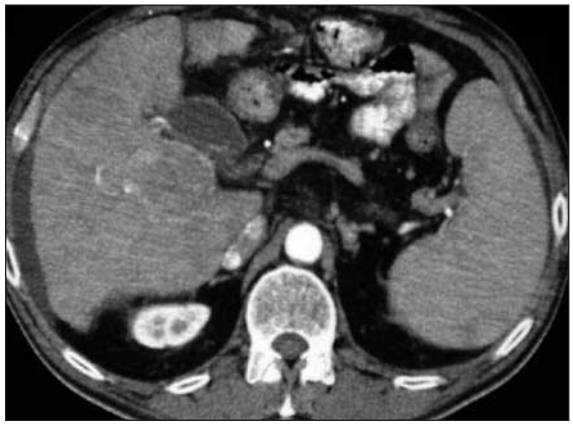
Case Report

A 65-year-old man with Child C alcoholic cirrhosis was referred to our unit for evaluation of a hepatic mass associated with raised α-fetoprotein levels (1500 U). Contrast-enhanced dual-phase (30 and 70 seconds) multidetector CT showed ascites and an enlarged liver, with diffuse signal intensity alteration, portal vein thrombosis, and a low-attenuating focal area of 56 mm in diameter in segments V through VIII, with inhomogeneous peripheral enhancement in the arterial phase (Figure 1A) and a low-density pattern in the portal phase (Figure 1B).

Magnetic resonance imaging showed a hyperintense lesion on the T2-weighted scan (Figure 2A); after delivery of a contrast agent bolus (0.5-mol/L gadobenate dimeglumine solution; MultiHance; Bracco SpA, Milan, Italy), the lesion showed a hyperintense rim in the arterial and portal phases (Figure 2B) on the T1-weighted scan and became inhomogeneously hyperintense in the late phase. Sonographic examination (Acuson Sequoia 512 system; Siemens Medical Solutions, Mountain View, CA) showed a mildly hyperechoic lesion 5 to 6 cm in diameter, with a peripheral halo in segments V through VIII, ascites, and portal vein thrombosis (Figure 3A).

Figure 1. A, Contrast-enhanced, arterial-phase CT scan shows a low-attenuating nodule of 5 to 6 cm in diameter with an inhomogeneous rim of enhancement in segments V through VIII. **B**, Contrast-enhanced, portal-phase CT scan shows a hypodense nodule.

A



B

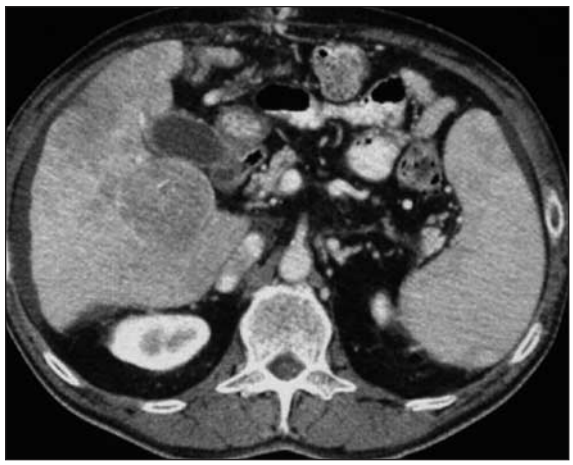
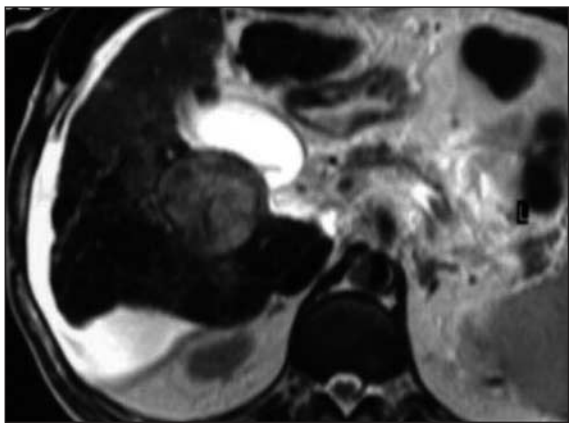


Figure 2. A, Precontrast T2-weighted magnetic resonance image shows a hyperintense nodule. **B**, Postcontrast T1-weighted gradient echo image shows a hyperintense rim in the portal phase.

A



B

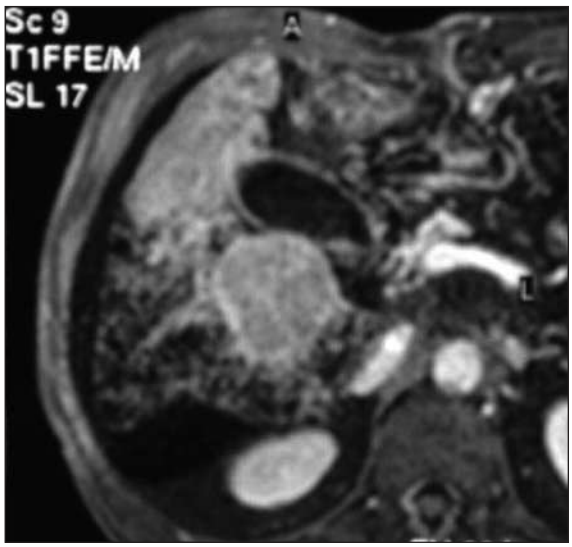
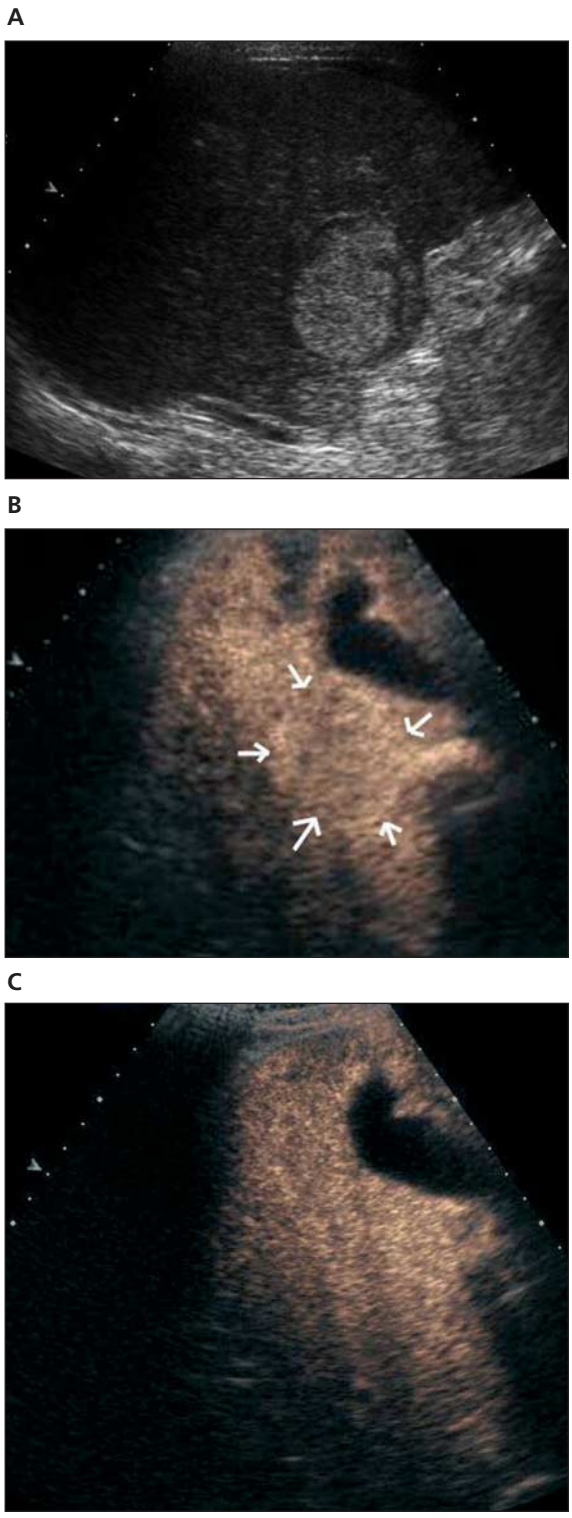


Figure 3. A, Baseline sonogram shows an inhomogeneously hyperechoic lesion with a thin peripheral halo. **B**, Contrast-enhanced, arterial-phase sonogram shows inhomogeneous enhancement with a hyperechoic rim (arrows). **C**, Contrast-enhanced, late-phase sonogram. The lesion appears isoechoic and is nearly indistinguishable from the adjacent parenchyma.



Contrast-enhanced sonography was performed by using the CPS technique at a low mechanical index (MI, 0.15). After delivery of an intravenous bolus of 2.4 mL of a 0.5% stabilized aqueous suspension of sulfur hexafluoride microbubbles with a phospholipidic shell (SonoVue; Bracco SpA), inhomogeneous enhancement of the lesion with a hyperechoic rim was observed in the arterial phase (Figure 3B); no notable washout occurred, and the enhancement persisted in the early portal phase. Afterward, the lesion became isoechoic to the adjacent parenchyma, and this pattern remained unmodified throughout the late phase (Figure 3C). These findings were surprising because they would suggest benignancy.

Finally, sonographically guided biopsy was performed, and histologic examination revealed undifferentiated HCC. The patient was not a candidate for any treatment because of portal vein thrombosis and general clinical conditions.

Discussion

The recent introduction of real-time, low-MI, contrast-specific sonographic techniques that produce images based on the nonlinear acoustic effects of the interaction of ultrasound with microbubble contrast agents has greatly increased the diagnostic performance of conventional sonography in liver imaging. The detection and characterization of focal liver lesions has been improved considerably, reducing the need for additional expensive imaging or invasive techniques.[1–4] The peculiar microcirculation of focal liver lesions is well depicted by second-generation contrast agents, and the ability of sonography to differentiate benign from malignant lesions has increased. In particular, in the late phase, benign lesions show appreciable contrast uptake, whereas no uptake is generally observed in malignant lesions.[1–4]

With the CPS mode, real-time imaging of contrast microbubbles is displayed either as a color map overlying the gray scale background of native tissue on the fundamental mode (the so-called "MIX mode") or as a color map without the background 2-dimensional native tissue ("CA mode" or color alone mode). The latter

mode can also be displayed in gray scale ("2D mode") simply by toggling the Balance key. The CPS is very sensitive in contrast agent depiction and has the ability to display the presence of contrast uptake/retention (in color), in particular within benign lesions such as hemangioma, adenoma, and focal nodular hyperplasia, which may completely disappear and become isoechoic to the adjacent liver parenchyma in the late phase[1–4]; however, contrast-enhanced sonographic techniques may be more perplexing in the evaluation of the contrast agent wash-out during the portal venous and late phases in the presence of HCC.

Tumor identification is improved by contrast agents, which emphasize the difference in echogenicity between normal and pathologic areas of the liver. The real-time evaluation of the wash-out during the portal and late phases plays an essential role in the diagnosis of malignant lesions, showing hypoechoic areas or filling defects within the normally echoic pattern of liver parenchyma.[1–4] Hepatocellular carcinoma is usually characterized by a hypervascular pattern, with hyperechoic enhancement during the arterial phase, which reflects tumor neoangiogenesis, followed by wash-out with a hypoechoic pattern during the portal and late phases[1–5]; however, well-differentiated HCC can sometimes maintain notable contrast retention in the portal and late phases, with an isoechoic pattern in comparison with surrounding parenchyma.[5,6] In these cases, the lack of wash-out can make the characterization of HCC quite difficult, and misinterpretations are possible.

In this regard, a recent article[6] reported different contrast echographic patterns of differentiated or undifferentiated HCCs in the late phases, suggesting that the more the lesion is well differentiated, the more it appears isoechoic in these phases, whereas undifferentiated HCC always appears hypoechoic. Conversely, in our patient, HCC was undifferentiated but appeared isoechoic in the portal and late phases. We hypothesize that portal vein thrombosis may have impaired the hepatic circulation, thus contributing to such an atypical finding. Unlike HCC, which has a nearly exclusive arterial blood supply, 70% to 75% of the blood supply of the normal liver is furnished by the portal vein. It follows that, after microbubble injection, the echo signal intensity of liver parenchyma becomes maximal in the portal phase. As cirrhosis advances, portal blood flow decreases, and hepatic arterial blood flow increases, as a part of a homeostatic mechanism.[7] Portal vein thrombosis hampers portal flow and consequently impairs the enhancement of liver parenchyma after the contrast agent bolus. Therefore, liver parenchyma may appear less echoic than normal, and the hypoechoic pattern of HCC due to portal wash-out is less evident, with a reduced echoic gap between the tumor and the surrounding parenchyma. At the same time, HCC has a nearly exclusive arterial blood supply, which means that microbubbles are detectable. This may be particularly true with low-MI imaging modes, which are very sensitive to microbubble depiction and minimally destroy microbubbles.[8]

It follows that, in our case and in similar cases, the high sensitivity to contrast agents, the long survival of microbubbles due to the low MI used, which allows their recirculation even in the late phase, and, hypothetically, the hemodynamic changes due to portal vein thrombosis may together impair the correct evaluation of wash-out and delayed contrast clearance inside the HCC nodule. Finally, although no firm conclusions can be drawn by our single-case observation, we hypothesize that a very sensitive imaging mode for microbubble signals, such as the CPS mode, may prevent a clear differentiation between HCC and benign nodular lesions in the presence of portal vein thrombosis.

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