Utility of Gd-EOB-DTPA-Enhanced MRI in Diagnosing Small Hepatocellular Carcinoma

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Key Words
Gd-EOB-DTPA-enhanced MRI · Hepatocyte function · Ultrasound · CT during arteriography · CT during arterial portography · Well-differentiated hepatocellular carcinoma · Small hepatocellular carcinoma

Abstract
We describe an 8-mm hepatocellular carcinoma (HCC) with hepatitis C virus-related cirrhosis in a 74-year-old woman. Ultrasound (US) revealed an 8-mm hyperechoic nodule in segment 6 of the liver. Contrast-enhanced computed tomography (CT) and US revealed no hypervascularity in the early phase and no washout in the late phase and the Kupffer phase, respectively. CT during arteriography revealed no hypervascularity and CT during arterial portography disclosed no perfusion defect. Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) revealed no hypervascularity in the early phase, but disclosed a defect in the hepatobiliary phase. Histologically, the nodule was diagnosed as well-differentiated HCC characterized by more than two-fold the cellularity of the non-tumorous area, with a high nuclear:cytoplasmic ratio, increased cytoplasmic eosinophilia, fatty change, and slight cell atypia with an irregular thin trabecular pattern. Our case demonstrates the utility of Gd-EOB-DTPA-enhanced MRI in the diagnosis of small HCC.
Introduction

Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) is a new liver-specific contrast agent used in magnetic resonance imaging (MRI). A bolus injection of Gd-EOB-DTPA allows the evaluation of tumor vascularity in a manner similar to evaluation with gadolinium-triamine pentaacetic acid (Gd-DTPA) [1]. Moreover, it begins to accumulate in normally functioning hepatocytes in the hepatobiliary phase [1, 2] 20 min after injection, thereby enhancing the liver parenchyma. On the other hand, tumors appear like hypointense lesions because they lack normally functioning hepatocytes [2, 3].

Here, we describe an 8-mm well-differentiated hepatocellular carcinoma (HCC) detected in the hepatobiliary phase (20 min after injection), whereas contrast-enhanced ultrasound (US) and computed tomography (CT) did not reveal hypervascularity in the early phase and washout in the late phase; also, CT during arteriography (CTA) and CT during arterial portography (CTAP) did not reveal hypervascularity and perfusion defect, respectively.

Case Report

A 74-year-old woman with hepatitis C virus (HCV)-related cirrhosis was admitted to Kobe Asahi Hospital in April 2008 for further examination of an 8-mm hyperechoic nodule in segment 6. HCV antibody and HCV RNA were positive, hepatitis B surface antigen and hepatitis B virus DNA were negative, and laboratory data on admission disclosed the following values: platelets 7.2 × 10^4/μl (normal 13.0–36.9), aspartate aminotransferase 26 IU/l (10–40), alanine aminotransferase 20 IU/l (5–40), thymol turbidity 18.5 U/l (0–4), zinc surface turbidity 13.7 U/l (2–12), indocyanine green retention rate at 15 min 7% (0–10), and γ-globulin 23.3% (10.6–20.5). The levels of tumor markers revealed the following: α-fetoprotein 7.1 ng/ml (0–9.9), protein induced by vitamin K absence II 42 mAU/ml (0–40).

US disclosed an 8-mm hyperechoic nodule in segment 6 (fig. 1). Contrast-enhanced CT revealed no hypervascularity in the early phase and no washout in the late phase. Contrast-enhanced US revealed no hypervascularity in the early vascular phase and no defect in the Kupffer phase. CTA revealed no hypervascularity and CTAP revealed no perfusion defect. Superparamagnetic iron oxide (SPIO)-MRI revealed isointensity in both T1 and T2 sequences. Gd-EOB-DTPA-enhanced MRI revealed no hypervascularity in the early phase, but disclosed a defect in the hepatobiliary phase (fig. 2).

Histologically, the nodule was diagnosed as well-differentiated HCC characterized by more than two-fold the cellularity of the non-tumorous area, with a high nuclear:cytoplasmic ratio, increased cytoplasmic eosinophilia, fatty change, and slight cell atypia with an irregular thin trabecular pattern (fig. 3). The HCC was treated with radiofrequency ablation, and the ablated HCC was confirmed by Gd-EOB-DTPA-enhanced MRI. Complete necrosis of the tumor was revealed by US-guided biopsy.

Discussion

HCC is known to arise multicentrically in cases of virally induced liver cirrhosis, developing from dysplastic nodules into HCC [4, 5]. When considering the most appropriate therapeutic approach, it is important to distinguish between dysplastic nodules and HCC. Although the usefulness of detecting hypervascular HCCs has been reported [1], neither hypovascular lesions nor lesions with weakly increased arterial flow have been evaluated to date. These latter nodules are difficult to evaluate in dynamic studies with Gd-DTPA. No significant quantitative difference is observed between HCCs and dysplastic nodules in terms of the enhancement ratios and the contrast-to-noise ratio [6]. A combination of CTA and CTAP, as well as SPIO-enhanced MRI, has been conducted to distinguish between these two entities [7, 8]. It is known that SPIO accumulates in some HCCs [8]. SPIO-enhanced MRI, however, is of limited use in the
evaluation of HCCs, being by itself insufficient for determining the therapeutic strategy for the treatment of HCCs. When a combination of CTA and CTAP is used [7], the blood supply is very informative in evaluating the malignancy of liver lesions. CTA and CTAP are too invasive, however, for routine application.

In our case, imaging studies by modalities such as contrast-enhanced US and CT revealed no hypervascularity in the early phase and no washout in the Kupffer phase and the late phase. CTA did not reveal hypervascularity, and CTAP did not reveal perfusion defect. We have emphasized the superiority of CT arteriportal angiography to contrast-enhanced CT and MRI in the diagnosis of HCC in nodules smaller than 20 mm [9]. We have also detected a 10-mm well-differentiated HCC showing perfusion defect at CTAP, when contrast-enhanced US, CT, and MRI revealed no hypervascularity in the early phase or washout in the late phase, and CTA showed no hypervascular stain [9]. In this study, however, even with CT arteriportal angiography, we were not able to detect the 8-mm HCC. Although the data remain preclinical, specific enhancement with Gd-EOB-DTPA has been reported for the differentiation of HCC [10]. Gd-EOB-DTPA-enhanced MRI provides additional diagnostic clues – the level of hepatocyte function and excretion [11]. We detected an 8-mm HCC with Gd-EOB-DTPA-enhanced MRI, showing a defect in the hepatobiliary phase (20 min after injection). Our case demonstrates the utility of Gd-EOB-DTPA-enhanced MRI in the diagnosis of small HCC, even of an 8-mm nodule, although all nodules recognized as hypointense in the hepatobiliary phase and diagnosed as HCCs are associated with potential misdiagnosis. In our case the well-differentiated HCC was confirmed histologically.

Further study is needed to compare the utility of Gd-EOB-DTPA-enhanced MRI with contrast-enhanced US, CT, and CT arteriportal angiography in the diagnosis of HCC in nodules smaller than 20 mm.
**Fig. 1.** US disclosed an 8-mm hyperechoic nodule in segment 6.

**Fig. 2.** Gd-EOB-DTPA-enhanced MRI disclosed a defect in the hepatobiliary phase.
**Fig. 3.** Histologically, the nodule was diagnosed as well-differentiated HCC characterized by more than two-fold the cellularity of the non-tumorous area, with a high N/C ratio, increased cytoplasmic eosinophilia, fatty change, and slight cell atypia with an irregular thin trabecular pattern.
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