□ CASE REPORT □

Well-differentiated Hepatocellular Carcinoma Detected as Hypovascularity by Only CT during Hepatic Arteriography

Jun Saito¹, Soo Ryang Kim¹, Masatoshi Kudo², Susumu Imoto¹, Kenji Ando¹,
Taisuke Nakajima¹, Katsumi Fukuda¹, Yumi Otono¹, Soo Ki Kim³, Takamitsu Komaki⁴,
Hirohisa Yano⁵, Osamu Nakashima⁵, Kayo Sugimoto⁶ and Toshiyuki Matsuoka⁷

Abstract

We describe a well-differentiated hepatocellular carcinoma (HCC) with alcohol-related liver cirrhosis in a 69-year-old man. Ultrasonography (US) disclosed a 10 mm hypoechoic nodule in segment 4; Sonazoid contrast-enhanced US and gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) revealed no defect in either the Kupffer phase or the hepatobiliary phase. Computed tomography during hepatic arteriography (CTHA), however, revealed a hypovascular nodule, but CT during arterial portography showed no perfusion defect. Histological analysis indicated a well-differentiated HCC. Thus, our detection of well-differentiated HCC disclosed by only CTHA attested to the efficiency of this modality, suggesting that it is more sensitive than Gd-EOB-DTPA-enhanced MRI.

Key words: well-differentiated hepatocellular carcinoma, imaging studies, Gd-EOB-DTPA-enhanced MRI, CT during hepatic arteriography, hypovascular tumor, Sonazoid contrast-enhanced US

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Introduction

The definitive diagnosis of nodular lesions detected by imaging techniques in the cirrhotic liver remains a critical challenge for clinicians. The issue is particularly complicated for small (1-2 cm) nodules, many of which may be preneoplastic with uncertain malignant potential (1), such as macroregenerative nodules, low-grade dysplastic nodules (LGDN), high-grade dysplastic nodules (HGDN), or more rarely, hemangiomas that are found in up to 42% of explanted livers (2-4).

Recently, clinicians have been able to conduct computed tomography (CT) scanning during angiography, CT during hepatic arteriography (CTHA) and CT during arterial portography (CTAP), thereby simultaneously acquiring data on lesions and intranodular blood flow (5, 6). Moreover, devel-

opment of the newly introduced diagnostic imaging techniques, Sonazoid contrast-enhanced ultrasonography (US) (7) and gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) (8), have provided higher degrees of detectability of small hepatocellular carcinoma (HCC).

Here, we describe a 10 mm well-differentiated HCC appearing as a hypovascular tumor, with alcohol-related liver cirrhosis, disclosed by only CTHA, whereas Sonazoid contrast-enhanced US and Gd-EOB-DTPA-enhanced MRI revealed no defect in either the Kupffer phase or the hepatobiliary phase; also, contrast-enhanced CT revealed no wash-out in the equilibrium phase.

Case Report

A 69-year-old man with alcohol-related liver cirrhosis was

¹Department of Gastroenterology, Kobe Asahi Hospital, Japan, ²Department of Gastroenterology and Hepatology, Kinki University School of Medicine, Japan, ³Department of Gastroenterology and Hepatology, Kyoto University, Japan, ⁴Department of Internal Medicine, Saiseikai-Tondabayashi Hospital, Japan, ⁵Department of Pathology, Kurume University School of Medicine, Japan, ⁶Department of Pharmacy, Kobe Asahi Hospital, Japan and ⁷Department of Radiology, Osaka City University Medical School, Japan

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Correspondence to Dr. Soo Ryang Kim, asahi-hp@arion.ocn.ne.jp

Figure 1. Imaging findings of US. (a) B-mode US reveals a 10 mm hypoechoic nodule in segment 4 (arrow). The hypovascular nodule is not visible in either (b) the early vascular phase (5 sec) or (c) the Kupffer phase (15 min) on Sonazoid contrast-enhanced US. Contrast-enhanced US imaging was performed with Xario SSA-660A, PVT-375BT probe (3.5 MHz) (Toshiba Medical Systems). PS-low; mechanical index: 0.2, frame rate: 15 fps, dynamic range: 45 dB, injection of Sonazoid: 0.0075 mL/kg

admitted to Kobe Asahi Hospital in July 2010 for further examination of a 10 mm hypoechoic nodule in segment four (S4). His alcohol consumption over 40 years was 360 mL/day. A physical examination on admission showed no remarkable abnormalities and no evidence of lymph adenopathy or splenomegaly. The serum was negative for hepatitis C virus antibody and hepatitis B surface antigen. Laboratory data disclosed the following values: platelets $10.2 \times 10^4/\mu\text{L}$ (normal, 13.1-36.2), total protein 7.0 g/dL (6.7-8.3), γ -glutamyl transpeptidase 281 IU/L (0-30), albumin 4.2 g/dL (4.0-5.0), total bilirubin 0.9 mg/dL (0.3-1.2), prothrombin time 82% without encephalopathy and ascites, classified as Child-Pugh classification A of cirrhosis. Alpha-fetoprotein (AFP), lens culinaris agglutinin A-reactive fraction of alpha fetoprotein (AFP L3) and protein-induced vitamin K absence (PIVKA II) were within normal ranges. A US-guided biopsy disclosed alcohol-related liver cirrhosis with pericellular fibrosis. B-mode US disclosed a 10 mm hypoechoic nodule in S4 (Fig. 1a). Sonazoid contrast-enhanced US revealed no hypervascular nodule in the early vascular phase (Fig. 1b) and no defect in the Kupffer phase (Fig. 1c). Plain CT showed no fatty liver or any nodule in the liver (Fig. 2a); contrast-enhanced CT revealed no enhanced nodule in the arterial phase (Fig. 2b) and no washout in the equilibrium phase (Fig. 2c); Gd-EOB-DTPA-enhanced MRI revealed no enhanced nodule in the arterial phase (Fig. 2d), and no defect in the hepatobiliary phase (Fig. 2e). CTHA, however, revealed a hypovascular nodule (Fig. 3a, b), but CTAP revealed no perfusion defect (Fig. 3c). A US-guided biopsy of the nodule was diagnosed as well-differentiated HCC characterized by more than two-fold the cellularity of the non-tumorous area, clear cell change and mild cell atypia (Fig. 4a, b). Immunohistochemical staining of CD34 in the nodule was positive in the sinusoidal blood space, implying capillarization compatible with well-differentiated

HCC (Fig. 4c, d). The organic anion transporter (OATP) 1B3 (9), being positive in both the nodule and the non-nodular lesion, was compatible with the absence of defect in the hepatobiliary phase as determined by Gd-EOB-DTPA-enhanced MRI (Fig. 5a, b).

Discussion

Confirmation of arterial hypervascularity by three imaging modalities (triphasic CT, triphasic MRI, and contrast-enhanced US), even in the absence of a significant (>400 ng/mL) rise in α -fetoprotein, is recommended by the European Association for the Study of the Liver as diagnostic criteria for HCC nodules larger than 2 cm in patients with cirrhosis (10). This recommendation for the management of HCC provides a rational approach to the problem but leaves some areas of uncertainty, particularly those concerning the interpretation of discordant vascularity, the use of imaging techniques in nodules smaller than 2 cm, the meaning of truly hypovascular nodules, and the management of those diagnosed as LGDN or HGDN at guided biopsy.

To resolve the areas of uncertainty, we previously evaluated the superiority of CT arteriportal angiography for nodules smaller than 2 cm, and concluded that the modality is superior to contrast-enhanced CT and contrast-enhanced MRI (11). Nonetheless, the status of imaging studies in the diagnosis of HCC smaller than 2 cm has changed with the introduction of new contrast agents for US and MRI. First, Sonazoid was exclusively approved in Japan in 2007 as a second-generation US contrast agent; second, Gd-EOB-DTPA, a new liver-specific contrast agent used in MRI, was approved in 2008. Taking these improvements into consideration, we evaluated the effectiveness of four imaging modalities (contrast-enhanced CT, Sonazoid contrast-enhanced US, Gd-EOB-DTPA-enhanced MRI, CT arteriportal angi-

Figure 2. Imaging findings of CT and MRI. (a) Plain CT reveals no fatty liver or any nodule in the liver. (b) Contrast-enhanced CT reveals no enhanced nodule in the arterial phase and (c) no wash-out in the equilibrium phase. CT imaging was performed with Somatom Emotion 16-Slice configuration (Siemens Japan). (d) Gd-EOB-DTPA-enhanced MRI reveals no enhanced nodule in the arterial phase and (e) no defect in the hepatobiliary phase. MR imaging at the hepatobiliary phase was performed with Gyroscan 10T-NT (Philips Medical Systems), Intera 1.0T version 12.1. THRIVE; TR/TE: 5.4/2.8 msec, FA: 20°, SENSE factor: 2, slice thickness: 6 mm (gap -2.5 mm), slice number: 70, matrix: 160×512

ography) in the diagnosis of HCC smaller than 2 cm. Consequently, the following patterns disclosed by these imaging modalities were deemed to be a conclusive diagnosis of HCC: 1) hypervascularity in the arterial phase and washout in the equilibrium phase (by contrast-enhanced CT), 2) hypervascularity in the early vascular phase and defect in the Kupffer phase (by Sonazoid contrast-enhanced US), 3) hypervascularity in the arterial phase and/or defect in the hepatobiliary phase (by Gd-EOB-DTPA-enhanced MRI) and 4) hypervascularity by CTHA and/or perfusion defect by CTAP (by CT arteriportal angiography). The results showed that the diagnostic sensitivity of CT arteriportal angiography was 88.2% in all nodules and 95.8% in moderately-differentiated HCC, with a significant difference between contrast-enhanced CT and CT arteriportal angiography ($p < 0.05$). No difference was observed, however, among Sonazoid contrast-enhanced US, Gd-EOB-DTPA-enhanced MRI and CT arteriportal angiography.

The combined sensitivity of Sonazoid contrast-enhanced US and Gd-EOB-DTPA-enhanced MRI in all nodules was 94.1% due to improvement in the diagnostic capabilities of each modality (12). For the diagnosis of nodules smaller than 2 cm, these two imaging modalities have provided higher sensitivity with Sonazoid CEUS and Gd-EOB-DTPA-enhanced MRI than with Sonovue contrast-enhanced US and contrast-enhanced CT (13), or with Sonovue contrast-enhanced US and gadolinium-enhanced MRI (14). Such sensitivity in the diagnosis of well-differentiated HCC was, however, not explicit with the use of those imaging modalities in the present study.

According to the classification by the International Working Party of the World Congress of Gastroenterology, he-

Figure 3. Imaging findings of CT arteriportal angiography. CTHA reveals a hypovascular nodule in both (a) the early phase (arrow) and (b) the late phase (arrow), (c) although CTAP does not reveal any perfusion defect. CTHA was performed using 40-60 mL of contrast medium at the rate of 2-3 mL/s into the common hepatic artery, scanned early phase (15 s) and late phase (60 s). CTAP was performed using 80-90 mL of contrast medium at the rate of 2-3 mL/s.

Figure 4. Histological findings of the US-guided biopsy specimens. (a) Well-differentiated HCC characterized by more than two-fold the cellularity of the non-tumorous area, clear cell change and mild cell atypia, and (b) non-nodular lesion (Hematoxylin and Eosin staining). (c) Capillarization is evident in the sinusoidal blood space, and (d) non-nodular lesion (immunohistochemical staining by CD34).

patic nodules in patients with chronic liver diseases are subdivided into regenerative nodules (mono acinus and multi

acinus), LGDN, HGDN, well-differentiated HCC, moderately-differentiated HCC and poorly-differentiated

Figure 5. Expression of OATP 1B3 is observed in both (a) the nodular lesion and (b) the non-nodular lesion.

HCC, in ascending order of histologic grades, representing a sequence of multistep hepatocarcinogenesis (1). In a sequence of multistep carcinogenesis, the differentiation of HGDN from well-differentiated HCC is pivotal. From the viewpoint of histopathology, consensus on the criteria of well-differentiated HCC has been established (15). From the viewpoint of imaging studies on early HCC, there is controversy among hepatologists engaged in the diagnosis of well-differentiated HCC. Some insist that Gd-EOB-DTPA-enhanced MRI is most sensitive in disclosing defect in the hepatobiliary phase (16) and others insist that CTAP with CT arteriportal angiography is the most sensitive in disclosing perfusion defect (11). Although defect disclosed by CTHA, implying hypovascular HCC, has been reported to occur before perfusion defect disclosed by CTAP (6), the finding has not been verified in the clinical setting. We described a 10 mm well-differentiated HCC disclosed by only CTHA as a hypovascular tumor, whereas Sonazoid contrast-enhanced US, contrast-enhanced CT and Gd-EOB-DTPA-enhanced MRI revealed no defect in the Kupffer phase and no washout in the equilibrium phase and no defect in the hepatobiliary phase; also, CTAP revealed no perfusion defect.

Concerning OATP 1B3, there was no difference of OATP 1B3 expression in either the nodule or the non-nodular lesion in the present case of well-differentiated HCC. That is compatible with two reports, describing that OATP 1B3 was highly expressed in some of moderately-differentiated HCC, whereas it was hardly observed in well-differentiated HCC (9, 17). Concerning insufficient quality of the images, the unhomogeneous enhanced area depicted with CTHA and Sonazoid contrast-enhanced US might be explained by pericellular fibrosis due to alcohol-related liver cirrhosis.

The present results demonstrated that CTHA is more sensitive than Gd-EOB-DTPA-enhanced MRI in the diagnosis of well-differentiated HCC, although no clinical trials have been undertaken to evaluate the sensitivity of the two above modalities in the diagnosis of well-differentiated HCC. Further study is needed to clarify the sensitivity of imaging studies in the diagnosis of well-differentiated HCC smaller

than 2 cm.

The authors state that they have no Conflict of Interest (COI).

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