Contrast-Enhanced Ultrasonography Using Levovist:
Usefulness of Diagnosis of Small Focal Nodular Hyperplasia Lesions

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Abstract
Differential diagnosis of focal nodular hyperplasia and hepatocellular carcinoma is clinically important because, while both are hypervascular tumors, they have vastly different prognoses. Because the spoke-wheel appearance is the primary characteristic of focal nodular hyperplasia, we attempted to detect this pattern in nodules smaller than 3 cm in diameter with contrast-enhanced ultrasonography using a contrast agent (Levovist). Four patients were examined with contrast-enhanced US: two of the patients were examined with Coded Harmonic Angio; the other two patients were examined with contrast-enhanced color and power Doppler US without harmonic imaging. Although the hepatic arteriogram showed the spoke-wheel appearance in only one tumor (diameter, 3 cm), contrast-enhanced US clearly demonstrated this characteristic in all four tumors, including three tumors that were less than 2 cm in diameter. Because it is noninvasive and can be carried out in an outpatient clinic, contrast-enhanced US is extremely useful for diagnosing small focal nodular hyperplasia lesions at sites that can be observed with US.

Keywords
contrast-enhanced color Doppler imaging, contrast-enhanced power Doppler imaging, focal nodular hyperplasia, harmonic imaging, Levovist

1. Introduction
The lesions of focal nodular hyperplasia (FNH) are rare benign hypervascular tumors of the liver and are usually discovered incidentally. Because they are benign, FNH, in principle, require no treatment. Hepatocellular carcinoma (HCC) is a malignant hypervascular tumor and is one of the most common malignancies in Japan. Differentiating FNH lesions from other hypervascular liver tumors, particularly those of HCC, is therefore clinically important. The principal characteristic of FNH is the spoke-wheel appearance, which is produced by the tumor's centrifugal blood supply. Angiography does not readily detect this characteristic radiologic finding in small FNH lesions, however. We therefore attempted to detect the spoke-wheel pattern of small FNH lesions with contrast-enhanced ultrasonography using Levovist.

2. Subjects and Methods
The patients were four women aged 40 to 69 years (mean, 52.5 years). None had a history of oral contraceptive use. Liver tumors were discovered incidentally in all the patients. Liver function test findings were normal, and tests for tumor markers were negative in three of the patients. One patient had an elevated γ-GTP level and tested positive for protein induced by vitamin-K antagonist-II resulting from administration of warfarin potassium. All the patients tested negative for hepatitis B virus surface antigen and hepatitis C virus antibody.

Levovist (Schering AG, Berlin) is an ultrasound contrast agent consisting of a galactose-palmitic acid microparticle mixture. We prepared Levovist by

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Received on February 12, 2002; Revision accepted on April 24, 2002

J Med Ultrasonics 2002; 29 (Autumn) : 99-104
shaking it for 10 seconds. Then, after allowing the mixture to stand for 2 minutes to reach equilibration, a total of 2.5 g (8.5 ml of a 300 mg/ml concentration) was injected manually through a 20-gauge cannula inserted into the antecubital vein at a rate of 1.0 ml/s and was flushed with 10 ml of a normal saline solution. In one patient examined with Coded Harmonic Angio, Levovist was administered at a concentration of 400 mg/ml.

We examined all four patients with contrast-enhanced US, and examined two of them with Coded Harmonic Angio (GE LOGIQ 700 EXPERT, GE Medical Systems, Milwaukee, Wis.). In Coded Harmonic Angio mode, a 348C convex probe was used at a mechanical index of 0.6 to 0.8, a transmission frequency of 2.0 MHz, and a receiving frequency of 4.0 MHz. The focal point was set below the bottom of the nodule. Images in the scanning plane were displayed in real time by slightly changing the scanning plane. Tumor vessels were continuously scanned in real time for about 20 seconds (early arterial phase) after the first microbubble signal intensity appeared in the liver parenchyma. Intermittent scanning or manual flash imaging was then performed to visualize tumor perfusion for 4 to 5 minutes after Levovist had been injected (late vascular phase).

The other two patients were examined using contrast-enhanced color and power Doppler US (SSD 5500 US system, Aloka, Tokyo) with a 3-MHz convex probe at a mechanical index of 0.6 to 0.8 and without harmonic imaging.

Continuous imaging visualized tumor vessels at 5 to 10 frames per second. Images were recorded on videotape beginning immediately after injection of Levovist. Helical CT was performed in all patients. Superparamagnetic iron oxide (SPIO)-MRI was performed in two patients, and enhanced MRI using gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA), in the other two. Hepatic arteriography was performed in three patients, but not in the patient who had been treated with warfarin potassium.

3. Results

Each of the patients had a single nodular tumor ranging from 1.3 to 3.0 cm in diameter. The ultrasonograms showed tumors to be slightly hypoechoic in two patients and isoechoic in the other two. Conventional color and power Doppler US showed flow signals as dots or spots within the tumor in all four patients. Contrast-enhanced color Doppler US showed flow signals as dots or spots within the tumor in all four patients. Contrast-enhanced color Doppler US clearly demonstrated the spoke-wheel pattern in one tumor but did not show it in the other. Contrast-enhanced power Doppler US demonstrated the spoke-wheel pattern in two tumors. Coded Harmonic Angio clearly revealed the spoke-wheel pattern at the early arterial phase and a dense stain at the late vascular phase (manual flash) in two tumors. Three tumors appeared isodense in unenhanced CT images; the other tumor appeared slightly hypodense. All four tumors were homogeneously enhanced in the early phase and isodense in the late phase on enhanced CT scan. SPIO-MRI showed isosignal intensity in one tumor and a slightly high signal intensity in another tumor. Two tumors were isointense on Gd-DTPA-enhanced MRI. The hepatic arteriogram showed the spoke-wheel appearance in only one tumor (diameter, 3 cm). Our diagnosis of FNH was based on radiologic findings and the results of clinical follow-up for 12 to 24 months (mean, 18 months).

Case 1: 42-year-old female (Fig. 1).

The hepatic arteriogram showed a hypervascular tumor in the posterior superior segment of the right hepatic lobe, but the spoke-wheel appearance was not clearly demonstrated at the arterial phase. Pre-enhanced US showed an isoechoic tumor (19 × 12 mm), and conventional power Doppler US showed a dotlike flow signal within the tumor. Coded Harmonic Angio demonstrated the spoke-wheel pattern at the early arterial phase (15 seconds) and a dense stain at the late vascular phase (manual flash, 180 seconds).

Case 2: 59-year-old female (Fig. 2).

Unenhanced CT scan showed an isodense tumor in the anterior inferior segment of the right hepatic lobe; enhanced CT scan, a hyperdense tumor in the early phase and an isodense tumor in the late phase; pre-enhanced US, an isoechoic tumor (diameter, 15 mm); and conventional power Doppler US, a dotlike flow signal within the tumor. Coded Harmonic Angio clearly demonstrated the spoke-wheel pattern in the early arterial phase (25 seconds) and a dense stain in the late vascular phase (manual flash, 180 seconds).

Case 3: 69-year-old female (Fig. 3).

The hepatic arteriogram showed a hypervascular tumor in the posterior inferior segment of the right hepatic lobe, but the spoke-wheel appearance was not visible at the arterial phase. Pre-enhanced US showed a hypoechoic tumor (13 × 6 mm); conventional power Doppler US, a spotty flow signal within the tumor; and contrast-enhanced power Doppler US, the spoke-wheel pattern.

Case 4: 40-year-old female (Fig. 4).

The hepatic arteriogram showed a hypervascular tumor with the spoke-wheel pattern in the caudate lobe; pre-enhanced US, a hypoechoic tumor (30 × 20 mm); conventional color Doppler US, a spotty flow signal within the tumor; and contrast-enhanced color Doppler US and contrast-enhanced power Doppler US, the spoke-wheel pattern.