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● *Original Contribution*

DIFFERENTIAL DIAGNOSIS OF ARTERIAL PHASE ENHANCED HEPATIC INFLAMMATORY LESIONS AND HEPATOCELLULAR CARCINOMAS WITH CONTRAST-ENHANCED ULTRASOUND

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Abstract—We aimed to investigate the enhancement patterns of contrast-enhanced ultrasound (CEUS) with SonoVue and determine the utility of this method for differential diagnosis between hepatic inflammatory lesions with arterial phase enhancement and hepatocellular carcinomas (HCC). Twenty-three patients with arterial-enhanced inflammatory liver lesions and 46 HCC patients were included. These lesions had been subjected to CEUS examination and confirmed by pathologic results or imaging follow-up for at least 1 y. In the arterial phase of CEUS, 65.2% of the inflammatory lesions showed patchy (slight enhancement with poorly defined margins) or centripetal enhancement, whereas 89.1% of the HCC lesions showed homogeneous or heterogeneous enhancement ($p < 0.001$). Moreover, 82.6% of the inflammatory lesions had poorly defined margins, and 78.3% were irregular in shape at the peak, whereas 87.0% of the HCC lesions had well-defined margins and 76.1% were regular (both $p < 0.001$). Feeding vessels were more frequently visualized in HCCs (71.7%) than in inflammatory lesions (26.1%, $p < 0.001$). Additionally, 88.2% of the internal non-perfused areas in inflammatory lesions were regular in shape, while 68.0% of these areas in HCCs had an irregular shape ($p < 0.001$). CEUS pattern analysis provides important information for differentiating inflammatory liver lesions and HCCs and is helpful for improving diagnostic accuracy. (E-mail: minhuachen@vip.sina.com) **© 2016 Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology**

Key Words: **Inflammatory liver lesion, HCC, Contrast-enhanced ultrasound, Differential diagnosis.**

INTRODUCTION

Currently, existing diagnostic ultrasound (US) techniques allow for limited evaluation of tissue characteristics beyond morphology. Contrast-enhanced ultrasound (CEUS) perfusion imaging of the liver has the potential to overcome this shortcoming. The use of CEUS technology can improve the differential diagnosis of liver lesions by providing information regarding perfusion patterns and vascular structures (Claudon et al. 2008, 2013; Hohmann et al. 2003; Quaia et al. 2004; Von Herbay et al. 2004). Focal inflammatory lesions of the liver are uncommon, benign disease entities that occur in patients with internal malignancies, parasitic infections, allergic conditions, drug hypersensitivity or hypereosinophilic syndrome. On CEUS imaging, some liver inflammatory lesions show arterial phase enhancement, late-phase washout and internal necrotic foci. These features are similar to those observed in hepatocellular carcinoma (HCC). When we began to use CEUS in our center, most of the inflammatory lesions with arterial enhancement were misdiagnosed as malignancy, and the patients underwent biopsy or surgery. The present study aimed to compare the perfusion features of inflammatory liver lesions with those of HCCs on CEUS to improve differential diagnosis.

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MATERIALS AND METHODS

Patients

This study was approved by the Institutional Review Board of the Peking University School of Oncology, and written informed consent was obtained from all patients before their CEUS examinations.

From April 2008 to January 2012, 37 consecutive cases with inflammatory liver lesions that were suspected to be malignant by conventional US underwent CEUS examination in our department. Of these, 23 cases with

arterial phase enhancement, which is often indicative of HCC, were included in the study. The other 14 cases showed typical patterns for liver abscesses or tuberculous necrosis and were excluded. During the same period, 385 patients with suspected malignant HCC based on conventional US underwent CEUS examination. Because there were many more HCC cases (385) than inflammatory cases (23), we randomly selected 46 cases from the HCC pool according to a 1:2 proportion. Using random number generator software, we set the number range between 1 and 385, and we ran the program 46 times. We evaluated the 46 HCC cases that corresponded to the 46 numbers, and these 46 HCC patients were regarded as the comparison group. One lesion in each patient was examined for CEUS evaluation.

The average sizes of the inflammatory lesions and HCCs were 4.0 ± 2.7 cm (1.2–9.7 cm) and 4.3 ± 2.1 cm (1.9–10.0 cm), respectively ($p > 0.05$). The inflammatory lesions were diagnosed by surgery (4 patients), biopsy (14 patients) and over 12 mo of follow-up (5 patients). The pathology results from surgical specimens showed parasitic infections in two cases and tuberculous infection in two other cases. The latter five patients for whom pathology results were not available were confirmed by other imaging methods (computed tomography [CT], magnetic resonance imaging [MRI]) over 1 y of progression-free follow-up. Pathologic diagnoses were obtained for all HCC patients.

Ultrasound instrument and contrast agent

Low mechanical index (MI) and real-time contrast-enhanced harmonic ultrasound with SonoVue (Bracco SpA, Italy) was performed in this study. The SonoVue suspension contains 8 μL/mL sulfur hexafluoride (SF6) stabilized by a phospholipid shell (microbubble concentration: 5 mg/mL). The mean micro-bubble diameter was 2.5 μm. The SonoVue suspension (2.4 mL) was administered through the cubital vein by bolus injection (over 1–3 s). The Technos DU8 (Easote, Italy), Aplio 80 ultrasound system (Toshiba, Japan) and LOGIQ 9 (General Electric, Milwaukee, WI, USA) were used for this study. The probe frequency was approximately 2.5–6.0 MHz. The MI used in CEUS scanning ranged from 0.04 to 0.12.

US and CEUS examination methods

Conventional gray-scale ultrasound of the liver was first performed to identify the number and location of the lesions. The size, shape, margin, echogenicity, echotexture and color Doppler imaging features of the lesions were documented. Regular lesions had a round shape with clear borders. A distinct difference between the lesion and the surrounding liver was considered to be a well-defined margin. At least two vessels inside the lesion on color Doppler indicated rich flow. CEUS was then conducted with a low MI. After injection of the contrast agent, the lesions were scanned with pulse inversion contrast-enhanced harmonic ultrasound. The perfusion pattern and echogenicity of the lesion were observed and recorded. After adequate diagnostic information regarding the target lesion was acquired, the whole liver was scanned quickly to detect any previously undetected lesions showing abnormal washout. Each CEUS scan was approximately 5–6 min in duration. Dynamic images were stored for later analysis.

Enhancement pattern analysis

All CEUS images and clips were retrospectively reviewed, and the perfusion patterns were evaluated (described in the Results section) by two blinded reviewers with at least 3 y of experience in liver CEUS. The reviewers were unaware of the findings obtained with other imaging techniques or of the pathologic and clinical data. In case of a discrepancy, the saved images were reviewed together and reevaluated to reach an agreement. Data obtained from patients with the two diseases were compared.

By our definition, the CEUS arterial phase begins with enhancement in the hepatic artery, and the peak occurs when the lesion reaches its highest echogenicity. The late phase begins when the liver parenchyma exhibits the most strongly enhanced echogenicity. Usually, the 360th second after contrast injection is defined as the end of CEUS because microbubbles are present in the liver for 6–8 min.

The CEUS features of liver lesions include the following: enhancement patterns in the arterial phase, lesion margin and shape at the peak of enhancement, lesion margin and shape in the late phase and shape and distribution of non-perfused areas inside the lesion. There were four arterial enhancement patterns observed in our data. Pattern 1 consisted of patchy enhancement when the lesion slowly filled with the contrast agent, and the lesion showed a mild increase in echogenicity with poorly defined margins. Pattern 2 consisted of centripetal enhancement when the lesion first enhanced in the periphery, which gradually moved to the center. Pattern 3 consisted of homogeneous enhancement in which the entire lesion filled quickly with the contrast agent and showed a significant increase in echogenicity compared to the adjacent liver. Pattern 4 consisted of heterogeneous enhancement, which included rapid enhancement with heterogeneous contrast distribution in the lesion and a significant increase in echogenicity compared to the adjacent liver. A feeding vessel was identified in the arterial phase when contrast was observed through the vessel from the hepatic hilum to the tumor. An area of non-perfusion was diagnosed if no contrast agent entered