Abstract

Introduction: Contrast-enhanced ultrasound (CEUS) uses second generation microbubble contrast agents and is considered to be a useful imaging method for focal liver lesions (FLLs) characterization. Aim: To observe if CEUS increases the diagnostic performance of benign FLLs as compared with standard ultrasonography examination (US). Patients and methods: This is a single centre study developed during September 2009- December 2011 in the Department of Gastroenterology and Hepatology, in Timisoara. We evaluated 386 benign FLLs diagnosed by means of CEUS. Before performing CEUS, all FLLs were examined by US and Power Doppler techniques. At CEUS, the benign nature of a lesion was established by the absence of washout in the portal and late phase. The typical features observed using contrast, allowed their classification in a particular type of pathology, according to the 2008 EFSUMB Guidelines. Results: From 386 benign FLLs, 81 (20.9%) of them were diagnosed in patients with chronic liver disease, while 305 (79.1%) were in patients without chronic hepatopathy. In 355 (92%) cases CEUS established a particular type of pathology. The most frequent lesions were: hemangiomas (37.5%), focal fatty alterations (24.8%), complex cysts (10.7%) and regenerative nodules (11.8%). Based on US we correctly estimated the positive diagnosis in 55.7% cases and using CEUS, the diagnostic performance increased up to 92%. Conclusions: In our study, by means of US the estimate positive diagnosis was made in 55.7% of cases. CEUS properly characterized 92% of benign FLLs and increased the diagnostic performance of these lesions, as compared with US.

Keywords: ultrasonography, contrast agents, benign liver lesions, vascular phases

Introduction

Contrast-enhanced ultrasound is an imaging method which uses second generation microbubble contrast agents, offering sensitive information regarding the blood flow and tissue perfusion, being utilized for the characterization of focal liver lesions. It is a safe and easily performed technique, which does not require ionizing radiation and with no risk of nephrotoxicity. This method is widely used in Europe and Asia [1].

Microbubble contrast agents are composed of tiny bubbles of an inert gas enclosed in a supporting shell, with a very good safety profile. In a retrospective study including more than 23,000 CEUS investigations from 28 Italian centres, Piscaglia et al [2] reported only two serious adverse events and no deaths.

Even if various types of FLLs exhibit very similar baseline characteristics in standard ultrasound examination, the CEUS typical patterns established by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) allow a precise diagnosis of FLL etiology [3]. The most important feature that allows the differentiation between malign and benign liver lesions is the persistence of contrast media in benign lesions in portal and late phases. The results of many published studies [4-9] report the usefulness of CEUS for the characterization of FLLs and to differentiate between malignant and benign FLLs.

Published studies showed [7, 10-12] a sensitivity and specificity higher than 95% for the diagnosis of benign liver lesions as hemangiomas, focal nodular hyperplasia or complex cystic liver lesions.
The aim of this study was to assess the usefulness of CEUS as compared with US examination for the diagnosis of benign FLLs in a large cohort of subjects.

**Patients and methods**

**Patients**

A retrospective monocentre study including 386 subjects (208 women and 178 men, mean age 54±12.5 years) with 386 benign FLLs diagnosed by CEUS was performed during a 28 month period (September 2009-December 2011).

Inclusion criteria were: FLLs identified by US and diagnosed as benign by means of CEUS.

Exclusion criteria were: FLLs in patients with/without oncologic history which presented malign FLLs documented by other imaging methods (contrast CT/MRI, biopsy), FLLs diagnosed as benign by CT and/or MRI before CEUS, FLLs which were not clearly visible on US, patients with NYHA III/IV heart failure.

All patients signed an informed consent before CEUS and the study was in accordance with the Helsinki Declaration of 1975.

**Ultrasound examination**

Ultrasound examination was performed before CEUS using a Siemens Acuson S2000™ ultrasound system (Siemens AG, Erlagen, Germany). A 3.5 MHz convex array probe was used.

Tumor location, size, echogenity and the suspected etiology of FLLs were described.

**CEUS**

CEUS was performed after performing US using a Siemens Acuson S2000™ ultrasound system (Siemens AG, Erlagen, Germany) by four experienced ultrasonographers.

CEUS was performed with a 3.5 MHz convex probe using a low mechanic index (<0.2) in order to minimize microbubble disruption. A 2.4 mL bolus of SonoVue (Bracco, Italy) was injected through a peripheral intravenous cannula, followed by a 5-mL saline flush. Lesions enhancement patterns were studied in 3 phases: arterial (10-30 seconds after injection), portal (30-120 seconds) and late phase (>120 seconds) according to EFSUMB recommendations [3]. The contrast appearance was visualized for at least 4 minutes.

The contrast vascular patterns were defined by comparing the enhancement behavior of the tumor with the surrounding liver parenchyma and were classified as follows: hyperenhancement (=the degree of enhancement of the lesion was more intense than that of the surrounding liver parenchyma), isoenhancement (=the degree of enhancement of the lesion was less than that of the surrounding liver parenchyma), rim-like enhancement (=peripheral enhancement of the lesion which was limited to less than 25% of the tumor) and wash-out (=the presence of hyper- or isoenhancement of the lesion in the arterial phase followed by hypoenhancement in the portal or late phases).

The diagnosis of different benign FLLs by CEUS was established according to typical vascular patterns presented by EFSUMB guidelines [3] (fig 1-3):

1. Hemangioma: centripetal fill-in enhancement in the arterial phase, partial/complete centripetal filling in portal phase and complete enhancement in the late phase;
2. Focal nodular hyperplasia (FNH): rapid arterial hyperenhancement with typical centrifugal radiating or “spoke-wheel” pattern, followed by homogeneous hyperenhancement in the late arterial phase with the persistence of hyperenhancement in the portal phase and iso/hyperenhancement in the late phase;
3. Hepatocellular adenoma: early and homogeneous hyperenhancement in the arterial phase, isoenhancement in the portal phase and iso/hypoenhancement in the late phase;
4. Focal fatty alterations: the same enhancement pattern with respect to the surrounding liver in all vascular phases;
5. Liver cysts: no contrast enhancement in any of the vascular phases;
6. Regenerative nodule: the same vascular pattern as the surrounding liver parenchyma in all three vascular phases;
7. Abscess: rim-like enhancement in the arterial phase, hypo/isoenhancing rim in portal phase and hypo-enhancing rim in the late phase.

**Statistical analysis**

Statistical analysis was performed using the MedCalc Software (MedCalc, Belgium). In case of numerical variables mean value and standard deviation were calculated. The Chi-square (X²) test (with Yates’ correction for continuity) was used for the comparison of two proportions expressed as a percentage. 95% confidence intervals were calculated for each predictive test. A p-value less than 0.05 was regarded as significant for each statistical test.

**Results**

All 386 FLLs presented hyper or isoenhancement in the portal or late phases being diagnosed as benign liver lesions. In 20.9% cases, the lesions were discovered in
patients with chronic liver disease, while 79.1% were in patients without underlining liver disease.

All vascular patterns expressed by benign FLLs on CEUS are presented in Table I.

In 31/386 FLLs (8%) we established their benign nature, but we could not determine a precise etiology.

The following benign FLLs were most frequent diagnosed by CEUS: hemangiomas – 133 cases (37.5%), focal fatty alterations – 88 cases (24.8%), regenerative nodules in cirrhotic patients – 42 cases (11.8%), liver cysts – 38 cases (10.7%), FNH – 23 cases (6.5%), hepatocellular adenoma – 15 cases (4.2%), abscess – 9 cases (2.5%), hematomas – 3 cases (0.9%) and necrotic areas – 4 cases (1.1%).

The estimated diagnosis using US examination coincided with the diagnosis established by CEUS in 198/355 liver lesions (55.7%).

The accuracy of US examination for diagnosis of different type of benign FLLs, as compared with CEUS as “gold-standard” method is presented in Table II.

The contribution of CEUS as compared with US for diagnosis of different type of benign FLLs is presented in Table III.

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**Table I. CEUS enhancement pattern of the FLLs included in the study**

<table>
<thead>
<tr>
<th>Vascular pattern</th>
<th>Hyper-enhanced</th>
<th>Iso-enhanced</th>
<th>Un-enhanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial phase</td>
<td>210 (54.4%)</td>
<td>138 (35.8%)</td>
<td>38 (9.8%)</td>
</tr>
<tr>
<td>Portal phase</td>
<td>174 (45.1%)</td>
<td>174 (45.1%)</td>
<td>38 (9.8%)</td>
</tr>
<tr>
<td>Late phase</td>
<td>169 (43.8%)</td>
<td>179 (46.4%)</td>
<td>38 (9.8%)</td>
</tr>
</tbody>
</table>

**Table II. The accuracy of standard ultrasound examination for diagnosis of benign liver lesions, using CEUS as “gold-standard”**

<table>
<thead>
<tr>
<th>Etiology of benign FLL</th>
<th>Nr of cases diagnosed by CEUS</th>
<th>Nr of cases suspected in standard US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemangioma</td>
<td>133</td>
<td>80 (60.1%)</td>
</tr>
<tr>
<td>Focal nodular hyperplasia</td>
<td>23</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td>Hepatocellular adenoma</td>
<td>15</td>
<td>1 (6.6%)</td>
</tr>
<tr>
<td>Focal fatty alterations</td>
<td>88</td>
<td>70 (79.5%)</td>
</tr>
<tr>
<td>Liver cysts</td>
<td>38</td>
<td>30 (78.9%)</td>
</tr>
<tr>
<td>Regenerative nodule</td>
<td>42</td>
<td>4 (9.5%)</td>
</tr>
<tr>
<td>Abscess</td>
<td>9</td>
<td>6 (66.6%)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>3</td>
<td>1 (33.3%)</td>
</tr>
<tr>
<td>Necrotic areas</td>
<td>4</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

**Fig 1.** CEUS enhancement pattern in liver hemangioma (centripetal fill-in enhancement in the arterial phase, hyperenhanced lesion in the portal and late phases)

**Fig 2.** CEUS enhancement pattern in focal nodular hyperplasia (rapid arterial hyperenhancement with “spoke-wheel” pattern in the arterial phase, hyperenhanced lesion in the portal and late phases)

**Fig 3.** CEUS enhancement pattern in focal fatty sparing (the same enhancement pattern with respect to the surrounding liver in the arterial, portal and late phases).
Discussions

Approximately 10 years ago, CEUS started to be utilized for the characterisation of focal liver lesions, now being used in the daily clinical practice in many European and Asian countries.

The German [8] and French multicentre studies [9] which included each more than 1000 FLLs evaluated by CEUS, showed approximately 95% sensitivity and 85% specificity for the differentiation between the malignant and benign nature of them. A recently published meta-analysis [13] which included 25 studies demonstrated that the summary receiver operating characteristic (SROC) curve for CEUS was similar with SROC curve for CT and MRI. Also, it was demonstrated that CEUS is a cost-effective imaging technique for the characterization of liver lesions [14,15].

Usually, benign FLLs are incidental ultrasound findings in subjects without an underlining liver disease. CEUS allows a reliable characterization and a precise etiology of a FLL in only approximately 5 minutes. Also, as compared with CT, CEUS is a non-irradiant imaging technique and the costs are significantly lower as compared with contrast CT and especially with contrast MRI. For these reasons, CEUS is the first line imaging method utilized in the case of suspected benign liver lesions in many European and Asian countries. Also, if the examination of a lesion by CEUS is conclusive, another imaging technique is not necessary.

Published studies [16-18] showed CEUS accuracy between 82% and 95% for the diagnosis of hemangioma. A similar accuracy was obtained in the case of FNH [19,20].

In our present study, the most common type of benign FLLs found in daily practice was hemangioma (37.5%), being in line with the results of other published studies [8,9,21], but as compared with the previously specified studies, the percentages of hepatocellular adenoma and FNH were lower in our cohort of subjects.

A precise etiology of benign liver lesions could the established in 92% of our FLLs, the results being similar with other published studies [17,22].

As compared with US examination, CEUS brought us supplementary information which allowed a precise characterization of FLLs in 44.3% of cases, our results being similar with these published by Wilson et al [23].

The most important contribution of CEUS, in comparison with US was observed for the diagnosis of hepatocellular adenoma and regenerative nodules in cirrhotic patients (>90% of cases were diagnosed only after CEUS), while in the case of fatty liver alterations and liver cysts, CEUS brought supplementary data in only 20% of cases.

| Table III. Comparison between CEUS contribution vs standard US for diagnosis of different type of benign liver lesions |
|--------------------------------------------------|-----------------|-----------------|
| Focal liver lesions                              | CEUS contribution for diagnosis | p value        |
| Hemangiomas vs. fatty liver alterations          | 39.9% vs. 20.5% | 0.004          |
| Hemangiomas vs. liver cysts                      | 39.9% vs. 21.1% | 0.06           |
| Hemangiomas vs. FNH                              | 39.9% vs. 73.9% | 0.005          |
| Hemangiomas vs. hepatocellular adenoma           | 39.9% vs. 93.4% | <0.0002        |
| Hemangiomas vs. regenerative nodules             | 39.9% vs. 90.5% | <0.0001        |
| Fatty liver alterations vs. liver cysts          | 20.5% vs. 21.1% | 0.87           |
| Fatty liver alterations vs. FNH                   | 20.5% vs. 73.9% | <0.0001        |
| Fatty liver alterations vs. hepatocellular adenoma| 20.5% vs. 93.4% | <0.0001        |
| Fatty liver alterations vs. regenerative nodules | 20.5% vs. 90.5% | <0.0001        |
| FNH vs. hepatocellular adenoma                   | 73.9% vs. 93.4% | 0.27           |
| FNH vs. regenerative nodules                     | 73.9% vs. 90.5% | 0.15           |
| Hepatocellular adenoma vs. regenerative nodules  | 93.4% vs. 90.5% | 0.84           |
| Liver cysts vs. FNH                              | 21.1% vs. 73.9% | 0.0001         |
| Liver cyst vs. hepatocellular adenoma            | 21.1% vs. 93.4% | <0.0001        |
| Liver cysts vs. regenerative nodules             | 21.1% vs. 90.5% | <0.0001        |


Conclusions

CEUS is a good diagnostic tool for benign liver lesions, bringing additional information in 44.3% cases as compared with US examination. Also, CEUS established a precise type of benign FLLs for most of the subjects (92%).

Conflict of interest: none

References