Contrast-enhanced ultrasound for the assessment of focal nodular hyperplasia – results of a multicentre study

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Abstract

Aim: Contrast-enhanced ultrasound (CEUS) has become a relevant imaging method for the evaluation of focal liver lesions (FLL). The aim of this study was to evaluate the performance of CEUS for the assessment of focal nodular hyperplasia (FNH) in a large study group. **Material and methods:** We performed a multicentre prospective observational study, which included successive CEUS examinations from fourteen Romanian centres. CEUS examinations were performed in de novo FLL, using low mechanical index ultrasound, following an intravenous bolus of 2.4 ml SonoVue. CEUS was considered conclusive for FNH if a typical pattern was present following contrast (rapid “spoke-wheel” enhancement during the arterial phase, hyperenhanced lesion during venous phase, hyper- or iso-enhanced in the late phase). In all cases a reference method was available (contrast enhanced CT or MRI or biopsy). The trial was registered in clinicaltrials.gov (Identifier NCT01329458). **Results:** During the 6 years study, 2062 “de novo” FLL were evaluated by CEUS. From this cohort, 94/2062 (4.5%) had a typical enhancing pattern for FNH as described in the EFSUMB guidelines. Contrast enhanced CT/MRI and biopsy diagnosed additional 15 FNH. From the 94 cases diagnosed as FNH by CEUS, in nine the final diagnosis was different (five of them adenomas). CEUS had 85% sensitivity, 99.5% specificity, 90.4% positive predictive value, 99.2% negative predictive value and 98.8% diagnostic accuracy for the diagnosis of FNH. **Conclusions:** CEUS is a sensitive and very specific method for the diagnosis of FNH.

Keywords: Contrast Enhanced Ultrasound; focal liver lesions; focal nodular hyperplasia; multicentre study

Introduction

Focal nodular hyperplasia (FNH) is the second most frequent benign liver tumour with a 3% estimat-

ed prevalence, more frequent in women (female: male prevalence 4:1) [1]. It is not really a tumour but a regenerative nodule as a reaction to a vascular congenital abnormality [2,3]. Most frequently it is discovered by chance by conventional ultrasound in asymptomatic women younger than 50, in 80-95% of cases as a solitary lesion, but in some cases multiple FNH can be found [4]. Considering their higher prevalence in women and the fact that they enlarge in women who use contraceptive drugs, FNH seems to be influenced by the hormone balance, even if hormones are not involved in their pathogenesis.

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From a pathological point of view, FNH include normal liver structures but with abnormal architecture. Typical for FNH is a fibrous scar (located in the centre, more rarely in the periphery), which includes an artery larger than usual, originating outside the nodule. This vascular disorder generates a regenerative nodule, which lacks the central terminal hepatic vein and has only capillarized sinusoids derived from the feeding artery [2]. This type of vascularization generates the typical aspect of FNH in contrast imaging.

On contrast enhanced ultrasound (CEUS), FNHs are hyper-vascular, appearing homogeneously hyper-enhancing in the arterial phase, with very rapid and centrifugal fill-in. This “spoke-wheel” pattern is essential for differentiating FNHs from adenomas, from hyper-vascular malignant lesions, or from high-flow haemangiomas [5,6]. An eccentric feeding vessel may be seen in approximately 30% of cases. Usually, FNHs are hyperenhancing in the portal phase and hyper or isoenhancing in the late phase [5,6]. The central scar can appear as hypoenhancing in the late phase [6,7]. At contrast enhanced-CT, FNH is hyperdense with an isodense aspect during the portal-venous phase. A hyperdense central scar is commonly seen in the late phase [8]. On unenhanced MRI, FNHs appear as isointense on T1-weighted images and iso- to slightly hyperintense on T2-weighted images [9]. The MRI aspect of FNH following liver-specific contrast is of a hyperintense lesion in the initial phase with an isointense aspect in the delayed phase, the central scar being enhanced in the late phases [10].

FNHs are usually asymptomatic, being discovered during routine conventional US examination. Finding a focal liver lesion (FLL) can be highly stressful for the patient and thus all available methods should be performed to elucidate its nature. FNH’s B-mode aspect is uncharacteristic; it can be isoechoic, slightly hyper- or hypoechoic, with the central scar visible in 70-80% of cases [11]. Baseline colour Doppler ultrasound can reveal the central vessel, originating from the centre to the periphery with a low resistance index and a high flow pattern [7].

In the latter years, CEUS has become a reliable imaging method for the evaluation of focal liver lesions. International and national guidelines define precise criteria for the diagnosis of FNH [6,12]. The aim of this study was to evaluate the performance of CEUS for the assessment of focal nodular hyperplasia in a large, prospective multicentre study, to collect useful information for the practitioner.

Material and methods

We performed a multicentre prospective observational study, during a 6-year period (April 2011-June 2017),

which included successive CEUS examinations from eight university centres (14 individual departments). The trial was registered in clinicaltrials.gov (Identifier NCT01329458).

Patients

We included consecutive patients (older than 18 years), with newly discovered FLL during B-mode irrespective of the FLL size. In all patients, B-mode ultrasound was performed followed by CEUS. Also, in all patients a second line imaging method (contrast enhanced CT or MRI) or a biopsy were available, considered as the reference method. Most MRI imaging studies were performed using gadolinium based contrast media. Only in inconclusive cases hepato-specific contrast media was used. Demographic data, history of chronic hepatitis or of previous cancers, as well as data regarding the indication for CEUS were recorded.

The exclusion criteria were: contraindications for CEUS (acute myocardial infarction, class III/IV heart failure, rhythm disorders, pregnant women); patients who refused to participate; easy to diagnose FLL by conventional US, such as simple cysts or hydatid cysts, multiple lesions suggestive for liver metastases, patients with known FLL (hepatocellular carcinoma following percutaneous treatment, follow-up of patients with known metastasis or other FLLs, etc.); patients in whom biopsy or second line sectional imaging methods were unavailable.

A dedicated website was developed (<http://study.umfcv.ro>) for this study. Data were registered online for each individual patient.

Informed consent for CEUS was obtained from every patient. The study protocol was approved by the local Ethical Committee of each centre and was in accordance with the Helsinki Declaration of 1975.

Conventional and contrast-enhanced studies

In each patient, B-mode US and CEUS were performed with the same high-end ultrasound machine (different for each centre) able to perform low-mechanical index examinations. We documented the type of ultrasound machine, the name of the operator and the amount of contrast agent used. CEUS was performed by experts from each centre (levels II and III according to the EF-SUMB classification), who were blinded to the CT/MRI or histology results.

Convex probes using a low mechanic index (0.09-0.11) were used. The US scan parameters (ie. focal zone, time gain compensation) were not changed during the CEUS study. One focus was placed below the lesion. We documented for each FLL the number, size, placement and US aspect on conventional B-mode ultrasound.

The contrast agent used was SonoVue® (Bracco SpA, Milan, Italy), a perfluoro gas containing agent, as

Fig 1. a) Slightly hypoechoic FLL in the right liver lobe. b) The FLL shows “spoke-wheel” pattern on Doppler US. c) CEUS, arterial phase – the lesion is completely hyperenhanced 11 seconds after bolus injection – excentric feeding artery also visible. d) CEUS, portal phase – the lesion is slightly hyperenhancing with visible central scar. e) CEUS, late phase – the lesion is iso/hyperenhancing with well visible central scar (arrow).

per standard protocol [6,12]. Lesions’ enhancement patterns were studied in 3 phases: arterial (10-30 seconds following contrast bolus), portal (30-120 seconds) and late phase (>120 seconds) [6,12]. In each patient, the contrast study duration was at least 5 minutes after bolus injection. To document the study, four video files no longer than 30 seconds each were captured, containing conventional B-mode examination, the arterial phase, the portal phase and the late phase.

CEUS vascular patterns were defined by comparing the FLL’s enhancement pattern to the surrounding liver parenchyma. We classified CEUS vascular patterns as: homogeneous hyperenhancement (the whole FLL showed homogeneous enhancement); heterogeneous hyperenhancement (mixed irregular areas of contrast enhancement were present); rim-like hyperenhancement (a peripheral hyperenhancement limited to less than 25% of the tumour); iso-enhancement (the FLL enhanced the same as the adjacent parenchyma from the same depth); hypoenhancement (the lesion enhanced less than the adjacent parenchyma at the same depth); wash-out (hypoenhancement in the portal or late phases preceded by hyper or iso-enhancement in the arterial phase).

A CEUS diagnosis of FNH was established after the contrast study based on the patterns described in guidelines [6,12]: rapid “spoke-wheel” enhancement during the arterial phase, hyperenhanced lesion during the ve-

nous phase, hyper or iso-enhanced lesion in the late phase, sometimes with the visualization of a central hypoechoic scar (fig 1). A CEUS examination was considered conclusive if the FLL had a typical enhancement pattern according to national and international guidelines [6,12] and inconclusive if not. The CEUS diagnosis was compared with the final diagnosis established based on all available imaging and clinical data: contrast enhanced CT, and/or MRI, and/or histology.

Statistical analysis

Statistical analysis was performed using the GraphPad Prism program, version 7.02 (GraphPad Software, La Jolla, USA). We assessed the accuracy of CEUS for FNH characterization. The sensitivity (Se) was calculated as true positive cases divided by the total number of cases in which the disease was present; the specificity (Sp) was calculated as true negative cases divided by the total number of cases in which the disease was absent; the positive predictive value (PPV) was calculated as true positive cases divided by all CEUS positive cases; the negative predictive value (NPV) was calculated as true negative cases divided by all CEUS negative cases and accuracy was calculated as the sum of true positive and true negative cases divided by the total number of cases. We included in the statistical analysis all cases reported; we considered the inconclusive CEUS cases as wrongly diagnosed.

Results

During the 6 years study, 2062 “de novo” FLL were evaluated by CEUS. Patients’ characteristics are presented in Table I.

From this cohort, 94/2062 (4.5%) had a typical enhancing pattern for FNH. Contrast enhanced CT/MRI and biopsy diagnosed additional 15 FNH (12 in cases labelled as inconclusive on CEUS and one each labelled by CEUS as haemangioma, adenoma and metastasis). From the 94 cases diagnosed as FNH by CEUS, in nine cases the final diagnosis was different (five of them adenomas, two of them hepatocellular carcinomas, one haemangioma and one focal fatty infiltration). Thus, the final diagnosis was FNH in 100 of the 2062 (4.8%) cases. The characteristics of patients with FNH are presented in Table II.

The indication for CEUS was in most FNH cases an incidentally found FLL 98% (98/100), in 1% (1/100) case it was the evaluation of a patient with known oncologic disease and in 1% (1/100) case it was an inconclusive CE-CT scan. At the moment of CEUS examination, none of the patients diagnosed by CEUS with FNH were known with underlying liver disease. However, two of them were later diagnosed with underlying cirrhosis and 2 with chronic hepatitis.

CE-MRI was the gold standard in 30% (30/100) cases. In 6% (6/100) patients histology was available – one of them after surgery performed for HCC.

By comparing CEUS with the reference method (either CE-CT, CE-MRI or histology) CEUS had 85% Se, 99.5% Sp, 90.4% PPV, 99.2% NPV and 98.8% diagnostic accuracy for the diagnosis of FNH.

Discussion

Focal liver lesions (FLLs) are frequently discovered during conventional B mode ultrasound (US) examination, either during a routine scan for various abdominal symptoms or during the follow-up of chronic liver disease or of oncologic patients. In most cases, only B mode US is not sufficient for a definite diagnosis. This is particularly true when FNH is involved, since its appearance is totally uncharacteristic, sometimes isoechoic, or slightly hyper- or hypoechoic, the most suggestive for the diagnosis being the central scar, which is visible only in 70-80% of cases [8,10,11]. Thus, a contrast imaging method or a histopathological exam are required to reach a final diagnosis. The time needed for scheduling, and the costs of contrast enhanced CT or contrast enhanced MRI are not negligible, the same is true regarding guided biopsy, which is also an invasive procedure. On the other

Table I. Patients’ characteristics

Number of patients	2062
Mean age (years)	52.4±7.5
Gender, women	914 (44.3)
Underlying chronic liver disease	727 (35.3%)
CEUS diagnosis	
Hepatocellular carcinomas	685 (33.2)
Hemangiomas	452 (21.9)
Metastases	418 (20.3)
Focal nodular hyperplasias	94 (4.5)
Regenerative nodules	84 (4.1)
Focal fatty infiltrations	70 (3.4)
Cholangiocarcinomas	57 (2.7)
Abscesses	45 (2.2)
Complex Cysts	43 (2.1)
Other benign lesions*	37 (1.8)
Adenomas	32 (1.6)
Fatty free areas	26 (1.3)
Other malignant lesions**	19 (0.9)

The results are expressed as number, number (%) or mean±SD. * pseudolesion, scar area, angiomyolipoma, hamartoma; ** lymphoma, hemangiosarcoma, hepatic epithelioid hemangioendothelioma.

Table II. The characteristics of patients with focal nodular hyperplasia (FNH)

Number of patients with FNH	100
Mean age	40.4±13.7 years
Gender, women	75 (75)
Underlying chronic liver disease	4 (4)
Size:	
≤ 35 mm	39 (39)
≥ 36 mm	61 (61)

The results are expressed as number (%) or mean±SD

hand, CEUS can be performed immediately after a conventional B mode US examination and thus a diagnosis can be established in minutes.

CEUS is a real-time imaging technique, which, similar to contrast enhanced CT or MRI, shows tissue perfusion, and is able to identify the type of FLL based on the enhancement pattern in arterial, portal and late vascular phases. The value of CEUS for the differential diagnosis of FLLs was proved in a German national multicentre study (DEGUM study) [13] and in a French national multicentre study (STIC study) [14], each including more than 1000 FLL and later in a Romanian multicentre study [15]. Meta-analyses demonstrated that CEUS accuracy is similar to contrast enhanced CT and MRI [16-18].

Other advantages of CEUS as compared with CT and MRI are the absence of radiation exposure (as in CT examination) and of side effects (no nephrotoxicity, no iodine exposure), and the lower costs [19,20]. Limitations of CEUS are linked to the limitations of US (poor acoustic window, uncooperative patients) and to the lesion’s

depth, since FLL located at more than 9 cm from the skin are difficult to examine due to attenuation [6,12]. However, if we compare the methods, we discover from the study of Bröker et al [21] that in a direct comparison between MRI with liver specific contrast and CEUS, MRI performed better than CEUS for the diagnosis of FNH and hepatocellular adenoma, CEUS having a sensitivity and specificity of 85% and 87%, positive predictive value (PPV) of 79% and negative predictive value (NPV) of 90%, while MRI reached 95% sensitivity, 95% specificity, 92% PPV and 97% NPV.

The first guidelines regarding the use of CEUS were issued in 2004 by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) [22], which were revised in 2008 [23], in 2012 [6] and in 2020 [24], the last two developed in cooperation with the World Federation for Ultrasound in Medicine and Biology (WFUMB), thus with universal validity. Regarding the dose of SonoVue, guidelines recommend the use of 2.4 ml (1/2 vial) for the characterization of FLL, even if in the last years, with the development of more performant US machines, doses as low as 1.2 ml are frequently used [25]. A too high dose can lead to apparition of artifacts (shadowing, over-enhancement of small structures and signal saturation, as well as “drowning” of small lesions in the signal of adjacent structures). A too low dose can lead to an insufficient quantity of microbubbles in the late phases, so that the wash-out cannot be observed. However, if the dose is not optimal, the injection can be repeated, with a higher or lower dose, as needed [25]. Furthermore, to better evaluate the wash-out, insonation can be avoided in the arterial and portal phase of the reinjection, especially useful for diagnosis of hepatocellular carcinoma [26].

According to published data, CEUS is an accurate method to characterise FNH. In the DEGUM study the accuracy for FNH was 95.5% [27], with 57.1% Se and 99.3% Sp. In the STIC study, CEUS had 82.5% Se and 94.3% Sp for the diagnosis of FNH [14]. The calculated pooled sensitivity for FNH was 88% in the Friedrich-Rust et al meta-analysis [18] and the Sp can go as high as 100% [14,28]. In another study that evaluated the accuracy of CEUS performed by two operators for the diagnosis of 85 biopsy proven FNH, CEUS had 80.9% Se, 95.7% Sp, 95.0% PPV, 83.3% NPV and 88.3% accuracy for operator one and 78.7% Se, 93.6% Sp, 92.5% PPV, 81.5% NPV and 86.2% accuracy for operator two. This study concluded that CEUS performed better than contrast enhanced CT for characterizing dynamic centrifugal filling or the “spoke-wheel” sign in small lesions [29].

In our study, the performance of CEUS to diagnose FNH was very good with excellent Sp (99.5%) and ac-

curacy (98.8%) and a slightly lower Se (85%). Regarding the misdiagnosed cases, most confusions were made with adenomas. Five cases diagnosed by CEUS as FNH were in fact adenomas and one case diagnosed by CEUS as adenoma was in fact FNH. The confusion is probably understandable since both types of FLL show rapid hyperenhancement in the arterial phase, but in adenoma the fill-in occurs initially at the periphery with very rapid centripetal filling, as opposed to the centrifuge filling seen in FNH.

Arterial phase can be better evaluated using parametric arrival time (PAT), a post processing modality of evaluation. In the portal phase, adenoma usually becomes isoechoic or, more rarely, remains slightly hyperechoic. Sometimes, in adenomas the washout occurs in the late phase, thus being false positive for malignancy [6,12]. The imaging diagnosis of adenoma is very difficult and often guided biopsy is needed. In the DEGUM study, CEUS correctly diagnosed 57.9% of the adenomas [13]. Computer-assisted diagnosis can also be used to improve the accuracy of differential diagnosis by CEUS between FNH and adenoma [30].

In the Roche et al study [31] were included 43 FNH and 20 adenomas, most lesions diagnosed based on the histopathological exam. The conclusion of this study was that CEUS had excellent Sp for diagnosing FNH (100%), but the Se varies according to the lesion's size: 93% for lesions ≤ 35 mm and 7.7% for lesions > 35 mm, the overall Se being 67.4 %. The authors explained this observation by the fact that larger FNH have an increased vascular supply and several feeding arteries and thus, the typical spoke-wheel pattern is not visible. The same observation, that FNHs with signs of centrifugal filling were smaller than those without the sign (3.1 ± 1.5 cm vs. 5.2 ± 3.2 cm, $p=0.000$) was made in the study by Wang et al [29]. In our study, the five FNH misdiagnosed as adenomas were 2.5 cm, 6 cm, 6 cm, 3 cm, 7.5 and 3.2 cm in diameter, respectively.

Even if both adenoma and FNH are benign lesions, it is important to be differentiated since in adenoma there is a risk of rupture (and subsequent bleeding) or malignant transformation.

MRI with liver specific-contrast seems to outperform CEUS in differentiating FNH from hepatocellular adenoma. In a study by Grazioli et al, MRI had 96.9% Se, 100% Sp, 100% PPV, 96.4% NPV, and 98.3% overall accuracy [32].

Two FLL diagnosed by CEUS as FNH proved to be hepatocellular carcinomas (HCCs). Both types of lesions have arterial hyperenhancement but in HCC there is a chaotic pattern [6,12]. Usually, HCCs show mild, late, or very late washout, correlated with the differentiation of

the tumour [33,34]. Well-differentiated HCCs show very late or no washout, thus the CEUS examination should take at least 4-5 minutes [35]. Thus, in well-differentiated HCCs, the CEUS aspect can be similar to that of FNH but there is a very important factor that should be taken into consideration: up to 90% of HCCs occur on a background of chronic liver disease with severe fibrosis and cirrhosis [36]. US based elastography, available in most US machines able to perform CEUS, should be used to rule in or rule out the presence of cirrhosis in a point of care US evaluation [37]. Thus, it is important to keep in mind that a new lesion on a cirrhotic liver, hyperenhancing in the arterial phase on CEUS, is probably HCC [35,38]. Computer assisted diagnosis [39] as well as parametric imaging could be used to improve the differential diagnosis by CEUS between FNH and HCC, the mean transit time being significantly longer in FNH than in HCC [40].

Both HCCs misdiagnosed as FNH were in patients with incidentally discovered FLL, who were not known with chronic liver disease, but in whom, starting from the HCC, compensated liver cirrhosis was diagnosed.

A limitation of our study is that the pathological exam was available only in a small number of cases (only 7 of the 100 FNH), but an advantage is the large number included and the prospective design of the study.

In **conclusion**, CEUS is an accurate method to diagnose FNH, the main difficulties occurring in differentiating FNH from adenomas, especially in large lesions.

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