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Contrast enhanced ultrasound for the diagnosis of liver hemangiomas – results of a Romanian multicentre study.

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Abstract

Background and aim: Contrast enhanced ultrasound (CEUS) has been proven to be a reliable method for the characterization of focal liver lesions (FLL). The aim of this paper was to evaluate the performance of CEUS for the diagnosis of liver hemangiomas in a large cohort of patients. **Material and method:** We performed a multicentre prospective study which included successive CEUS examinations from fourteen centers from Romania. 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 hemangioma if a typical pattern was present following contrast (centripetal fill in during the arterial phase, hyperenhanced lesion during venous and late phases). In all cases a reference method was available (contrast CT or MRI or biopsy). The trial was registered in clinicaltrials.gov (Identifier NCT01329458). **Results:** During February 2011 – May 2015, 1153 CEUS examinations were performed for the evaluation of de novo FLL. Out of the 1153 de novo FLL, 238 cases were diagnosed as hemangiomas by CEUS (typical enhancing pattern). Contrast CT/MRI and biopsy diagnosed additional 24 hemangiomas. From the 238 cases diagnosed as hemangiomas by CEUS, in 11 the final diagnosis was different. Considering contrast CT/MRI and biopsy as reference methods, CEUS had 90.4% sensitivity, 98.8% specificity, 95.4% positive predictive value, 97.4% negative predictive value, resulting in 96.9% diagnostic accuracy for the diagnosis of hemangiomas. **Conclusion:** CEUS is a sensitive and very specific method for the diagnosis of hemangiomas.

Keywords: Contrast Enhanced Ultrasound, focal liver lesions, hemangiomas

Introduction

Focal liver lesions (FLLs) are frequently found in clinical practice due to the widespread use of ultrasonography (US), either during a routine examination or during the follow-up in chronic hepatitis or in oncologic patients. Of course, a new FLL is a major concern for the patient and for the physician. Standard B mode US is not enough to establish a final diagnosis, excepting cystic lesions (simple cysts and some types of hydatid cysts) and focal fatty lesions [1]. Color and spectral Doppler US don't add much to the diagnostic of FLL since their ability to detect blood flow at the perfusion level is limited, even if they provide important information regarding the directional blood flow in large vessels. Until a decade ago differential diagnosis among different types of FLLs could be made by contrast enhanced Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), or by biopsy, each one with their advantages, but all sharing the same disadvantage: the time needed to reach a final diagnosis (scheduling issues as well as the time needed to prepare and examine a tissue specimen in biopsies).

Contrast enhanced ultrasonography (CEUS) is a real-time imaging technique, that can be performed immediately after a standard US examination, thus it is able to provide a reliable diagnosis a few minutes after the FLL is discovered. Similar to contrast agents used for CT or MRI, second generation US contrast agents are able

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to show tissue perfusion, and, based on enhancement patterns in arterial, portal, and late vascular phases, to identify different types of FLLs. The value of CEUS in diagnosing FLLs was demonstrated in two national multicentre studies (a German and a French one) [2,3], each including more than 1000 FLL, while CEUS accuracy was proved to be similar to those of contrast enhanced CT and MRI [4,5]. Furthermore, in 2004 the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) issued Guidelines and Recommendations concerning the use of CEUS [6] revised in 2008 [7] and in 2012 [8], the later developed in cooperation with the World Federation for Ultrasound in Medicine and Biology (WFUMB), thus with universal valability.

Hemangioma is the most frequent benign liver tumor, the prevalence varying according to different authors from 1-2% [9] to 20% [10], more frequent in women than in men (women:man ratio ranging from 2:1 to 5:1) [11]. They are often solitary, but in 40% of cases multiple lesions can be found in both liver lobes [12], with diameters ranging from a few millimeters to 15-20 cm, those larger than 5 cm being known as giant hemangiomas [13].

Hemangiomas are considered to be hamartomas, congenital vascular malformations resulting from the abnormal proliferation of endothelial cells, with incompletely understood etiology, but with certain hormonal influence on tumor growth (hemangiomas enlarge during pregnancy and estro-progestative treatment) [14,15]. Other suggested etiologic factors are genetic predisposition [16] as well as an autoimmune mechanism [17].

Microscopically, hemangiomas are composed of cavernous vascular spaces lined by a single layer of flat endothelium, filled with blood, separated by thin fibrous septae. The vascular spaces vary in size and may contain thrombi. In large hemangiomas collagenous scars or fibrous nodules may appear due to thrombosis [18].

Most hemangiomas are asymptomatic, being an incidental finding. Large hemangiomas can cause symptoms such as fullness, discomfort and pain in the right upper quadrant [19]. Acute abdominal pain in a patient with a large hemangioma should be suggestive of thrombosis or bleeding within the tumor and may be accompanied by abnormal liver function tests and fever [20].

In B mode US, hemangiomas typically appear as hyperechoic, well defined lesions, with or without small central regions with decreased echogenicity [21,22]. Another appearance highly suggestive of hemangioma is of a hypo- or isoechoic mass with hyperechoic periphery [23], an aspect encountered also in patients with fatty infiltration. Color Doppler does not improve the accuracy of B mode US since hemangioma blood flow can be seen by color Doppler only in 10 – 50 % of cases [24]. The same US aspect can be encountered in some malignant lesions, thus contrast second line imaging methods are needed to confirm the diagnosis, especially in high risk patients, such as cirrhotics or oncologic patients, in which a new FLL is found.

Until a few years ago available second line imaging methods were only contrast enhanced CT or MRI and Technetium-99m pertechnetate-labeled red blood cell pool studies. In recent years, CEUS became a valuable alternative of these techniques. **The aim** of this paper was to evaluate the performance of CEUS for the diagnosis of liver hemangiomas in a large cohort of patients.

Material and methods

A multicenter prospective study was conducted during 51 months (1st of February 2011 – 15th of May 2015) in 8 university centers (14 individual departments), and the trial was registered in clinicaltrials.gov (Identifier NCT01329458).

Patients

The study included consecutive patients (older than 18 years), with one to three newly discovered FLL during B-mode US, regardless of the FLL size. In all patients CEUS was performed and a second line imaging method (contrast CT or MRI) or biopsy were also available, considered to be the reference method. In all patients demographic data, as well as data regarding indication for CEUS, history of chronic hepatopathy or oncologic diseases were recorded.

We excluded from the study: patients who did not agree to participate; patients with contraindication for CEUS (acute myocardial infarction, class III/IV cardiac insufficiency, significant rhythm disorders, pregnant women); patients diagnosed with simple cysts or with hydatid cysts by B-mode ultrasound; patients with known FLL (hepatocellular carcinoma following percutaneous treatment, follow-up of patients with known metastasis or other FLLs, etc); patients in whom second line imaging methods or biopsy were unavailable.

A dedicated website (http://study.umfcv.ro) was developed by the University of Medicine and Pharmacy of Craiova for this study, and the collected data were registered online for each individual patient.

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

Conventional and contrast-enhanced studies

B-mode US and CEUS were performed in each patient with the same ultrasound machine. Different ma-

chines were used in different centers, but all had capabilities for low-mechanical index examinations. The amount of contrast agent, as well as the type of ultrasound machine and the operator, were also documented. All contrast studies were performed using dedicated contrast software of each ultrasound machine. CEUS was interpreted by experts from each center, which were blinded to the CT/MRI or histology results.

The number, size, location, and ultrasound pattern of FLL were documented after B-mode ultrasound. CEUS was performed with convex probes using a low mechanic index (0.09-0.11) in order to minimize microbubble disruption. Once set, the US scan parameters – such as focal zone and time gain compensation – were not changed throughout the study. One focus was positioned below the lesion.

The contrast agent used was SonoVue® (Bracco SpA, Milan, Italy), a perfluoro gas containing agent, provided as a sterile, lyophilized powder contained in a septum-sealed vial. Usually 2.4 mL of SonoVue® were injected through a peripheral intravenous cannula of sufficient size, followed by a 10-mL saline flush, as per standard protocol [7,8]. 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 [7,8]. The contrast study for each patient lasted 5 minutes after bolus injection and was documented by at least 4 video files no longer than 30 seconds each, containing: B-mode examination, the arterial phase, the portal phase, and the late phase.

The contrast vascular patterns were defined by comparing the FLL's enhancement behavior to the surrounding liver parenchyma and were classified as: homogeneous hyperenhancement – the whole FLL showed global homogeneous contrast enhancement; heterogeneous hyperenhancement – the FLL presented mixed irregular areas of contrast enhancement; rim-like hyperenhancement – a peripheral hyperenhancement limited to <25% of the tumor's diameter; isoenhancement – the FLL enhanced similarly to the adjacent parenchyma at 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 hemangioma was established after the contrast study based on the patterns described in the EFSUMB guidelines [7,8]: centripetal fill-in in the arterial phase, partial/complete centripetal filling and sustained enhancement in portal and late phases (fig 1). A CEUS examination was considered conclusive if, following contrast, the FLL had a typical enhancement pattern according to the EFSUMB guidelines [7,8], and inconclusive if the enhancement pattern was not in concordance with these guidelines. The CEUS diagnosis was compared with the final diagnosis which was established based on all available imaging and clinical data: contrast enhanced CT, and/or MRI, and/or histology.

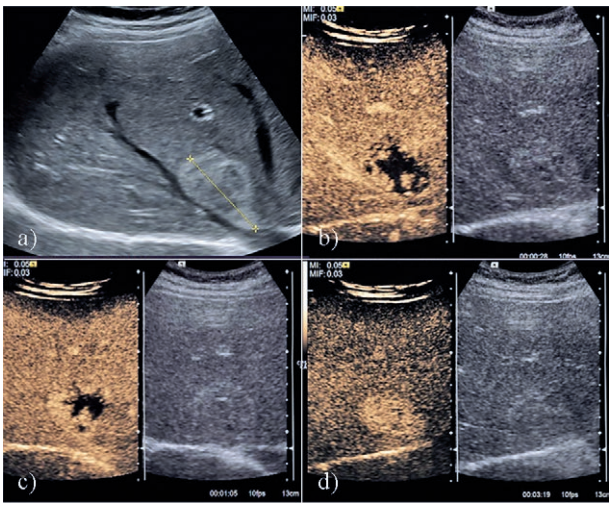

Fig 1. a) Hyperechoic, well delineated inhomogeneous nodule, situated in segment VIII of the liver; b) CEUS – arterial phase: nodular, peripheral enhancement of the nodule can be observed; c) CEUS – portal phase: centripetal peripheral enhancement continues; d) CEUS – late phase: the nodule is completely filled and hyperenhancing.

Statistical analysis

Statistical analysis was performed using the MedCalc program (MedCalc Software, version 12.3.0, Belgium). The accuracy of CEUS for FLLs' characterization was assessed in terms of lesion status and specific lesion type. 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, while the inconclusive CEUS cases were considered as wrongly diagnosed.

Results

During February 2011 – May 2015, 1153 CEUS examinations were performed for the evaluation of de novo FLL. Out of the 1153 de novo FLL, 238 cases were di-

agnosed as hemangiomas by CEUS (typical enhancing pattern). Contrast CT/MRI and biopsy diagnosed additional 24 hemangiomas (17 in inconclusive CEUS cases, 4 in cases diagnosed as hepatocellular carcinomas by CEUS, 2 in cases diagnosed as focal fatty infiltration by CEUS and 1 in a case diagnosed as dysplastic nodule by CEUS). From the 238 cases diagnosed as hemangiomas by CEUS, in 11 the final diagnosis was different: in 5 cases hepatocellular carcinoma, in 1 case adenoma, in 1 case focal nodular hyperplasia, 1 case dysplastic nodule, 1 case inflammatory lesion, 2 cases inconclusive.

Considering contrast CT/MRI as reference method, CEUS had 90.4% sensitivity, 98.8% specificity, 95.4% positive predictive value, 97.4% negative predictive value, resulting in 96.9% diagnostic accuracy for the diagnosis of hemangiomas.

Discussions

As showed above, hemangiomas are the most frequent benign tumors of the liver and thus frequently discovered in clinical practice, either during a "routine" US examination performed for unrelated pathology, or during the initial evaluation or follow up in patients with chronic hepatitis or oncologic diseases. Even if the B-mode US appearance of hemangioma is "typical" in most cases, the same US aspect can be found in patients with hepatocellular carcinoma (HCC) or liver metastases. Thus, a FLL suspected to be a hemangioma based on "typical" B-mode US aspect, found in a patient with liver cirrhosis (a risk factor for HCC) or with a malignant tumor (regardless of the primary location) should undergo a second-line imaging technique to confirm the diagnosis. In patients with no such history it is acceptable to repeat B-mode US after three or six months to document the FLL's stable aspect. Also, patients with known hepatic hemangioma who subsequently develop liver disease or extrahepatic malignancy should be further evaluated by second-line imaging methods [25].

Until recently, contrast enhanced CT and MRI were considered the best second-line imaging methods to confirm an US diagnosis of hemangioma. MRI is considered to be the best method since it is non-invasive and highly accurate, with approximately 90% sensitivity and 91-99% specificity [26]. The typical MRI appearance in hemangioma is a smooth, well-demarcated homogeneous mass that has low signal intensity on T1-weighted images and is hyperintense on T2-weighted images [26]. The presence of intratumoral fibrosis results in areas of low intensity on T2-weighted images. Administration of gadolinium results in early peripheral discontinuous nodular or globular enhancement on arterial phase with progressive centripetal enhancement or "filling-in" on delayed scans similar to that seen on CT scanning [25].

Technetium-99m pertechnetate-labeled red blood cell pool study (99mTc-RBC pool studies) is another technique useful for the diagnosis of hemangioma. Initial hypoperfusion is observed during arterial flow, followed by gradual increase of tracer peaking 30 to 50 minutes after the injection. The isotope is retained within the lesion on delayed images. Sensitivity of 99mTc-RBC pool studies for FLL larger than 2 cm varies from 69 – 92%, with almost 100% specificity [27].

Considering that contrast enhanced imaging methods are highly accurate for the diagnosis of hemangioma, biopsy is performed only in cases in which imaging techniques are not conclusive. According the American College of Radiology guidelines, liver biopsy should be performed only in indeterminate (after contrast CT/MRI) liver lesions >1 cm in diameter, in patients with a history of malignancy or of chronic liver disease [28]. Even if complications, especially bleeding, can occur following hemangioma biopsy, once the typical vascular hemangiomas are excluded, there is a surprisingly low risk of significant complications in atypical hemangiomas. The reason may be that thrombosis or fibrosis in the lesion, which makes the imaging appearance atypical, also reduces the potential for bleeding complications [29]. Ultrasound-guidance, normal bleeding parameters, suitable trajectory planning via a small cuff of normal liver may all contribute to the low complication rate [30].

Contrast CT and MRI are expensive and available only in specialized centers. CT is also an irradiating procedure, while contrast agents used for CT can trigger or worsen renal failure. SonoVue microbubbles are strictly intravascular (as opposed to contrast agents in CT and MRI that diffuse into the interstitium) and include hexafluoride sulfur, a biologically inert gas that is cleared through exhalation (not through the kidney as CT or MRI contrast agents), therefore it is not contraindicated in patients with renal failure [6-8].

Published data showed very good results regarding the diagnostic performance of CEUS for hemangioma. In the German multicentre study that included 1,349 patients with FLL in which CEUS was compared with biopsy in more than 75% of lesions, or with spiral contrast CT or contrast MRI, CEUS correctly diagnosed 82.2% of hemangiomas [2]. In the multicentre French study (STIC), which included 1034 FLL and in which CEUS was also compared to contrast spiral CT, contrast MRI or liver biopsy, considered to be the "gold standard", CEUS had 85.4% sensitivity and 93.7% specificity for the diagnosis of hemangioma [3].

In another multinational study on 134 patients in which CEUS was compared to contrast-enhanced CT and/or dynamic contrast-enhanced MRI, CEUS had 100% sensitivity and 87% specificity for the identification of focal nodular hyperplasia (FNH) and hemangioma, resulting in an accuracy of 94.5% [31].

In a recently published study, on 83 lesions, the accuracies of CEUS and contrast enhanced MRI in diagnosing hemangiomas were compared considering histology as the reference method. There were no significant differences in the diagnostic value between CEUS and MRI in terms of sensitivity (88.0% vs. 92.8%), specificity (99.0% vs. 99.4%), accuracy (97.3% vs. 98.4%), positive predictive value (93.6% vs. 96.3%), and negative predictive value (98.0% vs. 98.8%) ($p > 0.05$, all) [32].

Similar to the studies presented above, in our study CEUS was highly accurate (96.9%) for the diagnosis of hemangioma (90.4% sensitivity, 98.8% specificity, 95.4% positive predictive value, 97.4% negative predictive value). In our study contrast CT/MRI and biopsy diagnosed additional 24 hemangiomas: mostly (17 hemangiomas) in inconclusive CEUS cases, but also in cases misdiagnosed by CEUS (4 HCC, 2 focal fatty infiltration, and 1 dysplastic nodule). Also, from the 238 cases diagnosed as hemangiomas by CEUS, in 11 the final diagnosis was different: 5 HCCs, 1 adenoma, 1 focal nodular hyperplasia, 1 dysplastic nodule, 1 case inflammatory lesion, 2 cases inconclusive by contrast CT/MRI.

Which are the causes for misdiagnosis? In a paper that analyzed unclear FLL after CEUS in the German multicentre study, 31 benign lesions, from which 9 biopsy proven hemangiomas, were classified as malignant by CEUS and 86 lesions were unclear after CEUS (67 benign lesions iso- or hypoenhancing during the late phases, from which 20 hemangiomas) [33]. The authors suggested that hypo- or isoenhancement of hemangiomas in the late phases of CEUS could be due to the continuous insonation of the lesion which leads to bubble destruction, especially in the near field (fig 2). In our study, from the 24 hemangiomas additionally diagnosed by contrast CT/MRI, 11 were in inconclusive cases by CEUS (declared inconclusive due to hypoenhancement in the late phase even if centripetal, nodular fill in was observed in the arterial phase).

Apart from inconclusive cases by CEUS later diagnosed as hemangiomas by contrast enhanced CT/MRI or biopsy, the highest number of misdiagnosed cases were HCCs: 4 cases diagnosed by CEUS as HCCs and proven to be hemangiomas (all in patients with chronic hepatitis and cirrhosis) and 5 cases diagnosed by CEUS to be hemangiomas and proven to be HCCs by second-line imaging methods or biopsy (3 in patients with chronic hepatitis and cirrhosis). HCCs are lesions that show arterial hyperenhancement and wash-out in the portal and late phases [6-8]. The arterial enhancement in HCC is usually homogeneous, but it can also be heterogeneous, due to fatty degeneration or intratumoral necrosis [34,35], while in well-differentiated HCCs, wash-out can occur only in late phases [8,36]. Considering all of the above, we can speculate that the 5 HCCs misdiagnosed by CEUS as hemangiomas, were well-differentiated and thus the wash-out was not visible during the 5 minutes of evaluation. Regarding the 4 hemangiomas misdiagnosed by CEUS as HCCs, we can speculate that a pseudo wash-out was observed due to hyperinsonation as showed in the German study [33,34], while the arterial inhomogeneous hyperenhancement observed in these cases can be explained by arterio-venous and/or portal venous shunts, known to be present in 10% of hemangiomas [37]. Also, rapidly filling hemangiomas, usually smaller than 3 cm can be encountered in patients with cirrhosis in up to 16-18% of cases [30,38,39]

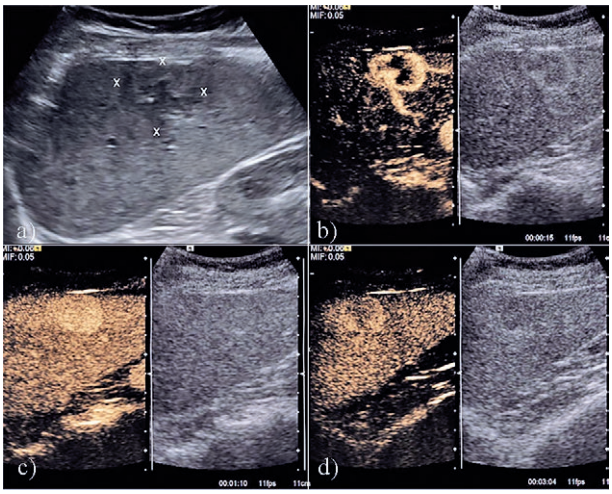

Fig 2. a) Isoechoic, inhomogeneous nodule, situated subcapsular in segment VI of the liver; b) CEUS – arterial phase: nodular, peripheral enhancement of the nodule can be observed; c) CEUS – portal phase: the nodule is completely hyperenhanced; d) CEUS – late phase: the nodule is hyperenhancing in the periphery, but the central area is hypoenhancing.

Previous studies demonstrated that CEUS accuracy for the characterization of FLL is comparable to that of contrast CT [40] and contrast MRI [41], and also that the use of CEUS as a first line imaging method when faced with a new FLL is cost-efficient [42,43]. Also the results of our study and of those mentioned above demonstrate very good accuracy for the diagnosis of hemangioma, so we can safely suggest to use CEUS a first-line imaging technique when faced with a suspected hemangioma based on standard B-mode US, even in high risk patients

in which clinical and serologic data should also be taken into consideration.

A limitation of our study is that we didn't include consecutive patients, but only those who met the inclusion criteria (having a second-line reference method: contrast CT/MRI or liver biopsy).

Conclusion

CEUS is a sensitive (90.4%) and very specific (98.8%) method for the diagnosis of hemangiomas, with an overall 96.9% diagnostic accuracy and should be considered as a first-line imaging technique when faced with a suspected hemangioma based on standard B-mode US, even in high risk patients.

Conflict of interest: none

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