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**Characterization of non traumatic focal splenic lesions using  
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Keywords:	ultrasonography, contrast agent, spleen, cyst, neoplasms

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Characterization of non traumatic focal splenic lesions using Contrast Enhanced Sonography

CEUS of the spleen in non traumatic focal lesions

For Peer Review

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7 **Purpose.** To compare the usefulness of contrast enhanced ultrasound (CEUS) with  
8 contrast enhanced computed tomography (CT) for assessing non-traumatic focal lesions  
9 of the spleen.  
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12 **Methods.** CEUS and CT findings in 22 patients with fever of unknown origin and  
13 ultrasound detected splenic focal lesions were analyzed retrospectively. CEUS was  
14 performed using an ultrasound unit equipped with a 3.6-Mhz probe and contrast media-  
15 analyzing software. A 4-ml bolus of second-generation contrast medium was used. The  
16 CEUS examinations comprised a 4-minute recording following injection of the contrast  
17 medium. Magnetic resonance imaging, splenic biopsy, or ultrasound follow-up were  
18 used to facilitate diagnosis if findings from CT were inconclusive.  
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27 **Results.** The final diagnoses were: 7 splenic infarcts, 5 hemangiomas, 3 lacerations, 2  
28 benign cysts, 1 lymphoma, 1 granuloma, 1 abscess, and 2 lesions of unknown etiology.  
29 CEUS and CT had the same specificity (77.2%). Both CEUS and CT failed to  
30 characterize nodular hypovascular lesions with a hypoenhancing pattern.  
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36 **Conclusions.** CEUS is as effective as CT for assessing non-traumatic focal lesions of the  
37 spleen. If CEUS findings are consistent with benign splenic lesions, CT seems to be of  
38 limited additional value.  
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44 **Keywords.** ultrasonography, contrast agent, spleen, cysts, neoplasms .  
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## Introduction

Focal lesions of the spleen incidentally detected by ultrasound (US) in a non-traumatic clinical scenario are not uncommon and may complicate a differential diagnosis. Contrast enhanced computed tomography (CT) is considered the primary tool of choice for assessing splenic abnormalities and sonography is generally not considered useful for determining the specific cause of these lesions.<sup>1</sup> The usefulness of contrast-enhanced ultrasound (CEUS) with a second generation sonographic contrast agent for differential diagnosis of benign and malignant focal abnormalities of the splenic parenchyma was recently described, but the actual utility of CEUS in a non-traumatic clinical setting remains controversial<sup>1-8</sup>. In the present study, we performed a retrospective comparison of CEUS and CT findings of non traumatic focal lesions incidentally detected by routine upper abdomen US examination in 22 patients admitted to the Infectious Diseases unit for fever of unknown etiology.

## Materials and Methods

### *Patients*

This study was approved by the local institutional ethics committee and written informed consent, according to legislative requirements, was obtained from each patient for CEUS and spleen biopsy.

Between February 2006 and September 2008 we investigated by CEUS of the spleen twenty-two patients (10 female and 12 males , median age 50 years , range 24 - 77) admitted to our unit because of fever of unknown origin and with US detected focal lesions of the spleen .

### *Ultrasound examination*

A GE Logic 5 ultrasound unit (General Electric-Connecticut USA) equipped with a contrast specific , continuous-mode software and a 3,6 Mhz transducer was used both for ultrasound standard examination and CEUS of the spleen.

## Contrast Enhanced Ultrasound examination

### *CEUS procedures and lesion diagnostic criteria*

CEUS was performed in harmonic mode with a mechanical index of 0.08 to 0.09. A 4-ml bolus of second-generation contrast medium ( Sonovue-Bracco, Milan) was used and injected in the antecubital vein. CEUS studies were analyzed on the basis of a review of reference clips stored in the sonographic unit. We identified three CEUS patterns using the surrounding splenic parenchyma as an in vivo reference: hypoenhancement, isoenhancement, and hyperenhancement, by scanning from 0 to 50 seconds during the early phase after injection, between 50 seconds and 120 during the parenchymal phase and between 120 seconds and 4 minutes after injection during the late phase. According to previous reports,<sup>1-8</sup> cystic lesions were considered to be malignant if enhancement of the cyst wall or septa was noted. Focal solid lesions were considered to be hemangiomas or hamartomas if we detected isoenhancement in all phases or if we detected hyperenhancement during the early phase (from 0-50 seconds) and isoenhancement during the late phase. A focal, nodular-shaped lack of enhancement in the late phase (hypoechoic lesions) after early enhancement was considered to suggest malignancy while absence of enhancement in all phases was considered to be due also to splenic granuloma or abscess<sup>1</sup>. Segmental subcapsular lesions of the spleen pointing toward the hilum with a hypoechoic pattern in all the phases were considered to be splenic infarcts, while irregular or branching parenchymal stripes constantly hypoechoic after contrast medium injection were considered to be spontaneous parenchymal lacerations (Fig.1).<sup>9-</sup>

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### *Clinical and radiological examination*

All patients underwent microbiological laboratory tests and abdominal and chest CT after CEUS examination for disease staging. Magnetic resonance imaging (MRI), US follow-up, or echo-guided spleen aspiration biopsy using a 22-gauge Chiba needle was performed if CT findings were inconclusive.<sup>12</sup>

### *Statistical Analysis*

Continuous variables are reported as the mean  $\pm$  standard deviation. Categorical factors are reported as percentages. Statistical calculations were performed with MedCalc software, version 9.6.0.0. (bvba, Mariakerke, Belgium)

### **Results**

The final diagnoses are summarized in Table 1. None of the patients had symptoms other than fever. US detected multiple focal lesions of the spleen (median size 4.7 cm, range 0.4-9 cm) in 4 patients. Baseline ultrasound showed no isoechoic lesions, hypoechoic lesions in 16 patients, hyperechoic lesions in 4 patients and anechoic lesions in 2 patients. CEUS showed anechoic nodular lesions without enhancement of the cyst wall or septa in 2 patients (Fig. 2a-2c) In 3 patients with nodular lesions, a persistent isoenhancement was noted in all phases, showing an enhancement pattern similar to that of the adjacent splenic tissue. In 2 patients hyperenhancing nodular lesions were detected only during the early arterial phase with rapid centripetal filling in and they became undetectable in the late phase.

Hypoechoic nodular lesions with an absence of enhancement in all phases was observed in 5 patients (Fig.3a-3c). Splenic CEUS showed persistent delayed hypoenhancement of segmental subcapsular lesions in 7 patients (Fig. 4a-4c) and of irregular parenchymal stripes in 3 patients. CEUS findings in lesions of all etiology are summarized in Table 2. According to these results, CEUS supported a diagnosis of benign cystic lesions in 2 patients, hemangioma in 5 patients, splenic infarct in 7 patients, and splenic lacerations in 3 patients. CEUS findings were confirmed by CT abdominal examination in all cases. Both CEUS and CT supported a final diagnosis in 17 of 22 patients (77.2%), and failed to characterize nodular splenic lesions in 5 patients with persistent hypoenhancing pattern. MRI was performed in one of these patients with inconclusive findings. Splenic aspiration biopsy was performed in 2 of these patients. The final diagnosis was splenic lymphoma infiltration and sarcoid granuloma. In 3 patients, US follow-up of monthly

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3 examinations for at least 1 year showed that the splenic lesions were benign.

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5 In two of these patients the diagnosis of a benign splenic tumor was most likely because  
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7 metastasised malignant diseases or extrasplenic pathology were ruled out by abdominal  
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9 CT, fever disappeared after few days of antibiotics therapy and monthly clinical and  
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11 ultrasound follow up during the first year showed no clinical symptoms and absence of  
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13 increase in size of the lesion. In one of these patients with a nodular splenic lesion of  
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15 unknown origin, blood culture and clinical follow-up allowed us to reach a diagnosis of  
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17 a small splenic abscess due to left heart endocarditis (Table 1).

## 18 19 20 **Discussion**

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22 The spleen is particularly suitable for CEUS studies because of its topography, small  
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24 size, homogeneous parenchyma, high vascularization, and intense and long-lasting  
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26 contrast enhancement.<sup>1-13</sup> Several reports demonstrated that CEUS of the spleen  
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28 significantly improves the diagnosis of parenchymal lacerations by enhancing the  
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30 detection of avascular areas during the late phase of the examination.<sup>9-11</sup> At the present  
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32 time, however, European CEUS guidelines warrant the use of this tool for only blunt  
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34 abdominal trauma and, in particular, to avoid CT or MRI during follow-up.<sup>14</sup> Reports of  
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36 the use of splenic CEUS to characterize non-traumatic focal lesions remain scarce. Some  
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38 authors have described a microbubble wash-out in the late-phase for a differential  
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40 diagnosis of malignant lesions, but the reliability of this diagnostic tool in clinical  
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42 practice is not yet confirmed. To date, however, there have been no studies to compare  
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44 CEUS with CT features in the assessment of focal lesions of the spleen. Three of 5  
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46 hemangiomas showed an enhancement pattern similar to splenic tissue, while 2 of 5  
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48 lesions showed a rapid and hyperechoic enhancement in the early-phase with centripetal  
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50 filling in. The splenic lymphoma we described appeared as a constantly hypoechoic  
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52 lesion, more easily defined during the late phase but without clear intralesional  
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54 microcirculation or rim enhancement in the early phase. Our findings indicated that a  
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3 persistent hypoenhancing CEUS pattern of nodular splenic lesions may also be common  
4 to benign lesions such as small abscesses or granulomas, so that differentiation  
5 of these lesions from malignant diseases is often not possible.<sup>8</sup> On the other hand, our  
6 data showed that CT has the same specificity as CEUS for the diagnosis of hypovascular  
7 solid lesions of the spleen because of the inability to characterize hypodense splenic  
8 nodules. The difficulty in making a differential diagnosis using CT and CEUS is  
9 probably due to the lack of a dual splenic vascular supply because double  
10 vascularization is useful for characterizing focal hepatic lesions using contrast-enhanced  
11 media.<sup>14</sup> Asymptomatic segmental-shaped hypovascular lesions of the spleen are often  
12 due to splenic infarcts. In patients with no history of abdominal trauma, irregular-shaped  
13 hypoenhancing parenchymal lesions may be due to spontaneous rupture of an enlarged  
14 spleen, which sometimes occurs as a complication of infectious diseases characterized  
15 by splenomegaly, such as mononucleosis and malaria, or during myeloproliferative  
16 diseases.<sup>15</sup> The unenhanced US patterns of mild spontaneous splenic lacerations in the  
17 absence of acute bleeding and perisplenic effusion do not differ from those of ischemic  
18 lesions and both these lesions may be difficult to distinguish from the surrounding  
19 splenic parenchyma. After contrast media injection, splenic infarct shows as a clear  
20 wedge-shaped lack of enhancement relative to the spleen capsule; while splenic  
21 lacerations appear as typical unenhanced branching stripes, usually perpendicular to the  
22 spleen surface. In our experience, CEUS of the spleen is as effective as CT for  
23 diagnosing these lesions in non-traumatic splenic pathology. Although abdominal CT is  
24 commonly used to rule out extrasplenic malignancy, most nodular lesions of the spleen  
25 are hypovascular and CT study seems to be of limited additional value to characterize  
26 focal lesions that have a benign pattern on CEUS. Finally CEUS might facilitate a rapid  
27 diagnosis and eliminate the need for CT contrast media and ionizing radiation during  
28 follow-up. CEUS of the spleen is simple, rapid, and safer and less expensive than CT  
29 and MRI. Based on the present findings, CEUS might be a useful first tool to  
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3 characterize lesions of the spleen detected incidentally by US and CEUS is as effective  
4 as CT for assessing this kind of lesion.  
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7 Conflict of interest statement

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9 All authors have no conflict of interest with regard to publication of this article.  
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## 12 13 **References**

- 14  
15 1. Catalano O, Sandomenico F, Vallone P, et al. Contrast-enhanced sonography of the  
16 spleen. *Semin Ultrasound CT MR*. 2006;27:426.  
17  
18 2. von Herbay A, Barreiros AP, Ignee A, et al. Contrast –Enhanced Ultrasonography  
19 with Sonovue differentiation between benign and malignant lesions of the spleen. *J*  
20 *Ultrasound Med* 2009; 28:421.  
21  
22 3. Görg C. The forgotten organ: Contrast enhanced sonography of the spleen. *Eur J*  
23 *Radiol* 2007; 187: 658  
24  
25 4. Peddu P, Shah M, Sidhu PS. Splenic abnormalities: a comparative review of  
26 ultrasound, microbubble-enhanced ultrasound and computed tomography. *Clin Radiol*  
27 2004;59:777.  
28  
29 5. Catalano O, Lobianco R, Sandomenico F, et al. Real-time contrast-enhanced  
30 ultrasound of the spleen: examination technique and preliminary clinical experience.  
31 *Radiol Med* 2003;106:338.  
32  
33 6. Görg C., Bert T. Contrast-enhanced sonography of focal splenic lesions with a  
34 secondgeneration contrast agent. *Ultraschall Med* 2005;26:470.  
35  
36 7. Görg C, Graef C, Bert T. Contrast-enhanced sonography for differential diagnosis of  
37 an inhomogeneous spleen of unknown cause in patients with pain in the left upper  
38 quadrant. *J Ultrasound Med* 2006;25:729.  
39  
40 8. Chiavaroli R, Grima P, Calabrese P, et al. Diagnosis of hepatosplenic sarcoidosis by  
41 contrast enhanced ultrasound guided needle biopsy. *Ultrasound* 2008;16:196.  
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3 9. Catalano O, Aiani L, Barozzi L, et al. CEUS in abdominal trauma: multicenter study.  
4  
5 Abdom Imaging 2009;34:225.  
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- 7 10. McGahan JP, Horton S, Gerscovich EO, et al. Appearance of solid organ injury with  
8  
9 contrastenhanced sonography in blunt abdominal trauma: preliminary experience. AJR  
10  
11 Am J Roentgenol 2006;187:658.  
12
- 13 11. Catalano O, Lobiano R, Sandomenico F, et al. Splenic trauma: evaluation with  
14  
15 contrastspecific sonography and a second-generation contrast medium. J Ultrasound  
16  
17 Med 2003;22:467.  
18
- 19 12. Cavanna L, Lazzaro A, Vallisa D, et al. Role of image-guided fine- needle aspiration  
20  
21 biopsy in the management of patients with splenic metastasis. World J Surg Oncol.  
22  
23 2007;5:13.  
24
- 25 13. Lim AK, Patel N, Eckersley RJ, et al. Evidence for spleen-specific uptake of a  
26  
27 microbubble contrast agent: a quantitative study in healthy volunteers. Radiology  
28  
29 2004;231:785  
30
- 31 14. Albrecht T, Blomley M, Bolondi L, et al. Guidelines for the use of contrast agents in  
32  
33 ultrasound. Ultraschall Med 2004;25:249.  
34
- 35 15. Görg, C., Cölle, J., Görg, K, et al. Spontaneous rupture of the spleen: ultrasound  
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37 patterns, diagnosis, and follow-up. Brit J Radiol 2003; 76 :704  
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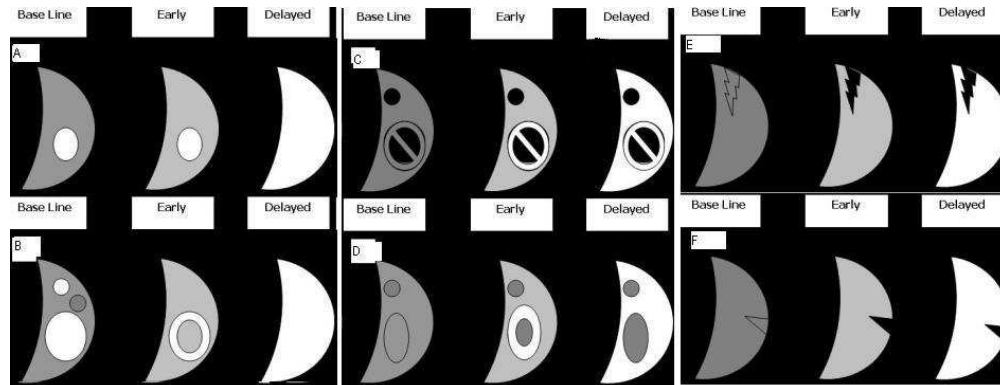


Figure 1.

Schematic display of the dynamic ultrasound contrast enhancement of splenic Hamartoma (A), Hemangioma (B), benign (upper) and malignant Cysts (C), Lymphoma (upper) and Metastasis (D), Laceration (E) and Ischemic lesion (F), during the base line, early and delayed phase.

249x96mm (96 x 96 DPI)

<b>FINAL DIAGNOSIS</b>	<b>CEUS</b>	<b>Abdominal CT</b>	<b>Abdominal MRI</b>	<b>Splenic Biopsy</b>	<b>Follow UP</b>	<b>Cases</b>
<i>Benign cists</i>	<b>diagnostic</b>	<b>diagnostic</b>	-----	-----	-----	2
<i>Haemangioma</i>	<b>diagnostic</b>	<b>diagnostic</b>	-----	-----	-----	5
<i>Splenic Infarct</i>	<b>diagnostic</b>	<b>diagnostic</b>	-----	-----	-----	7
<i>Lacerations</i>	<b>diagnostic</b>	<b>diagnostic</b>	-----	-----	-----	3
<i>Lymphoma</i>	inconclusive	inconclusive	inconclusive	<b>diagnostic</b>	-----	1
<i>Sarcoid</i>	inconclusive	inconclusive	-----	<b>diagnostic</b>	-----	1
<i>Granuloma</i>						
<i>Splenic abscess</i>	inconclusive	inconclusive	-----	-----	<b>diagnostic</b>	1
<i>Unknown cause (benign lesions)</i>	inconclusive	inconclusive	-----	-----	<b>diagnostic</b>	2
<b>Total</b>						22

Tab.1  
Ceus and CT diagnostic value for final diagnosis in all patients

	Haemangiomas	Lymphoma	Granuloma	Abscesses	Infarcts	Lacerations	Benign nodular lesions	Cysts
<b>n</b>	<b>5</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>7</b>	<b>3</b>	<b>2</b>	<b>2</b>
<b>Early phase (0-50 s)</b>								
<i>homogeneous</i>	3	0	0	0	0	0	0	0
<i>hyperechoic</i>	2	0	0	0	0	0	0	0
<i>hypoechoic</i>	0	1	1	1	7	3	2	2
<i>Enhancement pattern</i>	Centripetal filling-in(n =2)	None	None	None	Wedge shaped	Branching stripes	None	Round margin
<b>Parenchymal phase (50-120 s)</b>								
<i>homogeneous</i>	5	0	0	0	0	0	0	0
<i>hyperechoic</i>	0	0	0	0	0	0	0	0
<i>hypoechoic</i>	0	1	1	1	7	3	2	2
<i>Enhancement pattern</i>	None	None	None	None	Wedge shaped	Wedge shaped	None	Round margin
<b>Late phase (120-240 s)</b>								
<i>homogeneous</i>	5	0	0	0	0	0	0	0
<i>hyperechoic</i>	0	0	0	0	0	0	0	0
<i>hypoechoic</i>	0	1	1	1	7	3	2	2
<i>Enhancement pattern</i>	None	None	None	None	Wedge shaped	Wedge shaped	None	Round margin

Table 2  
Contrast Enhanced Ultrasound findings in lesions of all etiologies

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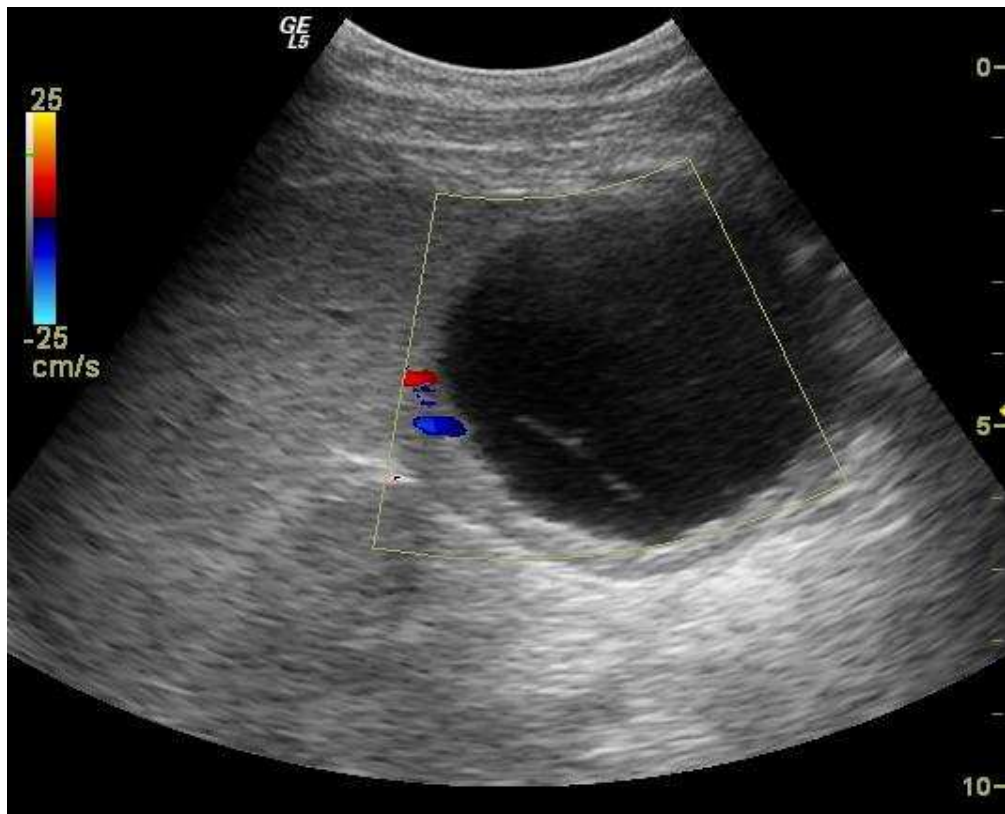


Figure 2a.  
Benign splenic cyst: Large avascular cystic lesion of the spleen with thick wall and fine septa by US color-doppler.  
140x114mm (96 x 96 DPI)

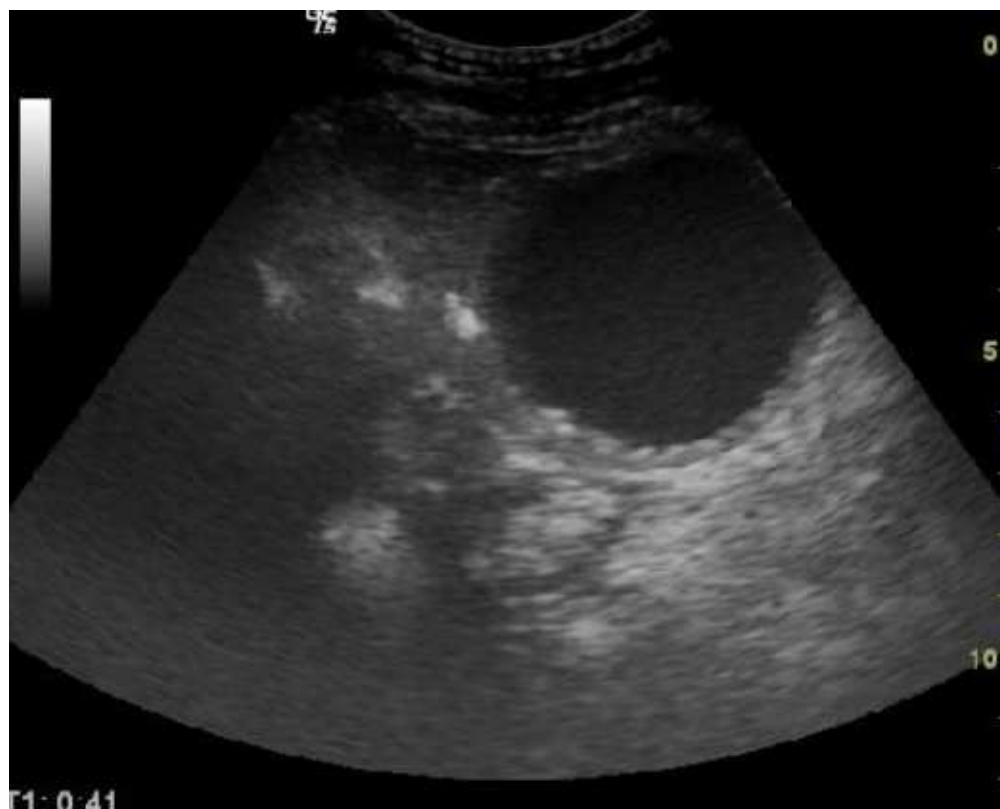


Figure 2b.  
Benign splenic cyst : CEUS shows no enhancement of wall and septa.  
138x110mm (96 x 96 DPI)



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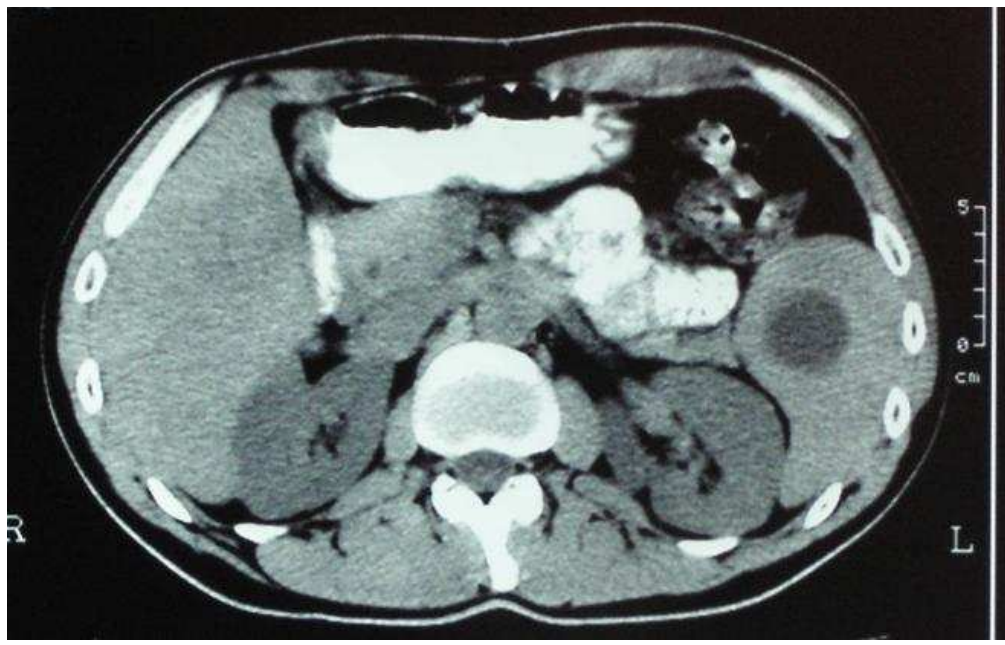


Figure 2c.  
Homogeneous hypodense cystic lesion by abdominal CT. study.  
173x109mm (96 x 96 DPI)

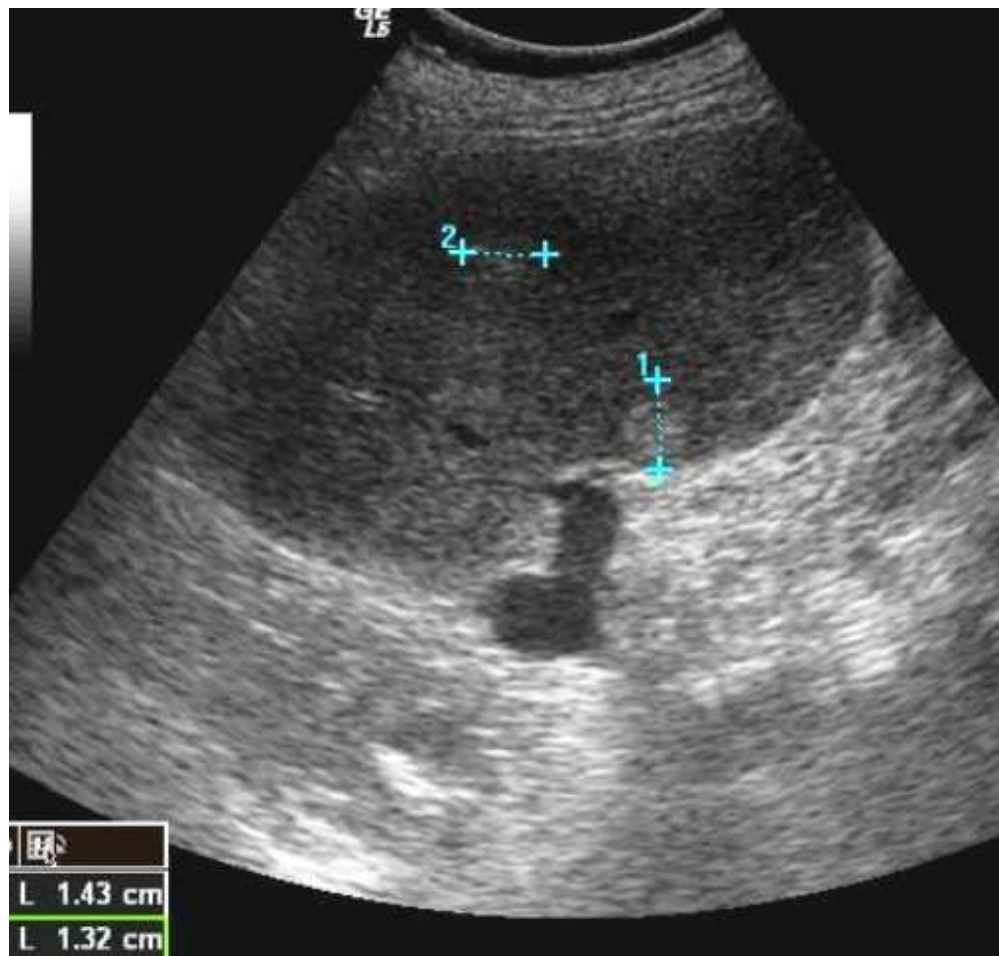


Figure 3a.  
Sarcoid granulomata of the spleen: Hyperechoic nodular lesions by US base line examination.  
134x127mm (96 x 96 DPI)



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Figure 3b.  
Splenic nodular lesions are hypoechoic during all the phases of CEUS study.  
142x120mm (96 x 96 DPI)

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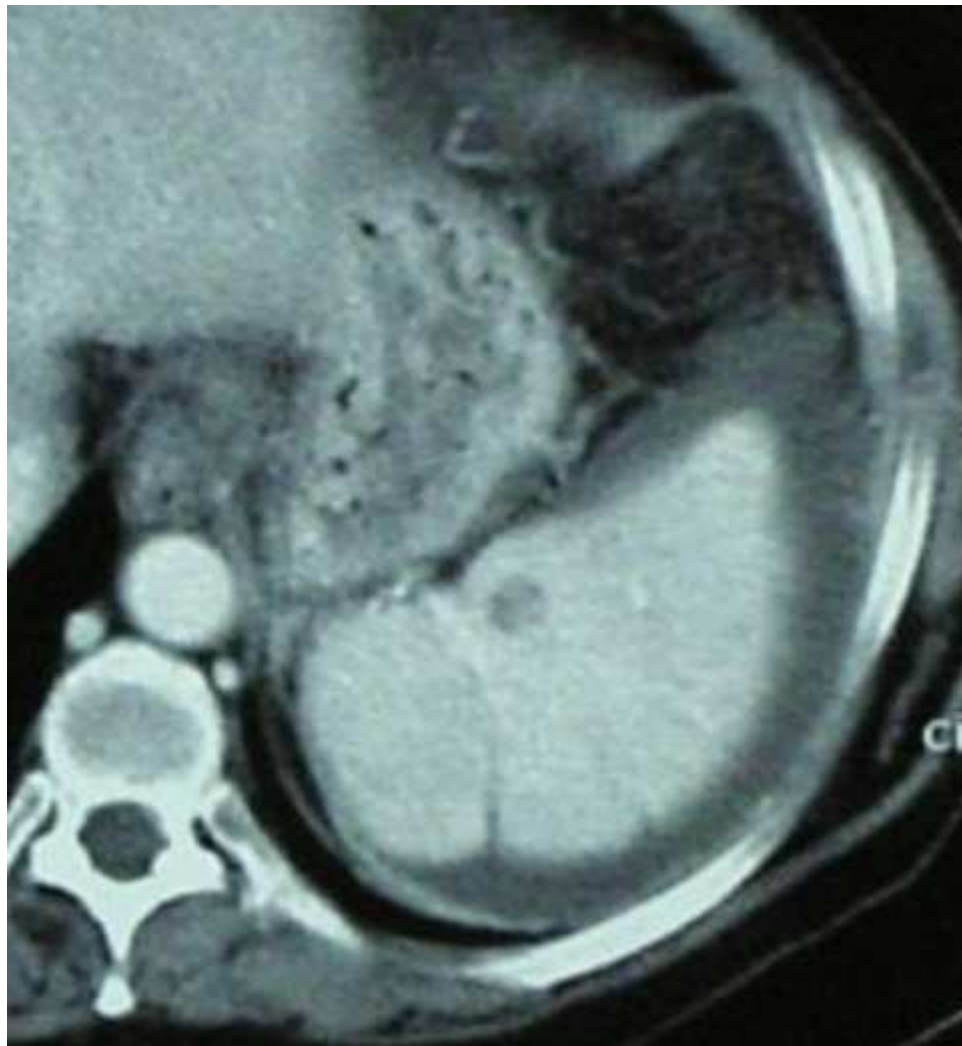


Figure 3c.  
Hypovascular nodular lesions by Abdominal CT.  
127x138mm (96 x 96 DPI)

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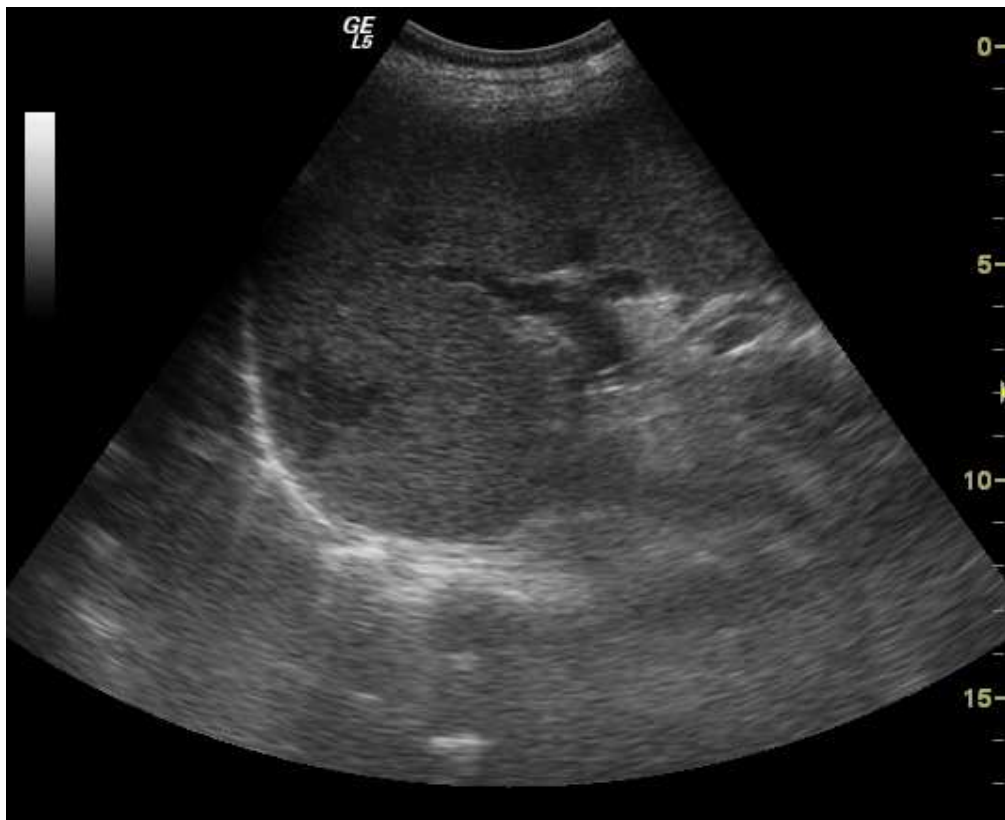


Figure 4a.  
Splenic infarct; US shows a segmental shaped hypoechoic lesion of the spleen.  
140x114mm (96 x 96 DPI)

view

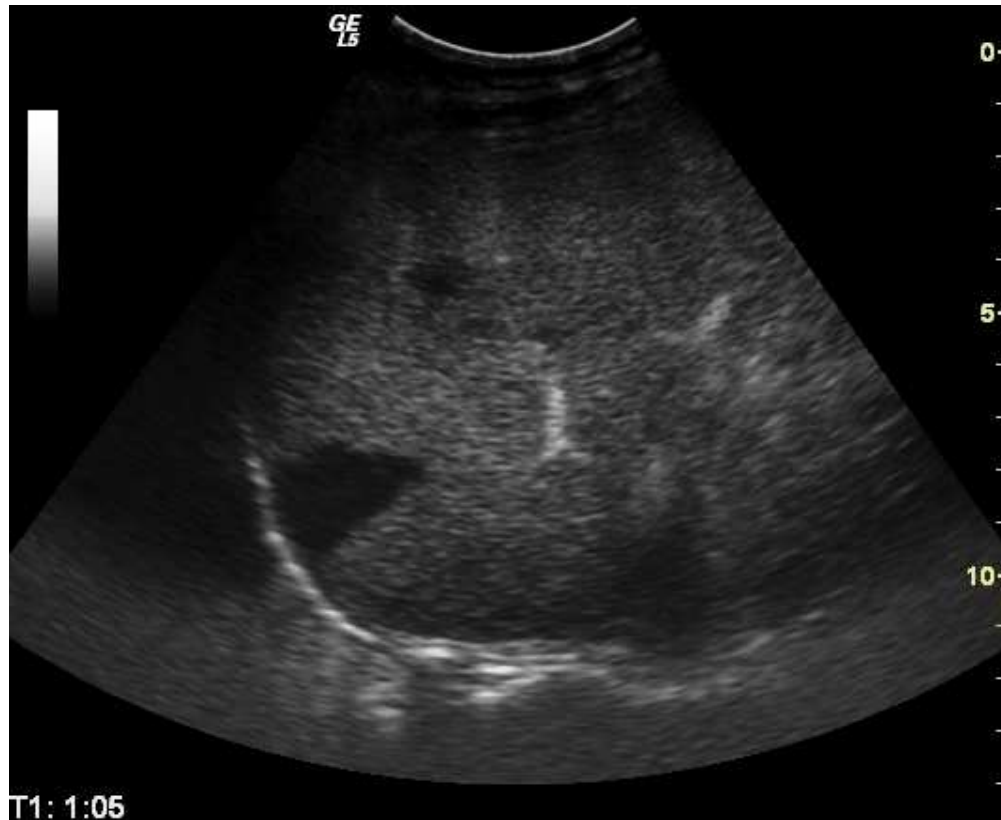


Figure 4b.  
CEUS shows two hypoechoic subcapsular lesion.  
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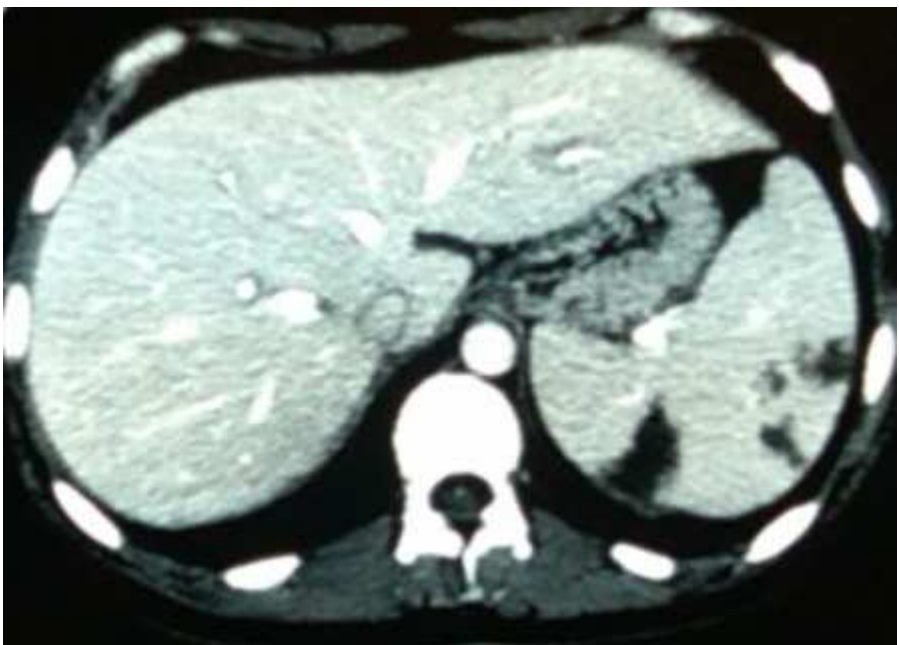


Figure 4c.  
Abdominal CT shows multiple hypodense subcapsular lesions of the spleen  
118x84mm (96 x 96 DPI)

Review

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3 Response to Comments from the Editor  
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6 MATERIALS and METHODS

7 1) I mentioned 3 CEUS patterns ; anechoic, isoechoic and hypoechoic, but i mean  
8 hypoenhancement, isoenhancement and hyperenhancement. I have made the  
9 correction throughout the text.  
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11

12 2) The statement has been reworded "*A focal, nodular-shaped lack of enhancement in  
13 the late phase (hypoechoic lesions) after early enhancement was considered to  
14 suggest malignancy while absence of enhancement in all phases was considered to be  
15 due also to splenic granuloma or abscess . "*  
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19 3) The statement in the abstract has been corrected "*Magnetic resonance imaging,  
20 splenic biopsy, or ultrasound follow-up were used to facilitate diagnosis if findings  
21 from CT were inconclusive.*"  
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25 4)The statistical software i used is not from USA. The maker of the software is from  
26 Europe " MedCalc software, version 9.6.0.0. (bvba, Mariakerke, Belgium)"  
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29 RESULTS:  
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32 5) I mean isoenhancement  
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35 6 I mean hyperenhancement of nodular lesion  
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38 7 I mean that all hyperenhancing nodular lesions with centripetal filling in in the  
39 early phase became undetectable in the late phase  
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41 The statements have been rewrote: "*in 3 patients with nodular lesions, a persistent  
42 isoenhancement was noted in all phases, showing an enhancement pattern similar to  
43 that of the adjacent splenic tissue . In 2 patients hyperenhancing nodular lesions were  
44 detected only during the early arterial phase with rapid centripetal filling in and they  
45 became undetectable in the late phase.*"  
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49 8) The statements "*Further studies are warranted to assess the  
50 reliability of CEUS in routine clinical practice. The present findings suggest that  
51 when CEUS features are consistent with benign splenic lesions, abdominal CT may  
52 be avoided, and CT studies and more expensive and invasive tools such as MRI and  
53 needle biopsy can be saved for  
54 patients with solid nodular hypovascular lesions. "* have been deleted.  
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Characterization of non traumatic focal splenic lesions using Contrast Enhanced  
Sonography

Keywords:  
ultrasonography, contrast agent, spleen, cyst, neoplasms

For Peer Review

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4 **Purpose.** To compare the usefulness of contrast enhanced ultrasound (CEUS)  
5 with contrast enhanced computed tomography (CT) for assessing non-traumatic  
6 focal lesions of the spleen.  
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9 **Methods.** CEUS and CT findings in 22 patients with fever of unknown origin and  
10 ultrasound detected splenic focal lesions were analyzed retrospectively. CEUS  
11 was performed using an ultrasound unit equipped with a 3.6-Mhz probe and  
12 contrast media-analyzing software. A 4-ml bolus of second-generation contrast  
13 medium was used. The CEUS examinations comprised a 4minute  
14 recording following injection of the contrast medium. Magnetic resonance  
15 imaging, splenic biopsy, or ultrasound follow-up were used to facilitate diagnosis  
16 if findings from CT were inconclusive.  
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19 **Results.** The final diagnoses were: 7 splenic infarcts, 5 hemangiomas, 3  
20 lacerations, 2 benign cysts, 1 lymphoma, 1 granuloma, 1 abscess, and 2 lesions of  
21 unknown etiology. CEUS and CT had the same specificity (77.2%). Both CEUS  
22 and CT failed to characterize nodular hypovascular lesions with a hypoenhancing  
23 pattern.  
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26 **Conclusions.** CEUS is as effective as CT for assessing non-traumatic focal  
27 lesions of the spleen. If CEUS findings are consistent with benign splenic lesions,  
28 CT seems to be of limited additional [value](#)  
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31 **Keywords.** ultrasonography, contrast agent, spleen, cysts, neoplasms.  
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## Introduction

Focal lesions of the spleen incidentally detected by ultrasound (US) in a non-traumatic clinical scenario are not uncommon and may complicate a differential diagnosis. Contrast enhanced computed tomography (CT) is considered the primary tool of choice for assessing splenic abnormalities and sonography is generally not considered useful for determining the specific cause of these lesions.<sup>1</sup> The usefulness of contrast-enhanced ultrasound (CEUS) with a second generation sonographic contrast agent for differential diagnosis of benign and malignant focal abnormalities of the splenic parenchyma was recently described, but the actual utility of CEUS in a non-traumatic clinical setting remains controversial.<sup>1-8</sup>

In the present study, we performed a retrospective comparison of CEUS and CT findings of non traumatic focal lesions incidentally detected by routine upper abdomen US examination in 22 patients admitted to the Infectious Diseases unit for fever of unknown etiology.

## Materials and Methods

### *Patients*

This study was approved by the local institutional ethics committee and written informed consent, according to legislative requirements, was obtained from each patient for CEUS and spleen biopsy.

Between February 2006 and September 2008 we investigated by CEUS of the spleen twenty-two patients (10 female and 12 males , median age 50 years , range 24 - 77) admitted to our unit because of fever of unknown origin and with US detected focal lesions of the spleen .

## Ultrasound examination

A GE Logic 5 ultrasound unit (General Electric-Connecticut USA) equipped with a contrast specific , continuous-mode software and a 3,6 Mhz transducer was used both for ultrasound standard examination and CEUS of the spleen.

## Contrast Enhanced Ultrasound examination

### CEUS procedures and lesion diagnostic criteria

CEUS was performed in harmonic mode with a mechanical index of 0.08 to 0.09. CEUS studies were analyzed on the basis of a review of reference clips stored in the sonographic unit. We identified three CEUS patterns using the surrounding splenic parenchyma as an in vivo reference: hypoenhancement, isoenhancement and hyperenhancement, by scanning from 0 to 50 seconds during the early phase after injection, between 50 seconds and 120 during the parenchymal phase and between 120 seconds and 4 minutes after injection during the late phase. According to previous reports,<sup>1-8</sup> cystic lesions were considered to be malignant if enhancement of the cyst wall or septa was noted. Focal solid lesions were considered to be hemangiomas or hamartomas if we detected isoenhancement in all phases or if we detected hyperenhancement during the early phase (from 0-50 seconds) and isoenhancement during the late phase. A focal, nodular-shaped lack of enhancement in the late phase (hypoechoic lesions) after early enhancement was considered to suggest malignancy while absence of enhancement in all the phases was considered to be due also to splenic granuloma or abscess<sup>1</sup>. Segmental subcapsular lesions of the spleen pointing toward the hilum with a hypoechoic pattern in all the phases were

**Deleted:** anechoic, isoechoic, and hypoechoic

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2 considered to be splenic infarcts, while irregular or branching parenchymal stripes  
3 constantly hypoechoic after contrast medium injection were considered to be  
4 spontaneous parenchymal lacerations (Fig.1).<sup>9-11</sup>  
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### 9 *Clinical and radiological examination*

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12 All patients underwent microbiological laboratory tests and abdominal and chest  
13 CT after CEUS examination for disease staging. Magnetic resonance imaging  
14 (MRI), US follow-up, or echo-guided spleen aspiration biopsy using a 22-gauge  
15 Chiba needle was performed if CT findings were inconclusive<sup>12</sup>.  
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### 20 *Statistical Analysis*

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22 Continuous variables are reported as the mean  $\pm$  standard deviation. Categorical  
23 factors are reported as percentages. Statistical calculations were performed with  
24 MedCalc software, version [9.6.0.0. bvba, Mariakerke, Belgium](https://www.medcalc.org/).  
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### 29 **Results**

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32 The final diagnoses are summarized in Table 1. None of the patients had  
33 symptoms other than fever. US detected multiple focal lesions of the spleen  
34 (median size 4.7 cm, range 0.4-9 cm) in 4 patients. Baseline ultrasound showed  
35 no isoechoic lesions, hypoechoic lesions in 16 patients, hyperechoic lesions in 4  
36 patients and anechoic lesions in 2 patients. CEUS showed anechoic nodular  
37 lesions without enhancement of the cyst wall or septa in 2 patients (Fig. 2a-2c).  
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45 In 3 patients with nodular lesions, [a persistent](#) isoenhancement was noted in all  
46 phases, [showing an enhancement pattern similar to that of the adjacent splenic](#)  
47 [tissue](#). In 2 patients, [hyperenhancing nodular lesion](#), was detected only during the  
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early arterial phase with rapid centripetal filling in and they became undetectable in the late phase.

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Hypoechoic nodular lesions with an absence of enhancement in all phases was observed in 5 patients (Fig.3a-3c). Splenic CEUS showed persistent delayed hypoenhancement of segmental subcapsular lesions in 7 patients (Fig. 4a-4c) and of irregular parenchymal stripes in 3 patients. CEUS findings in lesions of all etiology are summarized in Table 2. According to these results, CEUS supported a diagnosis of benign cystic lesions in 2 patients, hemangioma in 5 patients, splenic infarct in 7 patients, and splenic lacerations in 3 patients. CEUS findings were confirmed by CT abdominal examination in all cases. Both CEUS and CT supported a final diagnosis in 17 of 22 patients (77.2%), and failed to characterize nodular splenic lesions in 5 patients with persistent hypoenhancing pattern. MRI was performed in one of these patients with inconclusive findings. Splenic aspiration biopsy was performed in 2 of these patients. The final diagnosis was splenic lymphoma infiltration and sarcoid granuloma. In 3 patients, US follow-up of monthly examinations for at least 1 year showed that the splenic lesions were benign. In two of these patients the diagnosis of a benign splenic tumor was most likely because metastasised malignant diseases or extrasplenic pathology were ruled out by abdominal CT, fever disappeared after few days of antibiotics therapy and monthly clinical and ultrasound follow up during the first year showed no clinical symptoms and absence of increase in size of the lesion.

In one of these patients with a nodular splenic lesion of unknown origin, blood culture and clinical follow-up allowed us to reach a diagnosis of a small splenic abscess due to left heart endocarditis (Table 1).

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## Discussion

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The spleen is particularly suitable for CEUS studies because of its topography, small size, homogeneous parenchyma, high vascularization, and intense and long-

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2 lasting contrast enhancement.<sup>1-13</sup> Several reports demonstrated that CEUS of the  
3 spleen significantly improves the diagnosis of parenchymal lacerations by  
4 enhancing the detection of avascular areas during the late phase of the  
5 examination.<sup>9-11</sup> At the present time, however, European CEUS guidelines  
6 warrant the use of this tool for only blunt abdominal trauma and, in particular, to  
7 avoid CT or MRI during follow-up.<sup>14</sup> Reports of the use of splenic CEUS to  
8 characterize non-traumatic focal lesions remain scarce. Some authors have  
9 described a microbubble wash-out in the late-phase for a differential diagnosis of  
10 malignant lesions, but the reliability of this diagnostic tool in clinical  
11 practice is not yet confirmed.<sup>1-3</sup> To date, however, there have been no studies to  
12 compare CEUS with CT features in the assessment of focal lesions of the spleen.  
13 Three of 5 hemangiomas showed an enhancement pattern similar to splenic tissue,  
14 while 2 of 5 lesions showed a rapid and hyperechoic enhancement in the early-  
15 phase with centripetal filling in. The splenic lymphoma we described appeared as  
16 a constantly hypoechoic lesion, more easily defined during the late phase  
17 but without clear intralesional microcirculation or rim enhancement in the early  
18 phase. Our findings indicated that a persistent hypoenhancing CEUS pattern of  
19 nodular splenic lesions may also be common to benign lesions such as small  
20 abscesses or granulomas, so that differentiation of these lesions from malignant  
21 diseases is often not possible.<sup>8</sup> On the other hand, our data showed that CT has the  
22 same specificity as CEUS for the diagnosis of hypovascular solid lesions  
23 of the spleen because of the inability to characterize hypodense splenic nodules.  
24 The difficulty in making a differential diagnosis using CT and US is probably due  
25 to the lack of a dual splenic vascular supply because double vascularization is  
26 useful for characterizing focal hepatic lesions using contrast-enhanced media.<sup>14</sup>  
27 Asymptomatic segmental-shaped hypovascular lesions of the spleen are often due  
28 to splenic infarcts. In patients with no history of abdominal trauma, irregular-  
29 shaped hypoenhancing parenchymal lesions may be due to spontaneous rupture of  
30 an enlarged spleen, which sometimes occurs as a complication of infectious  
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2 diseases characterized by splenomegaly, such as mononucleosis and malaria, or  
3 during myeloproliferative diseases.<sup>15</sup> The unenhanced US patterns of mild  
4 spontaneous splenic lacerations in the absence of acute bleeding and perisplenic  
5 effusion do not differ from those of ischemic lesions and both these lesions may  
6 be difficult to distinguish from the surrounding splenic parenchyma. After  
7 contrast media injection, splenic infarct shows as a clear wedge-shaped lack of  
8 enhancement relative to the spleen capsule; while splenic lacerations appear as  
9 typical unenhanced branching stripes, usually perpendicular to the spleen surface.  
10 In our experience, CEUS of the spleen is as effective as CT for diagnosing these  
11 lesions in non-traumatic splenic pathology. Although abdominal CT is commonly  
12 used to rule out extrasplenic malignancy, most nodular lesions of the spleen are  
13 hypovascular and CT study seems to be of limited additional value to characterize  
14 focal lesions that have a benign pattern on CEUS. Finally CEUS might facilitate a  
15 rapid diagnosis and eliminate the need for CT contrast media and ionizing  
16 radiation during follow-up. CEUS of the spleen is simple, rapid, and safer  
17 and less expensive than CT and MRI. Based on the present findings, CEUS might  
18 be a useful first tool to characterize lesions of the spleen detected incidentally by  
19 US, and CEUS is as effective as CT for assessing this kind of lesion.

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#### Conflict of interest statement

All authors have no conflict of interest with regard to publication of this article.

#### References

- 1.Catalano O, Sandomenico F, Vallone P, et al. Contrast-enhanced sonography of the spleen. *Semin Ultrasound CT MR*. 2006;27:426.



2. von Herbay A, Barreiros AP, Ignee A, et al. Contrast –Enhanced Ultrasonography with Sonovue differentiation between benign and malignant lesions of the spleen. *J Ultrasound Med* 2009; 28:421.
3. Görg C. The forgotten organ: Contrast enhanced sonography of the spleen. *Eur J Radiol* 2007; 187: 658
4. Peddu P, Shah M, Sidhu PS. Splenic abnormalities: a comparative review of ultrasound, microbubble-enhanced ultrasound and computed tomography. *Clin Radiol* 2004;59:777.
5. Catalano O, Lobianco R, Sandomenico F, et al. Real-time contrast-enhanced ultrasound of the spleen: examination technique and preliminary clinical experience. *Radiol Med* 2003;106:338.
6. Görg C., Bert T. Contrast-enhanced sonography of focal splenic lesions with a second generation contrast agent. *Ultraschall Med* 2005;26:470.
7. Görg C, Graef C, Bert T. Contrast-enhanced sonography for differential diagnosis of an inhomogeneous spleen of unknown cause in patients with pain in the left upper quadrant. *J Ultrasound Med* 2006;25:729.
8. Chiavaroli R, Grima P, Calabrese P, et al. Diagnosis of hepatosplenic sarcoidosis by contrastenhanced ultrasound guided needle biopsy. *Ultrasound* 2008;16:196.
9. Catalano O, Aiani L, Barozzi L, et al. CEUS in abdominal trauma: multicenter study. *Abdom Imaging* 2009;34:225.
10. McGahan JP, Horton S, Gerscovich EO, et al. Appearance of solid organ injury with contrast enhanced sonography in blunt abdominal trauma: preliminary experience. *AJR Am J Roentgenol* 2006;187:658.
11. Catalano O, Lobiano R, Sandomenico F, et al. Splenic trauma: evaluation with contrast specific sonography and a second-generation contrast medium. *J Ultrasound Med* 2003;22:467.

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12. Cavanna L, Lazzaro A, Vallisa D, et al. Role of image-guided fine- needle aspiration biopsy in the management of patients with splenic metastasis. *World J Surg Oncol.* 2007;5:13.
  13. Lim AK, Patel N, Eckersley RJ, et al. Evidence for spleen-specific uptake of a microbubble contrast agent: a quantitative study in healthy volunteers. *Radiology* 2004;231:785
  14. Albrecht T, Blomley M, Bolondi L, et al. Guidelines for the use of contrast agents in ultrasound. *Ultraschall Med* 2004;25:249.
  15. Görg, C., Cölle, J., Görg, K, et al. Spontaneous rupture of the spleen: ultrasound patterns, diagnosis, and follow-up. *Brit J Radiol* 2003; 76 :704

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