

Article

## Contrast ultrasound LI-RADS LR-5 in Hepatic Tuberculosis: Case Report and Literature Review of Imaging Features

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## Abstract

**Background:** The liver is involved in disseminated tuberculosis in more than 80% of the cases while primary liver involvement is rare, representing < 1% of all cases. Hepatic tuberculosis (TB) can be treated by conventional anti-TB therapy, however, diagnosing this disease still remains a challenge. The diagnosis might be particularly difficult in patients with a single liver lesion that could be misdiagnosed as a tumor or other focal liver lesions. While computed tomography and magnetic resonance imaging findings have been described, there is a paucity of literature on contrast-enhanced ultrasound (CEUS) features of hepatic TB.

**Case Summary:** herein, we describe a case of a patient with tuberculous lymphadenopathy and chronic HCV-related liver disease who developed a single macronodular hepatic TB lesion. Due to the finding of a hepatocellular carcinoma (HCC) highly suggestive CEUS pattern, specifically a LR5 category according to the Liver Imaging Reporting and Data System (LI-RADS), and a good response to antitubercular therapy, a non-invasive diagnosis of HCC was made, and the patient underwent liver resection. We also review the published literature on imaging features of hepatic TB and discuss the diagnostic challenge represented by hepatic TB when occurs as a single focal liver lesion.

**Conclusions:** this report shows for the first time that CEUS pattern of hepatic TB might be misinterpreted as HCC and specific imaging features are lacking. Personal history and epidemiological data are mandatory in interpreting CEUS findings of a focal liver lesion even when the imaging pattern is highly suggestive of HCC.

**Keywords:** contrast-enhanced ultrasound (CEUS), Liver Imaging Reporting and Data System (LI-RADS), differential diagnosis, hepatocellular carcinoma (HCC), tuberculosis.

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## 1. Introduction

Hepatic tuberculosis (TB) is more common in men than in women with a 2:1 ratio. It affects mostly young patients in the second decade, although isolated hepatic TB is more common among 40 to 60 years-old patients than in younger patients. Around 15% of human immunodeficiency virus (HIV) positive patients are co-infected with tuberculosis [1].

Diagnosing hepatic TB can be challenging since it can have different imaging patterns and patients might be asymptomatic or present with unspecific constitutional symptoms such as fever, fatigue, weight loss, and night sweats, which can be present also in other systemic diseases, including solid cancers and lymphomas. Hepatic TB usually involve the liver tissue with multiple tiny miliary nodular lesions, whereas involvement as a single larger nodule is rare. Single macronodular hepatic TB is therefore at higher risk of being misdiagnosed as neoplastic lesions, therefore, histological confirmation might be necessary [1,2].

Hepatic TB can be classified as follows: a) primary acute pulmonary TB with liver involvement; b) miliary TB; c) primary TB of the liver; d) tuberculoma (abscess); and e) tuberculous cholangitis. Miliary TB is the most common presentation of hepatic TB and can be associated with splenic involvement. The patient can present with hepatomegaly with or without jaundice. The liver parenchyma might appear disseminated with small (<2 cm) isoechoic, hypoechoic, or rarely hyperechoic nodules on ultrasound [1-4]. Hepatic lesions could be as small as 0.5–2 mm and might not be recognizable on ultrasound scan, although the liver might have a coarse echotexture [2]. During the chronic stage, liver lesions might present with

calcifications [1-4]. Computed tomography (CT) and magnetic resonance imaging (MRI) features of hepatic TB lesions are non-specific, and several imaging patterns have been described. Multiple small hypodense hepatic lesions with or without peripheral enhancement can be observed on CT scan. On MRI, the hepatic TB lesions are hypointense on T1-weighted images and hyperintense on T2-weighted images. The differential diagnosis of hepatic miliary TB includes sarcoidosis, opportunistic fungal infections, metastasis, lymphoma, or other granulomatous diseases [1-4]. Macronodular or pseudotumoral hepatic TB can be observed at the ultrasound as single or multiple nodules with a diameter greater than 2 cm. The ultrasound pattern is unspecific, ranging from hypoechoic or hyperechoic to mixed echogenicity lesions with or without anechoic areas. The margins of the lesion might be poorly or well-defined. The features of the hepatic granuloma at CT scan can vary according to the stage of the disease [1]. The peripherally enhancing rim of the hepatic TB lesions at contrast enhanced CT or MR represents the granulation tissue, while the hypo or non-enhancing central core constitutes the necrotic portion of the lesion. In the acute stage low attenuating lesions with central enhancement may be observed, while in the chronic stage the enhancing areas are replaced by necrotic non-enhancing tissue. The “target sign” (ie, central calcification or punctate enhancement with surrounding hypoattenuation and ring enhancement) and the “cluster sign” (conglomeration of cystic lesions) on CT and MRI are suggestive but not pathognomonic for TB. The differential diagnosis of macronodular hepatic TB includes metastasis, pyogenic abscess, and primary liver tumors [1,5].

## 2. Case Presentation

We describe the case of a 41-year-old Pakistani man who has been living in Italy since 2018. In June 2019, the patient was admitted at our hospital because of 3-week-old fever of unknown origin associated with night sweats and unresponsive to broad spectrum antibiotics. Upon physical examination he presented with a painless, hard, and fixed mass in the right supraclavicular fossa compatible with lymphadenopathy. The supraclavicular mass had appeared a month earlier and was dimensionally stable over time. There were no other pathological findings at the physical examination. The patient had no history of weight loss, vomiting, or respiratory symptoms. A complete work-up was carried out including neck ultrasound, chest X-Ray, neck and chest contrast-enhanced CT, and fine needle aspiration of the lymphadenopathy of the right supraclavicular fossa. On microbiological examination, *Mycobacterium tuberculosis* polymerase chain reaction (PCR) amplification test was positive. The patient was diagnosed with tuberculous lymphadenopathy. Antibiotic therapy with Rifampin (R) 600 mg daily, Isoniazid (H) 300 mg daily, Pyrazinamide (Z) 1500 daily, and Ethambutol (E) 800 mg daily was started. In July 2019 a chest and neck enhanced CT scan revealed a right supraclavicular lymphadenopathy of 26x22 mm without pulmonary lesions. In August 2019 following the detection of raised liver enzymes (AST/ALT 2-3 x upper normal levels; ALP/GGT 1.5-2 x upper normal levels), chronic Hepatitis C virus (HCV)-related liver disease was diagnosed, genotype 3 (HCV RNA viremia was 950814

UI/ml), but liver ultrasound did not reveal focal liver lesions. In December 2019 a chest contrast-enhanced CT did not reveal mediastinal lymphadenitis, but in the inferior untargeted scans, it detected a subcapsular pluriconcamerate liver lesion of 33x30x28 mm with irregular profiles located at the segment fifth of unclear origin. The liver lesion was considered suspicious for malignancy. Abdominal ultrasound revealed a subcapsular inhomogeneous hypoechoic focal liver lesion of 3.5 cm x 2.9 cm in segment fifth (S5). (Figure 1, Panel A).

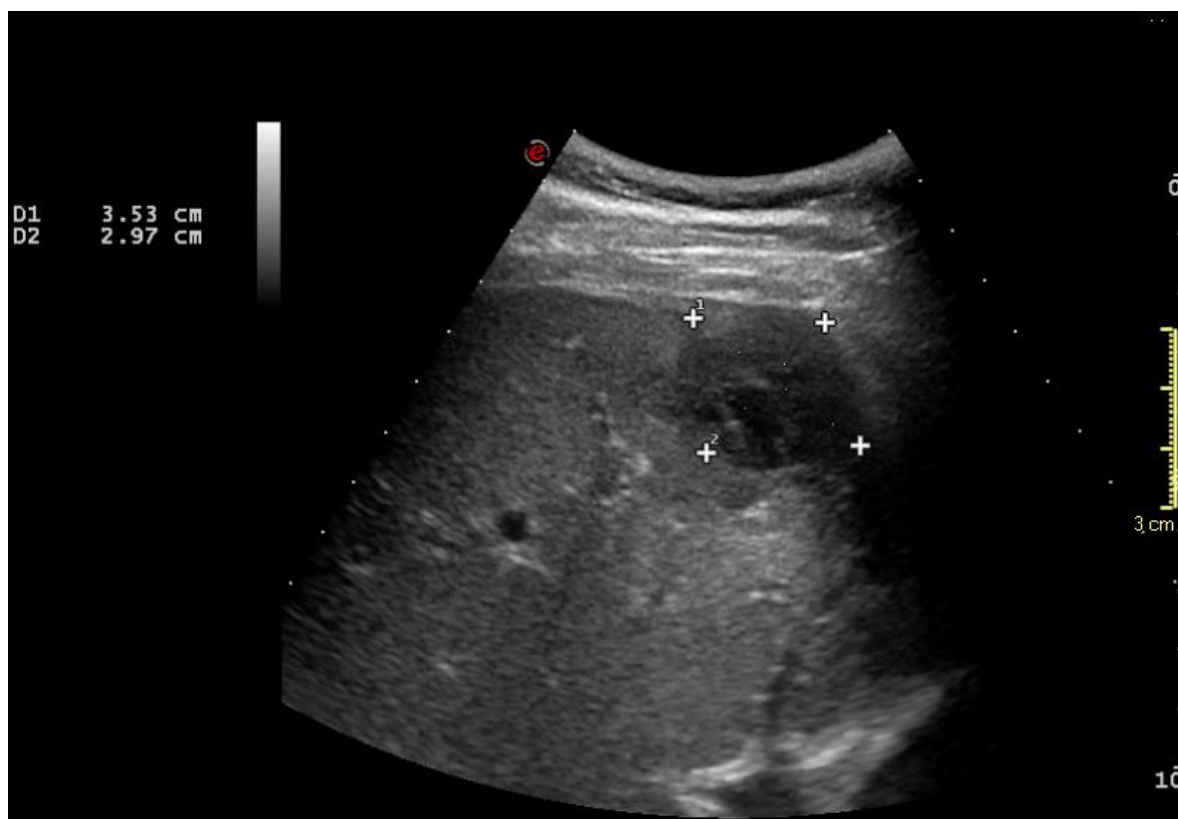


Figure 1 Panel A.

The liver stiffness determined using two-dimensional *shear* wave elastography (Aixplorer SuperSonic Imagine, S.A., Aix-en-Provence, France) was 10.9 kilopascal *that was* suggestive of advanced chronic liver disease (F4 fibrosis stage) [6].

Contrast enhanced ultrasound (CEUS) was performed to further characterize the liver lesion. After intravenous injection of 2.4 ml of SonoVue® injection, the hepatic lesion showed almost complete hyperenhancement in the arterial phase followed by late wash-out in the portal venous and late phases. (Figure 1, Panel B, C, D)

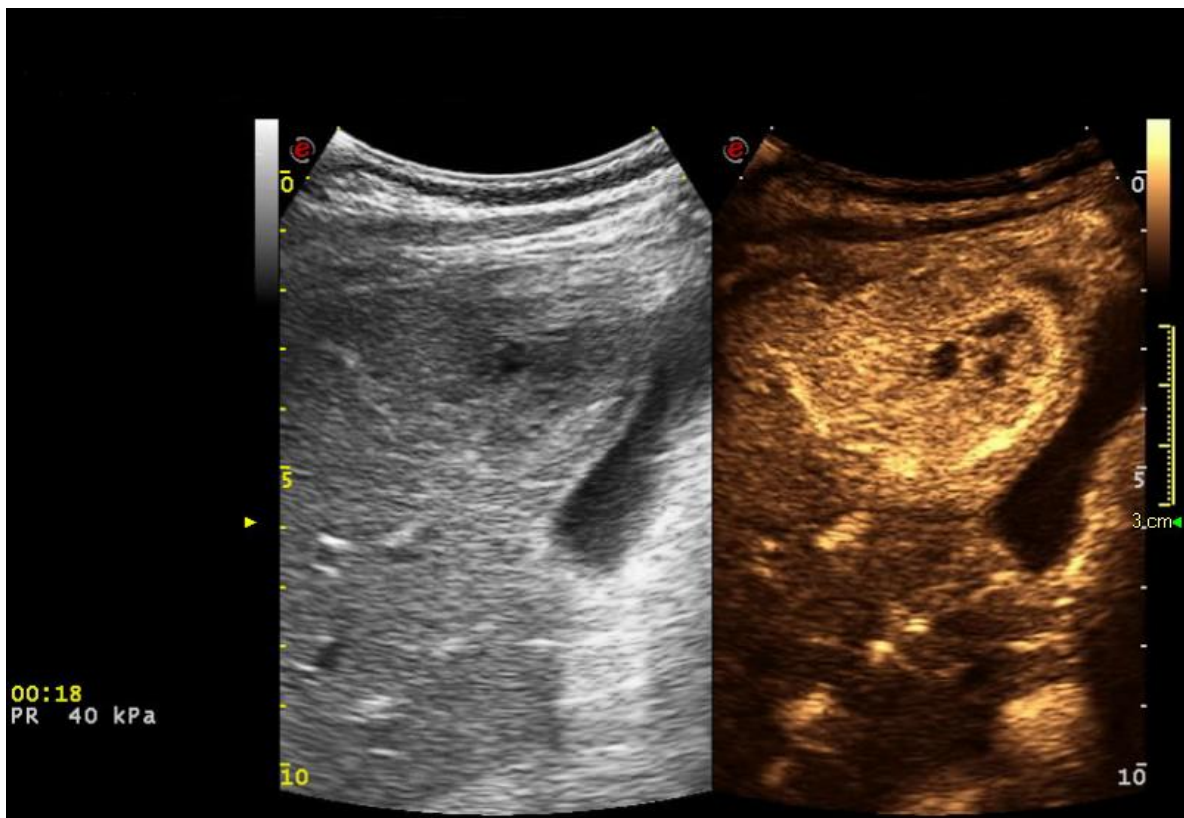


Figure 1 Panel B

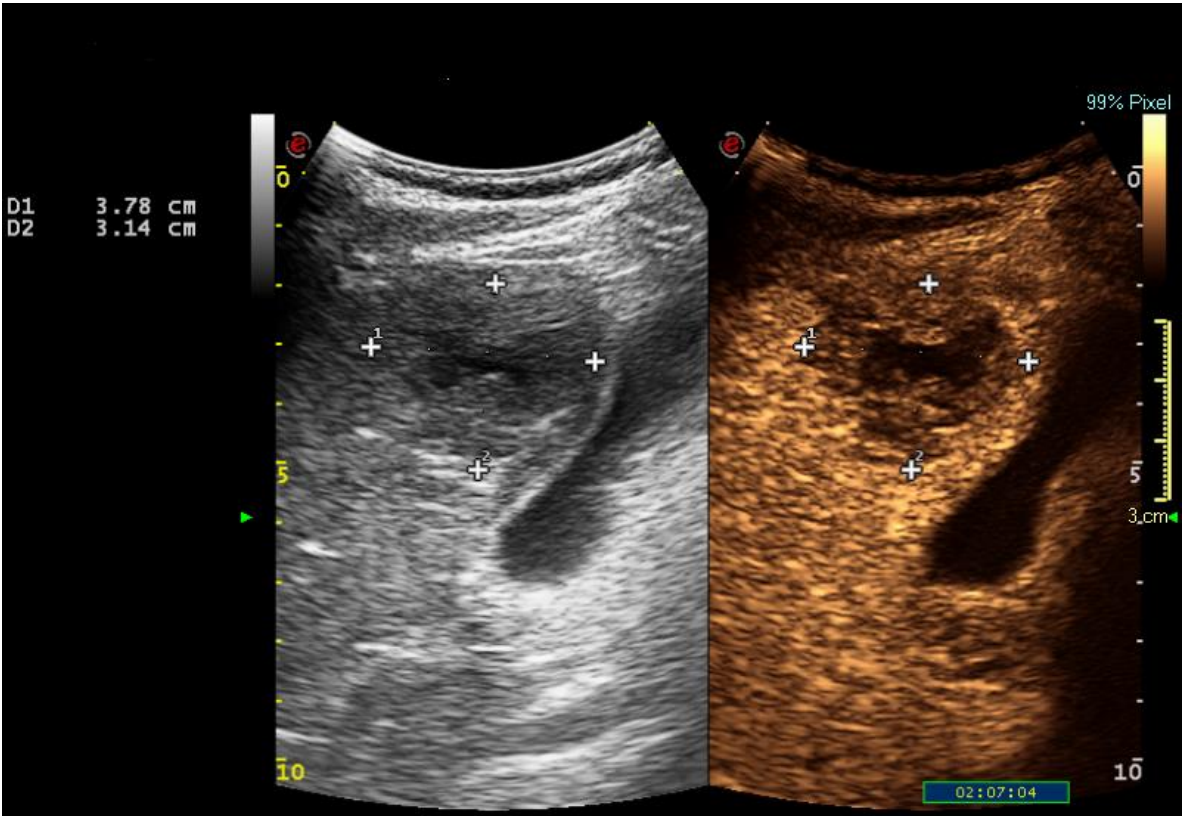


Figure 1 Panel C

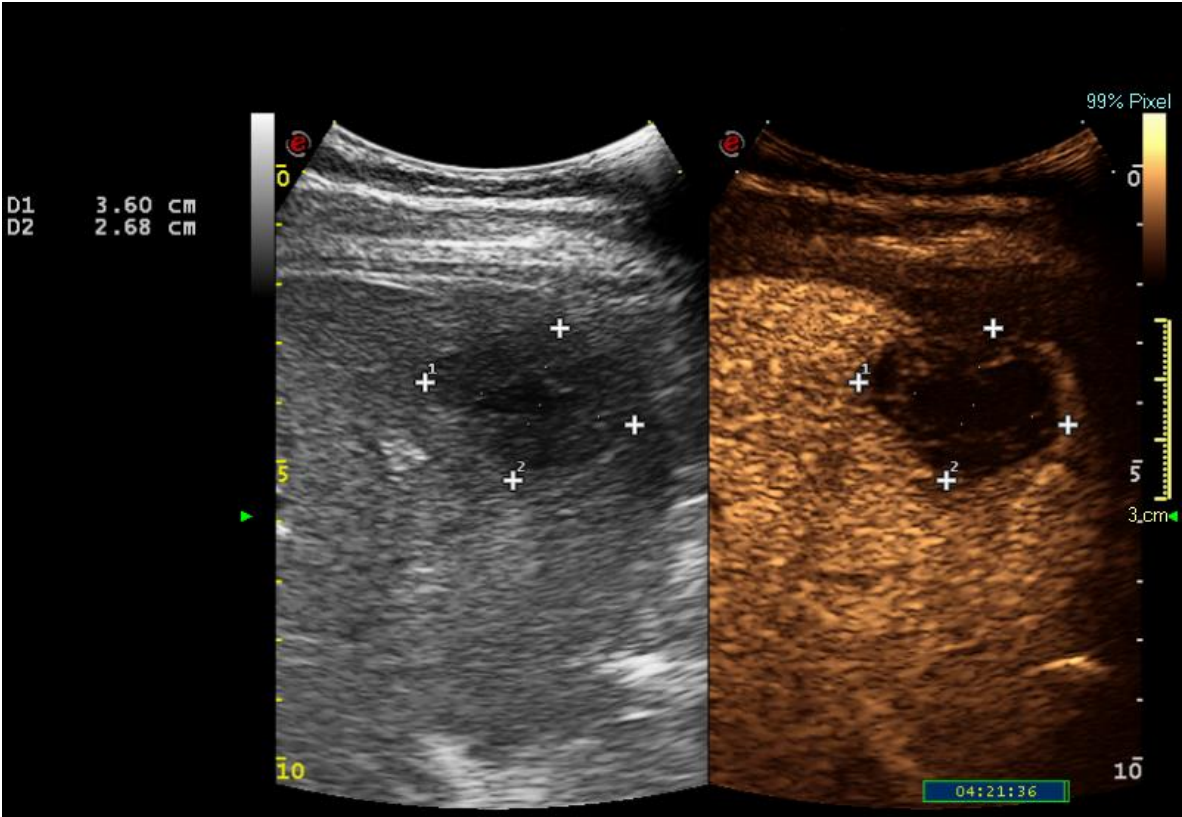


Figure 1 Panel D



The CEUS pattern of the hepatic lesion, according to the American College of Radiology Liver Imaging Reporting and Data System (LI-RADS®) used to classify lesions at risk of HCC, was compatible with LI-RADS LR5 category or definite HCC [7,8].

Due to the detection of a highly HCC specific CEUS pattern in the setting of advanced liver disease, according to current guidelines, a non-invasive diagnosis of HCC was assumed according to current guidelines [9].

As the location of the lesion was close to the gallbladder, liver biopsy was not performed and a decision for liver resection was taken.

In February 2020 the patient underwent wedge resection of the hepatic segment fifth (S5). Because of the macroscopic necrotic aspect, a complete bacteriological examination (including PCR and tissue culture for *Mycobacterium tuberculosis*) of the lesion tissue was performed together with histological examination of the resected liver tissue and of the pericholedochal lymph node. The resected hepatic lesion was characterized as an abscess with granulomatous inflammatory reaction with giant and necrotic cells. The examined liver tissue did not reveal malignant cells or Acid-Alcohol Resistant Bacilli (BAAR). The dissected pericholedochal lymph node was characterized as a reactive lymph node. The abscess content was BAAR negative and PCR positive for KB, sensitive to Rifampicin. The bronchial aspirate was negative for BAAR, PCR was negative for KB, and the mycobacterial culture was negative.

The patient was diagnosed with hepatic tuberculosis and therapy with R 600 mg daily, H 300 mg daily, and Levofloxacin 1000 mg daily was administered.

At 8 months of follow-up, the patient is still doing fine with no recurrence of focal liver lesions neither lymphadenopathy (Table 1).

Time	Event	Findings
June 2019	fever associated with night sweats	painless, hard, and fixed mass in the right supraclavicular fossa.
July 2019	Chest and Neck CT	Right supraclavicular lymphadenopathy of 26x22 mm.
	Fine needle aspiration of the lymphadenopathy of the right supraclavicular fossa; tissue culture and polymerase chain reaction (PCR) amplification.	Koch Bacillus isolated from both tissue culture and PCR
July 2019	Chest X-Ray	No signs of pulmonary TB. Diagnosis of tuberculous lymphadenopathy
July 2019	Starting treatment with Rifampin (R), Isoniazid (H), Pyrazinamide (Z), and Ethambutol (E)	Well tolerated
August 2019	Viral hepatitis serological markers because of elevated AST/ALT, ALP and GGT <i>elevations</i>	HCV-related chronic hepatitis (genotype 3)
October 2019	Abdominal ultrasound	No liver lesions
December 2019	Chest <i>contrast-enhanced</i> CT	No pulmonary neither lymphadenopathy TB. Subcapsular focal liver lesion in the fifth segment (S5) suspicious for malignancy
January 2020	CEUS to further characterize the focal liver lesion	Focal liver lesion with CEUS LI-RADS LR5 pattern (highly suggestive for HCC).
January 2020	2-dimensional <i>shear wave elastography</i> (because of detection of focal liver lesion)	Liver stiffness of 10.9 kPa (suggestive of advanced chronic liver disease).

February 2020	Liver wedge resection of the segment fifth (S5)	Abscess with granulomatous inflammatory reaction with giant and necrotic cells
February 2020	Histological examination and PCR for KB	No malignant cells; PCR positive for KB, sensitive to R; Diagnosis of hepatic TB
March 2020	Antibiotic therapy with R, H, and Levofloxacin was administered.	Well tolerated
April, May, October 2020	Clinical and biochemical re-evaluation	The patient was fine

Table 1 Patient history in timeline format

### 3. Discussion

With a burden of disease that accounts for more than 10 million new cases per year, of which less than two-thirds are reported, TB continues to be a major global health threat. TB is a rare disease in Western countries however, intravenous drug users, immunocompromised subjects, AIDS, and diabetic patients represent the most susceptible to infections. Pakistan, with a 6% of cases, is among the eight countries accounting for two-thirds of the total number of cases globally [10,11].

Despite the presence of such categories at greater risk, diagnosing hepatic TB can be challenging since it may display uncertain imaging patterns and the clinical manifestations may be quite variable.

Extrapulmonary TB represented 15% of the 7.0 million incident cases that were notified in 2018, ranging from 8% in the WHO Western Pacific Region to 24% in the Eastern Mediterranean Region. In northern Europe and the USA up to 40% of all cases of TB are extrapulmonary, and lymphadenitis is the most common

extrapulmonary presentation of tuberculosis [11]. Gastrointestinal TB constitutes nearly 10% of all extrapulmonary cases [12].

Hepatic TB is almost invariably associated with systematic dissemination of TB bacilli and is often unrecognized and missed because of its relatively nonspecific clinical presentations [1,3,11].

Imaging features of hepatic TB have been described using CT and MRI, and the imaging appearance of these lesions is considered as non-specific, and often, a histopathological or bacteriological confirmation is required [1,2,4,5,13-19].

CEUS, CT, and MRI are used in clinical practice for the characterization of liver lesions. However, imaging findings might be inconclusive or misleading in the diagnosis of hepatic TB (Table 2) [1,5,16,18-21].

**Table 2**

<b>Imaging</b>	<b>Contrast-enhanced ultrasound</b>	<b>Computed Tomography</b>	<b>Magnetic Resonance Imaging</b>
<b>Unenhanced scan</b>	Mainly hypoechoic but also isoechoic or hyperechoic nodules*	hypodense lesions <sup>o</sup>	hypointense on T1-weighted images, isointense or hyperintense lesions with a peripheral hypointense rim on T2-weighted images <sup>#</sup>
<b>Arterial phase</b>	Rim enhancement with a hypoenhanced or non-enhanced center or complete hyperenhancement of the lesion <sup>^</sup>	Peripheral contrast enhancement <sup>o</sup>	Rim heterogenous contrast enhancement
<b>Late phase</b>	Wash-out	Wash-out	Wash-out

### **Footnotes to Table 2**

*Comparison of imaging features of hepatic tuberculosis. All the imaging techniques can reveal a macronodular single lesion or multiple small miliary nodular lesions. \* The features may differ depending on the stage of the disease. ° CT imaging features of macronodular hepatic TB depends on the stage of the disease. Non-caseating granulomas appear hypodense on the unenhanced study and usually display no or minimal peripheral rim enhancement following intravenous contrast administration. Hepatic tuberculomas eventually tend to calcify, and the presence of calcified granulomas at CT in patients with relevant clinical history and in the absence of a known primary tumor should raise suspicion for tuberculosis. ^ The enhancement patterns on CEUS correlated with the different pathologic stages of the hepatic TB lesions, ranging from granulomatous lesions with or without caseation necrosis to fibrotic and calcified lesions. # Depending upon the stage of the disease.*

The diagnosis might be particularly difficult in patients with a single liver lesion, with underlying liver disease, without any history of TB nor signs of pulmonary TB. In such cases, histological and/or bacteriological confirmation might be needed to make an early diagnosis and start antibiotic therapy [13,21].

However, HCC is an unique entity as an imaging definite diagnosis can be achieved, not requiring histological confirmation. Therefore, if TB emerges in patients fulfilling the criteria for non-invasive diagnosis of HCC, corresponding to a typical contrast enhanced pattern in patients with cirrhosis a risk of misdiagnosis cannot be avoided.

Clinical conditions must therefore be heavily weighted to raise the suspicion of an alternative diagnosis.

Early diagnosis of hepatic TB is in fact important to reduce morbidity and mortality. It has been reported that patients can recover with anti-tuberculosis chemotherapy if the treatment is administered in the early stage [14].

A delayed or wrong diagnosis can instead cause the situation to deteriorate and lead to complications, requiring invasive treatment such as percutaneous drainage or surgery [16,18-20].

While CT and MRI findings have been described in some detail, there is a paucity of literature on CEUS features [1-5,18,19].

Due to a significant overlap with other common and similar appearing hepatic lesions, hepatic TB is often either misdiagnosed or labeled as indeterminate lesions. Several cases of hepatic TB lesions resembling primary or secondary liver cancer at the imaging have been described in literature, hence histopathologic and/or bacteriological diagnosis was needed [2,3,16-19].

However, the data on the CEUS features of hepatic TB are scarce. In the only study evaluating CEUS pattern of hepatic TB, most of the 24 hepatic TB lesions, were subcapsular, located on the diaphragmatic surface of the liver, and oval-shaped [22]. Almost 80% of the lesions had an inhomogeneous hypoechoic echogenicity and more than 90% had poorly defined margins on B-mode ultrasound. Lesions usually had no or very weak intralesional flow signal on Doppler ultrasonography. After the injection of contrast medium (SonoVue®), more than half of the lesions (54.2%)

presented a rapid and marked rim enhancement with a hypoenhanced or non-enhanced center in the arterial phase. About 37% of the lesions showed a transient inhomogeneous enhancement of the entire lesion during the arterial phase. The majority of the lesions showed a distinct contrast wash-out in the portal phase. The enhancement patterns on CEUS correlated with the different pathologic stages of the hepatic TB lesions, ranging from granulomatous lesions with or without caseation necrosis to fibrotic and calcified lesions [22].

To our knowledge, the HCC highly specific pattern CEUS LI-RADS LR5 has not been described previously in hepatic TB. Therefore, though very rare, the risk of misdiagnosis should be taken into account when using the LI-RADS algorithm, giving weight to the relevant clinical and epidemiological data, which might justify biopsy even in case of theoretically diagnostic pattern such as LI-RADS LR5.

#### **4. Conclusion**

This case initially misdiagnosed as HCC complicating HCV-related chronic liver disease confirms imaging polymorphism of hepatic TB and illustrates the difficulty in reaching a correct preoperative diagnosis. Due to the lack of specific clinical manifestations and imaging features, a good knowledge of personal history and epidemiological data is mandatory in interpreting CEUS findings of a focal liver lesion and for the differential diagnosis, even when the imaging pattern would be highly suggestive of HCC.

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