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Comments and illustrations of the WFUMB CEUS liver guidelines: Rare focal liver lesions – infectious (bacterial)

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Abstract

In this series of papers on comments and illustrations of the World Federation for Medicine and Biology (WFUMB) guidelines on contrast enhanced ultrasound (CEUS) the topics of bacterial infections are discussed. Improved detection and characterization of common focal liver lesions (FLL) are the main topics of these guidelines but detailed and illustrating information is missing. The focus in this paper on infectious (bacterial) focal liver lesions is on their appearance on B-mode and Doppler ultrasound and CEUS features. Knowledge of these data should help to raise awareness of these rarer findings, to think of these clinical pictures in the corresponding clinical situation, to interpret the ultrasound images correctly and thus to initiate the appropriate diagnostic and therapeutic steps in time.

Keywords: Guideline; carcinoma; focal nodular hyperplasia; abscess; parasitosis

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Introduction

The World Federation for Ultrasound in Medicine and Biology (WFUMB) has published guidelines on the use of contrast-enhanced ultrasound (CEUS) for the evaluation of focal liver lesions [1-5]. Improved detection and characterization of common focal liver lesions (FLL)

are the main topics of these guidelines. In recent years, conventional ultrasound (US) and CEUS features of less common FLL have been described in detail. The currently published papers with gold standard histology include hemangioma [6], focal nodular hyperplasia [7,8], hepatocellular adenoma [7-9], cholangiocellular adenoma [10], peliosis [11-13], cystadenoma and cystadenocarcinoma [14], hemangioendothelioma [15,16], metastases [4-12], hepatocellular carcinoma (HCC) in the non-cirrhotic liver [17,18], HCC [13-19], cholangiocellular carcinoma (CCC) [20-24]. Several of these are from multicenter trials [4,7-10,12], guidelines (EFSUMB) [13,14,25-36] and comments to these guidelines [20,21,37-43].

There are also several papers and reports on the more uncommon hepatic lesions. These include characterization of fibrolamellar hepatocellular carcinoma (fHCC) [19,20], very small HCC (HCC, sHCC <10 mm) [21], mixed HCC and CCC (mHCC/CCC) [22], nodular regenerative hyperplasia [23], sarcoma [24], inflammatory pseudotumour [25], sarcoidosis [26-29], tuberculosis [30,31], hydatid cysts [32-35], alveolar echinococcosis [33], schistosomiasis [36, 37], ascariasis [38,39], fasciolosis [40], clonorchis and opisthorchis [41], toxocariasis [42], bacillary angiomatosis [43], amyloidosis with spontaneous hemorrhage [44], as well as rare FLL in pediatric patients [45,46].

In this current paper series, we aim to summarize the US and CEUS features of rare FLL with limited reports and figures published in order to create a library of these rare lesions.

Actinomycosis of the liver

Actinomycosis is a rare form of chronic, granulomatous infection caused by gram-positive bacteria of the *Actinomyces* genus. There are 13 different species, but only 6 are associated with diseases in humans. The most common pathogenic species in humans is the *Actinomyces israelii* [47]. An infection with *Actinomyces israelii* is endogenous, because the species resides as a normal inhabitant on mucosal surfaces and gains access to deeper tissues via trauma, surgical procedures, or foreign bodies that disrupt the mucosal barrier [48]. In the abdomen, actinomycotic pelvic abscesses are believed to be related to intrauterine devices (IUDs) and typically affect the ileocecal region and appendix [49,50].

Hepatic actinomycosis is very rare and is often a secondary infection. The few related publications mostly consist of single-case reports. Hepatic involvement is present in 15% of patients with abdominal actinomycosis and is thought to result from the metastatic spread of abdominal infections at other sites via the portal vein [50]. Most of the recorded abscesses involve the right lobe of the liver, due to the drainage of the gut via the superior mesenteric vein. However, owing to the dual blood supply of the liver and via the biliary tree, hepatic actinomycosis can also be caused by pyogenic infection originating from other sites in the body [51]. Primary hepatic actinomycosis is a very rare condition, and should be considered only if there is no sign of primary involvement of the abdominal area or elsewhere within the body [52]. There are no characteristic clinical manifestations of actinomycosis in the liver (fig 1-3). The treatment for this condition is based on high dose, long-term courses (i.e., several months) of penicillin or alternative antibiotics such as erythromycin, cephalosporins or rifampicin to completely eradicate the infection. Pharmaceutical interventions alone may not suffice, and surgical treatment may be needed. This can involve the excision of necrotic tissues, drainage of abscesses, and removal of sinuses and fistulas [50].

Imaging

At ultrasound (US) imaging, the features observed in reported cases have mainly been of heterogenous mildly hypoechoic lesions with ill-defined borders. These non-specific features can be easily misdiagnosed for a primary liver cancer or metastatic liver cancer [47,50-56]. Occasionally, US may reveal mixed cystic and solid liver lesions and these features are difficult to differentiate from other acute bacterial liver abscesses, amebic abscesses, echinococcal cysts, or partially necrotic tumors [49,52,56]. As actinomyces bacteria are invasive and frequently cross anatomical boundaries, they typically penetrate the capsule of the liver and invade the surrounding tissue [49,50].

Only a few cases utilizing CEUS of the liver in patients with actinomycosis have been published. In one case, moderate contrast uptake during the arterial phase was noticed, with no washout during the portal venous phase and the delayed phase, along with an intense vascular signal in the surrounding liver parenchyma (rim-enhancement) [57]. The other case exhibited mild hyperenhancement in the portal venous phase and mild hypoenhancement in the late phase [58]. In another case, actinomycosis of the liver occurred secondary to a primary infection of the abdomen involving the ileocecal region. Mild hyperenhancement of the liver lesions were seen in the arterial phase, followed by washout of the contrast agent in the late portal venous and delayed phases, with a slight rim enhancement in the portal venous phase. In addition, 2 small lesions with no contrast enhancement were detected.

Owing to their non-specific presentation and non-descript symptoms (fever, abdominal pain and weight

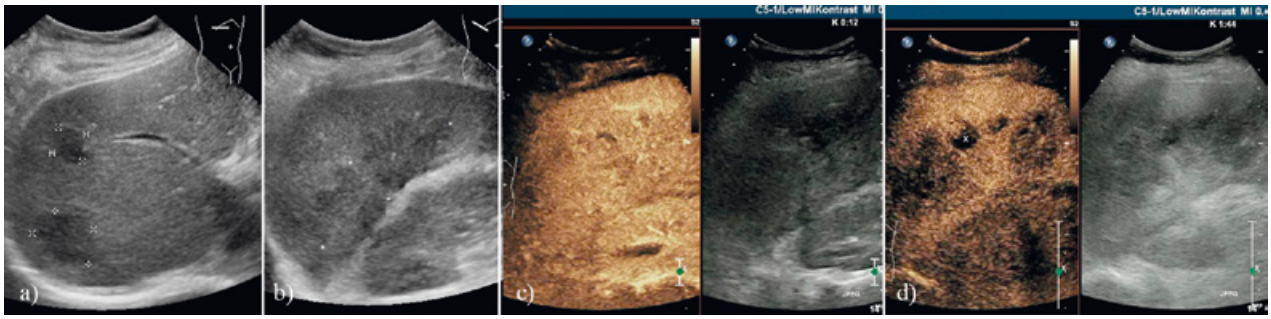

Fig 1. Actinomycosis of the liver (histological proven). 36 y/o female. Complaining about abdominal pain, fever and reduction of general constitution. B-mode ultrasound demonstrated hypoechoic lesions in the right lobe of the liver (a). As well as heterogenous isoechoic lesions with undefined borders (*) (b). All lesions were initially suspected to be primary liver cancer or liver metastasis of a cancer with unknown origin. Contrast enhanced ultrasound showed slightly reduced arterial enhancement (c) followed by a washout of the contrast-agent in late portal-venous phase and delayed phase. Two small lesions with no contrast enhancement (x) have been detected (d). Biopsy and histological evaluation showed Actinomycosis of the liver. Treatment with intravenous penicillin was initiated, which had to be changed to Tetracycline after allergic reaction. Clinical recovery was accompanied by substantial reduction of the inflammatory masses and abscesses in follow-up imaging.

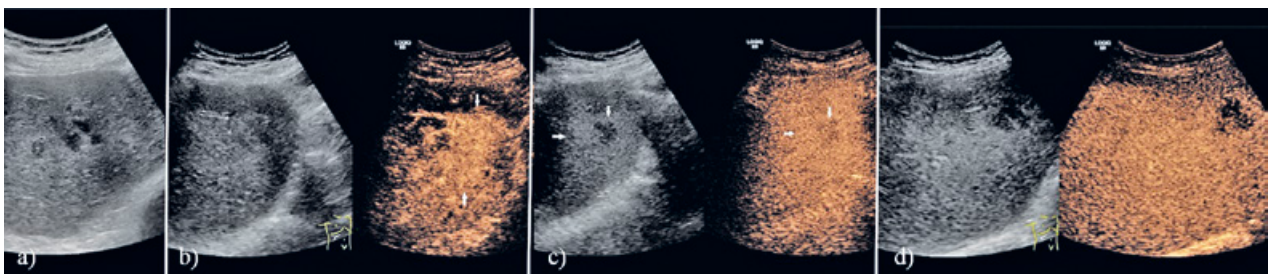

Fig 2. Actinomyces abscesses of the liver in a 72 y/o male with chronic calcifying pancreatitis. Current weight loss. Computer tomography showed a suspected pancreatic head tumor with multiple hypoechoic liver lesions. Endosonography did not show the lesion in the chronically calcified pancreatitis. A pro forma EUS-FNA of the pancreatic head was performed without evidence of malignancy. Ultrasound showed multiple hypoechoic lesions of the liver. These were suspicious for metastases. Ultrasound guided biopsy was performed. The pathological examination revealed actinomyces abscesses of the liver. The CEUS examination was performed with knowledge of the diagnosis before the start of several weeks of penicillin therapy. B-mode ultrasound showed multiple hypoechoic liver lesions. On careful examination, these were surrounded by a hyperechoic rim (a). At CEUS, both the hypoechoic lesions and the hyperechoic surrounding area are hyperenhanced in the arterial phase (arrows) (b). During the portal venous phase, the hypoechoic lesions showed a washout and were hypoenhanced (arrow), while the surrounding hyperechoic rim remained hyperenhanced (arrow) (c). In the late phase, the lesions were hypoenhanced (d). The hyperenhancement of the surrounding hyperechoic rim was an expression of hyperemia due to inflammation. After several weeks of penicilline therapy, the liver lesions were no longer detectable.

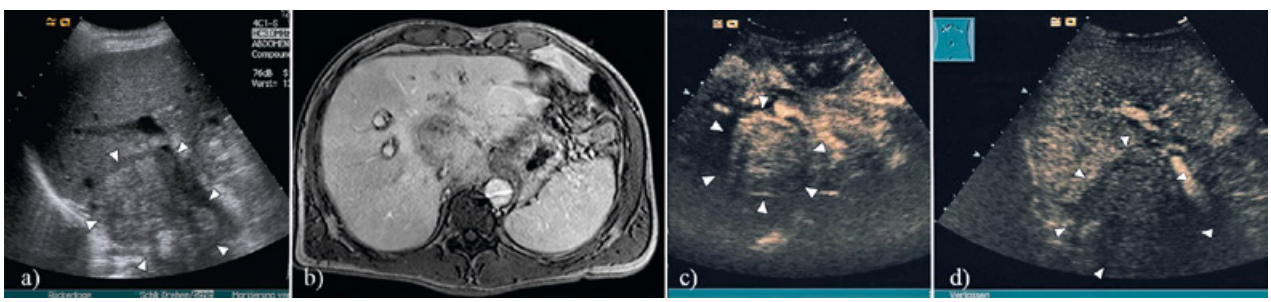

Fig 3. Primary hepatic actinomycosis (histological proven) in a 49 y/o male presenting with right upper abdominal pain and normal temperature. B-mode ultrasound showed a large heterogeneous lesion with irregular margins affecting the liver hilum (a). Magnetic resonance imaging revealed a heterogeneously hypoenhancing mass (b). Contrast-enhanced ultrasound revealed a slightly hyperenhanced lesion with well-defined margins during the arterial phase (c) and washout during the portal venous and late phase (d). Ultrasound-guided biopsy revealed actinomycosis. Computed tomography of the abdomen and the lungs as well as dental examination did not show further affected organs. Treatment with intravenous penicillin for 6 weeks followed by oral penicillin for 24 weeks resulted in complete remission.

loss) with a subacute to chronic course, imaging alone remains insufficient to make the correct diagnosis [54,55]. The definitive diagnosis is based on a pathohistological examination following a percutaneous biopsy or surgical resection and subsequent tissue cultures [53-55,59]. Actinomycosis tends to lead to a chronic and suppurative infection, resulting in fibrosis with draining sinuses that are pale yellow and often referred to as "sulfur granules." Furthermore, the walls of these masses are often described as "wooden" in consistency owing to the fibrosis [60].

Hepatic brucellosis

Brucellosis is one of the most common zoonosis worldwide; it is widespread in specific endemic areas such as the Mediterranean, Asia and South America, with more than 500 000 documented cases per year [61]. This multi-systemic disease is caused by Brucella, an intracellular gram-negative bacterium of the reticular-endothelial system. Brucellosis normally affects animals but can cause systemic infections in humans, most commonly the liver and spleen, in 30-60% of cases [62]. The infection occurs by direct or indirect exposure, typically contact with infected animals through the skin or mucous membranes, or by ingestion of contaminated food, particularly dairy products [63].

The diagnosis of brucellosis is based, in most cases, on a combination of clinical suspicion, serological markers, and radiological findings. The most frequent clinical symptoms are often non-specific and include malaise, asthenia, myalgia, arthromyalgia, fever, nausea, and anorexia. Laboratory tests commonly show an increase in inflammatory indices and cholestatic markers and occasionally an increase in aminotransferases. For the diagnosis of brucellosis in humans, various serological tests are used, among which the most common are Wright's serum agglutination test, Coombs anti-brucella antibody test, Rose Bengal test, and the complement fixation test.

While commonly presenting with multi-organ involvement, hepatic and splenic involvement predominate radiological findings, although patients are usually asymptomatic. On CT or MRI, splenic or hepatic abscesses can be identified and the additional finding of hepatosplenomegaly would also narrow the differential diagnosis. Ultimately however, the diagnosis of brucellosis requires validation by histological patterns or positive cultures on blood or tissue samples. The pathological evaluation is not entirely straight forward either where a predominating feature is caseating necrosis, but this can also be seen in epithelioid granulomas or other bacterial infections. The histological patterns show fibrosclerotic tissue with an intense inflammatory reaction.

Imaging

On imaging, a brucellosis abscess is usually solitary in nature, with a single lesion in 68% of the cases, usually localized to the right lobe in 71% of cases, measuring between 2 and 10 cm and has typical central calcification in 77% of cases [64]. Radiological investigations are fundamental in the diagnosis of a hepatic brucelloma. US and CT are the most common imaging modalities.

The association of ultrasound features with the presence of central calcification, peripheral necrosis and a positive Brucella agglutination tests would strongly support the correct diagnosis [65]. US appearance of a Hepatic brucelloma is of a hypoechoic and poorly defined lesion with a central fluid collection and calcification. This is a non-specific appearance and may require further evaluation with CT or MRI, and correlation with the laboratory tests.

CT allows for a volumetric assessment of the extent of the disease. However, small abscesses from the acute stage of brucellosis may be difficult to identify owing to limited contrast resolution. Brucella abscesses in the venous phase of contrast-enhanced CT demonstrates a hypodense pseudo-tumoral lesion within normal liver parenchyma with avidly enhancing areas in the arterial phase. There is often central calcification surrounded by fluid components.

MRI is very sensitive for early detection of liver infections [5], but not frequently used owing to availability in regions with higher incidence of brucellosis. At MRI, the brucellar abscess presents as a heterogeneous lesion with a hypointense signal on T1-weighted sequences and a hyperintense signal on T2-weighted sequences. After injection of contrast medium, enhancement of the walls of the abscess is observed and can persist during the delayed phase secondary to inflammation. Hypovascular regions peripheral to the abscess can be seen in some cases and may represent edema or necrosis with decreased perfusion.

The use of CEUS is recommended in the characterization of liver abscesses [5]. The typical pattern described is peripheral enhancement in the arterial phase, with hyper/isoenhancement of the rim in the portal venous phase and hypoenhancement in the late phase. The most typical feature is the complete absence of enhancement of the central necrotic area during all vascular phases. Diffuse hyperenhancement of the sub-segment(s) involved in arterial and late phase wash-out of the hepatic parenchyma surrounding the non-enhancing necrotic area have also been described. Septae, if present, may show enhancement in the arterial phase which is maintained in the portal venous phase.

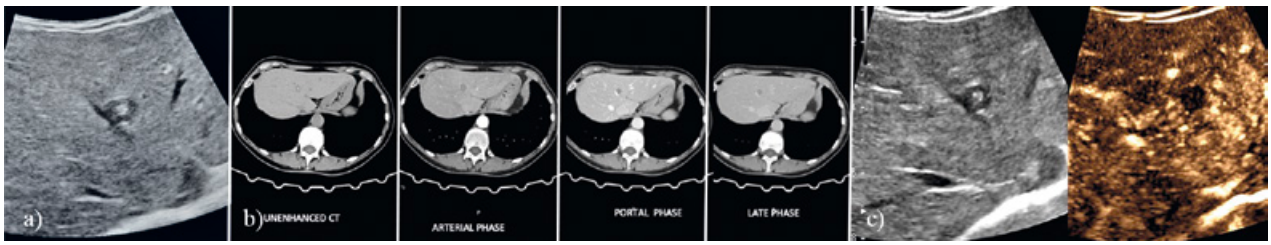

Fig 4. Brucellosis. 61-year-old woman underwent an ultrasound examination for abdominal colic. A focal lesion in segment IV of the liver with central calcification was detected (a). The CT study confirmed the central calcification and hypodensity of the lesion in all vascular phases (b). CEUS study showed complete absence of enhancement at all vascular phases, with confirmation at baseline of the presence of a central calcification (c). A chronic abscess was suspected at imaging and further history revealed that the patient had eaten unpasteurized cheese about 6 months earlier. The patient was referred to serological analysis for brucella, which confirmed the suspicion. Top-Tip: Central calcification of an avascular lesion was suspicious of a chronic abscess in the correct clinical scenario and Brucella infection has been considered. An active abscess would demonstrate peripheral arterial enhancement and hypoechoic rim washout.

To date, only one case of brucellar abscess evaluated with CEUS has been described in the literature [66]. In that report, US imaging showed an anechoic lesion in the right lobe surrounded by a hypoechoic peripheral rim of 1 cm and large central calcification. In the arterial phase, the lesion showed early and marked enhancement with larger dimensions than visualised on B-mode, with a non-enhancing central area. In the portal venous phase, superimposed perfusion of the surrounding hepatic parenchyma was described. In the late phase, wash-out was evident with a hypoechoic peripheral rim which was also evident on B-Mode (fig 4). As mentioned before, these imaging features are not specific and can also be seen with other granulomatous disease or infections such as tuberculosis, hydatidosis and histoplasmosis. The differential diagnosis would also include a chronic hematoma, calcified tumors or metastatic disease.

In summary, imaging plays a crucial role in the diagnosis of brucellosis. MRI has superior sensitivity compared to CT in characterizing brucellar abscesses and may detect smaller abscesses which are not obvious on CT [67]. CEUS is also able to find the pattern of brucellosis that is seen on CT and MRI with contrast and could therefore be utilized as the first-line investigation. The CEUS behavior of a brucellar abscess is non-specific but the vascular enhancement pattern on arterial and venous phase suggesting an abscess, presence of central calcification and serological tests all contribute to establish the diagnosis and thus initiation of the correct antibiotic treatment.

Bartonellosis

Bartonella henselae is the causative agent of cat-scratch disease (CSD) and other disorders, including hepatosplenic granulomatosis [68]. Hepatosplenic bartonellosis (HSB), also referred to as hepatosplenic CSD, is a granulomatosis that has rarely been reported in immunocompetent adults [69]. The main symptoms are fever, weight loss, abdominal pain, peripheral lymphadenopathy, and sweating. The median duration of symptoms before diagnosis is 30 days (with a range of 15–60 days; [69]. Serologic testing for the presence of antibodies to *B. henselae* is the most widely used test to confirm the diagnosis of CSD in a patient with signs and symptoms consistent with the illness [70]. Trimethoprim-sulfamethoxazole, rifampin, erythromycin, clarithromycin, azithromycin, doxycycline, ciprofloxacin and gentamicin are the agents of choice [70]. One large study, typically described circular lesion(s) in the liver (n=16, 16.7%), spleen (n=28, 29.2%), or both (n=52, 54.2%), with multiple lesions in 82 patients (85.4%) [69]. The lesions were <20 mm in 48 cases (50.0%), 20–50 mm in 23 cases (24.0%), and >50 mm in 3 cases (3.1%). US imaging was available for 35 patients and revealed hypoechoic lesions (n=33), while CT scans available for 64 patients found hypodense lesions (n=61). In 15 of these cases, there was contrast-enhancement but without a specific pattern. Magnetic resonance imaging, performed in 11 cases only, consistently described hypo-intense lesions on T1-weighted images and hyper-intense lesions on T2-weighted ones. Finally, positron emission tomography (PET)-CT was available in 14 patients and found metabolically active lesions [69] (fig 5).

Primary hepatic tuberculosis of the liver

Mycobacterium tuberculosis is a significant threat that causes over 10 million cases and 1.5 million deaths per year [71]. It is mostly prevalent in developing countries [72]. Tuberculosis (TB) is more common in immunocompromised patients, and its incidence is high in countries with a high prevalence of human immunodeficiency virus (HIV). Although TB predominantly affects

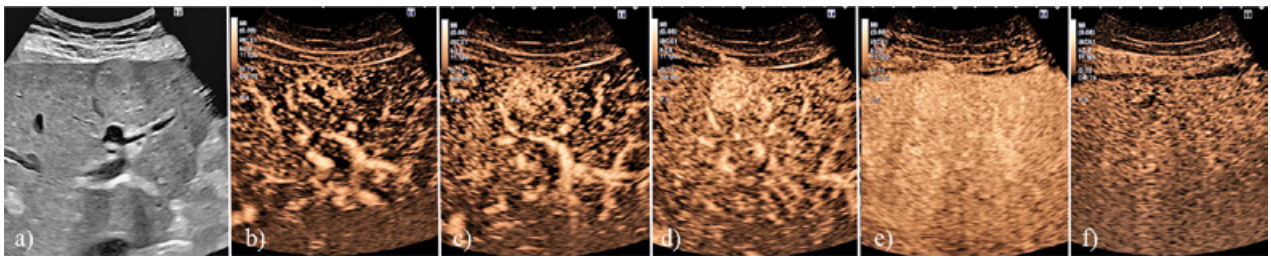

Fig 5. Bartonellosis. A 55-year-old man with first renal transplantation performed 3 months ago, presenting with an inflammatory biological syndrome with fever and loss of weight. An incidental focal liver lesion was discovered at the non-enhanced abdominal CT. Baseline US imaging detected a sub capsular isoechoic mass with a central hypoechoic area (a). CEUS in the arterial phase confirmed the presence of a focal liver lesion with a hyperenhancing rim and delayed central enhancement (b-d). During the portal venous phase, the lesion became iso-enhanced to the surrounding liver and during the late phase the FLL showed mild and late wash out (e,f). Liver Bartonellosis was diagnosed by the serologic tests while the liver tissue obtained from biopsy was negative.

the lungs, extra-pulmonary localizations are present in 15% of the cases [72], and liver localization is seen in 80% of cases of disseminated TB [73]. Primary hepatic TB is a rare manifestation of the disease. The most frequently presented clinical and laboratory findings in primary hepatic TB are fever, weight loss, abdominal pain, hepatomegaly, and elevated alkaline phosphatase level [74]. Levine et al [75] classified hepatic TB into five categories: miliary; granulomatous (in which the tubercles merge into aggregates of 1–4 cm); nodular (a single nodule); ductal and nodal (which obstructs the portal vein). Yu et al [76] proposed three classes: miliary, nodular, and serohepatic. The miliary pattern is the most frequent one encountered where US findings are typically of multiple small rounded hypoechoic lesions. Nodular TB presents with an isolated nodule, and it accounts for one-third of the cases of hepatic TB in one case series [77]. Serohepatic is the rarest form, presenting with multiple subcapsular lesions.

The first investigation for suspected hepatic TB is US, which often yields non-specific findings. Multiple round hypoechoic lesions characterize miliary TB, while nodular TB appears as a hypoechoic mass. Sometimes, the latter exhibits a heterogeneous pattern (i.e., hyperechoic center with anechoic areas). Furthermore, ill-defined margins may disguise the coalescence of multiple micronodules appearing as a solitary mass [78-80]. Other ancillary features which can be observed include lymph nodes and ascites.

A solitary liver tubercule has been examined in a small number of cases with CEUS, notably in Cao et al's case series [80]: during the arterial phase, 54.2% of the TB lesions displayed a rapidly enhanced peripheral rim with a hypo- or nonenhanced center, whereas 37.5% exhibited heterogeneous transient enhancement of the whole lesion. During portal venous phase, most lesions exhibited washout. The various CEUS patterns correlated with different pathologic stages of TB lesions: the hyperenhancement in the arterial phase represents inflammation, while the lack of central enhancement is due to necrosis and destruction of hepatocytes. Thus, the progression of the disease corresponds to decreasing perfusion in the arterial and late phases, until its complete absence, when necrosis occurs [80]. The average size of TB lesions in this study is significantly larger on the CEUS images compared to B-mode US.

Other imaging techniques such as CT and MRI are also usually performed when hepatic TB is suspected. In CT scans, hepatic TB presents with a non-enhancing, central, low-density lesion (owing to caseation necrosis) and a slightly enhancing peripheral rim that corresponds to the surrounding granulation tissue. On the other hand, MRI of hepatic TB typically reveals a hypo-intense nodule with a hypo-intense rim on T1-weighted imaging, and on T2-weighted imaging, a hypo-intense, isointense, or hyperintense nodule with a less intense rim [81]. A septated appearance (i.e., a "honeycomb" pattern) is often observed [71,77,79]. However, the imaging features of hepatic TB may include multiple lesions of varying densities, which indicates lesions at different pathologic stages of the condition; these include TB granuloma, liquefaction necrosis, fibrosis, or calcification [82]. Hepatic TB also presents with FDG avidity on F-18 FDG PET/CT, similar to malignant tumors [5]. In addition, F-18 FDG PET/CT is less useful in differentiating hepatic TB from other hepatic necrotic masses because FDG avidity may also be observed in necrotic tumors such as hepatocellular carcinoma, intrahepatic cholangiocellular carcinoma (iCCA), and metastases [83].

Overall, there are no characteristic imaging features for hepatic tubercular lesions, since they can mimic both primary liver malignancy and metastases. Misdiagnoses are not uncommon, and they are often corrected only after obtaining the surgical specimen [78,84,85]. To confirm the diagnosis, liver biopsy for histological evaluation, culture and TB polymerase chain reaction (PCR)

are the investigations of choice, along with clinical and radiological exclusion of extrahepatic disease [86]. In addition, CEUS provides helpful guidance for biopsy, especially for small lesions. It is essential to maintain a high index of suspicion, especially in endemic regions, so as to avoid unnecessary surgery and to begin prompt treatment in the form of anti-tubercular therapy (ATT) (fig 6-9).

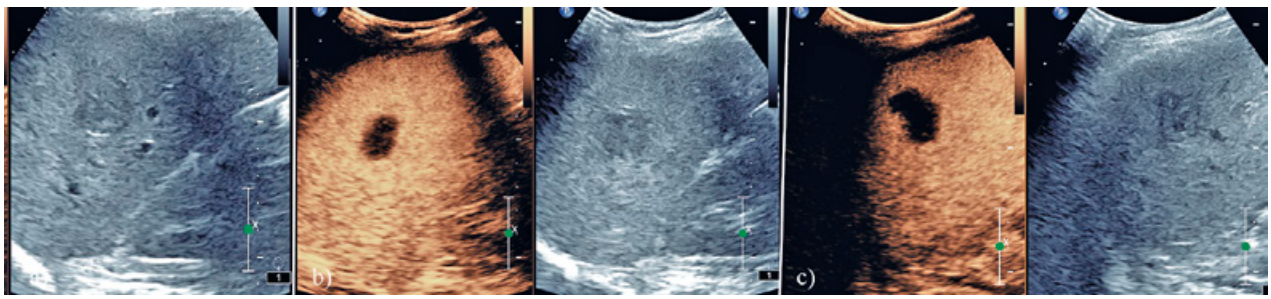

Fig 6. Hepatic tuberculosis. Isoechoic B-mode appearance and hypoenhancement in all phases (from the left to the right) representing the different appearance of hepatic tuberculosis.

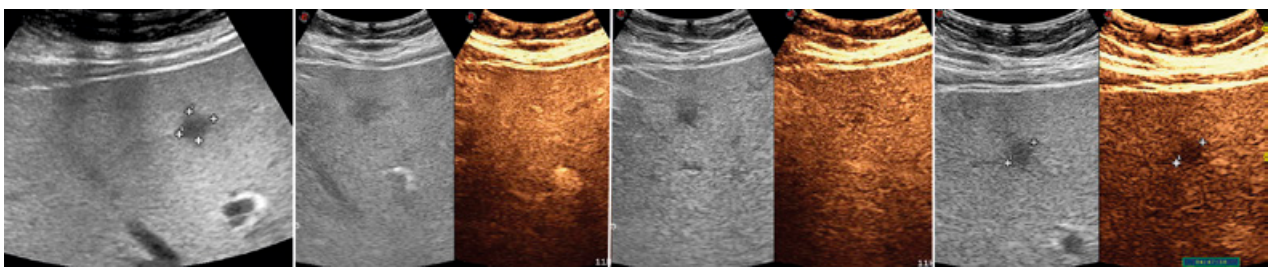

Fig 7. Hepatic tuberculosis. Hypoechoic nodules showing arterial phase contrast enhancement and wash out representing the different appearance of hepatic tuberculosis (CEUS phases shown from the left to the right).

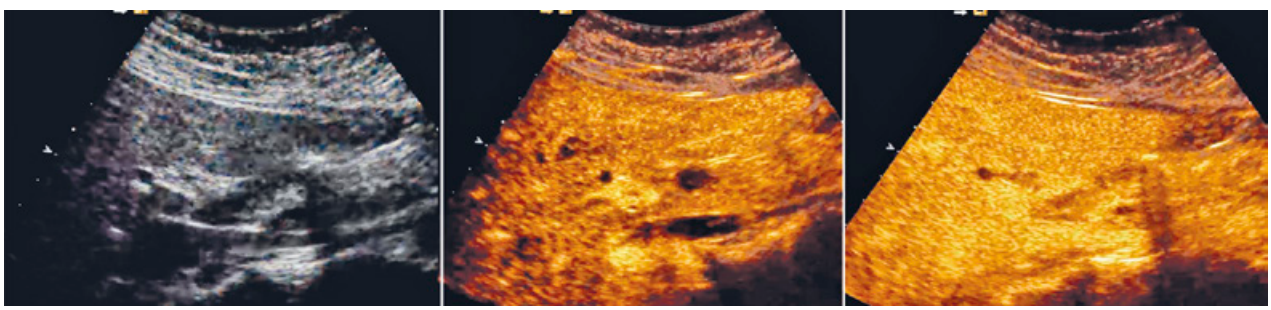

Fig 8. Hepatic tuberculosis. The most common manifestation of tuberculosis in the hepatobiliary system is peritoneal infiltration and perihepatic lymphadenopathy (CEUS phases shown from the left to the right).

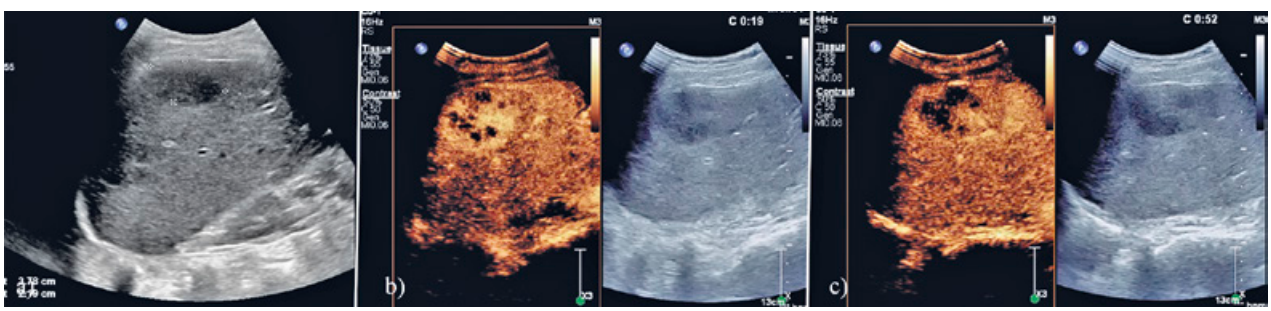

Fig 9. Hepatic tuberculosis (histological proven). 52 y/o female. Recurrent right lumbar pain for more than 10 days. No underlying disease. B-mode ultrasound with 37.8 x 21.9 mm hypoechoic focal liver lesion in the right liver lobe (a). Contrast enhanced ultrasound showed inhomogeneous hyper-enhancement with honeycomb-like non-enhancement area (b) and mild washout (c). Biopsy and histological evaluation showed hepatic tuberculosis. The patient underwent anti-tuberculosis therapy.

Melioidosis

Melioidosis is also known as pseudoglanders or Whitmore's Disease and was first described in 1912 by the pathologist Alfred Whitmore and his assistant surgeon C. S. Krishnaswami from autopsies of beggars and morphine addicts in Rangoon [87]. Melioidosis is endemic in tropical areas, specifically in Northeast Thailand and Northern Australia, but also in other regions of Southeast Asia, China, India and territories across the tropics. [88-97]. Melioidosis is endemic in regions which have tropical monsoon climates and abundant rainfall [90]. In Europe, melioidosis is usually imported from returning travelers.

The pathogen is the aerobic gram–negative bacterium *Burkholderia pseudomallei*. It is an environmental saprophyte and can be isolated from soil and surface water, especially in rice fields. It is abundant in soil at depths of >/= 10 cm from the surface but lives closer to the surface in the rainy season and is extremely resilient. The bacterium can even be detected in distilled water [88,97,98]. A modelling study calculated that there are round 165000 cases of melioidosis worldwide every year, 89000 are estimated to be fatal. It is believed that there is a wide range between suspected and registered cases [97].

The disease has a varied picture - from benign skin lesions to severe sepsis. Typical clinical manifestations are fever, pneumonia (36%) and abscesses (33%), which can occur in any part of the body. Typical abscess locations are the skin and subcutaneous tissue (21%), liver (18 - 46%), spleen (13%), lung (13%) and prostate. In most cases, there are multiple abscesses in one or more organs [88,89,99-101]. Neurological melioidosis, osteomyelitis, septic arthritis and genitourinary infections are all possible [94,97]. The detection of multiple abscesses in the liver and spleen in the tropics may be an indication of melioidosis. In the context of abscesses in melioidosis, the "*honeycomb sign*" and the "*necklace sign*" have been reported [88,89,102-105].

The disease may be acute or relapse after a latency of decades. Most people have an underlying predisposing disease, such as diabetes mellitus, chronic renal failure, chronic lung disease, thalassemia and other hematological disorders, alcoholism or other diseases with immune system deficiencies. Modes of transmission are inhalation or by direct contact between abraded skin and contaminated soil [88,99].

Burkholderia mallei is derived from *Burkholderia pseudomallei*, it is extremely infectious, mainly to solipeds but can occasionally infect humans. The US Centers for Disease Control and Prevention (CDC) have classified both bacteria as tier 1 select agents because of their biothreat potential [97].

A definitive diagnosis of melioidosis can be confirmed via culture or pathological results from the blood or infected organ. Unfortunately, cultures have low sensitivity for the detection of B. pseudomallei (60%) [106]. Serology testing by indirect hemagglutination (IHA) with a high (>1:640) or four-fold rising titer may also aid the diagnosis [107]. The indirect hemagglutination test on admission has a reported sensitivity of only 56% in Australia and 75% in Thailand [97,108,109]. Furthermore, in many endemic regions, the facilities for culture and identification of *Burkholderia pseudomallei* are often limited.

Imaging

Imaging studies such as US, CT, and MRI are helpful for early provisional diagnosis and guiding therapy. The intra-abdominal organ most commonly affected by melioidosis is the spleen, followed by the liver and kidneys. Intraabdominal abscesses are common in patients with melioidosis [88,89,99-101,110]. One or more abscesses were present in the liver and/or spleen in 33% of all the patients with melioidosis. Among them, multiple lesions were noted in 70% of cases with hepatic abscesses and 88% of cases with splenic abscesses. Evidence of abscess formation is often noted in either the lung on chest radiographs [111], or in the liver and spleen, diagnosed at US examination [112,113].

Abdominal US should be performed in all suspected cases: multiple small abscesses with a "target-like" appearance and larger multiloculated abscesses are a common finding in every organ [112].

On B-mode ultrasound and CT, multiple hypoechoic resp. hypodense lesions are seen in the liver and/or spleen, with multiple ring-shaped septa. The large lesions are typically multiloculated and multiseptated. Some liver lesions can be made up of asymmetric locules of varying sizes – "honeycomb sign" while others may exhibit a hypoechoic center with small symmetric peripheral locules in radial fashion – "necklace sign" [88,89,101]. Doppler signals can be detected in these lesions.

The "honeycomb sign" can also be found in non-melioid lesions, whereas the "necklace sign" is strongly associated with melioid hepatic abscesses [89,102,103,114]. Abscesses with the "honeycomb-sign" have also been reported in Klebsiella-associated abscesses [88]. The "honeycomb sign" however, has been reported to be a characteristic of melioidosis liver abscesses that are larger than 2 cm. Lesions larger than 5 cm have also been shown to have the "necklace sign" consisting of multiple peripheral radial loculations within large hypodense honeycomb lesions [88,102,115]. The "honeycomb sign", as a diagnostic indicator for melioidosis in liver abscesses which were greater than or equal to 2 cm, had an 85 %

sensitivity and 75 % specificity. In abscesses greater than 3 cm in size, the sensitivity and negative predictive value increased to 91 % [104]. As abscess size increases, the "honeycomb sign" is more predictive for melioidosis abscesses [104] particularly in endemic regions.

Splenic abscesses caused by melioidosis were mostly smaller than 3 cm, multiple and had no or minimal peripheral enhancement at CT [114]. Portal vein thrombosis have also been described [116,117].

In Laos, patients with fever underwent point-of-care US examination with simple portable black-and-white US equipment to check for abscesses of the liver, spleen, kidneys and prostate. In this study with 153 patients, which included 18 patients with melioidosis, 11 (61%) had an abscess at one or more sites, where five (28%) had both splenic and/or liver abscesses. The positive predictive value of abscesses for melioidosis was high at 93% (88–96%) [101]. Therefore, in endemic areas, the presence of abscesses in febrile patients should prompt empiric antibiotic therapy for melioidosis even in the absence of culture confirmation [101,118].

To the best of our knowledge, no CEUS studies or reports have been published. The only reported CEUS performed in a "honeycomb-sign" liver abscess secondary to cephalic duodenopancreatectomy showed a thin enhancing rim and some enhancing regular internal septa [119]. In other non-melioidosis associated abscesses with a honeycomb sign, the septa all showed hyperenhancement on CEUS [120].

Because of the high mortality rate, empirical antibiotic therapy is started in endemic regions when clinical symptoms of melioidosis are present, while waiting for confirmation by laboratory tests [100]. The detection of abscesses, especially liver abscesses with the "honeycomb" and in particular the "necklace sign" may be pathognomic of the disease and can be helpful in aiding the differential diagnoses of other febrile conditions [104]. The treatment of melioidosis is different from other pyogenic infections. First, intravenous therapy is given for 10-14 days, followed by an eradication phase of at least 12 and up to 20 weeks, to completely eliminate the bacteria. Effective antibiotics for the intensive first phase are ceftazidime or meropenem. For eradication, oral trimethoprim-sulfamethoxazole is used [97,104].

Conclusion

In this paper we showed examples of rare liver lesions in infectious diseases. We have to admit that these diseases are not rare in certain areas of the world but are termed rare, owing to the low proportion of liver involvement and subsequent lesions. It will be crucial for the investigator to have those lesions in mind since they do not appear very often.

All those lesions show a more or less typical clinical and imaging setting but cannot be diagnosed with a high positive predictive value by imaging alone. More importantly, exclusion of malignancy is essential and biopsy must be considered in most cases which will also aid the diagnosis of the causative pathogen.

In many demonstrated cases, CEUS imaging showed liver lesions which were hyperenhancing in the arterial phase with slightly hypoenhancement or isoenhancement in the late phase. Non-enhancing areas representing necrosis or abscesses are a main feature of these lesions as well. Overall, there is no clear differentiation between inflammatory or malignancy on imaging. CEUS using a strictly vascular contrast agent is able to discriminate between enhancement and no enhancement only.

Patients with a liver lesion showing features described above should be scheduled for a liver biopsy, in order to diagnose malignant liver disease or rare infectious lesions.

The investigator should always bear in mind that these diagnoses can only be ascertained histologically.

Conflict of interest: none

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