Comments and illustrations of the WFUMB CEUS liver guidelines: Peliosis hepatis and porphyria

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Introduction

The appearance of the most common benign and malignant liver tumors on ultrasound (US) and contrast-enhanced ultrasound (CEUS) is well known and reported in detail in the guidelines of the World Federation for Ultrasound in Medicine and Biology (WFUMB) [1-5].

It is usually not difficult to diagnose typical liver lesions such as typical haemangiomas or metastases on CEUS. However, problems may arise when rare lesions do not enter the differential diagnosis in the mind of the examiner when characterizing a lesion, owing to their poorly known or described imaging features on US and CEUS. For a large number of rare focal liver lesions (FLL), data already exist. Examples are nodular regenerative hyperplasia [6], inflammatory pseudotumour [7], peliosis [8-10], sarcoïdosis [11-14], cholangiocellular adenoma [15], cystadenoma and cystadenocarcinoma
Peliosis hepatis (PH) is a rare benign disease historically characterized by a proliferation of the sinusoidal hepatic capillaries with blood-filled cystic cavities of various sizes and irregular shapes [48]. It was first described by E. Wagner in 1861 [49]. In 1916, W. Schoenlack defined the term “peliosis” from the Greek word *pelios*, which means “reddish” or “bluish”) [50]. The pathogenesis and etiology of PH remains unclear, and it remains unidentified in 20-50% of all patients [51,52].

The cause may be secondary to an altered venous outflow tract with the consequence of damage to the walls of the sinusoids, dilatation of the sinusoids and dilation of the central vein of the hepatic lobule [53]. Peliosis hepatis is often associated with chronic wasting diseases. The diagnosis has been reported in patients suffering from tuberculosis, immunosuppressed patients [54-57], HIV [58-60], haemato-oncological diseases [61-65], but also in the context of pregnancy [8], oral contraceptives [8,66], anabolic steroids [64], azathioprine and chemotherapeutic agents.

Peliosis has also been reported in association with Bartonella species infection [56,60]. Bartonella henselae and Bartonella quintana cause the so-called bacillary peliosis in patients with AIDS.

Most commonly, Peliosis occurs in the liver but can also affect the spleen, bone marrow, lungs, abdominal lymph nodes, and other organs [59].

In most cases, the lesions are asymptomatic incidental findings on conventional imaging [67,68]. However, intrahepatic hemorrhage, liver rupture, and hemoperitoneum or acute liver failure have also been described [51,63,65,69-71].

In clinical practice, accurate preoperative diagnosis of PH may impact the immediate management of patients and prevent unnecessary surgery or biopsy [51].

**Imaging**

Imaging findings of focal PH may vary depending on the size, pathological presentation, and stage of the lesion [51,72]. It is typically difficult to make a clear distinction of PH from other hypervascular lesions through imaging studies alone [52]. Most cases are detected incidentally as a hypervascular tumor on cross-sectional imaging (CT, MRI, or US).

It has non-specific features on grey-scale abdominal US and can present as a homogeneous, hypoechoic lesion in patients with fatty livers, a hyperechoic lesion in those with healthy livers or a heterogeneous lesion if complicated by hemorrhage [51,73]. It is worth bearing in mind that any hepatic lesions with a hypoechoic rim must be suspicious for metastases [9,74].

With color Doppler US, it is possible to detect intravascular flow which typically has low-resistive indices on spectral Doppler US [75].

A series on the appearances of peliosis on US and CEUS in 24 patients has been reported by Dong et al [68]. These lesions were solitary in 70.8% and multiple in 29.2% [68]. On B-mode US, lesions were usually heterogeneously hypoechoic with well-defined margins but irregular shapes. There was no displacement of surrounding structures [68]. Color Doppler flow signals were detected in 41.7% [68]. On CEUS, in the arterial phase, mild heterogeneous enhancement was seen in 83.3%, centrifugal hyperenhancement in 12.5%, and isoenhancement in 16.7%. After 1 minute in the portal venous phase, 87.5% of the lesions were slightly hypoenhanced and washed out in the late phase [68]. While late-phase hyperenhancement is a typical feature of benign lesions in noncirrhotic livers [76,77], late-phase hypoenhancement of benign lesions are rarely found [4,5]. These exceptions include inflammatory infiltrations and pseudotumors.

Hypervascularized liver metastases and cholangiocellular carcinomas can be distinguished from PH based on their early and distinct washout. However, liver metastases of neuroendocrine tumors are an exception. A weak and late washout is indicative of HCC, but ancillary features of liver cirrhosis will usually be apparent.

There were three patients (12.5%) with phlebectatic variant of hepatic peliosis who had a highly enhanced area in the central part during the arterial phase, which then progressively spread centrifugally to the periphery during the portal venous and late phases [68]. The phlebectatic type of hepatic peliosis is due to aneurysmal dilatation of the central vein [78,79]. In contrast to
FNH, centrifugal enhancement in the portal venous and late phases was described here [68]. A similar contrast behavior with arterial centrifugal fill in and late phase enhancement has been reported by Loizides et al [9].

Gronlykke et al described multiple lesions with peripheral ring enhancement in the early arterial phase and centripetal filling, then centripetal enhancement and hyperenhancement in the late phase [8]. Contrast enhancement characteristics similar to metastases with peripheral hyperenhancement with central but not peripheral washout in the late phase has also been described in another case report [74].

The various observed appearances of peliosis lesions in the CEUS are listed in Table I.

Focal PH should be suspected when an incidentally detected focal liver lesion reveals no specific US features that clearly favor a diagnosis of common tumor-like hepatic lesions [81]. The lack of a mass effect would further support this diagnosis. The CEUS enhancement patterns of focal PH may also vary with any underlying diseases and the various stages of the blood components [72].

The characteristics of the disease in abdominal US, CT, MRI, angiography, and FDG-PET/CT have been previously described [72,82].

On unenhanced CT, peliotic lesions usually appear as multiple areas of low attenuation. However, they may show hyperattenuation to the liver parenchyma, presumably related to hemorrhage [51]. On contrast-enhanced CT, peliotic lesions may be hypoattenuating to the liver parenchyma. However, they tend to become increasingly isodense over time. In addition, some lesions may also have areas of increased attenuation [51]. Variants with centripetal and centrifugal enhancement have been described [51,78,83].

The signal intensity of lesions on MRI largely depends on the duration and status of the blood component. On T2 weighted imaged, peliotic lesions are usually hyperintense and hyperintense on T1w which may indicate blood. Hepatic peliosis causes persistent enhancement on delayed phase images [51,64,65,72,83,84]. However, isointense and hypointense lesions have also been reported [51]. On T1-weighted images post contrast injection, peliotic lesions usually show centrifugal enhancement patterns and rarely centripetal [51,83].

Ultimately, the definitive diagnosis of hepatic peliosis can only be confirmed histopathologically. Dilated sinusoidal spaces and hemorrhagic dilated spaces within the liver parenchyma are typical but this requires adequate tissue sampling which can be difficult owing to the dilated sinusoidal spaces involved. In addition, biopsy in peliosis is associated with a high risk of bleeding [85]. The aspirates can also be examined for Bartonella species especially in cases without predisposing factors and corresponding serology for Bartonella antibodies in the blood can also be carried out.

Dong et al concluded that hepatic lesions without a mass effect demonstrating mild heterogeneous arterial hyperenhancement with washout in the very late portal phase. However, they tend to become increasingly isodense over time. In addition, some lesions may also have areas of increased attenuation [51]. Variants with centripetal and centrifugal enhancement have been described [51,78,83].

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venous phase (after 1 minute) on CEUS are characteristics of hepatic peliosis [68]. However, these characteristics alone can be difficult to distinguish from other well-vascularized lesions and tumors. Hepatic peliosis should be considered in the differential diagnosis when the clinical context is not suggestive of malignancy or infection. The decision to biopsy should be made very responsibly because of the high risk of bleeding. In the case series by Dong et al, needle biopsy was performed with 18-G or 20-G needles in 41.7% of hepatic peliosis cases, with no mention of complications. All other patients underwent surgery, highlighting the difficulty in excluding suspected malignancy [68]. In individual cases, the lack of histologic assessment by needle aspiration may lead to a hemihepatectomy [86].

In asymptomatic patients with incidentally discovered liver lesions that show hyperenhancement in the late phase, a benign lesion can be assumed, and biopsy may not be necessary. The situation is different in symptomatic patients or patients with a history of malignancy in whom the focal liver lesion shows hypoenhancement in the portal venous and late phases. In these circumstances, the lesion should be assumed malignant until proven otherwise.

**Treatment**

Therapeutic strategies include treatment of the underlying disease, if possible. In the case of small asymptomatic findings, it is possible to wait. In the case of larger, complicated findings with hemorrhage, symptomatic or unclear findings that do not allow malignancy to be ruled out, surgical resection would be indicated.

Imaging assessment it thus highly important but usually requires a high degree of experience to make a confident diagnosis of peliosis conservatively (fig 1).

**Porphyria**

Porphyrias predominantly include hereditary metabolic disorders of heme biosynthesis, which are diagnosed and differentiated through specific biochemical patterns of porphyrins and porphyrin precursors found in urine, feces, and blood. Each type of porphyria is the result of a specific enzyme alteration in the pathway. The liver appears to be a central organ in the pathophysiology of porphyrias. Acute and non-acute, as well as erythropoietic and hepatic porphyrias can be subdivided according to etiology and clinical presentation [87-90].

**Acute hepatic porphyrrias (AHP)** include: acute intermittent porphyria (AIP), porphyria variegata (VP), hereditary coproporphyria (HCP), and 5-aminolevulinic acid dehydrase defect porphyria (ALAD-DP; Doss porphyria). These forms are characterized by an overproduction of presumably neurotoxic porphyrin precursors, the onset of which leads to intermittent, col-

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**Fig 1.** Peliosis. A 47-year-old female patient with incidental hypoechoic hepatic lesions. Visualization of the lesions on B-mode ultrasound in 2008 (A), 2017 (B), and 2020 (C). On contrast-enhanced ultrasound, the lesion showed mild arterial hyperenhancement after 30 s (D), with increasing hypoenhancement after 2 min (E) and 3 min (F). An ultrasound-guided biopsy was performed, and the diagnosis of peliosis was confirmed histologically.
icky abdominal pain as well as pain in the back and extremities, paresthesia and paralysis, vigilance disorders, seizures, hallucinations, and cardiovascular symptoms. Hyponatremia may occur secondary to inadequate ADH secretion (i.e., Schwartz-Bartert syndrome). Additional photosensitivity occurs in VP and HCP. Liver damage does not usually accompany AHP. Crucial to the diagnosis of PCT is the more than 4-fold increase in urinary excretion of 5-aminolevulinic acid (ALA) in ALAD-DP and of ALA and porphobilinogen (PBG) in all other acute porphyrias [87-89,91,92].

**Non-acute hepatic porphyrias** are porphyria cutanea tarda (PCT) and hepatoerythropoietic porphyria (HEP) [87-89].

**Non-acute erythropoietic porphyrias** include erythropoietic protoporphyria (EPP), X-linked protoporphyria (XLP), and congenital erythropoietic porphyria (CEP, M. Günther [93]).

In non-acute porphyrias, the accumulation of porphyrins in the liver and skin leads to photosensitivity and occasionally severe liver damage. The most common clinical forms of porphyrias are PCT, AIP, and EPP [87-89].

The cause of PCT is a sporadic or hereditary reduction in the activity of the uroporphyrinogen decarboxylase (Uro-D) in the liver. In this regard, PCT can be subdivided into several types as follows [87-89,94-96]:

- **Type I:** Sporadic or acquired form. The enzyme activity of hepatic Uro-D decreases during the active disease state. However, type-I PCT is only induced by external factors such as iron, drugs, estrogen, nicotine, chemicals, hepatitis C, HIV, and lupus erythematosus. Alcohol is one of the most important causative agents.

- **Type II:** Hereditary form of PCT with a family history; an autosomal dominant disorder with mutations on the Uro-D gene. However, most of the gene carriers do not display symptoms.

- **Type III:** Toxic form, characterized by its sporadic nature with a family history.

- **Type IV:** Hepatoerythropoietic porphyria (HEP), caused by a homozygotic defect on Uro-D.

In PCT, skin changes such as photosensitivity, bullae formation, and skin hyperpigmentation are observed, along with liver damage. Hepatic involvement is common. Most patients have abnormal liver function tests or exhibit only mild elevation of aminotransferase levels. Fatty liver degeneration and iron overload are noted in almost all cases. Liver cirrhosis and HCC may be induced by PCT, depending on the degree of liver involvement. However, decompensated cirrhosis is very rare [94]. Increases in porphyrin precursors and porphyrins may be secondary in patients without porphyria but with liver diseases, iron deficiency, and lead intoxication [87].

**Porphyrias and increased risk of hepatocellular carcinoma**

Patients with AIP are at increased risk for developing HCC without pre-existing chronic liver disease, especially liver cirrhosis. In addition, a rarer association exists between HCP, VP, and HCC that concerns symptomatic patients as well as latent carriers [90,97-101]. Kauppinen et al reported HCC as the cause of death in 9% of patients with AHP [97]. Innala et al conducted a screening over 15 years on AIP carriers in Sweden. They discovered that carriers over the age of 55 have a 100-fold increased risk of developing HCC. The authors recommend annual US screening for HCC in AIP gene carriers from the age of 50 and as long as therapeutic options are applicable with regard to concomitant diseases and age [101]. Deybach et al extend this screening recommendation to all AHP gene carriers, including those of AIP, VP, and HCP [90]. PCT and HCC are equally implicated. However, in this context, both HCC and PCT appeared because of an underlying liver disease such as chronic alcohol abuse, hepatitis C and B, or hemochromatosis, each contributing to fibrosis and cirrhosis. Currently, patients with PCT can benefit from etiopathogenetic treatments that reduce liver damage and halt the progression to liver cirrhosis.

**Imaging**

In AHP, the task of US is the differential diagnosis of acute abdominal pain and the screening for HCC. Meanwhile, with PCT, B-mode US may reveal hypoechoic round liver lesions, which exhibit the distinctive feature of a hyperechoic rim. The center of the lesions may be hyperechoic or isoechocic to varying degrees, and the hepatic vessels are not affected by the lesions. The lesions have no angioneogenesis and are isoenhanced on CEUS. If porphyria is already known, these lesions are indicative of liver involvement. If no porphyria is known to date, it makes sense to carry out a corresponding serological and urine diagnosis. Differential diagnosis are fat distribution disorders. In the case of PCT, it is important to assess the degree of liver damage during patient management, especially in cases of elevated liver values. B-mode US, elastography for fibrosis assessment, Doppler US for vascular assessment, and CEUS for liver lesions are available for this purpose. In the case of liver cirrhosis, screening with regard to HCC should be conducted (fig 2).

**Conclusion**

Liver lesions in porphyria have characteristic US and CEUS features., and should not be misclassified as liver
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Peliosis is a benign lesion. However, it can occur in various consumptive situations, in immunocompromised patients and tumor therapy. In this context, any new liver lesion is suspicious for tumor or metastases. The sonographic appearance is very diverse. Peliosis is non-vascular infiltrating and non-displacing, often hemorrhagic. Typical features in CEUS are a heterogeneous hyperenhancement in the arterial phase with a weak washout to the end of the portal venous phase, making differentiation from malignancy impossible.

In this case, US-guided biopsy may be indicated. Contrary to reports of increased bleeding risk, no complications occurred in the current work by Dong et al [68]. Another typical appearance is the phlebectatic variant with centrifugal enhancement in the arterial and portal venous phase. Although this has a pathognomonic enhancement pattern, the occurrence of this lesion is less common [68]. In the case of a planned biopsy, appropriate follow-up should be performed if the risk of bleeding is still considered to be increased. The pathologist should also be informed of the possible diagnosis of peliosis. Biopsies show sinusoidal dilatation without typical tissue cylinders.

Patients with PCT can show typical liver lesions characterized by a hyperechoic rim. The lesion itself can be isoechoic to the surrounding area, even slightly hyperechoic without vessel distortion. The lesions show no neoangiogenesis and are isoenhanced on CEUS. In this context, a liver biopsy is not necessary. If no porphyria is known to date, appropriate serological and urine diagnostics would be recommended. Patients with PCT, who often have underlying liver disease, need to be screened for the development of HCC. Patients with AIP have an increased risk of HCC even without liver disease. Therefore, these patients must also be monitored.

For the differential diagnostic assessment of liver lesions, it is important to consider and include the entire clinical context. The clinical data are important for deriving a suspected diagnosis from the US image. US images can be typical, such as the liver lesions in PCT or the phlebectatic variant of peliosis in CEUS. If there is even the slightest suspicion of peliosis, post-biopsy surveillance should be particularly intensified. Owing to the characteristic imaging features and combined with supporting clinical findings, biopsy should not be required for the diagnosis of porphyria lesions.

Knowledge of these ultrasound images should help to instigate appropriate further management.

References


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