Comments on and illustrations of the WFUMB CEUS liver guidelines: Rare malignant neuroendocrine and predominant epithelioid liver lesions

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Abstract

The diagnosis or rare, non-hematologic malignant lesions of the liver may be a challenge owing to the rarity of the disease, and is usually made by histological confirmation. Ultrasound with color Doppler and contrast-enhanced, if required, taking into account the clinical background of the patient, may help to focus the differential diagnosis. In this review, we describe the pathological and ultrasound features of rare malignant neuroendocrine and predominantly epithelioid liver lesions including primary neuroendocrine tumor of the liver, Invasive mucinous cystic neoplasm of the liver, and also hepatoblastoma.

Keywords: ultrasound; CEUS; primary neuroendocrine tumor; MCN-L; cystadenocarcinoma; hepatoblastoma

Introduction

The guidelines for the utilization of contrast-enhanced ultrasound (CEUS) in the assessment of focal liver lesions (FLLs) have been published by the World Federation for Ultrasound in Medicine and Biology (WFUMB) [1-5]. The primary focus of these guidelines revolves around improving the detection and characterization of prevalent FLLs. Comprehensive descriptions of both conventional ultrasound (US) including Doppler techniques [6] and CEUS features pertaining to atypical FLLs have emerged. Existing literature, supported by histological gold-standard, encompasses the study of cholangiocellular adenoma [7], peliosis [8-10], hemangiendothelioma [11,12], and hepatocellular carcinoma (HCC) in the non-cirrhotic liver. Numerous papers and reports have been published on these rare and specialized hepatic lesions. These encompass the characterization of fibrolamellar hepatocellular carcinoma [13,14], very small HCC (<10 mm) [15], mixed HCC and cholangiocellular carcinoma [16], nodular regenerative hyperplasia [17], sarcoma [18], inflammatory pseudotumour [19],
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primary liver tumors [50]. Edmondson reported the first case of a PHNET in 1958 [51]. This condition is predominantly found in adults and is more common in the right lobe of the liver, and it accounts for only 5% of all neuroendocrine tumors [52]. PHNETs are commonly found in people around the age of 50 years, with no gender predominance. Most tumors are singular, but they can also be multiple. Owing to the extremely slow growth of PHNETs, obvious clinical symptoms are rare unless they progress. Only a minority reveal the symptoms of classical carcinoid syndrome, such as skin flushing, diarrhea, and abdominal pain [53]. In terms of the various imaging features, it is always difficult to differentiate PHNETs from HCC or cholangiocarcinoma. Therefore, postoperative histological and immunohistochemical evaluation play an important role in diagnosing the disease. Furthermore, it is necessary to follow up with some patients for an extended period to exclude other diagnoses. Common pathological characteristics of primary neuroendocrine tumors include gray-yellow, well-defined, and multiple irregular hemorrhagic lesions or cystic areas. Through the hematoxylin–eosin staining method, insular, nested, trabecular, or mixed patterns of cell growth can be observed [54]. Approximately 70% of the tumors can be surgically removed, with a subsequent 5-year survival rate in approximately 78% of patients. For inoperable cases, various pharmacological treatments are available to control the disease, including systemic 5-fluorouracil, hepatic artery embolization, and octreotide therapy [54, 55].

Cross-sectional imaging

On contrast-enhanced computed tomography, contrast enhancement is observed in the arterial phase, with continuous enhancement into the venous phase [50]. The tumor density on CT images may be lower than that of the liver parenchyma. On Magnetic Resonance Imaging (MRI) (fig 1A,B), on T2-weighted and diffusion-weighted images, the PHNETs show a well-circumscribed, lobular or multiple-nodular mass with high signal intensity. Furthermore, the lesions are well-circumscribed, heterogeneous, and hypointense on T1-weighted images. Post contrast T1-weighted images, show marked enhancement of the solid tumor component in the early arterial phase, persisting enhancement in the portal venous phase, and high signal intensity or a clear defect in the 5-minute delayed hepatobiliary phase [56].

B-US and CEUS

On B-mode US, the lesions are visualized as hyperechoic (fig 1C) (60%) or mixed echoic (30%), inhomogeneous, and sometimes with cystic components [57]. The lesions may have a similar pattern to that of hemangiomas. However, in contrast to hemangiomas, vessels are detected in the lesions on color Doppler US (fig 1D). On CEUS, lesions commonly show marked arterial enhancement followed by washout in the portal and/or late phases (fig 1E-H) [58-60].

Invasive mucinous cystic neoplasm of the liver

Mucinous cystic neoplasm of the liver (MCN-L) and invasive mucinous cystic neoplasm of the liver (M- MCN-L) are extremely rare tumors of the liver. To date, less than 200 cases have been described in the literature [61,62]. They originate from the bile duct epithelium and are usually multilocular. These neoplasms present as solitary hepatic lesions consisting of multiple cysts with varying contents and surrounded by a thick capsule [62]. I-MCN-L (previously known as cystadenocarcinomas) are rare, with an incidence of 0.41% of all hepatic malignant epithelial tumors [62,63]. However, a high risk of up to 20% of malignant transformation has been described for MCN-L (previously known as biliary cystadenomas) [64]. Furthermore, the finding of benign areas in cystadenocarcinomas histologically, have led to the hypothesis that I-MCN-L develop via malignant transformation from MCN-L [62].
These tumors grow very slowly and can reach enormous dimensions before they are symptomatic. They frequently cause only non-specific abdominal symptoms, thus the diagnosis remains difficult despite the broad variety of imaging techniques available [62]. In some cases of cystadenomas as well as cystadenocarcinomas, tumor markers such as AFP, CEA, CA 125, or CA 19-9 may be elevated in serum or intracystic tissue. However, differentiation between benign and malignant cystadenomas is not possible using tumor markers alone [62,64]. Benign histology obtained by needle biopsy cannot exclude malignancy of the lesions because, in cystadenocarcinomas, benign and malignant tumor areas are often located side by side [62]. Currently, radical tumor resection with a negative margin is considered the treatment of choice, not only for malignant, but also benign cystadenomas of the liver, because it is not possible to distinguish between MCN-L and I-MCN-L radiologically or macroscopically. In addition, the high malignant transformation rate of MCN-L should be taken into account [62,64]. For patients with an inoperable or advanced tumor stage, radiotherapy and chemotherapy can be considered [65].

Cross-sectional imaging

A reliable differentiation between benign and malignant cystic hepatobiliary lesions is not possible based on current imaging modalities. In the diagnosis of biliary cystic liver tumors, the roles of US and CT have been described as complementary [62,64].

On CT (fig 2A), these tumors appear hypodense and show irregularly thickened walls, internal septa, and mucosal nodules. Individual areas may show different density values, and these are probably due to different concentrations of mucinous, serous, or partly hemorrhagic fluid [62]. Compared with US, CT provides a better overview and therefore better assessment of size, extension, and anatomic relationships with neighboring organs [62]. On contrast-enhanced CT, contrast enhancement is observed in the area of the septa and walls, and this is similar to that of the liver parenchyma. Intramural or septal calcifications may also be detectable [62].

On MRI (fig 2B), cysts present as homogeneous low intensity on T1-weighted images compared with the normal liver parenchyma. On T2-weighted images, they show high-intensity signal, similar to fluid-filled cavities and can be clearly demarcated from the normal liver tissue [62]. MRI is considered complementary to US and CT for the preoperative diagnosis of these tumors and the accurate assessment of the anatomical relationship of the tumor with neighboring organs [62,64].

B-US and CEUS

US is considered the method of choice in the preoperative diagnosis of hepatobiliary cystic tumors. The
lesions present as oval or roundish cystic masses with multiple septa (fig 2C). These may vary in number and thickness. Wall irregularities and nodular, papillary mucosal changes can also be seen on US and are relatively typical of cystadenomas and cystadenocarcinomas [62,64]. On CEUS, the septa and wall irregularities may demonstrate contrast enhancement (fig 2E, F).

**Hepatoblastoma**

Hepatoblastoma incidence rates are approximately 10.5 and 5.2 cases per million children under 1 year and between 1 to 4 years, respectively. Beyond these age ranges, the occurrence of hepatoblastoma are insufficient to establish a reliable incidence rate [66]. However, hepatoblastoma accounts for approximately 90% of hepatic malignancies in children aged below 5 years and is the most common type of liver malignancy in this age group [67,68]. Hepatoblastomas can be classified into two main subtypes: the more frequent epithelial type, and the mixed type, which is characterized by a combination of epithelial and mesenchymal components [69]. The mixed type accounts for approximately 20-30% of all hepatoblastoma tumors and exhibits a variable combination of the two components [69]. The main symptoms associated with hepatoblastoma include abdominal distension and
weight loss [68,70]. Typically, hepatoblastoma presents as a large solid mass with multiple compartments, varying in size, and may exhibit pseudocystic areas, necrosis, and calcifications. The diagnosis is aided by a significant increase in alpha-fetoprotein levels. CT and MRI are the primary methods used for oncological staging [68,71]. The specific role of CEUS in hepatoblastoma, particularly in follow-up examinations, has not been clearly defined [68].

**Cross-sectional imaging**

On CT, hepatoblastoma is typically visualized as a well-defined heterogeneous mass, which generally appears hypodense in comparison to the surrounding liver [72]. There are often occurrences of necrotic and hemorrhagic areas. Calcification may be present [72]. On MRI, a typical hepatoblastoma presents as a tumor with heterogeneously increased signal intensity on T2-weighted images, decreased signal intensity on T1-weighted imaging, and shows heterogeneous enhancement patterns during contrast administration. However, the tumor remains predominantly hypointense compared to the surrounding liver tissue throughout all phases of contrast enhancement. Additionally, calcifications may be present within the tumor mass, and variable incidences of hemorrhage and necrosis contribute to the heterogeneous patterns [73].

**B-US and CEUS**

On B-US, hepatoblastomas exhibit heterogeneity and variable echogenicity. Hepatoblastoma can present as a solitary dominant mass with accompanying satellite lesions, multiple nodules distributed throughout the liver, or rarely, as a diffusely infiltrative mass affecting the entire liver [74]. Calcifications may be observed [74]. Internal hemorrhage and necrosis are relatively common. Color Doppler US is a valuable modality for identifying potential invasion of the hepatic and portal veins [74]. On CEUS, the special features of hepatoblastoma include initial peripheral hyperenhancement during the arterial phase and pronounced wash-out in the subsequent late portal venous phase (fig 3, fig 4) [75].

**Conclusion**

Similar to common liver tumors, the diagnosis of the previously mentioned tumors should be made taking into account the clinical background of patients. Primary neuroendocrine tumors of the liver may mimic the appearance of a hemangioma on B-US. On CEUS, the wash-out may appear late owing to marked neoangiogenesis. Therefore, the lesion should be observed for at least 5 minutes. Hepatoblastomas are characterized by hyperenhancement and a marked wash-out phenomenon. Any cyst with enhancement of the septa or irregular walls on CEUS should be considered as a potential I-MCN-L requiring further evaluation.

**Conflict of interest:** none

**References**

- WFUMB in cooperation with EFSUMB, AFSUMB, AIUM, and FLAUS. Ultraschall Med 2020;41:562-585.
42. Zander T, Safai Zadeh E, Moller K, et al. Comments and illustrations of the WFUMB CEUS liver guidelines: Rare