Comments and illustrations of the WFUMB CEUS liver guidelines: Rare malignant hematological liver lesions

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Abstract

Diagnosing rare hematological malignancies in the liver is often challenging owing to their infrequency, and confirmation generally necessitates histological examination. Due to the rarity of these lesions, there are limited data concerning their appearance on ultrasound and, specifically, contrast-enhanced ultrasound. In this review, we describe the pathological and ultrasound features of several hematological malignant liver lesions, including lymphoma of the liver and chloroma. Furthermore, two specific forms of liver lymphoma are described: mucosa-associated lymphoid tissue (MALT) lymphoma and plasmacytoma of the liver.

Keywords: ultrasound; CEUS; diagnosis; liver; lymphoma; chloroma; plasmacytoma; hepatic MALT

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 (FLLs) [1-5]. Improved detection and characterization of common FLLs are the main topics of these guidelines. In recent years, conventional ultrasound (US) and CEUS features of less common FLLs have been described in detail [6-18]. In this current paper series, we aim to summarize the US and CEUS features of very rare FLLs for which limited reports and figures have been published, in order to create a library of these rare lesions.

In the case of underlying hematological malignancies, lymphatic systemic disease must be differentiated from hepatic involvement particularly in myeloid systemic disease, which is referred to as chloroma [19,20]. In clinical practice, if lymphatic systemic disease is di-
Primary hepatic lymphoma (PHL) is a very rare malignant tumor of liver, occurring in only 0.016% of all cases of non-Hodgkin lymphoma [21]. It can infiltrate liver tissue with no visible evidence of spleen, lymph nodes, bone marrow, or other lymphoid structure involvement [21]. PHL is typically diagnosed during the fourth to fifth decade, and it exhibits a higher occurrence in males than in females [22,23]. It is frequently associated with viral hepatitis B and C, Epstein–Barr virus, and human immunodeficiency virus (HIV) [22,23]. Notably, hepatitis C viral infection is prevalent, affecting 20–60% of patients with PHL [23]. Clinical symptoms, including right upper abdominal pain, weight loss, and fever, may be present in up to 50% of cases [23]. The majority of PHL cases belong to the B-cell lineage, with diffuse large B-cell lymphoma being the most commonly identified histological subtype [23]. Secondary liver involvement may be observed in approximately 50% of individuals with non-Hodgkin lymphoma and in roughly 20% of those diagnosed with Hodgkin disease [23]. Patients typically exhibit systemic manifestations, such as fever, night sweats, and weight loss. Hepatosplenomegaly and generalized lymphadenopathy are frequently observed during systemic examinations [23].

Imaging

Approximately 35-40% of cases of PHL present with multiple discrete hepatic lesions of varying sizes, with one dominant lesion typically observed [23]. In contrast, secondary hepatic lymphoma often shows a different pattern, with up to 90% of cases demonstrating either multifocal lesions or diffuse infiltration in the liver [23]. However, the lesions in both types show similar imaging features.

Cross-sectional imaging

On computed tomography (CT), the lesion typically appears uniformly hypodense on non-contrast-enhanced scans and occasionally, areas of necrosis and hemorrhage may be observed. Calcification is uncommon in the absence of treatment [23-25]. Different enhancement patterns have been identified on contrast-enhanced computed tomography (CECT). The majority of the lesions show minimal to no enhancement throughout all phases [23,25]. If enhancement is present, it is typically less pronounced than in the surrounding healthy liver tissue [23,25]. The second pattern involves enhancement at the rim of the lesion, whereas the central area does not enhance, resulting in a target-like appearance of the lesion [23,25,26]. On magnetic resonance imaging (MRI), the lesion typically appears homogeneously hypointense on T1-weighted images and hyperintense on T2-weighted images [25,27]. Signal intensity on T2-weighted images may exhibit heterogeneity due to the presence of hemorrhage and necrotic areas [23,24]. T2-hyointense tumors with a peripheral rim of hyperintensity have also been documented [23,24].

B-mode US and CEUS

On US, the lesion is usually well defined and appears hypoechoic (fig 1-4) or anechoic, occasionally resembling a cyst [23]. This is because lymphoma is a homogeneous tumor and generates very few internal reflections [23]. However, the absence of posterior acoustic enhancement can be a useful clue towards the solid nature of the lymphomatous lesion [23]. A strong perilesional or intralesional color flow signal can be detected with color Doppler imaging [28,29]. On CEUS, two-thirds of the cases show arterial homogeneous or inhomogeneous hyper-/isoenhancement with marked washout in the portal venous phase [23].

Primary hepatic lymphoma of the MALT type

MALT lymphoma, initially reported by Isaacson and Wright in 1983, is a type of low-grade malignant B-cell lymphoma [30]. MALT lymphomas develop in the context of persistent inflammation, often linked to infectious agents like Helicobacter pylori or autoimmune conditions like Sjögren’s syndrome [31]. The stomach is the most prevalent location for MALT lymphoma, often occurring in patients with chronic gastritis caused by H. pylori infection. Nevertheless, MALT lymphomas can also emerge in extranodal sites lacking lymphoid tissue. Primary hepatic MALT lymphoma is an exceedingly rare occurrence compared with other diagnosed hepatic lymphoma cases [32-34]. Consequently, limited information is available regarding its clinical progression, and there is a lack of precise definition for typical imaging findings.

The cause of primary hepatic MALT lymphoma remains unidentified; however, numerous reported cases have suggested a possible link to chronic inflammatory liver conditions, such as hepatitis B or C virus infections,
Fig 1. A 60-year-old female patient with an incidental hypoechoic liver. Visualization of the lesion on B-mode ultrasound (A). On contrast-enhanced ultrasound, the lesion shows mild arterial hyperenhancement after 15 s (B), with increasing hypoenhancement (washout) after 2 min (C) and 3 min (D). An ultrasound-guided biopsy was performed, and the diagnosis of a primary follicular lymphoma of the liver was confirmed histologically.

Fig 2. A 57-year-old male patient with previous allogenic kidney transplantation and multiple liver lesions on B-mode ultrasound (A). On contrast-enhanced ultrasound, the lesion shows arterial inhomogeneous isoenhancement after 17 s (B), with increasing hypoenhancement after 1 min (C) and 2 min (D). An ultrasound-guided biopsy was performed, and the diagnosis of a non-Hodgkin malignant lymphoma of the liver was confirmed histologically.

Fig 3. A 59-year-old female patient with hypoechoic periportal liver infiltration and known chronic lymphocytic leukemia in her medical history. Visualization of the lesion on B-mode ultrasound (A). On contrast-enhanced ultrasound, the lesion shows liver-like enhancement (isoenhancement) after 30 s (B), with hypoenhancement (washout) after 1 min (C) and 2 min (D). An ultrasound-guided biopsy was performed, and the diagnosis of chronic lymphocytic leukemia was confirmed histologically.

Fig 4. A 50-year-old patient with a hypoechoic hepatic mass (A) and known mycosis fungoides in their medical history. On contrast-enhanced ultrasound, the lesion shows arterial hyperenhancement after 17 s (B). After 1 min (C) and 4 min (D), the lesion showed progressive hypoenhancement (washout). Histologically, a diagnosis of hepatic mycosis fungoides was confirmed.
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steatohepatitis, and autoimmune hepatitis [29,35-39]. The primary standard treatment for early-stage H. pylori-associated MALT lymphoma in the stomach involves the eradication of H. pylori [36]. However, there is currently no consensus on the optimal treatment approach for MALT lymphoma located outside the stomach. Different methods, such as surgery, radiotherapy, chemotherapy, or a combination of these, have been utilized with encouraging results [36].

Cross-sectional imaging

On CT scans, the majority of cases were characterized by low density, with slight enhancement observed in CECT images [40]. On MRI, the lesions display low signal intensity on T1-weighted images and moderately high signal intensity on T2-weighted images [40].

B-mode US and CEUS

The lesions may show a hypoechoic echo pattern on B-mode US [35]. On CEUS, the lesions may show mild inhomogeneous hyperenhancement in the arterial phase with washout in the portal venous phase (fig 5) [35]. Despite its rarity, primary hepatic MALT-type lymphoma should be considered as a potential differential diagnosis for hepatocellular carcinoma (HCC), particularly in patients with chronic liver diseases and no underlying cirrhosis, as the imaging findings can be similar [35].

Plasmacytoma of the liver

Plasmacytoma is a malignancy of plasma cells, characterized by infiltration of the bone marrow with abnormal plasma cells and the excessive production of immunoglobulin or light chains [41]. Solitary plasmacytoma is an uncommon type of plasma cell dyscrasia characterized by either a single bone or extramedullary location. It constitutes approximately 3–5% of all plasma cell neoplasms [42,43]. The presence of plasma cells in the liver or spleen is associated with a more aggressive form than other forms of plasmacytoma, which typically necessitates intensive treatment, such as chemotherapy or consolidation therapy with autologous hematopoietic stem cell transplantation [43]. Although postmortem examinations reveal hepatic involvement in 30–40% of patients, diagnosing it before death is considerably less common [41,44]. Plasma cell infiltration in the liver can manifest in either diffuse or nodular patterns, with the former being the more prevalent [45]. Plasmacytoma of the liver can occur as a primary or secondary disease. In secondary hepatic plasmacytoma, myeloma cells proliferate in the bone marrow and circulate through the bloodstream, lymphatics, and the reticuloendothelial system. As a result, infiltrations of the liver may occur [41]. Primary hepatic plasmacytoma is an exceedingly uncommon liver tumor originating from plasma cells. Only a few cases have been reported without any primary lesions outside the liver or associated systemic disorders [46].

Histological changes like amyloidosis and myeloid metaplasia can lead to various clinical presentations. Liver lesions associated with myeloid metaplasia may manifest as hepatomegaly, jaundice, ascites, or fulminant liver failure, or they can be entirely asymptomatic, incidentally discovered during autopsy or imaging examinations [41]. Radiotherapy is considered to be the most suitable treatment for patients diagnosed with a localized extramedullary plasmacytoma. Additional experimental options being explored include surgery, combined chemotherapy, and stereotactic radiotherapy [43].

Cross-sectional imaging

Various CT enhancement patterns of hepatic plasmacytoma have been reported, including both hypoenhancement and hyperenhancement on single-phase scans, a haemangioma-like pattern, and the characteristic HCC pattern with arterial hyperenhancement and venous washout [47]. The MRI presentation of hepatic plasmacytomas also exhibits variability. On T1-weighted images, the lesions may demonstrate a slightly hypointense pattern compared with the liver or hyperintense margins.
with an eccentric isointense/hyperintense center [48,49]. Meanwhile, in T2-weighted images, they may show a homogeneously hyperintense pattern or hyperintense outer layer, accompanied by a hypointense margin and a hyperintense inner core [48,49].

**B-mode US and CEUS**

On US imaging, primary hepatic plasmacytoma usually appear as ill-defined, hypoechoic, heterogeneous lesions [49,50]. Cases describing lesions with a hyperechoic center and peripheral hypoechoic haloes or three layers (a hypoechoic rim, hyperechoic outer layer, and hyperechoic core, producing a “target-like” appearance) have been reported [48,49]. On CEUS, the lesions may demonstrate an arterial hyperenhancement with marked washout in portal venous and late phases (fig 6).

**Chloroma**

Chloroma, myeloid sarcoma, granulocytic sarcoma, and myeloblastoma are synonymous terms that describe extramedullary tumor aggregates of malignant myeloid progenitor cells [51]. Chloromas occur with an incidence of 3–8% in a number of hematologic disorders, such as acute and chronic myeloid leukemia, myelofibrosis with myeloid metaplasia, hypereosinophilic syndrome, and polycythemia vera [51-54]. Chloroma manifestation can occur in nearly all organs, although the most commonly reported to date has been in soft tissue, skin, bone, and lymph nodes [51]. Chloromas can also occur without bone marrow infiltration [51]. However, primary liver involvement without bone marrow involvement is described as extremely rare [55,56].

**Cross-sectional imaging**

On CT, hepatic chloromas typically appear hypodense and may show slight or even no contrast enhancement [57]. These nodules may imitate the appearance of an infection or abscess, or more frequently a malignant lymphoma [57]. On MRI, the masses typically present as T1-isointense to -hypointense and mildly T2-hyperintense, with common homogeneous enhancement [58]. However, no data are available regarding the description of the MRI patterns of hepatic chloroma.

**B-mode US and CEUS**

On B-mode US, chloroma lesions are predominantly hypoechoic [20]. The lesions may manifest either as round foci within the liver or as diffuse infiltration of the liver (fig 7). On CEUS, the chloroma may show inhomogeneous arterial iso-/hyperenhancement with parenchymal washout [20]. However, in some cases, a persistent arterial hyperenhancement without a washout in the portal venous and late phase may be present owing to marked neoangiogenesis.
Conclusion

On CEUS, hematological malignant lesions are characterized by marked arterial iso-/hyperenhancement owing to their pronounced neoangiogenesis. Therefore, these lesions may mimic the CEUS pattern of HCC and should be considered as a differential diagnosis in patients with an associated clinical background. However, in the majority of cases, these lesions reveal a rapid washout phenomenon in the portal venous and late phases. Ultimately, the definitive diagnosis is made by histological confirmation.

Conflict of interest: Some of the authors declare that they have received lecture honoraria and/or support for ultrasound courses by Bracco Imaging, Milan, Italy.

References

