Comments and illustrations of the WFUMB CEUS liver guidelines: rare benign hematological focal liver lesions (hepatic extramedullary hematopoiesis, Hemophagocytic lymphohistiocytosis, reactive lymphoid hyperplasia)

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Abstract
The manifestation of benign hematological infiltration in the liver is a challenge due to their rare occurrence and therefore, limited awareness and the general need for biopsy and histological confirmation. Owing to the rarity of these lesions, there are limited data concerning their appearance on ultrasound and, specifically, contrast-enhanced ultrasound.

In a series of papers, we have compiled the US and CEUS characteristics of rare FLL, where there are few reports and images available, in order to build up a library of these cases.

This paper describes the US and CEUS features of benign hematological FLL which include hepatic extramedullary hematopoiesis (EMH), hemophagocytic lymphohistiocytosis (HLH) and reactive lymphoid hyperplasia (RLH). Although these lesions occur rarely in the liver, their correct identification is imperative for appropriate patient’s management.

Keywords: hepatic extramedullary hematopoiesis; hemophagocytic lymphohistiocytosis; reactive lymphoid hyperplasia; liver tumor; contrast enhanced ultrasound

Introduction

Guidelines for the application of contrast-enhanced ultrasound (CEUS) for the assessment of focal liver lesions (FLL) have been issued by the International Federation for Ultrasound in Medicine and Biology (WFUMB) [1-7]. The guidelines’ primary goals are to improve detection and characterization of commonly encountered FLL. In-depth descriptions of the conventional ultra-
sound (US) and CEUS features of less common FLLs have also been published recently [8-20]. In a series of papers, we have compiled the US and CEUS characteristics of very rare FLL, where there are few reports and images available, in order to build up a library of these cases.

This paper describes the US and CEUS features of benign hematological FLL which include hepatic extramedullary hematopoiesis (EMH), hemophagocytic lymphohistiocytosis (HLH) and reactive lymphoid hyperplasia (RLH). Although these lesions occur rarely in the liver, their correct identification is imperative for appropriate patient’s management.

**Hepatic extramedullary hematopoiesis**

Extramedullary hematopoiesis (EMH) is defined as hematopoiesis taking place outside the bone marrow. The liver and spleen are the most common sites for EMH where it is physiological during fetal development, but pathological in adulthood. It is usually a compensatory mechanism owing to bone marrow dysfunction where the most common cause is myelofibrosis [21].

In a retrospective database review of 1933 patients with EMH conducted from 1975 to 2018, only 336 were not associated with myeloproliferative neoplasms. The causes included myelodysplastic syndromes (13% of the cases); acute myeloid leukemia (9%); hemolytic anemia (8%); thalassemia (7%); non-Hodgkin’s lymphoma (6%); immune thrombocytopenic purpura (6%); metastatic cancer (6%), most frequently from breast cancer; plasma cell neoplasms (4%); hereditary spherocytosis (3%); cirrhosis (2%); acute lymphoblastic leukemia (2%); chronic lymphocytic leukemia (2%); Hodgkin’s lymphoma (2%); and a spectrum of other hematological and non-hematological conditions. The most frequent areas of EMH were the spleen (53%), liver (25%), lymph nodes (6%), and the paraspinal region (5%) [22].

The increase in hepatic size owing to progression of hepatic EMH after splenectomy for thalassemia has also been described [23]. Extramedullary hematopoiesis can also occur in patients with malignant tumors, causing difficulties in differential diagnosis where hepatic EMH may be mistaken for metastatic lesions [24]. In a retrospective review, spanning a period from 1980 to 2017, 35 papers with 42 cases of EMH in patients with tumors were evaluated. The most common underlying malignancy was breast cancer (31%), followed by renal cancer (16.7%), lung cancer (14.3%), colon cancer (7.1%) and endometrial adenosarcoma (4.8%). Prostate carcinoma, adrenal carcinoma, endometrial carcinoma, cutaneous basal cell carcinoma, bladder carcinoma, Kaposi sarcoma, ovarian endometroid adenocarcinoma, ovarian leiomyosarcoma and melanoma represented 2.4% of the cases respectively. In the solid tumor group, EMH was most frequently encountered in the lymph nodes (19%) and the liver (16.7%), followed by the kidneys (14.3%), paraspinal region (9.5%), peritoneum (9.5%), and spleen (7.1%) [25]. The simultaneous histological confirmation of hepatic EMH with peliosis in a patient with colon carcinoma undergoing adjuvant chemotherapy has been described in one case report [21].

Sclerosing extramedullary hematopoietic tumor (SEMHT), formerly known as fibrous hematopoietic tumor or myelosclerosis, is another rare pseudotumor which can occur in patients with a history of chronic myeloproliferative disorders and may involve the skin, lungs, breasts, gastrointestinal tract, kidneys, lymph nodes and the thyroid gland. Wang et al reported hepatic involvement in which a CT scan revealed multiple ring-enhancing low-density lesions, where the differentiation from hemangiomas was difficult and the definitive diagnosis could only be made histologically [26]. EMH occurs when multipotential hematopoietic stem cells migrate out of the bone marrow to other areas of the body, typically as a result of bone marrow dysfunction or suppression [21,27]. Causes of EMH in patients with solid tumors include therapy-specific factors (e.g., administration of granulocyte colony-stimulating factor (G-CSF), extramedullary activation of circulating hematopoietic progenitor cells secondary to bone marrow suppression through chemotherapy and radiotherapy, and tumor-specific factors such as cytokines and paracrine growth factors released by the tumor [25].

**Imaging**

In patients with myelofibrosis and EMH, hepatosplenomegaly is the most common finding on imaging [28,29]. Moreover, such patients may develop non-cirrhotic portal hypertension due to sinusoidal infiltration and fibrosis, obliteration of the intrahepatic terminal portal venous branches or thrombosis of the portal vein. Additionally, increased splanchnic blood flow owing to splenomegaly is another factor which may contribute to portal hypertension in these patients [28,29]. In cases of hepatic EMH, hepatomegaly, splenomegaly, or hepatosplenomegaly are usually diagnosed ultrasonically.

Wong et al described the sonographic appearance of hepatic EMH in a series of 10 cases. The number of EMH lesions in the liver varied from single to multiple lesions. The lesions were mostly heterogeneous and predominantly hyperechoic; a small number were hyperechoic with central necrosis. EMH involvement of the periporal region was reported in only one case [23]. Bradley et al described the sonographic appearance of EMH in 2 cases.
In the first case, he reported a patient with a lung mass (which was later confirmed via bronchial biopsies to be a small cell carcinoma), where a liver ultrasound showed multiple large hyperechoic lesions, some of which demonstrated central necrosis. The spleen was normal in size but contained a solitary echogenic mass similar in morphology to those within the liver. A liver biopsy revealed hepatic EMH rather than the suspected metastases from the small cell lung carcinoma. In a second case, he reported a patient with Beta thalassemia presenting with right upper quadrant pain where ultrasound revealed a single, large, well-defined, inhomogeneous, hypoechoic solid mass in the liver measuring 15 cm in diameter without vessel invasion or features of cirrhosis. The histology confirmed the diagnosis of hepatic EMH [30]. Kwak et al described hepatomegaly and a single, large, ill-defined, inhomogeneous hypoechoic liver mass [31], while Tamiolakis et al similarly reported hepatomegaly with and a smaller lesion with the same ultrasound appearances lesion [24].

On unenhanced CT, hepatic extramedullary lesions have mostly been described as hypodense but may be hyperdense or heterogeneously hypodense. With enhanced CT, patchy enhancement of these lesions has been reported [23,31] while Lee et al reported intense enhancement of most of their lesions in the portal venous phase. On MRI, a homogeneously low signal on T1-weighted sequences and high signal on fat-saturated T2-weighted fast-spin echo images have been observed. There was no signal alteration between the in- and opposed-phased T1-weighted images. The lesion displayed homogeneous and intense enhancement in the arterial phase (20 seconds after the administration of gadolinium contrast) and enhanced persistently for five-minutes. There was no signal drop out in the mass on T2-weighted images obtained 10 minutes following the administration of a superparamagnetic iron oxide (SPIO) agent (SHU 5555, Resovist [32].

Ultimately, biopsy is needed for confirmation of the diagnosis (fig 1). Hematopoietic elements including erythroid, myeloid precursors, and megakaryocytes are definitive features of the condition. Hepatic EMH should be considered in the differential diagnosis whenever new liver lesions are encountered in patients with myelofibrosis or other underlying hematological diseases, as well as rarely in those with malignant non-hematological tumors (especially breast carcinoma) receiving bone marrow suppressive therapy.

Hemophagocytic lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) or hemophagocytic syndrome (HS) is a rare life-threatening hyperinflammatory syndrome characterized by abnormal excessive activation of the immune system. It is caused by impaired cytotoxic T-lymphocyte/natural kill (NK) cell activity and uncontrolled systemic proliferation of macrophages in all reticuloendothelial organs, producing pancytopenia, hypercytokinemia leading to hepatic injury with hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia. In cases of delayed diagnosis and therapy coagulopathy, disseminated intravascular coagulation and multiorgan dysfunction can occur [33]. HLH was initially described in 1952 by Farquhar and Claireaux and referred to as “familial hemophagocytic reticulosis” [34]. Depending on its etiology, HLH can be divided into the primary/genetic and secondary/acquired types [33,35,36]:

Primary HLH most commonly affects infants and children. This type of HLH is further subdivided into autosomal recessive/familial HLH, and HLH associated with primary immunodeficiency syndromes: Chediak-Higashi syndrome (LYST), Griscelli syndrome type 2, Hermansky-Pudlak syndrome type 2, X-linked lymphoproliferative disorder (XLP) type 1, X-linked prolif-
The secondary/acquired type of HLH is observed in the context of infections - viral (most commonly Epstein-Barr virus and cytomegalovirus), bacterial, fungal and parasitic; underlying autoimmune disorders or macrophage activation syndrome: systemic-onset juvenile idiopathic arthritis, Kawasaki disease, systemic lupus erythematosus and seronegative spondyloarthropathies; some metabolic disorders; and malignancies: which include (among others); peripheral T-cell/NK-cell lymphomas, anaplastic large cell lymphoma, acute lymphocytic leukemia, Hodgkin’s lymphoma, multiple myeloma, acute erythroid leukemia, prostate and lung cancer, and hepatocellular carcinoma.

While HLH affects 1% of adults with hematological malignancies, its incidence increases to 20% in some patients with B- and T-cell lymphomas [37]. Patients are often critically ill with a sepsis-like clinical picture. Signs and symptoms of HLH include [38]: fever, hepatosplenomegaly, cytopenia, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis in the bone marrow or lymph nodes, low or absent NK cell activity, hyperferritinemia and elevated soluble interleukin-2 receptor (CD25) levels. Diagnosis is based on the revised HLH-2004 guidelines [39,40].

Liver function impairment and hepatomegaly are present in 98% and 65% of cases respectively [41]. While it can simulate primary liver disease, HLH is a multisystem disorder involving multiple organs and has a characteristic immune dysfunction with high cytokine activity. Dong et al reported that the average interval from the earliest diagnosis of liver failure to a definitive diagnosis of HLH is 17 days, and 54% of the patients died during the follow-up period [42]. Liver biopsy of familial HLH can reveal activated macrophages with hemophagocytosis (any hemo poietic cell phagocytosed by the histiocytes, but most typically erythrocytes and/or platelets). Portal and sinusoidal lymphohistiocytic infiltrates and endothelialitis all correlate with clinical severity. Four histopathological patterns have been reported: chronic hepatitis-, leukemia-, histiocytic storage disorder- and neonatal giant cell hepatitis-like patterns [43].

Liver biopsy specimens of adult patients demonstrate well-preserved hepatic parenchyma, sinusoidal dilatation with portal and sinusoidal hemophagocytic histiocytosis, CD3+, CD8+, granzyme B+, and variable perforin+ T-cell rich infiltrates [33,44]. However, signs of hemophagocytosis in liver biopsies can nonetheless be found in adult patients regardless of whether they fulfil the diagnostic criteria for HLH [45].

Imaging

Reported abdominal US and CT sings in patients with HLH include hepatosplenomegalgy, gallbladder wall thickening, increased echogenicity of the portal areas, lymphadenopathy in the hepatoduodenal ligament, steatosis hepatitis, and ascites [38,46-49]. The sonographic signs are non-specific and must be correlated with the overall clinical context. Important differential diagnoses include sepsis, acute hepatitis, Wilson’s disease, myeloproliferative disorders, and various infectious diseases. Veno-occlusive disease of the liver is a rare complication of HLH or HS [50]. No pathognomic liver lesion specific for HLH have been reported.

Nakatsuka et al described liver lesions in a case of HS with veno-occlusive disease before initiation of immunosuppressive and chemotherapy. CT revealed multiple ill-defined hypodense liver lesions with no enhancement after contrast administration nor any mass effect of the adjacent vascular structures. The lesions were hypoechoic on the US examination, while high-intensity areas on T1-weighted images and low-intensity regions on T2-weighted images were visualized on MRI. The patient died despite immunosuppressive therapy, and an autopsy was performed. It was concluded that the hepatic lesions without mass effects were compatible with focal fatty infiltration due to the lipid-rich nature of the histiocytes [50]. Lymphoma infiltrations or metastases may naturally occur in the context of the causative hematological or oncolgical diseases of HLH, and their typical imaging characteristics may be present in US, CEUS, CT, and MRI scans [51]. Therapeutic approaches are complex and typically target immunosuppression.

Reactive lymphoid hyperplasia (RLH)

Reactive lymphoid hyperplasia (RLH) is a benign lesion that can occur in multiple organs including the lungs, skin, intestines, eye orbit and thyroid. Its occurrence in the liver is rare and was first described by Snover in 1981 [52]. To date, 100 cases of hepatic RLH, also known as pseudolymphoma, have been reported in the English-language literature [53]. This is a benign lesion characterized by a proliferation of polyclonal lymphocytes without atypia and with an active germinal center [54,55]. Its pathogenesis is unknown, although some authors speculate that it may be a reactive immune response to an infectious, inflammatory or tumoral process. More than 90% of cases occur in women over 50 years old, with an average age of 56 years [56]. More than one-third of all hepatic RLH patients present with underlying chronic liver disease, half of which are primary biliary cholangitis (PBC). Around 17% of the cases described
are linked to an autoimmune disease (Sjögren’s syndrome, autoimmune thyroiditis, Takayasu’s disease, antiphospholipid syndrome or CREST syndrome) and 26% to a malignant tumor (gastric, thyroid, uterine, ovarian, pancreatic, renal cell, cholangiocarcinoma or hepatocellular carcinoma) [56-59].

The potential association between hepatic RLH and an underlying malignancy has been hypothesized to be related to the production of cytokines/chemokines by such tumors [56-59]. Although these lesions are benign with no risk of malignant transformation, one case with progression to lymphoma has been described [60]. These lesions are peculiar in that they often resemble malignant lesions, appearing on dynamic imaging tests as hypervascular nodules that frequently present with washout in the portal venous phase [61,62]. Furthermore, hypermetabolic activity can be present and identified via FDG-PET mimicking that of malignant lesions [63,64]. The definitive diagnosis requires histology, where lymphoma remains a differential diagnosis and it may also share similarities with Castleman’s disease and PBC [54].

Imaging

The lesions are usually solitary and small in size (<2 cm, rarely exceeding 3 cm), multifocal FLH was described, however, in 15% of the cases. CT and MRI may reveal diffuse or perinodular arterial phase enhancement. Washout in the venous phase was described in at least 30% of the published cases and in at least 10.5% of cases with perinodular arterial enhancement, this phenomenon was also observed in the venous phase. This perinodular enhancement has been linked to lymphoid infiltration of the adjacent portal tracts [65,66] as well as to dilatation of the sinusoids surrounding the lesion in some cases [67]. On MRI, they are hyperintense on T2W and hypointense on T1W images [66]. Moreover, linear hyperintensity of the portal tract adjacent to the lesion has recently been described on diffusion-weighted imaging (DWI) which has also been associated with portal lymphoid infiltration [68]. On US imaging, they almost invariably appear as well-defined hypoechoic lesions [65,69]. The supplying vessel can be identified on Doppler in some cases.

The largest published series on hepatic RLH was reported by Dong et al [69] in which he and his colleagues described a series of 18 patients who underwent hepatic CEUS. Among these patients, RLH showed complete and homogeneous hyperenhancement in the arterial phase with early washout, that was evident at the end of the arterial phase or the beginning of the portal phase. In this early washout phase, a transient donut-like enhanced area, which became isoenhanced in the more advanced venous phase was observed. In addition, the size of the lesion in the arterial enhancement phase was larger than on the baseline B-mode US. The latter two features have also been associated with lymphoid cell infiltration of the portal tracts adjacent to the nodule. This infiltration could cause some portal obstruction that would secondarily produce an increase in arterial flow, which may thus be responsible for the hyperenhanced ring. During the preparation of this manuscript five histologically confirmed RLH lesions were analyzed in four women with an average age of 62.7 years, which is somewhat older than the average age described in previous published cases. Three patients had solitary lesions, and the fourth had two lesions with features of RLH (fig 2) [unpublished observations]. Two patients had a history of cancer (melanoma and squamous cell carcinoma of the tongue), and the other two had autoimmune diseases (type 1 diabetes mellitus and scleroderma). Furthermore, one patient had metabolic (dysfunction) associated fatty liver disease (MAFLD) without significant fibrosis. In three of the five

![Fig 2. Reactive lymphoid hyperplasia (RLH). B-mode US demonstrating a round, well-defined, hypoechoic lesion in the left hepatic lobe, measuring 12 mm in diameter (a). CEUS: Arterial phase showing an early diffuse enhancement, starting at 10 seconds (b). After enhancement, the lesion demonstrated a larger diameter than in B mode. Wash-out was seen at the end of the arterial phase at 22 seconds (c). The washout area is smaller than the enhancement area, although no clear hyperenhancing rim is identified.](image-url)
nODULES, MRI and/or CT revealed enhancement in the arterial phase with washout in the venous phase, suggestive of a malignant lesion. For the remaining two nodules, enhancement was observed in the arterial phase persisting into the end of the venous phase. In four of the five lesions, PET was positive with a SUVmax suggestive of malignancy. We performed US in four PET positive patients where two also underwent CEUS. The lesions in all cases were hypoechoic on greyscale. In the patient with multifocal lesions, we performed a study after the administration of SonoVue® to assess the two larger ones. Both had clear diffuse hyperenhancement in the arterial phase with early washout that was evident at the end of the arterial phase. One patient had a caudate lobe lesion. On CEUS, diffuse hyperenhancement was also observed in the arterial phase with early washout, albeit more faintly. The donut-like enhanced area at the beginning of the washout phase described by Dong was not identified in any of the cases. However, we did observe that the size of the lesion in the arterial enhancement phase was somewhat larger than on the baseline B-mode US. Since malignancy was suspected in all the cases, biopsy of the nodules was performed for three patients (two with the aid of transabdominal US and the nodule of the caudate lobe with endoscopic US guidance) and surgical resection in the fourth patient (fig 3). In the patient who had two nodules, both lesions were biopsied. The diagnosis was RLH in all the cases.

In conclusion, although RLH is a rare condition, it should be considered when a small, apparently malignant liver nodule is observed in middle-aged female patients, particularly if they have an underlying chronic liver disease, an autoimmune disease or a malignant tumor. However, metastatic lesions have similar enhancement patterns and are more common than RLH therefore they should always be considered until proven otherwise.

Conclusion

Rare benign hematological liver lesions (EMH, HLH, and ELH) should be considered in the appropriate clinical context. Unfortunately, these benign lesions often present in patients with underlying malignancies and their sonographic features of hypoechoigenicity on B-mode US and hyperenhancement/ washout on CEUS are nonspecific but mimic those of malignant lesions. Thus, histological examination is invariably required for the definitive diagnosis.

Conflict of interest: none

References


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