Contrast-enhanced sonographic appearances of two primary hepatic epithelioid angiomyolipomas

Running title: CEUS of hepatic epithelioid angiomyolipomas

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Abstract

Epithelioid hepatic angiomyolipoma (Epi-HAML) is a rare hepatic tumor frequently misdiagnosed as hepatocellular carcinoma (HCC). Unlike conventional angiomyolipoma (AML), Epi-HAML contains minimal amount of adipose tissue, which is a radiological distinguishing feature between AML and HCC. Two patients were referred for management of incidentally found hepatic lesions confirmed to be Epi-HAML on post-resection tissue analysis. CT and MRI findings were suggestive of HCC. Contrast-enhanced ultrasound demonstrated intratumoral shunting, a feeding artery and early draining hepatic vein. These findings should alert radiologists to the possibility of Epi-HAML.

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Furthermore, these features may be better assessed by CEUS due to its superior dynamic temporal resolution.

Introduction

Epithelioid hepatic angiomyolipoma (Epi-HAML) is a rare hepatic tumor which is frequently misdiagnosed as hepatocellular carcinoma (HCC). We present two cases of Epi-HAML with features seen on contrast-enhanced ultrasound (CEUS) relevant to the diagnosis.

HAML can be zsubcategorized according to dominant cell type; epithelioid, spindle, and intermediate forms. The majority of cases are found incidentally with abdominal discomfort being the most common symptom. Tumor markers (AFP, CEA, and Ca19-9) are usually in normal ranges. Epi-HAML has no established natural history though cases of metastatic and recurrent Epi-HAML have been reported in recent years. Less than 30% of Epi-HAMLs are diagnosed pre-operatively as they are frequently misdiagnosed pre-operatively as focal nodular hyperplasia (FNH) or hepatocellular carcinoma (HCC) with up to 65% being misdiagnosed as HCC.

Case one

A 62-year-old woman was found to have an incidental right hepatic lesion during the investigation of chronic cough. She had no abdominal or paraneoplastic symptoms. The patient had a history of SLE, asthma but no previous hepatitis. A multiphase hepatic CT demonstrated a subcapsular segment V mass that was isodense on the precontrast images, homogenously hyper-enhancing in the arterial phase, with an enlarged tortuous feeding artery and an early draining hepatic vein (Figure 1). There was no evidence of washout in the
portal venous or three-minutes-delayed phases. There was no calcification, capsular retraction, or biliary distension and the remainder of the liver was normal.

Hepatic MRI was performed without contrast due to previous allergic reactions and showed a mildly lobulated 25 x 16mm subcapsular segment V lesion. It was homogeneously hypointense on T1-weighted images and moderately hypointense on T2-weighted images. There was no evidence of intralesional fat or hemorrhage. CEUS was recommended.

Grayscale US examination demonstrated a homogeneous liver with normal echogenicity. The mass was homogeneously hypoechoic and extended to the hepatic capsule without evidence of capsular distortion. Pronounced vascularity was evident on Doppler interrogation. CEUS was performed with EPIQ 7G (Philips Healthcare, Andover, MA) and demonstrated vivid, homogeneous early arterial phase enhancement (Figure 2A), with the lesion enhancing almost simultaneously with the arrival of contrast in the feeding artery, 10 seconds post-injection. Early enhancement of an enlarged draining hepatic vein was noted (Figure 2B) before any significant hepatic parenchymal enhancement had occurred (12 seconds post-injection). The mass then demonstrated rapid washout centrally 24 seconds after the injection with persistent enhancement in the rim. These findings were in keeping with a malignant lesion with the differential diagnosis of a peripheral cholangiocarcinoma or a combined hepatocellular cholangiocarcinoma.

After a multi-disciplinary meeting and given the patient’s preference for surgical resection versus surveillance, a decision was made to proceed directly to an open right hemihepatectomy.

Macroscopically and microscopically the specimen was sharply circumscribed from the adjacent normal parenchyma and had no true capsule. There were some small areas of mature adipocytes,
epithelioid cells and scattered, thick-walled blood vessels consistent with the US appearance (Figure 3).

**Case two**

A 51-year-old woman was found to have segment VII and VIII hepatic lesions found incidentally during the investigation of thoracic spine pain, with unremarkable medical history.

A hepatic multiphase CT examination demonstrated a 4.6-cm lesion in segment VIII and a 1-cm lesion in segment VII lesion with the same features as those described in the patient of case 1 but without a clear feeding artery. On MRI examination the lesion in segment VIII was moderately hyperintense on T2 images with retention of contrast in the delayed phase while the segment VII lesion was isointense on T2 images with washout on the delayed phase.

CEUS of the liver performed using Acuson Sequoia (Siemens Healthineers, Malvern, PA) showed no evidence of cirrhosis. The segment VII lesion displayed marked, rapid and homogenous enhancement occurring at 8 seconds from injection with the entire lesion enhancing before any contrast had entered the hepatic parenchyma (Figure 4A). At 11 seconds, two large draining hepatic veins were clearly seen converging towards the main right hepatic vein, before any significant parenchymal enhancement had occurred (Figure 4B).

Core needle biopsy was performed under US guidance. Two passes were made in each lesion with 18-gauge cutting needles and a coaxial technique. Analysis of the core suggested the segment VII lesion to be an Epi-HAML and the segment VIII lesion to be a HAML. After management options for Epi-HAML were discussed, surgical resection of both segments was performed following pre-operative embolization with no complications.
On histopathological analysis, both lesions were found to have features of Epi-HAML. They were well-circumscribed with no true capsules but foci of infiltration into the surrounding parenchyma. Prominent vessels were scattered amongst epithelioid cells and mature adipose tissue (Figure 5). The surfaces of the lesions were necrotic and had changes consistent with the pre-operative embolization.

Discussion

Mature adipose tissue, along with an absence of a tumor capsule and a peripheral decreasing enhancement ring is a feature distinguishing HAML from HCC\(^1\), although this is not definitive as HCCs may contain fat deposits\(^5\). In contrast, Epi-HAML does not contain fat, which makes its diagnosis difficult.

Epi-HAML may have a pseudo capsule and is usually well-defined. On MRI, it is often hypointense on T1-weighted images and hyperintense on T2-weighted images and it is hypervascular on angiography\(^6\). These features are non-specific and are shared with HCC.

Hypoechoic, hyperechoic and mixed echogenicity appearances can be seen on US with a tendency towards mixed-echogenicity and hypoechoic appearances\(^7\) as opposed to a heterogeneous increased echogenicity seen in HAML. A six-patient case series investigating CEUS found that hyperenhancement in the arterial phase with washout in the late phase to be a common feature (67% in 121-360 seconds)\(^7\). This is a feature that is helpful but not diagnostic of Epi-HAML. The authors hypothesized that washout might have been delayed in those cases by the presence of sinusoids and vascular aberrancy.
The presence of hypervascularity is not specific for any individual liver pathology, and so the characterization of focal liver lesions is dependent upon constellations of findings. The imaging features of the Epi-HAML cases, hypervascularity and rapid washout on CEUS, are also suggestive of cholangiocarcinoma or combined HCC in patients with chronic liver disease.

In these two cases, the degree of hyperenhancement in the arterial phase was marked, occurring in the angiographic phase and being homogeneously distributed throughout the mass. There were two striking features of intralesional shunting: an enlarged feeding artery (due to reduced peripheral vascular resistance within the lesion) and early enhancement of a prominent draining hepatic vein. Both features were easily demonstrable on multiple modalities and are in keeping with the angiomatous component of the tumor. The presence of prominent vessels and shunting associated with HAML has been previously described \(^4,8\) and the presence of these vessels can be inferred by the feeding and draining vascular pathways.

An enlarged feeding artery has also been described in FNH as has the presence of draining veins\(^9,10\), although the draining vein is typically seen during the portal venous phase rather than during the arterial dominant phase as it is secondary to increased blood flow rather than due to shunting. A prominent and early draining vein has also been described in HCC, but the drainage of HCC is typically to the portal venous system, rather than to the hepatic veins.

We propose that there are some potentially diagnostic imaging features for Epi-HAML, which are well demonstrated on CEUS due to its excellent temporal resolution. These include strong homogenous angiographic phase enhancement, the presence of an enlarged feeding artery, and enlarged and early filling draining hepatic vein(s).


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Figure Legends

Figure 1: Case 1: 62-year-old woman with hepatic Epi-HAML in segment V. Arterial-phase CT scans demonstrate mass. Left: Arrow points to the tortuous feeding artery. Right: Arrow points to the draining vein.

Figure 2 Case 1: A) CEUS demonstrating enhancing lesion and feeding artery (arrow) 10 seconds post-injection of contrast.
B) CEUS shows early enhancement of mass-draining vein (arrow) 12 seconds post-injection of contrast.

Figure 3: Case 1: Photomicrograph shows epithelioid cells with clear to eosinophilic cytoplasm, with scattered thick-walled blood vessels. Note the lack of true capsule between lesion and adjacent liver (arrow) [AU: correct?] (40x magnification)

Figure 4: Case 2: 51-year-old woman with two hepatic lesions. A) CEUS examination of lesion in segment VII shows rapidly enhancing lesion at 8 seconds post-injection of contrast.
B) CEUS examination of lesion in segment VII shows two large mass-draining veins (arrows) appearing at 11 seconds post-injection of contrast.

Figure 5: Case 2: Photomicrograph of Epi-HAML in segment VII shows epithelioid cells with abundant eosinophilic cytoplasm, scattered thick-walled blood vessels (arrows) and mature adipose tissue. (40x magnification)
Contrast-enhanced sonographic appearances of two primary hepatic epithelioid angiomyolipomas

Running title: CEUS of hepatic epithelioid angiomyolipomas

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Abstract

Epithelioid hepatic angiomyolipoma (Epi-HAML) is a rare hepatic tumor frequently misdiagnosed as hepatocellular carcinoma (HCC). Unlike conventional angiomyolipomas (AML), Epi-HAML has minimal adipose tissue which is a radiological distinguishing factor for AML vs HCC. Two patients were referred for management of incidentally found hepatic lesions confirmed to be Epi-HAML on tissue analysis post-resection. CT and MRI findings were suggestive of HCC. Contrast-enhanced ultrasound demonstrated intratumoral shunting, a feeding artery and early draining hepatic vein. These findings should alert radiologists to the possibility of Epi-HAML. Furthermore, these features may be better assessed by CEUS due to its superior dynamic temporal resolution.

Introduction

Epithelioid hepatic angiomyolipoma (Epi-HAML) is a rare hepatic tumor which is frequently misdiagnosed as hepatocellular carcinoma. We present two cases of Epi-HAML with features seen on contrast-enhanced ultrasound (CEUS) relevant to the diagnosis.

HAML can be zsubcategorized according to dominant cell type; epithelioid, spindle, and intermediate forms. The majority of cases are found incidentally with abdominal discomfort being the most common symptom. Tumor markers (AFP, CEA, and Ca19-9) are usually in normal ranges. Epi-HAML has no established natural history though cases of metastatic and recurrent Epi-HAML being reported in recent years. Less than 30% of Epi-HAML is diagnosed pre-operatively with it frequently being mistaken as focal nodular hyperplasia (FNH) or hepatocellular carcinoma (HCC) pre-operatively with up to 65% misdiagnosed as HCC.

Case one
A 62-year-old woman was found to have an incidental right hepatic lesion on the investigation of chronic cough with her GP. She had no abdominal or paraneoplastic symptoms. This presentation was on a background of SLE, asthma and no previous hepatitis infection.

A multiphase hepatic CT demonstrated a subcapsular segment five mass that was isodense on the precontrast, homogenously hyper-enhancing in the arterial phase, with an enlarged serpentine feeding artery and an early draining hepatic vein (Figure 1). There was no evidence of washout on the portal venous or three minutes delayed phase. No capsular retraction, calcification or biliary distension and the remainder of the liver was normal.

Hepatic MRI was performed without contrast due to previous allergic reactions and showed a gently lobulated 25 x 16mm subcapsular segment V hepatic lesion. It was homogeneously T1 hypointense and moderately T2 hypointense. There was no evidence of intralesional fat or hemorrhage. A contrast-enhanced US or biopsy was recommended.

B mode ultrasound demonstrated a homogenous liver with normal echogenicity. The mass was homogenously hypoechoic and extended to the hepatic capsule without evidence of capsular distortion. Pronounced vascularity was evident on Doppler interrogation. Contrast-enhanced ultrasound was performed with EPIQ 7G (Philips Healthcare, Andover, Massachusetts) and demonstrated vivid, homogenous early arterial phase enhancement (Figure 2A), with the lesion enhancing almost simultaneously with the appearance of contrast in the feeding artery, being 10 seconds post-injection. Early enhancement of an enlarged draining hepatic vein was noted (Figure 2B) before any significant hepatic parenchymal enhancement had occurred (12 seconds post-injection). The mass then demonstrated rapid washout centrally 24 seconds after the injection with persistent enhancement in the rim. These findings were in keeping with a malignant lesion with a differential of a peripheral cholangiocarcinoma or a combined hepatocellular cholangiocarcinoma.
In view of discussion at a multi-disciplinary meeting and the patients own wishes on definitive surgery vs the possibility of surveillance, a decision was made to proceed directly to an open right hemihepatectomy.

Macrosopically and microscopically the specimen was sharply circumscribed from the adjacent normal parenchyma and had no true capsule. There were some small areas of mature adipocytes evident, epithelioid cells and scattered, thick-walled blood vessels consistent with the ultrasonographic appearance (Figure 3).

Case two

A 51-year-old woman was found to have segment 7 and 8 hepatic lesions on investigation of thoracic spine pain, with no significant pre-existing symptoms or medical conditions.

A hepatic multiphase CT demonstrated a 4.6cm segment 8 and a 1cm segment 7 lesion with similar features to the first patient without a clear feeding artery. MR of her liver was performed finding the segment 8 lesion to be moderately T2 hyperintense with retention of contrast in the delayed phase while the segment 7 lesion was T2 isointense with washout on the delayed phase.

CEUS performed using Acuson Sequoia (Siemens Healthineers, Malvern, Pennsylvania) showed a homogenous liver with no evidence of cirrhosis. The segment 7 lesion displayed marked, rapid and homogenous enhancement occurring at 8 seconds from injection with the entire lesion enhancing before any contrast had entered the hepatic parenchyma (Figure 4A). At 11 seconds, two large draining hepatic veins can clearly be seen converging towards the main right hepatic vein, with this occurring before any significant parenchymal enhancement has occurred (Figure 4B).

Biopsy was performed under ultrasound guidance with 17-gauge coaxial needles with three and two passes used to obtain 18-gauge cores from the segment 7 and 8 lesions respectively. Analysis of the cores suggested the segment 7 lesion to be an Epi-HAML and the segment 8 lesion to be a HAML.
Management options for Epi-HAML were discussed and surgical resection of both segments with pre-operative embolization was performed with no complications.

On histological analysis, both lesions were found to have features of Epi-HAML. They were well-circumscribed with no true capsules but foci of infiltration into the surrounding parenchyma. Prominent vessels were scattered amongst epithelioid cells and mature adipose tissue (Figure 5). The surfaces of the lesions were necrotic and had changes consistent with the pre-operative embolization.

Discussion

Mature adipose tissue, along with an absence of a tumor capsule and a peripheral decreasing enhancement ring is a distinguishing factor for HAML vs HCC\textsuperscript{1} though not definitive as HCCs may contain fat deposits\textsuperscript{5}. In contrast, Epi-HAML does not contain fat which makes diagnoses difficult.

Epi-HAML may have a pseudo capsule, is usually well-defined, is often hypointense on T1W1 and hyperintense on T2WI on MRI and is hypervascular on angiography\textsuperscript{6}. These features are non-specific and are shared with HCC.

Hypo, hyper and mixed echogenic pictures can be seen on US with a leaning towards mixed and hypoechoic\textsuperscript{7} as opposed to a heterogeneous hyperechoic picture seen in HAML. A six patient case series looking at contrast-enhanced US (CEUS) found hyperenhancement in the arterial phase with washout in the late phase a common feature (67% in 121-360 seconds)\textsuperscript{7}. This is a feature that is helpful but not diagnostic of Epi-HAML. The authors hypothesized that washout might have been delayed in those cases by the presence of sinusoids and vascular aberrancy.

The presence of hypervascularity is not specific for any individual liver pathology, and so the characterization of focal liver lesions is dependent upon constellations of findings. The imaging features of the Epi-HAML cases; hypervascularity and rapid washout on CEUS, are features suggestive of cholangiocarcinoma or combined HCC in patients with chronic liver disease.
In these two cases, the degree of hyperenhancement in the arterial phase was marked, occurring in the angiographic phase and being homogeneously distributed throughout the mass. There were two striking features of intralesional shunting; an enlarged feeding artery (due to reduced peripheral vascular resistance within the lesion) and early enhancement of a prominent draining hepatic vein. Both of these features were easily demonstrable on multiple modalities and in keeping with the effects of the angiomatous component of the tumor. The presence of prominent vessels and shunting associated with hepatic AML have been previously described \(^4,8\) and the presence of these vessels can be inferred by the feeding and draining vascular pathways.

An enlarged feeding artery has also been described in focal nodular hyperplasia as have the presence of draining veins\(^9,10\), although the draining vein is typically encountered during the portal venous phase rather than during the arterial dominant phase as it is secondary to increased blood flow rather than due to shunting. A prominent and early draining vein has also been described in hepatocellular carcinoma however a distinction is that the drainage of HCC is typical to the portal venous system, rather than to the hepatic veins.

We propose that there are some potentially diagnostic imaging features for EAML and that the excellent temporal resolution of CEUS can well demonstrate these. These features are i. vivid homogenous angiographic phase enhancement; ii an enlarged feeding artery; and iii and enlarged and early filling draining hepatic vein. These signs are better assessed with CEUS than cross-sectional imaging, due to the superior dynamic temporal resolution of ultrasound. These signs need to be reviewed in future descriptions of the cases to determine sensitivity, specificity and clinical utility.


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Figure Legends

Figure 1: Case 1: 62-year-old woman with segment V hepatic Epi-HAML: Axial arterial phase CT images demonstrating mass with serpentine feeding artery (left arrow) and draining hepatic vein (right arrow).

Figure 2A: Case 1: 62-year-old woman with segment V hepatic Epi-HAML: CEUS demonstrating enhancing lesion and feeding artery (arrow) 10 seconds post-injection of contrast.

Figure 2B: Case 1: 62-year-old woman with segment V hepatic Epi-HAML: CEUS demonstrating early enhancement of mass-draining vein (arrow) 12 seconds post-injection of contrast.

Figure 3: Case 1: 62-year-old woman with segment V hepatic Epi-HAML: Cut section under x40 magnification. Epithelioid cells with clear to eosinophilic cytoplasm, with scattered thick-walled blood vessels. Note the interface with a lack of true capsule between lesion and background liver (lower right).

Figure 4A: Case 2: 51-year-old woman with two hepatic lesions: CEUS of segment VII Epi-HAML demonstrating rapidly enhancing lesion at 8 seconds post-injection of contrast.

Figure 4B: Case 2: 51-year-old woman with two hepatic lesions: CEUS of segment VII Epi-HAML demonstrating two large mass-draining veins (arrows) at 11 seconds post-injection of contrast.

Figure 5: Case 2: 51-year-old woman with two hepatic lesions: Cut section of segment VII Epi-HAML under 40x magnification. Epithelioid cells with abundant eosinophilic cytoplasm, scattered thick-walled blood vessels (arrows) and mature adipose tissue.