Epithelioid hemangioendothelioma of the liver: the appearance on diffusion weighted and hepatobiliary phase magnetic resonance images

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Aims and objectives

Hepatic epithelioid hemangioendothelioma (HEHE) is a rare tumor of mesenchymal origin that has a low to intermediate malignant potential and is most commonly encountered in young and middle-aged females. The correct diagnosis of HEHE is of utmost importance, as the most common management of this neoplasm, contrary to the majority of other hepatic malignancies, is liver transplantation (LT). The disease is often multinodular and may mimic metastases from extra-hepatic malignancy. This may result in delay of correct diagnosis in some patients, although the knowledge of typical radiologic appearance of HEHE (multiple, peripheral, often subcapsular and confluent lesions, which may cause capsular retraction) should lead to inclusion of this entity in differential diagnosis in most of the cases. The definitive diagnosis of HEHE is based on histopathologic examination.

In recent years new magnetic resonance (MR) imaging techniques, including diffusion-weighted (DW) echo-planar imaging (EPI) and contrast-enhanced imaging with the use of hepatobiliary contrast agents, became widely available. Despite several published reports regarding MR imaging of HEHE [1-6] there is merely a single report including only three cases studied with DWI [5]. Moreover, to the best of our knowledge, there are no published articles regarding utilization of hepatobiliary contrast agents in this disease, therefore the behavior of HEHE after administration of these agents is not known. Since HEHE do not contain functioning hepatocytes, no significant contrast enhancement is expected during hepatobiliary phase, although this was never documented in radiologic literature. Therefore, the aim of this study was to determine if the appearance of HEHE on the state-of-the-art MR imaging including DW images and 3D dynamic contrast enhanced, 5-minutes delayed and hepatobiliary phase images may facilitate preoperative diagnosis and identification of potential candidates for liver transplantation.
Methods and materials

Patients

Between August 2008 and July 2012 six patients with HEHE underwent both CT and MR imaging at our institution and in all cases the final diagnosis was based on histopathological specimen.

There were 1 male and 5 females, with a mean age of 36.2 years (age range: 25-59 years). At the time of the diagnosis 3 patients had no remarkable clinical symptoms, whereas 3 presented with right-upper quadrant abdominal pain and one patient had swollen lower limbs.

Laboratory tests revealed no significant increase in the level of alpha-fetoprotein, carcinoembryonic antigen and cancer antigen 19-9.

Imaging

Magnetic Resonance Imaging

All MR examinations were performed on 1.5 T scanner (Magnetom Avanto, Siemens, Erlangen, Germany), using a phase-array multicoil system. All MR studies were performed according to the same protocol consisting of the following sequences: breath-hold T2-weighted turbo spin-echo (TSE) sequence with double echo (T2 TSE), respiratory-triggered T2-weighted TSE sequence with fat saturation (T2 TSE fat-sat), respiratory-triggered DW SE single shot echo planar (EP) sequence with b values of 50, 400 and 800s/mm², chemical shift imaging (in-out SGE) and 3D T1-weighted gradient recalled echo sequence (3D T1 GRE) with fat saturation before and after administration of contrast material.

In five patients contrast-enhanced MRI was performed after the infusion of Gd-BOPTA (Multihance, Bracco Diagnostisc, Milan, Italy) at a dose of 0.1 mmol/kg bodyweight, corresponding to 0.1 ml/kg bodyweight, immediately followed by a bolus of 20 ml of physiological saline (NaCl 0.9%). One patient underwent contrast-enhanced examination after intravenous administration of Gd-EOB-DTPA (Primovist, Bayer Schering, Berlin, Germany) at a dose of 25 mmol / kg body weight (0.1 ml / kg body weight), followed by a bolus of 20 ml of saline (NaCl 0.9%). Images were acquired during following phases: hepatic arterial (25-30 seconds postinjection), portal venous (60-70 seconds postinjection), equilibrium (90-120 seconds postinjection), delayed (5 minutes postinjection) and hepatobiliary (60-80 minutes delayed for Gd-BOPTA and 20 minutes delayed for Gd-EOB-DTPA).

Image analysis
All images were evaluated by two experienced radiologists who assessed the number of the lesions, their location, signal intensity characteristics on T1-weighted gradient-recalled echo (GRE) and T2-weighted turbo spin echo (TSE) images and contrast enhancement pattern on dynamic, delayed and hepatobiliary phase images. In case of disagreement a consensus interpretation was formed.

Apparent diffusion coefficient (ADC) of focal hepatic lesions were calculated by mono-exponential regression with following formula: $S = S_0 \cdot \exp(-b \cdot \text{ADC})$, where $S$ is the signal intensity after application of the diffusion gradient and $S_0$ is the signal intensity at $b=0$ s/mm$^2$\cite{7,8}. Three $b$ values (50, 400, 800 sec/mm$^2$) were applied for ADC calculation.

**Pathologic diagnosis**

The final diagnosis in all the patients was based on histopathological examination of the specimen, which was obtained during surgery in 3 of them and during diagnostic laparoscopy in remaining 3 patients. Immunohistochemically, staining for endothelial markers, including CD 31 and CD 34, was performed in all patients.
Results

Clinical course

Clinical course of disease, treatment and survival of analyzed patients are summarized in table 1. The extrahepatic spread was diagnosed in 2 patients (no. 1, 4); both had lung metastases and one (no. 1) had peritoneal and celiac lymph node metastases.

Three patients (no. 3, 5, 6) were treated with orthotopic liver transplantation. One of them (no. 6) died 12 weeks following transplantation (24 weeks after the initial diagnosis) due to acute pancreatitis subsequent to endoscopic retrograde pancreatobiliary angiography. In none of these patients recurrence of HEHE was observed in transplanted liver. Two other patients currently await liver transplantation (no. 2, 4) and one patient (no. 1) with disseminated, progressive disease (metastatic sites in lungs, peritoneum and celiac lymph nodes) was treated with Nexavar and died 33 months after the initial diagnosis.

In four patients who are alive (including 2 treated with liver transplantation) the disease is stable and no signs of progression are noted. In this group the mean survival time from initial diagnosis is 12.8 months (range: 4 - 38 months).

Imaging

Computed Tomography

Calcifications were depicted on CT scans in 1 patients. They were massive, located in subdiaphragmatic region of segments VII and VIII.

Magnetic Resonance Imaging

In four patients with more than 20 lesions the assessment of signal characteristics, morphology and quantification of each of them was not possible, therefore in this patients maximum of 10 lesions per patient were randomly selected for both qualitative and quantitative analysis. Ultimately, the final analysis included 55 lesions in 6 patients (from 7 to 10 lesions per patient).

The most common feature of HEHE, observed in 84% of tumor nodules, was progressive contrast enhancement, followed by subcapsular location (66%), confluent character (60%) (Fig. 1, 2) and, interestingly, hyper- or isointensity on hepatobiliary phase images (53%). The remaining 47% of lesions were hypointense on hepatobiliary phase images (Fig. 3). In 5 of 6 patients capsular retraction was observed (Fig. 2, 4).

All tumor nodules were hyperintense on T2-weighted TSE images. Among 55 analyzed lesions, 21 were inhomogenous, typically with markedly hyperintense center and moderately hyperintense outer zone (Fig. 1). In some lesions (n=10) there was additional
third, thin rim of low signal intensity, which was located externally or in-between two hyperintense zones (Fig. 4).

All lesions were hypointense on 3D T1-weighted GRE images and 12 of 55 analyzed tumor nodules demonstrated inhomogeneity with lower signal intensity in the center.

On the arterial phase images 25 of 55 analyzed lesions (46%) in demonstrated different degree of contrast enhancement, commonly with peripheral ring-like enhancement, although in some cases enhancing central dots or streaks were visible (Fig. 1). During portal venous phase 22 nodules (40%) showed at least two layers of varying enhancement, usually with peripheral hyperintensity and hypointense center. Progression of contrast-enhancement was best appreciated on 5-minute delayed images and was noted in 45 of analyzed tumor nodules (84%) (Fig. 1, 3).

Analysis of ADC demonstrated that the mean ADC value was \(1.423 \times 10^{-3}\ \text{mm}^2/\text{s}\) and a substantial variability of ADC values among investigated lesions was noted (range: \(0.94 - 2.1 \times 10^{-3}\ \text{mm}^2/\text{s}\)).

**Discussion**

Epithelioid hemangioendothelioma is an uncommon mesenchymal tumor, which may occur in the soft tissue, lung, bone, brain, small intestine and liver. Primary hepatic EHE is very rare tumor with reported incidence as low as less than 1 per million. It has low to moderate malignant potential and is presumed to affect most commonly young to middle-aged women. Clinical manifestation of HEHE is not specific and, most commonly, include right upper quadrant pain, hepatomegaly and weight loss. At the time of diagnosis majority of patients present with multifocal disease involving both hepatic lobes. Metastases may occur and usually involve lung, peritoneum, lymph nodes and bones [1, 5, 8]. Nevertheless, the prognosis is more favorable than in other hepatic malignancies and HEHE may be successfully treated with surgical resection or liver transplantation. Even though surgical resection is considered the treatment of choice only a small number of patients qualify for this procedure. In much more frequent cases of multifocal, non-resectable tumors, patients are treated with liver transplantation, which is presently the most common management. Reported 5-year patient survival rates were 75% and 54.5% after liver resection and liver transplantation, respectively.

Hence, distinguishing this tumor from other focal hepatic lesions, including metastases, multifocal hepatocellular carcinoma, peripheral cholangiocarcinoma, angiosarcoma and atypical hemangioma, is important in order to facilitate appropriate treatment, most commonly LT [1]. Even though the final diagnosis of HEHE requires pathological confirmation, radiologists should be aware of distinct imaging features of HEHE, which, in proper clinical setting and laboratory tests, may lead to accurate diagnosis. In this study accurate preoperative diagnosis was suggested by radiologists in 5 of 6 cases.
Our MR imaging findings regarding the appearance of HEHE were in the agreement with those reported previously in the literature, including the presence of multiple, coalescent lesions (60%), located mostly at the periphery, often in contact with liver capsule (66%). The majority of tumor nodules demonstrated progressive enhancement (84%), best depicted on 5-minute delayed contrast-enhanced MR images. Capsular retraction was depicted in 5 of 6 patients.

In recent years DW, chemical-shift and contrast-enhanced 3D T1-weighted GRE imaging have become the part of routine MR imaging protocol in most centers. Furthermore, the introduction of liver-specific contrast agents not only increased the sensitivity of MR imaging for detection of focal liver lesions, but also allowed for their more accurate differentiation. The knowledge of the appearance of HEHE on these relatively new MR techniques is very limited. There is just a single report on the implementation of DW imaging in three patients with HEHE [5] and, to the best of our knowledge, there is no data regarding appearance of this tumor during liver specific phase after injection of hepatobiliary contrast agent. Besides, the 5-minutes delayed MR images, best for the evaluation of progression of contrast enhancement, were systematically assessed in only four patients by Bruegel et al. [5]. Our study presents for the first time complex MR evaluation of HEHE at the state-of-the art MR imaging including diffusion-weighted images, high-resolution contrast-enhanced 3D T1-weighted GRE dynamic images, 5-minute delayed and hepatobiliary phase images.

In our study, analyzing the highest, so far, number of patients with HEHE using DW imaging, the mean ADC value of 55 tumor nodules (1.55 x 10^{-3} \text{ mm}^2/\text{s}) was higher than those of other types of malignant lesions, as reported in previous publications. This finding is similar to that described by Bruegel et al., who analyzed 30 lesions in three patients with HEHE and obtained even higher mean ADC value of 1.86 x 10^{-3} \text{ mm}^2/\text{s}.

Since HEHE is a tumor of vascular origin, lacking functioning hepatocytes, no up-take of hepatobiliary-specific contrast agent is expected in these lesions. However, to the best of our knowledge, this was never reported in the radiologic literature. Our report, analyzing for the first time the appearance of HEHE on hepatobiliary phase images after administration of liver specific contrast agents, revealed that the majority of these lesions (29 of 55) presented, surprisingly, with iso- or hyperintensity. We presume that this was due to marked and prolonged retention of contrast material in fibrous tissue in these lesions.
Fig. 1: 34-year-old woman with epithelioid hemangioendothelioma (patient 3). Axial T2-weighted fat-saturated axial turbo spin echo MR image shows multiple, inhomogenous, hyperintense lesions, most of them adjacent to liver capsule with distinctly increased signal intensity in the center.

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Fig. 2: 34-year-old woman with epithelioid hemangioendothelioma (patient 3). Axial DW-weighted respiratory-triggered MR image (b=800) shows multiple lesions with markedly hyperintense periphery.
**Fig. 3:** 34-year-old woman with epithelioid hemangioendothelioma (patient 3) ADC map reveals increased diffusion in all lesions, as compared to normal liver.

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**Fig. 4:** 34-year-old woman with epithelioid hemangioendothelioma (patient 3). Axial T1-weighted gradient recalled-echo MR image shows multiple hipointense lesions.

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Fig. 5: 34-year-old woman with epithelioid hemangioendothelioma (patient 3). Arterial phase, Gd-BOPTA enhanced, axial T1-weighted gradient recalled-echo MR image demonstrates central or peripheral rings of contrast enhancement.

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**Fig. 6:** 34-year-old woman with epithelioid hemangioendothelioma (patient 3). Five-minute delayed contrast enhanced axial T1-weighted gradient recalled-echo MR image demonstrates progression of contrast-enhancement in all lesions.

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Fig. 7: 34-year-old woman with epithelioid hemangioendothelioma (patient 3). Axial Gd-BOPTA-enhanced hepatobiliary phase T1-weighted gradient recalled-echo MR image shows retention of hepatobiliary contrast agent more than in the normal liver.

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Fig. 8: 25-year-old woman with epithelioid hemangioendothelioma (patient 1). Axial T2-weighted fat-saturated axial turbo spin-echo MR image shows large, coalescent, mostly subcapsular, hyperintense lesions in both liver lobes. Retraction of liver capsule and compensatory liver hypertrophy is noted. Ascites.

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Fig. 9: 25-year-old woman with epithelioid hemangioendothelioma (patient 1). Lesions are hyperintense on this axial DW-weighted respiratory-triggered MR image (b=800)
Fig. 10: 25-year-old woman with epithelioid hemangioendothelioma (patient 1). ADC map confirms increased diffusion in all lesions, as compared to adjacent liver.

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Fig. 11: 25-year-old woman with epithelioid hemangioendothelioma (patient 1). Axial Gd-BOPTA-enhanced hepatobiliary phase T1-weighted gradient recalled-echo MR image demonstrates increased retention of contrast agent.

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Fig. 12: 36-year-old woman with epithelioid hemangioendothelioma (patient 5). Arterial phase, Gd-BOPTA enhanced, axial T1-weighted gradient recalled-echo MR image shows multiple tumor nodules, majority of them located centrally. There is peripheral ring of enhancement in some lesions.

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Fig. 13: 36-year-old woman with epithelioid hemangioendothelioma (patient 5). Five-minute delayed contrast enhanced axial T1-weighted gradient recalled-echo MR image demonstrates progression of contrast enhancement in all lesions.

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Fig. 14: 36-year-old woman with epithelioid hemangioendothelioma (patient 5). On axial Gd-BOPTA-enhanced hepatobiliary phase T1-weighted gradient recalled-echo MR image some lesions are isointense and the other are mostly hypointense to the liver.

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Conclusion

HEHE may be difficult to differentiate from other hepatic lesion including metastases, multifocal HCC, peripheral cholangiocarcinoma and angiosarcoma. The most important imaging features, which help in diagnosing HEHE, are multiple, confluent nodules, often adjacent to liver capsule, showing peripheral, progressive enhancement and sometimes capsular retraction. Our study showed that the use of hepatobiliary phase and DW images have additional value in diagnosing HEHE. In appropriate clinical setting (young to middle-aged woman) identification of multiple lesions with malignant morphology of HEHE, which often demonstrate hyper- or isointensity during hepatobiliary phase and have higher ADC values than that of other liver malignancies (some in the range of benign lesions) may suggest correct diagnosis and help in qualifying patients for proper treatment, most commonly liver transplantation.
References