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Case Report

# Hepatic epithelioid hemangioendothelioma simulating liver metastasis: A case report

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ABSTRACT

*Introduction:* Hepatic epithelioid hemangioendothelioma (HEHE) is a rare tumor of vascular origin. Liver involvement is often multinodular simulating metastases. Herein, we report a rare case of HEHE mimicking liver metastases in a female patient.

*Case presentation:* A 43-years-old female patient, presented with complaints of pain in the right upper quadrant. Laboratory tests were all within the normal range. Abdominal ultrasound revealed multiple heterogeneous hypoechoic liver lesions. A thoracic and abdominopelvic computed tomography showed bilateral pulmonary micronodules with multiple hypodense hepatic nodules involving both lobes. Percutaneous ultrasound-guided biopsy with pathological study and immunohistochemistry staining revealed the diagnosis of hepatic epithelioid hemangioendothelioma.

*Discussion:* HEHE usually involves both liver lobes with three radiological presentations: single nodular, multiple nodular, or diffuse types, the diffuse type reflects an advanced stage. 3/4 of the cases are initially misdiagnosed as liver metastases or primary liver tumors. The pathological study with the immunochemistry stainings confirms the diagnosis. There is no standard treatment for HEHE due to its rarity and lack of prospective randomized studies.

*Conclusion:* HEHE is a rare tumor of vascular origin of unknown etiology with malignant potential and unpredictable course. The therapeutic management of this rare condition is not codified and is discussed on a case-by-case basis. Surgical treatment remains the best option with an excellent outcome.

## 1. Introduction

Epithelioid hemangioendothelioma is a rare tumor of vascular origin of unknown etiology with malignant potential and unpredictable course with a reported incidence of 1–2 of every 1 million people [1,2]. Liver involvement is often multinodular simulating metastases from a primary extrahepatic lesion and may delay diagnosis [3]. The clinical presentation and the radiological finding are heterogeneous and not specific making the pre-operative diagnosis difficult [2,3]. The final diagnosis is made upon pathological study and immunohistochemistry staining [3]. Herein, we report a rare case of hepatic epithelioid hemangioendothelioma (HEHE) mimicking liver metastases in a female patient. This case has been reported following the SCARE criteria [4].

## 2. Case report

A 43-years-old female patient, with a history of appendectomy 30 years ago, presented with complaints of vague, dull pain in the right upper quadrant without loss of weight or appetite. Abdominal examination revealed a slight tenderness in the right hypochondrium. Laboratory tests, including liver biochemical tests, routine blood examination, and serum tumor markers, were all within the normal range. Abdominal ultrasound revealed multiple heterogeneous hypoechoic liver lesions regarding both liver lobes. A thoracic and abdominopelvic computed tomography (CT) showed bilateral pulmonary micronodules with multiple hypodense hepatic nodules involving both lobes with heterogeneous enhancement, the largest measuring 33 ×

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52mm suggesting pulmonary and hepatic metastases of unknown origin (Fig. 1).

In order to obtain a definitive diagnosis, we performed a percutaneous ultrasound-guided biopsy. The pathological study and immunohistochemistry staining (CD31 +, CD34 +) revealed the diagnosis of hepatic epithelioid hemangioendothelioma (Fig. 2).

Following a discussion in a multi-disciplinary team (MDT) meeting, the patient was referred to the oncology department for chemotherapy. At three months follow-up; both liver, and pulmonary lesions remain stable without any regression.

## 3. Discussion

Described for the first time by Ishak et al., in 1984 [1]. HEHE seem to have a female predilection, with a female/male ratio of 3/2 [5]. Makhlouf et al. reported in their large study that HEHE tends to occur more frequently in the fourth and sixth decades with a mean age of 46.8 years [6]. The clinical presentation is heterogeneous and non-specific varied from asymptomatic patients to hepatic failure; according to Mehrabi et al. 25% of the patients were asymptomatic and the most common symptoms were right upper quadrant pain, hepatomegaly, and weight loss [5]. Both liver lobes are involved with a multifocal presentation in most of the reported cases [5]. Merhabi et al. reported that 90 among 246 patients had extrahepatic lesions at the time of the diagnosis and the lungs were the most common extrahepatic location [5]. The radiological findings HEHE finds three presentations: single nodular, multiple nodular, or diffuse types [7], the nodular type is observed in an early stage of the disease; however, the diffuse type reflects an advanced stage. HEHE appears frequently hypoechoic relative to the adjacent liver parenchyma on ultrasonography [8]. Mehrabi reported that 98% of the cases presented hypodense lesions on CT and only 1% presented hyperdense or heterogeneous mixed-density [5]. 96% of HEHE reported by Ganeshan et al. were located in the peripheral and subcapsular regions of the liver; capsular retraction was seen in 54 among 67 patients [9]. After administration of IV contrast, HEHE presents more frequently a peripherical enhancement in the arterial phase and a target appearance with a “halo sign” on the portal venous phase [5,9]. Alomari et al. [10] reported an interesting radiological finding on CT; the “lollipop sign”. This sign is the combination of the hypodense lesion that represents the candy and the occluded vessel that is likened to the stick of the lollipop [10]. This sign can be considered as a more characteristic finding of HEHE as it rarely occurs in most benign and malignant hepatic tumors [11]. On MRI, the most frequent finding is the heterogeneous high-T2-signal intensity [5,9,12]. 97% of the cases in the study of Ganeshan et al. had this radiological finding [9]. HEHE appears usually hypointense in T1-weighted [12]; according to Merhabi et al., 89% of the patients presented a low-T1-signal intensity [5]. In summary, the pre-operative diagnosis is difficult and challenging as the clinical presentation and the radiological finding are heterogeneous and not specific. The final diagnosis is made usually upon pathological and immunohistochemistry staining; HEHE displays an infiltrative growth pattern, with epithelioid, dendritic, and intermediate cells interspersed in a matrix rich in hyaluronic acid [5,13]. Immunohistochemical analysis reveals evidence of endothelial differentiation with the positivity of factor VIII-related antigen, CD34 and CD31 [14]. Nearly all the patients reported in the large study of Makhlouf et al. expressed factor VIII-related antigen; CD34 and CD31 were expressed in 94% and 86% of the cases respectively [6]. 75% of the cases are initially misdiagnosed as liver metastases or primary liver tumors [15]. Differential diagnosis includes hepatic hemangioma, hepatic angiosarcoma, hepatocellular carcinoma, cholangiocarcinoma, and metastatic tumors [5,6,15]. The most challenging differential diagnosis remains the hepatic angiosarcoma [6,15]. Both tumors show positivity for factor VIII-related antigen, CD34, and CD31 [6,15]. Immunohistochemical staining with CAMTA1 is more useful for the diagnosis of HEHE and may distinguish it from angiosarcoma [15]. There is no standard treatment for HEHE due to its rarity and lack of prospective randomized studies [5,16,17]. The options of treatment include liver transplantation, hepatectomy, chemotherapy, radiotherapy, and observation without treatment [5,17]. According to Merhabi et al., liver transplantation was the most common treatment modality (44.8%), followed by observation without treatment (24.8%), chemotherapy with or without radiotherapy (21.0%), and hepatectomy (9.4%) [5]. Liver resection is considered as the treatment of choice of HEHE and indicated mainly for single and resectable lesions, however, for the majority of the cases, the hepatectomy is not feasible due to multicentricity of the lesions or impossibility of R0 resection [16,17]. The 5-year-survival-rate after liver resection reported is 75% [5]. On the other hand liver transplantation is the ultimate treatment with an excellent outcome for non-resectable, multiple lesions, and involving both lobes [16]. Merhabi et al. [5] and Rodriguez et al. [18] reported a 5-year-survival-rate after liver transplantation of 54.5% and 64% respectively. In their large study, Lai et al. reported a disease-free survival rate at 1, 5, and 10 years of 88.7%, 79.4%, and 72.8% respectively [19]. Due to its rarity, there is no standard chemotherapy protocol [14]. Various chemotherapeutic drugs seem to be effective and provide a promising treatment method especially the vascular endothelial growth factor inhibitors, such as sorafinib, pazopanib, and bevacizumab [14].

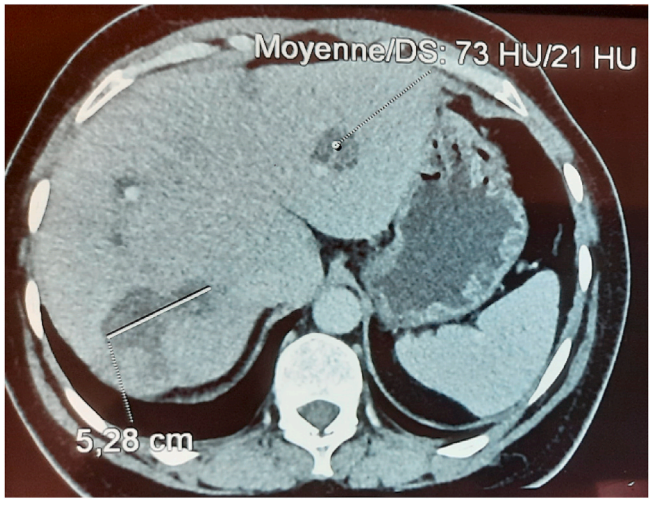


**Fig. 1.** CT scan showing hypodense hepatic nodules involving both lobes with heterogeneous enhancement.

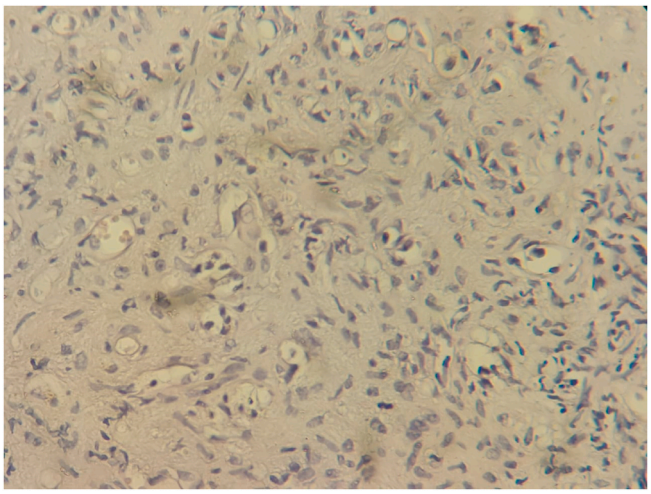

**Fig. 2.** Microphotograph showing hepatic parenchyma with tumor proliferation made up of isolated epithelioid cells with slightly to moderately atypical nuclei (HE X400).

Observation without treatment should not be considered as a standard in the management of HEHE and its indication remains unclear [5,16]; the 5-year-survival rate reported is only 4.5% [5]. Noh et al. reported that patients who underwent surgical treatment had significantly higher survival than those who underwent non-surgical treatment, moreover, the surgical treatment was the only independent prognostic factor for survival [20].

## 4. Conclusion

HEHE is a rare tumor of vascular origin of unknown etiology with malignant potential and unpredictable course. The clinical presentation is nonspecific and the radiological finding is unequivocal, resulting in multinodular involvement that can simulate metastatic lesions. The diagnosis is often established by histological examination with immunohistochemical study. The therapeutic management of this rare condition is not codified and is discussed on a case-by-case basis. Surgical treatment remains the best option with an excellent outcome.

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No ethical approval necessary.

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## Author contribution

Serji Badr, Ramdani Abdelbassir: Writing, review and editing of the manuscript.

Mirali Houda, Bouhout Tariq, Bennani Amal: Contributed for diagnose and treatment of the patient.

El Harroudi Tijani: Supervised the writing of manuscript.

## Consent of the patient

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

## Guarantor

Serji Badr and Ramdani Abdelbassir.

## Registration of research studies

Our paper is a case report; no registration was done for it.

## Provenance and peer review

Not commissioned, externally peer reviewed.

## Declaration of competing interest

The authors declared no potential conflicts of interests with respect to research, authorship and/or publication of the article.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102885.

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