



Case report

Hepatic epithelioid hemangioendothelioma a case report and literature review

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ABSTRACT

Introduction: Hepatic epithelioid hemangioendothelioma (HEHE) is a rare disease with a high probability of being misdiagnosed.

Case presentation: We present a case of a 38-year-old female patient found with HEHE by physical examination. The tumor was removed by surgery successfully, but then had recurrence after the operation.

Clinical discussion: We review the current literature on HEHE; its prevalence, diagnosis and treatment. And our opinion is that using fluorescent laparoscopy for HEHE may have an advantage in visualizing tumors, but there is still high possibility of false positives. It is recommended to use it correctly during operation.

Conclusion: The clinical presentation, laboratory and imaging index for HEHE were lacking in specificity. Therefore, diagnosis still depends mainly on pathology results, in which the most effective treatment is surgery. Besides, the fluorescent nodule which is not shown on images need to be analyzed carefully in order to avoid damage to normal tissue.

1. Introduction

HEHE has a worldwide incidence of <1 % of all liver malignancies, and its global prevalence was under 1 in 10 million [1]. It can occur at any age with an average age of occurrence at 41.7 years old. Females have a higher incidence with the male-to-female ratio being 2:3 [2]. Currently, no etiology of HEHE has been identified yet and it could be associated with oral contraceptives, alcohol exposure, and viral hepatitis [3]. Because the lack of specific imaging and laboratory examination features, HEHE is difficult to be diagnosed preoperatively [4].

A 38-year-old female was found with HEHE by physical examination. The tumor was removed by surgery successfully, but then had recurrence after the operation. The patient subsequently underwent a second surgery during which it was discovered the lesion could be visualized better by fluorescent laparoscopy but did in fact present false positives.

This work was reported to comply with the SCARE criteria [5].

2. Case presentation

A 38-year-old woman who underwent an abdominal computed tomography (CT), revealing a space-occupying lesion on the segment V of the liver. The patient underwent surgery for segment V tumor of liver in another hospital, and the pathological examination confirmed the tumor as a Hepatic Epithelioid Hemangioendothelioma (HEHE). Six months after the surgery, she came into our hospital with pain that appeared to be dull on the right hypochondrium and fatigue for treatment. No alcohol use, no oral contraception, no family history, no hepatitis, no tuberculosis or other infectious diseases were reported. In addition, the physical examination for the heart, lungs, abdomen revealed no abnormalities. All hematological investigations including liver function, α -fetoprotein (AFP), carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9) were within normal limits. Abdominal CT showed a slight low density shadow with patchy and unclear margins of

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about 28 mm × 17 mm in size at segment V of the liver. On the contrast enhanced imaging, the enhancement in the edge and inside of the lesion was shown to be flaky and flocculate (Fig. 1). Meanwhile, the tumor appeared as an abnormal signal shadow on contrast enhanced MR (MR), which is demonstrated with hypointense on T1-weighted images (T1WI), and slight hyperintense on T2-weighted images (T2WI) and fat

saturated T2-weighted images. In addition, The DWI images of the lesion showed a hyperintense at the edge and hypointense in the center, while in ADC images, a slight hypointense was observed at the edge and slight hyperintense in the center of the lesion (Fig. 1). The imaging showed that HEHE recurred in segment V of liver; although CT and MRI were in accord with the features of the disease at present, the findings were not

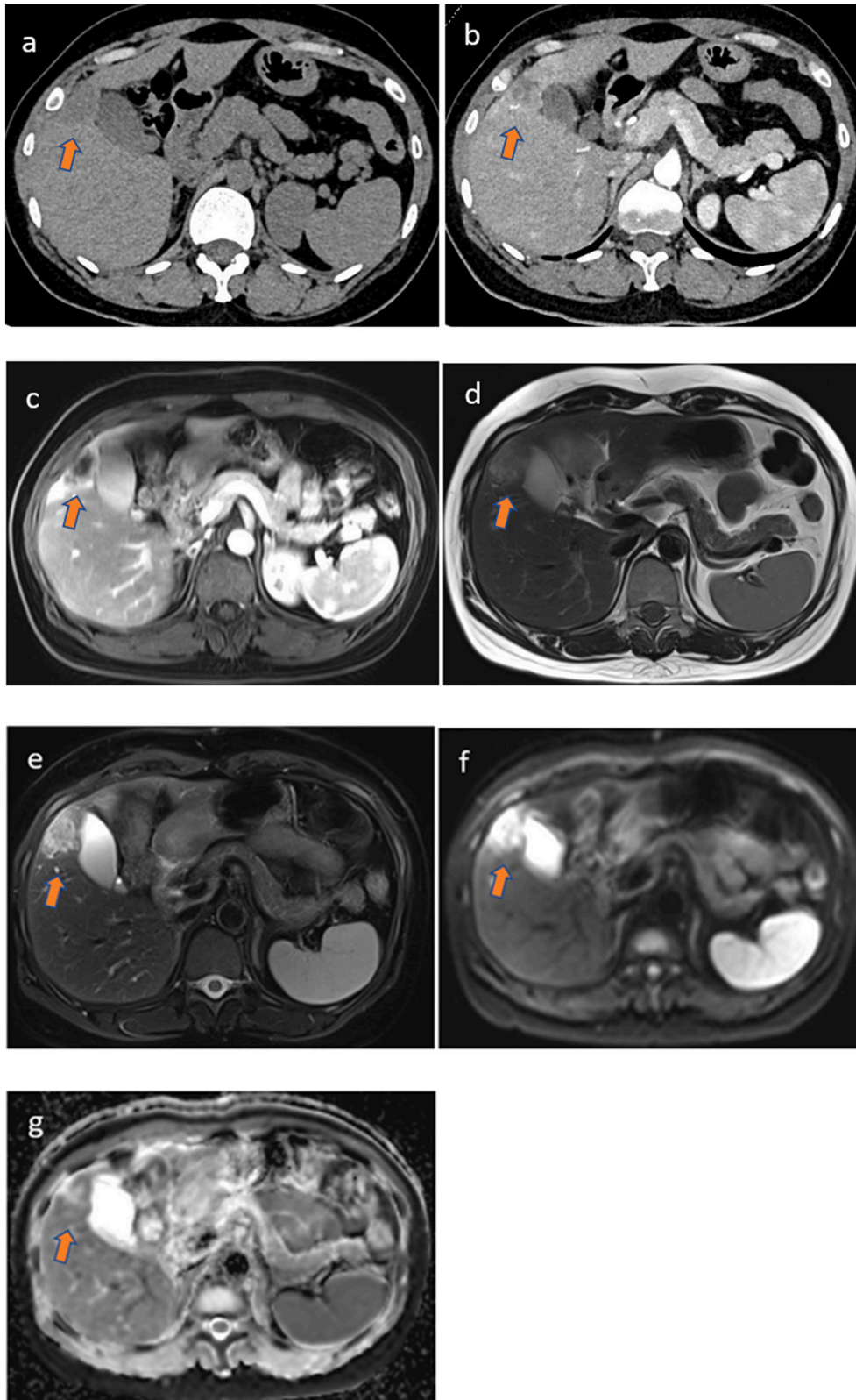


Fig. 1. (a) CT shows slightly low-density shadow about 28 mm × 17 mm in size at segment V with unclear margins. (b) On contrast-enhanced imaging, intense flaking and flocculence were discovered both at the peripheries and inside. The tumor showed hypointense in T1WI imaging (c) and slightly heavily hyperintense in T1WI and T2 lipid pressure (d, e). The signal seen on DWI is stronger on the peripheries compared to the center (f). The signal seen on ADC is stronger on the center compared to the peripheries (g).

typical and it was indicated that the lesion probably related to surgery for HEHE previously. Then, the patients were followed by fluorescence-guided laparoscopic surgery, in which a plurality of fluorescence-stained nodules were observed in the liver beyond the segment V of the liver. To exclude the possibility of intrahepatic metastasis or HEHE multiple lesions, the large nodules of segment III (4 mm diameter) of the liver were removed and frozen section biopsy were performed immediately to identify the lesion. no cancer or HEHE was confirmed. HEHE was confirmed through histologic and immunohistochemical analyses of the hepatic segment V tumor obtained after operation. The reexamination of contrast enhanced MR findings one and a half months later identified the postoperative changes, but no sign of an abnormal hyperintense of the hepatic parenchyma.

3. Discussion

3.1. Laboratory features

Laboratory data on 185 patients were reported in the study [1] on HEHE and 156 patients (84.3%) have abnormal results, with 15.7% having no abnormal results. No abnormalities have been noted with the blood biochemical indexes (blood routine, liver and kidney function, etc.), and tumor markers including AFP, CEA, CA 19-9 and so on of this patient.

3.2. Imaging features

HEHE can be divided into three types of imaging features: solitary lesion, multiple lesion, and diffuse nodular lesion, and multi-lesion type is the most common type of HEHE [6]. On non-contrast CT, the tumor appears as a low density lesion with a clear margin, while in contrast enhanced CT, the tumor appears with minor peripheral enhancement. Whether or not the tumor center can be strengthened depends on the components and degree of fibrosis of the tumor center. It can also show a sign of 'capsular retraction' according to a study [7]. MRI features of HEHE [8] are characterized by hypointense for T1WI, hyperintense for T2WI in the center and slight hyperintense in the periphery. Besides, HEHE show varying enhancement features in Contrast-enhanced MRI that may be enhanced according to blood supply in tumor, including the enhancement at the edge, peripheral enhancement during artery phase and infiltration enhancement at portal vein phase (similar to hemangioma) and may also be manifested as cyst with a dot appearance.

There is no cyst with a dot appearance in this case, and it is likely relate to the surgery of resection of segment V tumor. But CT shows a slight low-density shadow and MR showed hypointense in T1WI and slight hyperintense in T2WI and fat saturated T2-weighted images. These are all in line with the known characteristics of HEHE.

3.3. Histological and immunohistochemical features

HEHE histologically presents as nests and cords of epithelial-like

endothelial cells pervaded in a transparent mucus matrix. Another typical histological feature of HEHE is the presence of intracytoplasmic vacuoles, displaying the state of blister cells [9]. Immunohistochemical examination of HEHE shows positive expressions of tumor cell vascular endothelial cell markers such as CD31, CD34, CD10, D2-40, EGR, etc., or simultaneous expression of epithelial markers CK8/18 and EMA [10]. The tumor excision specimen can then be diagnosed based on the aforementioned characteristics, but genetic testing can be performed for small specimens that are difficult to diagnose should it be deemed necessary.

In this case, histopathological examination (Fig. 2) revealed that the tumor was composed of short strands or solid nests of rounded to slightly spindled endothelial cells. The individual tumor cells had large pleomorphic nuclei, prominent nucleoli and abundant eosinophilic cytoplasm, and the cytoplasm of each cell was light to acidophilic with small vacuoles. Foci of infarct lesion were noticed in certain regions. The boundary of the tumor was unclear and the tumor has infiltrated the liver sinusoids and liver parenchyma. The mature vessel lumen or pseudoalveolar architecture was formed locally. Immunohistochemical staining was positive for CD31, CD34, ERG, TFE3, and FLI-1 and negative for epithelial membrane antigen, cytokeratin, glypican-1, and hepatocyte. Ki67 proliferation index (Ki67 index) was >5%. Typical EHE tumors are not accompanied by mature vessel lumens. Molecular detection shows the fusion gene of WWTR1-CAMTA1 and immunohistochemical express CAMTA1. According to the literature report [11,12], some EHE can be seen clearly with the formation of vessel lumen. Molecular detection has YAP1-TFE3 fusion genes, immunohistochemical do not express CAMTA1, but can express TFE3. Due to the definition of forming vessel lumen and immunolabelling positive for TFE3, the pathological diagnosis is considered as EHE.

3.4. Treatment

Due to the fact that HEHE cases are rare, treatment studies of randomized controlled trials cannot be carried out. Thus, the treatment methods are diverse and difficult to generalize into a single method [13]. Currently, the treatment methods for this disease include liver transplantation, liver lesion resection, chemotherapy, and radiotherapy [14]. Meta-analysis [1] shows that the five-year survival rates of liver transplantation, liver resection, chemotherapy, and radiation therapy are 54.5%, 75%, 30%, and 4.5% respectively. A statistical report using 353 HEHE patient's data in the United States from 2004 to 2016 indicated [15] that the most common surgery performed was liver resection (90.8%). One-year overall survival (OS) from the group that underwent surgery and the group that did not undergo surgery was 86.6% and 61.0% respectively. The five-year OS was 75.2% and 37.4% respectively. The most common surgery performed were wedge resections and segmental resections (n = 86, 47.0%), followed by major liver resection (n = 82, 44.8%) and liver transplant (n = 15, 8.2%). Surgical excision is recognized as the best treatment, especially for small, single HEHE. Liver transplantation is the ultimate treatment for multifocal, diffuse,

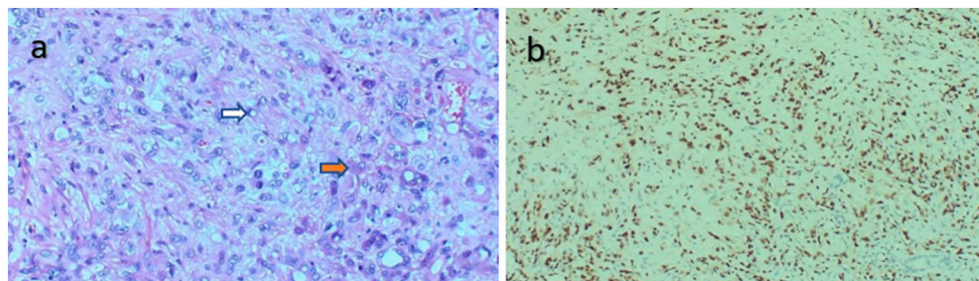


Fig. 2. (a) (200×) The tumor was composed of eosinophilic epithelioid cells (orange arrow) and blister cells (white arrow), and showing immature vessel lumen formation. (b) Immunohistochemistry for ERG shows positive.

unresectable and recurrent tumors [16].

In this case, surgical resection was selected. Multiple lesions were detected by indocyanine green-fluorescence imaging (ICG-FI) and the largest one was located in the liver's segment V (ICG was administered intravenously a day before surgery) (Fig. 3). The large fluorescent staining nodule in segment III (4 mm diameter) was then removed (Fig. 3). Frozen biopsy showed no clear signs of tumors. In the end, only the segment V resection was accomplished. It can be seen that fluorescence laparoscopy would help visualize HEHE lesions, but there are also false-positive (such as segment III fluorescent nodules in this case). Several research on liver tumor fluorescence imaging shows that the potential drawbacks of ICG-fluorescence imaging include a relatively high false-positive rate (approximately 40 %) [17]. The reason for the high false positive rate is due to the slow metabolism of ICG in cirrhotic liver, ICG retention in regenerative nodules, and the low contrast between regenerative nodules and tumor fluorescence signals [18]. Therefore, it is important to combine preoperative imaging with intraoperative fluorescent staining nodule, which will reduce the chance of misdiagnosis and false positive results.

4. Conclusion

As mentioned earlier, fluorescence laparoscopy has a false positive rate of up to 40 % and can only show superficial lesions that are within 8 mm from the surface of the liver. Therefore, patients should complete examinations such as ultrasound, CT, MRI and other related examinations pre-surgery to comprehensively evaluate their tumor distribution. Intraoperative ultrasonography (IOUS) has a good localized diagnosis for small, deep liver tumor lesions. For this reason, IOUS should be routinely used during surgery. Use radiofrequency ablation if IOUS results suggest radiofrequency ablation is appropriate (if the tumor is single, smaller than 2 cm in diameter [19]).

For the superficial lesions that can be visualized by fluorescent staining, the staining results alone are not a reliable reference standard for liver transplantation or liver resection. Therefore, frozen section biopsy should be combined with preoperative examinations to decide the operation mode. Liver transplantation may be considered when the results meet the Milan criteria (single hepatocellular carcinoma (HCC)

> 5 cm in diameter or up to 3 HCCs > 3 cm, together with vascular invasion [20]). At the same time, if new stained areas were found in fluorescent laparoscopy which were not found in the preoperative examination, it is necessary to be alert to the possibility that it is not a tumor. To prevent erroneous removals, biopsy results for the frozen section are needed to confirm the diagnosis. Should the result confirm that it is a tumor, surgical resection can then be performed.

Consent

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.

Ethical approval

The ethical committee approval was not required given the article type (case report).

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Guarantor

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CRediT authorship contribution statement

HL, JL and RZ assembled, analyzed, and interpreted the patient's data and case presentation. YL, QM, and QZ reviewed the literature. JL,

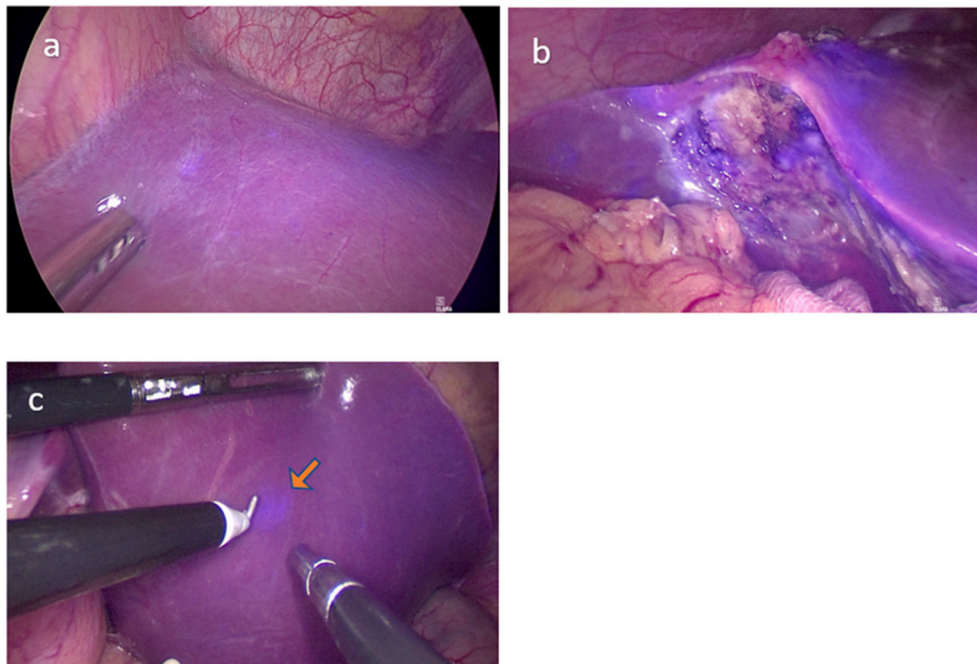


Fig. 3. During the surgery, multiple lesions were detected by ICG-FI (a) and the largest one was located on segment V (b). The fluorescent staining nodule in segment III is removed for diagnosis.

RZ, YL, QM, and QZ edited and critically revised the manuscript for intellectual content. All authors contributed to the writing of the manuscript. All the authors approved the manuscript for submission.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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