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Case Report

Primary hepatic epithelioid hemangioendothelioma masquerading as metastases: A rare case report ☆

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ABSTRACT

Epithelioid hemangioendothelioma (EHE) of the liver is an extremely rare malignant tumor of vascular origin, representing less than 1 % of all vascular tumors. Nearly 260 cases have been reported in English literature. Radiologically it is seen as multifocal lesions. It can be seen at different sites like lungs, bones, lymph nodes, breasts, and soft tissue. Often it is misdiagnosed with metastases, cholangiocarcinoma, or angiosarcoma. No definite treatment protocol is available due to its rarity, however, these malignancies are treated by radical resection of the tumor or liver transplant and/or chemotherapy. Here we present a primary hepatic epithelioid hemangioendothelioma (HEHE) which was mimicking metastases in a 42-year-old male who was treated with chemotherapy and radiotherapy. Sadly the patient expired after 1 year of complete course of treatment. Imaging features can help to improve the diagnostic accuracy of this tumor.

Introduction

It is a very rare malignant tumor with only 1 in 10 million people diagnosed with this rare cancer worldwide. It was first described by Ishak et al. [1] in the year 1984 as multiple nodular lesions in the liver. In the literature, nearly 260 cases have been described between the years 1996 and 2021 [2]. It is a tumor of vascular origin with low to intermediate malignancy [3]. It is detected between 30 and 50 years of age but can be seen in children and older people with sight predilection for females [4]. Patients present with non-specific clinical manifestations ranging from asymptomatic to hepatic failure. The etiology is unknown and can be associated with the use of oral contraceptives, alcohol intake, or viral hepatitis [5]. Radiological features can be mistaken for metastases, cholangiocarcinoma, hepatocellular carcinoma, and angiosarcoma. Thus the preoperative diagnosis of

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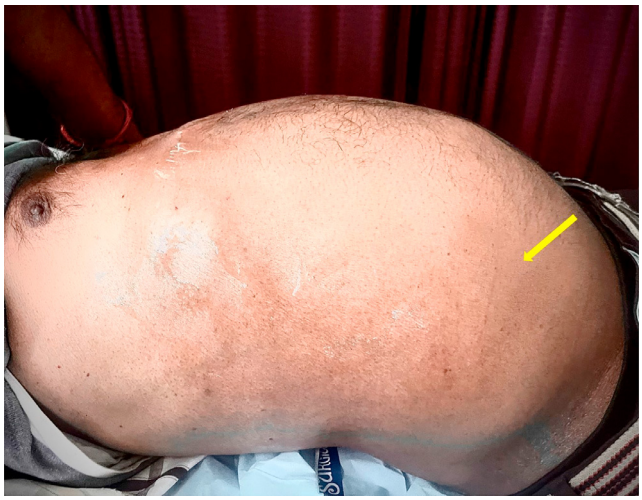

Fig. 1 – Clinical photograph depicting swelling of abdomen with palpable abdominal mass (yellow arrow).

this rare entity is difficult and many published cases were misdiagnosed [6,7].

Case report

A 42-year-old male, nonalcoholic, presented to our institute with a complaint of dull abdominal pain for 2 months. It was not associated with fever, yellowish discoloration of skin, or vomiting. Clinical examination revealed a palpable mass with tenderness in the epigastric region (Fig. 1). Hematological investigations showed elevated alkaline phosphatase, (serum glutamic pyruvic transaminase) SGPT and (serum glutamic oxaloacetic transaminase) SGOT with normal alpha fetoprotein, carcinoembryonic antigen (CEA) and Cancer Antigen 19.9. HBsAg and HCV Ag were negative. Other blood parameters were within normal limits. Abdominal ultrasound revealed hepatomegaly with multiple heterogeneously hypoechoic and mildly hyperechoic lesions of varying sizes in both lobes of the liver. On color Doppler, the lesions showed flow signals predominantly at the periphery (Fig. 2). On Shear wave elastography (SWE) the lesions showed stiffness with a minimum value of 140.8KPa and a maximum value of 159.0KPa (Fig. 3). Patient was further advised contrast-enhanced CT for further evaluation. It was performed with a 64-slice Philips Brilliance scanner, and 80 mL nonionic contrast (ultravist, 370 mg I/Ml) was injected with a rate of 4 mL per second through an 18G intravenous cannula. It demonstrated multiple well-defined heterogeneously hypodense lesions of varying sizes scattered diffusely in the liver, few of them coalescing to form a mass, largest exophytic mass measured ~ 15 × 19 × 13 cm involving the left lobe of the liver. These larger lesions showed central areas of hypodensity within. The largest lesion in the left lobe was compressing the pancreas and displacing it posteriorly, however, the fat plane was maintained. The right kidney was displaced inferiorly by the lesion in the right lobe of the liver with no evidence of infiltration. Major vessels showed no tumor thrombus (Figs. 4–6). Abdominal lymphadenopathy was not evident. Clinical suspicion of metastatic tumor or multifocal hepatocellular carcinoma was raised in this case. Patient was further evaluated with PET-CT to rule out any primary lesions elsewhere in the body. It showed heterogeneously increased pathologic FDG uptake [Standard Uptake Value max 10.9] in the hepatic lesions. No evidence of pathologic uptake was seen in the rest of the body suggestive of primary hepatic lesions (Figs. 7–9). Multiple hepatic lesions demonstrated characteristic peripheral uptake in the larger lesions, giving a ring of fire appearance (Fig. 10). He was advised image-guided biopsy for definitive diagnosis.

Microscopically, it demonstrated nests and cords of epithelial-like endothelial cells pervaded in a transparent mucus matrix with the presence of intracytoplasmic vacuoles, displaying the state of blister cells. On immunohistochemical examination positive expressions of tumor cell vascular

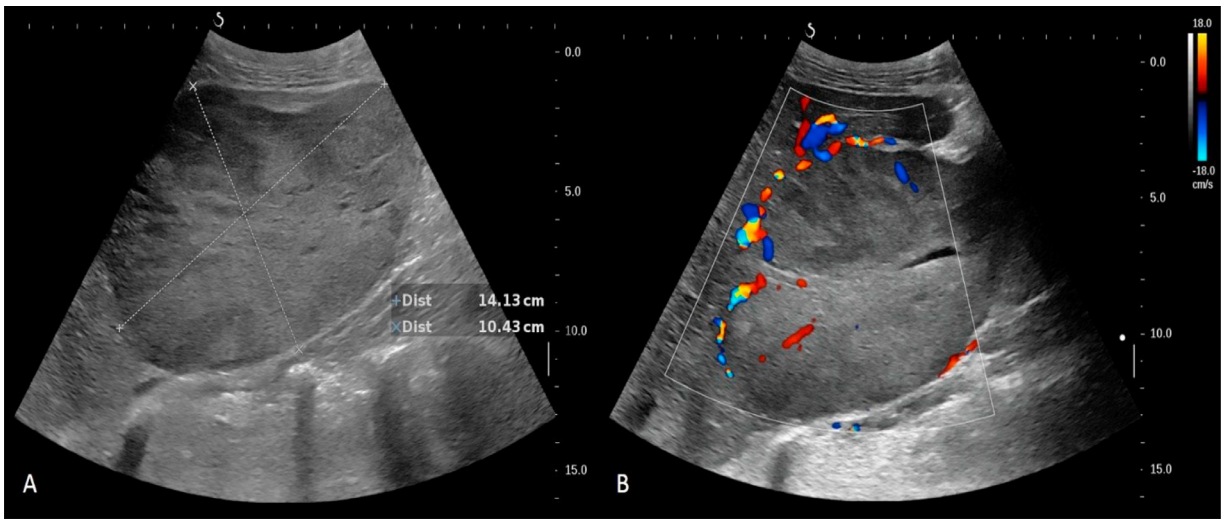

Fig. 2 – Hepatic Epithelioid Hemangioendothelioma: ultrasound showing (A) large heterogeneously hypoechoic space occupying lesion in the liver, (B) on color Doppler, flow signals are seen predominantly at the periphery of the lesion.

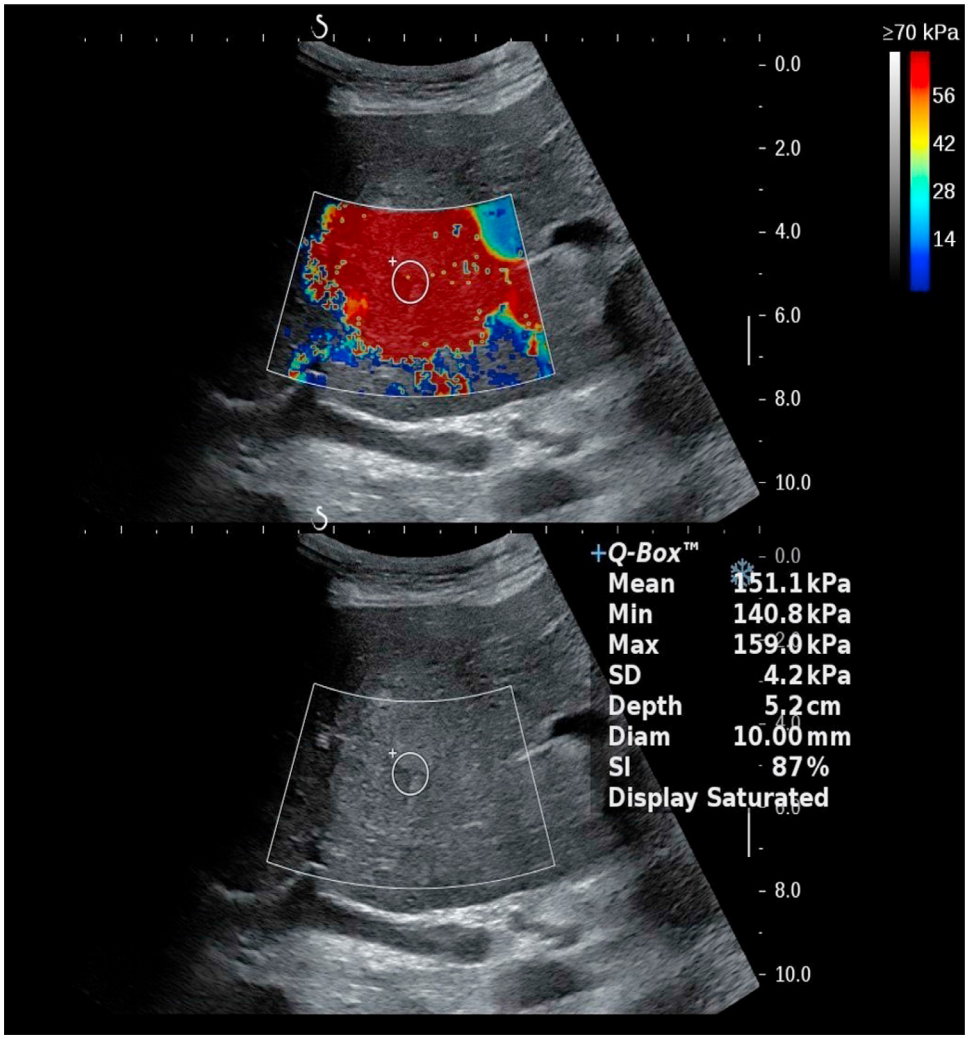

Fig. 3 – Hepatic epithelioid hemangioendothelioma: on color coded shear wave elastrography, the focused lesion is showing red color highly suspicious for malignancy, while the liver parenchyma is showing dark blue with SWE value in kilopascals.

endothelial cell markers such as CD31, CD34, EGR, and EMA were positive (Fig. 11).

The patient was treated with vincristine and bevacizumab. Unfortunately, the patient deteriorated even after the designed treatment and expired after 1 year.

Discussion

Clinical, radiological and pathologic diagnosis of this rare entity is demanding. Diagnosing on time is very important because long-term survival (5-10 years) is possible [8]. Clinical manifestation is variable. Some patient present with Budd-Chiari syndrome due to the involvement of the hepatic veins [9]. HBsAg positivity has been reported in few published cases [8,10], our patient was HBsAg negative. However, more cases are required to establish the relationship between HBV infection and HEHE occurrence. It is essential to know that this tumor may coexist with other liver tumors thus complicating the management of the patient. A case report of synchronous HEHE and HCC has been reported [11]. An aggressive case of multifocal HEHE in the background of Budd-Chiari syndrome with secondary cirrhosis and distant metastases was also reported [12]. The first known case of primary HEHE in cirrhotic liver was described by Shah et al. [13] in 2018.

Lesions on computed tomography can appear as single or multiple large masses or multifocal nodular lesions [2,14–17]. The lesions can vary in size from small nodules less than 10 mm to large masses measuring more than 10 cm in diameter, which was also evident in our case. Miller et al. found tumor nodules in peripheral distribution which coalesced as single masses exceeding 4 cm in size. These tumors were solid, predominantly hypoechoic on ultrasound [18]. Furui et al. [14] described nodular lesions as an earlier form of hepatic EHE which later slowly develop into the diffuse type. We have tried to use shear wave elastography to determine the stiffness of the lesion. The tumor demonstrated higher tissue stiffness which was suggesting malignancy. It is exhibited that malignant focal lesions were

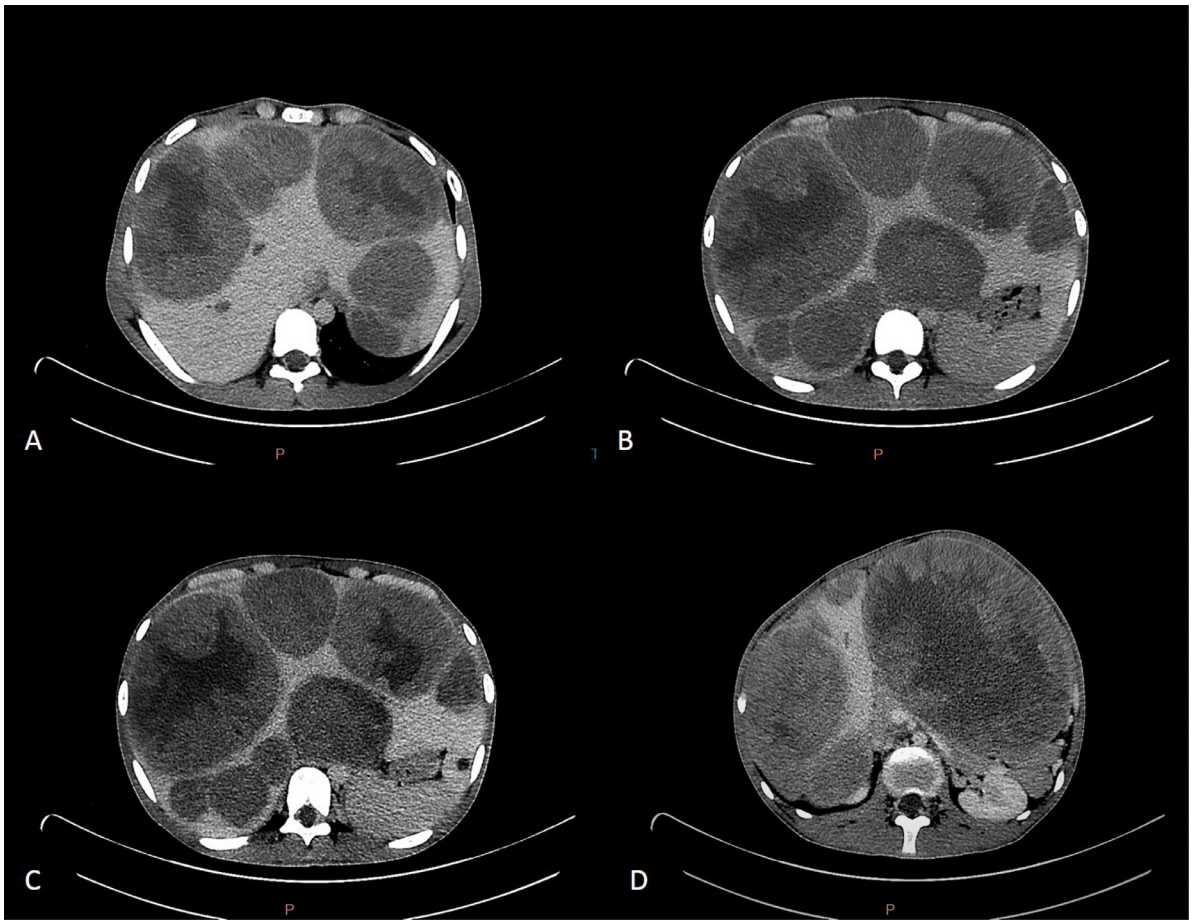

Fig. 4 – Hepatic epithelioid hemangioendothelioma: CT axial showing multiple heterogeneously hypodense lesions of varying sizes in the liver with areas of hypodensity within.

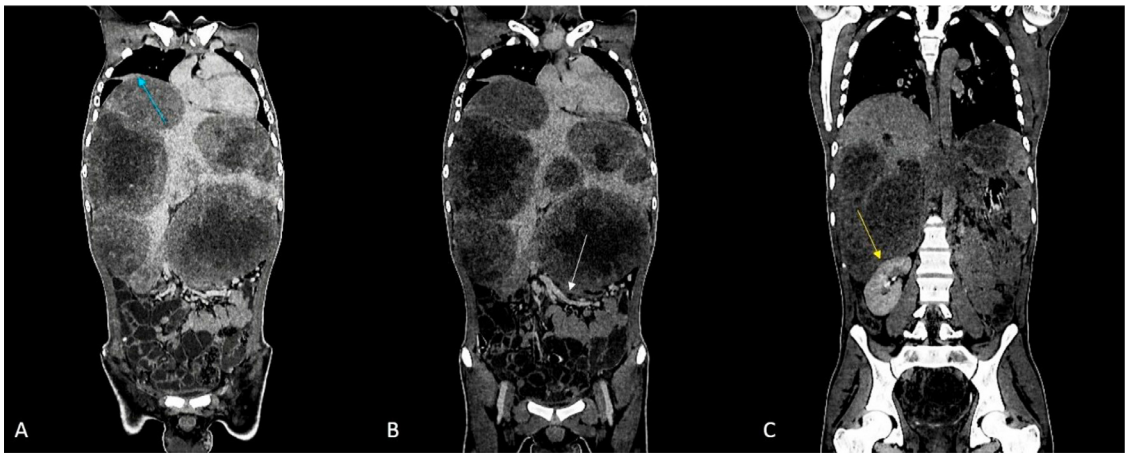

Fig. 5 – Hepatic epithelioid hemangioendothelioma: contrast enhanced CT coronal showing multiple heterogeneously hypodense lesions in the liver, (A) right hemi diaphragm is elevated (blue arrow), (B) the lesion displacing the portal vein inferiorly (white arrow), (C) right kidney is displaced inferiorly by the lesion (yellow arrow).

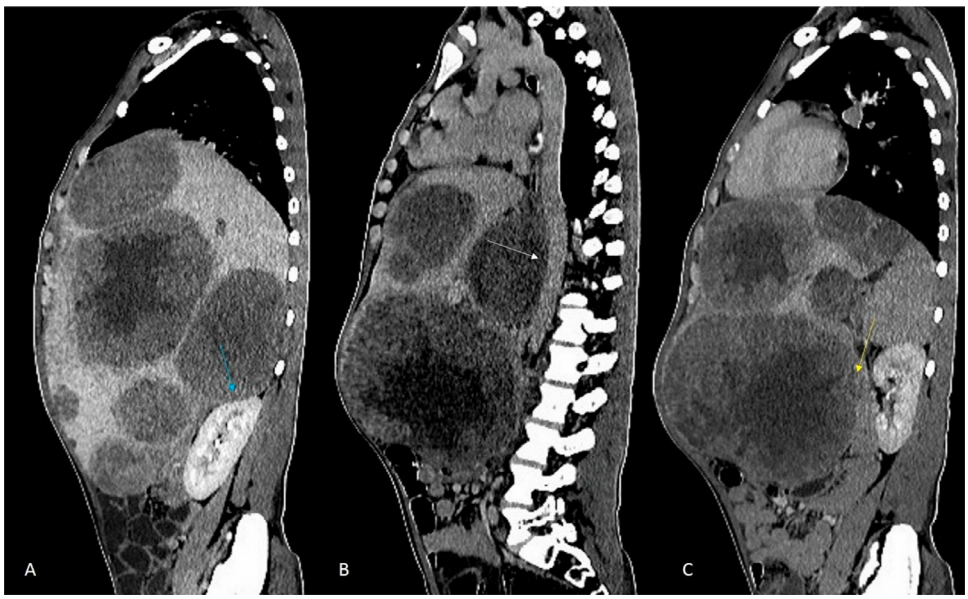

Fig. 6 – Hepatic epithelioid hemangioendothelioma: contrast enhanced CT sagittal showing multiple heterogeneously hypodense lesions with areas of hypodensity within (A) abutting the right kidney with maintained fat plane (blue arrow), (B) the lesion is in contact with the descending abdominal aorta (white arrow), (C) the left kidney is away from the lesion (yellow arrow).

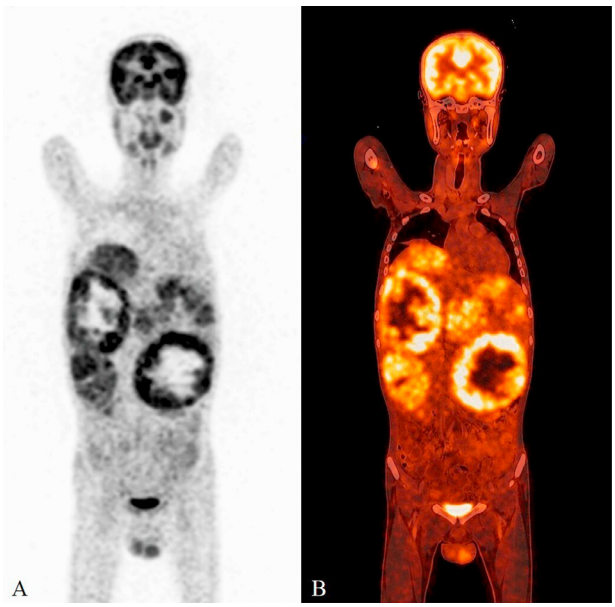

Fig. 7 – Hepatic epithelioid hemangioendothelioma: PET-CT coronal showing pathologic 18F-FDG uptake in the multiple hepatic lesions with characteristic peripheral uptake in the larger lesions giving a ring of fire appearance in fused image (B).

significantly stiff as compared to benign focal lesions. SWE has a high accuracy rate in distinguishing benign lesions from malignant ones with individual characterization of some malignant lesions like HCC, cholangiocarcinoma, and focal nodular hyperplasia [19–21]. A combination of conventional ultrasound and SWE using parallel testing improved the sensitivity to 100% with a specificity of 75% [22,21]. On the arterial phase, these lesions show marginal enhancement and become isodense to liver parenchyma [18]. Larger lesions demonstrated a halo or target pattern of enhancement [14,17]. Lin et al. [10] reported "halo" sign on contrast–enhanced CT in 38 (48%) of 79 lesions which were more evident in the portal-venous phase. Chen et al. [8] reported 24.3% of the lesions showed the target sign on plain CT, 37.8% lesions demonstrated the target sign with progressive enhancement rim on contrast study. The lesions adjacent to the capsule caused capsular retraction in few cases [10,16]. This radiological feature was absent in our case. Intratumoral calcification has also been reported [10,14]. On Magnetic resonance imaging, the lesions appear hypointense to normal liver parenchyma on T1 weighted images, heterogeneously hyperintense on T2 weighted images and hyperintensity with peripheral hypointensity on DWI [22,23]. Few lesions showed a peripheral halo or a target pattern of enhancement on contrast enhanced MRI and occasionally thin peripheral hypointense rim was seen [8,16,22,23]. Splenomegaly, ascites and pleural effusion were also reported in few cases [8] which was absent in our case. Mehrabi et al. [24] also reported extrahepatic spread to lung, peritoneum, lymph nodes and bone at the time of diagnosis. The radiological appearance of the tumor could be correlated with the pathologic characteristics in many ways. Histologically, the tumors comprise of substantial amounts of mucinous and dense stroma in the core with peripheral cellular zones. These findings might validate the low density in the center of the lesion and peripheral isodensity on plain CT, hypointense on T1WI, and hyperintense with peripheral hy-

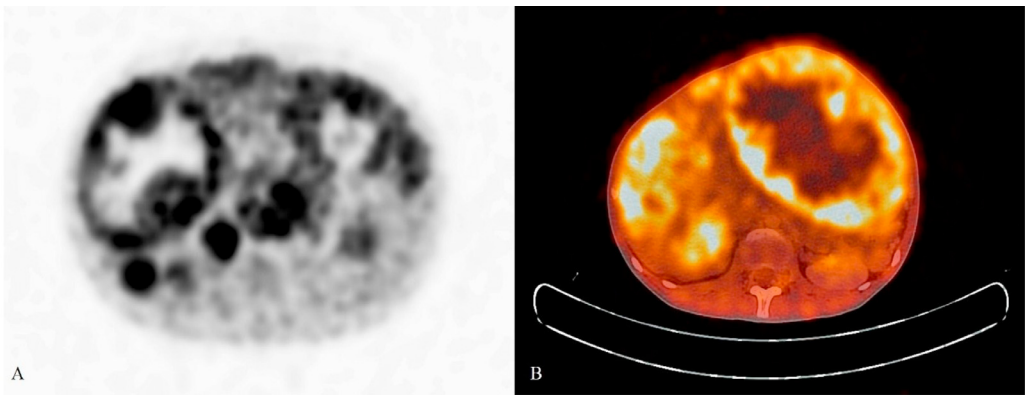

Fig. 8 – Hepatic epithelioid hemangioendothelioma: PET-CT axial showing pathologic 18F-FDG uptake in the hepatic lesions with characteristic peripheral uptake in the larger lesions in fused image (B).

pointensity on T2WI and DWI. Increased cellularity in the periphery of the tumor may explain the peripheral progressive–enhancement target sign on CECT. Halo appearance on CT or MRI could be due to infiltration of tumor and occlusion of hepatic sinusoids and small vessels which causes a limited avascular zone between the tumor and hepatic parenchyma [8]. These findings may represent an important diagnostic feature which could differentiate HEHE from intrahepatic multiple metastases, HCC, angiosarcoma, and cavernous hemangioma.

PET-CT may impart more information to help with the preoperative diagnosis. In the literature, not many reports have described the feature on PET-CT, however in our case, FDG PET scan 3D tracer uptake was noted in the multiple lesions with uptake in fused image. Larger lesions showed characteristic peripheral pathologic 18F-FDG uptake, giving ring of fire appearance in the fused image. In a case report by Hu et al. [25] described low glycometabolism in the hepatic lesions.

Histologically the tumor demonstrates epithelial like endothelial cells in the presence of intracytoplasmic vacuoles, exhibiting the blister cells [26]. On immunohistochemical, CD31, CD34, CD10, EGR, EMA and CK8/18 positivity is seen [27]. Molecular testing display the fusion gene of WWTR1- CAMTA1 which results from a t(1;3) (p36;q25) translocation and demonstrate CAMTA1 on immunohistochemical. Recently detected YAP1-TFE3 fusion is a distinctive variant of EHE [28]. The histological appearance can be flawed for primary or secondary carcinomas, angiosarcoma, schirrhous variant of HCC and other undifferentiated sarcomas [1,24,29]. These tumors are differentiated by a combination of histologic, immunohistochemical, and molecular attributes [30,31]. Epithelial markers like CK8 and CK18 may be expressed leading to misdiagnoses. Tumor shows invasion of the hepatic sinusoids which may be associated with necrosis [30,32].

At present the management of this rare disease includes liver transplantation or lesion resection, chemotherapy and/or radiotherapy [31]. In a study by Grotz et al. [33], liver resection was related to 86% of a 5-year overall survival while liver transplant was 73%. Liver transplantation was the commonest treatment option in 44.8% of patients in a study by Mehrabi et al. [24]. Liver transplantation is considered

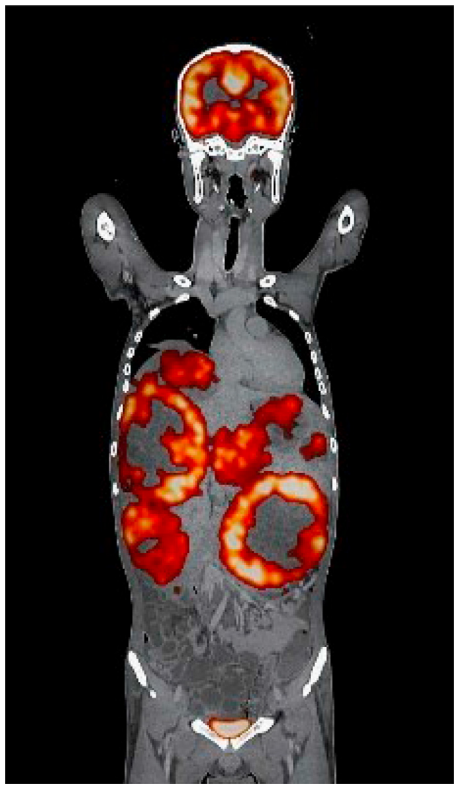

Fig. 9 – Hepatic epithelioid hemangioendothelioma: PET-CT coronal showing pathologic 18F-FDG uptake in the multiple hepatic lesions with characteristic peripheral uptake in the larger lesions, giving a ring of fire appearance.

when partial hepatectomy is not achievable. Lerut [34] found that 23.7% patients had recurrence following liver transplantation within a mean period of 49 months. Transhepatic arterial chemotherapy and embolization (TACE) and antiangiogenic therapy have been used in a few studies [2,24,35,36]. Vincristine, thalidomide, 5-flurouracil, interferon–alpha, doxorubicin, bevacizumab, sorafenib, and other monoclonal antibodies have been used as chemotherapeutic agents [30].

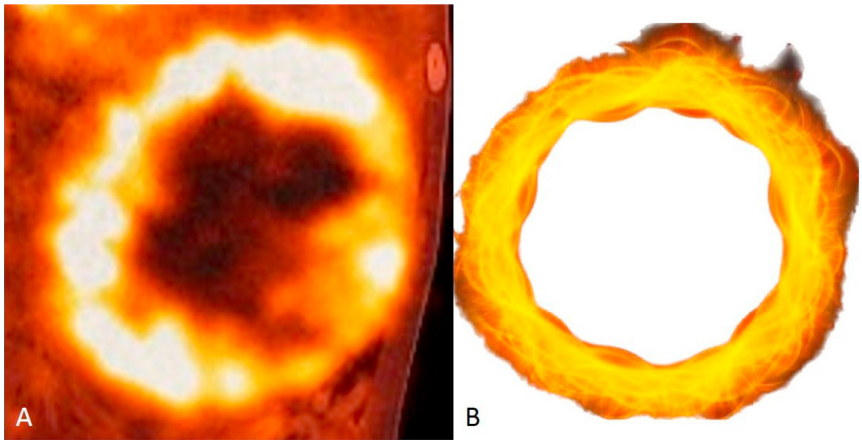

Fig. 10 – Diagrammatic depiction of characteristic peripheral uptake of 18F-FDG in the larger lesions (A), giving a ring of fire appearance (B).

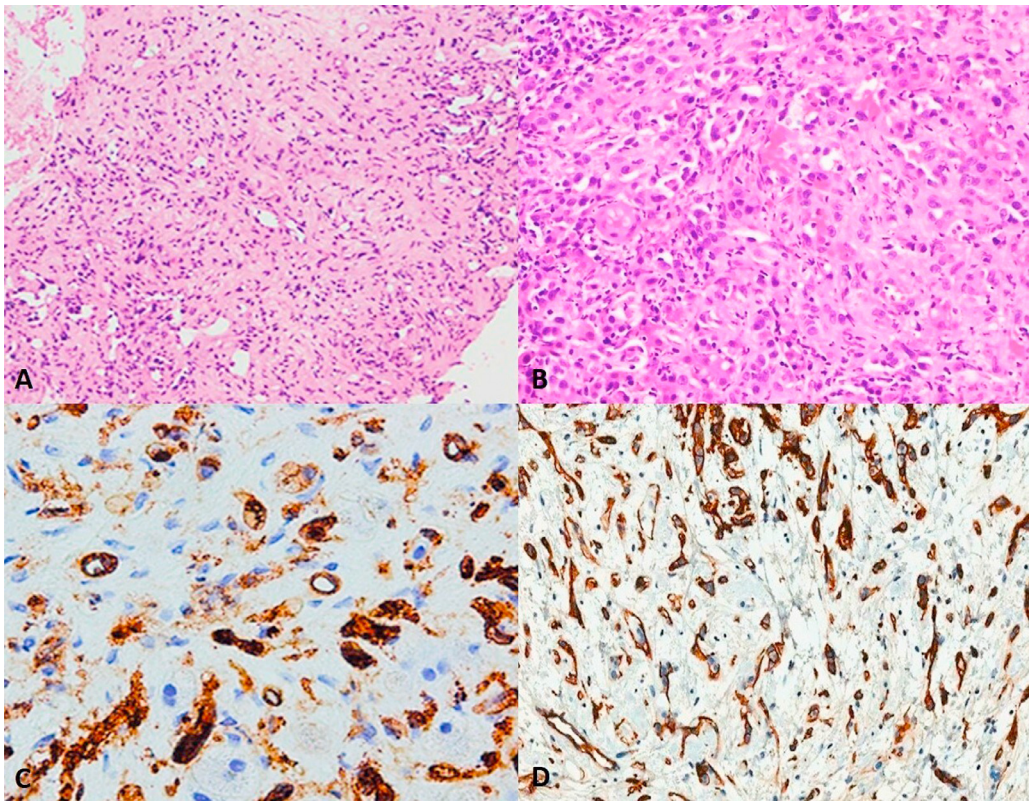

Fig. 11 – Hepatic epithelioid hemangioendothelioma: H&E (A-10x, B- 20x) reveals cords of epithelioid cells having cytoplasmic vacuoles and hyperchromatic nuclei, (C) CD 31positivity (D) CD34 positivity.

Rapid progression of the lesions are documented especially when the lesions are multifocal [37].

Conclusion

Hepatic Epithelioid hemangioendothelioma is an extremely rare tumor. Imaging features can help to improve the diagnostic accuracy of this tumor. It can only be confirmed by histopathological examination. However it should be considered in the differential diagnosis list of intrahepatic lesions which manifest as solitary or diffuse nodular lesions with a propensity for peripheral subcapsular nodular coalescence, together with the halo, target, ring of fire and capsular signs. Present management of this rare entity includes liver transplantation or lesion resection, chemotherapy and/or radiotherapy.

Patient consent

Written informed consent for the publication of this case report was obtained from the patient.

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