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CLINICAL CASE REPORT

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Synchronous Hepatic Epithelioid Hemangioendothelioma and Hepatocellular Carcinoma

First Case Report in the Literature and Challenges

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Abstract: We would like to report the first case in English literature, to the best of our knowledge, of a synchronous hepatic epithelioid hemangioendothelioma (HEHE) and hepatocellular carcinoma (HCC), as well as to address the current trends and challenges in the management of HEHE.

An otherwise well 58-year-old man was referred to his local hepatology service with elevated serum γ-GT levels. Imaging revealed bilobar liver lesions consistent with HEHE, a discrete left lobe lesion suspected as HCC, and multiple pulmonary nodules. Biopsies confirmed HEHE with pulmonary metastases. After multidisciplinary team discussions, the patient was admitted under our team and underwent an uneventful laparoscopic left lateral hepatectomy for suspected HCC, which was confirmed histologically.

As part of a watch-and-wait approach to metastatic HEHE, in the first follow-up (3 months postoperatively) the patient was clinically fine and the surveillance CT scan did not show recurrent disease.

By presenting this case, we aim to raise awareness that this rare entity can coexist with others, potentially complicating their management.

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Abbreviations: BCLC = Barcelona Clinic Liver Cancer, CT = computed tomography, EUS = endoscopic ultrasonography, GI = gastrointestinal, HCC = hepatocellular carcinoma, HEHE = hepatic epithelioid hemangioendothelioma, LR = liver resection, MRI = magnetic resonance imaging, OLT = orthotopic liver transplantation, US = ultrasonography.

INTRODUCTION

Hepatic epithelioid hemangioendothelioma (HEHE) is a rare malignancy of unpredictable clinical course without clear consensus management guidelines.[1] This report presents the first case of HEHE in synchrony with another primary liver malignancy and discusses its presentation and management in light of relatively limited evidence.

MATERIALS AND METHODS

A generally well, independent and asymptomatic 58-year-old man was referred to his local hepatology service for further investigation of elevated serum γ-GT levels. His history was notable for asthma and systemic hypertension, which were treated with tiotropium, seretide, amlodipine, and indapamide. In addition to excessive long-term alcohol consumption of 2 pints of beer daily, he had stopped smoking tobacco 25 years previously and had a biparental history of diabetes mellitus.

Clinical examination was remarkable for ascites, hepatosplenomegaly, and a small umbilical hernia in the absence of any stigmata of chronic liver disease, peripheral edema, or encephalopathy.

Investigations

Subsequent blood tests including full blood count, urea, electrolytes, liver biochemistry, α-fetoprotein, CA19-9, hepatitis viral serology, iron studies, ceruloplasmin, immunoglobulin, and autoantibody levels were unremarkable. Computed tomography (CT) and magnetic resonance imaging (MRI) at his local hospital revealed bilobar liver lesions consistent with HEHE, as well as a discrete 5 cm left lobe lesion suspected as hepatocellular carcinoma (HCC) on the basis of arterial hypervascularity and portal venous washout, in the context of a noncirrhotic liver (Figures 1–4). Subsequent endoscopic ultrasonography (EUS)-guided fine needle aspiration cytology of the suspected HCC lesion revealed features of a neoplastic process which was, however, not confirmatory of HCC. Additional biopsy samples of the right hepatic lobe yielded 3 cores of tissue with intact lobular architecture, mild steatosis, and a fibrous lesion confirmed as HEHE.

At this point, the patient was referred for further investigation and management to the regional tertiary hepatology center, where the MDT review suggested that one of the left lobe lesions was likely HCC based on imaging characteristics. This finding was in synchrony with bilobar HEHE associated with multiple pulmonary nodules.

The above investigations were supplemented with liver ultrasonography (US), as well as ultrasonographic elastography (FibroScan®), upper gastrointestinal (GI) endoscopy, and surgical open lung biopsy. US demonstrated moderate hepatic steatosis with multiple bilobar calcified focal lesions measuring 2.0–2.5 cm in diameter, as well as a 5 cm left lobe lesion with atherogenic echostructure surrounded by satellite lesions.

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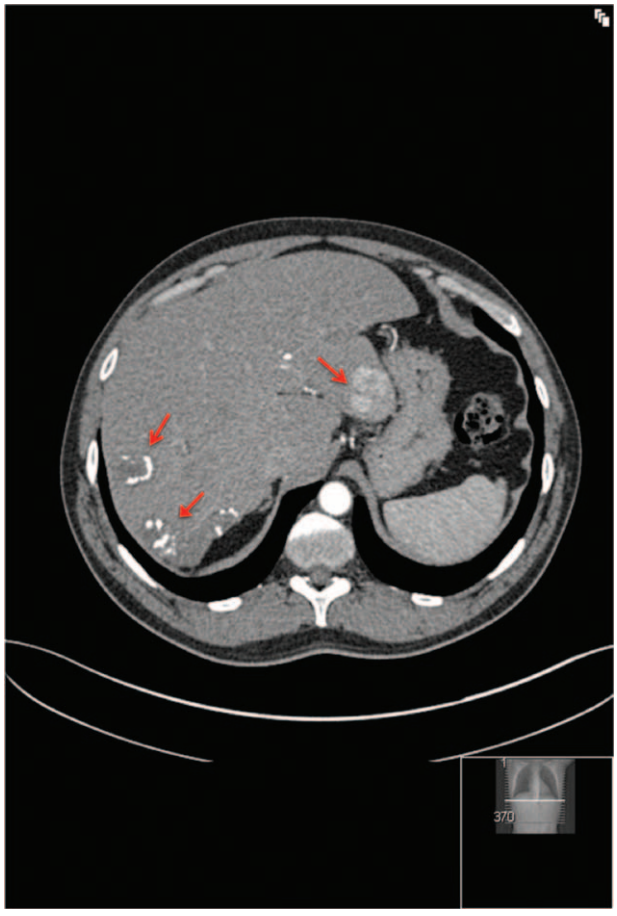

FIGURE 1. HEHE lesions (red arrows).

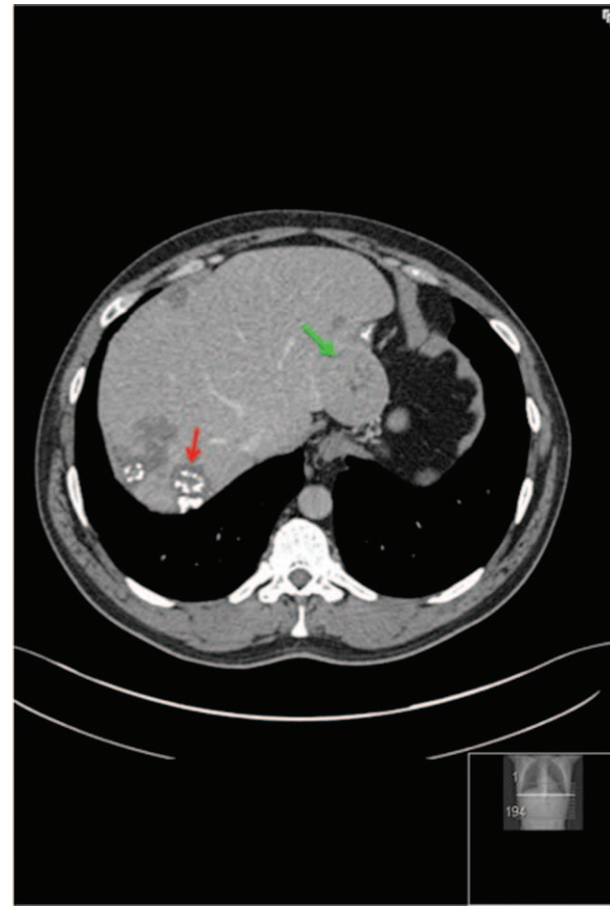

FIGURE 2. HEHE lesion (red arrow) and HCC (green arrow).

FibroScan® yielded a liver stiffness value of 5.0 kPa, which was compatible with the absence of fibrosis and cirrhosis. Upper GI endoscopy revealed mild portal hypertensive gastropathy and indentation of the gastric body by an external mass in the absence of varices. Finally, open surgical biopsy of the right upper and lower lung lobes produced tissue sections of nodular lung with a fibrous stroma, containing pleomorphic epithelioid cells. Some of the tumor cells had intracytoplasmic vacuoles. Immunohistochemistry revealed positive tumor cell staining for CD31, CD34, and factor VIII, whereas the MNF cytokeratin stain was negative. These findings led to the conclusion of HEHE with pulmonary metastases (Figure 5).

Treatment

After multidisciplinary team discussions around this unique case, the decision was made to proceed with resection of the possible HCC lesion alongside a watch-and-wait approach for the metastatic HEHE. Since the liver was not cirrhotic, we decided to treat the potential HCC on its own merit, which of course does not preclude transplantation as a future option. Furthermore, liver transplantation as a surgical alternative was considered but not favored, given the paucity of evidence on outcomes in patients with pulmonary HEHE metastases, as well as concerns that the coexistence of HCC might unacceptably reduce posttransplantation survival. An

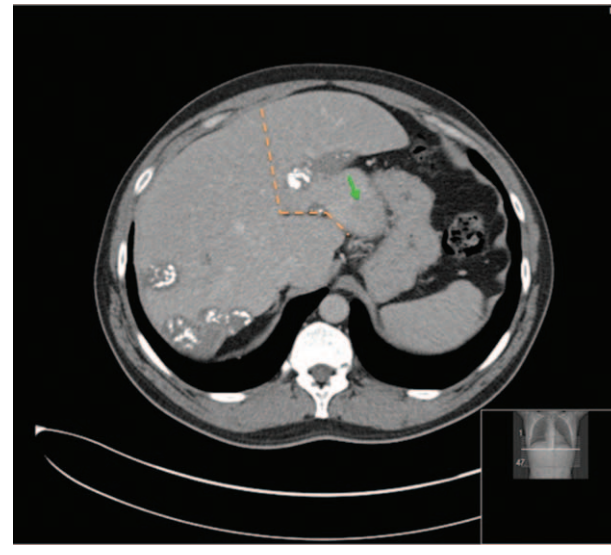

FIGURE 3. HCC (green arrow) and projected line of resection (dotted orange line). The caudate lobe was preserved.

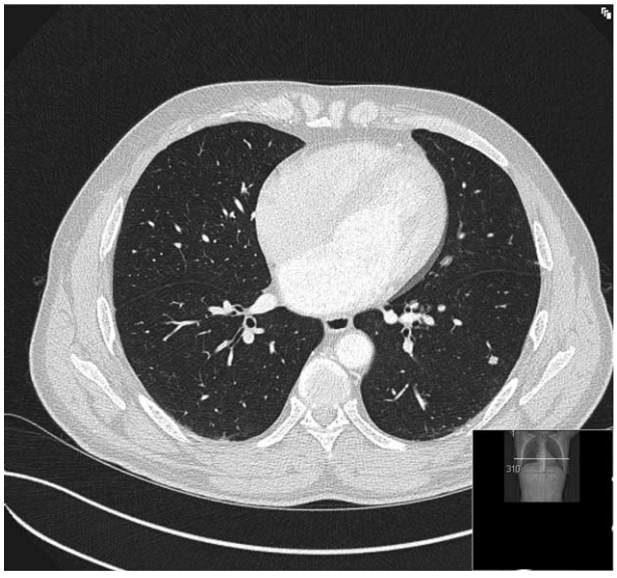

FIGURE 4. Multiple HEHE lung metastases.

additional consideration was the fact that the patient was asymptomatic from a HEHE standpoint and he was not willing to undergo a liver transplantation unless he would absolutely need it in the future. As such, the patient underwent an uneventful (duration 167 minutes and negligible blood loss) laparoscopic left lateral hepatectomy with primary umbilical hernia repair. The specimen (178 mm × 88 mm × 66 mm) was extracted through a 5 cm extension of the camera port incision.

RESULTS

Following surgery, the patient made an excellent recovery and was discharged on the 4th postoperative day. At 2 weeks he was asymptomatic and appeared well, with normal oral intake, stable weight, healthy healing incisions, and no evidence of a recurrent hernia.

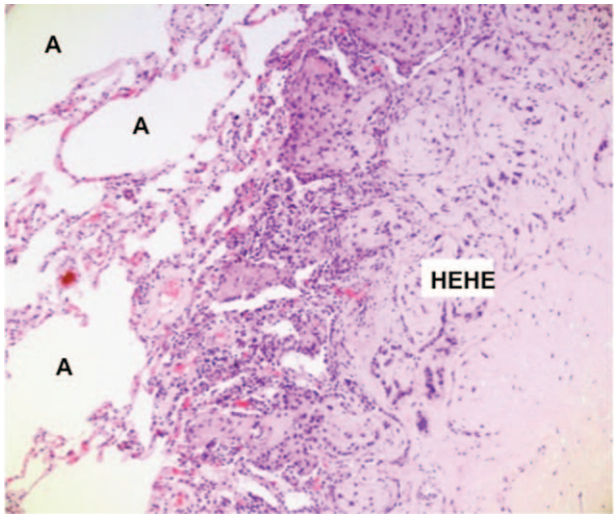

FIGURE 5. H&E-stained section showing alveolar parenchyma (A) replaced by the metastatic HEHE.

Pathological analysis of the resected specimen demonstrated 9 main tumors with 4 mm resection margins. The first tumor was confirmed as a moderately differentiated HCC surrounded by multiple satellite lesions without tumor bile necrosis or microvascular invasion (Figure 6). It stained positively for Hep Par 1 as well as polyclonal CEA (Figure 7). The remaining 8 tumors in the specimen had appearances ranging from predominantly fibrous to cellular and were arranged in cords or as small blood vessels with scanty mitoses but without microvascular invasion. These tumors stained positively for CD31 and CD34 in agreement with previous lung biopsy results and were therefore diagnosed as multiple HEHE deposits.

In the first follow-up (3 months postoperatively), the patient was clinically fine and the surveillance CT scan did not show evidence of recurrent disease. At that point, the perspective of publishing this case was discussed with the patient, who gave his full consent to proceed.

DISCUSSION

Epithelioid hemangioendothelioma is a rare vascular tumor of variable malignant potential (ranging from benign hemangioma to malignant angiosarcoma), which has been described in a variety of organs and which is termed HEHE when arising from the liver.[1] The earliest description of HEHE appears in the literature in 1982[2] and has since been reported on more than 400 occasions.[3]

HEHE predominantly afflicts women with a female-to-male ratio of 3:2 at a mean age of 41.7 years (ranging from 3 to 86 years) and represents <1% of all hepatic malignancies.[3,4] Although its etiology has not been firmly established, the suspected culprits are major liver trauma, hormones (ie, oral contraception), alcohol, viral hepatitis, and substances such as vinyl chloride, asbestos, and thorotrast.[5] Twenty-five percent of patients present asymptomatically, with the remaining 75% reporting right upper quadrant pain, weight loss, weakness, anorexia, nausea, jaundice, fatigue, and abdominal fullness in order of decreasing frequency. The clinician may correspondingly elicit hepatomegaly, an epigastric mass, ascites, or jaundice on examination.[5]

Blood tests commonly reveal mild elevations in bilirubin, alkaline phosphatase, and aspartate aminotransferase with normal tumor marker levels[5,6] and are therefore nondiagnostic.

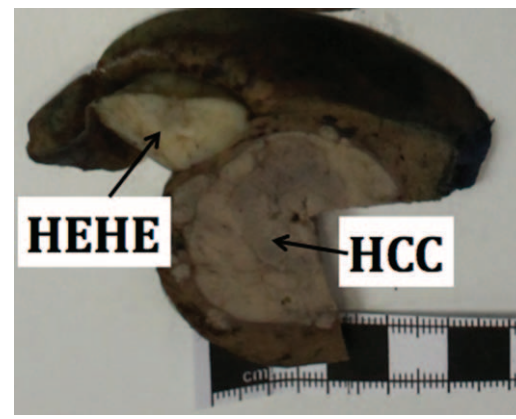

FIGURE 6. HEHE and HCC macroscopy. Grossly HEHE presents as a subcapsular, whitish, firm, circumscribed nodule with infiltrative borders whilst the HCC is a softer nodule, tan, pale-brown in colour. To the left of the main mass are smaller satellite nodules.

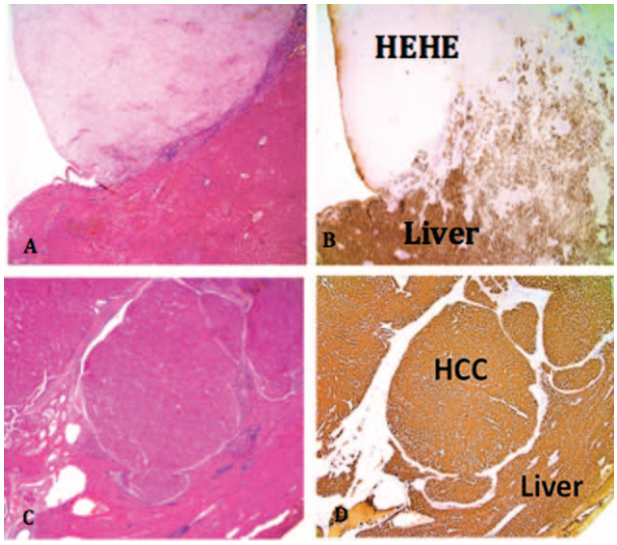

FIGURE 7. HEHE and HCC microscopy: (A and C) H&E-stained sections showing histological features of HEHE and HCC, respectively. (B and D) Immunostained-sections for Hep-PAR1 (marker for hepatocellular differentiation) showing negative expression in HEHE and positive staining in HCC. Note the infiltrative borders of the HEHE and pushing border of the HCC.

Imaging studies may demonstrate hepatosplenomegaly, signs of portal hypertension, focal calcification in 20% of tumors, and can serve to categorize the disease as either early (with nodular bilobar peripheral tumor distribution) or late (with a diffuse confluent tumor appearance).[6] In particular, MRI may detect the hallmark features of HEHE, which consist of peripheral confluent masses with capsular retraction and a halo or target enhancement pattern.[5] In a comprehensive literature review of 402 patients, Mehrabi et al determined that 87% of patients presented with multifocal bilobar disease, with extrahepatic involvement in 36.6% of cases. In metastatic disease, the lungs were the most common site, followed by regional lymph nodes, peritoneum, bone, spleen, and diaphragm.[3] For a definitive diagnosis of HEHE, immunohistochemical reactivity for factor VIII, CD31, CD34, and cytokeratins must be demonstrated.[5]

The establishment of clear treatment pathways for HEHE has been hindered by the rarity of this condition and the retrospective nature of most existing studies. Current management options include chemoradiotherapy, liver resection, liver transplantation, or a watch-and-wait strategy. Experience with nonsurgical treatment is reportedly of limited value,[6] therefore most studies have concentrated on either liver resection (LR) or orthotopic liver transplantation (OLT). It is generally agreed that LR should be considered only in limited disease,[4,5] whereas OLT should be considered in cases of multifocal disease even in the presence of extrahepatic disease as it has been shown to provide excellent outcomes.[5,6] A recent analysis of 110 cases in the United Network for Organ Sharing database by Rodriguez et al[7] has arrived at post-OLT 1- and 5-year patient survival rates of 80% and 64%, respectively. Similarly, an analysis of 59 cases in the European Liver Transplant Registry by Lerut et al[8] arrived at 1-, 5-, and 10-year survival rates of 93%, 83%, and 72% as well as disease-free survival rates of 90%, 82%, and 64% at 1, 5, and 10 years post-OLT. Only 2 patients in the latter study had pulmonary metastases at the time of OLT. The first patient underwent bilateral pulmonary resection after OLT and was disease free at 95 months post-OLT. The second one underwent double lung transplantation and α-interferon therapy and was well at 65 months post-OLT. Besides, the same publication reported recurrence of HEHE post-OLT, with additional pulmonary disease, in 4 patients.[8] As no clinical or histopathological prognosticators have been established, there is no consensus on the watch-and-wait approach. Some authors report long-term survival without therapy or advocate observation before committing to OLT,[9,10] whereas others have found survival rates of <50% within 22 years after diagnosis but caution on the unpredictable clinical course of HEHE.[3]

In contrast to HEHE, HCC is the most common primary hepatic malignancy, developing in the majority of cirrhotic patients and being the main cause of death within this group.[11] Symptomatology is such of chronic liver disease.[12] Lesions between patients or even within individual patients can be extremely heterogeneous at a molecular level and reliable biomarkers are currently lacking.[11] Biopsy carries a high false-negative rate (≤40%), and its diagnosis therefore relies heavily on contrast-enhanced imaging such as CT or MRI.[11] Management options for HCC include nonresectional ablative therapies (eg, radiofrequency ablation, microwave ablation, and transarterial chemoembolization), and surgical interventions such as LR and OLT.[12] While for HCC combined with cirrhosis there is a clear-cut treatment, based on consistently recommended decision-making tools like the Barcelona Clinic Liver Cancer (BCLC) staging system and the Milan Criteria, the management of HCC in a normal liver is still vague. The patient discussed above, having a single nodule with normal bilirubin would fall within the ''early stage'' BCLC group and therefore be considered for resection with curative intent.[11] Furthermore, LR was favored toward OLT as this was a unique case where the benefits and implications of OLT were unclear.

HCC has been described in synchrony with other malignancies including gallbladder adenocarcinoma, intrahepatic cholangiocarcinoma, renal cell carcinoma, oro-esophageal squamous cell carcinoma, as well as colorectal liver metastases[13–18] but has never been reported to coexist with HEHE. Conversely, HEHE has not yet been described in synchrony with any other malignancy. To our knowledge, this is therefore a unique case of synchronous metastatic HEHE and localized HCC, associated with challenges in both its diagnosis and treatment. By presenting this case, we aim to raise awareness that this rare entity can coexist with others, potentially complicating their management.

To conclude, HEHE can present in otherwise well patients with an unpredictable clinical course. Management of rare and potentially fatal conditions must be carefully considered by a multidisciplinary team. HEHE may appear in synchrony with other malignancies. Specifically for the liver, awareness must be increased if it is abnormal and harbors a lesion which cannot be clearly specified as HEHE.

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