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Case Report

A rare case of hepatic epithelioid hemangioendothelioma misdiagnosed as liver cancer

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Abstract: Hepatic epithelioid hemangioendothelioma (HEHE) is a malignant vascular endothelium-derived tumor featuring the histological characteristics of epithelial and vascular endothelial cells. The disease is very rare, with insidious onset. Its etiology and pathogenesis is not clear. Because of its complex and nonspecific clinical manifestations, HEHE is often misdiagnosed as liver cancer or other liver diseases. We report a case who had no specific symptoms and was initially diagnosed as liver cancer, but was finally confirmed to be HEHE by pathology. The patient's main clinical manifestations were abdominal distention and chronic large volume bloody ascites. Computed tomography and magnetic resonance imaging (MRI) scan of the patient's liver suggested abnormal multiple liver nodules, peritoneal and omental lesions. Positron emission tomography-computed tomography indicated the possibility of liver cancer. This case was clinically suspected of liver cancer, but CT and MRI imaging features did not support it. By transumbilical endoscopic surgery (TUES) and ultrasound-guided liver biopsy, we finally diagnosed HEHE at late stage, with extensive peritoneum and omentum metastasis. Like others reported, diagnosis of HEHE can be challenging. In our case, although it has the imaging features of vascular lesions, but was not correctly identified due to the absence of experience of radiologists and physicians resulted by its rare incidence. By presenting this case and extracting the image features, we aim to raise the awareness of HEHE in the future.

Keywords: Hepatic epithelioid hemangioendothelioma, computed tomography, magnetic resonance imaging

Introduction

Hepatic epithelioid hemangioendothelioma (HEHE), is a very rare malignant vascular endothelium-derived tumor, with histological features of epithelial and endothelial cells [1]. The first report by Weiss et al. [1] in 1982 characterized epithelioid hemangioendothelioma as a pathological histotype. The first retrospective study of 34 HEHE patients, by Ishak et al. [2], was published in 1984. Incidence of the disease is very low, with less than 1 in 1 million individuals worldwide. The female-to-male prevalence is 3:2 [3].

The clinical manifestations of HEHE are heterogeneous, varying from asymptomatic and nonspecific symptoms to obvious portal hypertension or even liver failure, about 60-80% of patients are misdiagnosed as primary liver cancer, or metastasis, tuberculosis, abscess, or parasites of the liver [4]. Although modern imaging technologies, including computed tomography (CT) and magnetic resonance imaging (MRI), can display the radiographic features of HEHE, but the medical staff often do not understand their imaging characteristics due to the rareness of the disease, and consequently render misdiagnosis. A definitive diagnosis always depends on fine needle biopsy of the liver and histological verification, including positive immunohistochemistry results of endothelial markers such as cluster of differentiation CD34, CD31, vimentin, and factor VIII are usually positive.

The present paper reports a rare case of HEHE with atypical symptoms of massive bloody ascites as the main manifestation. According to the symptoms and imaging features, we initially suspected liver cancer or cirrhosis, and finally diagnosed HEHE by transumbilical endoscopic

Table 1. Clinical features of HEHE patient

Test item		Value
Blood routine	White blood cell count	13.28 × 10^9/L ↑
	Red blood cell count	4.24 × 10^{12}/L
	Platelet count	359 × 10^9/L ↑
	Hemoglobin	123 g/L ↓
	Neutrophil	0.727
	Lymphocyte	0.107 ↓
Liver function	Alanine transaminase	64 μL ↑
	Aspartate transaminase	84 μL ↑
	Total bilirubin	33.8 μmol/L ↑
	Direct bilirubin	21.4 μmol/L ↑
	Total protein	58.4 g/L ↓
	Albumin	23.5 g/L ↓
	Globulin	34.9 g/L ↑
	Albumin-to-globulin ratio	0.7 ↓
	Total bile acid	36.3 μmol/L ↑
	Glutamyl transpeptidase	235 μL ↓
	Alkaline phosphatase	846 μL ↓
Coagulation	Prothrombin time	15.5 s ↑
	Activated partial thromboplastin time	57.2 s ↑
	Fibrinogen	4.79 g/L ↑
Ascites	Lactic dehydrogenase	169 U/L
	Glucose	6.25 μmol/L
	Adenosine deaminase enzyme acid	5.4 U/L
	Albumin	10.5 g/L

surgery (TUES) and ultrasound-guided liver biopsy. Through the diagnosis and treatment of the following case, We summarized its clinical symptoms and imaging features, which will be helpful for the diagnosis in the future. Since the disease is very rare, it is of great significance to raise awareness of physicians and radiologists to help correctly identify the disease.

Case report

A 46-year old man was admitted to the hospital in September 6, 2014 due to increased abdominal circumference and abdominal distension for more than one month. The patient did not have abdominal pain, diarrhea, chills, fever, night sweats, nose bleeding, or gum bleeding. He had worked in coal mining management for more than 10 years and had a drinking history of more than 20 years (Ethanol content is about 45 g/day). He denied a history of hepatitis or tuberculosis. The physical examination at admission showed body weight loss, visible facial telangiectasia, abdominal distension, visible abdominal vein, abdominal tension, slightly higher positive xiphoid tenderness, and no rebound tenderness. The liver was 5 cm subxiphoid process, hard, uneven and tender. There was no pain in the liver area with percussion and shifting dullness was positive.

Blood and liver function examination results are summarized in **Table 1**. Laboratory examination indicated nonspecific liver damage with evidently elevated aspartate transaminase, alanine transaminase, Glutamyl transpeptidase, alkaline phosphatase, total bilirubin, and direct bilirubin. Ascites routine examination revealed a large number of red blood cells, lymphocytes, and a few degenerated shedded mesothelial cells. Biochemical tests of ascites were: lactic dehydrogenase 169 U/L, glucose 6.25 μmol/L, adenosine deaminase enzyme acid 5.4 U/L, and albumin 10.5 g/L. Ascites pathological examination found no cancer cells. No bacterial growth was shown in ascites culture. Abdominal ultrasound revealed cirrhosis, ascites, and intrahepatic multiple hypoechoic nodules. Alpha-fetoprotein, carcinoembryonic antigen, and carbohydrate antigen 19-9 were normal. Ferritin was 402.6 ng/mL. Cancer antigen 125 was 272.64 KU/L and elevated. Erythrocyte sedimentation rate was 29 mm/hr. Hepatitis full examination revealed positive hepatitis B e antibody (HBeAb) and hepatitis B c antibody (HBcAb). Hepatitis B virus DNA was less than 10 copies/mL. Tuberculosis IgG was positive (+). T-SPOT.TB was positive. Tests of autoimmune liver disease, connective tissue disease, and parasites were all negative. Renal function, blood glucose and lipid were normal.

Gastroscopy showed no esophageal and gastric varices. Colonoscopy showed no abnormalities. Whole abdominal enhanced CT scan (**Figure 1A**) showed irregular liver contour, imbalanced lobe, larger left lobe, widened liver crack, and a large low-density shadow in the right lobe with less clear edge. Enhanced scan

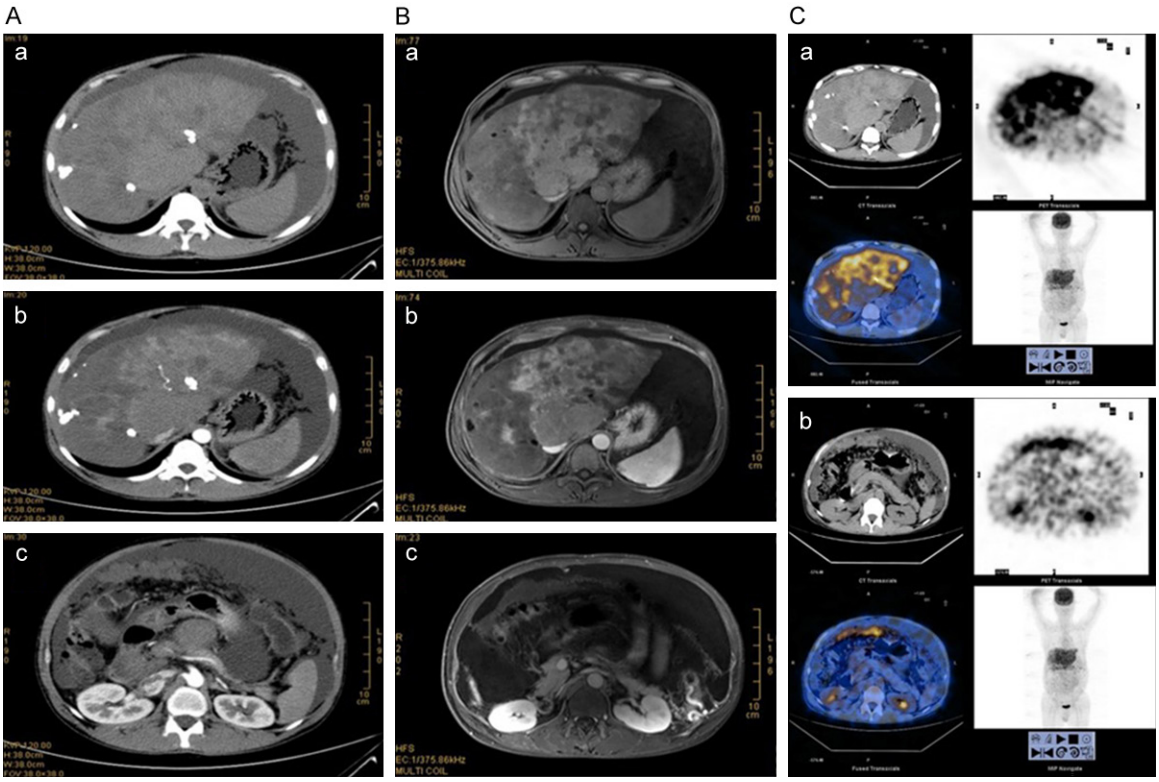

Figure 1. Imaging features of liver, peritoneal and omentum lesions. A. Whole abdominal CT+ enhanced scan (a-c) showed irregular outline of liver, imbalanced lobe with larger left hepatic lobe. The liver showed multiple patchy irregular hypodense lesions and the right lobe showed low density lesions with less clear edge. Enhanced scan showed mostly no enhancement or only peripheral enhancement. Liver parenchyma showed multiple patchy calcification. Peritoneum, omentum and mesentery appeared extensive thickening and partial omentum showed pie-like changes. A lot of peritoneal fluid was seen. (a) Unenhanced phase; (b) Arterial phase; (c) Omentum, peritoneal lesions. B. Hepatobiliary and pancreatic spleen MRI scan+ enhancement (a-c) showed reduced liver volume, imbalance of the proportion of each lobe segment, significantly increased caudate lobe, uneven liver parenchyma signal, large areas of relatively low signal foci in left liver lobe and the outer periphery of the right liver, In enhanced scan strengthening was not obvious. The peritoneum, omentum and mesentery appeared extensive thickness, significantly enhanced strengthening. And a lot of peritoneal fluid was seen. (a) Unenhanced phase; (b) Arterial phase; (c) Omentum, peritoneal lesions. C. PET-CT scan results. (a) Diffuse liver flake, nodular, lumpy uptake lesions; (b) Peritoneum and omentum showed significantly thickening.

showed edge enhancement and delayed scan showed a slow strengthening streak. The portal vein and vena vein and its branches were normal. The peritoneum, omentum, and mesentery showed extensive thickening. A lot of fluid was seen in the peritoneum. The hepatobiliary, pancreatic, and spleen enhanced MRI (**Figure 1B**) indicated reduced liver volume; significantly widened liver crack; increased caudate lobe; and large areas of relatively low signal foci in the left liver lobe and the right hepatic outer peripheral portion, within which short T1-segment T2 signal lesions of multiple nodules was seen. Enhanced scan strengthening was not obvious and delay scanning showed the sheet of slow strengthening shadow. Portal vein and its branch were normal. There was no expansion of the extrahepatic and intrahepatic bile duct. Peritoneum, omentum and mesentery were thickening and significantly enhanced with a lot of peritoneal fluid. CT/MRI imaging features did not indicate primary or secondary liver cancer, and had some characteristics of vascular lesions, such as low density lesions, enhanced scan without enhancement or only edge enhancement, and some lesions had calcification. But at that time, it was suspected of sclerotic hemangioma, tuberculosis or other malignant lesions.

To clarify the nature of the liver and peritoneal lesions, we used PET-CT (**Figure 1C**), and it

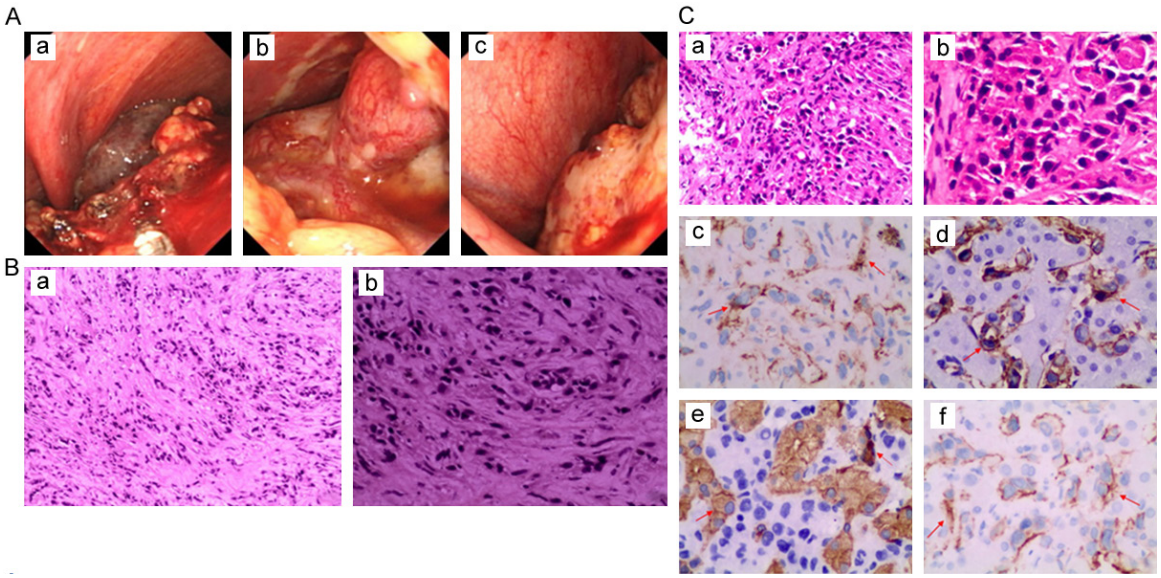

Figure 2. TUES, histopathology and immunohistochemistry of the liver and Omentum. A. TUES findings. a. Liver was purple-brown and hard; the omentum showed nodular thickening. b-c. Omentum appeared thickened, hardened, and with mass-like hyperplasia. Tortuous vessels and scattered purple blood blisters can be seen. B. Omentum histopathology showed tissue fibers and myofibroblast hyperplasia, inflammatory cell infiltration, among which there were a small number of cells with large stained nuclei. a. Omentum HE × 100; b. Omentum HE × 200. C. Liver histopathology showed scattered short spindle-shaped and large polygonal nuclear-stained cells in a gland-like arrangement, with necrosis and myxoid changes. a. Liver Tissue HE × 200; b. Liver Tissue HE × 400; c. Immunohistochemical Liver Tissue F8(+) × 400; d. Immunohistochemical Liver Tissue CD34(++) × 400; e. Immunohistochemical Liver Tissue Vimit (+++) × 400; f. Immunohistochemical Liver Tissue CD31(+) × 400.

showed a diffuse liver flake and nodular, lumpy slightly low density shadow, indicating malignant liver lesions, with liver, peritoneum, and omentum metastasis. However, the image features and tumor marker results did not support this suspicion, hence, we applied abdominal exploration and liver biopsy. Due to the large amount of ascites and coagulation dysfunction, liver biopsy turned out to be infeasible to proceed, therefore transumbilical endoscopic surgery (TUES) was performed to finish abdominal exploration and peritoneal biopsy. The surgery showed massive red muddy intraperitoneal ascites (**Figure 2A**), and dark green, hard liver with blunt edge. In the right upper abdomen was a hardened and thickened omentum, partial white mass hyperplasia, densely covered tortuous vessels, and scattered purple blood blisters. Small white nodules were scattered in the right lower quadrant of abdomen. We took 16 biopsies from lesions in the peritoneum and omentum. Rapid pathological examination results showed large atypically-shaped nuclei among the fibrous tissues. Routine pathological examination showed tissue fibers and myofibroblast hyperplasia, and inflammatory cell infiltration, among which there were a small number of cells with large stained nuclei. Based on these results, cancer could not be excluded (**Figure 2B**).

Through TUNES, we temporarily eliminated the ascites, and completed the ultrasound guided liver biopsy in September 30, 2014. Liver lesions showed scattered short spindle and large polygonal nuclear stained cells in a gland-like arrangement, with necrosis and myxoid changes (**Figure 2C**). Tumor cell hyperplasia and focal dysplasia were seen with interstitial myxoid degeneration. Red blood cells and the formation of cavities were in the tumor tissue. Immunohistochemistry results were as followings: tumor cell CD34(++), CD31(+), factor VIII (focal +), vimentin (+++), CD10(+++), carcinoembryonic antigen (+-), cytokeratin (CK;-), CK7 (-), CK20(-), CK19(-), S100(-), actin (-), hepatocyte (-), caudal type homeobox2 (CDX2;-), MOC31(-), and Ki-67 (about 5%). The immunohistochemical results confirmed epithelioid hemangioendothelioma.

The incidence of epithelioid hemangioendothelioma is very low and HEHE is even rare. There

is currently no effective treatment for this disease. This patient was administered thalidomide anti-angiogenic therapy, intraperitoneal 5-FU chemotherapy, and hyperthermia. The initial dose of thalidomide was 50 mg QN (at bedtime), increased to 100 mg QN after 1 week and to 150 mg QN after 2 weeks. 5-FU intraperitoneal chemotherapy and hyperthermia were applied once a week with 1 g 5-FU intraperitoneal treatment each time.

At 3 weeks, the ascites had turned from bloody turbid to clear and yellowish, and ascites routine examination revealed a significant reduction in the number of red blood cells. The ascites amount also decreased relative to admission. However, the patient's liver injury aggravated 2 weeks after discharge and he died of liver failure after more than one month stay in a local hospital.

Discussion

Epithelioid hemangioendothelioma, is a rare malignant tumor of vascular origin, with histological features of epithelial cells and endothelial cells [1]. Its etiology and pathogenesis is not clear and may be related to exposure to chemical substances (such as vinyl chloride and asbestos), oral contraceptives [5], progesterone imbalance, hepatitis B virus infection, alcoholism, liver injury, or genetic susceptibility [5-8]. In the present case, the patient had long been engaged in coal mining work and had a history of exposure to harmful substances including asbestos dust and vinyl chloride, which may be related to the pathogenesis of HEHE.

HEHE in CT/MRI imaging has characteristic features [9]. The lesions are often in the liver subcapsular region which can be a single nodule or diffuse nodular lesions, often accompanied by calcification. Enhanced scan shows edge enhancement or only strengthening with a halo sign and the envelope retraction symptom. At an advanced stage, HEHE shows diffuse liver disease or peritoneum, omentum metastasis, and has a poor prognosis. The imaging features of HEHE are quite different from primary and secondary liver cancer, with a strong diagnostic value, but because of the rare incidence of this disease and lack of understanding of the characteristics of its image, it is often misdiagnosed. Histopathologically, HEHE is characterized by epithelial cells and dendritic cells with nuclear atypia and mitosis. HEHE is characterized by lumen formed within the cytoplasm, which may contain red blood cells, and is similar to signet ring cells. The tumors contain mucinous hyaline fibrous stroma, and a few have intratumoral progressive fibrosis or calcification. Tumor endothelial cell proliferation can cause occlusion of the sinusoidal, portal, or liver vein, which will result in ischemic liver degeneration and necrosis. The liver pathology of the present case had the above features, and immunohistochemistry for CD34, CD31, vimentin, and factor VIII were positive. Moreover, since TUES is less invasive than traditional laparoscopic surgery and without scar, it facilitated the diagnosis of peritoneal and omentum metastasis in this case. The case also met the criteria for the highly invasive pathological tissue types of HEHE.

Because HEHE is a rare disease, investigations of the clinical efficacy of treatments are few. There are scattered reports of partial liver resection, liver transplantation, chemotherapy (5-FU, cyclophosphamide, and thalidomide), anti-angiogenic therapy (VEGF monoclonal antibody), interferon, and others. Treatment depends on the stage of the disease [10]. If liver transplant is not feasible, antiangiogenic chemotherapy is recommended.

Thalidomide has anti-inflammatory, immunosuppressive, anti-tumor, and anti-angiogenic effects. There have been some successful cases using thalidomide in the treatment of HEHE [10, 11]. In our case, we selected thalidomide for treatment, and initially the patient responded. After 3 weeks, the color of ascites became clear and the patient felt better, with symptoms of bloating because of slow ascites accumulation. But finally the patient died of diffuse liver disease and liver failure.

In conclusion, HEHE is a very rare disease and lack of specific clinical manifestations makes early diagnosis difficult. HEHE may be suspected in patients with multiple liver nodules, unexplained ascites, peritoneum and omentum involvement, multiple calcifications, low-density lesions of no enhancement or only peripheral enhancement in CT/MRI and other imaging, and who do not meet the criteria for primary or secondary liver cancer. The final diagnosis

depends on pathology. Greater awareness of the disease, early diagnosis, and early treatment are the keys to improve the prognosis.

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Disclosure of conflict of interest

None.

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