

Case Report

Hepatic epithelioid hemangioendothelioma metastasized to the peritoneum, omentum and mesentery: a case report

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Received March 3, 2015; Accepted April 15, 2015; Epub May 1, 2015; Published May 15, 2015

Abstract: Epithelioid hemangioendothelioma (EHA) is a malignant vascular tumor derived from endothelial cell often misdiagnosed as Hepatic carcinoma on the basis of radiological features. Till now etiology of this rare curiosity is unknown but it is related with use of oral contraceptives pills (OCP), liver trauma, exposure to vinyl chloride and hepatitis. We herein report on a case which failed to be diagnosed by cytopathology, computed tomography (CT) and magnetic resonance imaging (MRI). Patient was a 46 yr old man presented with abdominal distension for a month. Initial liver function test (LFT) was increased whereas renal function test (RFT) and alpha-fetoprotein (AFP) were normal. His abdominal ultrasound revealed multiple hypoechoic nodules and multiple liver calcifications. Subsequently laparoscopic omental biopsy and Ultrasound guided liver biopsy was done showing the neoplastic cells scattered in fibrous stroma. The immunohistochemistry for endothelial tumor cells stained positive for Vimentin (+++), CD10 (+++), CD34 (++), CD31 (+), Factor VIII antigen (focal) (+) and low proliferative activity for ki-67. Our case is very interesting in which patient admitted with nonspecific symptoms of abdominal pain and diagnosed to be a Malignant Hepatic EHA metastasized to the peritoneum, omentum and mesentery. The patient was on thalidomide 50 mg/day and increased to 100 mg/day. 5-Fluorouracil (FU) intraperitoneal chemotherapy and other symptomatic and supportive treatment was given to the patient. Our case highlights on the importance of immunohistopathological diagnosis, compare the radiological findings of this disease and discuss the treatment strategy with review of available literature.

Keywords: Epithelioid hemangioendothelioma, hepatic, peritoneum, metastasis, histopathology, immunohistochemistry

Introduction

Hepatic EHA is a rare low grade malignant vascular tumor which was first described by Weiss and Enzinger in 1982 [1, 2]. It has prevalence of 1 per 100,000 in the general population [3, 4]. The most common location for this tumor is lower extremity followed by upper extremity with an indolent clinical course. The clinical symptom is non-specific varying from asymptomatic to abdominal pain, abdominal distension, weight loss [5, 6], hepatic failure to death. Lung, peritoneum, lymphnodes, and bone were the most common sites of extrahepatic involvement at the time of diagnosis [3]. Most of the time the initial diagnosis is erroneous. Radiological imaging may be helpful in the earlier detection of this disease but the diagno-

sis depends entirely on histopathological staining of the cells combined with immunohistochemistry. All the patients of hepatic EHA is treated either with surgical resection or liver transplantation [7]. Recently new systemic drugs such as thalidomide, bevacizumab are used as an antiangiogenic agent in the treatment of hepatic EHA [8, 9]. Immunotherapy, radiotherapy and chemotherapy have seen to be less effective.

Case report

A 46 yrs middle aged man presented with history of abdominal distension for a month. He was alcoholic for more than 20 yrs and was allergic to pollen. He had no past H/o Diabetes, Hypertension, Hepatitis or Tuberculosis (TB). There was no exposure to drugs or radiation. No

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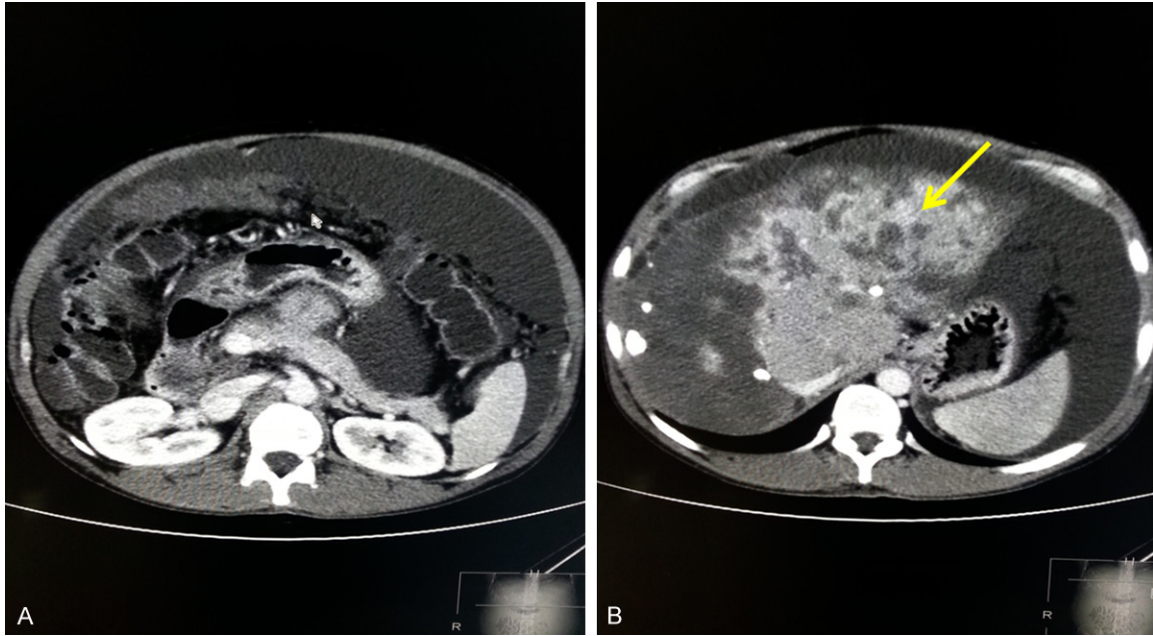


Figure 1. A. Computed Tomography scan of the abdomen demonstrate massive peritoneal thickening, nodular change and a large intraperitoneal effusion. B. A large number of nodules within the liver can be seen, low-density mass lesions (arrow) with intraperitoneal effusion.

loss of weight. Physical examination showed engorgement of jugular vein and mild edema of lower limbs. Systemic examination was unremarkable except shifting dullness was positive. Initial laboratory tests revealed ALT-65 U/L, AST-98 U/L, ALP 511 U/L, TBIL-31.6 Umol/L, DBIL-17.5 Umol/L, ALP-31.9 Umol/L, TP-73.2 g/l. Tumor markers including AFP, HCG, PSA, CA19-9 were all within normal limits but CA125 was positive. Serum surface antigen for hepatitis B and Anti HCV were negative. Initially the renal function test was normal but it started to deteriorate showing possibility of hepatorenal syndrome. The total protein and albumin values are protein 55.4 g/L ↓, albumin 24.1 g/L ↓.

The chest x-ray showed Left lower pulmonary infection showing increased in WBC count. Subsequently endoscopy and colonoscopy were done. Endoscopy showed chronic non atrophic gastritis with bile reflux. Colonoscopic polyp biopsy of rectum showed tubular adenoma with focal epithelial hyperplasia.

An abdominal ultrasonography revealed multiple hypoechoic nodules in the liver and multiple liver calcifications. The pathological nature of disease could not be determined.

Contrast enhanced CT revealed changes suggestive of liver cirrhosis, multiple lesion of

abnormal density in the liver and thickened peritoneum, omentum and mesentery with ascites (**Figure 1**). The patient was diagnosed as TB? liver carcinoma? MRI revealed multiple lesions in both hepatic lobes. Periphery of lesion showed abnormal signal. The tumor was diagnosed to be a sclerosing hemangioma.

The FNAC result was inconclusive which showed ascites with large number of RBC, a few lymphocytes and shedding of the mesothelial cells degeneration. The malignancy of tumor could not be ruled out. Patient underwent laparoscopic omental biopsy which showed myofibroblastic proliferation, infiltration of inflammatory cells with a few large hyperchromatic nuclei. Ultrasound guided 18G biopsy needle was punctured into the left lateral lobe of the liver hypoechoic area. Patient was stable during intraoperative and postoperative period. The biopsy result showed active spindle and polygonal tumor cells proliferation with focal atypical hyperplasia and interstitial myxoid degeneration, necrosis with visible red blood cells. The tumor cells expressed positive for CD10 (+++), vimentin (+++), CD34 (++), CD31 (+), CEA (+/-), factor VIII antigen (focal) (+), low ki-67 proliferative activity and negative for CK, CK7, CK20, CK19, S-100, act, hepatocyte, CDK-2, MOC-31. **Figures 2, 3** are representative imag-

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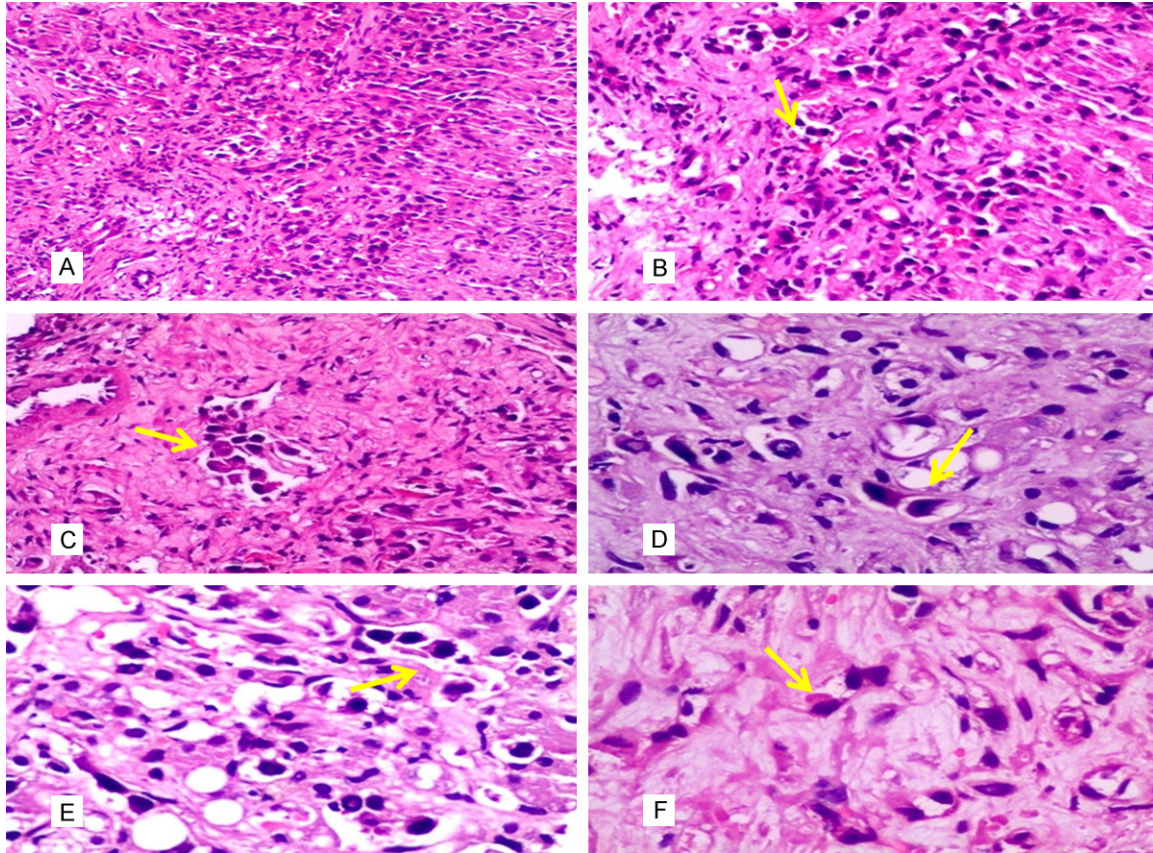


Figure 2. Histopathology of hepatic epithelioid hemangioendothelioma (A-E: Liver tissue & F: omentum tissue). A. Pleomorphic tumor cells with rounded and polygonal shaped nuclei embedded in myxochondroid and sclerotic stroma in liver tissue (magnification $\times 100$). B. Tumors cells with intracytoplasmic lumina containing red blood cell (arrow) (magnification $\times 200$). C. Neoplastic tumor cell (arrow) (magnification $\times 200$). D. Scanty tumor cell with hyperchromatic nuclei (arrow) (magnification $\times 400$). E. Tumor cells (arrow) (magnification $\times 400$). F. Intracytoplasmic lumina with red cell (arrow) (magnification $\times 400$).

es of the typical features of epithelioid hemangioendothelioma in histopathology and immunohistochemistry.

The tumor was diagnosed as malignant EHAE with wide metastasis to peritoneum, omentum and mesentery. The patient was on thalidomide 100 mg/day. Intravenous 5-FU chemotherapy was given. Albumin was continuously added due to decrease in total albumin. As cost of treatment was high patient asked for help to the government. Everything was explained to the patient including treatment effect and poor prognosis. Despite patient's critical condition he got discharged on his own demands with tablets thalidomide and asked to pay attention to take rest, proper exercise, high protein diet and to follow up with blood routine examination, LFT, RFT and electrolytes test. The final diagnosis during discharge was 1) Hepatic EHAE with metastasis to peritoneum, omentum

and mesentery 2) Alcoholic cirrhosis (decompensated) with hypoproteinemia 3) Chronic non atrophic gastritis 4) Chronic colitis 5) Colon polyps 6) Pneumonia.

Discussion and conclusion

EHAE was first described by Ishak in 1984 from the series of 32 patients [10]. It is described as a rare vascular tumor between intermediate and malignant potential in most of the article, but according to WHO classification it is added to malignant neoplasm. Till today there are less than 500 cases reported in the literature. This metastatic peculiar vascular tumor can occur primary in liver, lungs, breast, clival, wrist, cervical, kidney, gastric, oral [5, 11-14] In our case liver EHAE metastasized widely to peritoneum, omentum and mesentery showing multiple organ dysfunction syndrome (MODS). EHAE has no age or gender prediction. It is more common

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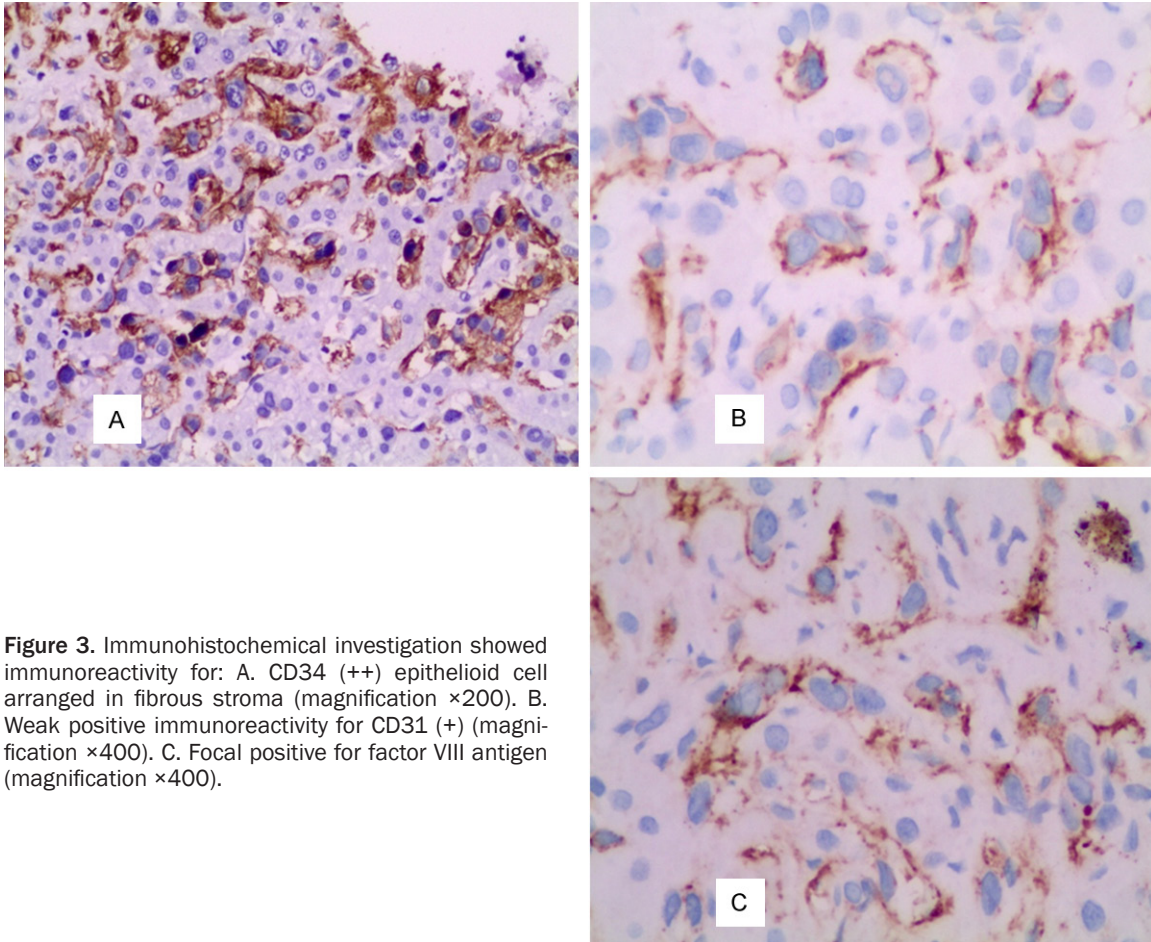


Figure 3. Immunohistochemical investigation showed immunoreactivity for: A. CD34 (++) epithelioid cell arranged in fibrous stroma (magnification $\times 200$). B. Weak positive immunoreactivity for CD31 (+) (magnification $\times 400$). C. Focal positive for factor VIII antigen (magnification $\times 400$).

is female (male to female ratio, 2:3) [3, 11, 12] and usually occurs in middle age women. We have a male patient in our case. The etiology of this disease is undetermined but it has been related to use of OCP (in case of female) [15], exposure to vinyl chloride, hepatitis, ascites and liver trauma [16-18]. In our case, patient is diagnosed as alcoholic cirrhosis with ascites. So these factors can be related to the disease. The serology marker for hepatitis was negative except for anti HEV (+) which was nonsignificant. The other risk factors explained above are not related to our patient.

The clinical manifestation of this disease is so diversified. Sometimes patients are asymptomatic. Most of the time EHAE is detected incidentally and is asymptomatic in 22% to 25% of patients. Some present with abdominal distension, abdominal pain, weight loss, jaundice, hepatosplenomegaly, portal hypertension, Budd-Chiari syndrome to severe hepatic failure [3, 19]. In our case the patient had no specific symptoms except for abdominal distension for

a month. At the time of diagnosis, 87% of patient have bilobar disease and extrahepatic involvement was observed only in 36.6% of patients. The lungs (8.5%), regional lymph nodes (7.7%), peritoneum (6.1%), bone (4.9%), spleen (3.2%), and diaphragm (1.6%) were the most common sites of extrahepatic involvement [3]. In present case there is metastasis to peritoneum, omentum & mesentery and both lobes are involved. 85% of patients have increased abnormality in AKP (68.6%), GGT (45.1%), AST (28.6%), ALT (23%), Bilirubin (19.9%) [3]. Our patient showed increased value of all of this laboratory test. The tumor markers, alpha-fetoprotein, carcinoembryonic antigen, cancer antigen19-9 are also negative as in our case. They are only useful for excluding other primary and secondary hepatic tumors and are not specific markers for diagnosing EHAE but cancer antigen 125 is positive here.

Hepatic EHAE is classified pathologically into solitary nodular or diffuse nodular types evolving from the former [11]. In (66.3%) of cases a

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hypoechoic pattern is found in ultrasound [11]. Some of the literature explained the hypoechoic nodules in the ultrasound. A heterogeneous pattern is present in 22.5% of EHAE whereas both hyperechoic and hypoechoic is rare [6, 20]. Ultrasonography in our patient showed multiple hypoechoic nodules in the liver and multiple liver calcification. Sometimes hypoechoic pattern resembles that of the hemangioma which may/can misdiagnose the case.

On CT scan the lesions presented as solid, inhomogeneously hypodense nodules with a ring like low density border or lower density centre. MRI manifestation on T1W1 image were hypointense with lower signal intensity in the centre, T2W2 image demonstrated intermediate to high signal intensity. The Capsular retraction sign caused by an intense fibroproliferation and Halo sign due to central coagulative necrosis are the important CT and MRI manifestation which provide accuracy of the diagnosis [2, 19]. CT findings in our patient was suggestive of liver cirrhosis. There are multiple lesions of abnormal density in the liver with thickened peritoneum, omentum and mesentery. All of these findings were suggestive of hepatic carcinoma and tuberculosis but the test result for AFP and TB was negative. MRI showed multiple lesion in both hepatic lobes, Periphery of the lesions showed abnormal signals. Case was misdiagnosed to be a sclerosing hemangioma. EHAE is often misdiagnosed as metastatic carcinoma, cholangiocarcinoma, hepatocellular carcinoma, sclerosing carcinoma or angiosarcoma [1, 21].

The diagnosis depends on the histopathological staining of cells. Tumors cells consists of intracytoplasmic lumina occasionally containing RBC, appear as Signet ring like structure [11, 18]. The stroma is fibrous with myxohyaline areas. The tumor is composed of epithelioid, dendritic or intermediate cells in a fibromyxoid stroma [11]. Immunohistochemically neoplastic cells of EHAE express the endothelial marker such as CD31, CD34, CD10, Vimentin, Factor VIII antigen [2, 12, 16, 19, 22, 23]. In our case immunohistochemical staining for endothelial marker such as Vimentin and CD10 are strongly positive whereas CD31, CD34, factor VIII antigen is weakly positive. Other marker of muscle and neural differentiation are negative and a low proliferative fraction on Ki67 staining helps to exclude other angiosarcoma. In a

microarray study, Higgins et al. proposed that using an immunohistochemical panel including FKBP12 combined with CD34 and CD31 yields 93% diagnostic sensitivity among 14 hemangi endothelioma. GLUT1 and FKBP12 are the two novel IHC marker in the diagnosis of malignant vascular tumor (MVT) including epithelioid hemangi endothelioma [24]. Podoplanin which is immunoreactive to D2-40 antibody could be useful for the diagnosis of Epithelioid hemangi endothelioma. It is expressed in EHAE with 78% sensitivity [23]. It is also concluded that CD10 has a sensitivity of 78% and specificity of 70% of EHAE [22]. In our case CD10 and Vimentin are strongly expressed as compared to other endothelial marker.

Currently there is an increased use of fine needle aspiration cytology (FNAC) in the diagnosis of EHAE but our case failed to diagnosed by FNAC. The FNAC result was inconclusive. Even sometimes USG guided liver biopsy fails to diagnose a case of EHAE [4, 25] due to limitation of sample but in our case diagnosis of Hepatic EHAE was done by sample taken from USG guided liver biopsy on the basis of histopathological findings and confirmed by IHC.

As symptoms, the prognosis of disease varies widely exhibiting slow growing lesion to a rapidly progressive disease but the prognosis is better comparing with other malignant hepatic tumor [17]. At present there is no standard treatment but Orthotopic Liver transplantation is the ideal treatment for this disease specially in case of diffuse kind of variety or in the presence of metastatic disease while liver resection can be done in case of single nodular type. For successful resection of a local or distance recurrence of EHAE early detection of tumor is very necessary. Prolonged survival (5-28 yrs) has been reported after surgical resection or liver transplantation [6]. Chemotherapy, radiotherapy and immunotherapy have seen to be less effective and usually resistant. Metronomic cyclophosphamide has been purposed as a new therapeutic palliative option to treat metastatic and nonoperative hepatic EHAE [26]. In some article It is reported that sorafenib may have the advantage over other antiangiogenic agents because of its dual anti tumor activity [9]. In present case the patient was on thalidomide 50/mg /day and then increased to 100 mg/day. Metastatic hepatic EHAE has been shown to be treated successfully by the use of

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thalidomide by blocking the proliferation of the malignant vascular endothelial cells [27]. So, Thalidomide is the choice of drug to treat for metastatic and non-operable hepatic EHAE as in our case.

In summary EHAE has very unclear etiology, diversified symptoms, indolent course which makes it very difficult to diagnose. Radiological imaging and FNAC are though helpful but diagnosis depends entirely on the histopathologic findings. Vimentin, CD10, CD31, CD34 and factor VIII antigen are the most important IHC markers for the diagnosis of EHAE. The important histopathologic findings like intracytoplasmic lumina with red blood cells with polygonal and spindle tumors cell in fibromyxoid are very specific in this disease. Multiple hypoechoic nodules in liver with peritoneal and mesenteric thickening with normal AFP, CEA, TB test and serology marker can suggest the differential diagnosis of Hepatic EHAE. Our case presented as nonspecific abdominal symptoms which has been progressed to peritoneum, omentum and mesentery with multiple organ involvement. So as the disease outcome is unpredictable, early diagnosis and treatment is very necessary.

Acknowledgements

This study was supported by the clinic big data research funding of Central South University.

Disclosure of conflict of interest

None.

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