Hepatic epithelioid hemangioendothelioma: A misdiagnosed rare liver tumor

L'hémangioendothéliome épithélioïde du foie : une tumeur hépatique rare à ne pas méconnaître

Hepatic epithelioid hemangioendothelioma (HEHE) is a very rare vascular neoplasm of the liver that arises from endothelial cells, with an estimated incidence of 1–2 in 1,000,000 [1]. The clinical presentation is heterogeneous, varying from absence of symptoms to portal hypertension and liver failure [1]. Radiological imaging may be helpful in the earlier detection of this disease but the diagnosis depends entirely on histopathological staining of the cells combined with immunohistochemistry. The management of this uncommon liver tumor remains debated especially for bilobar disease extent into the liver and in the case of extrahepatic spreading [2]. Due to the rarity of the disease and its natural history with a usually indolent course relative to other hepatic malignancies, the effectiveness of curative strategy is still difficult to define [2].

Herein, we report an intriguing case of a HEHE in a 24-year-old male.

Clinical observation

A 24-year-old male patient presented to our department with a history of recurrent abdominal pain in the right upper quadrant. He was a non-smoker and did not consume alcohol. His medical history started 6 years earlier when he presented to the emergency department with the same complaint. The pain was mild to moderate, unrelated to food intake, position or respiration. An abdominal ultrasound and a computed tomography (CT) were performed, which revealed multiple focal lesions in the liver (figure 1). The diagnosis of atypical hepatic hemangiomas was suspected and a magnetic resonance imaging (MRI) of the liver was indicated. However, the patient was lost to follow-up. When he was admitted to our department, abdominal examination revealed a slight tenderness in the right upper quadrant and a splenomegaly of 3 cm below the left costal margin. Routine haematological and biochemical investigations were normal. Liver function tests were within normal values including alkaline phosphatase (66 U/L), g-glutamyl transpeptidase (36 U/L), aspartate aminotransferase (18 U/L), alanine aminotransferase (26 U/L) and bilirubin levels (18 umol/L). Prothrombine time and albumin level were normal (86% and 38 g/L respectively). An abdominal ultrasound was scheduled which showed several hypoechoic nodules, regarding both liver lobes, with an irregular echogenic outline and multiple calcifications (figure 2). Viral markers for hepatitis B and C viruses were negative. Tumor markers including cancer embryonic antigen (CEA), alpha-fetoprotein (AFP) and carbohydrate antigen (CA) 19–9 were all within normal limits. MRI of the liver was performed afterward. T1-weighted images showed hypointense peripheral bilobar lesions; T2-weighted images showing hyperintense lesions with capsular retraction and signs of portal hypertension (figure 3). In order to obtain a definitive diagnosis, we performed a percutaneous ultrasound-guided biopsy. The histopathology report revealed fusiform tumor cells embedded in myxochondroid and sclerotic stroma in liver tissue associated with irregular anastomosis of vascular channels (figure 4).
cells stained positive for factor VIII-related antigen as well as the endothelial markers CD31 and CD34. The overall immunohistochemical findings supported the diagnosis of hepatic epithelioid hemangioendothelioma. Extrahepatic metastasis was not observed. The patient was enlisted and waiting for a liver transplantation.

**Discussion**

HEHE is a rare tumor of vascular origin. It was first reported in 1984 by Ishak et al. in a series of 32 patients [3]. Till today, there are less than 500 cases reported in the literature [2]. The World Health Organization classifies HEHE as a malignant tumor with low/intermediate aggressiveness [4]. Patients with HEEH have a female predominance, at a ratio of 1.6, with a mean age of presentation of approximately 42 years [1]. We have a young male patient in our case. The etiologic factors remain unclear, but association with contraceptive pills, exposure to vinyl chloride, viral hepatitis or major hepatic trauma is assumed to play a role in the pathogenesis of HEHE [5,6]. Recently, a specific translocation t(1;3)(p36.3;q25) has been hypothesized to be unique for HEHE but the pathway of how the resulting fusion transcript leads to oncogenesis is not yet elucidated [7]. None of these risk factors were related to our patient. The clinical presentation of this disease is very diversified. HEHE is detected incidentally in 22 to 25% of cases [1]. Among symptomatic patients, the most common clinical manifestations are non-specific, including right upper quadrant pain, jaundice and weight loss [1]. A complicated clinical presentation, such as Budd-Chiari syndrome, portal hypertension or liver failure, seems to be correlated with the presence of diffuse and bilobar form of the disease [2]. Spontaneous rupture of tumor was reported but was extremely rare [8]. The exact mechanism is unclear and is often related to rapid expansion and central necrosis, tumor venous invasion, abdominal trauma and pressure of the diaphragm [8]. Non-specific symptoms and the rarity of HEHE, make the diagnosis of this entity very challenging especially the preoperative diagnosis. For these reasons, approximately 60 to 80% of patients with HEHE are initially
misdiagnosed as metastatic carcinoma, hepatocellular carcinoma, cholangiocarcinoma or other types of vascular lesions preoperatively [1,2,8]. At his first presentation, our patient was misdiagnosed as liver hemangiomas. The diagnosis was reassessed after he presented with portal hypertension. This latter complication may develop when massive tumor cells invade blood vessels [2]. Laboratory parameters are also non-specific. The most common abnormalities are increased alkaline phosphatase (68.6%), g-glutamyl transpeptidase (45.1%), aspartate aminotransferase (28.6%), alanine aminotransferase (23%) and bilirubin (19.9%) [1]. Serum alpha-fetoprotein, carcinoembryonic antigen and cancer antigen 19–9 are generally within normal values [1]. The tumor markers have no significant value for the diagnosis of HEHE [1]. Their only potential role is the excluding of other primary and secondary liver tumors with the limitations of their sensitivity and specificity. Our patient did not show any increased value of all of these laboratory tests. Pathologically, there are three types of growth patterns in the gross appearance of HEHE:

- multiple nodules;
- diffuse nodules;
- a single mass [9].

The nodular subtype is present in early stages and is characterized by the imaging of multifocal nodules. With time, these nodules grow and eventually coalesce, forming large confluent masses preferentially involving the peripheral liver, that is, the diffuse subtype [9]. The present case proves this particular aspect of HEHE. In fact, our patient had initially multinodular lesions, which evolved, 6 years later, into diffuse peripheral ones. Regarding imaging, there exist great heterogeneities in the features of HEHE. HEHE was classified into three types according to the number of lesions/solitary nodule, multifocal nodule and diffuse types. Typically, hepatic lesions are hypointense on US, with low density on CT, and are usually hypointense on T1-weighted images and hyperintense on T2-weighted images [10]. Typical imaging features, including the ‘white target-like’, ‘black target-like’, ‘lollipop’ and ‘strip-like’ signs, capsular contraction, submarginal distribution, may contribute significantly to the definitive diagnosis of HEHE [10]. The ‘white target-like’ sign is defined by a nodular enhancement in the central part of the lesion in the arterial phase surrounded by ring-like enhancement in the portal venous and delay phases [10]. The ‘black target-like’ sign correlates with peripheral enhancement with central low signal intensity in the arterial phase and enhanced lesions surrounded by a thin hypointense ring in the portal venous and delay phases. The ‘strip-like’ sign is a low density or heterogeneous signal intensity lesions involving regions of part or the whole liver, coalescent lesions and lollipop sign is a gradual enhancement along central vessels. Exceptions from the above findings are very frequent [10]. Contrast-enhanced ultrasound (CEUS) has improved detection of multifocal HEHE, which showed typical enhancement patterns with hyperenhancement in the arterial phase and hyperenhancement in the portal venous and late phases [11]. Therefore, CEUS can help to determine the malignant nature of HEHE [11]. CEUS can be considered at least equal to, and in some ways (real time observation, no radiation, less expensive) superior to, CT and MRI as a diagnostic tool [11].

In our case, imaging features included multiple bilobar hypointense lesions with multiple calcifications on US, MRI showed peripheral signal abnormalities of the liver associated with a capsular retraction and features of portal hypertension. Histologically, HEHE appears as nests or cords of epithelioid endothelial cells spreading within sinusoids. Another classical histological feature of these tumors is the presence of intracellular vascular lumina that sometimes contain red blood cells [12]. Immunohistochemically, neoplastic cells of EHEAE express the endothelial marker such as CD31, CD34, CD10, Vimentin, Factor VIII antigen [12,13]. Other marker of muscle and neural differentiation are negative and a low proliferative fraction on Ki67 staining helps to exclude other angiosarcoma. In our case, immunohistochemical staining for CD31, CD34 and factor VIII were positive. At the time of diagnosis, extrhepatic involvement is observed 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%) are the most common involved sites of [1]. Our patient did not have any extrhepatic involvement. Currently, there is no standard therapeutic algorithm for HEHE, but conventional treatments of HEH include surgical resection or OLT [14,15]. In fact, only surgery can provide cure in HEH. OLT is considered the ideal treatment for this disease especially in case of diffuse type even in cases of metastatic disease, except for the pediatric population.

**Figure 4**

Photomicrography shows fusiform tumor cells embedded in myxochondroid and sclerotic stroma in liver tissue associated with irregular anastomosis of vascular channels.
The efficiency of OLT as the treatment of choice for HEHE has been documented in two big studies, one from the United States and one from Europe [14, 15]. But the shortage of organs available for transplantation makes the choice of resection inevitable in cases where complete resection is feasible especially in case of single nodular type [16]. Chemotherapy, radiotherapy and immunotherapy have seen to be less effective but can be considered as the treatment of choice for patients with metastasis [15, 16]. It has been reported that sorafenib may have the advantage over other antiangiogenic agents because of its dual anti tumor activity [10]. In our case, in spite of a preserved hepatic function and the good clinical condition of the patient, liver transplantation was decided due to the extensive hepatic involvement associated with portal hypertension. As symptoms, the prognosis of disease varies widely. Whereas some patients present a rapidly progressive disease, others may remain stable for several years. Prognosis of HEH was closely related to the choice of treatment [8]. The 5-year survival rate was 54.5% after liver transplantation, 30% after chemotherapy or radiotherapy, 75% after hepatic resection and was 4.5% without treatment [8]. Spontaneous rupture of HEHE was reported in the literature as a possible life threatening complication [8]. In summary, HEHE has very unclear etiology, diversified symptoms, variable natural history with a highly unpredictable clinical course [17]. In fact, the diagnosis of this tumor is challenging for the pathologist and the management disappointing for the clinician. The history of our patient affords interesting information about the diagnosis and the clinical course of HEHE. The occurrence of a liver tumor in young adults, particularly the presence of multiple intrahepatic tumors associated with good clinical condition and a slow growth pattern can orientate the diagnosis of HEHE. Some suggestive imaging tumoral features such as slow growing lesions in peripheral location, extension to the liver capsule with capsular retraction, a tendency for tumoral nodules to merge with each other and intratumoral calcifications may be diagnostic clues.

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References


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