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Our experience of liver Epithelioid Hemangioendothelioma: from a misdiagnosis to liver transplantation with long term follow-up

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Abstract: Malignant Hepatic Epithelioid hemangioendothelioma (HEHE) is an uncommon vascular tumor of intermediate malignant potential. HEHE is a rare tumor and it is difficult to diagnose for surgeons, hepatologists, radiologists and pathologists. So, misdiagnosis with a delay of the treatment is not uncommon.
We describe a case of a young woman with a diagnosis of HEHE made 6 years after the first evidence of liver mass with a very long term follow-up after surgical treatment.
She had two diagnoses of Hepatocellurar carcinoma (HCC) and a diagnosis of Cholangiocarcinoma after three different fine needle biopsies. After clinical observation, a new laparoscopic core biopsy was performed. In a first time approach, considering clinical and radiological patterns, a diagnosis of Budd-Chiari Syndrome was finally made.
For that the patient underwent an orthotopicliver transplantation (OLTx).
The surgical sample histological analysis allowed a definitive diagnosis of HEHE.
At last, at follow up 7 years after three OLTx the patient is still alive and in good health with no evidence of recurrence.

Keywords: Hepatichemangioendothelioma, liver transplantation, laparoscopic liver surgery

1 Introduction

Epithelioid hemangioendothelioma is an uncommon vascular tumor of intermediate malignant potential. Malignant hepatic epithelioid hemangioendothelioma (HEHE) is a rare variant with an incidence of <0.1 per 100,000 individuals worldwide usually appearing as multiple nodules involving both hepatic lobes and can be misdiagnosed on the basis of its radiologic patterns [1-6]. Origin and pathogenesis of these tumors should be well addressed but some tumors of endothelial cells like hamangiomas, hemangiosarcomas arise from early or late Endothelial Progenitor Cells (EPCs) [7]. Endothelial progenitors express several molecular markers and are involved in angiogenesis processes [8-12]. Nonspecific symptoms such as right upper quadrant discomfort and weight loss are frequent. Also, abnormal liver function and routine laboratory tests are usually inconclusive. Normal serum tumor markers, including AFP, CEA, Ca19.9 and Ca125 do not exclude other primary and secondary liver tumors [3,4]. In the majority of patients, the tumor is first discovered incidentally during imaging studies and the absence of experience of surgeons, radiologists and histopathologists due to the rarity of HEHE can make the diagnosis of this entity very challenging. Misdiagnosis is not a rare event with sometimes catastrophic consequences. We report a case of a young foreign Caucasian woman referred to our Department on April 2006 at the age of 23 years with three previous different misdiagnoses (on three fine needle biopsies and on one laparoscopic

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core biopsy) before the definitive and correct diagnosis of an HEHE was made and a definitive treatment with orthotropic liver transplantation (OLTx) carried out.

2 Case report

A female patient on November 2001 was hospitalized in her country for upper abdominal pain and underwent an ultrasound scan and a CT scan showing a hypertrophic liver with multiple solid bilateral lesions. For this reason a fine needle liver biopsy was performed with a diagnosis of fibrolamellar hepatocellular carcinoma (HCC).

She was in good health condition until May 2003 when a new CT scan showed an increase in number and dimensions of liver bilateral lesions with an invasion of right portal branch, hilar lymph nodes and significant splenomegaly (18 cm of longitudinal diameter). A second fine needle biopsy was performed confirming the previous diagnosis of (HCC).

In March 2004 a third fine needle liver biopsy was performed and a diagnosis of Cholangiocarcinoma was made.

For this reason, the oncologist decided to start chemotherapy with desametasone and cisplatin with no radiological response according to RECIST criteria.

In April 2006 the patient came to our country and was referred to our Department of Hepatobiliary Surgery and Liver Transplantation.

The patient was symptomatic with severe hepatomegaly. Laboratory tests were within normal limits including alkaline phosphatase, glutamyltranspeptidase, aspartate aminotransferase, alanine aminotransferase, bilirubin and Ca 19.9. Hepatitis serology was also negative.

We evaluated the patient by a CT-scan which showed several hypodense solid nodules regarding both liver lobes. These findings suggested the presence of multifocal HCC but without the characteristic CT scan contrast enhancement. A severe splenomegaly associated with portal hypertension was also reported.

An EGDS showed esophageal varices (F2). Hepatic veins occlusion was also observed by a cavography. Based on the above evidence the hypothesis of a suspected HCC on a Budd-Chiari Syndrome was proposed.

For this reason on May 2006 we decided to peform multiple laparoscopic guided core biopsies of the liver to exclude the presence of HCC.

The biopsies analyzed by a senior pathologist showed normal liver so we decided to start an evaluation for OLTx on the basis of a diagnosis of Budd-Chiari Syndrome.

On August 2007 the patient was transplanted with a right split liver with segment 4 from a 20 years old cadaveric female donor with a total ischemic time of 10 hours and 30 minutes.

The patient started an immunosuppressive regimen with steroids and Tacrolimus according to our policy.

The histologic examination (Figure 1) and immunostaining (Figure 2) of the liver indicated the presence of an HEHE.

The postoperative course was characterized by an ischemic necrosis of the segment 4 with sepsis, biliary fistula and biliary peritonitis, so on November 2007 we performed a necrosectomy of the segment 4.

The postoperative course was critical with a severe sepsis and liver failure. Two weeks after OLTx the patient was re-transplanted with a whole liver from a 48 female donor with a total ischemic time of 6 hours and 20 minutes.

The immunosuppressive regimen was continued as above.

Ten days after the second OLTx, due to ahepatic artery thrombosis, we re-confectioned the arterial anastomosis. Two days later the patient underwent a new liver transplant (thirdOLTx) with a whole liver from a 73 years female donor due to the presence of another arterial thrombosis. Total ischemic time was of 7 hours and 30 minutes.

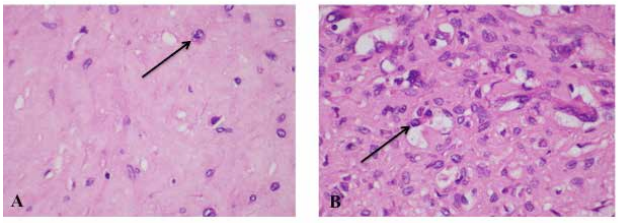

Figure 1: Histochemical features of lesion using Hematoxilin & Eosin-staining. (A)Scantly and abundant myxohyaline stroma. Epithelioid cells appears vacuolized (arrow).Original magnification x 20.(B) Epithelioid cells contained vacuoles signet rings cells-like. Marked nuclear pleomorphism was also observed (arrow). Original magnification x 40.

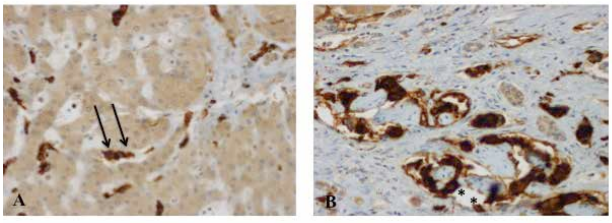

Figure 2: Immunoistochemical findings using ABC/HRP method. A strong immunostaining for CD34 was observed. Neoplastic cells expressed CD34 in sinusoids (arrows) (A) and in the lumen of stromal vessels (asterisks) (B).Original magnification x 20.

The patients had an intraoperative cardiac arrest but the postoperative course was uneventful.

The immunosuppressive regimen was the same of the previous twoOLTx with a steroids withdrawal after 3 months.

At the last follow-up on October 2014 the patient was in excellent health conditions without recurrence.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Informed consent: Informed consent has been obtained from all individuals included in this study.

3 Discussion

HEHE is a very rare tumor with a very low incidence reported for the first time in 1984 by Ishak et al. in a series of 32 patients [4]. It appears more often in women with a male to female ratio of 2:3 during the 4th decade of life [3]. Pathogenesis of these tumors is still unclear. The origin of tumors of endothelial cells was recently demonstrated to be like hamangiomas and hemangiosarcomas from early or late EPCs [7]. EPCs are derived either from the bone marrow and/or the arterial wall to replace dysfunctional endothelial cells [8-12]. EPCs play a pivotal role in blood perfusion of ischemic and tumoral tissues using different mechanisms [13-23].

For its rarity it is impossible to start prospective randomized studies and all the available publications are based on retrospective analysis and/or small cases series.

Many authors stressed the unpredictable course of the disease.

Disease progression varies widely from very low to very long term follow-up with also cases of total spontaneous regression [1,5,24-28].

In most of the cases, the disease is asymptomatic or the symptoms are only mild and unspecific.

The most commonly reported symptoms include abdominal pain or right sub-costal discomfort related to hepatomegaly.

Frequently the disease involves both lobes of the liver with an extra-hepatic extension in 36.6% of the patients [3]. The most commonly extra-hepatic localizations are lungs (8.5%), lymph nodes (7.7%), peritoneum (6.1%), bones (4.9%), spleen (3.2%), and diaphragm (1.6%) [3]. Liver transplantation is the treatment of choice in patients with bilobar intrahepatic lesions spread without an extrahepatic involvement [24].

Nonspecific symptoms and the lack of experience of surgeons, radiologists, and histopathologists, due to the rarity of HEHE, make the diagnosis of this entity very challenging. For these reasons approximately 60% to 80% of patients with HEHE initially are misdiagnosed [1,29-31].

Also, the radiological pattern can mimic other diseases. The disease can be separated in two subtypes regarding the radiological aspect. The nodular subtype is present in early stages and is characterized by the imaging of multifocal hypodense nodules as in our case. Over time, these nodules grow and eventually coalesce, forming large confluent masses preferentially involving the peripheral liver characterizing the diffuse subtype [31].

This heterogeneity regarding imaging features of HEHE leads to a greater incidence of misdiagnosis.

In our case, imaging features included multiple bilobar hypodense lesions but without a characteristic enhancement after contrast injection for HCC with a severe portal hypertension and a caval compression at cavography induced us to make a diagnosis of suspected HCC in patient with a Budd Chiari Syndrome; we excluded the diagnosis of HCC by the mean of laparoscopic core biopsies. Laparoscopic liver surgery is now wide used with very low morbidity in experienced hands [32].

Definitive diagnosis of HEHE requires histopathologic examination and is very challenging on frozen sections. The tumor comprises dendritic and epithelioid cells that often contain vacuoles *signet ring cells*-like representing intracellular lumina. The neoplastic cells are dispersed in a stroma that varies from scanty to abundant. Immunohistochemically neoplastic cells are positive for CD34, an endothelial marker [33]. Usually, epithelioid cells infiltrate sinusoids. In the hepatic parenchyma surrounding the tumor there are areas with Budd-Chiari-like features.

In patients with HEHE, parenchymal abnormalities are irregularly distributed and sampling variability is almost inevitable. Therefore, the specificity of the diagnosis mainly depends on precise tumor localization and a biopsy specimen of sufficient size. In our case the laparocopic biposy was probably done on a site of normal liver surrounding the tumor.

HEHE is characterized by highly variable clinical courses. There are reports of patients succumbing within months after diagnosis in contrast with reports of milder clinical course. For example we founded a patient alive 27 years after diagnosis without treatment and another patient recovering with complete spontaneous regression

[1,34]. However, the indication to an aggressive treatment was documented in the meta-analysis by Mehrabi et al [3] .

The absence of evidence of any kind of tumor induced us to make a diagnosis of Budd-Chiari Syndrome due to the clinical and radiological patterns. Budd-Chiari Syndrome may occur in several conditions with venous occlusion related to hematological disorders or liver tumors as in our case. It is not infrequent that the coalescence of multiple hypodense liver lesions can mimic a Budd-Chiari Syndrome with a delay in the diagnosis [35].

In our case the patient is alive 13 years after the first evidence of the disease (on November 2001) and 7 years after the correct diagnosis and treatment.

Mehrabi et al analyzed the survival rates of 434 patients in relation to the given treatment with a 5-year survival rates. He reported the survival after liver transplantation, local or systemic chemo- and radiotherapy and no treatment of 55%, 30% and 0%, respectively [3]. Although local resection is not excluded from the therapeutic algorithm, it is only feasible in a small portion of patients because the great majority (81%) of patients have multifocal lesions at the time of diagnosis [3].

Lerutet al presented the data from the European Liver Transplant Registry (ELTR) of OLTx in 59 patients with HEHE and an average follow-up of 78.5 months. In 17% of patients, extrahepatic lesions were found before OLTx or during the transplantation [36].

Our patient shows no extrahepatic involvement, even with the extended time period between the beginning of symptoms and the definitive diagnosis and treatment.

Moreover, we can find in the meta-analysis from Mehrabi et al that the most common treatment was OLTx (44.8%) with no absolute contraindications forOLTx even in presence of limited extrahepatic focal lesions. The 1-year disease free survival is the 81.31%.

In the ELTR registry recurrence-free survival observed at 1 year, 5 years, and 10 years of follow-up was 90%, 82%, and 64%, respectively with a recurrence-related mortality of 15.3% (Lerut et al).

Moreover, the ELTR data confirmed that survival was not affected by lymph node metastases, prior treatment, nor the presence of extrahepatic disease [36].

Similar results are reported from the United States experience based on the United Nations for Organ Sharing (UNOS) database about 110 OLTx for HEHE28.

4 Conclusion

HEHE due to is rarity is a very challenging diagnosis. Based on our case report a young female with positive imaging findings with multiple liver hypodense lesions in addition with a good clinical conditions, slow course of the disease, absence of chronic liver disease, normal tumor markers, and normal laboratory parameters should be suggestive for HEHE.

Moreover, and incorrect diagnosis of more severe neoplasm such as Cholangiocarcinoma or HCC can exclude the patients from definitive treatments.

OLTx when feasible is the best option for HEHE with very long term overall and disease free survival.

Conflict of interest statement: Authors state no conflict of interest

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