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Hepatic Epithelioid Hemangioendothelioma: A Case Report of An Extremely Rare Tumour

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Abstract:
Epithelioid hemangioendothelioma is a very rare vascular tumour, with fewer than 500 cases described worldwide. Diagnosis is often multifocal or at an advanced stage with non-specific symptoms. Pathological examination by biopsy is crucial to confirm the diagnosis. The liver is the most frequent site of predilection, followed by the lungs and bones.
The etiology of hepatic epithelioid hemangioendothelioma is poorly understood and is not linked to chronic liver disease, with a heterogeneous and unpredictable course depending on the individual. Given the rarity of this cancer, there are no established treatment standards for this type of tumor of intermediate malignancy. Surgical resection is performed in the case of unifocal disease, and orthotopic liver transplantation remains an option in the case of multifocal and/or unresectable disease, with high survival rates and disease free survival (DFS). Transcatheter arterial chemoembolization (TACE) and chemotherapy/radiotherapy regimens are other treatment possibilities. However, surveillance may be proposed for asymptomatic patients with a slow progression.
We report the case of a patient followed for a multifocal EHE with pulmonary metastases, discovered following pain in the right hypochondrium. Morphological and immunohistochemical examination confirmed the diagnosis of hepatic epithelioid hemangioendothelioma. Given the moderate symptoms, surveillance was recommended for our patient with a good clinical course and radiological stability for 3 years.

Keywords: Epithelioid hemangioendothelioma, Liver, Lung metastasis, Active surveillance, Systemic therapy.

Introduction:

Epithelioid hemangioendothelioma (EHE) is a rare mesenchymal tumor composed of epithelioid or histiocytoid cells with endothelial features of low to intermediate malignancy, which can often be confused with other solitary fibrous tumors such as angiosarcoma[1,2]. It was first described in 1982 by Weiss and Enzinger[3]. 434 cases of HEH have been reported from 1984 to 2006 with only 252 cases of liver primitive disease[1–8]. The median age of onset is 36[9,10], and the incidence remains higher in women than in men [11]. 45.1% of cases have multifocal or metastatic disease at the time of diagnosis, with the liver being the most common site, followed by the lungs and bones[4,12]. The course of epithelioid hemangioendothelioma is variable, ranging from indolent to more aggressive[1,2]. Serous effusions and

bone metastases have been reported as poor prognostic factors[12–14].

Symptoms at the start of the diagnosis are variable and depend on the site of the cancer; in the case of hepatic epithelioid haemangioendothelioma, they include pain (40%), a palpable mass (6 to 24%), and weight loss (9%)[12,15,16]. Admittedly, the majority of patients have asymptomatic disease at the time of diagnosis, and the disease is detected incidentally in the form of a solitary or multifocal mass on imaging[12]. The biopsy is used to confirm the diagnosis by morphological and immunohistochemical study of the expression of endothelial differentiation markers, such as CD31, CD34, factor VIII-related antigen, ERG, and FLI-1[17]. Surgery with complete resection of the tumor or liver transplantation is the first-line treatment for disease localized to the liver, and other treatments such as chemotherapy, radiotherapy, or transarterial chemoembolization may be offered, although active surveillance may be proposed in certain situations.

Case presentation:

We report the case of a young, 25-year-old female patient whose father died of gastric cancer. Since March 2020, she has presented with right hypochondrium pain evolving in a context of moderate deterioration of her general condition, and a thoracoabdominopelvic CT scan was performed. Abdominal CT scans before and after injection of portal contrast showed a liver of normal size and morphology, with regular contours and multiple nodular, well-limited lesions of variable shape and size in the periphery. Some of these lesions are hypodense in spontaneous contrast, and others are isodense in the hepatic parenchyma, but all show annular and centripetal enhancement, delimiting a necrotic center that does not enhance in the portal period (Figure 1).

However, there were no other associated lesions. There was no mass effect on the intrahepatic bile ducts and no peri-lesional oedema. The portal trunk, hepatic veins, and gallbladder were without abnormality. Thoracic scans showed multiple smooth, regularly contoured, randomly arranged bilateral pulmonary nodules and micronodules. A liver biopsy showed a morphological appearance initially suggestive of epithelioid hemangioendothelioma. Immunohistochemical complement confirmed this diagnosis, with anti-CD34 and anti-CD31 antibodies returning positive.

Anti-HBV and anti-HCV viral serologies came back negative. A blood test showed microcytic hypochromic anemia, which was supplemented with iron, and a normal liver function test. In view of the patient's moderate symptoms, it was recommended that she be monitored closely for 3 months, and after 1 year of clinical and radiological stability, she should be monitored every 6 months. The patient is in good clinical condition with stable disease 3 years after diagnosis.

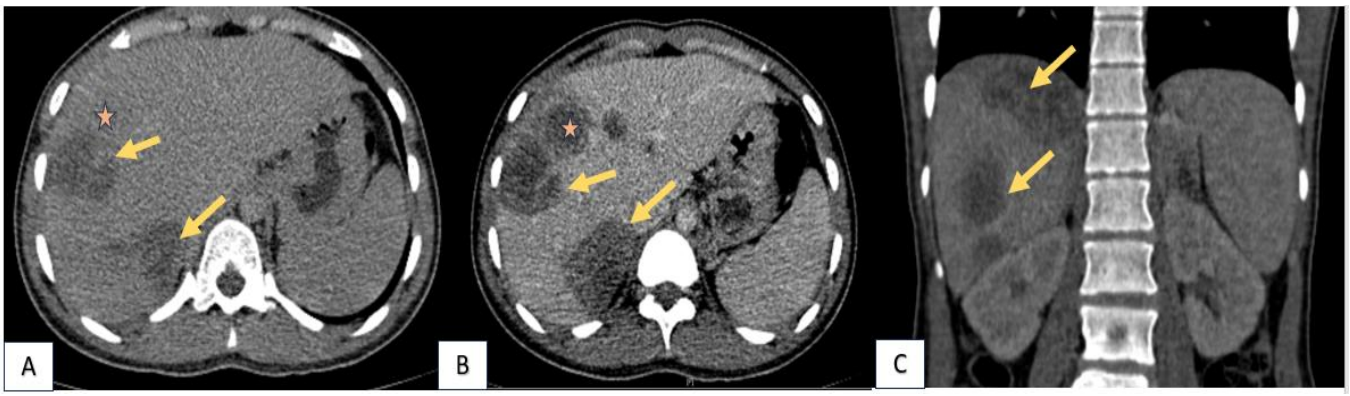

Figure 1: Axial CT sections without injection (A) and after axial (B) and coronal injection (C) show spontaneously hypodense peripheral lesions that enhance in a ring-like fashion after

injection of contrast medium (yellow arrows) and other iso-dense lesions showing the same enhancement as the other lesions (star).

Discussion:

The etiology of hepatic epithelioid hemangioendothelioma remains unknown, despite the involvement of certain risk factors such as alcohol consumption, use of oral contraceptives, exposure to vinyl chloride, asbestos, or the radioactive compound thorium dioxide, major trauma to the liver, viral hepatitis, or primary biliary cirrhosis[6,9].There are no clearly validated pathological or molecular prognostic factors for EHE. It is characterized by chromosomal translocation involving chromosomes 1 and 3; t(1;3) (p36; q25) was detected in epithelioid hemangioendothelioma, resulting in the formation of a WWTR1-CAMTA1 fusion gene in approximately 90% of cases[11].Nuclear CAMTA1 expression is identified in the majority of EHE cases, whereas other epithelioid mesenchymal neoplasms such as benign epithelioid vascular tumors, epithelioid angiosarcoma, and epithelioid sarcoma are negative for CAMTA1[18],and 10% of cases are characterized by YAP1-TFE3 gene fusion[19]. In our patient, genetic testing could not be performed, so the diagnosis was made on the basis of immunohistochemical, histological, and imaging characteristics. As in our case, it has been shown that multinodular lung involvement is associated with longer survival, unlike the pleural form[14]. No standard treatment strategy has yet been defined. Active surveillance is recommended as a first-line treatment for asymptomatic metastatic, locally advanced, or inoperable EHE[20], or in patients for whom surgery is not an option due to co-morbidities or technical problems[21]. And although active surveillance has never been formally studied, some experienced centers are considering it as a therapeutic option before starting treatment[12,13,16,20]. In a group of 15 patients with hepatic EHE, prolonged disease stability in 33% of patients and regression in 40% were reported by Onishi et al.[22] .Furthermore, Kitaichi et al. also showed spontaneous tumor regression in three of 21 patients (14.3%) followed by metastatic EHE in the lung[23]. Another patient had a complete response to his EHE under simple monitoring in 12 months, with no signs of recurrence for at least 16 months after confirmation of complete regression of the lesions[24]. In addition, 4 patients underwent active surveillance with a follow-up of 61.4 months, with only one patient dying more than 10 years after diagnosis at the age of 85 [25]. The mechanisms of spontaneous regression of EHE remain unknown and probably involve immune mechanisms in the development and regression of this disease[9,21]. A complete surgical resection is proposed for patients with stable unifocal disease with an indolent course or limited locoregional involvement for whom surgery would not be too morbid. However, in the case of unresectable, symptomatic, and/or rapidly progressive disease, orthotopic liver transplantation may be proposed[21], whose long-term results are excellent, with 10-year survival rates of around 74%[26]. Transarterial chemoembolization (TACE) may be a treatment option for extrahepatic EHE, with better survival and lower morbidity observed in four patients who received TACE compared with five patients who underwent liver resection or transplantation[27]. However, patients with pleural effusion, marked systemic symptoms, or liver failure as a result of the tumor will require systemic treatment, even though no standard medical approach is currently established and the typical protocols used to treat sarcomas have a limited role in this disease[25,28].

In an international retrospective study conducted by twenty sarcoma reference centers, 73 patients diagnosed with advanced EHE who had received systemic therapies were included. 33 patients treated with anthracycline-based regimens, 11 with weekly paclitaxel, 12 with pazopanib, 15 with INF-α 2b, and 27 with other agents (Ifosfamide,Gemcitabine+Docetaxel,Oral Cyclophosphamide) were included.

Anthracycline-based regimens, which are the first-line standard in soft tissue sarcomas, showed low activity in advanced EHE with an ORR of 3% and a m-PFS of 5.5 months; similarly, limited activity was seen with weekly paclitaxel with an ORR of 9% and a m-PFS of 2.9 months; and pazopanib which showed no response with a m-PFS of 2.9 months, while INF-α 2b resulted in an ORR of 7% and a m-PFS of 8.9 months[29]. Cioffi et al. reported no objective response in 16 patients treated with doxorubicin, with a PFS of 4.8 months[27]. Also, Youssaf et al.[25] showed no objective response with antracyclines with only partial response (PR) observed (ORR:3%), with stable disease being the best response with an m-SSP of 5.5 months in 6 patients treated with doxorubicin and 2 patients treated with liposomal doxorubicin. Paclitaxel showed clinical benefit but no objective response, with a median treatment duration of three months in accordance with angiosarcoma[25].

This shows that the treatments indicated for sarcomas are less active, which means that new therapeutic modalities need to be sought, especially in the case of aggressive EHE.

Data on the activity of anthracycline-based treatment regimens are limited. In contrast, 2 responses were reported with doxorubicin in 1997 and 2010, in two patients with metastatic EHE[30,31]. Similarly, two other authors each reported an objective response to liposomal doxorubicin. Kelly and O'Neil described the case of a patient with multifocal epithelioid hemangioendothelioma with bone involvement, treated with liposomal doxorubicin 45 mg/m2 every 3 weeks; the disease was controlled for 24 months before his general condition deteriorated[32]. Grander et al. reported a partial response lasting 18 months in a patient with hepatic epithelioid hemangioendothelioma[33] .

With regard to other therapeutic protocols, prolonged stabilization of 72 months has been reported with gemcitabine in a patient with disease refractory to the doxorubicin-ifosfamide combination[34], a partial response with the carboplatin-pemetrexed-bevacizumab combination[35], and stability in 1 of 3 patients treated with cyclophosphamide-etoposide or cyclophosphamide-vinblastine[25], and three patients received 5-FU in combination with interferon with stable disease as a good response[25].

The use of antiangiogenic drugs has been tested in this group of patients in retrospective studies or small series, given that EHE and angiosarcoma express vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR)[36]. In a phase II study conducted by the Groupe Français des Sarcomes, 2 out of 15 patients with EHE showed partial responses to Sorafenib[37]. Two out of 7 patients had a partial response, and four out of 7 had stable disease on Bevacizumab[38]. On the other hand, no objective response was shown by the use of antiangiogenic agents such as pazopanib, sunitinib, axitinib, or semaxinib, with stable disease being the best response[25]. The last two TKIs have been tested in ongoing clinical trials and have shown prolonged disease stabilization of up to 25 months with clinical benefit[25].

Salech et al.[39] describe a case of a patient with HEH metastatic to the lungs who was treated with oral thalidomide therapy and presented no evidence of disease progression after 9 years of follow-up. In addition, Mascarenhas et al. reported a stable disease as well as symptomatic relief in a case of HEH with extensive pleural and pulmonary metastases treated with thalidomide[40], and Kassam and Mandell[7] incorporated thalidomide to a chemotherapeutic scheme aiming to achieve an anti-angiogenic effect.

Sirolimus, an inhibitor of the rapamycin (mTOR) pathway, was used in 12 patients, which resulted in a high proportion of long lasting tumor responses[41].

Non-steroidal anti-inflammatory drugs and anti-allergic drugs have also shown responses[42–44].

A patient followed for EHE with pulmonary metastases reported a complete remission following initiation of cyclophosphamide CMC at the daily dose of 50 mg for 2 years, then stopped due to hematological complications, and progression was seen 3 months after discontinuation of CMC[45]. Another case of a patient diagnosed with HEH lung metastasis reported by the same author, CMC was introduced in third line and a partial response was achieved during 6 months and treatment interruption was due to recurrence of dyspnea[45].

In 2011,a study assessed the clinical interest of using metronomic cyclophosphamide in 26 advanced or metastatic soft tissue sarcoma, including one metastatic HEH[46].CMC was associated with a 26.9% response rate, and a complete response of the liver metastases of the HEH patient was observed. Altogether, these reports confirm the efficacy of CMC in this rare disease.

Data on selective internal radiation therapy (radioembolization) (SIRT) are lacking, with only one report of a case followed up for diffuse, unresectable multifocal EHE that described a significant remission 2 months after SIRT was performed[47].

More thorough studies are essential to learn more about this extremely rare disease. Clinical trials are limited. Recently, the identification of alterations in FGF-R and ROS1 could lead to the development of targeted treatments[48].

Conclusion:

In this case, the stability of a metastatic EHE in the lung has been demonstrated following monitoring with therapeutic abstention.

Medical oncologists should not over-treat this type of disease, especially in the presence of asymptomatic disease with a slow progression, and should consider inclusion in clinical trials if available. However, in the case of clinically symptomatic or aggressive disease, a therapeutic approach similar to that used for angiosarcoma may be necessary, without necessarily achieving good response rates, but rather stabilizing the disease as a good response without being a therapeutic standard.

Thanks to advances in molecular biology, the majority of EHEs now have a WWTR1-CAMTA1 fusion gene, which may guide future therapies.

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