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Hepatoepithelioid hemangioendothelioma (HEHE): A comprehensive review of pathogenesis, characteristic features, diagnostic strategies and treatment approaches with the emphasis of surgical therapies

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Abstract

Introduction: Hepatoepithelioid hemangioendothelioma (HEHE) is a rare, low-grade malignant vascular tumor that can occur in multiple parts of the body but primarily affects the liver. It is marked by the presence of endothelial cells showing characteristics of both vascular and epithelial cells. The tumor typically appears as a vascularized tumor, displaying different levels of abnormal cell features. Despite developing and improving diagnostic methods, misdiagnosis remains a challenge due to its overlapping features with other tumors which primarily affect the liver.

Aim of Study: This review aims to summarize current knowledge on the clinical and radiological manifestations, diagnostic challenges, and treatment managements of HEHE with a focus on surgical therapies and possible signs of recurrence.

Materials and Methods: A comprehensive review of the literature on hepatoepithelioid hemangioendothelioma was performed using the PubMed database.

Results and Conclusions: Hepatoepithelioid hemangioendothelioma progression is unpredictable, as both benign and malignant variants can occur. Due to its rarity and variability in both clinical and radiological presentation, accurate diagnosis of this tumor is challenging for clinicians. Currently, there is no universally accepted standard treatment protocol as a consequence of low prevalence of HEHE. Despite this, liver transplantation remains a therapeutic management of choice, particularly for patients with widespread or non-resectable disease. Nonetheless, long-term management is essential, involving regular monitoring, imaging studies, and liver function assessments to detect any signs of recurrence or emerging complications. More large-scale, long-term studies are needed to optimize management strategies for HEHE.

Keywords: Hepatoepithelioid hemangioendothelioma, HEHE, liver tumor, orthotopic liver transplantation, liver resection, surgical therapies

HEHE - hepatoepithelioid hemangioendothelioma
EHE - epithelioid hemangioendothelioma
PHVMs - primary hepatic vascular malignancies
Et al. - and others
OCPs - oral contraceptives pills
CA 19-9 - carbohydrate antigen 19-9
AFP - alpha-fetoprotein
CEA - carcinoembryonic antigen
US - ultrasonography
CT - computed tomography
MRI - magnetic resonance imaging
LRx - liver resection
LTx - liver transplantation
FNA - fine needle aspiration
IHC - immunohistochemistry
HCC - hepatocellular carcinoma
Arg-1 - Arginase-1
HepPar-1 - Hepatocyte Paraffin-1

CK – cytokeratin

OLT - orthotopic liver transplantation

RFA - radiofrequency ablation

MWA - microwave ablation

SBRT – stereotactic body radiotherapy

TACE - transarterial chemoembolization

OS - overall survival

DFS - disease-free survival

ELTR - European Liver Transplant Registry

MILS - minimally invasive surgical techniques

VEGF - vascular endothelial growth factor

IFN-α2b - interferon-alpha 2b

1. Introduction:

Hepatic epithelioid hemangioendothelioma (HEHE) is a rare, low-grade malignant vascular tumor characterized by epithelioid and histiocytoid endothelial cells embedded within a myxoid or fibrotic stroma. It is considered a liver-specific variant of epithelioid hemangioendothelioma (EHE), a broader category of vascular neoplasms, distinguished by its exclusive localization within the hepatic parenchyma. Although the exact etiology of HEHE remains unclear, it is hypothesized to originate from endothelial progenitor cells capable of differentiating into both endothelial and epithelioid-like phenotypes. HEHE, alongside angiosarcoma and hemangiopericytoma, belongs to the group of primary hepatic vascular malignancies (PHVMs), collectively accounting for less than 1% of all hepatic tumors [1].

While HEHE primarily affects the liver, extrahepatic metastases may occur, most commonly involving the lungs, peritoneum, lymph nodes, and bone marrow [2,3,5,8]. One of the major challenges in HEHE management is the limited availability of large-scale, long-term studies, which hinders the establishment of standardized diagnostic and therapeutic protocols. Current evidence is largely derived from case reports and small series, leaving many aspects of the disease - particularly its clinical behavior and optimal management - poorly defined. The aim of this review is to

provide a comprehensive overview of the pathogenesis, clinicopathological features, diagnostic methods, and therapeutic strategies in HEHE, with particular emphasis on surgical treatment modalities and indicators of recurrence.

2. Epidemiology:

Primary hepatoepithelioid hemangioendothelioma is a rare vascular tumor, with an incidence of less than 0.1 per 100,000 population [4]. The disease was first described in 1984 by Ishak et al. in a case series involving 32 patients [7]. Epidemiologically, HEHE most commonly affects middle-aged individuals, with a higher prevalence in women, although it can occur at any age [2]. Clinically, the disease often follows a more indolent course compared to other primary malignant hepatic neoplasms [8].

3. Pathogenesis:

Definitive etiology and pathogenesis of HEHE are not widely understood so far [3]. Exposure to vinyl chloride, asbestos, thorotrast, a history of major trauma to the liver, viral hepatitis, primary biliary cirrhosis, alcohol consumption and the use of oral contraceptives pills (OCPs) have been suggested as potential risk factors for HEHE, although the association remains unclear [1,11-15,19] due to the fact that HEHE cases without medical history of hepatic damage or systemic disease have also been described in the literature [3]. The tumor is characterized by numerous atypical features, encompassing clinical manifestations, radiological imaging, and histopathological characteristics [8].

Despite its usual low malignant potential and more indolent clinical course of the disease compared to other PHVMs neoplasms, the absence of definite risk factors does not allow to outline a solid and cost-effective screening program in target populations. For these reasons, about 30% of patients present diffuse or metastatic disease at the time of diagnosis [3,4,22,23].

4. Characteristics of HEHE:

In recent years, increasing efforts have been made to better characterize the clinical course, radiologic features, and therapeutic strategies associated with HEHE. However, current understanding of this rare malignancy remains limited due to the scarcity of available data [18]. Given the highly variable and unpredictable nature of HEHE progression, contemporary research has focused on enhancing diagnostic accuracy - particularly in distinguishing HEHE from other primary hepatic tumors - to inform and optimize treatment planning. Prognostic factors for HEHE are still not well established. Nonetheless, some studies suggest that the presence of clinical symptoms at diagnosis, advanced patient age, and elevated serum CA 19-9 levels may be associated with poorer outcomes [26].

4.1 Clinical features:

The core problem of identifying HEHE is that 25% of patients reported in the literature are asymptomatic [17]. In numerous instances, the lesions are discovered incidentally during imaging performed for unrelated indications, in the absence of prior hepatic disease or systemic illness. Clinical symptoms are often nonspecific and may manifest with abdominal discomfort especially right upper quadrant pain, hepatomegaly, jaundice, unintentional weight loss and also less common are weakness, anorexia, epigastric mass, ascites, nausea/emesis, and fatigue [3,8].

Some patients may also exhibit biochemical evidence of liver dysfunction, such as elevated hepatic enzymes and other parameters that assess the function and health of the liver. The most frequently elevated parameters included alkaline phosphatase, γ-glutamyl transpeptidase, aspartate aminotransferase, alanine aminotransferase, and bilirubin. Common tumor markers - such as alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA 19-9) remain within normal limits in most patients, indicating limited utility in diagnosis beyond excluding other primary or metastatic hepatic malignancies [8]. In some cases, complications such as portal hypertension may occur [10].

According to the analysis of 23 HEHE cases reported between January 2015 and December 2020 metastasis may be most commonly presented in the lung, regional nodes, peritoneum, and ascitic fluid [4]

4.2 Radiological features:

HEHE typically presents as incidentally discovered multifocal lesions with peripheral or subcapsular growth pattern [3] exhibiting heterogeneous contrast enhancement across both lobes [1,16]. As the disease progresses, the lesions may grow and coalesce into larger and more-complex masses. These characteristic features of HEHE allow us to divide the disease into two types - nodular and diffuse [3]. The nodular type of HEHE indicates an early stage of the disease compared to the diffuse type, which is characteristic of an advanced stage of the tumor [8].

The first examination that tends to be done is abdominal ultrasonography (US). It may reveal multiple nodules or scattered areas of decreased echogenicity compared with the liver parenchyma. Furthermore, the most common type of echogenicity in imaging of this mass is a hypoechoic pattern [8]. US is not the first-line examination for the diagnosis due to HEHE's nonspecific appearance in this examination.

Computed tomography (CT) imaging typically reveals that the tumor originates as multiple discrete hepatic nodules, which progressively enlarge and coalesce into confluent masses, with a predilection for peripheral hepatic distribution. Advanced disease is often accompanied by hypertrophy of uninvolved liver segments and splenomegaly. Hepatosplenomegaly is the consequence of mechanisms of compensation and reflects the extensive hepatic involvement [16]. In the computed tomography with contrast, nodules (<2 cm) typically exhibit homogeneous enhancement rather than the larger lesions which demonstrate peripheral or heterogeneous enhancement [23].

Noncontrast computed tomography imaging shows lesions with low-density, and subcapsular ones may show associated capsular retraction [3,4]. Retraction of the liver capsule because of fibrosis and compensatory hypertrophy of the unaffected liver segments may be diagnostic clues. Calcifications or cysts are less commonly seen [3].

Usually there are no specific imaging features of the nodular type of HEHE in CT but diffuse type is much more suggestive if following criteria are met.

Characteristic imaging features of the diffuse type in CT:

- large and slow-growing tumor
- peripheral distribution in the liver
- no bulging of the liver capsule
- peripheral enhancement of contrast
- hypervascularized, central lesions with a tendency to merge
- no sign of the portal or hepatic veins
- compensatory hypertrophy of the unaffected liver segments
- portal hypertension
- splenomegaly
- calcifications

Furthermore one of a few HEHE features, but still worth mentioning because of its specific correlation with the tumor and the fact that it may be discovered in CT scanning is “lollipop sign”. It is described by a series of case reports and it is thought that it is caused by an enhancing vein terminating at the periphery of a hypodense mass [3,4].

Another possible imaging examination is magnetic resonance imaging (MRI). In MRI the lesions are typically hypointense on T1-weighted image and heterogeneous to hyperintense on T2-weighted image [3,8,23].

Scintigraphic imaging techniques with ^{99m}Tc, gal-lium-67, and indium-leukocyte also have been useful in the diagnosis of HEHE. Low-uptake pattern has been demonstrated through the majority of analysed HEHE cases. Scintigraphy shows the areas affected by the disease with no or barely no perfusion, and the areas with normal perfusion do not show any signs of involvement by the tumor.

The examination may be performed in patients who have contraindications to the use of iodine radiomarkers administering during CT [8]. Moreover, scintigraphic imaging may play a valuable role in the staging process for patients undergoing liver resection (LRx) or particularly liver transplantation (LTx) [8].

4.3 Histopathology and cytology:

Macroscopically, hepatoepithelioid hemangioendothelioma typically presents as multifocal hepatic nodules with ill-defined margins. The lesions may vary in color,

appearing white, light brown, yellow, or yellow-brown. On palpation, the nodules usually exhibit a firm to rubbery consistency. The cut surface may demonstrate a gritty texture, particularly in cases with calcifications. The tumor is often multifocal, with individual lesions ranging in size from 0.2 cm to 18 cm. Although the size of a single lesion can vary considerably, the average diameter reported is approximately 5.6 cm.

On core needle biopsy, HEHE exhibits an infiltrative growth pattern composed of a heterogeneous population of neoplastic cells, including epithelioid, dendritic, and intermediate forms.

A characteristic histopathological feature of HEHE is the infiltration of hepatic sinusoids by tumor cells, which often leads to hepatocellular atrophy [1,3,4]. The extracellular matrix is typically abundant. In older or more advanced lesions, features such as sclerosis, calcification, and necrosis may be observed. Accordingly, HEHE is often mistaken for sclerosing hemangioma or sclerosing forms of adenocarcinoma, including cholangiocarcinoma [8]. Progressive stromal fibrosis is commonly seen and is hypothesized to contribute to the tumor's indolent clinical course.

According to Ishak's hypothesis, although the neoplastic cells recapitulate primitive vascular structures, the dense sclerosis induced by the tumor may occlude or obliterate native hepatic vasculature. Consequently, the tumor cells may become deprived of their blood supply, potentially limiting further progression [3].

Fine-needle aspiration (FNA) cytology of HEHE remains poorly documented in the literature, with available data primarily limited to a series of case reports [3]. Cytologic smears are typically described as paucicellular to moderately cellular, containing spindled and epithelioid cells, either isolated or arranged in clusters. The cytoplasm of neoplastic cells may range from scant to abundant, while nuclei are generally round to oval, often with multiple small nucleoli [3]. Despite these cytomorphologic findings, no definitive correlation between histological features and clinical course has been established for hepatic lesions, including HEHE [3].

HEHE typically expresses endothelial markers, which support its vascular origin. It stains positive for CD31, CD34 by immunohistochemistry (IHC). The expression of factor VIII-related antigen (von Willebrand factor) which is the evidence of endothelial differentiation may be observed in almost 100% of cases, but the degree of staining between cells within a lesion can be highly variable. Immunohistochemical

staining for the endothelial markers CD31 and CD34 are positive in 94% and 86% of cases, respectively [3,8,24]. Other IHC stains that can be positive include factor XIIIa, vimentin, and type IV collagen [3].

4.4 Molecular patterns:

Molecular studies have contributed significantly to the characterization of HEHE, offering insights that may enhance diagnostic accuracy and facilitate the development of more personalized therapeutic strategies. Given the genetic heterogeneity of HEHE, incorporating molecular profiling into the differential diagnostic process is of particular importance. A study analyzing 39 cases of epithelioid hemangioendothelioma identified two principal molecular subtypes: the more prevalent WWTR1-CAMTA1 fusion and the less common, but clinically more aggressive, YAP1-TFE3 fusion [1,4,28].

The translocation t(1;3)(p36.3;q25), which leads to the WWTR1-CAMTA1 fusion gene product, is the most frequently observed genetic alteration in HEHE and is typically associated with a more indolent disease course [3]. Immunohistochemical analysis has shown that nuclear expression of CAMTA1 is present in the majority of HEHE cases, whereas other epithelioid mesenchymal tumors generally lack this marker, making it a useful diagnostic tool in equivocal cases. [29].

However, despite the association of the WWTR1-CAMTA1 fusion with slower disease progression, studies have not demonstrated a significantly improved prognosis in affected patients [4]. This suggests that while molecular subtyping aids in the classification and understanding of HEHE, it may not yet serve as a reliable prognostic indicator on its own.

5. Diagnostics:

The diagnosis of HEHE remains difficult due to the lack of specific clinicopathological features, characteristic features throughout the imaging studies and the comprehensive data in the existing literature [10,18]. Unfortunately, diagnostic inaccuracies are common in cases of HEHE, as reported multiple times in the literature. Importantly hepatic nodules may be misinterpreted. In this paper researchers

showed that malignant cell clusters were misdiagnosed as normal hepatocytes and it may finally lead to delayed diagnosis and initiation of appropriate therapy [11].

Although an increasing number of studies suggest that specific imaging features may aid in the identification of HEHE, a definitive diagnosis still requires histopathological confirmation via liver biopsy, as imaging alone is insufficient to reliably differentiate HEHE from other hepatic lesions [1,5,6]. A critical step in establishing an accurate diagnosis of HEHE is the detection of factor VIII-related antigen (von Willebrand factor) expression, which serves as a key marker of endothelial differentiation. Nonetheless, tumor histology, including nuclear pleomorphism and mitotic count, has limited prognostic value, as it does not reliably reflect the biological behavior of the neoplasm [15]. Notably, the typically low mitotic activity observed in EHE may serve as a helpful feature in its differential diagnosis [38].

One study suggested a potential correlation between the mitotic activity of tumor cells and the tendency of HEHE to exhibit aggressive behavior. However, this association has not been conclusively established, highlighting a need for further investigation to clarify the prognostic relevance of mitotic activity in this rare vascular malignancy [15].

6. Differential Diagnosis:

Due to its non-specific imaging characteristics and the absence of distinct serological markers HEHE may be misdiagnosed as other hepatic tumors, including both benign and malignant entities. It is estimated that in 60% to 80% of cases, HEHE is not diagnosed and cannot be treated properly [8]. Its radiological appearance can mimic metastatic disease or other vascular lesions. The most common misdiagnoses include hepatocellular carcinoma (HCC), angiosarcoma, cholangiocarcinoma, sclerosing hemangioma and metastasis of another cancer [4,8,12,15].

In the differential diagnosis of HEHE versus metastatic tumors, it has been observed that on hematoxylin-eosin staining, HEHE tends to preserve portal tracts and exhibits a pattern of intravascular growth, whereas metastatic carcinoma typically does

not. This histological feature may serve as a valuable diagnostic clue supporting the identification of HEHE [3].

It has been demonstrated that the use of hepatocellular markers such as hepatocyte paraffin-1 (HepPar-1), Arginase-1 (Arg-1), and Glypican-3 can aid in the differential diagnosis, as these markers are highly sensitive and specific for hepatocellular carcinoma - especially Arg-1, which was not positive for any cancer other than HCC in the study. These markers are typically negative in HEHE, which helps to distinguish it from HCC [37].

Furthermore, the observation that cytokeratin (CK) expression - particularly CK AE1/AE3, CK8/18, CK19, and CK7 - can be either negative or only focally and weakly positive in HEHE may aid in differentiating it from metastatic carcinomas [38]. However, the potential for cytokeratin positivity in HEHE poses a diagnostic challenge, as it may lead to misclassification as an epithelial neoplasm, particularly in distinguishing it from metastatic adenocarcinomas or cholangiocarcinoma [4,38]. Immunohistochemical analysis and staining for epithelial differentiation markers plays a critical role in differentiating HEHE from other neoplasms.

7. Treatment:

Liver resection (LRx), orthotopic liver transplantation (OLT), radiotherapy, chemotherapy, hormone therapy, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and surveillance are among the therapeutic options available for the management of HEHE [20]. Due to the rarity of this tumor, an optimal and standardized treatment strategy has yet to be clearly defined. The therapeutic approach should be tailored to the individual patient, taking into account the anatomical location, tumor size, number of nodules, the presence of vascular invasion, the presence of extrahepatic disease, rate of disease progression, the severity of clinical symptoms, and the patient's response to prior treatment [8,39]. Surgical intervention - particularly LRx and LTx - has been associated with favorable long-term survival in selected patients. However, surgery is not feasible in all cases, primarily due to the multifocal nature of the disease or anatomical constraints that preclude

complete resection [8]. Analysis of the available literature suggests that key factors guiding treatment selection include tumor size, number of lesions, extent of dissemination, growth rate, presence of systemic symptoms, and the feasibility of achieving clear surgical margins. These parameters help determine whether LRx, LTx, or conservative management is the most appropriate strategy [1].

7.1 Surgical treatment:

The choice of surgical modality is primarily determined by the stage and extent of the disease [35]. Initial case series of HEHE were published in the early 1990s, and since then, both radical LRx and OLT have emerged as first-line treatment options. LRx is typically considered for patients with localized and resectable disease, whereas OLT is reserved for those with unresectable or multifocal tumors.

Due to the rarity of HEHE, most recent studies are retrospective clinical analyses, as prospective trials remain largely unfeasible. This limitation significantly hampers the development of standardized clinical management guidelines. Nevertheless, several studies - including the analysis by Grotz et al. [19] - have compared overall survival (OS) and disease-free survival (DFS) between patients undergoing LRx and those treated with OLT.

LRx demonstrated 5-year OS and DFS rates of 86% and 62%, respectively, while LTx achieved corresponding rates of 73% and 46%. Data from the research paper by Mehrabi et al. (2006) further support the efficacy of surgical interventions in the management of HEHE, reporting 5-year survival rates of 54.5% following LRx and 75% following LTx [8]. In a more recent study, Noh et al [44] evaluated 79 HEHE patients.

The results indicated that surgical treatment (LRx or LTx) had significantly higher 5-year survival rates than those who underwent non-surgical treatment (88% vs 49%). Collectively, the available evidence underscores that surgical intervention remains a highly important therapeutic approach in the management of resectable HEHE and offers favorable outcomes in appropriately selected patients [21].

7.1.1 Orthotopic liver transplantation (OLT):

Hepatoepithelioid hemangioendothelioma is often characterized by a multifocal or diffuse pattern of hepatic involvement, which frequently renders surgical resection infeasible due to the number or anatomical distribution of lesions. In such scenarios, OLT is regarded as one of the primary therapeutic strategies.

Due to the lack of well-designed, long-term studies involving large patient cohorts, and the limited feasibility of prospective study designs, most therapeutic approaches remain largely experimental. However, LTx is widely regarded as the preferred nonoperative treatment for HEHE, particularly in cases with multifocal or bilobar hepatic involvement [1,5,35]. Accordingly, OLT is recommended for patients with bilobar HEHE, even in the absence of cirrhosis, despite challenges such as limited donor availability and the risks associated with long-term immunosuppression [2,12–14,19]. Furthermore, LTx should be considered at an earlier stage of the disease, particularly in younger patients and those with substantial intrahepatic tumor burden, given the high probability of recurrence following LRx.

Previous data indicate that survival rates post-transplantation for HEHE are generally positive. Data from the European Liver Transplant Registry (ELTR) support this position, indicating that post-transplant survival outcomes in HEHE patients are highly favorable. According to the ELTR, the 5-year survival rate following LTx for HEHE is approximately 80%, with a recurrence rate of 24.8% [8].

A retrospective study evaluated the efficacy of LTx with regard to long-term survival and the risk of disease recurrence. The study included 18 patients who underwent OLT between 2000 and 2018. Transplantation was indicated based on the multifocal nature or extensive intrahepatic spread of the tumor. The mean post-transplant follow-up period was 65 months. Survival outcomes were favorable, with rates of 94% at 1 year, 82.6% at 5 years, and 41.3% at 15 years. Importantly, no cases of recurrence were observed during the follow-up period.

These findings support the notion that LTx can achieve durable, recurrence-free survival in patients with HEHE - even in the presence of extrahepatic metastases, such as to the lungs - provided there is no evidence of overt tumor aggressiveness. In light of the limited efficacy of available systemic therapies, OLT should be considered the treatment of choice for carefully selected patients with advanced HEHE [5].

Further evidence from other studies has focused on evaluating survival outcomes, recurrence patterns, and prognostic indicators following OLT [35]. These data confirm that long-term remission is attainable, even in cases with extrahepatic dissemination—an outcome rarely observed in oncology. Importantly, prognostic factors such as vascular invasion, lymph node metastases, and a short interval between diagnosis and transplantation were identified as significant predictors of post-transplant recurrence. Therefore, these parameters should be carefully considered in the selection process for transplantation candidates [35]. Other authors have also emphasized that OLT significantly improves prognosis in HEHE patients [18].

The three main risk factors for post-transplant recurrence in HEHE include microvascular invasion, short waiting time for transplantation (≤120 days), and lymph node invasion at the time of OLT. These factors are incorporated into the HEHE-LT score, which stratifies patients into low and high-risk groups. This scoring system helps guide post-transplant management. Patients with a score between 0 and 2 had a significantly better 5-year DFS than patients with a score of 6-10 (93.9% vs 38.5%) [43].

In terms of surgical technique, the authors also point to the growing importance of minimally invasive surgical techniques (MILS) – such as laparoscopy or thoracoscopy – in HEHE resections [35]. These methods offer similar oncological results with a lower rate of complications, shorter hospitalization time and faster recovery [35].

7.1.2 Liver resection (LRx):

A pivotal 1996 study analyzing 127 previously reported cases demonstrated a 5-year OS rate of approximately 55.5% among patients treated with radical LRx or OLT - a markedly superior outcome compared to other primary hepatic malignancies [9]. This favorable prognosis established surgical intervention as a key therapeutic strategy in HEHE management.

However, subsequent case reports have described instances of rapid disease progression following partial LRx. This paradoxical response may be explained by the tumor's sensitivity to hepatotropic growth factors, which are released during the liver regeneration process and could potentially stimulate tumor proliferation [30].

Nevertheless, surgical resection remains the standard of care for patients with resectable disease, provided that anatomical and clinical factors permit complete tumor removal [18].

Notably, the most favorable post-resection outcomes are observed in patients with low-grade, small tumors and no evidence of metastasis at the time of diagnosis [1]. Conversely, patients with bilobar or infiltrative disease generally have poorer outcomes due to higher recurrence rates and the more aggressive nature of such tumors.

As a result, LRx is typically reserved for patients with stable or slowly progressing unifocal or limited locoregional disease that is technically resectable [19,39]. The main goal is to achieve complete tumor resection with clear surgical margins. Supporting a more individualized approach, one study suggested that LRx or LTx may be indicated in patients demonstrating disease progression during a short-term observation period (1–3 months), as such progression may reflect a more aggressive tumor phenotype warranting early intervention [31].

Moreover, postoperative monitoring has shown that serum levels of vascular endothelial growth factor (VEGF) - frequently elevated in HEHE patients - tend to decrease following surgical resection. Although this observation suggests that VEGF may serve as a potential biomarker of treatment response, its prognostic value remains uncertain and warrants further investigation [4].

7.2 Systemic treatment:

Currently, no standardized systemic therapies for HEHE are supported by definitive treatment guidelines. Systemic treatment is considered an alternative option in cases of multifocal disease or when surgical intervention is contraindicated. Conventional chemotherapeutic agents, including anthracycline-based regimens, paclitaxel, and pazopanib, have demonstrated limited efficacy in managing HEHE.

Nevertheless, emerging clinical evidence indicates that immunomodulatory and targeted therapies - such as interferon-alpha 2b (IFN-α2b), anti-VEGF agents (including bevacizumab, sorafenib, pazopanib, and thalidomide), and the mTOR inhibitor sirolimus (rapamycin) - may provide clinical benefit in selected patient populations.

A case study investigated the therapeutic outcome of a combined approach involving perioperative IFN-α2b administration and LRx in the treatment of HEHE. In this case, the patient received IFN-α2b both before and after segmental LRx. Clinical follow-up and imaging studies performed over a three-year period post-treatment revealed no evidence of disease recurrence, metastasis, or new HEHE lesions. This favorable outcome suggests that adjunctive immunotherapy may play a role in selected clinical scenarios - particularly when LRx is technically feasible but LTx is contraindicated or unavailable [27].

Despite these promising observations, the overall efficacy of systemic therapy in HEHE remains uncertain and requires further investigation through prospective studies [21].

7.3 Radiotherapy:

Available literature indicates that most cases of radiotherapy were administered in combination with chemotherapy, making it difficult to assess the independent efficacy of radiotherapy alone. The impact of radiotherapy on inhibiting the pulmonary spread of HEHE has been investigated; however, the intervention did not yield a favorable outcome [8,36].

According to global consensus on diagnosis and treatment, stereotactic body radiotherapy (SBRT), a local ablative technique, may serve as a therapeutic option in cases of unresectable unifocal or oligometastatic disease [39].

7.4 Chemotherapy:

Previous studies have demonstrated that unresectable HEHE responds poorly to both chemotherapy and radiotherapy. Nonetheless, thalidomide has exhibited limited clinical benefit in the treatment of metastatic HEHE, presumably due to its antiangiogenic properties [8,26]. During thalidomide therapy, disease stability was maintained, with no radiological evidence of either lesion progression or regression. Furthermore, case reports suggest that multimodal treatment strategies may improve quality of life and potentially prolong survival in selected patients [24].

In addition, there is evidence indicating that primary HEHE may respond to pegylated liposomal doxorubicin [25]. In a case series involving 20 patients, 13

received metronomic chemotherapy regimens consisting of vinblastine, methotrexate, tamoxifen, and propranolol. Serial computed tomography imaging conducted during follow-up demonstrated either disease stability or progression, with no instances of radiologic regression. The median follow-up duration was 24 months (range: 1–72 months), and the reported overall 3-year survival rate was 74.6% (range: 52.8%–100%) [4].

Despite these isolated reports of partial effectiveness, recent systematic reviews confirm that conventional chemotherapy provides minimal therapeutic benefit in the management of HEHE [4,7,8]. Moreover, chemotherapy has been shown to be largely ineffective in patients with disseminated disease [8].

A comparative analysis of treatment modalities - including LRx, LTx, and conservative approaches such as chemotherapy demonstrated that conservative management was associated with the poorest outcomes, with a 5-year OS rate of only 29% [19].

7.5 Radiofrequency ablation (RFA) and microwave ablation (MWA):

RFA and MWA, as well as SBRT, are local ablative techniques that may serve as therapeutic options in cases of unresectable unifocal or oligometastatic disease. Moreover, these modalities may be applied in patients with unifocal lesions who are not suitable candidates for surgery, as well as in individuals presenting with recurrent hepatic nodules following LRx or LTx.

Furthermore, these interventions can function as bridging therapies for patients awaiting LTx [39].

7.6 Transarterial chemoembolization (TACE):

TACE is considered a bridging or palliative treatment option for patients with extensive hepatic involvement who are awaiting LTx or are not immediate candidates for surgical intervention [8]. In one study, 10.2% of patients received TACE, with a reported mean OS of 90.8 months, suggesting a potential survival benefit compared to other non-surgical treatment modalities. However, TACE is not without risks. Its adverse effects - including hepatic decompensation and hypoxia - may upregulate angiogenic factors, thereby stimulating the proliferation of residual tumor cells and

contributing to disease recurrence. Consequently, TACE appears most suitable for patients with preserved liver function and adequate hepatic reserve [41].

To enhance therapeutic efficacy, TACE has been combined with antiangiogenic agents such as IFN-α2b, sunitinib, thalidomide, sorafenib, and bevacizumab. This combination is thought to exert a synergistic effect by reducing angiogenic stimulation and inhibiting neovascularization, thus offering a promising strategy in patients who are either awaiting or ineligible for LTx [41].

7.7 Surveillance:

There are several reports of long-term survival in patients with stable HEHE who did not receive any treatment. Findings from the analysis of these case reports support surveillance without active intervention as a viable management strategy for patients with stable disease confirmed by serial imaging studies. Given the rarity of HEHE, its unpredictable clinical course, and the limited availability of organ donors, a watchful waiting approach may be considered a reasonable initial strategy in carefully selected cases [17].

However, due to the small number of such reports and their anecdotal nature, these cases cannot reliably justify a generalized strategy of active surveillance without initiating treatment. Importantly, there are also documented cases of patients who died within two weeks of diagnosis [8].

At the current stage, the malignant potential of HEHE cannot be accurately assessed early in the disease course, making it critical to initiate the most appropriate and potentially beneficial treatment as early as possible.

8. Postoperative Follow-Up and Recurrence Patterns:

There is currently no standardized protocol for post-transplant monitoring or established recommendations for re-imaging in patients with HEHE following LTx. According to the study by Mehrabi et al. (2006), most recurrences occurred more than two years after transplantation [8]. Three main causes of post-transplant tumor recurrence and treatment failure have been identified: errors during pre-transplant evaluation, accelerated tumor progression under immunosuppressive therapy, and the absence of effective antitumor treatment following surgery [8].

Several risk factors associated with recurrence after LTx include tumor rupture, macrovascular invasion, and the presence of hilar lymph node metastases [39]. Notably, a history of tumor rupture is considered a major contraindication to transplantation due to its strong association with post-transplant recurrence [39].

Despite the limited data in this area, current surveillance strategies typically rely on the optimization of immunosuppressive therapy combined with contrast-enhanced CT imaging every six months [46]. A low-dose immunosuppressive regimen initiated early after transplantation, followed by steroid withdrawal, is recommended to minimize the risk of acute liver rejection, reduce long-term adverse effects, and potentially lower the risk of tumor recurrence. Moreover, this approach supports improved wound healing following the complex surgical procedures involved in LTx.

Given the elevated risk of recurrence, particularly in cases with vascular invasion, the use of the mTOR inhibitor everolimus in combination with a reduced dose of tacrolimus is advised. This dual regimen offers both immunosuppressive and antitumor benefits in the post-transplant setting [47]. Importantly, recurrent graft disease should be managed aggressively, as long-term survival remains achievable in many patients [44].

9. Conclusions:

Hepatoepithelioid hemangioendothelioma is a rare, low-grade malignant vascular tumor that can occur in multiple parts of the body, but primarily affects the liver. It is marked by the presence of endothelial cells showing both vascular and epithelial characteristics. It is usually diagnosed incidentally and has an uncertain prognosis due to the unpredictable clinical course. HEHE most often affects middle-aged individuals, with a higher prevalence in women. Clinically, radiologically, and even histologically HEHE can be mistaken for other benign or malignant vascular and epithelial neoplasms. Therefore, vigilance - along with supportive immunohistochemistry - is essential for accurate diagnosis in biopsy specimens [4].

HEHE is characterized by a more indolent course compared to other primary malignant liver tumors. However, imaging findings are not specific enough to establish a definitive diagnosis [3,4]. Careful evaluation of imaging studies is essential.

CT and MRI examinations are more sensitive than US, so they are recommended as the first-line radiological tools for both the detection and monitoring of HEHE [8].

Nonetheless, imaging alone cannot provide a definitive diagnosis. These modalities may only suggest the presence of HEHE and serve as adjuncts to diagnosis. A final diagnosis requires histopathological examination combined with immunohistochemical profiling, which is crucial before appropriate treatment can be initiated. Misdiagnosis may result in delayed therapy [1]. Immunohistochemical staining for epithelial differentiation markers continues to play a critical role in distinguishing HEHE from other hepatic neoplasms. However, molecular studies have identified two main genetic subtypes of HEHE: the more common WWTR1-CAMTA1 fusion and the less frequent but more aggressive YAP1-TFE3 fusion. These molecular alterations not only correlate with the distinct morphological patterns observed in HEHE but may also carry prognostic significance and suggest the need for a tailored therapeutic approach [28,29]. Given the rarity and heterogeneity of HEHE, diagnostic and therapeutic strategies should be individualized, with consideration of disease progression rate, severity of clinical manifestations, and patient response to prior treatments [4,5].

According to recent studies, surgery remains the main therapeutic approach of HEHE. LRx is preferred for localized, resectable disease, whereas OLT is reserved for unresectable or multifocal tumors. Both treatment modalities require careful patient selection, considering factors such as the patient's overall health status, size of the tumor, and graft availability [4,5].

Although LRx may be beneficial for some patients—particularly those seeking to avoid long-term immunosuppression - it is often limited by the multifocal nature of HEHE and its unpredictable clinical course. Consequently, OLT is generally considered a more effective therapeutic option. Importantly, neither extrahepatic disease nor lymph node involvement are contraindications to LTx [1,32,33]. However, the presence of bone metastases should be regarded as a limiting factor [34].

To date, no universally accepted criteria exist for selecting ideal transplantation candidates. Nevertheless, the development of the HEHE-LT score represents a promising tool, as it stratifies patients according to recurrence risk and may facilitate a more informed and individualized approach to transplantation [43]. Even though

surgical intervention offers the potential for long-term survival, it is not a viable option for all patients. For patients who are not candidates for surgery, systemic therapies may be considered.

However, their efficacy remains limited and is not well established [21]. Furthermore, available evidence suggests that systemic chemotherapy, TACE, RFA, and radiotherapy are largely ineffective and should not be recommended as first-line treatments for HEHE [36]. Future advancements in personalized medicine and the development of targeted therapies may significantly improve outcomes for patients with HEHE and other rare hepatic tumors [18].

Due to the tumor's unpredictable nature and limited treatment options, further research is needed to identify prognostic and predictive biomarkers and novel therapeutic targets [39]. Interdisciplinary collaboration and the establishment of centralized registries will be essential to creating standardized guidelines for this rare but potentially curable disease [1].

Disclosure

Author's contribution:

Conceptualization: [AS],[OM],[KP]
Methodology: [AS],[KB],[ASu]
Software: [AS],[ASu],[KP]
Check: [AS],[ASu],[OM]
Formal analysis: [KB],[ASu],[MP]
Investigation: [AS],[KB],[MP]
Resources:[ASu],[KP],[OM]
Data curation: [AS],[KP],[OM]
Writing - rough preparation: [AS],[KB],[MP]
Writing - review and editing: [KP],[OM],[ASu]
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Declaration of the use of AI and AI-assisted technologies in the writing process:
Artificial intelligence (AI) tools such as ChatGPT were employed in this research to assist in refining the academic English language of the manuscript. Their purpose was to ensure clarity, consistency, and adherence to scientific writing standards. AI tools were used strictly for additional linguistic polishing-focused on proper grammar, style, and clarity of the text in presenting the results. Importantly, these tools were used only as support under the direct supervision of the authors. All final interpretations, classification of findings, and conclusions were determined exclusively by human experts with formal training in clinical medicine. The role of AI was limited to enhancing the efficiency of language refinement, pattern recognition, and data processing, and it did not replace human judgment in the analytical process.

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