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DIAGNOSIS OF HEPATIC EPITHELIOID HEMANGIOENDOTHELIOMA: CHALLENGES AND CURRENT APPROACHES

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Abstract: Hepatic epithelioid hemangioendothelioma (HEHE) is a rare malignant vascular neoplasm with unpredictable clinical behavior and variable morphology, whose incidence is extremely low. Its nonspecific clinical presentation and the absence of specific laboratory markers make diagnosis a major challenge, often leading to errors and delays in treatment. This study aims to critically review the current diagnostic approaches to HEHE, highlighting the main clinical, radiological, histopathological, and immunohistochemical findings. Through a systematic review of the recent literature, evidence was analyzed that reinforces the role of advanced imaging techniques—such as magnetic resonance imaging and PET/CT—and immunohistochemical analysis with endothelial markers (CD31, CD34, factor VIII, among others) in differentiating HEHE from other liver neoplasms. Despite diagnostic advances, early identification still depends on a high degree of clinical suspicion and multidisciplinary integration. The absence of standardized protocols and the rarity of the disease reinforce the need for further clinical studies and international collaboration.

INTRODUCTION

Hepatic epithelioid hemangioendothelioma (HEHE) is a rare malignant vascular neoplasm characterized by unpredictable clinical behavior and variable morphological presentation. With an estimated incidence of only 1 to 2 cases per million inhabitants, HEHE originates from vascular endothelial cells and manifests predominantly in the liver, although it may present systemic involvement in advanced cases. (Kou et al., 2020) Its clinical presentation is highly heterogeneous, posing a substantial challenge for early diagnosis and individualized therapeutic planning. (Atyah; Sun; Yang, 2024)

This neoplasm is part of the spectrum of vascular sarcomas and is classified as a low- to moderate-grade malignant tumor with the potential for systemic dissemination. It can present in solitary, multiple nodular, or diffuse forms, the latter generally associated with a worse prognosis. (Atyah; Sun; Yang, 2024; Kou et al., 2020) The etiopathogenesis of the disease remains poorly understood, and there are currently no systemic agents specifically approved for its treatment, with refractoriness to conventional therapies used for sarcomas being common. (Stacchiotti et al., 2021)

Although imaging methods—such as ultrasonography, magnetic resonance imaging, and PET/CT—contribute to the identification of characteristic patterns of the disease, definitive diagnosis depends on histopathological findings and immunohistochemical confirmation of endothelial markers, such as CD31, CD34, CD10, vimentin, and factor VIII antigen. (Kou et al., 2020) This diagnostic requirement, combined with the rarity of the tumor, makes it difficult to establish standardized clinical protocols, making the management of HEHE highly dependent on clinical experience and specialized centers.

Regarding therapeutic options, hepatectomy and liver transplantation are the most effective approaches in localized cases. In advanced or metastatic situations, some chemotherapy modalities have been used with varying results, although there is no international consensus on the best approach. (Kou et al., 2020; Stacchiotti et al., 2021) In this context, an international consensus meeting promoted by the European Society for Medical Oncology (ESMO) in 2020 brought together experts from several continents to outline evidence-based therapeutic guidelines with the aim of standardizing the clinical management of the disease and optimizing patient outcomes. (Stacchiotti et al., 2021)

Given this scenario, it is imperative to conduct clinical studies and systematic reviews that consolidate existing knowledge about HEHE. This article aims to present a critical and updated review of the main aspects related to the diagnosis of this neoplasm, highlighting its clinical particularities, the challenges in histopathological identification, and the limitations of current therapeutic approaches.

METHOD

This study is a literature review aimed at identifying, analyzing, and synthesizing contemporary diagnostic approaches to hepatic epithelioid hemangioendothelioma (HEH), a rare and difficult-to-detect vascular neoplasm. The search was performed in the PubMed database using the following keywords: "Epithelioid Hemangioendothelioma," "Diagnosis," and "Treatment."

Articles published in the last five years, available in full, written in English, and addressing the diagnosis of HEH from different perspectives, including radiological and histopathological findings and differential diagnostic strategies, were included. Original studies, systematic reviews, case reports with clinical relevance, and guidelines from specialized societies were prioritized.

Duplicate publications, articles outside the scope of the proposed theme, studies focusing exclusively on therapy or animal experimentation, as well as those not indexed in the PubMed database, were excluded. This selection aimed to ensure methodological rigor and up-to-date information, ensuring the quality of the proposed analysis.

RESULTS AND DISCUSSION

The literature review revealed that HEHE presents a highly nonspecific clinical picture, which contributes to delayed diagnosis and a high rate of initial diagnostic error. Approximately 25% of cases are asymptomatic, and about 40% are identified incidentally, often already in advanced stages and with a bilateral or even diffuse multinodular pattern, with extrahepatic involvement in 36% to 45% of patients, including sites such as the lungs, lymph nodes, bones, spleen, and central nervous system. (Atyah; Sun; Yang, 2024)

With regard to imaging tests, HEHE has demonstrated specific characteristics in advanced modalities. Conventional ultrasonography reveals hypoechoic lesions, while contrast-enhanced ultrasonography (CEUS) shows early arterial enhancement with subsequent washout in the portal and late phases, suggesting malignancy. Magnetic resonance imaging (MRI), in turn, showed a typical target sign on T2-weighted images, as well as a sign called "lollipop," related to vascular obstruction associated with tumor growth. Positron emission tomography (PET/CT) with 18F-FDG proved useful in detecting metastases and assessing tumor metabolic activity. Greater uptake was observed in tumors with high cell density, while more fibrotic lesions showed reduced uptake, highlighting its potential application in assessing tumor aggressiveness and therapeutic monitoring. (Kou et al., 2020)

Histologically, HEHE is characterized by nests and strands of epithelioid endothelial cells embedded in myxoid or hyaline stroma, often with intracytoplasmic lumina. The presence of three cell subtypes—epithelioid, dendritic, and intermediate—associated with positivity for endothelial markers such as CD31, CD34, factor VIII, vimentin, and collagen IV was consistent in the studies evaluated. (Kou et al., 2020) Additionally, increased proliferative indices, such as Ki-67 above 10%-15%, correlated with greater tumor aggressiveness.

Immunohistochemical analysis also demonstrated value in differentiating HEHE from neoplasms with similar morphology. Focal expressions of pancytokeratin, the presence of CAMTA1 or TFE3, and the absence

of INI1 loss were useful in distinguishing it from entities such as epithelioid sarcoma ( ), angiomyosarcoma, pseudomyogenic hemangioendothelioma, and malignant mesothelioma. (Stacchiotti et al., 2021)

The diagnosis of HEHE represents a considerable challenge in clinical practice due to its nonspecific clinical presentation, silent evolution, and morphological patterns that mimic other liver neoplasms. The high rate of misdiagnosis reported in the literature—reaching up to 80% of cases—reveals an urgent need for more specific and accessible diagnostic strategies. (Atyah; Sun; Yang, 2024) The difficulties are compounded by the absence of typical laboratory changes and radiological similarity to other liver tumors, such as hepatocellular carcinoma, cholangiocarcinoma, and metastases.

Correct interpretation of imaging findings is critical for the recognition of HEHE. Advances in techniques such as CEUS, MRI with specific agents (such as Gd-EOB-DTPA), and PET/CT with 18F-FDG have contributed significantly to the characterization of hepatic lesions. The presence of a target sign on T2-weighted images and the lollipop sign, described as the abrupt termination of vessels at the margin of the lesion, are relatively specific findings and should be valued in patients with multiple liver lesions of uncertain etiology. (Kou et al., 2020)

In the histopathological field, the epithelioid morphology and cellular heterogeneity of HEHE require careful correlation with immunohistochemical data. The consistent expression of endothelial markers, such as CD31, CD34, and factor VIII, contributes to the diagnosis, although the focal pattern of pancytokeratin can cause confusion with carcinomas. (Stacchiotti et al., 2021) In addition, markers such as CAMTA1 and TFE3, associated with specific genetic fusions, emerge as promising tools in distinguishing HEHE from morphologically similar tumors, such as epithelioid angiosarcoma, where these expressions are absent.

Early identification of HEHE still depends on a high degree of clinical suspicion and integration between clinical, radiological, and histopathological findings. The reviewed literature highlights emblematic cases of diagnostic error with significant therapeutic implications, such as ineffective chemotherapy administration and delays in curative procedures such as hepatectomy or liver transplantation. (Atyah; Sun; Yang, 2024) These reports reinforce the importance of careful differential diagnosis, especially in the face of multifocal liver lesions in young patients or those without liver cirrhosis.

It is concluded that, although advances in imaging techniques and immunohistochemical methods have improved the diagnostic accuracy of HEHE, there is still a long way t to go to ensure the early and correct identification of this rare entity. The standardization of diagnostic protocols, including the use of molecular biomarkers and artificial intelligence-based algorithms, may represent a promising future for improving the diagnosis and prognosis of HEHE.

CONCLUSION

The diagnosis of hepatic epithelioid hemangioendothelioma remains a significant challenge, marked by its nonspecific clinical presentation, similarity to other liver neoplasms, and lack of well-defined clinical protocols. Although advances in imaging and immunohistochemistry techniques have improved diagnostic accuracy, the error rate remains high, highlighting the importance of early clinical suspicion and a multidisciplinary approach.

Standardization of diagnostic methods, including the incorporation of molecular biomarkers and emerging technologies such as artificial intelligence, may represent a valuable tool for the future management of HEHE. Investments in research, specialized training, and collaboration between reference centers are essential to improve patient prognosis and consolidate evidence-based guidelines for this rare neoplasm.

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