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CONTEMPORARY THERAPIES IN THE TREATMENT OF HEPATIC EPITHELIOID HEMANGIOENDOTHELIOMA

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Abstract: Hepatic epithelioid hemangioendothelioma (HEHE) is an extremely rare malignant vascular neoplasm with heterogeneous clinical behavior and difficult therapeutic management. This bibliographic review aims to review the most current scientific evidence on contemporary therapies used in the treatment of HEHE, highlighting the advances and challenges still present in clinical practice. A structured search was carried out on the PubMed database, covering publications from the last five years on the diagnosis, treatment and prognosis of the disease. The results show that although liver resection and liver transplantation remain the main therapeutic strategies, there is growing interest in systemic and locoregional therapies, including antiangiogenic agents, interferon alfa-2B, sirolimus, radiofrequency ablation and transarterial chemoembolization. However, the scarcity of standardized guidelines, the clinical heterogeneity of HEHE and the lack of approved systemic therapies make it difficult to establish uniform conduct and compromise clinical outcomes. This highlights the need to broaden health professionals' knowledge of the disease and to encourage robust research that contributes to the construction of more effective and personalized therapeutic protocols.

INTRODUCTION

Hepatic epithelioid hemangioendothelioma (HEHE) is a malignant vascular neoplasm with heterogeneous clinical behavior and an extremely low incidence, estimated at 1 to 2 cases per million inhabitants, characterized as a low to moderate grade malignant tumor and classified as a translocated and ultra-rare sarcoma, which can vary into three types: solitary, multiple and diffuse (Atyah; Sun; Yang, 2024; Kou et al, 2020; Stacchiotti et al., 2021) Derived from vascular endothelial cells, HEHE has an epithelioid morphology, often accompanied by a fibromyxoid stroma,

and may contain cytological elements such as cells with dense cytoplasm, mild nuclear pleomorphism, nuclear grooves and intranuclear pseudoinclusions, as well as intracytoplasmic lumens. (Atyah; Sun; Yang, 2024)

Although the liver is the most frequently affected site, epithelioid hemangioendothelioma (EHE) can manifest in various organs, including the lungs, bones and soft tissues, showing a widely variable clinical spectrum. (Atyah; Sun; Yang, 2024) This anatomical and histopathological heterogeneity is directly reflected in the prognosis and therapeutic strategies, which are inconsistent given the lack of well-established clinical guidelines. (Stacchiotti et al., 2021)

The obscure etiology is a challenging characteristic of HEHE. The exact involvement of potential risk factors and the mechanism of development have yet to be defined. Relevant genetic alterations such as the WWTR1-CAMTA1 fusion have been investigated; however, they are only applicable as diagnostic markers and their influence on therapeutic efficacy is largely unknown. (Atyah et al., 2024)

Although the etiology and characteristic clinical manifestations of HEHE are unknown, HEHE has a characteristic appearance on imaging, including ultrasonography, magnetic resonance imaging and positron emission tomography/computerized tomography (Kou et al., 2020). The definitive diagnosis of HEHE is based on histopathological analysis and the immunohistochemical expression of endothelial markers such as CD31, CD34, CD10, vimentin and factor VIII antigen, with radiological findings - such as those obtained by ultrasound, MRI and PET-CT - being considered complementary and often suggestive. (Kou et al., 2020), 2020) The disease usually manifests in young female adults, between the third and fourth decade of life, and its presentation can vary from a solitary liver lesion to multifocal or diffuse forms, with degrees of malignancy ranging from low to moderate. (Atyah; Sun; Yang, 2024)

Despite diagnostic advances, the treatment of HEHE remains challenging. Hepatectomy and liver transplantation are still the main therapeutic approaches in resectable cases. However, there are growing reports on the use of chemotherapy and systemic therapies, especially in the face of tumor inoperability or recurrence, offering a promising therapeutic option. Nevertheless, HEHE is refractory to most of the antitumor agents used in conventional sarcomas, which aggravates the therapeutic scenario and contributes to the unsatisfactory results observed in some patients (Kou et al., 2020; Stacchiotti et al., 2021).

Faced with the scarcity of approved treatments and the lack of standardized guidelines, an international consensus meeting organized under the aegis of the European Society for Medical Oncology (ESMO) in 2020 brought together more than 80 experts from different continents with the aim of outlining evidence-based guidelines for the management of primary and metastatic HES. The collaboration also involved representatives of patient groups, such as the EHE Group and the Sarcoma Patient EuroNet (SPAEN), reinforcing the need for a multidisciplinary and patient-centered approach (Stacchiotti et al., 2021).

In view of the above, it becomes imperative to gather and critically analyze the recent literature on hepatic epithelioid hemangioendothelioma, with a special focus on the contemporary therapies available, their clinical outcomes and the challenges yet to be overcome. This article aims to discuss current therapeutic approaches in the treatment of HEHE, contributing to a better understanding of the disease and helping to develop more effective and personalized clinical approaches.

METHODOLOGY

This literature review aims to synthesize the most recent evidence related to diagnostic and therapeutic approaches to hepatic

epithelioid hemangioendothelioma, with an emphasis on the contemporary strategies discussed in the scientific literature. To identify the relevant studies, a structured search was carried out in the PubMed database, covering publications from the last five years. The descriptors "Hepatic epithelioid hemangioendothelioma", "Treatment" and "Diagnosis" were used in combination to ensure the thematic scope of the search.

Articles available in full that directly or indirectly addressed the diagnosis and/or treatment of hepatic epithelioid hemangioendothelioma were considered eligible. Publications in different languages were included, as long as they were accessible, methodologically clear and of recognized scientific relevance. Original studies, narrative reviews and update articles were accepted. Exclusion criteria included duplicate publications, studies outside the proposed scope and articles not available on the PubMed database.

RESULTS AND DISCUSSION

HEHE is a rare malignant vascular neoplasm with variable clinical behaviour and a generally indolent course, which makes early diagnosis and the definition of a standardized therapeutic protocol difficult. The literature shows that the approach must be individualized, taking into account factors such as location, number of liver lesions, presence of extrahepatic metastases and the patient's clinical performance. Therapeutic approaches include liver resection, liver transplantation, locoregional therapies, systemic therapies and even active surveillance in certain selected cases (Stacchiotti et al., 2021).

The absence of treatment guidelines is HEHE's biggest challenge. Generally, surgical approaches are recommended due to the benefits of prolonged survival and improved prognosis. However, only a minority of patients are eligible for resection, while liver transplants face severe donor shortages and long waiting lists (Atyah et al., 2024). Patients with intrahepatic metastases and liver dysfunction may have a worse prognosis compared to those without these conditions. Surgical intervention, whether liver resection or transplantation, may be indicated regardless of the existence of extrahepatic metastasis (Zhao; Yin, 2022).

Resective surgery is considered the first line of treatment in patients with localized and resectable disease, especially in cases of unifocal tumours. When performed with negative surgical margins (R0), resection can offer five-year survival rates of over 70%. On the other hand, in multifocal or bilobar cases, this approach becomes technically unfeasible and other therapeutic alternatives need to be evaluated (Kou et al., 2020). For patients without a surgical option, a variety of non-surgical treatments (such as anti-angiogenic agents, interferon alfa-2B and sirolimus) can be presented with promising potential. However, relevant studies face limitations such as small sample sizes and lack of prospective designs.(Atyah et al., 2024) Meanwhile, no active systemic agents are currently approved specifically for HEHE, which is typically refractory to antitumor drugs used in sarcomas. (Stacchiotti et al., 2021).

Liver transplantation (LT) is widely indicated in cases of non-resectable multifocal disease and is considered one of the few options with curative potential. A multicenter study has shown that patients undergoing HT have an overall survival comparable to that observed in liver resections, even in the presence of stable lung metastases, which suggests that HEHE has a peculiar biological behavior, distinct from other malignant liver neoplasms (Zhao; Yin, 2022).

In some cases, especially when HEHE is slow-growing and the patient is in good clinical condition, active surveillance can be consi-

dered. This approach, although still controversial, has been shown to be valid in well-selected situations, with reports of tumor stability for several years, without the need for immediate intervention (Stacchiotti et al., 2021).

Locoregional therapies, such as radiofrequency ablation and transarterial chemoembolization, have been used adjunctively or palliatively, especially in patients who are not candidates for surgery or transplantation. Although not curative, these modalities can slow down the progression of the disease and improve quality of life (Kou et al., 2020).

In addition to surgical options, the evolving role of systemic therapies has affected the approach to treating unresectable HEHE. Given the inherent vascular component of the tumor and the high expression of vascular endothelial growth factor, numerous studies of anti-angiogenic agents, such as sorafenib, pazopanib and lenvatinib, have been carried out in recent years. Phase I and II clinical trials and series of case reports have shown that all these agents can stabilize tumour growth in situ and, in some cases, even induce partial responses. The latter has recently been used as bridge-based neoadjuvant therapy for liver transplantation with success to avoid toxicity and adverse interactions with post-transplant immunosuppressants in advanced cases without a surgical option (Telli et al., 2020, Kounis et al., 2022).

Another approach under study is the use of immunotherapy. Interferon-alpha 2b (IFN--α2b) modulates both innate and adaptive responses and has demonstrated antitumor effects by transmitters. Used alone or in combination with mTOR-targeted agents sirolimus, IFN-α2b was associated with disease stabilization and in a small subset disease regression (Liu et al., 2022).

In addition, minimally invasive locoregional therapies have been introduced to complement the surgical arsenal. One such modality is irreversible electroporation (IRE). IRE delivers high-voltage electrical pulses to induce cell membrane rupture and apoptosis without the side effects of induced heat seen in thermal ablation. This technique is particularly advantageous in lesions close to larger vascular structures or bile ducts, where standard thermal ablation carries an increased risk of collateral damage. Initial multicenter studies showed high technical success and promising local control with IRE and provided an adjuvant treatment for patients who were not good candidates for most surgeries (Dijkstra et al., 2024).

Finally, the therapeutic choice must be multidisciplinary and patient-centered, taking into account both the biological characteristics of the neoplasm and individual clinical aspects. Despite recent advances, there are still significant gaps in the understanding of HEHE, and more prospective studies are needed to define more consistent prognostic criteria and therapeutic algorithms (Zhao; Yin, 2022).

CONCLUSION

The last decade has witnessed remarkable advances in the diagnosis and treatment of hepatic epithelioid hemangioendothelioma. The introduction and integration of sophisticated diagnostic techniques - including contrast-enhanced ultrasound (CEUS), hepatocyte-specific contrast-enhanced MRI, FDG-PET/CT, ICG-FI and molecular genetic profiling - have significantly increased our ability to detect, characterize and stage this rare vascular tumor. Diagnostic improvements have translated into more precise treatment strategies, allowing doctors to distinguish candidates for curative surgical resection or liver transplantation from those better treated with systemic or locoregional therapies. Emerging therapeutic approaches - notably the use of anti--angiogenic agents, immunomodulatory therapies and non-thermal ablative techniques such as irreversible electroporation - further

enrich the therapeutic arsenal available for the treatment of unresectable or advanced HEHE. Continued research into molecular pathogenesis, developments in imaging technology and ongoing multi-institutional collaborative clinical trials should drive the evolution of personalized treatment protocols. The integration of genetic and radiomic data into prognostic models and treatment algorithms thus promises to refine current management and launch intractable enhancements and immunotherapy therapies. Therefore, the future of HEHE management is set to benefit enormously from continuous innovation and interdisciplinary collaboration, which ultimately translates into improved quality of life.

Despite decades having passed since its discovery, hepatic epithelioid hemangioendothelioma (HEHE) remains a major challenge, both due to its unpredictable clinical behavior and the lack of well-established therapeutic protocols. Increasing knowledge and awareness of HEHE among health professionals is essential to improve the early recognition of this rare tumor and drive the development of more consistent research, as well as the creation of clinical guidelines that effectively guide the management and treatment of affected patients.

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