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Diaphragm epithelioid hemangioendothelioma: a rare case report

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Abstract

Background Epithelioid Hemangioendothelioma (EHE) is an extremely rare malignancy originating from endothelial cells, with an incidence rate of less than 1/100,000. To date, there have been no documented cases of Diaphragm EHE in the English or Chinese literature. EHE can manifest in various organs throughout the body and lacks distinctive clinical features, often leading to misdiagnosis. Given its rarity, there is currently no standardized treatment protocol, management options include radiotherapy, chemotherapy, and targeted therapy. In this report, we present a case study of a 75-year-old male patient who presented with a 6-month history of cough, sputum production, chest tightness, and pleural effusion. A biopsy of the diaphragm mass and immunohistochemical analysis of the pleural fluid confirmed the diagnosis of EHE. The patient underwent chemotherapy combined with targeted therapy, however, unfortunately experienced disease progression.

Case summary In March 2023, a 75-year-old male patient was admitted to our hospital with persistent cough for over two months accompanied by sputum production and chest tightness. The patient was diagnosed with Diaphragm EHE accompanied by pleural effusion and received treatment at our institution. We initiated combination chemotherapy using albumin-bound paclitaxel and cisplatin along with intrapleural infusion of bevacizumab as an anti-angiogenic drug. After one cycle of treatment, significant control over the pleural effusion was observed which prompted us to administer systemic treatment through intravenous infusion using albumin-bound paclitaxel, cisplatin, and bevacizumab. Unfortunately, the patient's condition continued to deteriorate.

Conclusion When accompanied by pleural effusion, EHE often demonstrates rapid disease progression.

Keywords Case report, Rare, Diaphragm, Epithelioid hemangioendothelioma

Introduction

Epithelioid hemangioendothelioma (EHE) is an exceptionally rare form of vascular sarcoma, primarily characterized by the epithelioid subtype. It commonly presents as a low-grade or well-differentiated vascular sarcoma affecting multiple organs including the liver, bones, skin, and soft tissues [1, 2]. This malignancy follows an aggressive clinical course with a tendency for local recurrence and regional lymph node metastasis [1]. It predominantly affects males aged 60–79 years [1, 3]. The clinical presentation and radiological findings of EHE lack specificity [4, 5], leading to frequent misdiagnosis. Consequently,

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diagnosing this uncommon tumor poses significant challenges. The etiology and pathogenesis of EHE remain elusive but may potentially be associated with oral contraceptive usage and abnormal secretion of estrogen and progesterone [2, 6]. In this report, we present the case of a 75-year-old male patient who presented with persistent cough, sputum production, chest tightness, and pleural effusion over a period of six months. A biopsy of the diaphragm mass along with immunohistochemical analysis of the pleural fluid confirmed the diagnosis of EHE. Despite receiving two cycles of chemotherapy combined with targeted therapy, there was progressive disease advancement in our patient.

Case presentation

Chief complaints

In March 2023, a 75-year-old male patient was admitted to the hospital with a persistent cough, sputum production, and chest tightness that had lasted for over two months.

History of present illnes

On March 13th, 2023, the patient underwent advanced computed tomography (CT) scans of the thorax, abdomen, and pelvis, revealing the presence of two mass lesions located on the right diaphragmatic surface. The distinction between the diaphragm, pericardium, adjacent pleura, and liver parenchyma was observed to be unclear. The adjacent hepatic tissue was compressed, and the enhanced imaging demonstrated significant enhancement along the margins, accompanied by irregular internal enhancement. Subsequently, on March 23rd, 2023, the patient underwent a CT-guided biopsy of the diaphragmatic mass. Microscopic examination indicated the presence of a tumor composed of elongated spindle-shaped cells, with areas of necrosis. Immunohistochemical staining demonstrated positivity for CD31, ERG, CD99, CK, Bcl2, and focal positivity for SMA. However, the staining was negative for STAT6, CD34, S-100, Desmin, EMA, WT1, D2-40, Calretinin, BerEP4, TTF-1, NapsinA, and ALK. The proliferative marker Ki-67 exhibited a slightly elevated index of approximately 10%. These findings were consistent with the diagnostic features of EHE, a neoplasm characterized by low-grade malignancy (Fig. 1).

History of past illness

The patient had been diagnosed with type 2 diabetes for over a decade and was currently undergoing long-term glycemic control with acarbose, achieving commendable glycemic stability.

Personal and family history

The patient had a 20-year history of smoking, averaging 10 cigarettes daily, and a concurrent 20-year history of alcohol consumption, ranging from 50 to 100 g per day. Unfortunately, there was no available information regarding the patient's family medical history.

Physical examination upon admission

Height: 174 centimeters, weight: 50 kg, ECOG (Eastern Cooperative Oncology Group) score: 1, NRS (Numerical Rating Scale) score: 2. Upon percussion, bilateral dullness was noted, and upon auscultation, diminished breath sounds were detected.

Laboratory examinations

Clinical examinations indicated no significant deviations in hematological analyses, urinalysis, tumor markers (Carbohydrate tumor CA153: 22.16U/ml; Carbohydrate tumor CA199: 2.18U/ml; Alpha-fetoprotein: 0.79ng/ml; Carcinoembryonic antigen: 1.05ng/ml; Neuron-specific enolase: 40.90ng/ml), or electrocardiography.

Imaging examinations

On March 13, 2023, the patient underwent enhanced CT scans that revealed two mass lesions on the right diaphragmatic surface, measuring 5.8×3.1 cm and 4.8×1.9 cm, with indistinct borders between the diaphragm, pericardium, adjacent pleura, and liver parenchyma. These findings suggested the presence of tumor lesions with potential invasion of neighboring structures and a high probability of bilateral pleural metastasis. The adjacent liver tissue appeared compressed, and enhanced scanning revealed significant enhancement at the edges, accompanied by irregular internal enhancement. The patient exhibited right pneumothorax, resulting in approximately 30% compression of the right lung, as well as a minor pneumothorax on the left side, causing approximately 10% compression of the left lung (Fig. 2). Following two cycles of treatment, the patient experienced disease progression. On May 27, 2023, enhanced CT scans demonstrated an increase in the size of the two masses on the right diaphragmatic surface, measuring approximately 6.3×6.4 cm and 3.1×6.2 cm, with invasion of adjacent structures and potential bilateral pleural metastasis. Furthermore, there was a noticeable escalation in the amount of fluid present in the right pleural cavity compared to previous scans (Fig. 2).

Diagnosis

The patient was diagnosed with EHE, a low-grade malignancy, along with malignant pleural effusion. The clinical staging was performed independently, without reliance on external references.

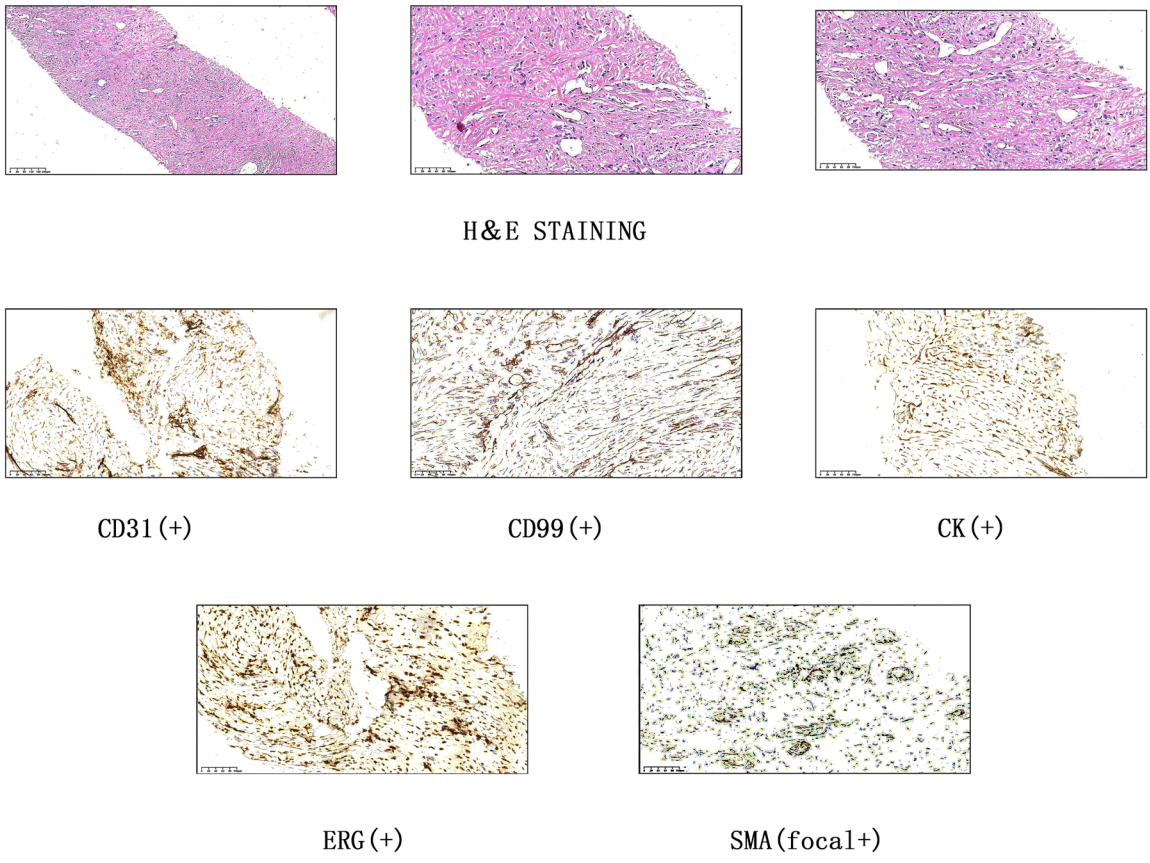

Fig. 1 Pathology results of the biopsy. HE images demonstrated that the epithelioid tumor cells were arranged in cords and beams within a dense collagenous stroma. The tumor cells exhibited a relatively uniform epithelioid morphology, with cytoplasm that was abundant and stained eosinophilic to lightly. Clear cytoplasm, round nuclei, and small nucleoli were observed focally. Additionally, focal areas displayed cellular polymorphism and mitotic figures, while necrosis was also evident in certain regions

Treatment

A multidisciplinary consultation was conducted, which included specialists from general surgery, hepatobiliary surgery, and cardiothoracic surgery. All experts concurred that surgical intervention was not advisable. Additionally, the department of interventional diagnosis and treatment determined that interventional embolization was not a viable option, as the tumor was situated above the diaphragm outside the liver, and there was no clearly identifiable feeding vessel.

On April 3, 2023, the patient underwent thoracentesis to drain the pleural effusion and subsequently received an intrathoracic infusion of 300 mg of bevacizumab. On April 5, 2023, chemotherapy was administered, consisting of 400 mg of paclitaxel albumin-bound and 90 mg of cisplatin. On April 30, 2023, the patient received systemic treatment with 400 mg of paclitaxel albumin-bound, 90 mg of cisplatin, and 375 mg of bevacizumab. All these treatments were conducted at the prestigious Chengdu Fifth People's Hospital.

Outcome and follow-up

After completing two cycles of treatment, CT scans indicated disease progression, evidenced by the enlargement of the diaphragmatic tumor and an increase in pleural effusion. The patient reported increased breathlessness. A thoracentesis procedure was subsequently performed, and pathological examination revealed a small number of atypical epithelioid cells. Immunohistochemically, these cells were positive for CD31, focal ERG, and CK, with a Ki-67 index of around 30%. However, they were negative for CEA, TTF-1, D2-40, and MC. The morphological features and immunophenotype of the tumor cells were consistent with those of EHE. The patient then underwent transarterial embolization of the diaphragmatic tumor at a different medical facility. A month later, on July 5, 2023, enhanced CT scans showed the presence of two slightly high-density masses on the right diaphragmatic surface, measuring approximately 11.6×5.9 cm and 7.0×3.0 cm, with signs of invasion into adjacent structures. Bilateral pleural metastasis and potential lymph node metastasis in the bilateral cardiophrenic angle were also observed.

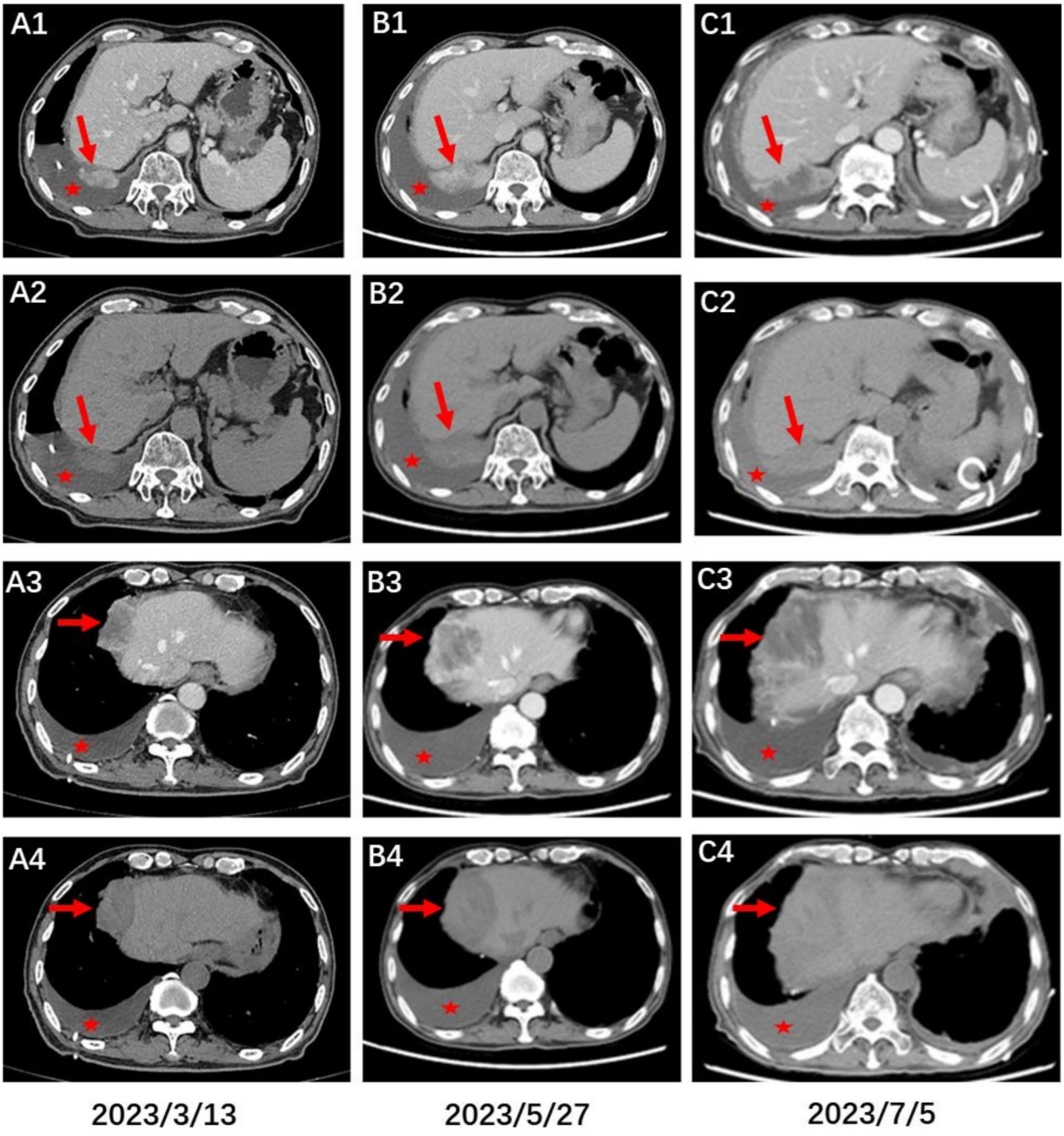

Fig. 2 Changes in right diaphragmatic tumors during treatment on CT scans. A1-4 exhibited two mass lesions (A1, A2, A3, and A4; denoted by red arrows) on the right diaphragmatic surface in both non-contrast CT scans (A2, A4) and contrast-enhanced CT scans (A1, A3). These were accompanied by right pleural effusion (marked by red asterisks). Following two cycles of treatment, B1-4 revealed enlargement of the two mass lesions (red arrow) on the right diaphragmatic surface and an increase in right pleural effusion (A1, A2, A3, and A4; indicated by red arrows). One month later, C1-4 demonstrated further enlargement of the two tumors on the right diaphragmatic surface (red arrows) and a further increase in right pleural effusion (red asterisks)

Additionally, partial destruction of the ribs and sternum on the left side, along with possible bone metastasis, were noted (Fig. 2). The assessment of treatment efficacy indicated further disease progression. Tragically, the patient passed away on July 23, 2023, with a Progression-Free-Survival (PFS) of less than one month and an Overall Survival (OS) of four months.

Discussion

EHE, an exceptionally rare and invasive neoplasm, primarily presents in the dermis and connective tissues [7]. Instances of EHE occurring in the diaphragm are exceedingly rare. Currently, the prevalence of EHE stands at less than 1 per 100,000 [8]. However, an analysis conducted by Liu et al. [1] on the SEER database, the largest publicly accessible patient cohort, revealed an incidence rate of approximately 0.23 per 100,000. This study also indicated a higher occurrence among individuals aged 60–79, predominantly males, while being infrequent in children. Our patient, a 75-year-old male, aligns with this demographic profile.

Currently, there is a scarcity of comprehensive descriptions concerning the imaging characteristics of EHE, due to its tendency to manifest in various organs throughout the body, with the liver, lungs, and bones being the most commonly reported sites. The specific computed tomography (CT) and magnetic resonance imaging (MRI) features of EHE located in the diaphragm have yet to be fully elucidated. In this particular instance, the lesions were delineated as consolidated masses with slightly increased density on the right diaphragmatic surface. To prevent potential misdiagnosis or oversight of this condition, numerous scholars have advocated for the combined use of CT, MRI, and 18 F-FDG positron emission tomography/CT (PET/CT) to enable timely and accurate identification of the disease [9–11].

EHE displays unique morphological features, marked by the presence of plump spindle cells and primitive epithelioid cells that are arranged in fascicular patterns and nest-like structures [12]. Morphologically, EHE cells possess the ability to mimic other epithelial tumors, thereby necessitating supplementary immunohistochemical and molecular analyses for a conclusive diagnosis. Immunohistochemically, the tumor cells exhibit the expression of vascular endothelial markers, including CD31, CD34, ERG, Ki-67, as well as cytokeratin [6, 13]. The emergence of targeted RNA sequencing has enabled the identification of recurrent gene fusions, such as FOS, FOSB, YAP1, and WWTR1, in EHE [14]. This advancement has refined tumor classification and improved the precision of vascular tumor diagnosis.

An optimal treatment strategy for EHE has not yet been established, with most cases being reported as isolated instances. Surgical resection may be considered for localized lesions. However, EHE can also manifest in uncommon organs such as the spleen, and in such cases, embolization followed by resection has been employed in various organs, including the liver, in the presence of vascular malformations [15, 16].In our specific case, the patient's inability to undergo surgical intervention due to the presence of multiple lesions undoubtedly increased the complexity of treatment. Certain medications [17, 18], including anti-angiogenic agents, interferon, thalidomide, mTOR inhibitors (such as everolimus and sirolimus), and the MEK inhibitor trametinib, have demonstrated clinical efficacy in impeding tumor progression. They have shown varying levels of effectiveness, resulting in different survival outcomes.According to documented reports [19], it has been noted that four patients diagnosed with EHE have demonstrated significant therapeutic benefits when treated with bevacizumab across different settings. Notably, one patient experienced a remarkable progression-free survival of at least 18 months while undergoing thalidomide therapy. However, in the case of hepatic EHE, despite receiving a combination treatment of vincristine and bevacizumab, the patient unfortunately passed away from the disease within a year [20]. After the administration of sirolimus in conjunction with interferon, a favorable clinical outcome was achieved, resulting in a significant reduction in the size of a substantial liver lesion, exceeding 15 centimeters, following an eight-month treatment period in a case of hepatic EHE [21]. Tumor stability was maintained for a period of 24 months through the monotherapy use of anlotinib. Additionally, another patient with hepatic EHE exhibited tumor regression after just three months of combination therapy that included interferon [22]. Furthermore, a partial response to treatment was observed when utilizing a combination of doxorubicin, ifosfamide, and methotrexate [23]. In a unique case of pulmonary EHE, the patient completed 5 cycles of chemotherapy using albumin-bound paclitaxel and carboplatin, followed by maintenance therapy with pembrolizumab, which demonstrated significant efficacy [24]. In a separate instance involving renal EHE, the patient received 16 cycles of toripalimab treatment, resulting in a minimum of 13 months of progression-free survival [25].

Considering the limited availability of data on EHE research, a standardized treatment protocol is currently lacking, which underscores the need for additional studies to determine effective therapeutic strategies, evaluate their efficacy, and assess their safety profiles. EHE displays a moderate to low level of differentiation and carries the potential for metastasis, making the prognosis uncertain. As a result, identifying independent risk factors for EHE presents a significant challenge. Existing scholarly reports indicate that factors such as gender, age, pathological parameters (including necrosis, nuclear

grade, and mitotic activity), and atypical histology do not exert a significant influence on prognosis. Rather, it is the involvement of the pleura, lymph nodes, or the presence of distant metastases that contributes to a less favorable prognosis. Patients with pleural involvement or lymph node metastases exhibit a more aggressive clinical course, with survival rates beyond five years being only 22% and 30% respectively. This stands in stark contrast to the survival rate of over 70% observed in patients who do not exhibit these two adverse factors [12]. Intriguingly, the presence of molecular gene fusions may also play a role in determining survival outcomes in EHE [26]. The genetic signature of EHE predominantly involves the recurrent WWTR1-CAMTA1 gene fusion, which is observed in the majority of cases. Additionally, there exists a small subset with distinct morphology and characteristics associated with the YAP1-TFE3 gene fusion. Notably, a study revealed a lower 5-year overall survival rate for individuals with the WWTR1-CAMTA1 fusion compared to those with the YAP1-TFE3 fusion (58% vs. 86%) [12]. Regrettably, the detection of gene fusions involving WWTR1-CAMTA1 and YAP1-TFE3 was not conducted for this specific patient, thereby impeding the achievement of an accurate prognosis at the time of initial diagnosis. However, it is noteworthy that personalized therapeutic approaches for EHE may exhibit potential, given that genetic alterations beyond the disease-defining gene fusion were identified in more than half of the sequenced patients, with 22% demonstrating putative oncogenic alterations [12].

Conclusion

The scarcity of EHE impedes our understanding of its biological dynamics and therapeutic potential. Currently, there is no universally accepted treatment for patients with distant metastasis. Consequently, it is imperative that we intensify our research into EHE, exploring its biodynamic properties in greater depth and seeking out more effective diagnostic techniques and treatment strategies. Specifically, we must focus on patients with distant metastasis. By fostering multidisciplinary collaboration, we can conduct clinical research and trials, and strive to develop a treatment plan that gains widespread acceptance. This will improve the quality of life and prognosis for patients.

Abbreviations

EHE	Epithelioid Hemangioendothelioma
ECOG	Eastern Cooperative Oncology Group
NRS	Numerical Rating Scale
CT	Computed tomography
MRI	Magnetic resonance imaging
PET/CT	Positron emission tomography/CT

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-024-05536-7.

Supplementary Material 1

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Author contributions

QY and SL wrote the main manuscript text .LZ and SST prepared Figs. 1 and 2. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Consent to publication

The spouse of the patient had consented to our candid discussion regarding the patient's health condition and had authorized the dissemination of said information in a published format.

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