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Pulmonary Epithelioid Hemangioendothelioma: Case report and a brief review of the literature

Gabriella Piedra [6], Francisco Comas [2], Ivana Ranjan [2], John Hanna [5], Donnah Encaoua [3], Shane Ganga [4], Michael Mitchell [3], Jessica Jahoda [1, 2] and Mohamed Aziz [1, 3, *]

[1] *Research Writing and Publication (RWP), LLC, NY, USA.*
[2] *American University of the Caribbean School of Medicine, USA.*
[3] *Ross University School of Medicine, Barbados.*
[4] *St. George's University School of Medicine, Grenada.*
[5] *Medical University of the Americas, Nevis, West Indies.*
[6] *Universidad Iberoamericana (UNIBE), Santo Domingo, Dominican Republic.*

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Abstract

Pulmonary Epithelioid Hemangioendothelioma (PEHE) is an uncommon endothelial cell-derived vascular tumor of the lung. It is a form of Epithelioid Hemangioendothelioma (EHE), a low to intermediate-grade malignant vascular sarcoma which may be aggressive and can metastasize. It presents with a wide range of clinical and radiological findings, including bilateral lung nodules and pleural effusion. Diagnosis of PEHE is challenging due to its rarity and similarity to other benign and malignant vascular lesions. It is essential to distinguish PEHE from other vascular lesions of an epithelioid nature, particularly epithelioid angiosarcoma, which has a distinct prognosis and treatment options. Molecular analysis has now conclusively demonstrated this difference by detecting typical gene fusions, such as that of WWTR1-CAMTA1, which is not identified in angiosarcoma. However, even though molecular pathogenesis has been more clearly understood, PEHE lacks a universal treatment regimen, and management is often personalized, depending on therapies such as mTOR inhibitors.

The present case illustrates the challenges in diagnosis, variable clinical progression, and the ongoing need for greater awareness among medical professionals regarding PEHE to facilitate earlier diagnosis, improve therapeutic strategies, and enhance patient outcomes for this rare tumor.

Keywords: Epithelioid Hemangioendothelioma; Pulmonary; Angiosarcoma; Challenging Diagnosis; Treatment

1. Introduction

PEHE is a rare vascular tumor of endothelial origin. It is an unpredictable and heterogeneous disease in terms of clinical progression and presentation. [1] PEHE has an estimated incidence rate of less than one in a million; thus, it may pose a diagnostic challenge to practitioners, often appearing similar to more common pulmonary processes or being incidentally discovered. This is a rare disease, and its diverse clinical manifestations, which include the absence of symptoms, as well as non-specific respiratory symptoms such as cough, dyspnea, and chest pain, are one of the causes of diagnostic delays and difficulties. [2]

Radiologically, PEHE is typically seen as multiple, bilateral lung nodules, and it has a heterogeneous appearance on images, which makes its primary diagnosis more challenging. The final diagnosis of EHE is largely based on

* Corresponding author: Mohamed Aziz

histopathological examination, particularly molecular studies that demonstrate the characteristic gene fusions, such as WWTR1-CAMTA1 or YAP1-TFE3. This molecular validation is important, as it differentiates PEHE from other epithelioid vascular abnormalities, particularly the higher-grade entity epithelioid angiosarcoma, which represents a significant prognostic and therapeutic distinction. [3]

This molecular confirmation plays a critical role in distinguishing between PEHE and other epithelioid vascular lesions, and particularly the more aggressive epithelioid angiosarcoma. This distinction has important clinical implications, both in terms of prognosis and treatment planning. [4]

No standardized treatment protocol has been established for PEHE because it is an infrequent and unpredictable condition. Management is typically a multidisciplinary process, and treatment decisions are made individually, depending on the extent of the disease, its symptoms, and progression. [5] In localized tumors, therapeutic interventions may include watchful waiting and surgical treatment. In contrast, for advanced or metastatic disease, treatment may include systemic therapies, such as targeted therapies, including mTOR inhibitors. [6] We report this case to illustrate the complexity of diagnosis, the evolving concept of its molecular basis, and the persistent challenges in treating PEHE, highlighting the need to raise awareness in the medical community to enhance timely diagnosis and improve patient outcomes.

2. Case presentation

A 59-year-old man reported to his primary care physician with a history of an intermittent, non-productive cough, dyspnea on exertion that had been gradually increasing over six months. First, his symptoms were explained by the fact that he smoked two packs every day for twenty years, which he stopped four years ago. He never took up medical treatment until the symptoms began to impact his normal life.

Of importance to his medical history, he had localized colon adenocarcinoma 5 years prior to presentation and was treated with a right hemicolectomy, a T3N1M0 disease with three lymph nodes positive. He had completed adjuvant FOLFOX chemotherapy and was not found to have recurrence on observation colonoscopies and imaging. The family history was not notable for malignancy. Physically, he appeared well and was experiencing slight respiratory distress with an oxygen saturation of 92% on room air. Pulmonary examination showed that the breath sounds were decreased in the right base and dulled to percussion, which is characteristic of pleural effusion. The remainder of his examination was not remarkable, and he had no lymphadenopathy, hepatomegaly, or peripheral edema.

Radiography revealed bilateral nodules in the lungs and right pleural effusion. A CT scan of the chest (high-resolution) revealed five nodules, three in the right lung (the biggest nodule was 3.2 cm) and two in the left lung (the biggest nodule was 1.8 cm), with ground-glass halos. There was also moderate right pleural effusion. PET-CT showed low-grade FDG uptake in the pulmonary lesions and absence of extrathoracic disease.

Therapeutic thoracentesis produced 800 mL of bloody pleural effusion, and cytologic analysis showed suspicious atypical cells. A CT-guided biopsy of the largest nodule on the right side allowed for a detailed examination of the tissue. Histopathological analysis revealed groups, sheets, and clusters of epithelioid cells in cords, as well as excessive sclerotic stroma, and normal intracytoplasmic vacuoles containing red blood cells. (Figure 1 A, B, C, D). The immunohistochemistry (IHC) of the tumor was positive for CD31, CD34, Fli-1, vimentin, Factor VIII, and CD10. The negative markers included cytokeratins, TTF-1, CD68, S-100, LCA, and P53. The proliferation marker Ki-67 was 15% nuclear stain. The diagnosis was established based on histomorphology supported by IHC confirmatory studies; molecular confirmation was not required.

The case was discussed during a multidisciplinary tumor board meeting. Since there were multiple nodules with a maximum size of 3.2 cm and bloody pleural effusion, surgical resection was not a viable curative treatment. This patient was considered not a surgical candidate, whereas cases with one localized tumor could be removed surgically with a good long-term outcome. Treatment was instead shifted to controlling symptoms and disease progression using systemic therapies. Since there is no standard PEHE treatment, both Bevacizumab and apatinib are anti-angiogenic medications that may be explored and considered, but whose efficacy is primarily reported via case studies. The patient was treated with sirolimus, which was tolerated and resulted in stabilization after three weeks. Mouth sores and skin rash were mild side effects that resolved in six weeks. Hyperlipidemia was observed and atorvastatin was prescribed; subsequently, lipid parameters returned to normal. The patient also received palliative radiation for symptomatic bone lesions.

Three months of follow-up imaging showed stable disease with a mild attenuation of the ground-glass appearance around the nodules. The pleural effusion was mild, and his dyspnea was significantly relieved. He was able to resume light recreational activities. The six-month follow-up demonstrated stabilization of the disease, a slight reduction in the largest nodule (2.2 cm), and the presence of a mild pleural effusion that was under control.

At 18 months of treatment, the patient presented with the development of lower back pain and slight deterioration with gradual fatigue. Surveillance radiography revealed a patient with stable pulmonary disease, but new lytic lesions in the L3 and T12 vertebrae, and areas of focal increased FDG uptake on PET scans. Metastatic EHE with the same features as the primary tumor was confirmed by bone biopsy. There was no evidence of hepatic or brain involvement in other common sites on hepatic and brain MRI. Combination therapy involving Bevacizumab, with continued sirolimus, was added to intensify treatment. Vertebral lesions palliative radiotherapy alleviated a high degree of pain, such that opioid medications could be stopped in four weeks. Zoledronic acid was started for bone protection.

The combination therapy was tolerated, and the mild toxicity was manageable, with hypertension being controlled with lisinopril and infrequent proteinuria necessitating changes in dose. A six-month follow-up revealed that the bone metastases were stable with sclerotic alterations indicating some response to treatment, and the pulmonary disease remained stable. Fourteen months after metastatic diagnosis and treatment, clinical and radiographic follow-up indicated an increasing size of pulmonary nodules and the recurrence of large pleural effusion, leading to respiratory failure, and the patient expired.

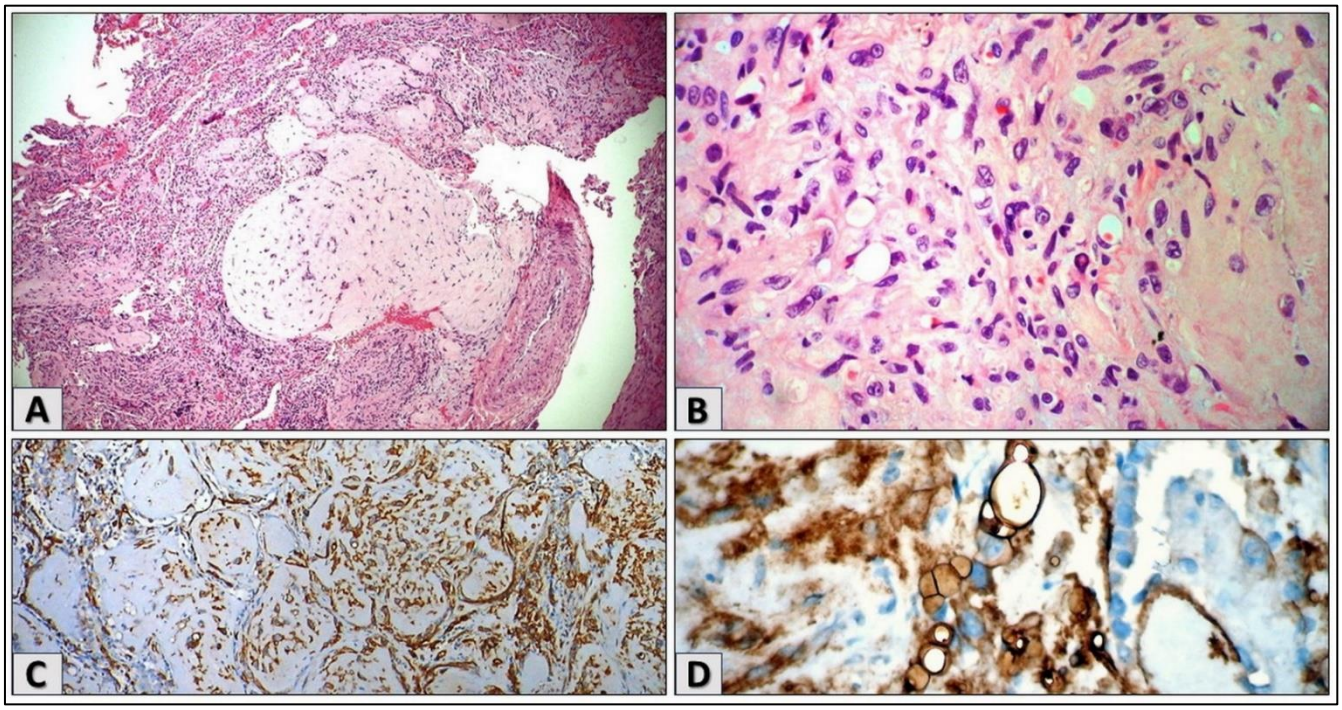

Figure 1 Histomorphology of pulmonary epithelioid hemangioendothelioma (PEH)

- **1A** Low power view showing increased cellularity at the periphery and abundant eosinophilic stroma (HandE stain X20)
- **1B:** Intermediate power view showing eosinophilic stroma with many cells displaying prominent cytoplasmic vacuoles and intravacuolar red blood cells (HandE stain X40)
- **1C:** Tumor cells positive for CD34
- **1D**: Tumor cells positive for CD31

3. Discussion

3.1. History, epidemiology, risk Factors, and WHO classification

Before PEHE was formally classified in 1982 by Weiss and Enzinger, it had only been described as an atypical tumor exhibiting characteristics intermediate between those of hemangioma and angiosarcoma. [1] The first to gain some understanding of this atypical tumor were Dail and Liebow, who identified these nodules as intravascular bronchiolo-alveolar tumors (IVBAT) in 1975. [3] Later in 1979, Corrin and his team detected Weibel-Palade bodies within the cells, which contained proteins such as von Willebrand factor (vWF), indicating their endothelial cell origin. [3] That same year, Rosai named these findings histiocytoid hemangioma based on their characteristic proliferation of histiocytoid endothelial cells. [3]

Most recently, in the WHO classification (5th edition, 2020) of Soft Tissue and Bone Tumors, EHE is categorized as a vascular tumor. More precisely, the existing description of the WHO defines EHE as a locally invasive vascular tumor with a potential for metastasis. [7] This classification is a development of previous WHO classifications. It is worth noting that this tumor was first graded (grade I) as benign in the 2007 classification by the WHO. EHE was re-classified in 2016 as grade III (malignant). [8] The tumor is currently classified as a locally aggressive tumor that may metastasize. [9] Specific molecular features, including the presence of fusion genes such as WWTR1-CAMTA1 or YAP1-TFE, also characterize EHE. [3], which have helped elucidate the pathogenesis of the tumor and contribute to its diagnosis. The new reclassification of EHE represents an advancement in understanding the biological behavior of EHE, where the lesion exhibits intermediate malignant potential between benign vascular lesions and high-grade angiosarcomas.

PEHE preferentially presents in adults with female gender predominance with three distinctive CT patterns: lung nodules, pulmonary reticulonodular opacities, and diffuse infiltrative pleural thickening. [10] PEHE occurs in fewer than one in a million people, with a broad age range from 7 to 85 years old and a median age of approximately 50. Research indicates that younger patients are more likely to have the YAP1-TFE3 fusion gene (median age, 34), whereas older patients tend to have the WWTR1-CAMTA1 fusion gene (median age, 51). There is a slight female predominance, and no hereditary cases have been reported. Research on the risk factors for EHE is still evolving and has not yet been fully explored. Some cases are linked to Bartonella infection, although the cause remains unknown in other cases. EHE can affect a single organ or multiple organs, with 36-60% of patients experiencing systemic disease. [3] Poor survival is associated with factors like age >80, African-American or American Indian/Alaska Native race, respiratory involvement, and symptoms like fever, fatigue, and weight loss. Soft tissue EHE responds better to surgery; however, outcomes can vary depending on the location of the tumor. [11]

3.2. Diagnosis: Pathology, immunohistochemistry, and molecular considerations

PEHE is a very rare tumor of blood vessels that has an intermediate potential for spreading. It is a diagnosis that requires multiple tests and methods to be determined. It begins with radiological images, which must then be confirmed with tissue samples, tests on those samples, and, in some cases, molecular tests.

The initial evaluation of suspected PEHE typically involves a chest x-ray and a CT scan of the chest. These tests often show a variety of bilateral pulmonary nodules. They can be small, a few millimeters to a few centimeters in size. Some can have small calcifications, appear on the surface of the lung, or have fluid around them, especially in advanced disease. [12] [13] MRI may be used to analyze the lesion further, especially if there is concern for chest wall or mediastinal invasion. ^18F-fluorodeoxyglucose positron emission tomography/computed tomography (^18F-FDG PET/CT) may also be performed. PEHE may have mild or moderate FDG uptake. This test can also be used to provide information about the presence of disease, disease activity, or disease progression. [14]

To determine a conclusive diagnosis, a tissue biopsy is necessary. The sample can be procured via CT-guided core biopsy, transbronchial biopsy, or video-assisted thoracic surgery (VATS), depending in part on the location of the lesions. [15] Most histologic examinations show a magnetic myxohyaline stroma with epithelioid endothelial cells. These cells may be eosinophilic and even contain intracytoplasmic vacuoles that contain erythrocytes (although this is not very common). The key histologic element of PEHE is the formation of primitive vascular channels, which leads to the development of cytoplasmic vacuoles and lumina. [16]

To confirm that the neoplasm is of endothelial origin and to differentiate PEHE from metastatic carcinoma, mesothelioma, or other sarcomas, immunohistochemistry is particularly helpful. Tumor cells have been shown to consistently express endothelial markers, such as CD31, CD34, or factor VIII–related antigen (the most reliable and common being CD31, which displays the strongest membranous staining). Epithelial markers (such as cytokeratins and

epithelial membrane antigen (EMA) may be expressed in small amounts in some instances, but do not constitute the majority. [1]

Even more precise improvements in diagnostics have been made with the addition of molecular testing. Most epithelioid hemangioendotheliomas have the recurrent gene fusion, WWTR1-CAMTA1. Less frequently, tumors may carry a YAP1-TFE3 fusion. Detecting these alterations with reverse transcription–polymerase chain reaction (RT-PCR), fluorescence in situ hybridization (FISH), or next-generation sequencing (NGS) can be particularly valuable when morphology is ambiguous or when PEHE must be differentiated from histologic mimics. [4]

3.3. The Big Question: Why is this case not an epithelioid angiosarcoma?

Malignant vascular neoplasms represent a diverse array of tumors derived from the endothelial cells. Among them, EHE and epithelioid angiosarcoma (EAS) represent two distinct clinical and pathological entities that share a common histogenetic origin but exhibit significant differences in biological behavior, histologic characteristics, and clinical outcomes. [2]

EHE belongs to the group of low- to intermediate-grade vascular tumors. Its biology is typically less aggressive than that of angiosarcoma, and patients generally have a better clinical outcome. One of the diagnostic hallmarks of EHE is its frequent association with a very specific genetic alteration: the CAMTA1-WWTR1 gene fusion. This molecular footprint is a potent diagnostic marker that can differentiate EHE from other vascular lesions, particularly angiosarcoma, in which this fusion is generally absent. [3]

Table 1 Key differences between EHE and epithelioid angiosarcoma

Feature	**Epithelioid Hemangioendothelioma (EHE)**	**Epithelioid Angiosarcoma (EAS)**
Malignancy Grade	Low-to-intermediate grade. Its behavior is variable and can range from benign-like too slow-growing malignant.	High-grade malignancy with highly aggressive behavior.
Genetic Signature	Defined by specific chromosomal translocations, most commonly the \(WWTR1-CAMTA1\) gene fusion. A less common variant has a \(YAP1-TFE3\) fusion.	Does not possess the characteristic gene fusions found in EHE. Genetic studies show large-fragment gains and deletions, a key distinction from EHE.
Clinical Behavior	Characterized by a slow, often indolent, course. In some cases, it can be fatal due to spread, but it does not spread as often or as rapidly as angiosarcoma.	Has a poor prognosis due to rapid growth, high rates of local recurrence, and early metastasis, particularly to the lungs, bone, and lymph nodes.
Pathology and Histology	Exhibits a characteristic microscopic appearance of cords, strands, and nests of epithelioid cells in a fibrous or myxoid stroma. The tumor cells may contain primitive, vacuolated vascular lumens.	Displays a high degree of cellular atypia, high mitotic activity, and necrosis. The tumor cells are large and polygonal (epithelioid) and may form solid sheets.
Diagnosis	Diagnosis is confirmed by identifying the characteristic genetic fusion, such as \(WWTR1-CAMTA1\), usually via molecular testing (e.g., FISH or PCR).	Diagnosis relies on clinical, radiological, and histopathological findings, often supported by immunohistochemical staining for vascular markers.
Treatment	Treatment is highly individualized. It may involve watchful waiting for slow-growing tumors, surgical resection, or targeted therapies. A liver transplant may be an option for extensive liver involvement.	Requires aggressive treatment, typically involving radical surgical resection, radiation therapy, and chemotherapy. Prognosis is poor even with treatment.

*Compiled from references 2, 3, 5, 9, 14, and 17

EAS has been distinguished from EHE as a high-grade vascular neoplasm, showing marked nuclear atypia, high mitotic activity with a much more aggressive clinical behavior, and worse outcome. This aggressive nature is manifested with its rapid development and risk for widespread metastasis, resulting in significantly poor patient overall survival rates. From a genetic point of view, angiosarcoma typically does not have the CAMTA1–WWTR1 gene fusion, but rather shows

more complex and chaotic genetic changes, including MYC amplifications (especially in radiation-related cases) and mutations in genes such as TP53. This lack is a key diagnostic discriminator, strongly favoring an EHE diagnosis if this fusion is present. For this reason, the molecular testing is crucial for differentiating these two tumors. [3] [17]

Angiosarcoma is histologically defined by its more destructive and infiltrative growth pattern, characterized by disorganized and anastomosing vascular channels, greater nuclear atypia, a high level of mitosis, and necrosis. [17] Conversely, typical classic EHE presents as cords and nests of epithelioid cells within a characteristic myxohyaline or sclerotic stroma. A characteristic feature of EHE, but not the only one, is the presence of intracytoplasmic vacuoles, or blister cells, which are primitive vascular lumina. [17] Although both tumors are positive on endothelial markers such as CD31 and Factor VIII, they do not differentiate based on these markers alone. [15]

A precise distinction of these two tumors, with an extensive assessment of genetic, histological, clinical, and radiological characters, is mandatory for appropriate patient treatment and prognostic determination. Further investigation of the molecular paradigm of these tumors will enhance our diagnostic and therapeutic armamentarium, thereby increasing patient survival. Table 1 summarizes the key differences between EHE and epithelioid angiosarcoma.

3.4. Pathogenesis and pathophysiology

A good example of a fusion-based malignancy is the pathogenesis of EHE. It does not arise from many mutations but rather from one and a distinctive chromosomal translocation. This is approximately 90 percent of the t (1;3) (p36; q25) translocation, which fuses the WWTR1 gene to the CAMTA1 gene. The other 10 percent of the cases are defined by a YAP1-TFE3 fusion [18]

Both YAP1 and WWTR1 (an encoder of the protein TAZ) are important downstream effectors of the Hippo signaling pathway, an essential regulator of cell growth, proliferation, and organ size. In a healthy condition, TAZ and YAP are phosphorylated and inactivated by the Hippo pathway and are subsequently trapped in the cytoplasm. The formation of the TAZ-CAMTA1 or YAP-TFE3 fusion proteins, however, bypasses this important control mechanism. The resulting fusion proteins become resistant to the negative feedback of the Hippo pathway and accumulate in the nucleus, where they function as highly potent, constitutively active transcription factors. These unregulated transcription activities promote the abnormal proliferation and tumor growth of endothelial cells, a characteristic of EHE, which validates these fusions as the most important oncogenic factors in the disease. [18]

Other hypotheses for the pathogenesis of this neoplasm, reported in the literature, discussed a possible causal relationship between chronic Bartonella infection and the development of this rare vascular tumor in immunocompetent patients. [19] Some authors also believe that hormonal significance plays a role in this disease, as the disease is observed to have a greater incidence in women. Additionally, hormone receptor expression has been reported in the literature, and a recent case report described the recurrence of EHE during pregnancy. [20]

3.5. Management and prognosis

EHE of pulmonary (PEH) or hepatic (HEH) origin, is a rare neoplasm that typically follows a highly variable clinical course. Surgical resection for localized, resectable disease is the primary treatment modality, and its long-term results are excellent, particularly in cases of soft tissue or single-organ disease. [21] No therapy is often the advice in asymptomatic, unresectable, or indolent disease, “no therapy” is often the advice, specifically in pulmonary presentations with no adverse features. [5] Systemic therapy is reserved for symptomatic, multifocal, or high-grade disease, such as in advanced, widespread, or metastatic disease, in which surgery is not feasible; in these cases, systemic therapy is a viable option. While conventional chemotherapies remain of questionable benefit, there are reports discussing the use of the VEGFR-2 inhibitor, apatinib. One report describes a patient treated with incremental doses of apatinib who showed symptomatic and imaging improvement, albeit becoming progressive after one month. [6] Further, there was another report of successful disease stabilization for a patient with liver and lymph nodes involvement by apatinib combined with chemotherapy (doxorubicin and cyclophosphamide) that yielded marked symptomatic control and stable response for 2 years; this case further supported the possible role of targeted therapy in controlling the lymphatic dissemination. [24]

The prognosis of the PEHE varies considerably. The 5-year overall survival rate ranges widely, from approximately 60% (47–71%) [22] to higher estimates (~73–90%) in some series characterized by more indolent, asymptomatic patients. [22] Some patients remain alive for more than 20 years, while others, especially the patients with hemorrhage symptoms, pleural effusion, anemia, and weight loss, progress rapidly, and the median survival is less than 1 year. [23] A 5-year survival rate of 2% was reported in patients with pleural hemorrhagic effusion, compared with 73% in patients

without effusion, in one study. [23] Other poor prognostic factors are male sex, symptomatic disease, metastases, and lymph node involvement. [22]

3.6. Relating the literature to the findings in our case

The insidious onset of cough and dyspnea in our patient is typical of the non-specific and mixed onset symptoms frequently described in the literature of PEHE. Although most PEHE patients are asymptomatic, having been identified incidentally on imaging, symptomatic presentation, as in our case, is well-described and usually represents more progressive disease or pleural involvement. The fact that our patient had a large bloody pleural effusion, a characteristic that in various studies has indicated a poorer prognosis, further demonstrates how serious the presentation is and how difficult PEHE is to diagnose due to its wide clinical spectrum. Radiologically, the bilateral pulmonary nodules seen on the CT scan in our patient are the typical imaging characteristic of PEHE, which is in line with many published case series. The peripheral distribution and size of these nodules are characteristic. However, the secondary finding of pleural effusion highlights the importance of thorough imaging evaluation in capturing the entire scope of the disease. The low to moderate uptake on PET/CT is not pathognomonic. However, it also correlates with the metabolically indolent character of PEHE compared to more aggressive malignancies, as reported in the literature. [14]

In our case, as in the medical community in general, diagnosis was based upon a multi-pronged approach. Suspicion on imaging and clinical background was confirmed by histopathological and IHC analysis, where typical epithelioid cells were present in a myxohyaline stroma. In difficult cases, molecular analysis can provide a definitive diagnosis by identifying the WWTR1-CAMTA1 or YAP1-TFE3 mutations, which are found in most cases of EHE. Molecular testing was not required as a clear diagnosis was achieved by histomorphology and IHC studies. [4] [15]

Relating the treatment and prognosis of our patient to the available literature sheds light on the challenges as well as new approaches to managing PEHE. Considering that no standard treatment regimen has been developed yet, the customized approach to our patient represents the existing state of PEHE treatment. Of particular interest is the first phase of disease control on sirolimus, an mTOR inhibitor. The application of mTOR inhibitors in PEHE is increasingly supported by the literature, as the mTOR pathway is commonly impaired in such tumors, either directly or indirectly by the fusion proteins. [6] Although the disease is very rare, and thus there are no large-scale randomized controlled trials, a large number of case reports and small series have shown clinical benefit and disease control with mTOR inhibitors, especially in patients with advanced or metastatic disease. [3] The patient's reaction, despite the presence of adverse prognostic factors at the time of presentation, supports the possible effectiveness of this selective method.

However, the next step of bone metastases that necessitates a shift to combination therapy with sirolimus and Bevacizumab demonstrates the vagaries and the propensity to alteration of PEHE. The anti-VEGF agent Bevacizumab (targeting angiogenesis, which is highly important in tumor development) has demonstrated some potential in combination with mTOR inhibitors in a few refractory cases of vascular tumors. [24] This flexible treatment plan, which involves palliative radiation of symptomatic bone lesions, aligns with the pragmatic and multidisciplinary approach that many PEHE patients require.

PEHE may have an indolent or aggressive overall prognosis, and the survival of our patient evidences this aspect over a long period despite the presence of metastases. Some patients progress very quickly, and others, like our patient, can remain very stable over long periods. However, the disease is advanced, and it is necessary to ensure that they are regularly monitored and that the therapeutic regimen is adjusted according to the individual disease pattern and reaction to treatment. It can be of particular interest, thus, as an example of considering the peculiarities of PEHE management in the context of the small evidence-based regimes, with references to the knowledge of its molecular basis and to a specific treatment plan.

3.7. What have we learned from this case?

This case offers some important learning points in the diagnosis and treatment of PEHE. First, it highlights the need to be highly suspicious of rare malignancies in patients with non-specific respiratory symptoms and a history of a prior, unrelated cancer. Cough and dyspnea might have been easily overlooked at the initial presentation, but continued research ultimately led to the correct diagnosis.

Second, this case provides a graphic example of the changeable and unpredictable clinical course of PEHE. Although the patient had poor prognostic indicators, such as symptomatic disease and a bloody pleural effusion, sirolimus, an mTOR, inhibitor, was able to induce an extensive period of disease control in the patient. This highlights the potential effectiveness of therapies targeting angiogenesis and cell growth pathways, despite the lack of data from large-scale clinical trials.

Lastly, this case supports the idea that despite a certain phase of stability, PEHE can change, and a flexible and dynamic treatment approach is required. The next phase of treatment for metastatic disease involves a combination therapy (sirolimus and Bevacizumab) and palliative radiation, representing a multidisciplinary and frequently personalized approach that can help increase patients' survival and preserve quality of life in those with advanced PEHE. The Case is a good practical example of how to navigate the complex aspects of a rare, unpredictable vascular tumor.

4. Conclusion

Overall, this case report presents the experience of a patient with PEHE, a rare vascular tumor, in a careful and detailed manner. This case will highlight the diagnostic difficulties that PEHE presents due to its non-specific clinical presentation, mixed radiologic appearances, and the fact that molecular diagnostics are essential in providing a definitive diagnosis and distinguishing PEHE from more aggressive imitators, such as angiosarcoma. Moreover, this report highlights the lack of a unified treatment regimen for PEHE. It presents a customized, adaptive therapeutic strategy that incorporates focused therapy using mTOR inhibitors and anti-angiogenic agents, resulting in significant disease control despite unfavorable prognostic factors. This case is a useful tool for the medical community to increase awareness of the complexities of PEHE, its unpredictable clinical progression, and the shifting approaches to its management, ultimately helping to improve awareness and increase care for future patients with this ultra-rare malignancy.

Abbreviations

Pulmonary Epithelioid Hemangioendothelioma (PEHE); Epithelioid Hemangioendothelioma (EHE); Epithelioid angiosarcoma (EAS; Immunohistochemistry (IHC)

Compliance with ethical standards

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Disclosure of conflict of interest

All authors make the following declarations

- **Payment/services information:** All authors have declared that they received no financial support from any organization for the submitted work.
- **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of ethical approval

Ethical review and approval were not required for this study involving human participants. The paper has been sufficiently anonymized to maintain the patient's confidentiality.

Statement of informed consent

Consent for the publication of this Case was obtained from the patient.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

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