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CASE REPORT

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A case of primary pleural epithelioid hemangioendothelioma achieving stable disease with paclitaxel treatment: A case report and literature review

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Abstract

Epithelioid hemangioendothelioma (EHE) is a rare vascular neoplasm with a clinical behaviour that falls between a benign hemangioma and a high-grade angiosarcoma. Pleural EHE is exceptionally rare, and its prognosis is grim, with most patients experiencing survival of less than 1 year. Here, we present a case of pleural EHE in a 45-year-old woman with a month-long history of right-sided pleuritic chest pain. Chest computed tomography revealed consolidation, atelectasis of the right lung, right pleural thickening, and pleural effusion. She underwent video-assisted thoracoscopic surgery for decortication and was diagnosed with conclusively pleural EHE, showing a CAMTA1 rearrangement. Paclitaxel treatment, administered once weekly on days 1, 8 and 15 of a 28-day cycle, resulted in a stable disease after 12 cycles. Managing patients with pleural EHE is challenging because there are still no established standard treatments. Our case achieved 11-month progression-free survival following paclitaxel treatment.

KEYWORDS

CAMTA1, epithelioid hemangioendothelioma, paclitaxel, pleural effusion, pleural malignancy

INTRODUCTION

Epithelioid hemangioendothelioma (EHE) is an uncommon vascular tumour characterized by an intermediate malignancy and is, positioned between benign hemangioma and aggressive angiosarcoma. This disease can manifest in any body part, but primarily targets the liver, lungs, and soft tissues. It shows a higher prevalence in women than in men, typically affecting middle-aged adults.[1] Notably, cases of pleural EHE are exceedingly rare, occurring in older adult men. For pulmonary EHE, the 5-year survival rate is approximately 60%, ranging from 47% to 71%.[2] Contrarily, pleural EHE patients generally have a survival span of <1 year, averaging between 9.6 and 10 months.[1,3,4] Here, we present a case of pleural EHE in a 45-year-old woman who presented with right-sided anterior pleuritic chest pain.

CASE REPORT

A 45-year-old woman presented with a month-long history of right-sided anterior pleuritic chest pain that progressively radiated to her right back. Accompanying symptoms included a significant weight loss of 7 kg within the same period. Her medical history was notable for the absence of smoking or any systemic diseases. Initially diagnosed with right lower lobe pneumonia, she received empirical antibiotic treatment, but it failed to alleviate her pain. Subsequently, she developed dyspnea, severely limiting her ability to perform physical activities. She reported no fever, cough with purulent sputum, orthopnea, paroxysmal nocturnal dyspnea, or pitting edema.

Physical examination revealed diminished breath sounds and dullness to percussion over the right hemithorax. Chest X-ray, shown in Figure 1A, demonstrated right pleural effusion and atelectasis in the right lower lung. Thoracentesis

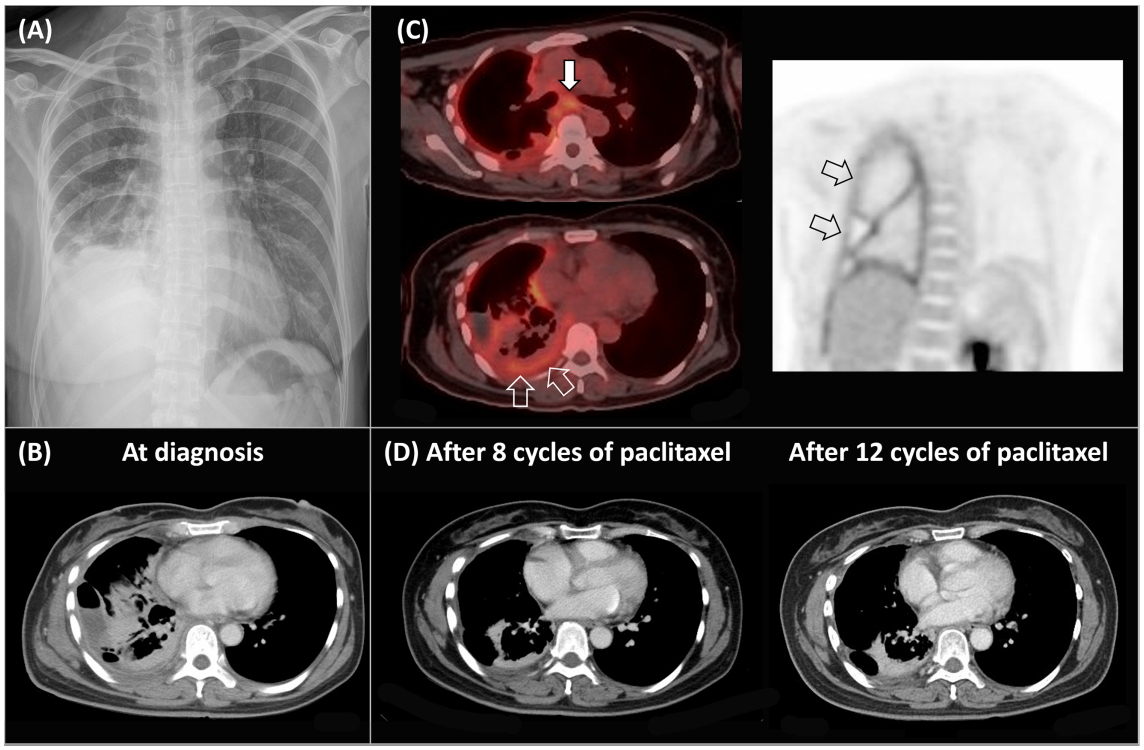

FIGURE 1 (A) Chest-x ray showing right pleural effusion and right lower lung atelectasis. (B) Computed tomography (CT) of the chest at the time of diagnosis showed sublobar consolidation and atelectasis with interlobular septal thickening, right pleural thickening, and loculated right pleural effusion. (C) Positron emission tomography (PET) showed mild-to-moderate hypermetabolism along the right pleura (open straight arrows) and mild-to-moderate hot spots at the subcarinal lymph nodes (solid straight arrow). Maximum intensity projection (MIP) PET images showed a fludeoxyglucose (FDG)-avid tumour along the right pleura and fissures. (D) Computed tomography (CT) of the chest after 8 and 12 cycles of treatment with paclitaxel indicated a stable disease.

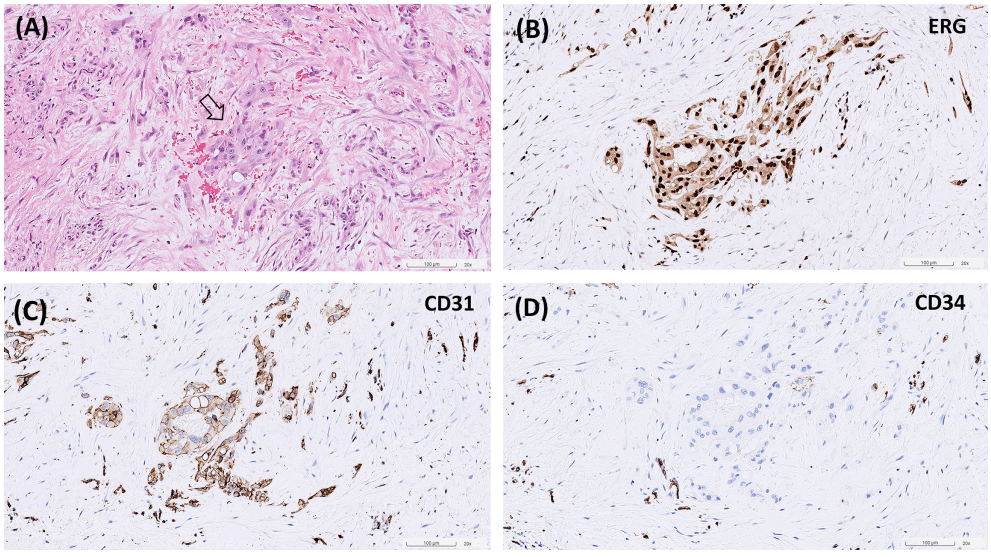

FIGURE 2 (A) Haematoxylin and eosin staining showed atypical epithelioid cells arranged in irregular small nests within a myxohyaline stroma (open straight arrow). The atypical cells exhibited moderate amounts of eosinophilic cytoplasm, frequent cytoplasmic vacuoles, pleomorphic nuclei, occasional distinct nucleoli, and increased mitoses (four mitotic figures/10 mm^2). (B) and (C) Immunohistochemical staining showing the atypical cells with diffuse positivity for ERG and CD31. (D) Rare atypical cells showing CD34 positivity.

was performed, which revealed an exudative pleural effusion. Pleural fluid analysis revealed a nucleated cell count of 398/μl, with a differential comprising polymorphonuclear cells (15.0%), neutrophils (16.2%), lymphocytes (46.2%), and monocytes (21.3%). Chest computed tomography (CT) revealed sublobar consolidation and atelectasis with

interlobular septal thickening, ground-glass opacities in the right middle and lower lobes, right hilar lymphadenopathies, pleural thickening, loculated right pleural effusion (see Figure 1B), and an elevated right diaphragm. She then underwent decortication by video-assisted thoracoscopic surgery.

Histological examination revealed clusters of atypical epithelioid cells characterized by pleomorphic nuclei and intracytoplasmic lumina, occasionally containing erythrocytes. The cells were set within a myxohyaline stroma and demonstrated an increased mitotic activity (four mitotic figures/10 mm^2) (Figure 2A). Immunohistochemical staining revealed that these cells were negative for cytokeratin, TTF1, p40, PAX8, GATA3, and calretinin, which diminished the likelihood of carcinomas and mesothelioma. Conversely, the morphological features, in combination with ERG and CD31 positivity (Figure 2B,C), were most consistent with EHE. CD34 was weakly positive (Figure 2D). Fluorescence in situ hybridization (FISH) testing indicated a CAMTA1 rearrangement, confirming the diagnosis of pleural EHE. Positron emission tomography (Figure 1C) revealed mild-to-moderate hypermetabolism in the right pleural and fissural regions, along with a similar activity in the right hilar and subcarinal lymph nodes. No metastatic lesions were detected.

The patient was started on chemotherapy with paclitaxel at 80 mg/m^2 once weekly on days 1, 8, and 15 of a 28-day cycle. After eight cycles, chest CT revealed less pleural effusion and improvement in pleural thickening. (Figure 1D). The regimen was then switched to oral cyclophosphamide (50 mg daily); however, this led to a recurrence of chest pain. Approximately 3 weeks later, the treatment reverted to paclitaxel. Following the 12th cycle, a chest CT suggested a stable disease (SD) (Figure 1D).

DISCUSSION

EHE, initially identified in 1975 by Dail and Liebow as an intravascular, bronchiolar, and alveolar tumour of the lung (IVBAT), underwent a nomenclature revision in 1982. Weiss and Enzinger reclassified it as an 'epithelioid hemangioendothelioma', a term reflecting its distinctive characteristics. This tumour comprises of endothelial cells with an epithelioid or histiocytoid morphology. Clinically, EHE occupies a position on the spectrum of angiogenic tumours, intermediate between benign hemangioma and malignant angiosarcoma.[5] EHE can manifest in various anatomical locations. In cases with single-organ involvement, the reported locations included the liver (34%), bone alone (21%), lung alone (19%), and other sites (26%).[6] Primary pleural EHE is a rare condition with diverse clinical presentation, and its management approaches can vary significantly. The largest case series report of pleural EHE published in 2022 reported 50 cases. Among these cases, the average patients' age was 53.72 ± 15.98 years, with a male predominance of 70%. The most common clinical symptoms of pleural EHE include pleuritic chest pain, dyspnea, productive cough and weight loss.[7]

The histopathological hallmark of EHE is the presence of distinctive cytoplasmic vacuoles, which may compress the nucleus, giving a signet-ring appearance to the tumour cells. The tumour cells characteristically express endothelial markers, including CD31 and CD34, and often show positivity for ERG, an endothelial transcription factor. Notably, EHE demonstrates negative staining for markers including mucicarmine, TTF-1, p40, PAX8, and GATA3,[5] and the mesothelial markers WT1 and calretinin are not expressed.[8] A defining genetic aberration in EHE pathogenesis is the t(1;3) translocation, resulting in WWTR1 (located on chromosome 3q25) and CAMTA1 (located on chromosome 1p36) fusion. This fusion event is considered pivotal in EHE tumorigenesis. Such specific genetic alterations can be detected by FISH testing.[9] A minority of EHE cases exhibit the Yes-associated protein 1 (YAP1)–transcription factor E3 (TFE3) fusion gene. This fusion leads to the overexpression of TFE3, a transcription factor. The YAP1–TFE3 fusion is considered a rare event occurring in a limited number of EHE cases.[5]

The treatment modalities for EHE lack a standardized approach, with various studies exploring a spectrum of strategies. These include surgery, chemotherapy, radiotherapy, target therapy, and combination therapy, and some cases have adopted for a watchful waiting strategy.[7]

Lavacchi et al. documented a case series in which surgical interventions such as pleural decortication, pleurectomy, resection, or pneumonectomy were performed on 13 patients. Following surgery, most patients undergo postoperative systemic therapy, including chemotherapy, bevacizumab, pazopanib, or interferon, with or without radiotherapy. The clinical outcomes and survival rates varied among these patients, with post-surgery survival ranging from several months to over 2 years.[10] According to expert opinion, surgical resection is the preferred treatment for cases with confirmed unifocal disease or reasonably limited locoregional metastases that are technically resectable.[11]

A previous retrospective international case series reviewed the data of 73 patients with locally advanced or metastatic EHE undergoing systemic therapy. These patients were categorized into the following five groups based on the treatment received: anthracycline-based regimens, paclitaxel, pazopanib, interferon (IFN), and others. It is worth noting that >70% of patients in both the anthracycline-based regimen and paclitaxel groups had not received any prior systemic therapies. Although partial response (PR) was achieved in only 3% and 9% of patients in the anthracycline-based and paclitaxel groups, respectively, a significant number of patients achieved SD (76% and 55%, respectively). The median progression-free survival (PFS) was 5.5 and 2.9 months for anthracycline-based and paclitaxel therapies, respectively, whereas the median overall survival (OS) was 14.3 and 18.6 months, respectively.[12] The proportions of patients receiving IFN-α who achieved PR and SD were 7% and 73%, respectively.

However, patients receiving pazopanib had lower PR and SD rates. Among the patients who received other systemic regimens, two cases treated with oral cyclophosphamide attained SD. Unfortunately, these findings underscore the lack of established standard medical therapy for EHE.[12] The present case achieved SD following paclitaxel treatment, resulting in a PFS of at least 11 months.

Anti-tumour activity has also been observed with thalidomide, multi-tyrosine kinase inhibitors, vascular endothelial growth factor receptor inhibitory properties, and mechanistic target of rapamycin inhibitors.[11] A previous retrospective case series conducted in Italy reviewed the data of 38 patients with advanced EHE who were administered continuous-dosing of sirolimus (5 mg daily). A prerequisite for treatment initiation was the occurrence of disease progression within the 6 months preceding the start of therapy. PR and SD were achieved in 10.8% and 75.7% of the patients, respectively. The median PFS and OS were 13 and 18.8 months, respectively. However, the presence of serosal effusions has been confirmed as an adverse prognostic indicator linked to a shorter survival, and treatment with sirolimus demonstrates restricted efficacy within this subgroup.[13]

Notably, our case involves a relatively young woman, a demographic uncommon in previously reported cases. Additionally, we highlight the early use of surgery for diagnosis. The disease is limited to the pleura and mediastinal lymph nodes, and has not progressed to metastasis, suggesting a potential link to a more favourable PFS with paclitaxel treatment than reported in the literature. However, the absence of randomized clinical trials comparing various treatment regimens leaves us uncertain about the potential benefits of incorporating alternative treatment methods.

In conclusion, owing to its rarity and non-specific clinical manifestations, pleural EHE is frequently underrecognized and initially misdiagnosed. When encountering a patient who presents with unilateral pleuritic pain and exhibits signs of pleural thickening, pleural EHE should be considered a potential differential diagnosis. The absence of standard therapy for EHE makes managing pleural EHE particularly challenging. Our report details the case of a 45-year-old woman with confirmed pleural EHE, showing CAMTA1 rearrangement, who achieved SD through paclitaxel treatment. In the future, more research, registries, and clinical trials are essential to develop effective treatments for this disease.

AUTHOR CONTRIBUTIONS

Chun-Ying Chou: Contributed to the literature search and drafted the manuscript. **Hsiang-Wei Hu**: Contributed to the pathological diagnosis, pathological interpretation, and figures. **Tom Wei-Wu Chen**: Contributed to the concept of work and revision of the manuscript. **Shu-Yung Lin**: Provided a substantial contribution to the study concept and revised the manuscript. All authors have reviewed and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained from the patient for the publication of this manuscript and the accompanying images.

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