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**Effective combined therapy for pulmonary epithelioid hemangioendothelioma: A case report**

Zhang XQ *et al*. A case of P-EHE

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**Abstract**

BACKGROUND

Pulmonary epithelioid hemangioendothelioma (P-EHE) is a rare disease. Thus far, consensus on a standard treatment for P-EHE has not been established given its low incidence worldwide. Apatinib combined with chemotherapy with doxorubicin/cyclophosphamide has been used as an effective combination treatment for human malignancies. However, the efficacy of this combination has not been reported in P-EHE cases.

CASE SUMMARY

We present the case of a 64-year-old woman with chest tightness, cough, and chest pain. Computed tomography showed multiple unresectable pulmonary nodules. She had been misdiagnosed with lung carcinoma and underwent gefitinib treatment at a hospital. Subsequently, the patient underwent a cardiothoracic surgery for further disease investigation. CD31, CD34, and Vimentin expression were detected in the resected nodule specimens by immunohistochemical analyses, and pathological analyses confirmed the diagnosis of P-EHE. Following this, four cycles of apatinib combined with chemotherapy with doxorubicin/cyclophosphamide were initiated. The patient demonstrated stabilization of multiple bilateral nodules and showed a dramatic improvement in the clinical presentation after combination treatment. The patient could not tolerate the side effects of chemotherapy. Therefore, she then continued apatinib monotherapy, which is ongoing to date. The patient was stable at the last follow-up after 24 mo.

CONCLUSION

Apatinib combined with chemotherapy with doxorubicin/cyclophosphamide may be an effective therapeutic option for P-EHE treatment.

**Key words:** Pulmonary epithelioid hemangioendothelioma; Apatinib; Doxorubicin; Cyclophosphamide; Combination therapy; Prognosis; Case report

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**Core tip:** Pulmonary epithelioid hemangioendothelioma (P-EHE) is a rare disease. Patients with P-EHE demonstrate multiple unilateral or bilateral nodules that are often misdiagnosed as lung cancer or suspected to represent lung metastases. Meanwhile, currently, no standard treatment for this rare disease exists, and patients with P-EHE show a poor prognosis. Therefore, an effective therapeutic strategy for these patients is urgently required.

**INTRODUCTION**

Pulmonary epithelioid hemangioendothelioma (P-EHE) is a rare vascular tumor, which was first identified by Dail and Liebow in 1975 and was believed to be an intravascular bronchioloalveolar tumor of the lung[1]. Most patients with P-EHE show diverse clinical manifestations such as cough, chest pain, pleural effusion, and dyspnea, and the minority of patients are asymptomatic[2,3]. Multiple nodules in both lungs are usually identified on imaging, and unilateral P-EHE is often initially misdiagnosed as bronchogenic carcinoma[4]. Thus, immunohistochemical analysis is critical for the diagnosis of P-EHE. CD31, CD34, and Vimentin are vascular antigen markers that contribute to the diagnosis of P-EHE[5-7]. P-EHE accounts for 12% of all EHE cases and P-EHE prognosis is unpredictable; for patients with symptoms such as pleural effusion, chest pain, chest tightness, and cough, the prognosis is very poor, with a median survival time of 12 mo or less[3,8]. Meanwhile, no standard treatment for patients with these multiple unresectable lesions currently exists. In this study, we discuss the case of a 64-year-old patient with P-EHE, from P-EHE confirmation to effective combination therapy.

**CASE PRESENTATION**

***Chief complaints***

A 64-year-old woman was admitted to the Affiliated Hospital of Jiangnan University with obvious chest tightness, chest pain, and cough, and multiple pulmonary nodules were identified on imaging.

***History of present illness***

She previously visited another hospital with chest pain, chest tightness, and cough. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) showed abnormal FDG accumulation (Figure 1), and she was suspected to have lung metastasis. She was administered with gefitinib (250 mg/d) for 2 mo as treatment. However, her clinical manifestations persisted, and the number of pulmonary nodules did not decrease significantly.

***History of past illness***

Her medical history was unremarkable.

***Family history***

The patient had no family history of hereditary diseases or cancer.

***Physical examination upon admission***

On admission to our hospital, the body temperature of the patient was 37 °C with a pulse rate of 94 beats per minute (bpm); her respiratory rate was 25 breaths per minute and blood pressure was normal. The pain score was 8 on a scale of 1-10. She was slightly short of breath, and lung sounds were absent in the right middle and lower lung lobes. Her heart sounds were normal on auscultation.

***Laboratory examinations***

Hematological analysis showed a white blood cell count of 11.9 × 109/L, with 75.8% of neutrophils; an erythrocyte sedimentation rate of 75 mm/H; and a C-reactive protein level of 59.17 mg/L. Carcinoembryonic antigen levels were normal.

***Imaging examinations***

Lumbar CT showed diffusely scattered, high-density, non-calcified nodules, up to 13 mm in diameter, in both lungs. Pulmonary nodules were distributed along the tracheal vascular bundle, and the right lung had suffered serious damage with right pleural effusion (Figure 2A).

***Medical management***

A biopsy of bronchial samples from the basal segment of the right lower lobe revealed collagen fibers and inflammatory cell infiltration. Further, alveolar lavage fluid was extracted and analyzed *via* high-throughput gene expression analysis for infectious pathogens, and *Burkholderia* and *Propionibacterium* genera were identified. Following this, the patient underwent a cardiothoracic surgery, wherein two nodules of the left upper lobe were removed for further investigation. Immunohistochemical analysis of these nodules revealed positive expression of CD31, CD34, and Vimentin (Figure 3).

**FINAL DIAGNOSIS**

A pathological examination confirmed the diagnosis of P-EHE.

**TREATMENT**

The patient was first suspected of having a pulmonary infection based on the results of the high-throughput gene expression analysis of the alveolar lavage fluid; thus, she was treated with meropenem (2 g/q 8 h) for 14 d as per the Sanford Guide to Antimicrobial Therapy. Thoracic CT showed an only minor improvement in the multiple nodules and pleural effusion, following which, immunohistochemical staining of the resected nodule specimens confirmed the diagnosis of P-EHE. The subsequent therapeutic strategy included four cycles of apatinib combined with chemotherapy. Chemotherapy was started with doxorubicin (40 mg/m2; day 1) and cyclophosphamide (450 mg/m2; days 1-3), along with 250 mg daily dosage of apatinib.

**OUTCOME AND FOLLOW-UP**

The patient showed mild resolution of chest tightness and cough at 2 mo after two cycles of apatinib combined with chemotherapy. The clinical status of the patient showed a dramatic improvement with resolution of chest pain, chest tightness, and cough at 4 mo after four cycles of combination therapy. Finally, the patient became completely asymptomatic at 5 mo after four cycles of combination therapy. Meanwhile, the multiple pulmonary nodules were stable in both size and density on CT scan at the 8-month follow-up after combined treatment (Figure 2B). The patient was under the combined therapy for 4 mo; she had grade III-IV leukopenia and mild nausea after chemotherapy. She could not tolerate the side effects of chemotherapy and refused to continue the administration of doxorubicin + cyclophosphamide further. Thus, after 4 mo of apatinib combined with chemotherapy, she only continued apatinib monotherapy, which has been continued to date. The patient remained stable both in terms of lung nodule number and clinical status at the subsequent 2-year follow-ups (Figure 2C).

**DISCUSSION**

EHE demonstrates a low-to-intermediate grade malignancy and has metastatic potential with the lung and liver being the most commonly affected organs. EHE not only has composition of solid nests and short cords of epithelioid endothelial cells in myxohyaline stroma, but also shows the presence of increased mitotic activity and necrosis and greater nuclear atypia[8,9]. Tanas *et al*[10,11] reported that *WWTR1*/*CAMTA1* gene fusion is a biological characteristic of P-EHE. Another hypothesis for this rare disease is that chronic *Bartonella* infection maybe have a causal relationship with EHE[12]. P-EHE with an epithelioid appearance has minor or nonspecific pulmonary clinical manifestations, but many patients are asymptomatic and bilateral multiple nodules are often incidentally observed by imaging. However, given its rare incidence, there is no consensus on P-EHE treatment; surgical resection should be performed if possible. A previous report describes a P-EHE case with multiple nodules wherein 32 pulmonary nodules were resected, and the patient was still alive 11 years after the surgery[13]. However, most patients with unresectable bilateral multiple nodules are usually treated with chemotherapy, anti-angiogenic treatment, or radiotherapy.

Several cases of chemotherapy treatment for unresectable P-EHE have been reported, showing variable efficacies. In a previous study, patients with P-EHE who underwent chemotherapy with carboplatin, paclitaxel, and bevacizumab showed short-term stabilization for 10 mo[14]. In another report, after the fourth cycle of chemotherapy with carboplatin, pemetrexed, and bevacizumab in a P-EHE patient, left pleural effusion was well-controlled with a 90% reduction[15]. [Geramizadeh](https://www.ncbi.nlm.nih.gov/pubmed/?term=Geramizadeh%20B%5BAuthor%5D&cauthor=true&cauthor_uid=24753647) reported that a patient who received mesna, doxorubicin, ifosfamide, and dacarbazine (MAID regimen) showed long-term stability for more than 6 mo[16]. Further, a patient who underwent three cycles of chemotherapy with paclitaxel showed the involvement of other organ nodules such as mediastinal lymph nodes and liver nodules on CT imaging. The patient was alive for 7 mo after a confirmed diagnosis of P-EHE[17]. In another study, a P-EHE patient was treated with azathioprine and prednisone without any response. Thereafter, the patient did not undergo any further treatment, and showed no evidence of disease progression for 6 years[18]. Different chemotherapy regimens have demonstrated varying efficacies and periods of disease stability in P-EHE.

Vascular endothelial growth factor (VEGF) and VEGF receptor have been reported on P-EHE cells[19,20]. Apatinib, which selectively binds to VEGFR-2 as a tyrosine kinase inhibitor, exerts broad spectrum anti-tumor effects[21]. A P-EHE patient who received apatinib for a month showed dramatic improvements in clinical presentation and on CT imaging. However, the patient’s disease progressed, and his clinical status gradually aggravated after dose escalation; the patient survived for 6 mo[22]. Another patient was reported to receive pazopanib treatment and achieved disease stability for a period of 24 mo[23]. Thus, the use of VEGF inhibitors may be a reasonable therapeutic strategy for patients with P-EHE.

Radiation therapy is ineffective because of the slow growth of P-EHE, but is used as a symptomatic palliative treatment against pain caused by bone involvement in bone metastasis[24,25]. Sardaro *et al*[26] reported a patient with P-EHE presenting with vertebral metastasis (L3 and L4 vertebrae), wherein a course of radiotherapy with individual doses of 200 cGy/d for 5 d/wk was administered, and the patient’s lumbar pain was resolved.

Cyclophosphamide and doxorubicin have been used for lung carcinoma[27]. In our case, we used apatinib and four cycles of chemotherapy with doxorubicin and cyclophosphamide to treat P-EHE. The patient could not tolerate the side effects of chemotherapy, and only accepted apatinib treatment thereafter. CT scan showed the stabilization of multiple bilateral nodules in our patient, and a dramatic improvement in the clinical presentation was observed. The patient has been alive for more than 24 mo as of today.

**CONCLUSION**

We present the case of a patient with P-EHE who was treated with apatinib combined with chemotherapy (doxorubicin and cyclophosphamide). The patient demonstrated stabilization of bilateral multiple nodules and a dramatic improvement in the clinical presentation. This case presentation aids the efforts to find an effective treatment strategy for P-EHE.

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**Footnotes**

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**Figure Legends**

**图片包含 照片, 不同, 白色, 一群

描述已自动生成Figure 1 18F-fluorodeoxyglucose positron emission tomography/computed tomography.** A: 18F-fluorodeoxyglucose positron emission tomography shows abnormal accumulation of fluorodeoxyglucose throughout the chest, with no other significant findings in the body; B-D: Computed tomography scan of the thorax reveals multiple pulmonary nodules with different sizes.

图片包含 照片, 甜甜圈, 不同, 白色

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**Figure 2 Comparison of chest images before and after treatment.** A: Chest computed tomography (CT) scan on lung window shows diffusely scattered, round, non-calcified nodules in both lungs before treatment; B and C: CT scans at the 8-mo follow-up (B) and 24-mo follow-up (C) after combined treatment. CT image demonstrates stabilization of bilateral multiple nodules both in size and density.

躺在地上

描述已自动生成

**Figure 3 Immunohistochemical findings.** A: Tumor cells, in a short strip form and with epithelial cell features, have no nuclear division and contain abundant eosinophils in the cytoplasm (× 20). B and C: Immunohistochemical analyses for CD34 (B) and CD31 (C) are positive both in the cytoplasm and the tumor cell membrane (× 40); D: Immunohistochemical analysis for Vimentin reveals positivity in the cytoplasm (× 40).