

Apatinib for the treatment of pulmonary epithelioid hemangioendothelioma

A case report and literature review

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Abstract

Rationale: Pulmonary epithelioid hemangioendothelioma (P-EHE) is a rare tumor, with no established standard treatment. Overexpression of vascular endothelial growth factor receptor 2 (VEGFR-2) has been reported in some P-EHE patients. Apatinib, a new small molecule tyrosine kinase inhibitor that specifically targets VEGFR-2, has therapeutic benefits in some advanced tumors. However, its efficacy in P-EHE cases has not been reported.

Patient concerns: Herein, we presented a 44-year-old man with recurrent hemoptysis for approximately 9 years.

Diagnoses: After hospitalization, relevant examinations were conducted. The disease was subsequently diagnosed as P-EHE.

Interventions: The patient underwent pulmonary lobectomy, but subsequently developed multiple metastases. Within the tumor, CD31, CK, and Vimentin were found to be positive, while CD34 was negative. Apatinib was initially administered 250 mg daily doses and after 1 month was increased to 500 mg daily.

Outcomes: He showed noticeable symptomatic improvements and positive imaging changes in the first month of treatment. However, the disease progressed in the following month, despite the increased apatinib dose.

Lessons: Apatinib is possibly a new treatment for P-EHE. However, further clinical trials are necessary to confirm an effective dose and the efficacy and safety of apatinib in P-EHE treatment.

Abbreviations: CT = computed tomography, EHE = epithelioid hemangioendothelioma, P-EHE = pulmonary epithelioid hemangioendothelioma, TKI = tyrosine kinase inhibitor, VEGFR = vascular endothelial growth factor receptor.

Keywords: apatinib, chemotherapy, lung cancer, pulmonary epithelioid hemangioendothelioma, VEGFR inhibitors

1. Introduction

Pulmonary epithelioid hemangioendothelioma (P-EHE) is a rare tumor. It was originally described as an intravascular, bronchiolar, and alveolar tumor (IVBAT) of the lung in 1975 by Dail and Liebow.^[1] The term “epithelioid hemangioendothelioma” (EHE)

was introduced in 1982 by Weiss and Enzinger, which shows its biological features between both hemangioma and angiosarcoma.^[2] EHE was classified as a low- to intermediate-grade malignant vascular tumor, with metastatic potential, in the recent World Health Organization (WHO 2015) classification.^[3] The tumor has a low prevalence and preferentially occurs in females in an approximately 3:1 gender.^[4] The clinical behavior of EHE tumors is unpredictable, with the lungs and liver being the most frequently affected organs. The clinical manifestations of P-EHE are heterogeneous, with majority of patients being symptomatic with weight loss, cough, hemoptysis, chest pain, pleural effusion, or dyspnea.^[5,6] P-EHE typically manifests with bilateral lung and multiple pleura nodules that are usually discovered incidentally by imaging. Biopsy, histology, and immunohistochemistry are essential for diagnosis. The typical macroscopic appearance of EHE is rubbery or having a cartilage-like consistency, with a gray-white to yellow-brown cut surface. The typical microscopic appearance, usually showing low-grade atypia, includes hypercellular periphery of the nodules, hyalinization, hypocellular, necrosis, or calcification of the nodule centers. The nuclei are round or oval with abundant cytoplasm. Lumens formed by the epithelioid tumor cells that contain red blood cells may be observed. Vascular antigens, such as CD31, CD34, Fli-1, or Ulex-1, are expressed in most P-EHE, while CD31 is relatively specific and sensitive. Other antigens, such as vimentin, CK, and EMA, are also partially expressed in P-EHE.^[7-9] However, considering its rarity and unpredictable clinical behavior, a standard treatment for this malignancy has not been established, without

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Ethical approval is not necessary because that it is a case report and literature review, and we do not use any special methods.

Informed consent is not given because that the patient is died, and the use of entirely anonymized CT images does not contain any identifying marks and is not accompanied by text that might identify the individual concerned.

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a large clinical trial to guide therapy having been conducted. Surgical resection, radiotherapy, and chemotherapy have been reported to treat P-EHE, but these modalities have shown varying effectiveness. The significant risk factors for P-EHE include: male gender, cough, hemoptysis, chest pain, multiple unilateral nodules, pleural effusion, and metastases to multiple sites.^[6] The clinical outcome of P-EHE is variable, which ranges from spontaneous regression without treatment to rapid disease progression and death, even with aggressive intervention and management. Kitaichi et al analyzed 21 P-EHE patients throughout Asia using questionnaires. Survival ranged from 0.5 to 12.0 years during the follow-up period, with 3 cases being classified as partial spontaneous regression.^[5] Bagna et al^[10] reported a 5-year survival probability of 60% in 75 P-EHE patients, with those having poor prognosis factors showing a median survival of less than 1 year. Therefore, it is prudent to develop novel therapies for EHE. Given the vascular endothelial origin of EHE, inhibitors of vascular endothelial growth factors (VEGF) can be considered promising treatment options for multifocal EHE that does not qualify for surgical intervention.^[11] Moreover, vascular endothelial growth factors receptor-2 (VEGFR-2) was reported to be overexpressed in some cases of P-EHE.^[12] Apatinib, a tyrosine kinase inhibitor (TKI) that selectively binds to VEGFR-2, exerts broad anti-tumor effects,^[13] which is a potential treatment for this refractory tumor. To the best of our knowledge, this is the first case of metastatic P-EHE treated with apatinib. We also reviewed the literature in the current report by summarizing treatments and outcomes for P-EHE, with a discussion on the effect of VEGFR inhibitors in P-EHE cases.

2. Case report

A 44-year-old man was admitted to our hospital on May 26, 2016 due to recurrent hemoptysis for approximately 9 years. The patient had been in good health until 2007, when coughing with small amounts of bright red blood, without obvious sputum and fever, presented. He was suspected of pulmonary tuberculosis at that time and treated with antituberculosis pharmacotherapy. However, the patient had poor compliance and used the prescribed medicine for 1 month. Hemoptysis repeated with small amounts of bright red blood until October 2015, when the hemoptysis presented with approximately 100 mL of blood on one occasion. He was admitted to another hospital, where a thoracic computed tomography (CT) scan showed a round 5.1 × 4.9 cm nodule in the right middle lobe of the lung, with several small nodules surrounding the larger nodule, as well as presenting with a right encapsulated pleural effusion with pleural calcification, without hilar and mediastinal lymphadenopathy. After a period of administering medication for the nodules, the patient felt no improvement and was subsequently transferred to another hospital for surgery. Lobectomy of the right lung middle lobe, with an empyema evacuation and pleural decortication, was conducted in January 2016. Postoperative histopathological examination showed chronic, inflammatory changes with cavity formation, scattered multinucleated giant cells, mass fibrinoid necrosis, and moderate heterocyst of the excisional pulmonary tissue. Immunohistochemical examination revealed that CD31, CK, and Vimentin were positive and CD34 was negative. Antiacid stain, PSM stain, and PAM stain were all found to be negative. The patient was subsequently diagnosed with P-EHE. Two months after surgery, the hemoptysis relapsed and gradually worsened. The patient sought treatment at several other hospitals, but did not obtain a

favorable therapeutic effect. On May 26, 2016, the patient coughed 3 times with bright red blood and sputum, had chest pain and dyspnea, and was therefore admitted to our hospital.

The patient worked at a rubber company and did not smoke, but did consume 150 to 200 mL of wine on a daily basis for almost 30 years; he had no other peculiar medical history. The patient's father died of lung cancer.

The patient's temperature was 36.1°C, the pulse was 82 bpm, respirations were 21 breaths per minute, blood pressure was 128/75 mm Hg, and his pain score was 6 on a 10 scale.

On physical examination, the patient appeared fatigued and pale. An old oblique scar, about 20 cm in length, was observed on his right chest. Neither lymphadenopathy nor rash was detected. Breath was slightly short and rough sounding, but this was absent in the right middle and lower lung.

Hematologic laboratory and blood chemical tests were unremarkable. The urine test showed microalbuminuria and a stool test showed the presence of occult blood (2+). A thoracic CT scan was performed on May 26, 2016 (Fig. 1), showing increased bilateral lung markings and diffuse lesions, including multiple ill-defined nodules, with the largest (2.1 × 2.4 cm) surrounded by ground-glass opacities and multiple bilateral chest wall and pleural thickening. A cephalic CT scan and a liver ultrasound showed multiple metastases. After a multidisciplinary consultation, considering the patient had no chemotherapeutic and radiotherapeutic indications, and since other VEGFR inhibitors had been reported for the treatment of EHE, he was prescribed apatinib monotherapy with an initial daily dose of 250 mg. The patient began to take apatinib on May 31, 2016. Dramatically, hemoptysis, chest pain, and dyspnea markedly decreased after the 1-month of apatinib administration, with no side effects being observed. Another thoracic CT scan was performed on June 28, 2016 (Fig. 2), showing bilateral lung wild markings that were more clear than before, and the multiple nodules had decreased in

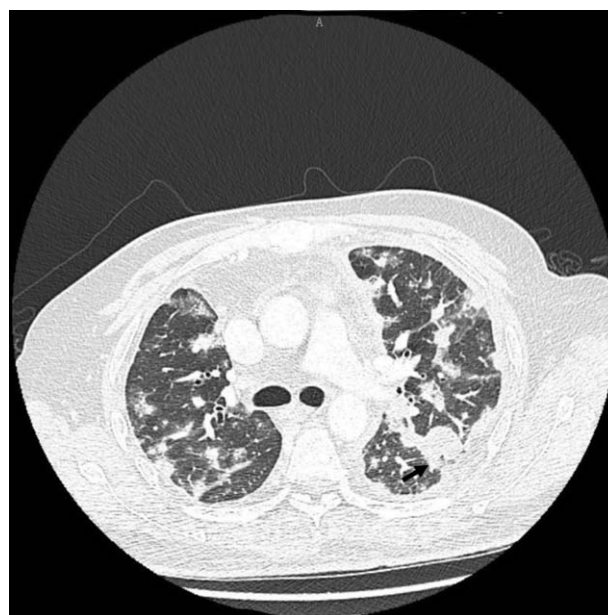


Figure 1. Thoracic CT reveals increased bilateral lung markings and diffuse lesions, including multiple ill-defined nodules, with the largest one (the arrow, 2.1 × 2.4 cm) surrounded by ground-glass opacities and multiple bilateral chest wall and pleural thickening. CT = computed tomography.

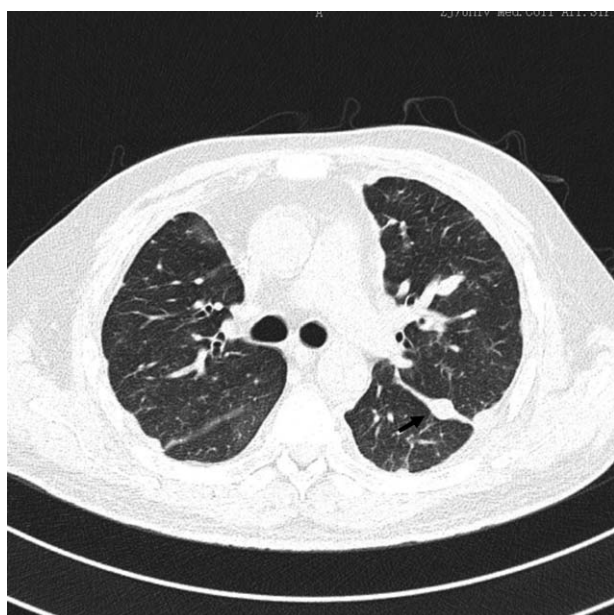


Figure 2. Thoracic CT reveals bilateral lung wild markings that were more clear than before, and the multiple nodules had decreased in size, the largest one (the arrow, 0.8 × 1.2 cm), with unnoticeable surrounding ground-glass opacities and less pleural thickening.

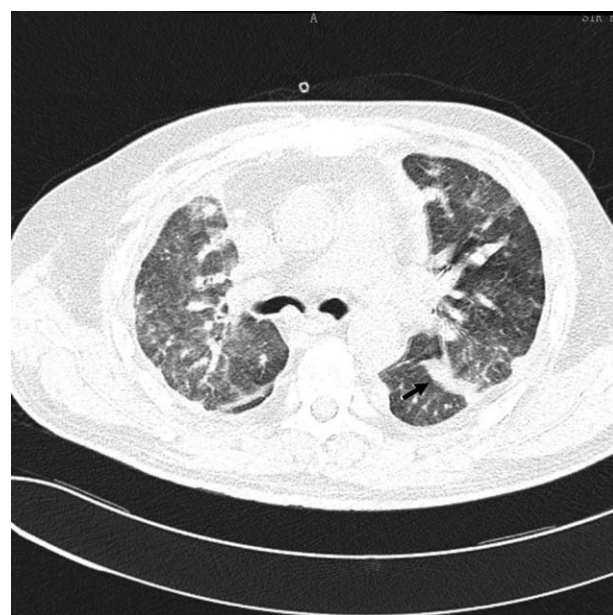


Figure 3. Thoracic CT reveals once again diffuse lesions of bilateral lungs, which were more obvious than previously, with multiple ill-defined nodules, the largest one (the arrow, 1.4 × 2.1 cm), surrounded by ground-glass opacities.

size with less pleural thickening. As the patient seemed to improve, the apatinib dose was increased to 500 mg daily on July 1, 2016. Unfortunately, the patient suddenly coughed about 200 mL of bright red blood on July 3, 2016 with a blood pressure of 150/105 mm Hg. Hypertension was controllable. Selective embolization of the bronchial artery was operated on July 8, 2016, but the patient coughed bright red blood again on July 10, 2016. The general condition of the patient precipitously declined with progressive asthenia, dyspnea, and chest pain. A third thoracic CT scan was performed on July 17, 2016 (Fig. 3), showing once again diffuse lesions of the bilateral lungs, which were more obvious than previously, with multiple ill-defined nodules surrounded by ground-glass opacities and an additional mass in the right lower chest wall invading the liver with several new small mediastinal lymphadenopathies. Soon after, rash, chest tightness, ecchymosis, headache, inability to use the right limbs, and a deflection of the left angle of the mouth developed one after the other. His disease progressed and the treatment was terminated. Six months after surgery, the patient died of respiratory failure (Table 1).

Table 1
Timeline of patient's management.

Date	Event
2016-05-26	Visited our hospital
2016-05-31	Apatinib 250 mg daily chemotherapy
2016-06-28	CT showed good response to apatinib
2016-07-01	Apatinib 500 mg daily chemotherapy
2016-07-03	Hemoptysis relapsed
2016-07-08	Selective embolization of bronchial artery
2016-07-10	Apatinib was stopped
2016-07-17	CT showed disease progressed

CT = computed tomography.

3. Discussion

A standard treatment and consensual management for P-EHE are not presently available because of its low incidence and heterogeneous clinical manifestations. Therefore, we reviewed the case reports of P-EHE published in English, focused therapy and survival years and excluded studies did not state detailed patient information (Table 2).^[4,6,7,14-62] In total, 63 patients were included, comprised of 22 males and 41 females. Age ranged from 13 to 76-years-old, with a mean age of 43.6 years. Nineteen patients (30%) had unilateral pulmonary nodules, and 44 (70%) had bilateral pulmonary nodules, and 26 (41%) had extrapulmonary metastases. In asymptomatic patients, watchful follow-up without intervention is 1 clinical option. Conservative therapy without treatment on some asymptomatic patients has been reported, with one of these patients maintaining a complete response and another was still alive after 10 years without treatment.^[4,44] Jinghong and Lirong^[40] reported an interesting P-EHE case with a unilateral dominant mass. The patient had been asymptomatic without treatment for approximately 23 years, before she began to cough and then underwent a lobectomy. Surgical resection alone is an available option, being proposed on the condition that the lesions are unilateral or limited, which typically results in a positive outcome since no extrapulmonary metastases are present. Notably, extensive lung resection offers the same survival as a wedge resection.^[10] Since only 9% of patients present with lymph node metastasis, the prognostic value of lymph node invasion and resection remains unclear.^[63] Baba et al^[45] reported the longest follow-up case, which had no recurrence of 8 years after surgery, while Adamane et al^[16] reported a 20-years-old boy who died on the 5th postoperative day. However, in some patients with bilateral multiple nodules that cannot be completely resected, surgery remains a treatment option, but is usually followed by chemotherapy or radiotherapy, according to the condition of the patient. Radiation therapy is considered ineffective for P-EHE, because of the tumor's slow

Table 2**Summary of the pulmonary epithelioid hemangioendothelioma case reports in the current literatures.**

Author (year)	n	M/F	Age	Pulmonary nodules	Metastasis	Therapy	Survival years
Calabrese et al ^[14] (2016)	1	0/1	20	Bilateral	Liver	None, paclitaxel	4.5 y
Abdalla et al ^[15] (2016)	1	0/1	42	Unilateral	None	Bevacizumab, radiotherapy	8 mo
Rojas-Vigott et al ^[4] (2016)	1	1/0	47	Unilateral	None	None	4 y (alive)
Adamane et al ^[16] (2016)	1	1/0	20	Bilateral	Bone	Surgery	1 wk
Soo et al ^[17] (2016)	2	1/0, 1/0	59, 62	Unilateral, unilateral	Mediastinum, brain	None, traditional treatment	2 wk, 1 mo
Ro et al ^[18] (2016)	1	1/0	76	Unilateral	Skin	Surgery	6 mo (alive)
Semenisty et al ^[19] (2015)	1	0/1	62	Bilateral	Liver	Pazopanib	2 y (alive)
Sakata et al ^[20] (2016)	1	1/0	46	Bilateral	None	None	1 mo
Desie et al ^[21] (2015)	3	0/1, 0/1, 0/1	45, 23, 49	Bilateral, bilateral, bilateral	Liver, bone, bone	Surgery, interferon-2 α , surgery, interferon-2 α , surgery	10 y, 7 y (alive), 1 y (alive)
Haro et al ^[22] (2015)	1	0/1	42	Bilateral	None	None	4 y (alive)
Salijskva et al ^[23] (2015)	1	0/1	36	Bilateral	None	Surgery, paclitaxel	6 mo
Kim et al ^[24] (2015)	1	1/0	50	Bilateral	None	Surgery	1.5 y (alive)
Eguchi et al ^[25] (2015)	1	0/1	54	Bilateral	Liver	Surgery	11 y (alive)
Albores et al ^[26] (2014)	1	0/1	40	Bilateral	None	Surgery, gemcitabine+, taxotere+adriamycin	5 mo
Donfut et al ^[27] (2014)	1	1/0	56	Unilateral	None	Cisplatin+ifosfamide+, gemcitabine, cisplatin +taxotere, surgery, radiotherapy	2 y (alive)
Geramizadeh et al ^[28] (2014)	1	0/1	60	Unilateral	None	Surgery, doxorubicin+, ifosfamide +dacarbazine	6 mo (alive)
Mucientes et al ^[29] (2014)	1	1/0	19	Bilateral	Spleen, vertebra	Surgery, sorafenib	3 mo
Nizami et al ^[30] (2014)	1	0/1	13	Bilateral	Liver	Etoposide+carboplatin+, sorafenib	died soon
Sardaro et al ^[31] (2014)	1	0/1	46	Bilateral	Spleen	Surgery, radiotherapy, interferon-2 α , ifosfamide+, epirubicin	1 y
Shao et al ^[7] (2014)	4	1/0, 0/1, 0/1, 0/1	54, 54, 46, 30	Bilateral, unilateral, unilateral, bilateral	None, none, none, none	Surgery, surgery, surgery, surgery	7 y (alive), 3 y, 6 mo (alive), 5 mo (alive)
Tan et al ^[32] (2014)	1	0/1	58	Bilateral	None	Doxorubicin, suninibin	4 mo
Ye et al ^[33] (2013)	3	1/0, 0/1, 0/1	40, 54, 44	Bilateral, bilateral, bilateral	Brain, none, none	Carboplatin+paclitaxel+endostar, carboplatin +paclitaxel+bevacizumab carboplatin +paclitaxel	6 mo, 15 mo, 25 mo
Palfoldi et al ^[34] (2013)	1	0/1	42	Bilateral	Bone	Carboplatin+etoposide, docetaxl, pharmorubicin	Stable disease
Gaur et al ^[35] (2012)	1	1/0	35	Bilateral	Bone, mediastinum	Radiation, bevacizumab+, paclitaxel +zoledronic acid	6 mo (alive)
Tochigi et al ^[36] (2011)	1	0/1	50	Unilateral	None	Surgery	25 mo (alive)
Ryu et al ^[37] (2011)	1	1/0	41	Unilateral	None	Surgery, epirubicin+cyclophosphamide	10 mo (alive)
Mizuno et al ^[38] (2011)	2	0/1, 0/1	30, 67	Bilateral, bilateral	None, none	Surgery, surgery	12 mo (alive), 6 mo (alive)
Mizota et al ^[39] (2011)	1	0/1	59	Unilateral	Liver, brain,	Surgery, carboplatin+, paclitaxel +bevacizumab	6 mo
Jinghong et al ^[40] (2011)	1	0/1	20	Bilateral	None	None, surgery	23 y (alive)
Haruki et al ^[41] (2011)	1	0/1	28	Bilateral	None	Surgery	10 mo, (alive)
Cazzuffi et al ^[42] (2011)	1	1/0	67	Bilateral	Liver, spleen	Surgery	8 mo (alive)
Ye et al ^[43] (2010)	1	0/1	55	Bilateral	Liver	None	7 months
Okamura et al ^[44] (2010)	1	0/1	19	Bilateral	None	None	10 y (alive)
Baba et al ^[45] (2010)	1	0/1	51	Bilateral	None	Surgery	8 y (alive)
Kim et al ^[46] (2010)	1	0/1	44	Bilateral	Liver, bone	None, surgery, radiotherapy, carboplatin +paclitaxel+zoledronic acid, carboplatin +paclitaxel+bevacizumab	2 y
Darbari et al ^[47] (2010)	1	0/1	33	Unilateral	None	Surgery	3 y (alive)
Reich et al ^[48] (2010)	1	0/1	15	Bilateral	None	Surgery	3 mo (alive)
Ouadnoui et al ^[49] (2009)	1	1/0	45	Unilateral	None	Surgery	30 mo (alive)
Shang et al ^[50] (2009)	1	0/1	40	Unilateral	Bone	Surgery	1 mo
Schattenberg et al ^[51] (2008)	3	0/1, 1/0, 0/1	44, 68, 30	Bilateral, bilateral, bilateral	Liver, none, none	Surgery, surgery, ifosfamide+adriamycin, radiotherapy, surgery	16 mo (alive), 2 y (suicide), 3 y (alive)
Radzikowska et al ^[52] (2008)	1	0/1	62	Bilateral	None	Interferon-2 α	6 mo (alive)
Saleiro et al ^[53] (2008)	1	1/0	39	Bilateral	None	Interferon-2 α	9 mo
Bahrami et al ^[54] (2008)	1	1/0	37	Unilateral	Pericardium, skin	Radioerapy, cisplatin+etoposide	11 mo
Watanabe et al ^[55] (2008)	1	1/0	53	Unilateral	None	None, surgery	8.5 y (alive)
Belmont et al ^[56] (2008)	1	1/0	41	Bilateral	None	Surgery, cisplatin+etoposide, interferon-2 α , carboplatin+, paclitaxel+bevacizumab	13 mo (alive)
Anagnostou et al ^[57] (2007)	1	0/1	36	Bilateral	None	None	2 y
Amin et al ^[6] (2006)	1	0/1	70	Unilateral	None	Surgery	31 mo (alive)
Chen et al ^[58] (2006)	1	0/1	58	Bilateral	Mediastinum	None, radiotherapy, carboplatin+etoposide	20 y (alive)
Iwashima et al ^[59] (2005)	1	0/1	51	Bilateral	None	None	24 mo (alive)
Hanada et al ^[60] (2003)	1	1/0	45	Unilateral	None	None	66 mo
van Kasteren et al ^[61] (1995)	1	1/0	10	Bilateral	Bone, liver	Radiation, doxorubicin	21 y
Miettinen et al ^[62] (1987)	1	0/1	17	Bilateral	Retropertoneum	Surgery	24 y

F = female, M = male.

growth and radiobiological characteristics, but it can be used as a symptomatic palliative treatment to control bone metastasis presentation or relieve pain associated with bone involvement.^[10,64] Various chemotherapies, which also show variable effectiveness, have been reported for unresectable or metastatic P-EHE cases. Paclitaxel or platinum-based chemotherapy tends to be the most utilized chemotherapy regents. Paclitaxel alone did not stop progression in 2 cases.^[14,2,3] A combination chemother-

apy of carboplatin and paclitaxel resulted in short-term stable disease with no change in the nodule size for 1 patient, but this effect was not observed in another patient.^[33,46] Platinum combined with etoposide was used in a P-EHE patient after 20 asymptomatic years.^[58] The same combination chemotherapy resulted in progressive disease in 3 other patients,^[30,54,56] but showed partial regression in another patient.^[34] Although ifosfamide and anthracyclines are commonly used in the

Table 3**Vascular endothelial growth factor inhibitors and their best response to epithelioid hemangioendothelioma in the literatures.**

VEGFR inhibitor	Author (year)	N	Best response
Pazopanib	Kollar et al ^[66] (2017)	1	CR
		1	PR
		4	SD
		3	PD
		1	Unknown
Sorafenib	Bally et al ^[67] (2015)	1	SD
	Kobayashi et al ^[69] (2016)	1	PR
	Chevreau et al ^[70] (2013)	1	PR
		3	SD
Sunitinib	Sangro et al ^[68] (2012)	1	SD
		1	SD
		1	SD
	Prochilo et al ^[72] (2013)	1	SD
	Tilkach et al ^[73] (2012)	1	SD

CR=complete response, PD=progressive disease, PR=partial response, SD=stable disease.

treatment of patients with advanced soft tissue sarcomas, their effect on P-EHE remains unclear. van Kasteren et al^[61] reported an advanced P-EHE patient who poorly tolerated doxorubicin, which did not result in stopping tumor progression. Schattenberg et al and Sardaro et al each reported a patient who showed no response to chemotherapy consisting of adriamycin or epirubicin with ifosfamide, respectively.^[31,51] Although Geramizadeh et al^[28] reported a patient treated with postoperative chemotherapy including doxorubicin, ifosfamide, mesna, and dacarbazine was stable during 6 months of follow-up, this may due to unilateral nodules and no metastasis. Since P-EHE has a vascular origin, bevacizumab, interferon-2 α , sorafenib, and sunitinib have been administered to patients with advanced P-EHE. Belmont et al^[56] reported the first case of a P-EHE treated with carboplatin, paclitaxel, and bevacizumab, as a third choice postoperative chemotherapy, which resulted in stable disease for at least 13 months. The same combination chemotherapy improved patients' systems and obtained disease stabilization in 2 cases,^[33,39] but failed to stop disease progression in 1 case.^[46] Considering its antiangiogenic activity, interferon-2 α also has been used in several cases, with disease stabilization observed, but the adverse response of interferon therapy should be paid attention.^[52] Both sorafenib and sunitinib are VEGFR inhibitors that have antiangiogenic ability, but P-EHE patients did not respond to them in a few case studies.^[29,30,32] However, another VEGFR inhibitor, pazopanib, was given to a P-EHE patient for more than 2 years, which resulted in stable disease.^[19] Combination chemotherapy, including antiangiogenic drugs, appears to benefit P-EHE patients. However, further large studies are needed to determine the efficacy of these treatments for P-EHE patients.

In addition, these 3 VEGFR inhibitors, sorafenib, pazopanib, and sunitinib, were previously reported in the treatment of other EHE cases (Table 3). All of these agents are multitargeted tyrosine kinase inhibitors acting not only on the VEGFR-1/2/3 tyrosine kinases but also other targets.^[13,65] Kollar et al^[66] retrospectively studied 10 EHE patients who were treated with pazopanib, and found a clinical benefit (response or stable disease) rate of 60% and a median progression-free survival of 26.3 months. While Bally et al^[67] reported that pazopanib resulted in a longer period of disease stabilization (over 8 years) for 1 patient. Durable stabilization was also observed in sorafenib therapy, with partial response for 5 years and stable disease in almost 2 years being observed in previous reports.^[68,69] In a phase 2 study of

progressive EHE patients treated with sorafenib, the 2-, 4-, 6-, and 9-month progression-free survival was 84.6% (11 of 13), 46.4% (6 of 13), 38.4% (5 of 13), and 30.7% (4 of 13), respectively.^[70] In contrast, only 3 EHE patients who were treated with sunitinib have been previously reported, with stabilization lasting about 10 months, 2 years, and 6 years, respectively.^[71-73] In total, the clinical benefit rate of VEGFR inhibitors was 55.1% (16 of 29), with several observed adverse events, not including bleeding, but was manageable in the limited literature of EHE. However, the VEGFR expression level of these EHE patients who benefited from VEGFR inhibitors is unknown.

In our clinical case, we used apatinib monotherapy since the patient had multiple organ metastases and could not tolerate conventional chemotherapy. Apatinib, a small molecule acting as a TKI of vascular endothelial growth factor receptor that selectively binds to VEGFR-2, is one of the latest developed oral administered, antiangiogenic agents that can potentially treat a variety of advanced solid tumors.^[13] Moreover, Stacher et al^[12] reported VEGFR-2 overexpression in 5 of 8 P-EHE cases. In addition, we have reviewed the biology of VEGFR-1, -2, and -3. The precise function of VEGFR-1 is still under debate. One proposition is that VEGFR-1, both the membrane-bound form and the soluble form, is a negative regulator of VEGFR action, serving as a decoy receptor preventing VEGF binding to VEGFR-2.^[74] VEGFR-2 plays an important role in the development of angiogenesis and hematopoiesis,^[74] and appears to mediate the vast majority of the known cellular responses to VEGF.^[75] Furthermore, heterodimerization with VEGFR-2 is necessary for VEGFR-3 to exert its function^[76]. Considering the key role of the VEGF-VEGFR system, especially VEGFR-2 in angiogenesis and metastasis of tumor, the application of targeted therapy may be feasible in P-EHE patients. To the best of our knowledge, this is the first report of apatinib monotherapy to treat P-EHE. After receiving apatinib for about a month, the patient showed dramatic improvement in the clinical status, as well as on CT imaging (Fig. 2). However, the patient's disease progressed and his general status gradually deteriorated after dose escalation. Previously, a phase III trial of apatinib in advanced gastric cancer patients reported an adverse event rate of bleeding of 19.9% for any grade and 3.4% for grade 3 or 4 bleeding with a daily dose of 850 mg.^[77] Therefore, this may be the cause of the hemoptysis observed in our case. However, EHE tumors have a wide spectrum of behavior from indolent to aggressive, so there is uncertainty as to whether the increased dose or tumor characteristics contributed to the patient's deterioration. Therefore, it is important to balance chemotherapy dose and tumor control. When the vascular origin of P-EHE is considered, targeted antiangiogenic agents, such as apatinib and others, appear to be beneficial for treatment. However, more studies are needed to identify the clinicopathological features of patients who benefit from VEGFR inhibitors, as well as whether 1 particular VEGFR inhibitor is optimal for a specific patient with EHE.

In conclusion, antiangiogenic therapy may be a promising treatment for advanced P-EHE due to the expression of VEGFR-2 in this malignancy. Apatinib as a targeted therapy may have a more promising role in treating selected advanced P-EHE patients than multitargeted agents acting on various tyrosine kinases. However, further studies using large sample sizes are required to determine the safety and efficacy of apatinib for treating P-EHE.

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