

CASE REPORT

Open Access

# Pazopanib for metastatic pulmonary epithelioid hemangioendothelioma—a suitable treatment option: case report and review of anti-angiogenic treatment options

Valeriya Semenisty<sup>1</sup>, Inna Naroditsky<sup>2</sup>, Zohar Keidar<sup>3</sup> and Gil Bar-Sela<sup>1\*</sup>

## Abstract

**Background:** Epithelioid hemangioendothelioma is a rare vascular tumor of borderline or low-grade malignancy. The lungs and liver are the two common primary organs affected. Metastatic disease was reported in more than 100 cases in the literature. However, no firm conclusions can be determined for recommended treatment options.

**Case presentation:** The current case presents a patient with metastatic pulmonary epithelioid hemangioendothelioma to the cervical and mediastinal lymph nodes, lungs and liver that has been treated with pazopanib for more than two years with PET avid complete metabolic response in the mediastinum and lungs, and long-lasting stable disease. Target therapies that block VEGFR have a logical base in this rare malignancy.

**Conclusions:** The current case is the first to report objective, long-lasting response to pazopanib.

**Keywords:** Epithelioid hemangioendothelioma, Pulmonary, Pazopanib, VEGFR

## Background

Pulmonary epithelioid hemangioendothelioma (PEH) was first described by Dail *et al.* in 1983, who called it an intravascular bronchioloalveolar tumor [1]. Development of immunohistochemical techniques confirmed its endothelial lineage, and Wiess *et al.* subsequently suggested the current name, “epithelioid hemangioendothelioma” [2]. Immunohistochemistry for PEH showed diffuse cytoplasmic staining of the malignant cells, with some or all of the vascular-endothelial markers (CD31, CD34 and factor VIII) [3].

Epithelioid hemangioendothelioma (EHE) is a rare vascular tumor of borderline or low-grade malignancy. The lungs and liver are the two common organs for primary EHE, but it can spread through the bloodstream to other sites, such as bone and soft tissue. According to a literature review, nearly 100 cases have been described, mainly discussing a differential diagnosis [4]. The treatment options in metastatic disease are not well

established. The current case presents a patient with metastatic PEH that was treated with pazopanib as first line of treatment.

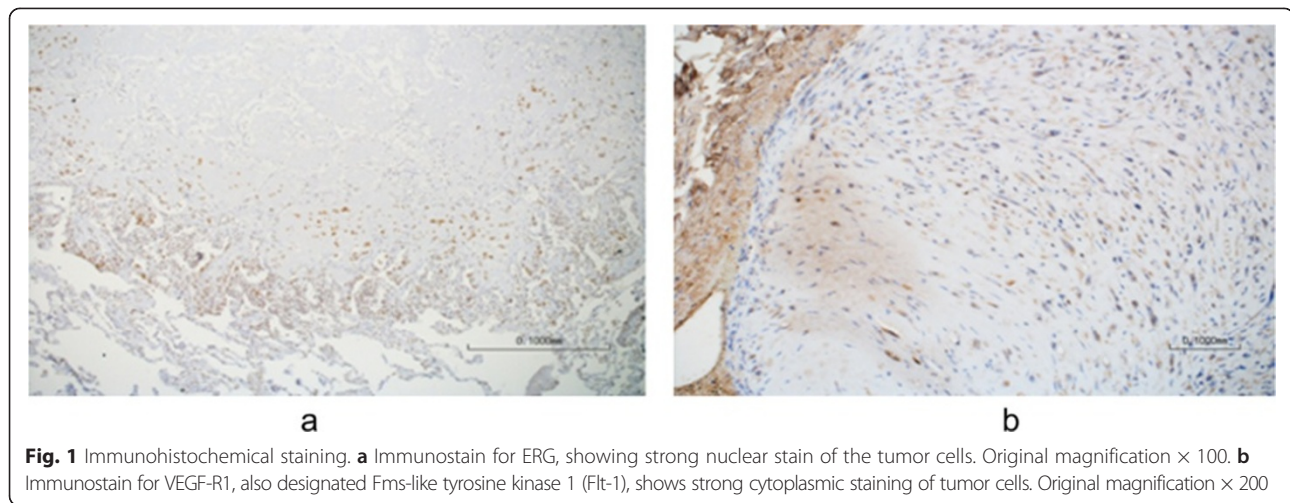
## Case presentation

In December 2011, a 62-year old woman was referred to our Emergency Department with a history of progressive chest pain in the preceding 3 months. She had no prior medical history, was a non-smoker, and denied any history of cardiovascular diseases. CT scan revealed multiple nodules in both lungs up to 6 mm in diameter, multiple cervical lymph nodes up to 10 mm, and unclear lesions in the liver.

For pathological diagnosis, the patient underwent thorascopic surgery with wedge resection of two lesions from the right lung. Immunohistochemical (IHC) stains demonstrated positive staining for endothelial markers CD31, CD34, FLI-1, and ERG, representing epithelioid hemangioendothelioma. The stain for ERG is shown in Fig. 1a. IHC was performed also for vascular endothelial growth factor receptor 1 (VEGFR1), and was found to be strongly positive (Fig. 1b).

\* Correspondence: g\_barsela@rambam.health.gov.il

<sup>1</sup>Integrated Oncology and Palliative Care Unit, Rambam Health Care Campus and Technion-Israel Institute of Technology, POB 9602, Haifa 31096, Israel  
Full list of author information is available at the end of the article



In March 2012, before treatment was started, for final evaluation of unclear liver lesions, 18F-FDG PET-CT was performed and showed increased pathological uptake of 18F-FDG in the pulmonary nodules, cervical and mediastinal lymph nodes, and the liver (Fig. 2a, b).

Following the advanced disease shown by the PET-CT and the patient's dyspnea, treatment with pazopanib in the standard dose of 800 mg orally once daily was started in April 2012. The treatment was given for more than 2 years without any side effects, except grade I fatigue. Other treatment options, such as interferon-alpha or chemotherapy, were discussed with the patient before treatment but were postponed by the patient due to concerns of possible side effects.

Since the disease had been initially demonstrated on PET scan, FDG-PET-CT was performed again in February 2013 and demonstrated disappearance of the pathological uptake in the mediastinal lymph nodes and in the lung lesions, with reduced metabolic response in the liver (Fig. 2c, d). The last FDG-PET-CT in June 2014 showed stable disease, without changes compared to February 2013.

## Discussion

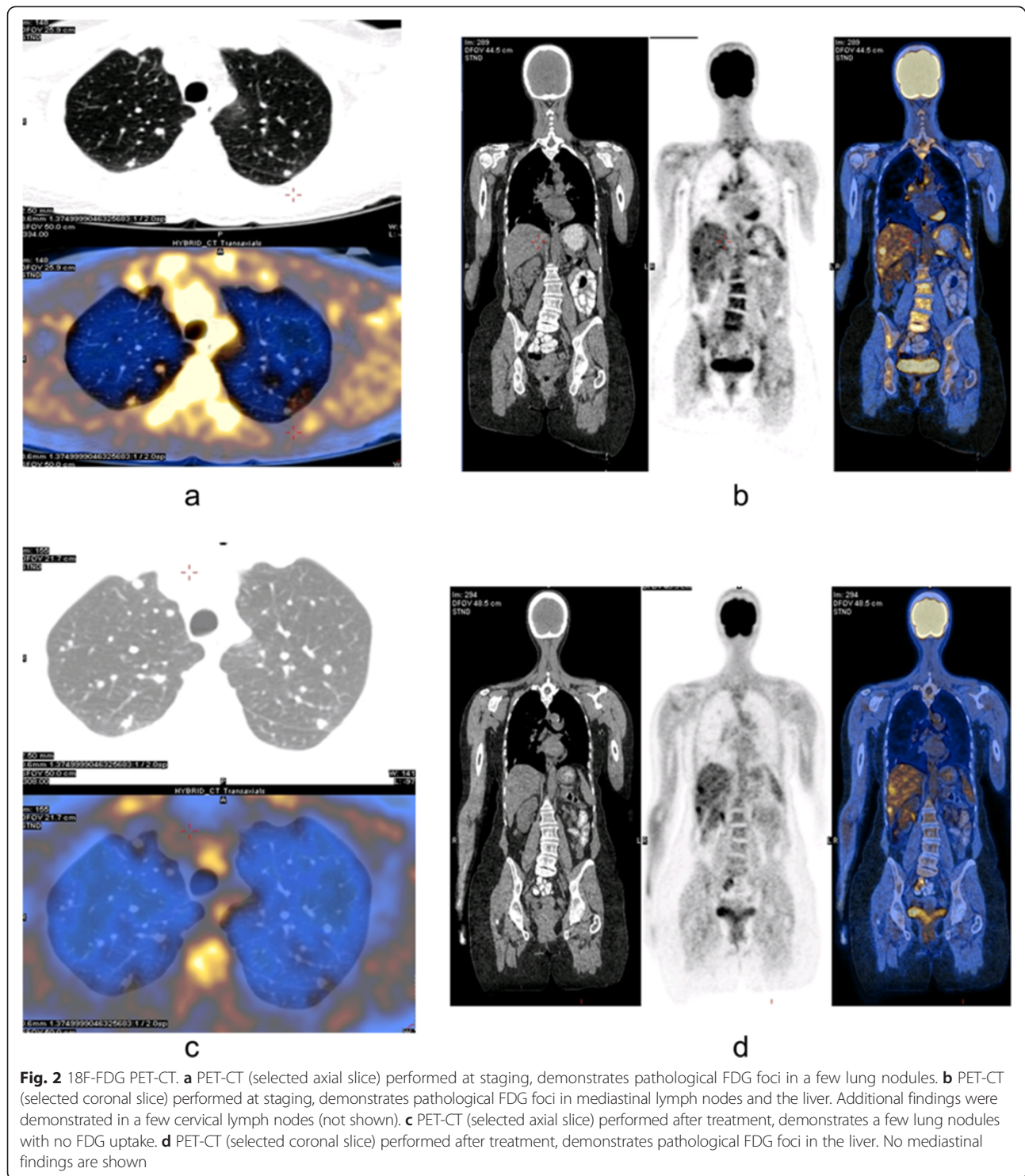
According to a literature review, only 108 cases of this rare tumor involving the lungs have been published. The largest series of PEH published in 2006 contained 93 cases. The authors found an average age of  $40.1 \pm 17.3$  years, with a female predominance of 73 %. Almost half the patients (49.5 %) were asymptomatic at diagnosis. Reported symptoms were dyspnea and cough (18.3 % each), chest pain (16 %), hemoptysis and weight loss (6.5 % each) [4].

Epithelioid hemangioendothelioma can be primary in the lung or pleura, or it may arise in liver, soft tissue or bone. The prognosis is very unpredictable, with life expectancy ranging from 1 to 15 years [5].

The poor prognostic factors of PEH include the presence of respiratory symptoms or pleural effusion at diagnosis, extensive intravascular, endobronchial or interstitial tumor spreading, hepatic metastases, peripheral lymphadenopathy, or the presence of spindle cells in the tumor [2]. However, the worst prognosis was for patients with pleural effusion or hemoptysis, with a median survival of less than 1 year [4]. The current patient had several poor prognostic factors (respiratory symptoms, hepatic metastases, and peripheral lymphadenopathy).

There is no established standard treatment for PEH, due to the rarity of the disease. Surgical resection should be performed if possible. In asymptomatic patients with diffuse lesions, watchful waiting is an acceptable option [1, 6]. Radiotherapy is not effective in certain patients due to the slow growth of the tumor cells, and chemotherapy appears to have little effect [7–9]. A few cases reported response or stable disease following immunotherapy treatment with interferon alpha [10–14].

Although its etiology remains unknown, immunohistochemical and electron microscopy studies have revealed that PEH is of endothelial origin [3]. Lymphatic dissemination is extremely rare, thus supporting the endothelial origin of the tumor. Vascular endothelial growth factor (VEGF) and the VEGF receptor were found on PEH tumor cells [15, 16], suggesting that VEGF inhibitors may be a potential treatment for PEH. In a review published a few years ago, anti-angiogenesis agents in angiosarcoma and EHE are discussed but, except for specific activating mutations in VEGFR2, which may be effectively targeted by VEGFR TKIs in some angiosarcomas, the biological mechanisms underlying the activity of these agents in angiosarcoma and EHE are poorly understood [17]. However two small phase II studies were performed with anti-angiogenic drugs in EHE. In a study by Agulnik *et al.*, testing the effect of bevacizumab alone in angiosarcoma



and EHE, seven patients with EHE were included; two had partial response (PR) and four had stable disease (SD) [18]. In a sub-group report of 15 patients with EHE who were included in the phase II study of the French Sarcoma group testing the effect of sorafenib in sarcoma patients, only two had PR and five had SD [19].

Pazopanib is a second-generation tyrosine kinase inhibitor with highly selective activity against VEGFR, PDGFR, and c-KIT, which has demonstrated significant clinical benefit in a variety of malignancies, especially for the treatment of metastatic renal cell carcinoma [20]. The PALETTE (Pazopanib Explored In Soft Tissue



Sarcoma) study was the first randomized phase III trial demonstrating the efficacy of this anti-angiogenic agent in pretreated soft tissue sarcoma (STS) patients, and 10 % of the patients in the pazopanib group had low-grade sarcomas [21].

In the current case, the patient is still on treatment with pazopanib, with partial response after a few months and prolonged stable disease for up to 24 months based on follow-up with a CT-PET-FDG scan. Considering that chemotherapy is generally ineffective in epithelioid hemangioendothelioma, angiogenesis inhibition is a reasonable approach to manage patients with metastatic EHE.

In a literature review for PEH cases and different target anti-angiogenic medication, only eight patients who received chemotherapy and bevacizumab were found [6, 9, 15, 16, 22–24]. Those cases are summarized in Table 1. Partial response was reported in one case only, with the combination of paclitaxel and carboplatin [22]. Other reports of target therapy treatment in this entity were not found.

Although the mechanism of action of thalidomide and its analog, lenalidomide, is not fully understood, they are believed to have immunomodulatory as well as anti-angiogenic properties that logically can fit the treatment of

this rare malignancy. A PubMed search using “thalidomide” and “hemangioendothelioma” identified five case reports [25–29], while “lenalidomide” and “hemangioendothelioma” identified only two case reports [30, 31]. However, none of these had primary thoracic involvement. These cases are also summarized in Table 1, which shows that two cases had partial responses that lasted up to 9 years in one case and another two patients had stable disease lasting up to 7 years.

## Conclusions

In conclusion, based on the presentation of VEGFR1in pulmonary epithelioid hemangioendothelioma cells, target therapies that block VEGFR have a logical base in this rare malignancy. The current case is the first to report objective, long-lasting response to pazopanib.

## Consent

Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

**Table 1** Summary of patients with epithelioid hemangioendothelioma treated with anti-angiogenic therapy

First author (ref)	No.pts.	Median age	Gender	Treatment medications	Response
Gaur S [6]	1	35	M	Bevacizumab, Nab-Paclitaxel	SD
Belmont [22]	1	41	M	Bevacizumab, Carboplatin, Paclitaxel	PR
Kim [15]	1	44	F	Bevacizumab, Carboplatin, Paclitaxel	PD
Lopes [16]	1	51	M	Bevacizumab, Carboplatin, Etoposide	PD
Mizota [23]	1	59	F	Bevacizumab, Carboplatin, Paclitaxel	PD
Ye [9]	1	44	F	Bevacizumab, Carboplatin, Paclitaxel	SD
Lazarus [24]	1	42	M	Bevacizumab, Paclitaxel	PD
	1	42	M	Carboplatin, Etoposide	PD
Salech [25]	1	40	F	Thalidomide	PR
Raphael et al. [26]	1	53	F	Thalidomide	SD
Kassam et al. [27]	1	13	F	Thalidomide	PD
Bolke et al. [28]	1	47	M	Thalidomide	PD
Mascarenhas et al. [29]	1	52	M	Thalidomide	PR
Pallotti et al. [31]	1	73	M	Lenalidomide	SD
Sumrall et al. [30]	1	31	F	Lenalidomide	SD
Agulnik et al. [18]	2	NA	NA	Bevacizumab	PR
	1	NA	NA	Bevacizumab	PD
	4	NA	NA	Bevacizumab	SD
Chevreau et al. [19]	5	NA	NA	Sorafenib	SD
	2	NA	NA	Sorafenib	PR
	8	NA	NA	Sorafenib	PD

PR partial response, PD progressive disease, SD stable disease

**Competing interests**

The authors declare that they have no competing interests.

**Authors' contributions**

VS - drafted the manuscript; IN - pathology review; ZK - imaging review; GBS - treated the patient and helped to draft the manuscript. All authors read and approved the final manuscript.

**Acknowledgements**

The authors thank Mrs. Myrna Perlmutter for her help in the preparation of this paper. Funding for this service was provided by the Division of Oncology, Rambam Health Care Campus, Haifa, Israel.

**Author details**

<sup>1</sup>Integrated Oncology and Palliative Care Unit, Rambam Health Care Campus and Technion-Israel Institute of Technology, POB 9602, Haifa 31096, Israel.

<sup>2</sup>Institute of Pathology, Rambam Health Care Campus and Technion-Israel Institute of Technology, Haifa, Israel. <sup>3</sup>Department of Nuclear Medicine, Rambam Health Care Campus and Technion-Israel Institute of Technology, Haifa, Israel.

Received: 12 November 2014 Accepted: 29 April 2015

Published online: 13 May 2015

**References**

- Dail DH, Liebow AA, Gmelich JT, Friedman PJ, Miyai K, Myer W, et al. Intravascular, bronchiolar, and alveolar tumor of the lung (IVBAT). An analysis of twenty cases of a peculiar sclerosing endothelial tumor. *Cancer*. 1983;51:452–64.
- Weiss SW, Ishak KG, Sweet DE, Enzinger FM. Epithelioid hemangioendothelioma and related lesions. *Semin Diagn Pathol*. 1986;3:259–87.
- Gray MH, Rosenberg AE, Dickersin GR, Bhan AK. Cytokeratin expression in epithelioid vascular neoplasms. *Hum Pathol*. 1990;21:212–7.
- Amin RM, Hiroshima K, Kokubo T, Nishikawa M, Narita M, Kuroki M, et al. Risk factors and independent predictors of survival in patients with pulmonary epithelioid haemangioendothelioma. Review of the literature and a case report. *Respirology*. 2006;11:818–25.
- Rosengarten D, Kramer M, Amir G, Fuks L, Berkman N. Pulmonary epithelioid haemangioendothelioma. *Isr Med Assoc J*. 2011;13:676–9.
- Gaur S, Torabi A, O'Neill TJ. Activity of angiogenesis inhibitors in metastatic epithelioid hemangioendothelioma: a case report. *Cancer Biol Med*. 2012;9:133–6.
- Van Kasteren ME, Van der Wurff AA, Palmén FM, Dolman A, Misere JF. Epithelioid haemangioendothelioma of the lung: clinical and pathological pitfalls. *Eur Respir J*. 1995;8:1616–9.
- Azumi N, Churg A. Intravascular and sclerosing bronchioloalveolar tumor. A pulmonary sarcoma of probable vascular origin. *Am J Surg Pathol*. 1981;5:587–96.
- Ye B, Li W, Feng J, Shi JX, Chen Y, Han BH. Treatment of pulmonary epithelioid hemangioendothelioma with combination chemotherapy: report of three cases and review of the literature. *Oncol Lett*. 2013;5:1491–6.
- Erasmus JJ, McAdams HP, Carraway MS. A 63-year-old woman with weight loss and multiple lung nodules. *Chest*. 1997;111:236–8.
- Roudier-Pujol C, Enjolras O, Lacrolique J, Guillemette J, Herbreteau D, Leibowitch M, et al. Multifocal epithelioid hemangioendothelioma with partial remission after interferon alfa-2a treatment. *Ann Dermatol Venereol*. 1994;121:898–904.
- Radzikowska E, Szczepulska-Wojcik E, Chabowski M, Onisz K, Langfort R, Roszkowski K. Pulmonary epithelioid haemangioendothelioma—interferon 2-alpha treatment—case report. *Pneumonol Alergol Pol*. 2008;76:281–5.
- Marsh Rde W, Walker MH, Jacob G, Liu C. Breast implants as a possible etiology of epithelioid hemangioendothelioma and successful therapy with interferon-alpha2. *Breast J*. 2005;11:257–61.
- Demir L, Can A, Oztop R, Dirican A, Bayoglu V, Akyol M, et al. Malignant epithelioid haemangioendothelioma progressing after chemotherapy and interferon treatment. *J Cancer Res Ther*. 2013;9:125–7.
- Kim YH, Mishima M, Miyagawa-Hayashino A. Treatment of pulmonary epithelioid hemangioendothelioma with bevacizumab. *J Thorac Oncol*. 2010;5:1107–8.
- Lopes T, Clemente S, Feliciano A, Lourenço I, Costa A, Gil DJ. Pulmonary epithelioid hemangioendothelioma -rarity, diagnosis and treatment difficulties. *Rev Port Pneumol*. 2009;15:1167–74 (in Portuguese).
- Park MS, Ravi V, Araujo DM. Inhibiting the VEGF-VEGFR pathway in angiosarcoma, epithelioid hemangioendothelioma, and hemangiopericytoma/solitary fibrous tumor. *Curr Opin Oncol*. 2010;22:351–5.
- Agulnik M, Yarber JL, Okuno SH, von Mehren M, Jovanovic BD, Brockstein BE, et al. An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. *Ann Oncol*. 2013;24:257–63.
- Chevreau C, Le Cesne A, Ray-Coquard I, Italiano A, Cioffi A, Isambert N, et al. Sorafenib in patients with progressive epithelioid hemangioendothelioma. *Cancer*. 2013;14:2639–44.
- Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med*. 2013;369:722–31.
- van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2012;379:1879–86.
- Belmont L, Zemoura L, Couderc LJ. Pulmonary epithelioid haemangioendothelioma and bevacizumab. *J Thorac Oncol*. 2008;3:557–8.
- Mizota A, Shitara K, Fukui T. Bevacizumab chemotherapy for pulmonary epithelioid hemangioendothelioma with severe dyspnea. *J Thorac Oncol*. 2011;6:651–2.
- Lazarus A, Fuhrer G, Malekiani C, McKay S, Thurber J. Primary pleural epithelioid hemangioendothelioma (EHE)—two cases and review of the literature. *Clin Respir J*. 2011;5:e1–5.
- Salech F, Valderrama S, Nervi B, Rodriguez JC, Oksenberg D, Koch A, et al. Thalidomide for the treatment of metastatic hepatic epithelioid hemangioendothelioma: a case report with a long term follow-up. *Ann Hepatol*. 2011;10:99–102.
- Raphael C, Hudson E, Williams L, Lester JF, Savage PM. Successful treatment of metastatic hepatic epithelioid hemangioendothelioma with thalidomide: a case report. *J Med Case Rep*. 2010;4:413.
- Kassam A, Mandel K. Metastatic hepatic epithelioid hemangioendothelioma in a teenage girl. *J Pediatr Hematol Oncol*. 2008;30:550–2.
- Bölke E, Gripp S, Peiper M, Budach W, Schwarz A, Orth K, et al. Multifocal epithelioid hemangioendothelioma: case report of a clinical chamaeleon. *Eur J Med Res*. 2006;11:462–6.
- Mascarenhas RC, Sanghvi AN, Friedlander L, Geyer SJ, Beasley HS, Van Thiel DH. Thalidomide inhibits the growth and progression of hepatic epithelioid hemangioendothelioma. *Oncology*. 2004;67:471–5.
- Sumrall A, Fredericks R, Berthold A, Shumaker G. Lenalidomide stops progression of multifocal epithelioid hemangioendothelioma including intracranial disease. *J Neurooncol*. 2010;97:275–7.
- Pallotti MC, Nannini M, Agostinelli C, Leoni S, Di Scioscio V, Mandrioli A, et al. Long-term durable response to lenalidomide in a patient with hepatic epithelioid hemangioendothelioma. *World J Gastroenterol*. 2014;20:7049–54.

**Submit your next manuscript to BioMed Central and take full advantage of:**

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at  
www.biomedcentral.com/submit

