International Journal of Innovative Research in Medical Science (IJIRMS)
Volume 05, Issue 02, February 2020,
https://doi.org/10.23958/ijirms/vol05-i02/828

Case report

Pazopanib in Pulmonary Epithelioid Hemangioendothelioma: Report of a Case

Ibtihal Ahalli [1], Karima Oualla [1], Loubna Hejjane [1], Raihana Boujarnija [1], Kaouthar Messoudi [1], Adil Mai [2], Fatima Zahrae Er Reggad [3], Lamiaa Amaadour [1], Zineb Benbrahim [1], Samia Arifi [1], Badr Alami [2], Laila Chbani [3], Nawfel Mellas [1]

[1]Department of Medical Oncology, Hassan II University Hospital, Fez, Morocco
[2]Radiology Department, University Hospital Hassan II, Fez, Morocco
[3]Anatomical Pathology and Cytology Laboratory, University Hospital Hassan II, Fez, Morocco

Corresponding author: Ibtihal Ahalli; *ahalli.ibtihal@gmail.com*

Received 31 December 2019; Accepted 25 January 2020; Published 21 February 2020

Abstract

Pulmonary epithelioid hemangioendothelioma (PEH) is a rare vascular tumor of borderline or low-grade malignancy, Vascular endothelial growth factor (VEGF) and the VEGF receptor were found on PEH tumor cells, suggesting that target therapies that block VEGFR have a logical base in this rare malignancy. We report a 25 years old woman with a pulmonary hemangioendothelioma, treated with pazopanib, the only anti angiogenic registered agent for sarcoma, with clinical improvement of symptoms and durable stabilization for more than two years of lung tumor.

Introduction

Pulmonary epithelioid hemangioendothelioma (EHE) is a rare disease, the prevalence of EHE is reported to be less than one in 1 million[1]. It was originally published the first time by Dail and Liebow in 1975, and it was taken as an intravascular bronchial-alveolar carcinoma[2].

In 1982 it was differentiated from bronchioalveolar carcinoma by Weiss and Enzinger[3,4].

It is a rare vascular tumor of low to intermediate malignancy. It affects preferably lung, liver and soft tissues. The usual presentation is incidental in middle-aged women who have single or multiple pulmonary nodules. The imaging diagnosis is complex and granulomatous or metastatic diseases should be excluded. Histology is similar to angiosarcoma and epithelioid sarcoma among others [9].

The electron microscopy techniques used by Weldon-Linne et al, as well as the immunohistochemical techniques by means of the detection of specific tumor markers for factor VIII and CD34, have facilitated the diagnosis [5].

The 2015 WHO Classification of Tumors of the Lung, Pleura, Thymus and Heart, has a significant change involving recognition of usefulness of WWTR1-CAMTA1 fusions in diagnosis of pulmonary EHE. The new information regarding this tumor is recognition of a translocation involving the WWTR1 and CAMTA1 genes and prognostic factors [6].

This update was based on the recent recognition that a recurrent t (1;3) (p36.3; q25) chromosomal translocation is characteristic of EH [7].

Prognosis remain unclear, although indicators of poor prognosis include the presence of respiratory symptoms, male gender, older age and multi-organ disease [1].

There is no standard treatment for PEH but curative resection is the preferred treatment option where possible, for metastatic or inoperable disease, the treatment options are not well established.

The aim of this work is to report the rarity of pulmonary epithelioid hemangioendothelioma, describe the clinical, radiological, and pathological features, in addition to the therapeutic management.

Case presentation

A 25-year-old woman, history of celiac disease since childhood stabilized by a gluten-free diet, non-smoker, the main symptom was a sharp pain in the chest radiating to the left shoulder. The physical examination was normal.

A chest CT scan revealed the presence of a lung mass in the parenchyma of the left superior lobe, with necrotic component, occluding the left bronchus, invading the left pulmonary artery 5mm from its origin in the trunk of the pulmonary artery, comes into contact with the arch of the aorta and the left superior pulmonary vein but without signs of invasion, and coexisting multiple nodules scattered in both lungs (Fig. 4). Abdomino-pelvic CT scan did not show distant metastases.

Surgical lung biopsy which was performed thoracoscopically and histological examination of the nodules revealed an epithelioid cell with eosinophilic cytoplasm and intracytoplasmic vacuolization (Fig. 1,2).

On immunohistochemical analysis, the tumor cells were immunoreactive to CD31 and negative for cytokeratin, CD 79a, CD 99, the desmin and myogenin, Ki67 estimated at 10% (Fig. 3).

These findings are consistent with the pulmonary HEE.

Treatment with pazopanib at a dose of 800mg per day was started in February 2018.

Tolerance was favorable and the clinical benefit was rapidly noticed with particularly chest pain control, allowing an improvement in patient's quality of life.

The CT scan after three months of treatment showed a stable disease. Treatment was continued and still ongoing. After 2 years of treatment at the same dose, the patient is still keeping the clinical benefit with reduction of the tumor process by 7%.

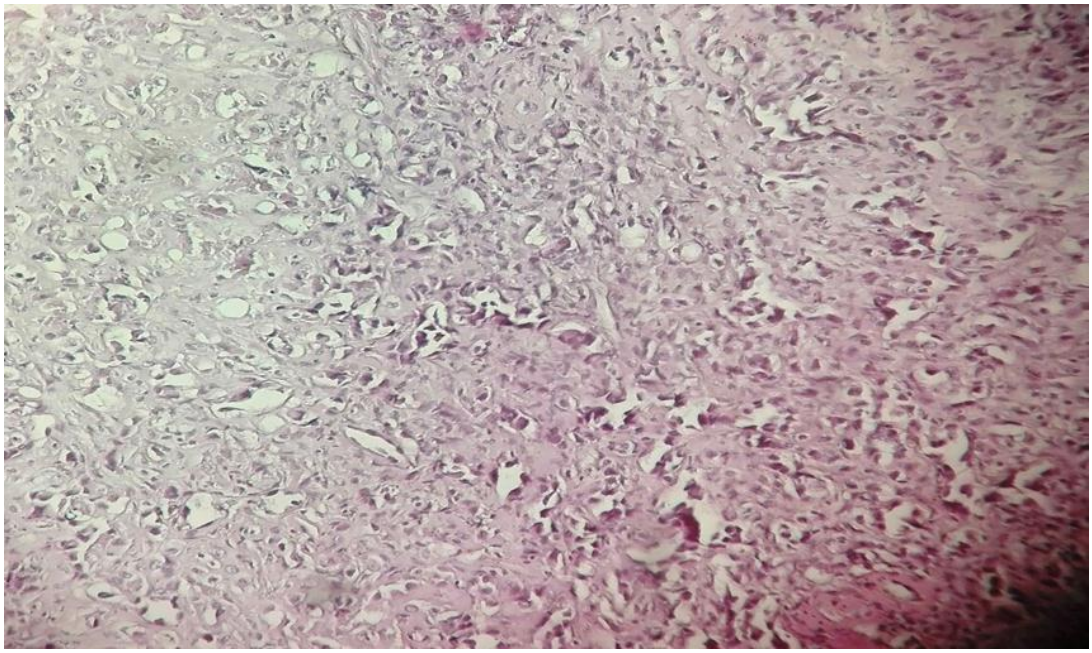

Fig 1: Epithelioid and spindled cells (HESx10)

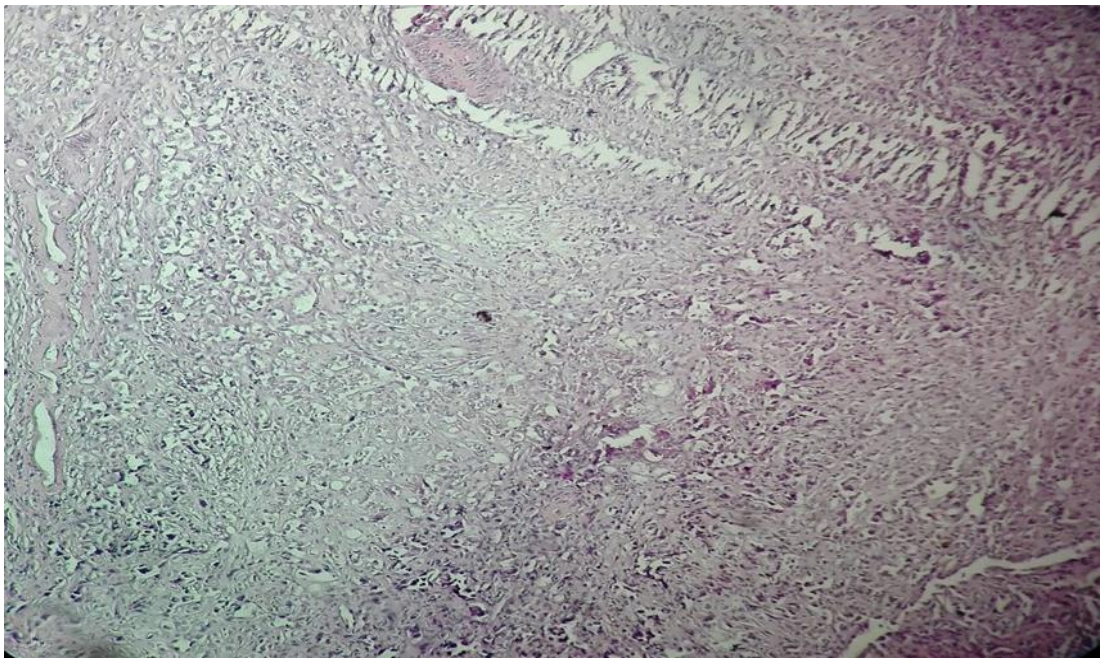

Fig 2: Epithelioid haemangioendothelioma (HESx200)

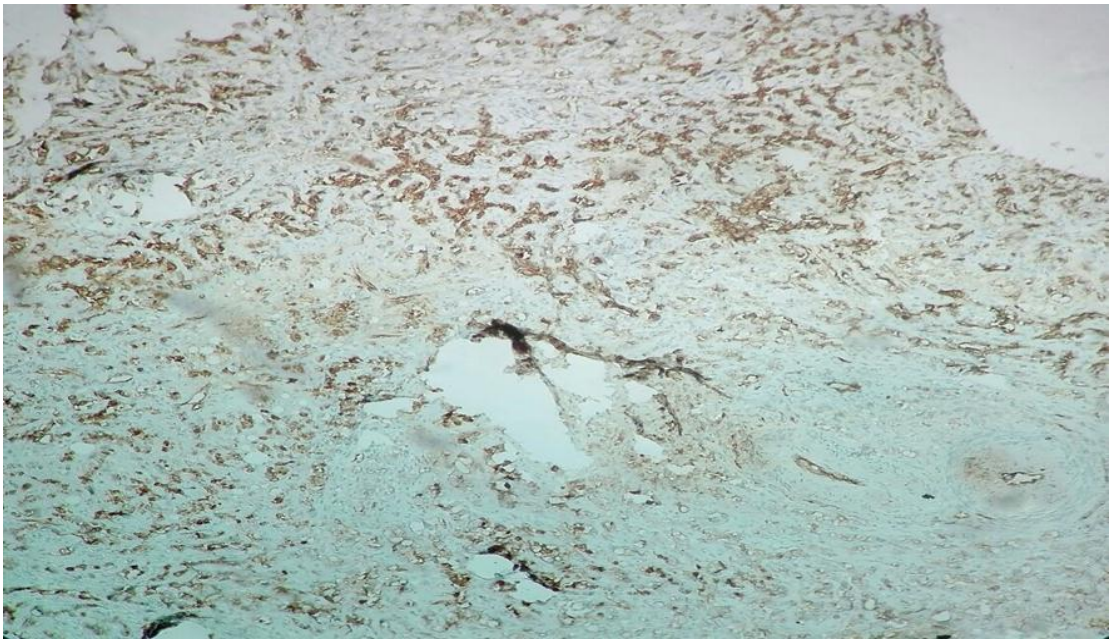

Fig 3: Immunohistochemistry highlights that the tumor cells are positive for vascular markers CD31

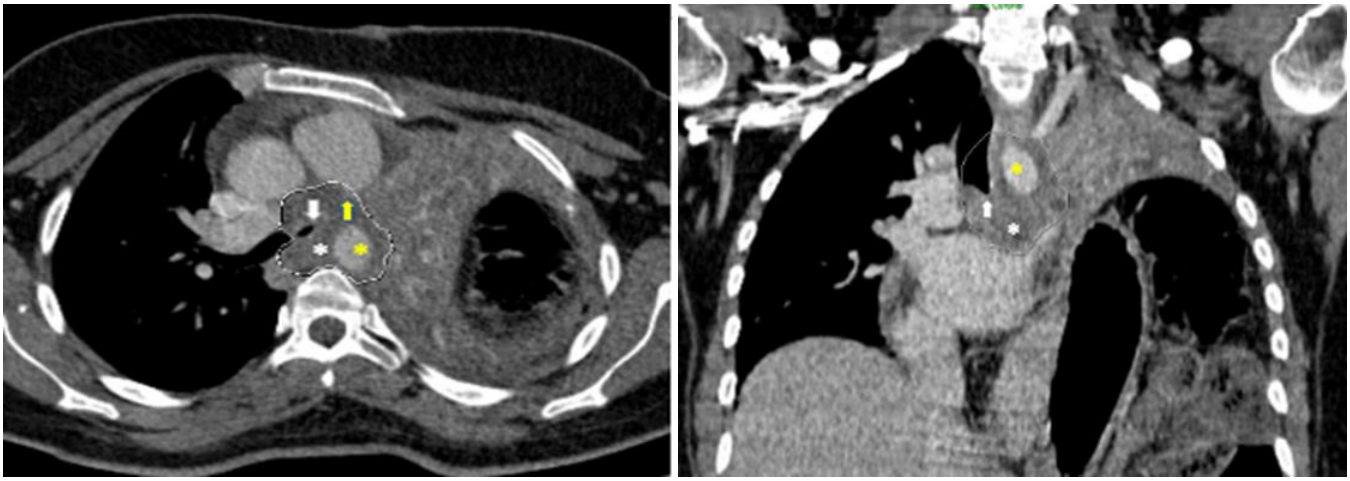

Fig 4: Thoracic CT injected in axial sections (A) with coronal reconstruction (B): not well-defined tissue process (white star), invasive and occluding the left bronchus (white arrow) and the left branch of the pulmonary artery (yellow arrow), encompassing the descending aorta (yellow star).

Discussion

The prevalence of this entity is near to one in a million habitants, only a hundred cases of this rare tumor involving the lungs have been published, there is a female predominance (1M/4F) with an average age of 40.1 ± 17.3 years[1].

Although many patients (49,5%) are asymptomatic at the time of diagnosis, the most frequent symptoms include dyspnea and cough (18.3 % each), chest pain (16 %), hemoptysis and weight loss (6.5 % each). Imaging studies have an important role in the diagnosis of EHE[8].

The prognosis is very unpredictable, with life expectancy ranging from 1 to 15 years[15]. 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[9].

However, the worst prognosis was for patients with pleural effusion or hemoptysis, with a median survival of less than 1 year[1]. The current patient had one poor prognostic factors which is extensive intravascular and endobronchial tumor spreading.

There is no established standard treatment for PEH, due to the rarity of the disease. Surgical resection should be performed if possible[10]. In asymptomatic patients with diffuse lesions, watchful waiting is an acceptable option[11]. Radiotherapy is not effective in certain patients due to the slow growth of the tumor cells, and chemotherapy appears to have little effect[12]. A few cases reported response or stable disease following immunotherapy treatment with interferon alpha[13-14-15].

Little is known about the pattern of activation of the VEGF–VEGFR pathway in EHE. Overexpression of VEGF, VEGFR2, and VEGFR3 has been observed in pulmonary EHE samples[16]. Case reports of EHE treated with interferon, thalidomide, and celecoxib show that patients can achieve disease stabilization with these antiangiogenic agents[17,18]. These findings suggest that the VEGF–VEGFR pathway may also be dysregulated in EHE.

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[19].

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[20].

Based on the presentation of VEGFR1in pulmonary epithelioid hemangioendothelioma cells, target therapies that block VEGFR have a logical base in this rare malignancy. some cases in the literature report objective, long-lasting response to pazopanib[21,22].

In the current case, the patient is still on treatment with pazopanib, with partial response after a few months and prolonged stable disease. Considering that chemotherapy is generally ineffective in epithelioid hemangioendothelioma, angiogenesis inhibition is a reasonable approach to manage patients with inoperable or metastatic EHE.

Conclusion

Pazopanib demonstrated a long stabilization of PEHE, with improvement in clinical status. It is a promising therapeutic option in patients with HEH. Further research and prospective studies are required to contribute to the data regarding the natural history and pazopanib effectiveness in this rare tumor.

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