

# Epitheloid Hemangioendothelioma of the Lung in Children – A Case Report and Review of the Literature

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## ABSTRACT

**Background:** Epitheloid Hemangioendothelioma (EHE) is a rare vascular tumor and occurrence in childhood is uncommon. Patients have unspecific symptoms and are often accidentally identified on chest X-ray. There is no established standard treatment.

**Case presentation:** A 4-year-old boy with pulmonary EHE was presented initially with abdominal pain and dyspnoea. Due to the involvement of both lungs, operative intervention was not possible and off-label therapy with a tyrosine-kinase-inhibitor (Pazopanib) was started. Despite a good initial response, the boy died after 6 months.

**Conclusions:** To our knowledge, this is the youngest child with pulmonary EHE ever reported in the literature.

## Introduction

Epitheloid Hemangioendothelioma (EHE) is a rare vascular tumor. It was first reported by Dail and Liebow in 1975, who called it an intravascular bronchioloalveolar tumor. [1] Occurrence in children is uncommon and so far only 7 pediatric cases have been published. These patients usually present with unspecific symptoms, and an abnormal chest X-ray finding leads to the diagnosis. [2] Clinical symptoms of pulmonary EHE include dyspnoea, productive cough and hemoptysis. [3] Due to the rarity of the disease, there is no established standard treatment. Surgical resection should be performed in case of solitary occurrence, and radio- and chemotherapy have no beneficial effects. [2] New treatment options include an anti-angiogenic therapy with selective activity against the vascular endothelial growth factor receptor (VEGF) on the tumor cells [3].

## Case Presentation

A 4-year-old boy presented to our emergency department with a two week-history of abdominal pain and dyspnoea without fever. Chest X-ray showed a postero-basal infiltrate and pleural effusion on the left side. Blood tests revealed mildly elevated inflammatory markers (CRP 13 mg/l, ESR 28 mm/h) and a thrombocytosis (669 G/l).

Suspecting pneumonia the child was initially treated with amoxicillin, but there was no improvement in clinical symptoms, inflammatory markers or radiological findings. Suspecting atypical pneumonia, clarithromycin was

**Table 1:** Children with pulmonary epitheloid hemangioendothelioma, reported by the literature.

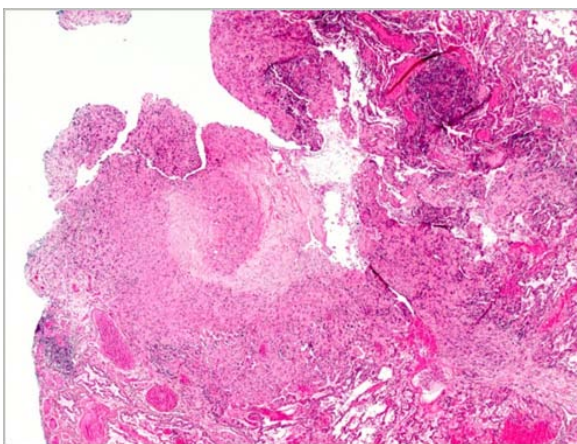
Case	Authors Journal Year of publication	Sex	Age	Symptoms	Site	Therapy	Metastases	Follow-Up
1	Rock et al. Pediatr Pulmonol 1991	F	7y	scoliosis, small right hemithorax	lung, liver	NA	NA	NA
2	Roepke et al. Arch Pediatr Adolesc Med 1997	F	12y	productive cough, hemoptysis	lung, liver	NA	NA	NA
3	Madhusudhan et al. Indian J Pediatr 2010	M	11y	hemoptysis, pain in right hypochondrium dyspnoea, cough	lung, liver	steroids	NA	NA
4	Reich et al. J Pediatr Hematol Oncol 2010 (Ref.2)	F	15y	NA	lung: right lung	NA	NA	NA
5	Flucke et al. Diagnostic Pathology 2014 (Ref. 5)	F	9y		lung, multifocal	CT	pleura	DOD, 0.5y
6	Flucke et al. Diagnostic Pathology 2014 (Ref. 5)	F	10y	NA	lung, multifocal	CT, RT	chest wall	DOD, 0.5y
7	Nizami et al. Ann Saudi Med 2014 (Ref. 4)	F	13y	dyspnoea, cough, weight loss	lung, pleura, liver	CT	liver	DOD
Our case		M	4y	abdominal pain and dyspnoea	lungs	CT	pleura	DOD, 0.5 y

**Abbreviations:** [NA] Not available; [CT] Chemotherapy; [RT] Radiotherapy; [DOD] Death of disease

**Figure 1: Chest-CT.**

Huge pleural effusion on the left side. Multiple diffuse limited nodules on both sides.

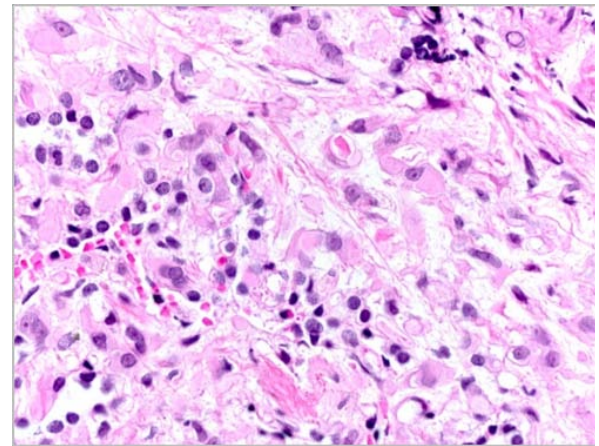
added without any improvement. Subsequently, the child was referred to our department, where a computer tomography (CT)-scan showed an extensive pleural effusion on the left side with multiple ubiquitous pulmonary nodules throughout both lungs (Figure 1). Flexible bronchoscopy showed no mucosa inflammation, and broncho-alveolar lavage was negative for *Mycobacterium tuberculosis*. Investigation of pleural fluid obtained by thoracentesis also revealed no *Mycobacterium tuberculosis*, but showed atypical cells. Consequently thoracoscopy with biopsy of several peripheral pulmonary nodules was performed: The nodules were scattered over all lobes of the right lung, some were retracted and some were bulged. Histological work-up of the tissue was highly suspicious for EHE with immuno-histochemical evidence of endothelial markers. Reference patho-histology at the University of Kiel (Germany) confirmed the diagnosis (Suppl. Figure 1, 2). Positron emission tomographic (PET)-CT was negative for further metastases outside the lungs (Suppl. Figure 3). Due to the numerous nodules in both lungs, surgical intervention was not possible. After appropriate discussion with the parents, an off-label therapy with pazopanib, a second-generation tyrosine-kinase-inhibitor was started. Pazopanib has a highly selective activity against the vascular endothelial growth factor receptor (VEGFR), which is over expressed on pulmonary epitheloid hemangioendothelioma tumor cells.



**Figure 1 and 2: Histopathology**

**Figure 1:** Moderately well delimited, eosinophilic, tumor nodules with few cells and slightly fibrotic center, rich in mucopolysaccharids; HE, 2.5x.

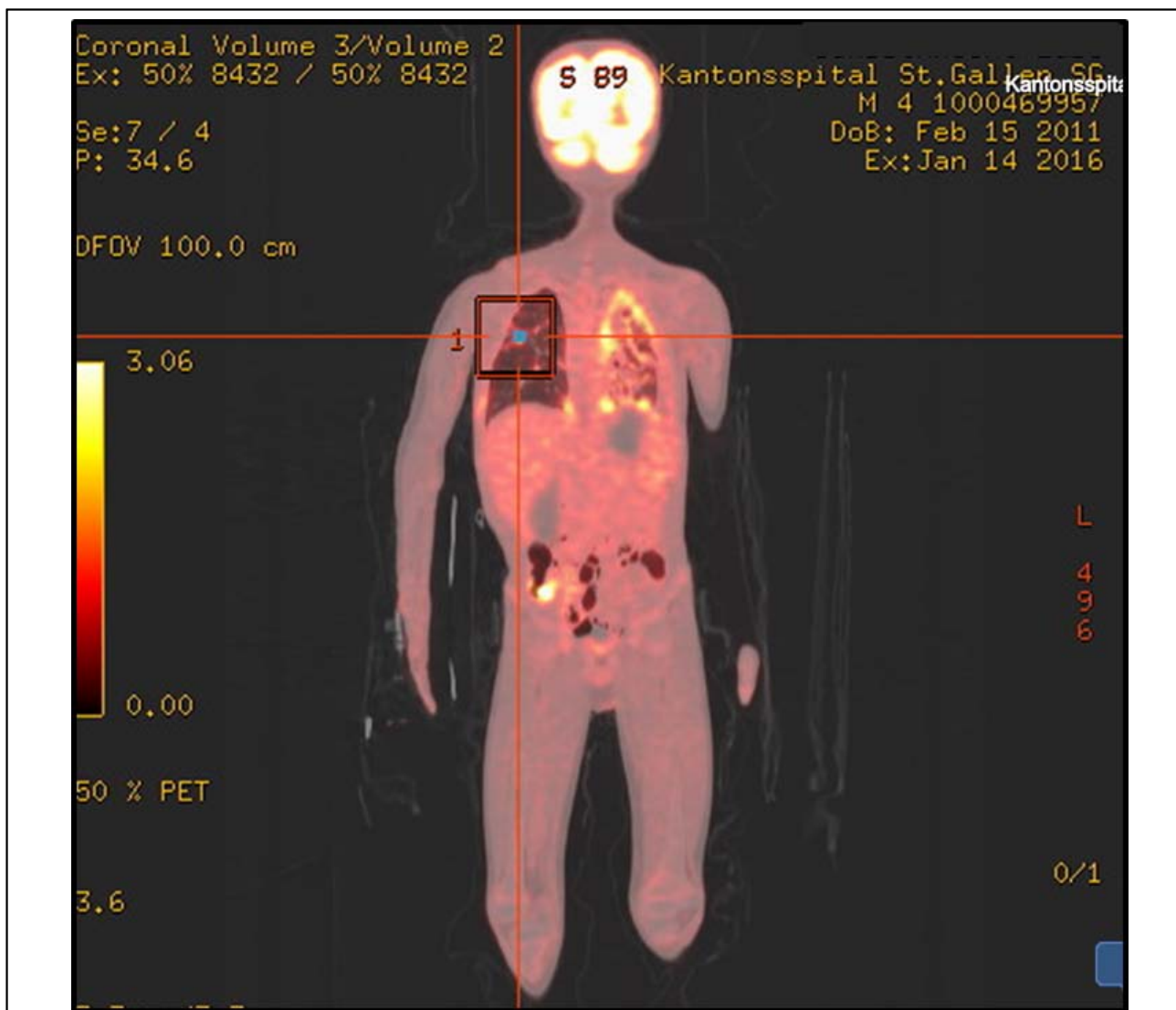
The therapy was well tolerated, the CT-scan two months later showed a decrease of the existing pulmonary nodules of around 20%. However, exertional dyspnoea persisted and the further clinical course was marked by progressive deterioration of the boy's general condition of unknown origin with increasing pain, loss of weight and developing of dyspnoea at rest. In agreement with the parents, a palliative approach to therapy was initiated and the boy died within two weeks.



**Figure 2:** The cells may form a central lumen (rudimentary neoplastic intracellular lumina) with or without erythrocytes or erythrocyte fragments; HE, 40x.

## Discussion

Pulmonary epitheloid hemangioendothelioma (EHE) is a rare lung tumor characterized by the proliferation of epitheloid endothelial cells. [2] Overall, pulmonary EHE is four times more common in young females than in males. [4] According to our review of the literature, only seven cases of children with a pulmonary EHE have been reported to date, the youngest was a seven-year-old girl (Table 1). To our knowledge, our case of a four-year-old boy with an EHE of both lungs and the pleura, is the youngest case ever reported. Children with pulmonary EHE present with unspecific symptoms with an abnormal chest X-ray finding leading to further diagnostic investigations. [2] In our patient abdominal pain and dyspnoea were the predominant symptoms. In the literature, 4 of the 7 reported cases (Table 1) had pulmonary symptoms such as dyspnoea, productive cough and hemoptysis.



**Figure 3: Positron emission tomographic (PET)-CT.**

Pathological fluorodeoxyglucose (FDG) uptake along the entire left pleura with pleural effusion and multiple FDG-uptake in pulmonary nodules on both sides. No distant metastases.

The CT-scan of chest usually shows multiple nodules with perivascular distribution and irregular margins. There is often no evidence of hilar or mediastinal lymphadenopathy. [4] Distant metastases of pulmonary EHE are frequent. Involved sites include the liver, followed by pleura, lymph nodes, kidney, spleen, bowel, gingiva, skin and bone. [2] All in all, it is difficult to determine whether the neoplasm is multi-centric or a primary lesion with metastasis to other areas. A Fluorodeoxyglucose (FDG) PET-CT is a useful tool for detecting high metabolic activity in the pulmonary nodules with uptake of FDG as a sign of malignancy. [4] It is thus also useful to detect metastases.

The etiology of EHE is not yet clear. On molecular basis, different angiogenic stimuli lead to an increased endothelial proliferation. [5] A new hypothesis suggests a chronic infection with Bartonella [1].

The prognosis of a pulmonary EHE is very unpredictable. The mean survival is 4.6 years, ranging from 6 months to 24 years. [1] Poor prognostic factors include the presence of respiratory symptoms or pleural effusion at diagnosis, as seen in our patient. Other poor prognostic factors are the presence of extensive intravascular, endobronchial or interstitial tumor spread, hepatic metastases, peripheral lymphadenopathy or the presence of spindle cells in the tumor [3].

Due to the rarity of the disease, there is no established standard treatment [3]. Surgical resection should be performed in case of a solitary lesion or in the presence of only a few lesions. [2] In asymptomatic patients with diffuse lesions, watchful waiting is suggested to be an acceptable option. [3] The management of patients with bilateral pulmonary nodules has not yet been standardized. Therapies which have been attempted, including mitomycin C, 5-fluorouracil, cyclophosphamide, vincristine, tegafur or cisplatin, have shown no beneficial effects. [2] Radiotherapy is not effective in certain patients due to the slow growth of the tumor cells. [3] Immunotherapy treatment with interleukin-2 and interferons has been tried with variable results. Recently, vascular endothelial growth factor (VEGF) and the VEGF receptor have been identified on the EHE tumor cells. Pazopanib, a second-generation tyrosine-kinase-inhibitor with highly selective activity against VEGFR, has been used in adult patients with metastatic EHE. [3] In our patient we used this new anti-angiogenic medication off-label with only a temporarily good response.

### Conclusion

In conclusion, pulmonary epithelioid hemangioendothelioma is a rare lung tumor which can also affect children as young as 4 years old. There is no standard therapy and the outcome is unpredictable.

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