# Pulmonary Epithelioid Hemangioendothelioma

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**ABSTRACT:** Pulmonary epithelioid hemangioendothelioma (PEH), previously known as "intravascular bronchoalveolar tumor," is a rare vascular malignancy with an unpredictable prognosis. Treatment can vary from observation in asymptomatic patients to surgery in patients with resectable disease or chemotherapy in patients with disseminated disease. This report describes the clinical, radiological and pathological features of three cases of PEH and a review of the current literature.

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**KEY WORDS:** pulmonary epithelioid hemangioendothelioma (PEH), intravascular bronchoalveolar tumor, lung cancer, transbronchial biopsy

Pulmonary epithelioid hemangioendothelioma, previously known as "intravascular bronchoalveolar tumor," is a rare tumor of the lung [1]. PEH can be primary in the lung and pleura, or it may arise in the liver, soft tissue or bone. Most patients have multiple bilateral nodular lesions. Diagnosis is usually made by surgical lung biopsy. Epithelioid hemangioendothelioma is characterized histologically by the presence of round or spindle-shape endothelial cells with abundant cytoplasm embedded in a fibromyxoid stroma; some of the cells may demonstrate intracellular lumina. Definitive diagnosis requires positive immunohistochemical staining for endothelial markers. The prognosis is very unpredictable, with life expectancy ranging from 1 to 15 years. There is no single effective treatment, although spontaneous regression and variable response to chemotherapy are reported.

We describe three cases of PEH, their clinical presentation, radiological and pathological findings, and variable management and outcome.

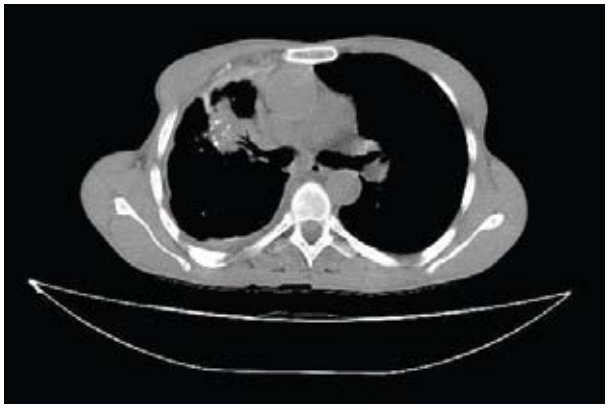
## PATIENT DESCRIPTIONS

### PATIENT 1

A 55 year old woman, non-smoker, complained of right-sided chest and shoulder pain of 6 months duration without dyspnea, fever or cough. Breathing exacerbated the pain. On physical examination a friction rub was audible over her right lung base. Chest X-ray demonstrated a large right upper lobe infiltrate. Computed tomography scan revealed a right upper lobe mass with calcifications and several smaller additional lesions throughout both lungs and a small right pleural effusion [Figure 1]. Thoracocentesis was not diagnostic and three bronchoscopies performed in another institution yielded inadequate tissue with fragments of bronchial wall only. A repeat bronchoscopy showed marked swelling and irregularity of the bronchial mucosa of the anterior segment of the right upper lobe. Endobronchial and transbronchial biopsy showed epithelioid tumor cells arranged in a single layer and in poorly formed vascular structures in a homogeneous eosinophilic stroma. Some of the cells had intracytoplasmatic vacuoles. Immune staining was positive for FLI-1 and CD 31 and negative for TTF-1 and CK 5/6. These histological and immunohistochemical findings are diagnostic of PEH.

The patient was not suitable for surgical resection and was referred for oncologic consultation. She was treated with pegylated interferon for 6 months, followed by doxorubicin. She also received radiation therapy for painful bony metastases in the right shoulder and femur. Follow-up 2 years later showed gradual slow enlargement of the pulmonary nodules. The patient's primary symptom continues to be non-specific chest pain and she requires large doses of analgesics for pain relief.

**Figure 1.** CT scan of the chest, showing a right hilar mass involving the right upper lobe with calcifications and irregular margins.



PEH = pulmonary epithelioid hemangioendothelioma

**PATIENT 2**

A 50 year old woman, non-smoker, complained of dyspnea and chest pain for several months. CT scan demonstrated a large left hydropneumothorax with collapse of the left lower lobe. Abdominal and pelvic CT scans were normal. Thoracocentesis revealed numerous lymphocytes and a few mesothelial cells, but no malignant cells. Bronchoscopy with biopsies was not diagnostic. Thoracotomy was performed with evacuation of left pleural effusion and decortication of the left lung. There was no identifiable palpable pulmonary parenchymal lesion for biopsy. Markedly thickened parietal and visceral pleura on the left side was decorticated and sent for pathological examination. Histological examination revealed malignant epitheloid neoplasm composed of large tumor cells arranged in cords and nests, some with single intracytoplasmic vacuoles embedded in a hyaline myxoid matrix. Tumor cells were seen to invade adipose tissue. No intracytoplasmic mucin was identified on mucicarmine-stained sections. On immunohistochemical studies, the tumor cells were immunoreactive for CD31 and CD34, weakly reactive with carcinoembryonic antigen, and negative for pancytokeratin, CD15, BarEP4, TTF-1, calretinin and CK5/6. These findings were diagnostic of PEH.

The patient was treated with analgesics and the chest pain gradually subsided. Magnetic resonance imaging of the chest was performed revealing enhancement with gadolinium, suggesting invasion of the chest wall by the tumor. One year after the diagnosis, the radiological and clinical status of the patient remained unchanged. The patient continues medical follow-up but without specific treatment.

**PATIENT 3**

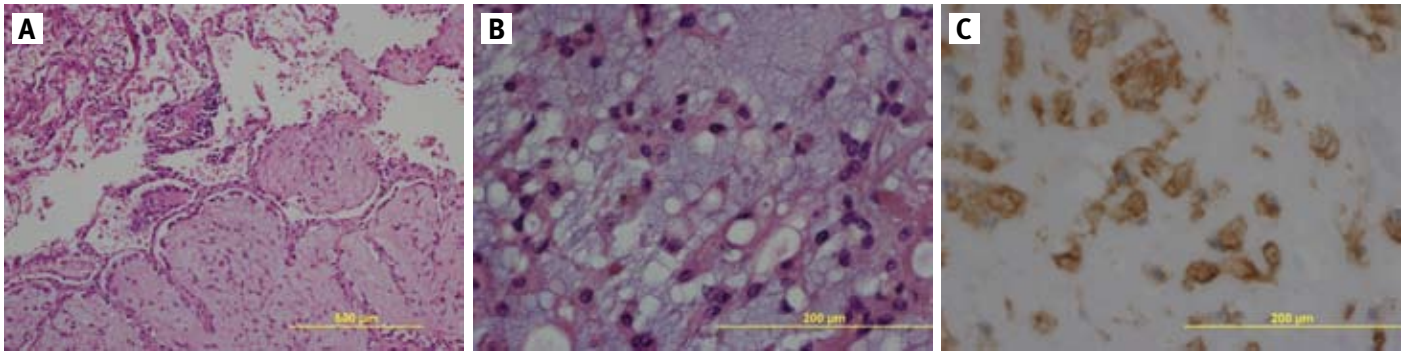
A 49 year old man, non-smoker, complained of shortness of breath on exertion of 1 year duration. At presentation, the dyspnea had become worse and was associated with pain over the posterior chest. He had a cough productive of brown sputum but no hemoptysis. Chest X-ray and CT scan showed bilateral lung nodules and right pleural effusion. Complete blood count demonstrated eosinophilia of 11.8%. Thoracocentesis revealed an exudate with 87% eosinophils. Cultures and cytology were negative. Bronchoscopy, performed with bronchoalveolar lavage, demonstrated 8% eosinophils. Brushing and transbronchial biopsies demonstrated inflammatory response with many eosinophils and no evidence of malignancy. The patient was treated in another institute for 8 months with prednisone for a presumptive diagnosis of chronic eosinophilic pneumonia. His symptoms became progressively worse. Another bronchoscopy with biopsies was not diagnostic and open lung biopsy was performed. Multiple lesions in the lungs and pleura were observed at surgery. Pathologic examination revealed multiple lung nodules. Some were sub-pleural and some had central necrosis. Histologically, there was proliferation of histiocytic-like tumor cells with eosinophilic cytoplasm, round nucleus, but without atypical morphology. Some of the cells demonstrated intracytoplasmic vacuoles. On immunohistochemical studies, the tumor cells were immunoreactive to vimentin and CD34 [Figure 2]. Stains for cytokeratin, S-100, CD-68 and factor VIII were negative. These finding were diagnostic of PEH. The patient died from acute pulmonary embolism before antitumor therapy could be initiated.

## DISCUSSION

Pulmonary epithelioid hemangioendothelioma was first described by Dail et al. [1] who called it intravascular bronchioloalveolar tumor. Development of immunohistochemical techniques confirmed its endothelial lineage, and Weiss et al. [2] subsequently suggested the current name, "epithelioid hemangioendothelioma."

The lungs and liver are the two organs most frequently involved by epithelioid hemangioendothelioma, but it can

**Figure 2. [A]** Histologic section of the periphery of a pulmonary epithelioid hemangioendothelioma. Nodules of tumor extend into adjacent alveoli as papillary process. Tumor cells in the nodules are embedded in a myxoid matrix. (Hematoxylin & eosin x10)
**[B]** Higher magnification of the tumor reveals vacuolation of some of the tumor cells, representing primitive angiogenesis. (H&E x40)
**[C]** Tumor cells show brown cytoplasmatic staining with immunohistochemical antibody to CD31. (x40)



spread through the bloodstream to other sites such as bone and soft tissue. It is a tumor of borderline malignancy with a clinical course intermediate between hemangioma and angiosarcoma. Differential diagnosis includes other lung malignancies, especially non-small cell lung carcinoma and inflammatory diseases like sarcoidosis or organizing pneumonia. Infectious disease, particularly tuberculosis, should be ruled out in the appropriate clinical scenario.

A recent review found 15 studies of this rare tumor involving the lungs [3], and the largest series published in 2006 contained 93 cases collected from the literature [4]. In that report the mean age of patients suffering from PEH was 40.1 ± 17.3, and 73% were females. Most patients were asymptomatic (49.5%). Other reported symptoms were dyspnea and cough (18.3% each), chest pain (16%), hemoptysis and weight loss (6.5% each). Two of our patients complained of dyspnea, one had productive cough and all had chest pain. All three patients presented with an indolent course developing over several months prior to diagnosis.

Delayed diagnosis can be explained in part by the difficulty in diagnosing PEH. Several diagnostic procedures were needed in our patients, five in the first patient, three in the second patient and four in the third. The diagnosis was made on open lung biopsy in two of our patients, as reported in most cases in the literature. One patient was diagnosed with transbronchial biopsy. This is only the fourth case of PEH diagnosed by transbronchial biopsy reported in the literature [5,6].

Radiographically, the presence of multiple nodules in both lungs, usually less than 2 cm in diameter, is the characteristic finding in PEH. Unilateral ground-glass, linear or nodular opacities and pleural effusion have also been reported [7]. In two of our patients bilateral lung nodules were present. One patient presented with massive pleural involvement without significant parenchymal findings.

The pathological characteristics of PEH typically include nodules with a hypocellular sclerotic or necrotic center. Infectious and autoimmune processes can yield similar findings and must be considered in the differential diagnosis [8].

Immunohistochemical analysis is pivotal for the diagnosis of PEH. Immunohistochemical staining of the malignant cells with CD31, CD34, factor VIII and/or FLI-1 confirm the endothelial lineage of PEH. FLI-1 is the most specific endothelial immune marker of PEH in the correct morphologic context [9]. CD31 and CD34 were positive in two of our patients and FLI-1 was positive in one. Microbiological studies were negative, which excludes Mycobacterium or fungal infection.

The natural history of PEH is hard to predict. Unfavorable prognostic factors include loss of weight, anemia, pulmonary symptoms and, particularly, pleural hemorrhagic effusions and hemoptysis [10]. In patients with pleural effusion or hemoptysis, the median survival is less than 1 year. Furthermore, Amin and colleagues [4] found that respiratory symptoms and the presence of pleural effusion were independent negative predictors of survival. Our patients suffered from respiratory symptoms, two complained of dyspnea and one had a productive cough. They had pleural effusion, which places them in the poor prognostic group.

Because of the rarity of PEH, there is no standard treatment. Treatment can vary from observation in asymptomatic patients, surgery in patients with resectable disease, to chemotherapy in patients with disseminated disease. The most common treatment, when feasible, is tumor resection. Surgical resection of solitary lesion or a number of lesions seems to provide a long remission period and recurrence can be treated with resection when possible. In one report, a 17 year old girl was operated on for a solitary well-circumscribed pulmonary parenchymal tumor and reoperated ten times for multiple similar recurrent pulmonary tumors over a period of 24 years [11]. Although several chemotherapeutic agents have been tried, there are insufficient data to recommend a specific drug regimen. In one report carboplatine plus etoposide brought about complete remission [12], and in one patient treatment with azathioprine was associated with stabilization of disease [13]. Interferon-alpha has anti-angiogenic activity and there are incidental reports regarding the effectiveness of this treatment in PEH patients with partial or complete response [14-16]. One of our patients received interferon treatment for 6 months with stabilization of the disease; however, the clinical potential of anti-angiogenic treatment such as interferon for PEH needs to be investigated further [17]. Spontaneous regression in patients with PEH has been reported. Thus, observation and close follow-up is an option in asymptomatic patients [7].

Respiratory failure as a result of increasing size and number of lung nodules is the most common cause of death in PEH, although some patients die due to extrapulmonary spread. Death from sepsis, myocardial infarction or other malignancy has also been reported. One of our patients died following acute pulmonary embolism.

In conclusion, we describe three cases of PEH, a rare vascular tumor of low to intermediate grade malignancy. In this report, we emphasize the variable course of PEH and the difficulties in diagnosing this tumor and discuss new therapeutic options in this disease.

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## References

1. Dail DH, Liebow AA, Gmelich JT, 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 (3): 452-64.

2. Weiss SW, Ishak KG, Dail DH, Sweet DE, Enzinger FM. Epithelioid hemangioendothelioma and related lesions. *Semin Diagn Pathol* 1986; 3 (4): 259-87.

3. Schattenberg T, Kam R, Klopp M, et al. Pulmonary epithelioid hemangioendothelioma: report of three cases. *Surg Today* 2008; 38 (9): 844-9.

4. Amin RM, Hiroshima K, Kokubo T, 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 (6): 818-25.

5. Cronin P, Arenberg D. Pulmonary epithelioid hemangioendothelioma: an unusual case and a review of the literature. *Chest* 2004; 125 (2): 789-93.

6. Shang A, Wang X. Pulmonary epithelioid haemangioendothelioma mimicking central lung cancer. *Respirology* 2009; 14 (3): 452-5.

7. Kitaichi M, Nagai S, Nishimura K, et al. Pulmonary epithelioid haemangioendothelioma in 21 patients, including three with partial spontaneous regression. *Eur Respir J* 1998; 12 (1): 89-96.

8. Case Records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Hemoptysis in a 20-year-old man with multiple pulmonary nodules. *N Engl J Med* 2000; 342 (8): 572-8.

9. Gill R, O'Donnell RJ, Horvai A. Utility of immunohistochemistry for endothelial markers in distinguishing epithelioid hemangioendothelioma from carcinoma metastatic to bone. *Arch Pathol Lab Med* 2009; 133 (6): 967-72.

10. Bagan P, Hassan M, Le Pimpec Barthes F, et al. Prognostic factors and surgical indications of pulmonary epithelioid hemangioendothelioma: a review of the literature. *Ann Thorac Surg* 2006; 82 (6): 2010-13.

11. Miettinen M, Collan Y, Halttunen P, Maamies T, Vilkko P. Intravascular bronchioloalveolar tumor. *Cancer* 1987; 60 (10): 2471-5.

12. Pinet C, Magnan A, Garbe L, Payan MJ, Vervloet D. Aggressive form of pleural epithelioid haemangioendothelioma: complete response after chemotherapy. *Eur Respir J* 1999; 14 (1): 237-8.

13. Ledson MJ, Convery R, Carty A, Evans CC. Epithelioid haemangioendothelioma. *Thorax* 1999; 54 (6): 560-1.

14. Roudier-Pujol C, Enjolras O, Lacronique J, et al. Multifocal epithelioid hemangioendothelioma with partial remission after interferon alfa-2a treatment. *Ann Dermatol Venereol* 1994; 121 (12): 898-904.

15. Erasmus JJ, McAdams HP, Carraway MS. A 63-year-old woman with weight loss and multiple lung nodules. *Chest* 1997; 111 (1): 236-8.

16. Radzikowska E, Szczepulska-Wójcik E, Chabowski M, Oniszh K, Langfort R, Roszkowski K. Pulmonary epithelioid haemangioendothelioma – interferon 2-alpha treatment – case report. *Pneumonol Alergol Pol* 2008; 76 (4): 281-5.

17. Calabrò L, Di Giacomo AM, Altomonte M, et al. Primary hepatic epithelioid hemangioendothelioma progressively responsive to interferon-alpha: is there room for novel anti-angiogenetic treatments? *J Exp Clin Cancer Res* 2007; 26 (1): 145-50.