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Case Reports

# Pulmonary Epithelioid Hemangioendothelioma

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ABSTRACT

Epithelioid hemangioendothelioma is a multifocal tumor that rarely metastasizes. It is difficult to diagnose and is most often an incidental finding in young asymptomatic women. It has a heterogeneous radiologic pattern. The most important diagnostic information is histologic confirmation of Weibel-Palade bodies or immunohistochemistry based on specific tumor markers such as factor VIII and CD34. We report the case of a 73-year-old woman in whom multiple pulmonary nodules detected by chance in a radiograph were subsequently diagnosed as epithelioid hemangioendothelioma.



## Hemangioendotelioma epitelioide pulmonar

RESUMEN

El hemangioendotelioma epitelioide es una enfermedad de difícil diagnóstico, descrita como un tumor multicéntrico y de escasa actividad metastásica, que aparece con mayor frecuencia en mujeres jóvenes asintomáticas y como un hallazgo casual. El patrón radiológico es heterogéneo. El dato más importante para su diagnóstico es la confirmación histológica de cuerpos de Weibel-Palade, o bien la inmunohistoquímica, con marcadores tumorales específicos como el factor VIII y CD34. Presentamos el caso de una mujer de 73 años en quien de forma casual se detectaron, en una imagen radiológica, nódulos pulmonares múltiples que posteriormente se diagnosticaron como esta entidad tumoral.



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## Introduction

Epithelioid hemangioendothelioma (EHE) is an uncommon condition that was first described by Weiss and Enzinger[1] in 1982. It is a multifocal tumor that originates in endothelial cells and mainly involves the lung, liver, and soft tissue. Its most common form of presentation is as solitary or multiple bilateral pulmonary nodules. It is slow growing and an incidental finding in women aged less than 40 years. The initial radiologic presentation is suggestive of granulomatous processes or metastatic disease. The first cases were thought to be a variation of bronchoalveolar carcinoma known as intravascular bronchoalveolar tumor. Other possible differential diagnoses are angiosarcoma, Kaposi sarcoma, liposarcoma, epithelioid sarcoma, and angiolymphoid hyperplasia.

Diagnostic confirmation of this entity was a controversial matter for some years until electron microscopy and immunohistochemistry made it possible to identify Weibel-Palade bodies in the cytoplasm of its cells. The characteristic image of nests or strands is usually obtained in a medium-sized vessel or a large vein. Most of these tumors present scant mitotic activity. They spread centrifugally towards the wall, partially destroying the tunica media and filling the lumen with amorphous eosinophilic matter. Positivity for the specific tumor markers factor VIII, *Ulex europaeus*, and CD34 has made diagnosis much easier.[2] EHE is a slow-growing tumor that rarely metastasizes despite its intravascular origin. It remains stable for years. Metastatic disease is seen in a low proportion of patients with primary lung disease (15%), and in a somewhat higher proportion in patients with primary liver disease (25% to 35%).[3]

We present the case of a patient scheduled for surgery to correct a prolapsed uterus. During the preoperative study, a plain radiograph revealed several bilateral pulmonary nodules, despite the absence of clinical manifestations or evidence of a primary tumor.

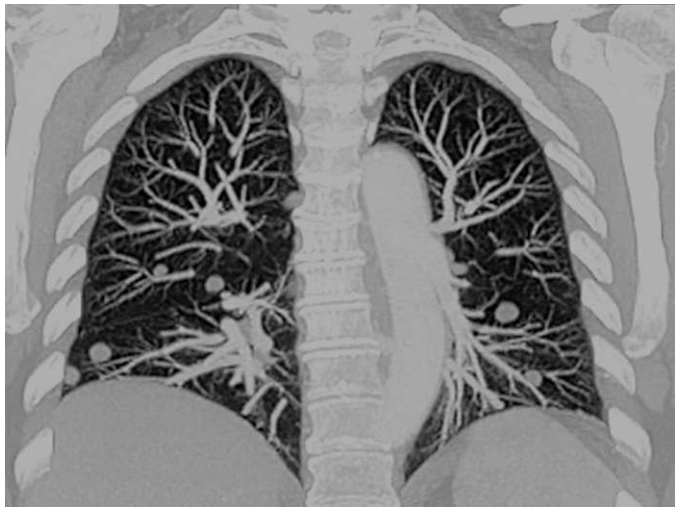

**Figure 1.** Computed tomography scan showing multiple pulmonary nodules. The resected nodules are highlighted.

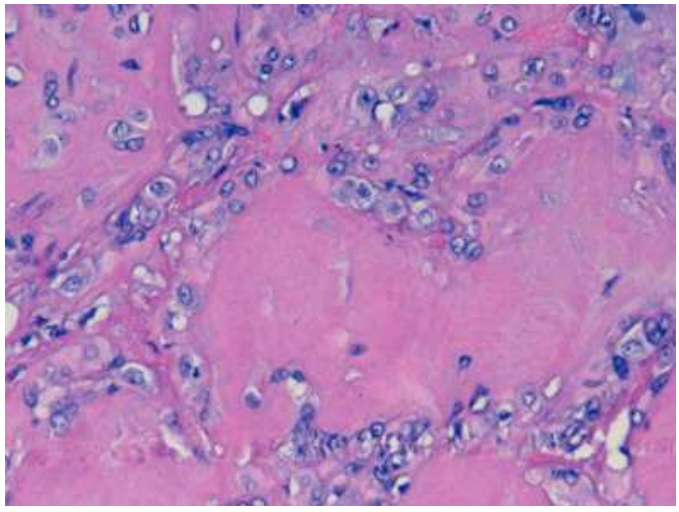

**Figure 2.** Histology reveals vascular neoplastic cells arranged in nests within a hyaline matrix.

## Case Description

A 73-year-old woman was referred to our department for evaluation of multiple pulmonary nodules revealed by a chest radiograph. She had no history of lung disease or cancer. She was asymptomatic and her physical examination was unremarkable. A complete laboratory workup—CYFRA, thyroglobulin, carcinoembryonic antigen, cancer antigen [CA] 125, CA 15/3, CA19/9, and α-fetoprotein—was normal. Computed tomography (CT) of the chest, abdomen, and pelvis revealed multiple pulmonary nodules of between 0.5 cm and 1 cm in both hemithoraxes (Figure 1), with no evidence of a primary tumor. Endoscopy of the upper digestive tract, colonoscopy, and mammography showed no abnormal findings. Positron emission tomography revealed bilateral pulmonary nodules with low glucose uptake, and no uptake in other areas.

A CT scan performed 2 months later revealed no significant changes in the size or number of the nodules, thus indicating that the disease was not aggressive. Surgery of the pulmonary lesions was by standard 3-port video-assisted thoracoscopy: 2 nodules were resected from the right lower lobe (Figure 1), and a third was removed from the middle lobe.

Histopathology showed the nodules to be a vascular tumor composed of epithelioid endothelial cells arranged in small nests within a hyaline and myxoid matrix (Figure 2). Immunohistochemistry revealed them to express the markers CD31, CD34, and factor VIII. The diagnosis of pulmonary EHE was confirmed. As the CT scan performed 6 months after diagnosis revealed no significant changes in the size of the nodules, a conservative approach was adopted.

## Discussion

Pulmonary EHE is an endothelial tumor that has long been difficult to classify. It has been described as granulomatous, inflammatory, or tumoral, and both benign and malignant.

In our patient, several examinations were unable to demonstrate the existence of a primary tumor, and radiographic images remained virtually unchanged during subsequent monitoring. The differential diagnosis pointed to conditions ranging from neoplastic processes such as lymphoma or multiple myeloma, bronchoalveolar carcinoma, epithelioid sarcoma, angiosarcoma, or metastasis, to pulmonary infarction, opportunistic infections of the type caused by *Nocardia*, *Histoplasma*, and mycobacteria, or even granulomatosis and rheumatoid nodules. Therefore, a biopsy of the pulmonary nodules was performed using thoracoscopy and a definitive diagnosis was reached after histopathology testing.

Treatment of the disease is controversial. Complete local removal of the tumor is the approach of choice, when situation and location allow. However, where surgery is not possible, the medical literature offers scant options for effective chemotherapy. Some investigators have used the MAID chemotherapy regimen, which is recommended for soft tissue sarcoma and is composed of mesna, doxorubicin, ifosfamide, and dacarbazine (mesna is a renal protector and

dacarbazine has been withdrawn due to increased toxicity), although the response was unsatisfactory.

In our case, the lack of symptoms, slow course of the disease, and the multifocal nature of the tumor (which prevented resection) led us to opt for clinical follow-up. A new radiologic checkup was carried out 6 months later, and no changes were observed compared with the previous study.

The outcome of these tumors is unpredictable. They usually progress slowly and insidiously, and they rarely metastasize,[4] although new multifocal nodules may be observed over time.

Pulmonary EHE usually survives for periods of up to 15 years. However, some are more aggressive, can infiltrate the pleura or mediastinum, and are accompanied by initial symptoms such as dyspnea, cough, chest pain, and hemoptysis leading to early death due to pulmonary hypertension, alveolar bleeding, hemoptysis, and respiratory failure.[2] Tumors with such a poor prognosis include pleural EHE, which is less common and more typical of men aged 55 to 70 years. Pulmonary EHE, on the other hand, progresses with severe symptoms from onset and has a high mortality.[5]

Therefore, EHE must be considered an intermediate malignant tumor of uncertain outcome. It can progress silently and asymptomatically for years, and can survive for long periods. On the other hand, onset can be with vascular compromise that slowly and inexorably destroys the lung until the patient dies of respiratory failure or massive hemoptysis in a short period of time. Some authors associate poor outcome with the onset (as early as at diagnosis) of respiratory symptoms, hemoptysis, and interstitial infiltrates on radiograph[6] and hemorrhagic pleural effusion, as well as extensive intravascular and endobronchial spread.[7] Other authors claim that no morphologic criteria can predict the malignant potential of this disease.[8] The histologic and radiologic factors that can predict a better or poorer prognosis with this disease continue to be studied.

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