

CASE STUDY

Central nervous system metastases of a pulmonary epitheloid haemangioendothelioma

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ABSTRACT: The case of a 55-yr-old male with a right pleural effusion and multiple bilateral nodules is reported. A diagnostic thoracotomy was necessary to obtain a definitive histological diagnosis.

During the postoperative course, the subject's neurological condition deteriorated and multiple cerebral mass lesions were discovered. The pathological analysis of both lung and cerebral tumours revealed an atypical endothelial cell proliferation; vascular immunohistochemical markers, such as factor VIII and CD34, were strongly positive. His general condition remained poor and the patient died 18 months after the initial diagnosis.

The final diagnosis was pulmonary epitheloid haemangioendothelioma with synchronous central nervous system dissemination, the first time the authors believe that association has been reported. Little is known of the prognosis and treatment of these tumours, due to their rarity. Negative prognostic factors appear to be the presence of symptoms, pleural effusion or multifocal presentations. Treatment should include surgical resection if possible; chemotherapy appears to have little effect. Watchful waiting is an acceptable option, especially in asymptomatic patients.

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Epitheloid haemangioendothelioma (EHE) is a rare tumour of endothelial origin, with an intermediate course between haemangioma and conventional angiosarcoma. Its two main locations include the liver and the lung, although it has been described in many other locations. Pulmonary EHE usually manifests itself as multiple bilateral nodules in middle-aged patients and tends to follow a prolonged clinical course; dissemination outside the pulmonary parenchyma is rare. The case of a 55-yr-old male with a pulmonary EHE who developed central nervous system dissemination, a unique association, is reported here. The diagnostic criteria of the malignancy and scant evidence regarding prognostic factors available in the literature are reviewed. The therapeutic options available are also presented.

Case report

A 55-yr-old male developed haemoptysis and pleuritic pain in the right hemithorax in June 2001. Apart from heavy smoking and a slight thrombocytopenia attributed to the use of metamizol, his past medical history was unremarkable. He had no history of risk factors for human immunodeficiency virus infection, tuberculosis or exposure to tuberculosis, exposure to industrial dusts or travel outside Spain. A chest radiograph performed at the University Hospital La Fe, Valencia, Spain, showed a right sided pleural effusion alongside multiple bilateral nodules (fig. 1). Thoracic computed tomography (CT) confirmed these findings, revealing a 6.9×4.1 cm liquid collection in the left lower lobe suggestive of pleural

empyema and multiple bilateral nodules of different sizes, highly suggestive of metastasis (fig. 2). However, a fibro-bronchoscopy failed to reveal any abnormalities, as did the pleural liquid analysis, which showed only haematic material. Two transthoracic needle biopsies of the collection were also negative for malignant cells. In order to obtain a definitive histological diagnosis, the patient was admitted to University Hospital La Fe, Valencia, Spain, in October 2001 to carry out a diagnostic thoracotomy.

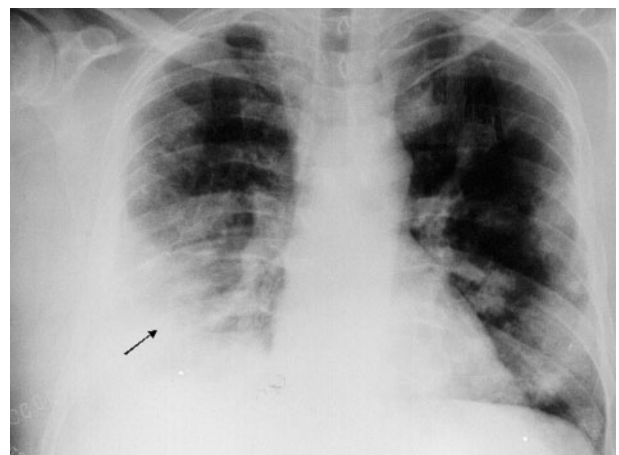


Fig. 1. – Chest radiograph shows a right sided pleural effusion (arrow) alongside multiple parenchymal nodules in both lungs.

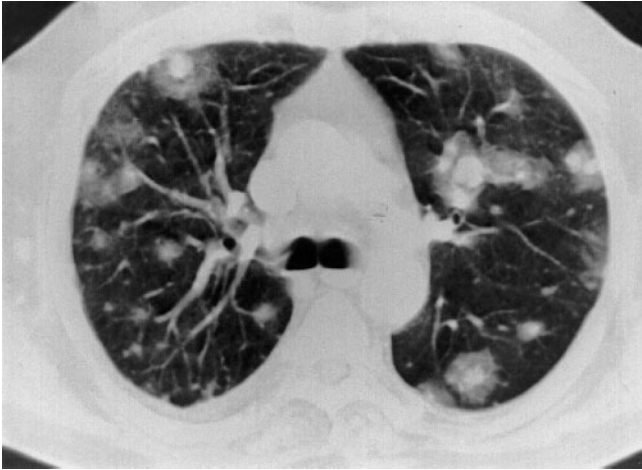


Fig. 2.—Computed tomography section shows multiple bilateral nodules of varying sizes. The nodules are well-delineated and have a homogeneous matrix.

The surgical exploration revealed a highly vascularised tumour in the left lower lobe with apparent metastatic dissemination throughout the pulmonary parenchyma. However, the initial pathological analysis of the nodules only showed foci of pulmonary infarcts with central microabscessification, surrounded with areas of organised pneumonia and endothelial and alveolar proliferation and hyperplasia; in some points, the alveolar cells showed cellular atypias and mitoses. The surrounding stroma was highly cellular, with abundant histiocytes. No evident malignant cells could be seen (fig. 3). An organised fibrinous pleuritis was also noted. All these histological changes could be secondary to systemic or infectious causes, such as mycobacteria or fungi.

The patient's clinical course soon deteriorated with the appearance of fever and headache. The neurological examination showed nominal aphasia, right homonymous hemianopsia and a severe gait impairment. A brain magnetic resonance imaging showed multiple subcortical hemispheric lesions with ring morphology and surrounding oedema (figs 4 and 5). Analysis of the cerebrospinal fluid showed no initial abnormalities. With the suspicion of disseminated mycobacterial infection, empirical treatment with dexamethasone, isoniazid, rifampicin and etambutol was begun. Due to

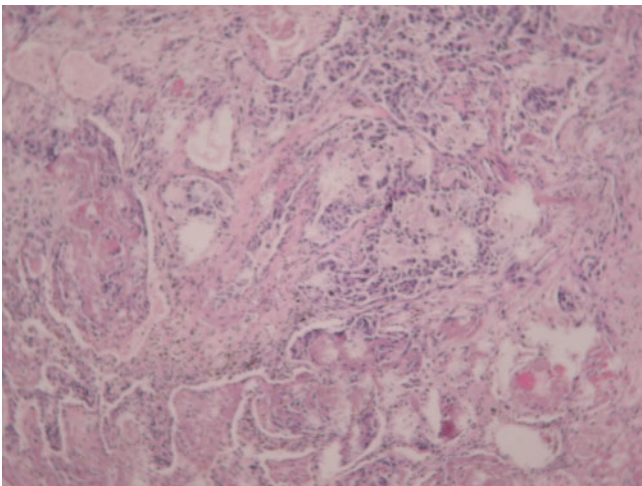


Fig. 3.—The histological analysis of the lung tumour, with the haematoxylin-eosin stain, shows several areas of coagulative necrosis surrounded by areas of intense alveolar and endothelial proliferation.



Fig. 4.—Computed tomography section of the brain shows multiple nodular lesions strongly suggestive of metastasis.

the extremely unusual evolution, a biopsy of one of the brain lesions was performed.

The brain biopsy showed the same endothelial proliferation as the lung lesion with atypical cells and some mitoses. The immunohistochemical studies performed in both biopsies (including the alveolar component of the lung lesion) showed negativity for cytokeratin, epithelial membrane antigen (EMA) and thyroid transcription factor 1 (TTF-1) and strong positivity for vimentin and the vascular markers factor VIII and CD34 (fig. 6). All microbiological studies for mycobacteria, fungi and bacterial pathogens were negative. A standard battery of autoantibodies was also negative. Thus, the final pathological diagnosis was pulmonary EHE with central nervous system dissemination.

The clinical state of the patient remained poor, with an Eastern Cooperative Oncology Group performance status of 3. Symptomatic treatment with corticosteroids and major opioids was begun. Holocraneal irradiation for a total dose of 30 Grays was given, with little improvement in his neurological impairment. He remained wheelchair-bound until his death in January 2003, 18 months after the initial diagnosis.

Discussion

EHE is a rare tumour of endothelial origin, which has been described primarily in the liver [1] and in the lung [2]. In its pulmonary form, it was originally described by DAIL and LIEBOW [3] as "intravascular bronchioalveolar tumour"; these authors noted the tumour's remarkable propensity to invade pulmonary vessels and small airways. Since then, <50 cases

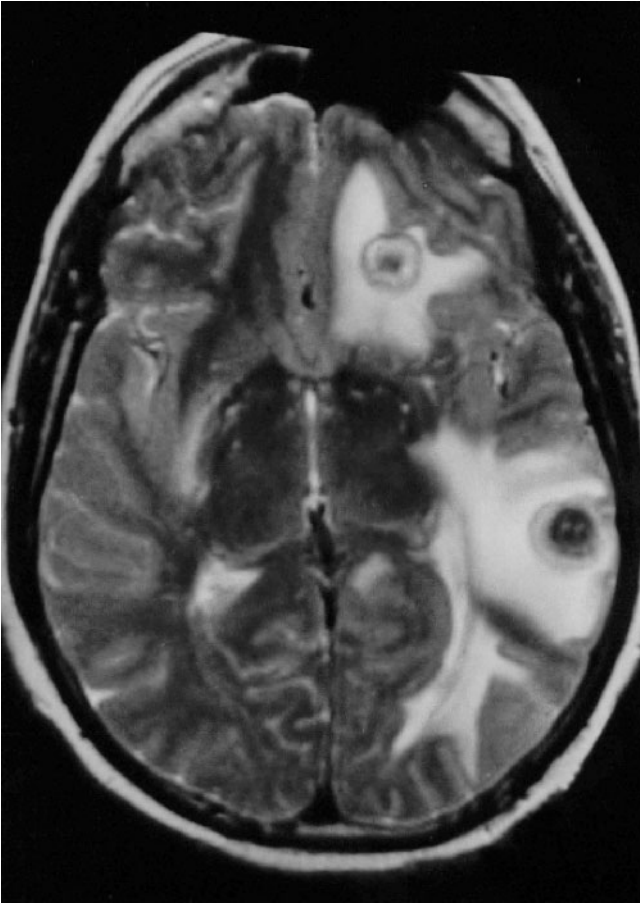


Fig. 5.—T1-weighted magnetic resonance imaging section through the brain shows multiple nodular lesions with ring-like morphology. Note that all lesions are surrounded by perifocal oedema.

have been described in the literature worldwide. It is a tumour of borderline malignancy, which tends to follow an intermediate course between haemangioma and conventional angiosarcoma [4].

In the typical pulmonary forms, EHE presents with non-specific symptoms, such as chest pain, cough or sputum, or it

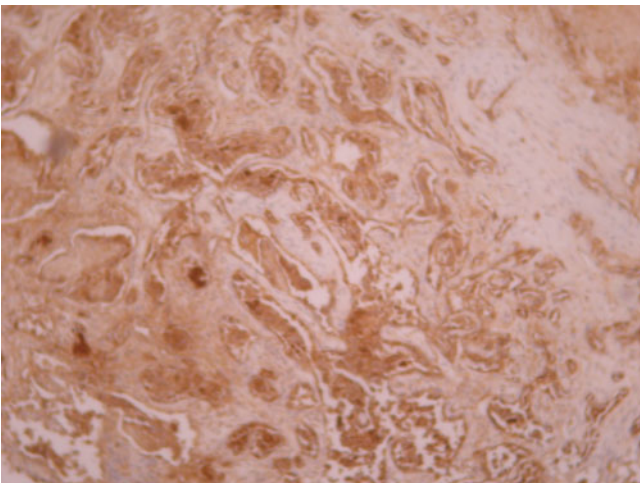


Fig. 6.—The immunohistochemical study for factor VIII presence in the lung tumour shows intense positivity for this vascular marker.

may remain asymptomatic [2, 5]. It usually affects middle-aged patients, with a female predominance, although cases in children and in the elderly have been described [2, 5, 6]. Multifocal nodular densities up to 2 cm in diameter, with well- or ill-defined margins, are the most common feature of pulmonary EHE on chest radiography [2, 7]; these are often mistaken for metastatic disease but they show little or no growth on serial radiography. The presence of a pleural effusion or hilar or mediastinal lymphadenopathy is rare [7, 8]. The thoracic CT usually reveal more nodules than those in the chest radiography. In long-standing cases, extensive calcification of the nodules and interstitial involvement can be seen [9].

The pathological characteristics of pulmonary EHE are more distinctive in the lung than in other locations because of the zonal pattern of the pulmonary nodules. The centre of the nodule is typically sclerotic, necrotic and hypocellular and it may resemble an infarct, a microabscess, a hyalinised granuloma or even a hamartoma. The periphery of the nodule is composed of an hypercellular and sclerotic stroma and clusters of neoplastic cells with few morphological signs of malignancy that grow as polypoid tufts into alveolar spaces [2, 4, 5, 10, 11]. Many autoimmune and infectious processes can produce a similar pathological picture of central coagulative necrosis and atypical endothelial and intra-alveolar cell growth, so all these causes should be ruled out before a definitive diagnosis is made [12].

In this case, the immunohistochemical study was pivotal for the correct diagnosis, showing negativity for epithelial markers, such as EMA, TTF-1 and cytokeratin, and strong positivity for vimentin (a mesenchymal marker), factor VIII and CD34 (both vascular markers). All microbiological studies were negative, thus ruling out infection by mycobacteria or fungi.

Due to the rarity of the tumour, its natural history is difficult to predict. In typical pulmonary cases, it appears to follow a protracted clinical course, with death after a variable length of time usually resulting from respiratory insufficiency due to substitution of the healthy pulmonary parenchyma [2, 4, 5, 13]. However, some authors have observed partial spontaneous regressions of the lesions [5]. Lymphatic dissemination is extremely rare, supporting the endothelial origin of the tumour. Haematogenous metastases are also rare and have been described especially in the liver but also in the skin, serosa, spleen, tonsils, retroperitoneum and kidney [2, 5, 10, 14, 15]. However, the authors believe this is the first case reported of a pulmonary EHE with a synchronous massive dissemination to the central nervous system.

Prognostic factors in pulmonary EHE have been difficult to validate, due to the small number of patients involved. In DAIL *et al.* [2], a report of 17 patients with pulmonary EHE, negative prognostic factors appeared to be respiratory symptoms at presentation, extensive lymphangitic spread, pleural invasion, hepatic metastases and peripheral lymphadenopathy. In the largest series (21 patients) published to date by KITAICHI *et al.* [5], an unfavourable prognosis was associated with pleural effusion on chest radiography, fibrous pleuritis with extrapleural proliferation of tumour cells and spindle tumour cells at histology; surprisingly, liver involvement was not associated with a worse prognosis.

Treatment can vary from observation in asymptomatic patients, surgery in the few patients with resectable disease or chemotherapy in widely disseminated disease [2, 4, 5, 10, 13]; these options should be discussed with the patient. However, the chemotherapy to be used is still a matter of debate. The notion of pulmonary EHE as a chemoresistant disease is probably still true [2, 5]. The authors have only found a case of complete remission of a pleural EHE after treatment with chemotherapy (carboplatin and etoposide) [16] and a partial

remission of a widely disseminated EHE with a year's treatment of α -2A interferon, suggesting a possible role of immunotherapy [17].

In conclusion, this case study reports the first case of a pulmonary epitheloid haemangioendothelioma with synchronous central nervous system dissemination. Prognosis of this disease, especially if disseminated, remains poor and treatment is usually unsatisfactory. Novel therapeutic strategies are urgently needed, which could include new chemotherapeutic agents or the use of immunotherapy.

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