

Epithelioid Haemangioendothelioma of the Lung Presenting with Pulmonary Nocardiosis

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Abstract. *Epithelioid haemangioendothelioma of the lung is a rare tumour, originally described as intravascular bronchioalveolar tumour. The typical clinical findings are those of bilateral multiple pulmonary nodules in young or middle aged Caucasian women. Pulmonary nocardiosis is an unusual disease affecting patients with immunodeficiency or chronic obstructive lung disease. The first case of pulmonary epithelioid haemangioendothelioma (PEH) associated with pulmonary nocardiosis, in a 36-year-old woman presenting with progressive dyspnoea and fever, is described. The neoplasm was diagnosed by thoracoscopic lung biopsy and the histological diagnosis was confirmed by immunohistochemistry and electron microscopy. Pulmonary nocardiosis was confirmed by lung tissue culture. Following treatment with antibiotics, the patient's respiratory symptoms subsided. Two years after diagnosis she was asymptomatic and chest CT scans showed stable neoplastic disease.*

Pulmonary epithelioid haemangioendothelioma (PEH) is the current term for a rare neoplasm originally described by Dail and Liebow in 1975 as intravascular sclerosing bronchioalveolar tumour (IVBAT) of the lung (1). Immunohistochemistry (2) and electron microscopy (3) have revealed the vascular origin of the neoplasm. It is a low-to-intermediate grade malignancy composed of short cords and nests of epithelioid endothelial cells embedded in a hyalinized stroma and extending into the alveoli, bronchi and blood vessels. PEH is typically seen as multiple bilateral lung nodules usually discovered incidentally in Caucasian young or middle aged women, although cases in children and in the elderly have also been described (4, 5). In a recent literature

review, PEH was twice as common in women than men and the mean age of the patients was 39.7 years (4). To date approximately 120 cases of PEH have been reported (4-18).

The clinical presentation of PEH is usually indolent and almost half of the patients are asymptomatic (5). Symptomatic patients may present with dyspnoea, pleuritic chest pain due to pleural effusion, a mild non-productive cough, haemoptysis and clubbing. Up to 42% of the patients have anaemia (4). PEH may rarely present with alveolar haemorrhage or as thromboembolic disease. Up to 10% of patients may have substantial liver involvement (4, 19).

A case of PEH presenting with pulmonary nocardiosis is reported. To the best of our knowledge, this is the first case of PEH presenting with symptoms of an opportunistic infection.

Case Report

A 36-year-old woman was referred to our hospital because of dyspnoea and mild pyrexia. Her symptoms have started ten days before admission when she developed slowly progressive dyspnoea and fever up to 38°C. Her prior medical history involved a deep vein thrombosis of the femoral vein and a severe respiratory infection eight and seven years ago, respectively. The patient was a 36-pack/year smoker and had a free family history.

On physical examination, she had enlarged right clavicular lymph nodes, prolonged expiration, systolic murmur of the tricuspid valve and hepatomegaly. The full blood count revealed hypochromic microcytic anaemia and the blood smear showed anisocytosis and poikilocytosis. The biochemical and coagulation tests were normal while all immunological blood tests proved negative.

A chest radiograph revealed multiple, bilateral, nodular opacities. No hilar or mediastinal lymph node enlargement, or pleural effusion could be observed. On spirometry, a mild obstructive ventilatory defect, reversible with bronchodilators, was identified. The patient's pulmonary function tests revealed forced expiratory volume in 1 second (FEV1) of

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73.1% and forced vital capacity (FVC) of 97.5% of the predicted values, respectively. A chest CT revealed multiple, bilateral, nodular, non-calcified, mostly ill-defined lesions, varying in size from a few mm to 1 cm. No pleural effusions, interlobular septal thickening, atelectasia, cavities or pycnosis were detected. There were no enlarged lymph nodes or osteolytic lesions (Figure 1a). Upper-abdomen CT did not show any abnormalities.

A thoracoscopic lung wedge biopsy was performed. Tissue cultures were negative for *Mycobacterium tuberculosis*, *Mycobacterium avium intercellulare*, *Actinomyces*, fungi and routine bacteria. RT-PCR, performed to confirm the absence of mycobacteria, was also negative. Nevertheless, tissue culture revealed *Nocardia asteroides*.

Pathological gross examination of tissue specimens from the left upper (5x3.5x2.5 cm) and left lower lobe (4x2x1.7 cm) revealed 8 well circumscribed, round, firm, white-gray nodules, measuring 1-6 mm in greatest diameter. Histology showed eosinophilic nodules with a center composed of hypocellular hyalinized fibrous tissue, while at their periphery, groups of epithelioid neoplastic cells with oval nuclei and intracytoplasmic lumina were extending into the alveoli or surrounding blood vessels (Figures 2a-2c). Mitoses were not detected. Larger nodules showed central necrosis. The non-neoplastic lung parenchyma did not show significant histological changes. Special stains for amyloid, acid fast bacilli, bacteria and fungi were negative. In particular, *Nocardia asteroides* infection could not be confirmed histologically. Immunohistochemical stains for endothelial markers Factor VIII, CD31 and CD34 (Figure 2d), vimentin and progesterone receptor (Figure 2e) were positive in the tumour cells, while immunostains for cytokeratin markers, epithelial membrane antigen, carcinoembryonic antigen, α -smooth muscle actin, CD68 and estrogen receptor were negative. Electron microscopical examination confirmed the endothelial nature of the neoplastic cells some of which contained Weibel-Palade bodies (Figure 2f). The final pathological diagnosis was that of pulmonary epithelioid haemangioendothelioma.

Based on the tissue culture results of *Nocardia asteroides* infection, the patient received an oral combination of trimethoprim-sulfamethoxazole and her symptoms improved. The patient did not receive any treatment for PEH and two years following diagnosis was asymptomatic. Her follow-up CT scans showed stable neoplastic disease (Figure 1b).

Discussion

Pulmonary nocardiosis is an unusual opportunistic infection in humans and predominant risk factors are an immunocompromised state, corticosteroid therapy and underlying pulmonary pathology, including chronic obstructive lung disease (20, 21). Many patients suffering from nocardiosis are HIV-positive (20). Our patient was HIV-negative, but she

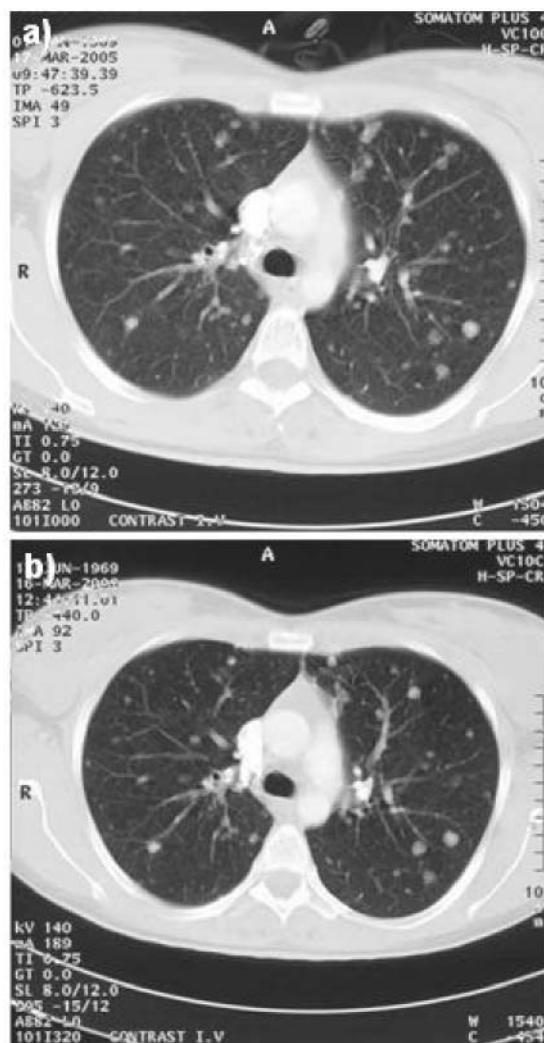


Figure 1. Chest computed tomography scans: a) at presentation: multiple bilateral small lung nodules; b) 1 year after presentation: there are no significant differences in the size and number of nodules.

had the predisposing factors of an immunocompromised state and pulmonary pathology due to PEH.

Imaging studies of PEH, characteristically demonstrate multiple, bilateral nodules measuring 1-2 cm. However, PEH may present as a solitary lung mass (5, 6, 22, 23). Occasionally, the nodules of PEH may appear calcified (22) and pleural effusion secondary to the pulmonary lesions is not uncommon (19, 24). The radiographic appearance in pulmonary nocardiosis varies (25). Interestingly, the disease may also present as multiple, bilateral lung nodules which occasionally may show cavitation (25, 26).

The main differential diagnosis of PEH is from metastatic cancer. Differential diagnosis of multiple pulmonary nodules also includes a variety of benign non-neoplastic conditions, such as infection with pathogens, sarcoidosis, organizing infarcts,

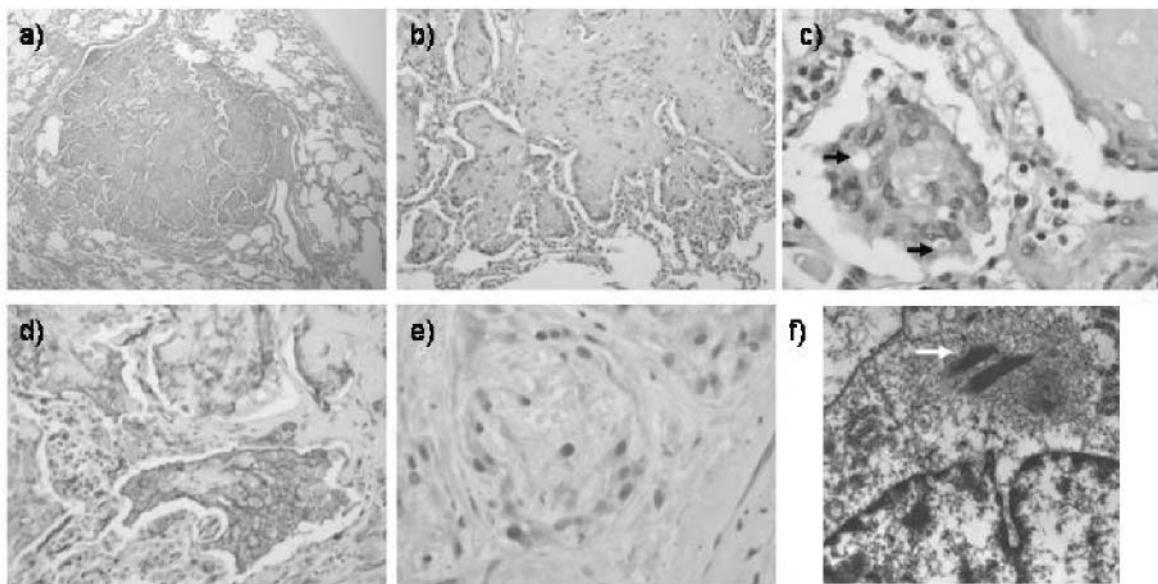


Figure 2. *a)* An eosinophilic hypocellular nodule of epithelioid hemangioendothelioma of the lung, Haematoxylin and eosin stain (H&E), *x25*, *b)* at the periphery of the nodule, tumour grows into alveolar spaces, H&E, *x100*, *c)* bland neoplastic cells grow in a hyalinized stroma, have oval nuclei and intracytoplasmic lumina which occasionally contain a red blood cell (arrows), H&E, *x200*, *d)* intense immunostaining for CD34 in tumour cells, *e)* nuclear immunopositivity for progesterone receptor in neoplastic cells; mild cytoplasmic immunostaining is also noted, *x400*, *f)* electron micrograph showing tumour cell with intracytoplasmic Weibel-Palade bodies (arrow), *x23,600*.

amyloid nodules, hamartomas, connective tissue diseases including vasculitides (Wegener's type) and pulmonary rheumatoid nodules. Langerhans cell histiocytosis may present with similar imaging features. Benign neoplasms such as sclerosing haemangioma and chemodectoma and malignant neoplasms such as primary lung carcinoma and epithelioid sarcoma may also be considered (4, 5, 19). The final diagnosis is based on histological evaluation of specimens obtained by transbronchial biopsy or, most often, thoracoscopic wedge biopsy, and is confirmed by immunohistochemistry (4, 5). Cytological diagnosis on fine needle aspiration biopsy material is also feasible (6, 15). The possibility of lung metastases of a primary epithelioid haemangioendothelioma should be excluded since this tumour may also arise in the liver, soft tissue and bones (4, 5, 24, 27). However, distinction between multifocal disease and metastatic progression is difficult.

Surgical resection is proposed as the treatment of choice in symptomatic PEH patients with unilateral single or multiple nodules (4), but there is no single effective treatment in cases of bilateral multiple nodules. Asymptomatic patients may not be treated and should be closely followed-up (4, 24). The response to chemotherapy varies, while treatment with mitomycin C, 5-fluorouracil, cyclophosphamide, vincristine or tegafur was of no benefit (24). In one case a complete response was achieved using carboplatin and etoposide (28). Variable response to treatment with α -2a interferon, corticosteroids or azathioprine has also been reported (4, 5). Radiation therapy does not seem to be effective in PEH (4).

The presence of hormonal (estrogen and progesterone) receptors in a few PEH cases raises the possibility of hormonotherapy as a potential treatment in selected patients (29, 30). Lung transplantation should be evaluated in patients with vascular aggressiveness, pleural haemorrhagic effusion and anaemia (4). Treatment with sulfonamides or trimethoprim-sulfamethoxazole is usually effective in pulmonary nocardiosis (20, 21).

The prognosis of PEH is unpredictable. The usual course is slow progression finally resulting in restrictive respiratory failure and death. Life expectancy varies from 1 to 15 years, depending on tumour aggressiveness (4, 5). In a recent meta-analysis evaluating the outcome of 80 reported cases of PEH, the median 5-year survival was 60% (range 47% to 71%) (4). Loss of weight, anaemia, pulmonary symptoms and particularly pleural haemorrhagic effusions are significant factors of poor prognosis, with a median survival of less than 1 year (4, 5).

The lack of clear standards for treatment due to the rarity of the tumour, the partial-to-complete spontaneous regression of PHE seen in some patients (24) and the absence of significant poor prognostic factors in our case, led us to the decision not to treat but closely follow-up our patient. Her concurrent pulmonary nocardiosis was successfully managed with antibiotic treatment and the patient remains asymptomatic two years following diagnosis of PEH. Interestingly, in our case, PEH tumour cells expressed progesterone receptors, making hormonal therapy

a possible therapeutic choice if the disease shows signs of progression in the future.

In conclusion, a case of PEH predisposing to the development of pulmonary nocardiosis is reported. Our diagnosis of PEH was confirmed by immunohistochemistry and electron microscopy, while pulmonary nocardiosis was diagnosed by lung tissue culture. Awareness of the presentation findings of PEH may allow the clinician to consider this unusual tumour in the differential diagnosis of multiple lung nodules, even in the presence of concurrent infectious lung disease.

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