

CASE STUDY

Epithelioid haemangioendothelioma of the lung: clinical and pathological pitfalls

M.E.E. van Kasteren*, A.A.M. van der Wurff**, F.M.L.H.G. Palmen†,
A. Dolman*, J.F.M.M. Miseré**

Epithelioid haemangioendothelioma of the lung: clinical and pathological pitfalls. M.E.E. van Kasteren, A.A.M. van der Wurff, F.M.L.H.G. Palmen, A. Dolman, J.F.M.M. Miseré. ©ERS Journals Ltd 1995.

ABSTRACT: In 1973, a 10 year old boy presented with numerous bilateral lung nodules, diagnosed as histiocytosis X by open lung biopsy. The patient was treated with prednisone until 1984. In 1993, he developed severe pain in the neck. A biopsy of the spine revealed the same tumour morphology as was seen in the lung in 1973. Immunohistological examination of the former and present biopsy led to the definitive diagnosis of epithelioid haemangioendothelioma of the lung with metastases to spine and liver.

Epithelioid haemangioendothelioma of the lung is a rare soft tissue tumour of vascular origin, readily mistaken for carcinoma or, as in this case, histiocytosis. The tumour has an intermediate malignant potential. Although metastases of epithelioid haemangioendothelioma of the lung are well-known, metastatic spread to bones, as in our case, has not previously been mentioned in the literature.

Eur Respir J., 1995, 8, 1616–1619.

*Dept of Internal Medicine, **Dept of Pathology, †Dept of Respiratory Diseases, St. Elisabeth Hospital, Tilburg, The Netherlands.

Correspondence: A. Dolman
Dept of Internal Medicine
St. Elisabeth Hospital
Hilvarenbeekse weg 60
5022 GC Tilburg
The Netherlands

Keywords: Epithelioid haemangioendothelioma
lung
metastases

Received: September 19, 1994

Accepted after revision February 26 1995

Epithelioid haemangioendothelioma (EH) is an uncommon vascular tumour with an epithelioid or histiocytoid appearance, originating from endothelial cells [1, 3]. Normally, this tumour is of borderline malignancy running a relatively benign course [3, 4]. The principal locations are soft tissue (especially the extremities), bone, liver and lung. In the lung, the tumour is often multifocal, bilateral, and usually affects young people (average age 39 yrs, range 12–61 yrs) with a predominance for women (male:female 1:4) [3–5]. Initially most patients have no symptoms and diagnosis may be suspected on routine chest roentgenogram. Although EH of the lung is a relatively slow growing tumour, extensive pulmonary involvement, intrathoracic spread and systemic metastases, mainly to the liver, have been documented.

We present a case of EH of the lung, which was initially mistaken for histiocytosis X and finally diagnosed 20 yrs later, when extensive dissemination had occurred.

Case report

In 1973, a 10 year old boy was admitted to our hospital because of dyspnoea. A chest radiograph showed multiple parenchymal nodules and an open lung biopsy was performed.

The biopsy (2.5 × 1.0 × 0.5 cm) showed small foci of epithelioid cells with oval nuclei and abundant eosinophilic cytoplasm (fig. 1). The nucleus had a coarse chromatin pattern and one or more nucleoli. Anisokaryosis was prominent. The cells were localized around vessels and bronchioles. Mitoses were not seen. There was a sparse lymphoplasmocytic infiltrate, with a few eosinophilic granulocytes and many iron-containing macrophages. The reticulin stain showed a solid insular, sometimes tubular pattern. A diagnosis of histiocytosis X was made.

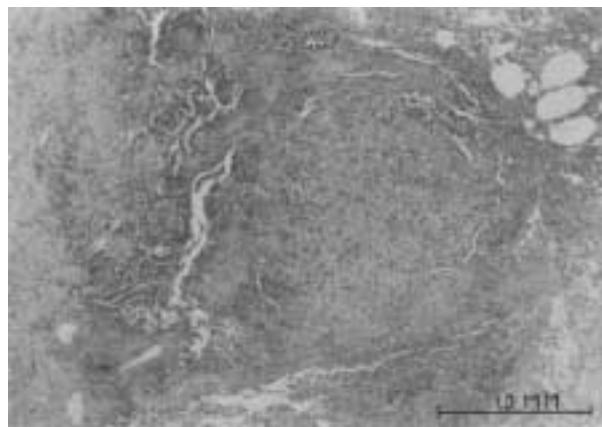


Fig. 1. – Biopsy of the lung taken in 1973, which shows a tumour nodule composed of epithelioid cells. There are remnants of alveoli within the nodule. (Haematoxylin and eosin stain; magnification ×25).

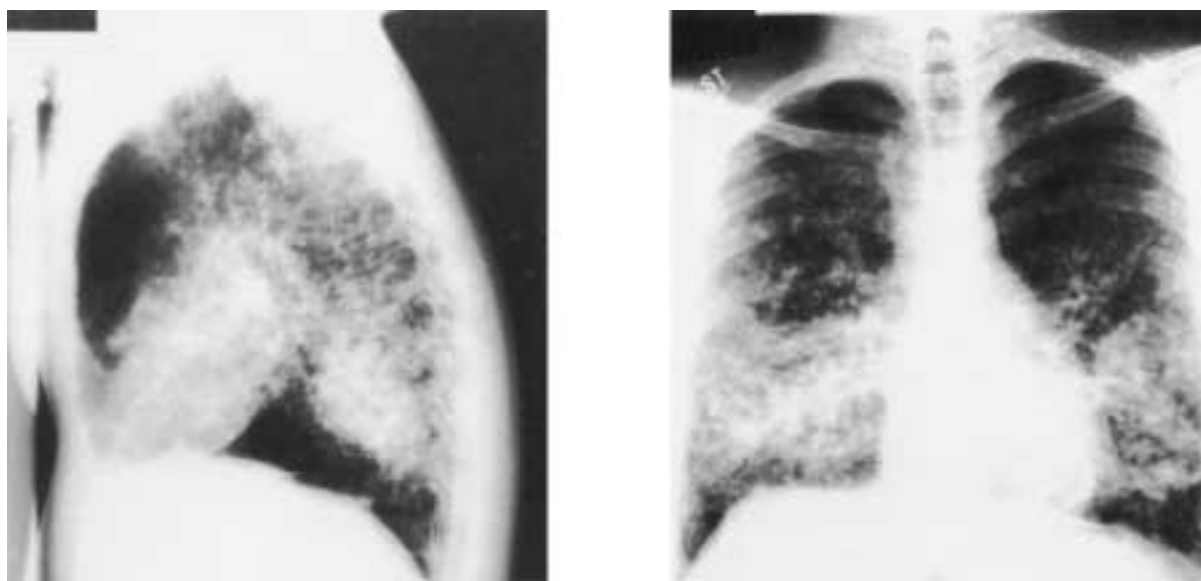


Fig. 2. – Radiograph from 1984, when the patient's pulmonary condition was stable, shows a bilateral nodular interstitial pattern. The roentgenological picture had not changed throughout the years.

The patient was treated with prednisone until the age of 21 yrs (1984). Thereafter, his pulmonary condition, which was checked twice yearly by chest radiography (fig. 2) and lung function tests, remained stable.

In February 1993, at the age of 30 yrs, he visited a neurologist because of severe pain in the neck and paraesthesia of his fingers. A roentgenogram and magnetic resonance imaging (MRI) of the cervical spine showed a tumour, with complete destruction of the corpora of C6-Th1 and extracorporal spread. The patient was referred to our hospital for neurosurgical exploration. At admission, physical examination revealed a patient with a slight dyspnoea, who was sweating excessively. No cardiac murmurs were heard and over the lungs there was a slight wheezing. The liver was palpable. Surprisingly, no neurological abnormalities were found. A second MRI of the whole spine showed destruction of the corpora C6-Th1 with compression of the spinal cord and multiple, partly calcified, lesions in several thoracic and lumbar corpora, suggestive of metastases. A chest roentgenogram indicated a nodular pattern as in former radiographs. At abdominal echography, two calcified nodules highly suggestive of metastases were found in the liver. The patient was prescribed 2.5 mg prednisone *t.i.d.* Surgical exploration of the cervical tumour was performed and a biopsy was taken from the corpus of C6. Before a histological diagnosis was made, radiation therapy was initiated (4,000 cG in 4 weeks).

The biopsy (fig. 3) showed an osteoclastic lesion in which, apart from extensive necrosis, the same tumour morphology was seen as in the former lung biopsy. Mitoses were not seen. Immunohistochemical characterization was performed on the biopsy of the spine and, retrospectively, on the biopsy of the lung from 1973. In both cases, there was a strong positivity for vimentin.

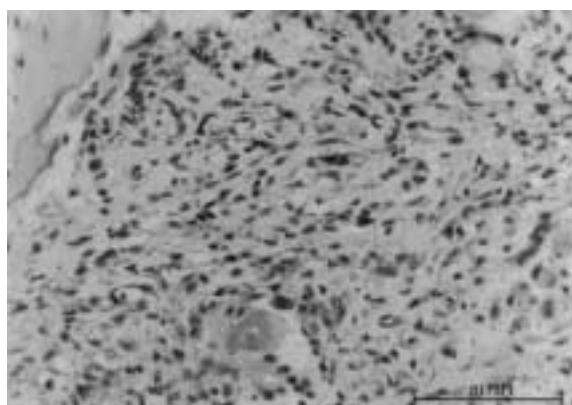


Fig. 3. – Biopsy of the cervical spine taken in 1993, which shows an osteoclastic lesion with irregular vascular spaces and pleomorphic cells. Note bone destruction in upper left corner. (Haematoxylin and eosin stain; magnification $\times 250$)

In particular, the lung biopsy showed strong positivity for the endothelial marker factor VIII and Ulex. Both biopsies were negative for different keratin antibodies, leucocyte common antigen (CD45), desmin, actin and the macrophage marker CD68. Specific monoclonal antibodies such as prostate specific antigen, thyroglobulin, alpha-foetoprotein, and an anti-melanoma marker were all negative.

Both biopsies were sent to the soft tissue consultation board of The Netherlands (J.A.M. van Unnik, Ch.E. Albus Lutter) who also sent the slides to J. Rosai (Memorial Sloan-Kettering Cancer Center, New York, USA). They all agreed with the diagnosis of epithelioid haemangioendothelioma involving both lungs and spine.

Despite radiation therapy, the patient developed a tetraparesis and his clinical condition worsened. Because of the progressive and disseminated character of the

tumour, chemotherapy was initiated. The patient received two courses of doxorubicin (140 mg) every three weeks. The chemotherapy was badly tolerated and showed no effect on tumour growth. Three months after the first visit to our clinic (almost 21 yrs after his first admittance for pulmonary complaints) the patient died of cachexia and respiratory insufficiency.

At autopsy, numerous, partly necrotic tumour nodules were found in both lungs, with diameters ranging 0.2–3.0 cm. Nodules with the same appearance were seen in the left kidney (subcapsular 0.9 cm), pancreas (1.0 cm), left adrenal gland (3.0 cm) and liver (2.0 and 1.0 cm). The nodules in the liver showed extensive calcification. Multiple tumour foci in the spine and para-aortic lymph nodes were also seen. Between the tumour nodules of the lungs, mild emphysema was microscopically visible.

Discussion

This case report is an example of an extraordinarily protracted course with fatal outcome of an epithelioid haemangioendothelioma of the lung.

Several articles have been published concerning patients with multiple bilateral nodular lung lesions on chest radiograph, microscopically consisting of epithelioid tumour cells expressing endothelial marker profiles [4, 6–9]. This tumour was initially known as “intravascular bronchioloalveolar tumour” (IVBAT). VERBEKEN *et al.* [8] suggested that IVBAT as well as a unique soft tissue tumour of endothelial origin, named epithelioid haemangioendothelioma by WEISS *et al.* [3], could be different manifestations of one and the same tumour.

In the original cases described by DAIL *et al.* [4], the mean survival of epithelioid haemangioendothelioma of the lung was 4.6 yrs, with a range of 6 months to 15 yrs. TEO *et al.* [10] reported a case with a 20 year survival, and MIETTINEN *et al.* [11] described a 17 year old girl who died of respiratory failure 24 yrs after 10 recurrent epithelioid haemangioendotheliomas were excised.

Most patients die from pulmonary insufficiency as a result of increasing size and number of tumour nodules. A small group succumbs because of extrapulmonary spread of the tumour [5]. Distant, sometimes calcified, metastases have been described mainly in the liver. DAIL *et al.* [4] also reported metastases in kidney and spleen. Bone metastases are quite common in EH of the extremities but, to our knowledge, extensive bone metastases of EH of the lung, as in our patient, have not previously been documented.

The diagnosis of EH can be a pitfall for the clinician as well as the pathologist. Most patients are asymptomatic or have aspecific symptoms, such as cough, dyspnoea, chest pain and malaise [12]. The roentgenological findings, *i.e.* multiple bilateral nodules up to 3 cm in diameter often suggest other diseases [4, 5]. In adults, these lesions are frequently mistaken for metastases or granulomatous diseases [3, 5, 12]. In childhood, diseases such as histiocytosis X may be considered. Often

histological examination leads to the correct diagnosis. This tumour, however, was initially mistaken for histiocytosis X because of the histiocytoid morphology of the cells. In 1973, a marker profile of the lung biopsy could not be determined because of lack of specific immunohistochemical technology. Nowadays, with the help of monoclonal antibodies, the vascular origin of the tumour cells can easily be deduced and the correct diagnosis of epithelioid haemangioendothelioma can be made. The histiocytoid appearance of the endothelial cells prompted ROSAI *et al.* [13] and LAI *et al.* [14] to group tumours as angiolymphoid hyperplasia, histiocytoid haemangioma of the testis, epithelioid haemangioma, and probably spindle cell haemangioendothelioma, under one heading of histiocytoid haemangiomas (the unifying concept).

Although immunohistochemical technology makes differentiation from histiocytosis X easy, differentiation from angiosarcoma and sclerosing haemangioma can pose more problems. Unlike angiosarcoma, EH does not show necrosis, significant cytonuclear atypia or a high mitotic index, and runs a relatively benign course. Sclerosing haemangioma, on the other hand, is a benign tumour without cytonuclear atypia and mitotic figures. Therefore, SCOTT and ROSAI [15] stress the fact that haemangioendotheliomas are in a continuum between haemangioma and epithelioid angiosarcoma.

Therapeutic options of EH of the lung are rare. When the lesions are small and limited in number, which is seldom the case, surgical resection is recommended by some authors [3]. Others advise an anticipatory policy in asymptomatic patients [4]. Radiotherapy is hardly ever effective because of the slow growth of the tumour cells. Although several chemotherapeutic regimens have been tried, no success has been documented [3, 4]. In our patient, radiation therapy and chemotherapy were not effective. He died 5 months after admission and almost 21 yrs after he first presented with pulmonary complaints.

References

1. Haelst v. UJG, Pruszczyński M, Cate t. LN. Ultrastructural and immunohistochemical study of epithelioid hemangioendothelioma of bone: coexpression of epithelial and endothelial markers. *Ultra Struct Pathol* 1990; 14: 141–149.
2. Weiss SW, Enzinger FM. Epithelioid hemangioendothelioma. *Cancer* 1982; 50: 970–981.
3. Weiss SW, Ishak KG, Dail DH, Sweet DE, Enzinger FM. Epithelioid hemangioendothelioma and related lesions. *Semin Diagn Pathol* 1986; 3 (4): 259–287.
4. 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: 452–464.
5. Eggleston JC. The intravascular bronchioloalveolar tumor and the sclerosing hemangioma of the lung: misnomers of pulmonary neoplasia. *Semin Diagn Pathol* 1985; 2 (4): 270–280.
6. Borlee-Hermans J, Bury Th, Grand JL, Jardon-Jeghers C, Rademecker M. Intravascular bronchioloalveolar tumour. *Eur J Respir Dis* 1985; 66: 344–346.

7. Sherman JL, Rijkwalder PL, Tashkin DP. Intravascular bronchioloalveolar tumor. *Am Rev Respir Dis* 1981; 123: 468-470
8. Verbeken E, Beyls J, Moerman P, Knockaert D, Goddeeris P, Lauweryns JM. Lung metastasis of malignant epithelioid hemangioendothelioma mimicking a primary intravascular bronchioalveolar tumor: a histologic, ultrastructural and immunohistochemical study. *Cancer* 1985; 55: 1741-1746.
9. Weldon-Linne CM, Victor TA, Christ ML, Fry WA. Angiogenic nature of the intravascular bronchioalveolar tumour of the lung: an electron microscopic study. *Arch Pathol* 1981; 105: 174-179.
10. Teo SK, Chiang SC, Tan KK. Intravascular bronchioalveolar tumour: a 20 year survival. *Med J Aust* 1985; 142: 220.
11. Miettinen M, Collan Y, Halttunen P, *et al.* Intravascular bronchioloalveolar tumor. *Cancer* 1987; 60: 2471.
12. Sicilian L, Warson F, Carrington CB, Hayes J, Gaensler EA. Intravascular bronchioalveolar tumor (IVBAT): case report. *Respiration* 1983; 44: 387-394.
13. Rosai J, Gold J, Landy R. The histiocytoid hemangiomas: an unifying concept embracing several previously described entities of skin, soft tissue, large vessels, bone and heart. *Hum Pathol* 1979; 10: 707-730.
14. Lai FM, Allen PW, Yuen PM, Leung PC. Locally metastasizing vascular tumor: spindle cell, epithelioid, or unclassified haemangioendothelioma? Single case report. *Am J Clin Pathol* 1991; 96: 660-663.
15. Scott GA, Rosai J. Spindle cell hemangioendothelioma: report of seven additional cases of a recently described vascular neoplasm. *Am J Dermatopathol* 1988; 10 (4): 281-288.
16. Allen PW, Ramakrishna B, MacCormac LB. The histiocytoid hemangiomas and other controversies. *Pathol Annu* 1992; 27: 51-87.