Thoracic Cancer ISSN 1759-7706

CASE REPORT

Four-year natural clinical course of pulmonary epithelioid hemangioendothelioma without therapy

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Keywords
Epithelioid; hemangioendothelioma; observation.

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Received: 29 August 2014;
Accepted: 13 October 2014.

doi: 10.1111/1759-7714.12192

Thoracic Cancer **6** (2015) 544–547

Abstract

Pulmonary epithelial hemangioendothelioma is a rare low to intermediate malignant vascular tumor originating from vascular endothelial cells. The therapy for this disease, if possible, is surgical resection. However, there is no standard treatment for patients with multiple unresectable lesions. We present the case of a 42-year-old woman treated with a natural clinical course of hemangioendothelioma for four years without therapy. The nodules have increased in number and size extremely slowly, and the patient is alive and asymptomatic four years after diagnosis.

Introduction

Pulmonary epithelioid hemangioendothelioma (PEH) is a rare low to intermediate malignant vascular tumor representing 12% of all epithelioid hemangioendothelioma (EHE) cases, with single-organ involvement seen in 19% of cases.[1,2] Therapy for this disease is surgical resection if the lesions are resectable. However, there is no standard treatment for patients with multiple unresectable lesions. Chemotherapy is often selected as a therapy for multiple lesions, but there is no effective regimen. Regular follow-up without therapy is an option for asymptomatic patients with multiple lesions. We experienced a case of PEH and present its clinical course over four years without therapy.

Case report

A 42-year-old female non-smoker was found to have multiple abnormal nodules incidentally via a chest X-ray. She was asymptomatic and had no concomitant disease or family history of pulmonary disease. Chest computed tomography (CT) revealed multiple pulmonary nodules with well-defined margins in both lungs. A 5.0-cm thyroid nodule extended to the anterior mediastinum. Positron-emission tomography exhibited an increased uptake of 18F-fluorodeoxyglucose (maximum standardized uptake value of 2.17) in the thyroid tumor. She was clinically diagnosed with thyroid carcinoma and pulmonary metastasis. She underwent hemithyroidectomy, and the diagnosis was benign adenomatous goiter. She was advised to undergo surgical resection of the pulmonary nodules for tissue diagnosis at our hospital, and a diagnostic lung biopsy of the right lower lobe (S6) was performed (Fig 1a). Histological findings reported a hyalinized component in a normal alveolar space. Some tumor cells in the hyalinized component had intracytoplasmic vacuoles (Fig 1b). Immunohistological staining of the tumor cells was positive for CD34 and factor VIII antibodies and negative for CD31 antibody (Fig 1c,d). The postoperative diagnosis of the nodule was PEH.

The patient declined therapy and has received regular follow-up chest CTs and X-rays for four years. Over this period, the tumors have increased extremely slowly in number and size (Fig 2). The largest lung nodule, which increased in size from 8.9 mm to 9.4 mm, had a tumor-doubling time of 18 528 days. The number of nodules has increased from over 60 to over 90, but no pleural effusion or

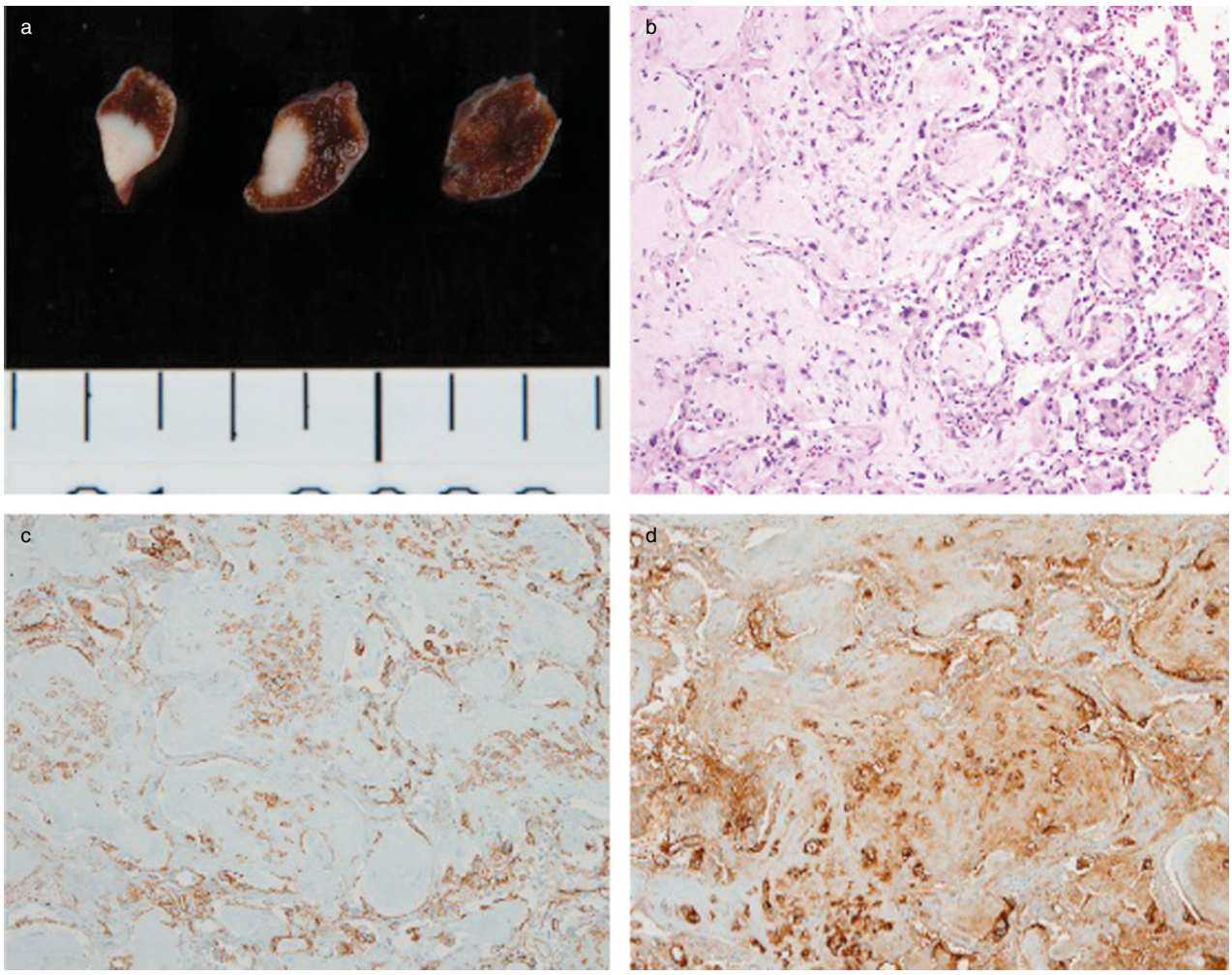

Figure 1 (**a**) One of lung nodules in the right lower lobe (S6). (**b**) Hematoxylin-eosin stain shows atypical epithelioid cells with hyalinized component in normal alveolar space (×200). (**c**) Immunohistological staining shows CD34 positive, and (**d**) factor VIII positive tumor cells.

other changes have been noted, and the patient is alive and asymptomatic four years after diagnosis.

Discussion

EHE is multicentric in origin, typically arising in the lung, liver, and other soft tissues and bone. Multi-organ involvement occurs in 36% of cases, single-organ involvement in 64%. PEH is rare, accounting for 19% of cases of single-organ involvement and 12% of all EHE cases.[1,2] By 2006, 15 reviews and 93 case reports on PEH have been reported.[2] PEH occurs in patients younger than 40 years of age and is four times more common in women than in men.[3] In most cases, this disease is an incidental finding in asymptomatic patients upon physical examination but is often accompanied by symptoms such as coughing, shortness of breath, and/or hemoptysis. PEH is often mistaken for lung carcinoma or metastasis or granulomatous disease. In our case, the disease was clinically diagnosed as metastasis of thyroid carcinoma.

Disease prognosis is unpredictable. Life expectancy ranges from one to 15 years. In cases with symptoms such as shortness of breath, pleural effusion, and weight loss, prognosis is so poor that median overall survival is 12 months or less.

Surgical resection should be performed if possible. Five-year overall survival in cases of surgical treatment has been reported to be 60%.[4] However, there is no established therapy in cases of multiple unresectable nodules. Regular follow-up without therapy has often been employed in asymptomatic patients with diffuse lesions. Survival of 10 years or more without therapy has been reported in two cases.[5,6] The time to exacerbation was more than 12 years in one case report;[6] in another, it was 10 years until one of multiple tumors, which was enlarging and showed a significant 18F-fluorodeoxyglucose uptake, was surgically resected.[5]

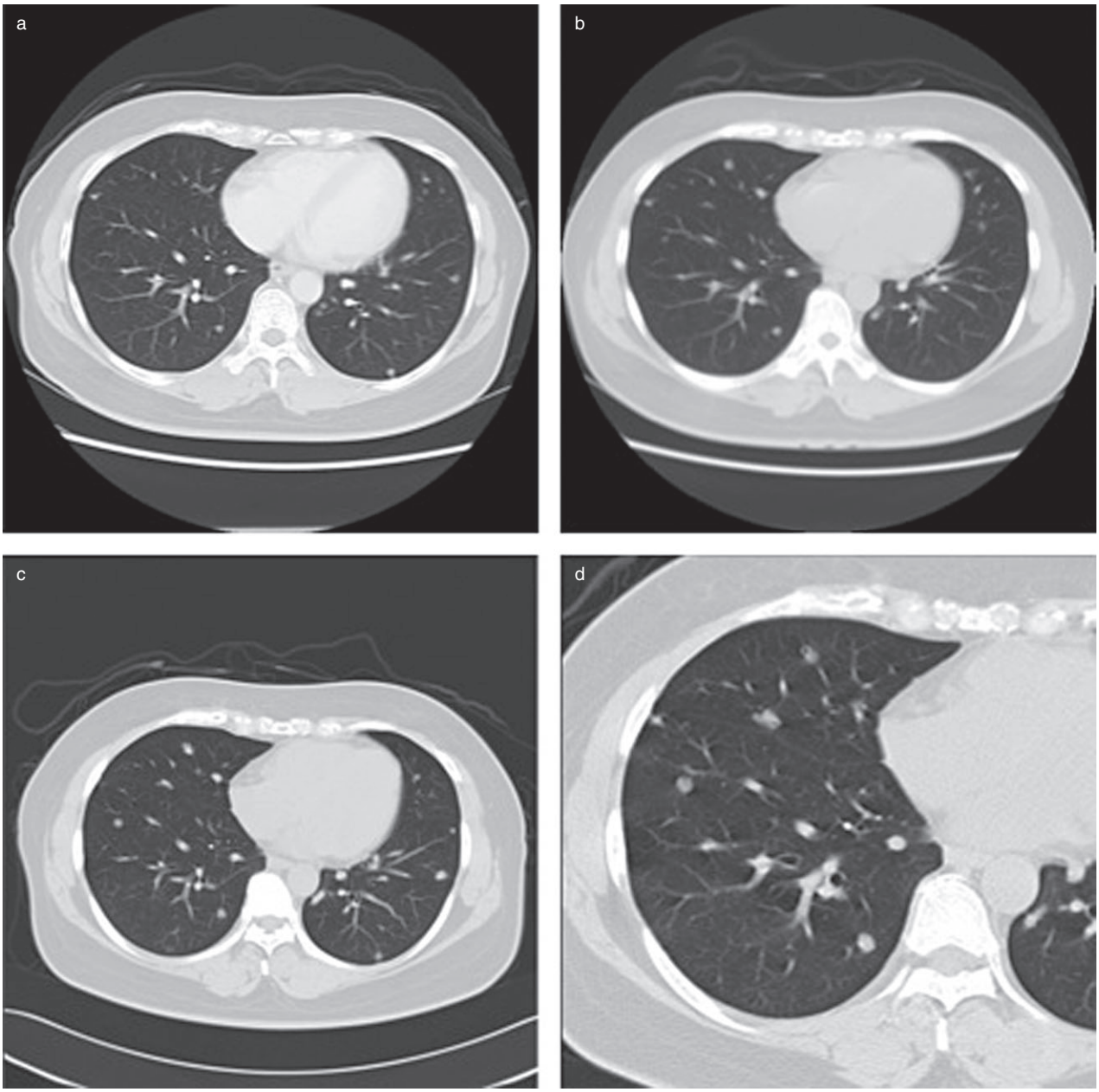

Figure 2 Chest computed tomography showing the four-year natural clinical course. (**a**) Before biopsy, (**b**) one year after biopsy, and (**c**) four years after biopsy. (**d**) Magnified image of pulmonary lesions four years after biopsy.

To date, chemotherapy with Interferon-α, Carboplatin, Paclitaxel, and Bevacizumab have been attempted.[7] In particular, there are five case reports of PEH treated with bevacizumab, a monoclonal antibody that blocks human vascular endothelial growth factor-A (VEGF-A).[7,8] The chemotherapeutic effects were partial response in one case, stable disease in one case, and progressive disease in one case. In another case, an effect was unable to be assessed because of side effects.[8] These results are small in number but promising, and the new VEGF-A-targeting chemotherapeutic agents, bevacizumab and Sorafenib,[9] are expected to be effective.

Since our patient's diagnosis, we have checked pulmonary lesions with yearly CT scans. Although the size and number of pulmonary nodules are increasing, they are doing so extremely gradually. The patient's clinical examinations have been unremarkable, and she is alive without symptoms four years after diagnosis. In asymptomatic patients, we therefore suggest a treatment strategy of careful observation of the

number and size of tumors with a chest CT at a minimum of once yearly. For symptomatic patients, or those who experience disease exacerbation, we recommend therapy, such as chemotherapy. Considering the low to intermediate malignancy of this disease, observation is an option for PEH patients without symptoms.

Disclosure

No authors report any conflict of interest.

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