

## Pemetrexed for epithelioid haemangioendothelioma of the pleura

Shingo Kanemura<sup>1</sup>, Kozo Kuribayashi<sup>1</sup>, Yumiko Moriya<sup>1</sup>, Shigeki Shimizu<sup>2</sup>, Tohru Tsujimura<sup>2</sup> & Takashi Nakano<sup>1</sup>

<sup>1</sup>Department of Respiratory Medicine, Hyogo College of Medicine, Hyogo, Japan.

<sup>2</sup>Department of Pathology, Hyogo College of Medicine, Hyogo, Japan.

### Keywords

Epithelioid hemangioendothelioma, malignant pleural mesothelioma, pemetrexed, pleura, pleural effusion.

### Correspondence

Kozo Kuribayashi, Department of Respiratory Medicine, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan, E-mail: kuririn@hyo-med.ac.jp

Received: 5 April 2016; Revised: 22 August 2016; Accepted: 25 August 2016; Associate Editor: Helen Davies.

*Respirology Case Reports*, 4 (6), 2016, e00191

doi: 10.1002/rcr2.191

### Abstract

A 31-year-old woman presented with a 2-month history of dull left back pain. Chest roentgenography revealed pleural thickening in the left lung apex, whereas chest computed tomography showed a left pleural effusion with diffuse pleural thickening. Based on these findings, malignant mesothelioma was suspected. Video-assisted thoracoscopic pleural biopsy was performed, and subsequent staining of the specimen revealed negative results for anti-cytokeratin antibodies and positive results for vascular endothelial immunohistochemical markers. Therefore, a diagnosis of epithelioid hemangioendothelioma (EHE) was made, and chemotherapy with carboplatin, pemetrexed, and bevacizumab was initiated. After the fourth course of treatment, the disease was well controlled with a 90% reduction of the left pleural effusion. This case is very rare in that the EHE originated from the pleura. Additionally, there has been no report of pemetrexed for treatment of EHE.

### Introduction

Epithelioid hemangioendothelioma (EHE) was first reported as intravascular bronchioloalveolar tumour by Dail and Liebow in 1975 [1]. EHE is a rare slow-growing neoplasm, which can occur in any organ but is found most often in the lung and liver. Reports of primary pleural EHE are very rare. Although pulmonary EHE is a rare entity in nature, with a relative increase in occurrence in women and has a slow progression, pleural EHE is more common among men than among women and has a poor prognosis [2]. Here, we describe a case of pleural EHE that presented with pleural effusion, mimicking malignant pleural mesothelioma (MPM). The patient's disease was well controlled after four cycles of chemotherapy with carboplatin, pemetrexed, and bevacizumab.

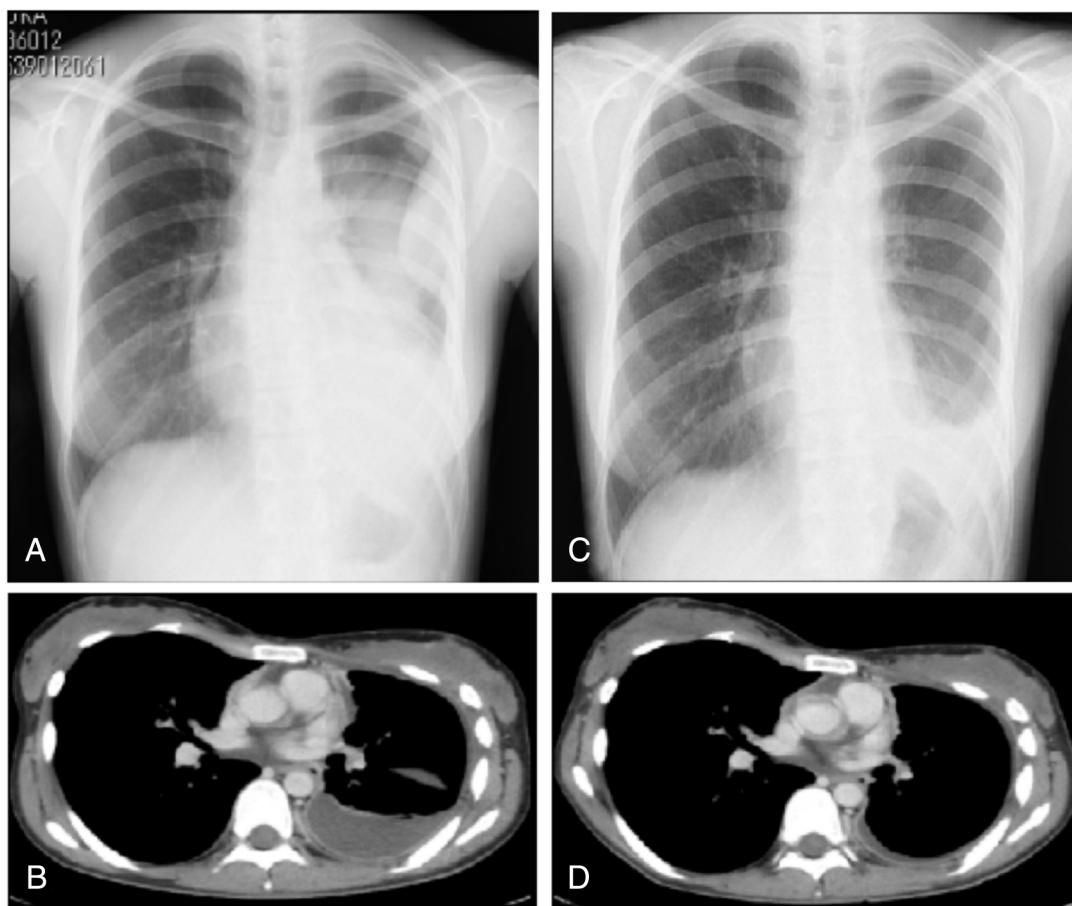
### Case Report

A 31-year-old Japanese woman presented with a 2-month history of dull left back pain. She was admitted to a nearby hospital after chest roentgenography revealed pleural

thickening in the left lung apex (Fig. 1A). Chest computed tomography (CT) showed a left pleural effusion with diffuse pleural thickening, leading to suspicion of MPM (Fig. 1B). Video-assisted thoracoscopic pleural biopsy was performed, and she was referred to our hospital for further examination.

The patient had no relevant medical, family, occupational, or smoking history. On physical examination of the respiratory system, breath sounds over the left hemithorax decreased. Left-sided back pain was aggravated with palpation. Further examination revealed no digital clubbing, skin eruptions, or palpable lymphadenopathy. Positron emission tomography (PET)-CT demonstrated low-grade 18-fluorodeoxyglucose (FDG) uptake in the left pleural thickening, but a metastatic lesion was not observed (Fig. 2A).

MPM was doubted after staining of the biopsy specimen with haematoxylin and eosin. Histologically, the tumour was characterized by chains and cords of epithelioid cells distributed in a myxohyaline stroma that had spread through the entire thickness of the parietal pleura and invaded the adipose tissue and vessels in the chest wall (Fig. 2B-I). The cells had irregularly shaped nuclei and



**Figure 1.** (A, B) Left pleural thickening and encapsulated pleural effusion in the left lung before chemotherapy. (C, D) Left pleural effusion decreased and left pleural thickening was stable after 4 months.

vacuolated cytoplasm. Little mitosis of tumour cells and partial intracytoplasmic lumen formation containing red blood cells was observed (Fig. 2B-II). The presence of intracytoplasmic lumens containing red blood cells favoured EHE over epithelioid mesothelioma. Therefore, we carried out immunohistochemistry assays for vascular markers (CD34, CD31, and factor VIII) and mesothelial markers (calretinin, WT-1, and D2-40). Immunohistochemically, the tumour cells were negative for AE1/AE3, CAM5.2, calretinin, WT-1, CEA, and TTF-1, and positive for D2-40, vimentin, CD34, CD31, and factor VIII. Based on these findings, a diagnosis of EHE was made (Fig. 2B-III).

Chemotherapy with carboplatin (area under the curve, 6), pemetrexed (500 mg/m<sup>2</sup>), and bevacizumab (15 mg/kg) was initiated. After the fourth course of treatment, the pleural effusion had decreased by 90% but the pleural thickening had not changed (Fig. 1C, D). Thus, the regimen was changed to pemetrexed and bevacizumab for maintenance chemotherapy in order to obtain disease

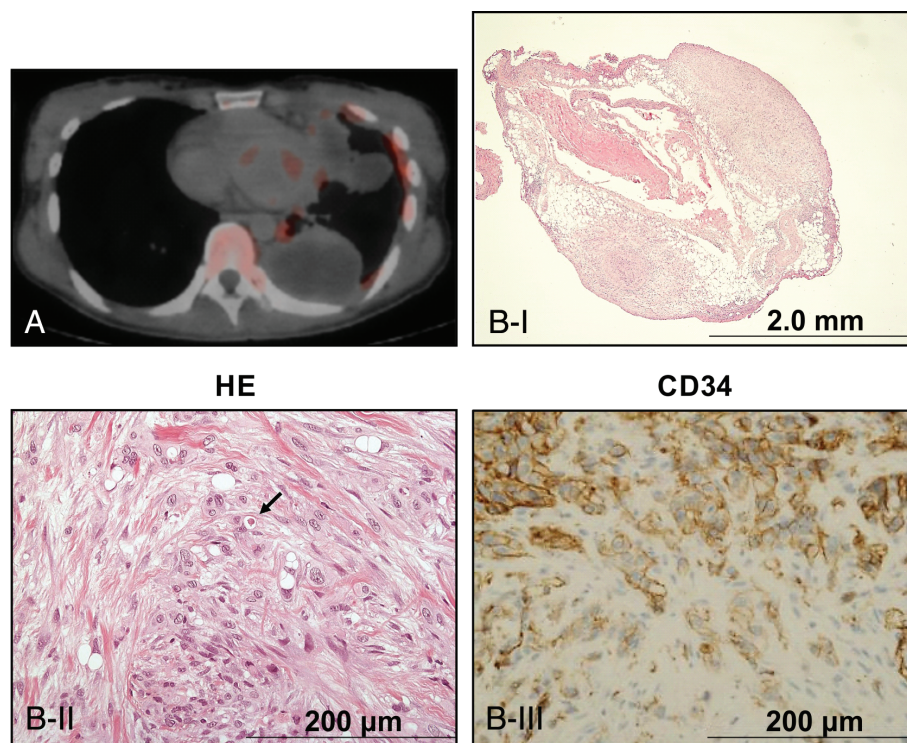
control. The patient remained stable for 6 months, and no adverse events occurred after eight cycles of pemetrexed and bevacizumab. At the same time, good pain control was obtained.

## Discussion

EHE is a rare vascular tumour of low- to middle-grade malignancy, which can occur in any part of the body, including the liver, bone, soft tissue, and skin. Pulmonary EHE (PEH) is more common among women than among men, and approximately half of the cases are aged 40 years or less. Patients are often asymptomatic, and diagnosis is established following discovery of multiple pulmonary nodules. To date, there have been less than 200 cases of PEH, with an average age of onset of approximately 35 years [3].

Primary pleural EHE is less common, with only 30 cases reported to date, including our patient [3]. Of these cases, 21 were men and 9 were women, and the mean age of onset was 45.7 years (range, 31–85 years). Twenty-eight of

**Figure 2.** (A) 18-Fluorodeoxyglucose (FDG) positron emission tomography-computed tomography showed increased FDG avidity in the left pleura. (B-I) Histologically, the surgical biopsy images showed that the tumour cells had spread through the entire thickness of the parietal pleura and invaded the adipose tissue and vessels in the chest wall. (B-I) Intracytoplasmic lumens containing red blood cells are indicated by the arrow. (B-II) Chains and cords of epithelioid cells were distributed in the myxohyaline stroma. The cells had irregularly shaped nuclei and intracytoplasmic lumens containing red blood cells, suggesting epithelioid hemangioendothelioma. Positive staining was observed for vascular markers, including CD34.



30 patients had symptoms at presentation, including chest pain, dyspnoea, weight loss, and cough.

The radiologic features of pleural EHE are similar to those of MPM. Furthermore, in this case, the patient's symptomatic deterioration was reflected by radiologic evidence of disease progression. Immunohistochemical analysis is useful for differentiation from other malignancies, with EHE demonstrating negative results for calretinin and cytokeratin, and positivity for CD34, CD31, and factor VIII. EHE is a slow-growing tumour that rarely metastasizes, and has a 5-year survival probability of approximately 60%. However, the prognosis of EHE with pleural effusion is poor, with a 5-year survival rate of 2% reported in previous reviews [4]. Treatment with various chemotherapeutic agents, including carboplatin, paclitaxel, thalidomide, etoposide,  $\alpha$ -interferon, gemcitabine, and/or doxorubicin, has previously been reported for pulmonary EHE [4]. Although there have been many reports of alternative treatments for EHE, there is no established effective therapy for EHE. Bevacizumab is a recombinant humanized antibody against vascular endothelial growth factor. In a previous report, a patient with EHE showed dramatic improvement after treatment with bevacizumab [5]. Furthermore, chemotherapy including carboplatin, pemetrexed, and bevacizumab is known to be effective for MPM, but there has been no report of pemetrexed for treatment of EHE.

MPM is the most frequent mesenchymal tumour affecting the pleura. Pemetrexed, a multitargeted antifolate, is a

key drug in the treatment of MPM. As EHE may involve the pleura diffusely and mimic the gross appearance of diffuse MPM, we suggest that new multitargeted antifolates should be considered for patients with advanced pulmonary EHE.

### Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

### References

1. Dail DH, and Liebow AA 1975. Intravascular bronchioloalveolar tumor. *Am. J. Pathol.* 78:6a–7a.
2. Ha SY, Choi IH, Han J, et al. 2014. Pleural epithelioid hemangioendothelioma harboring CAMTA1 rearrangement. *Lung Cancer* 83:411–415.
3. Salijevska J, Watson R, Clifford A, et al. 2015. Pleural epithelioid hemangioendothelioma: literature summary and novel case report. *J. Clin. Med. Res.* 7:566–570.
4. Wethasinghe J, Sood J, Walmsley R, et al. 2015. Primary pleural epithelioid hemangioendothelioma mimicking as a posterior mediastinal tumor. *Respirol. Case Rep.* 3:75–77.
5. Belmont L, Zemoura L, and Couderc LJ 2008. Pulmonary epithelioid haemangioendothelioma and bevacizumab. *J. Thorac. Oncol.* 3:557–558.