Epithelioid hemangioendotheliomas of the lung and pleura: Report of three cases

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Summary  Epithelioid hemangioendothelioma (EHE) is a rare malignant neoplasm of endothelial origin with an unpredictable clinical course and prognosis. Primary epithelioid hemangioendotheliomas of the lung and pleura, in particular, are extremely rare. The clinical and radiological manifestations mimic those of mesothelioma and metastatic adenocarcinoma, and an accurate pathological diagnosis is important for appropriate clinical management. Herein, we report one pulmonary and two pleural cases of epithelioid hemangioendothelioma. All three patients were symptomatic at presentation. The symptoms included cough, dyspnea, chest pain, and vocal palsy. Pleural effusion was noted in both pleural cases. Wedge resection was performed in the patient with multiple pulmonary nodules. The postoperative recovery was uneventful. The patient regained normal pulmonary function and was able to return to work after the operation. Both patients with pleural lesions underwent surgical excision of the tumors. Bony metastasis occurred in one of the patients and local recurrence developed in the other. In the previously reported cases and our experience, pleural EHE tends to have more aggressive behavior than tumors in other locations.

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1. Introduction

Epithelioid hemangioendothelioma (EHE) is a rare, well-differentiated vascular endothelial neoplasm. The clinical behavior of EHE is between hemangioma and angiosarcoma. Pulmonary involvement of EHE is even rarer. It was first reported by Dail and Liebow in 1975 as an intravascular bronchioloalveolar tumor.1 Four years later, Corrin et al2

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demonstrated using immunohistochemistry that EHE was of endothelial origin. The tumor cells reacted to vascular markers such as CD31, CD34, factor VIII, and Friend leukemia integration-1 (FLI-1). Pulmonary EHE typically manifests as bilateral multiple pulmonary nodules in young or middle-aged women. Although many affected patients are asymptomatic, some present with pleuritic pain, dyspnea, and cough. We present a classic case of pulmon-ary EHE in which the patient’s pulmonary function was normal after operation.

EHE of the pleura is also extremely rare, and has a poor prognosis because of aggressive involvement of the pleura and the impossibility of complete surgical resection. The radiological and histopathological characteristics resemble those of metastatic adenocarcinoma or mesothelioma. There are at present 12 reports of EHE of the pleura in the literature. Herein, we report two more well-documented cases of pleural EHE. Both patients underwent tumor excision as well as radiotherapy and chemotherapy to treat their recurrent or metastatic lesions. The pathological diagnosis was independently confirmed by at least two senior pathologists after reviewing hematoxylin-and-eosin-stained tissue sections and immunohistochemical staining.

The ability to recognize and differentiate these tumors based on the knowledge of their full morphological spectrum is important because they have different courses and require different management strategies from those of similar-looking tumors.

2. Case report

2.1. Clinical manifestations

2.1.1. Case 1

A 54-year-old man presented with a 1-month history of dry cough after visiting a local medical hospital. The cough did not abate, therefore, an X-ray was taken and showed abnormal findings. Then, the patient was referred to our chest outpatient department for further evaluation. Computed tomography (CT) and positron emission tomography (PET) scans revealed multiple small nodules measuring up to 1.0 cm in diameter scattered throughout both lung fields (Figure 1A). The nodules did not show increased uptake of 2-[18F]-fluoro-2-deoxyglucose (FDG). No other lesions suggestive of a primary disease were found. The patient had normal pulmonary function (forced vital capacity (FVC) 3.19 L and 100% predictive value (PRED), forced expiratory volume in one second (FEV1) 2.69 L and 103% PRED, FEV1/FVC 84%). The preliminary diagnosis was pulmonary metastasis from an unknown primary carcinoma. The patient, therefore, underwent video-assisted thoracic surgery and wedge resection. The postoperative chest X-ray did not show obvious progression of lung nodules, and no chemotherapy or radiotherapy was administered. The patient was able to return to work after the operation and at 16 months’ follow-up there was no evidence of disease recurrence.

2.1.2. Case 2

A 42-year-old man presented to a hospital elsewhere with chest pain and a 6-month history of productive cough. An X-ray and CT scan showed pleural effusion and irregular thickness of the left pleura with small nodularities. The preliminary diagnosis was mesothelioma or metastatic carcinoma. A pleural biopsy was performed, and a definitive diagnosis of plural EHE was made based on histopathology of the biopsy specimen. The patient was transferred to our thoracic surgical department. The CT scan performed at that time revealed pleural thickness with residual tumor (Figure 1B). Preoperative pulmonary function testing revealed suboptimal pulmonary function, but showed normal carbon monoxide diffusing capacity (DLCO) (FVC 2.14 L and 59% PRED, FEV1 1.96 L and 65% PRED; FEV1/FVC 91%, DLCO 22.0 mL/mm Hg/min, and 108% PRED). The patient underwent pleurectomy. Intraoperative findings included the presence of diffuse and irregular thickening of the left visceral pleura with tight adhesion to the parietal pleura. Fragmented pleural tissues measuring up to 20.0 cm × 5.0 cm × 1.5 cm in size were removed. Gross examination of the resected tissues showed grayish cut surfaces with ill-defined firm nodules. At 5 months’ follow-up, metastatic bony lesions on the thoracic spine were noted. The patient underwent radiotherapy and chemotherapy, but did not respond well to treatment. At 14 months’ follow-up, the metastatic bony lesions were still present.

2.1.3. Case 3

A 27-year-old man presented with a 3-month history of dry cough, hoarseness, and chest tenderness. The CT scan revealed a pleural mass and left hemidiaphragm paralysis (Figure 1C and 1D). A PET scan showed increased uptake of FDG. Intraoperative findings included a poorly defined, fibrotic lesion measuring 3.7 cm × 2.0 cm × 2.0 cm in size in the left pleura of the lung apex. The tumor adhered to the internal jugular vein and carotid artery. It was partially dissected and separated from the vessels. The patient received postoperative radiotherapy with a radiation dose of 6600 cGy in 33 fractions as initial therapy. However, pleural effusion and tumor recurrence were noted 5 months after the therapy. Pulmonary function tests showed a restrictive ventilation defect but normal diffusing capacity (standardized for alveolar volume) (FVC 2.32 L and 45% PRED, FEV1 2.02 L and 47% PRED, FEV1/FVC 87%, DLCO/VA 5.47 mL/mm Hg/min/L and 117% PRED). The patient then underwent pleurectomy and chemotheraphy with doxorubicin and cisplatin. He was monitored for 7 months after the pleurectomy and showed no evidence of a new lesion. Nonetheless, the patient developed repeated episodes of pneumonia and died of septicemia 18 months after the initial diagnosis.

2.2. Pathologic findings

Three pulmonary nodules measuring up to 1.0 cm in diameter were resected from Patient 1. The tumors were white and elastic with a chondromyxoid consistency. Microscopically, the pulmonary nodules were made up of plump epithelioid cells in a homogenous myxofibrous stroma (Figure 2A). The tumors showed an intra-alveolar growth pattern with tumor cells mainly in the alveolar spaces. Some tumor cells had intracytoplasmic vacuoles containing...
red blood cells (Figure 2B), which raised the possibility of endothelial differentiation.

The pleural tumors in Patients 2 and 3 were poorly defined, with tan and relatively fibrous cut surfaces. The microscopic features of the two pleural tumors were similar. The hyalinized stroma was infiltrated by small nests or cords of epithelioid cells (Figure 3A). The tumor cells had uniform round or ovoid eccentric nuclei and a moderate amount of pink cytoplasm. Intracytoplasmic vacuoles and mildly atypical nuclei were seen (Figure 3B). The most likely differential diagnoses included metastatic adenocarcinoma, malignant mesothelioma, or other rare pleural tumors. Immunohistochemical studies were useful in making the definitive diagnosis (Table 1). The tumors were positive for endothelial markers, such as CD31, CD34 (Figure 4), or FLI-1, supporting the diagnosis of EHE.

Figure 1  Computed tomography and X-ray. (A) Multiple small tumor nodules (arrows) in both lung fields (Patient 1). (B) Pleural tumor (arrow) with irregular thickening of the left pleura (Patient 2). (C) A poorly defined nodule (arrow) in the apex of the left pleura, with extension into the anterior mediastinum (Patient 3). (D) Chest X-ray showed elevation of the left diaphragm (arrowhead) and tumor (arrow) in the paraspinal region of the left lung apex with increased opacity (Patient 3).

Figure 2  Photomicrographs of pulmonary EHE (Patient 1). (A) Tumor cells grew in alveolar spaces with myxofibrous stroma (H&E, original magnification 100×). (B) Plump epithelioid tumor cells showed intracytoplasmic vacuoles containing erythrocytes (arrow) (H&E, original magnification 400×). EHE = Epithelioid hemangioendothelioma; H&E = hematoxylin and eosin.
3. Discussion

EHE is a rare vascular tumor with intermediate malignant potential, and occurs at a variety of tissue sites including skin, soft tissue, liver, bone, and lung. Less common sites include serosal membranes such as peritoneum and pleura. In previously reported cases, pulmonary EHE occurred predominantly in asymptomatic young women, in whom it was diagnosed incidentally. In contrast, pleural EHE most commonly affects older men, who are often symptomatic at presentation. All three of our patients were men aged 27–54 years, and all presented with cough and chest pain. Patient 3 experienced hoarseness due to left vocal cord palsy, which is a rare presentation of pleural EHE.

In patients with pulmonary EHE, chest radiographs or CT scans commonly show multiple, small nodular lesions in both lungs, as in patient 1. Usually, metastatic carcinoma or pulmonary hamartoma is suspected before pulmonary biopsy or wedge resection is performed. Pleural EHE lacks significant roentgenographic features, but manifests as nodular or diffuse thickening of the pleura and pleural effusion. A definitive preoperative diagnosis is difficult to establish without biopsy.

Microscopically, pulmonary EHE usually features epithelioid nests in a myxoid or chondroid stroma. The differential diagnoses include metastatic adenocarcinoma and pulmonary hamartoma with chondroid elements. The histological features most characteristic of EHE tumors are intracytoplasmic vacuoles with red blood cells within the lumens. EHE tumor cells are positive for endothelial markers and are usually negative for epithelial and chondroid cell markers. Pleural EHE commonly displays fibrous or hyalinized stroma with scant epithelioid cells, or occasionally, spindle cells, arranged as small sheets, cords or even glandular structures. In our patients, the differential diagnoses included metastatic adenocarcinoma, malignant mesothelioma, and sclerosing epithelioid fibrosarcoma.

Tumor cells of sclerosing epithelioid fibrosarcoma do not react with epithelial or vascular markers. The specimens in our patients were negative for cytokeratin and calretinin, proteins that are usually expressed in carcinoma and mesothelioma. The reactivity to vascular markers confirmed the diagnosis of EHE.

Immunohistochemistry is helpful in the diagnosis of EHE. The endothelial markers characteristic of EHE include CD31, CD34, factor VIII, and *Ulex europaeus* agglutinin 1 (UEA-1). CD31 and CD34 have also been shown to be sensitive markers for the presence of endothelial differentiation. The specimens from Patients 1 and 2 in our series showed positive staining for both antibodies. Interestingly, the tumor specimens in Patient 3 stained positively for CD 31 but negatively for CD34. A positive immunohistochemical stain of FLI-1, recently reported as

<table>
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<th>Table 1</th>
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<tr>
<td>Antibodies</td>
<td>Major reactivity</td>
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<tr>
<td>CD31</td>
<td>Endothelial cell</td>
</tr>
<tr>
<td>CD34</td>
<td>Endothelial cell</td>
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<tr>
<td>FLI-1</td>
<td>Endothelial cell</td>
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<tr>
<td>AE1/AE3</td>
<td>Epithelial cells</td>
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<td>Vimentin</td>
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<td>Calretinin</td>
<td>Mesothelial cell</td>
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<tr>
<td>S-100</td>
<td>Peripheral nerve sheath cell, melanocyte, chondrocyte</td>
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Results: +: positive reactivity; —: no reaction; AE1/AE3 = Cytokeratin AE1/AE3; FLI-1 = Friend leukemia integration-1; ND = not done.

a Most antibodies have multiple applications. This column lists the reactivity of antibodies used for differential diagnosis in our patients.
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the first nuclear marker of endothelial origin, supported the diagnosis. Focally weak positivity of cytokeratin has been described in cases of EHE.\textsuperscript{7} Although cytokeratin positivity makes it difficult to differentiate EHE from carcinoma, cytokeratin staining is usually focal and weaker than vimentin staining. None of the tumor specimens from our patients expressed cytokeratin.

Most EHE tissue samples display bland-looking nuclei and nearly no mitotic activity. Occasionally, they exhibit areas of nuclear atypia and mitoses (rarely more than 1 mf/10 high power fields), and/or focal necrosis. Such histological features are correlated with a more aggressive clinical course. Epithelioid angiosarcoma must be considered when nuclear pleomorphism, increased mitotic figures, and extensive necrosis are present.\textsuperscript{8}

EHE is an indolent tumor with a tendency for local recurrence and metastasis. Distant metastases are usually seen in regional lymph nodes, liver, bowel, soft tissue, and skin.\textsuperscript{7,9} The natural history of EHE is difficult to predict and ranges from rapid progression to a silent course even without treatment. Because of the rarity of pulmonary and pleural EHE, there is no standard treatment for these conditions. Complete surgical resection is the first choice of treatment when possible. However, in most cases, the lesions are multifocal or poorly defined, and curative excision is impossible. Various investigators have reported the use of radiotherapy or chemotherapy with doxorubicin, vincristine, carboplatin, and etoposide for treatment of inoperable or metastatic cases,\textsuperscript{10} and several practitioners have reported partial or complete remission with interferon.

The 5-year survival rate for patients with pulmonary EHE is about 60\% (range, 45–71\%). The presence of anemia, weight loss, pulmonary symptoms, and especially hemorrhagic effusion, are associated with poorer prognoses.\textsuperscript{10} In our series, Patient 1 had no significant history of poor prognostic factors. He had a smooth postoperative course and returned to work after the operation. In our experience, and according to the literature, however, pleural EHE tends to have a more aggressive clinical course.\textsuperscript{5,8} There were no obvious mitotic figures or tumor necrosis in the pleural tumors in Patients 2 and 3, but Patient 2 developed metastasis to the thoracic spine, which responded poorly to radiotherapy and chemotherapy. Patient 3 required radiotherapy and chemotherapy with doxorubicin and cisplatin for treatment of a recurrent lesion. The patient’s pleural effusion resolved and there was no new growth after six courses of chemotherapy. Unfortunately, the patient developed repeated episodes of pneumonia and died of septicemia 18 months after the initial diagnosis.

In summary, the clinical features of pleural EHE differ from those of pulmonary EHE. Pleural EHE usually develops in men, who are symptomatic at presentation, and has a more aggressive clinical course than EHE arising in the lung or other sites.\textsuperscript{5,8} The clinical, radiological, and histomorphological features of EHE mimic those of metastatic adenocarcinoma and malignant mesothelioma, but the management and prognosis of those tumors are significantly different from the tumors they mimic. EHE must be suspected in cases of pleural epithelioid tumors that do not exhibit cytokeratin. Acute awareness of the morphologic features and immunohistochemical characteristics of EHE will help establish an accurate diagnosis of this tumor.

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References