Case Report

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Pulmonary Multinodular Epithelioid Hemangioendothelioma with Mixed Progression and Spontaneous Regression during a 7-Year Follow-Up: A Case Report and Review of Imaging Findings

7년간 추적관찰에서 진행과 자발적 퇴행을 함께 보인 폐의 다결절성 상피양 혈관내피종: 증례 보고 및 영상 소견 고찰

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Pulmonary epithelioid hemangioendothelioma (PEH) is a rare vascular tumor of borderline or low-grade malignancy, and its prognosis is unpredictable. Herein, we describe the case of a 47-year-old asymptomatic female with a diagnosis of multinodular PEH. During a 7-year follow-up, the nodules with large size and high ^{18}F-fluorodeoxyglucose uptake in the initial study showed progression with increasing sizes; however, most small nodules (size < 1 cm) demonstrated spontaneous regression with peripheral rim or nodular calcification. The patient underwent surgical resection for an enlarged nodule. Of note, it is unusual for an individual to have mixed progression and regression concomitantly, which may be helpful in predicting the prognosis.

Index terms Hemangioendothelioma, Epithelioid; Computed Tomography, X-Ray; Positron Emission Tomography Computed Tomography

INTRODUCTION

Pulmonary epithelioid hemangioendothelioma (PEH) is a rare vascular neoplasm between benign vascular tumor and high grade malignant tumor in the lung. It is often diagnosed asymptomatically in middle-aged patients and tends to be more common in female (1). It usually appears as multiple pulmonary nodules that show little or no growth in serial chest radiographs or CT. The prognosis varies with spontaneous regression, and some have blood vessels, lymphatics, pleural cavities, and distant hematogenous spreads.

There have been only a few reports providing data of the behavior and morphologic changes of PEH during a long term follow up. The present article describes a case of multinodular PEH in a patient with Sjögren's syndrome, comparison of initial and follow-up CT and ^{18}F fluorodeoxyglucose (FDG) PET/CT features between the nodules demonstrating progression and spontaneous regression during a 7-year follow up.

CASE REPORT

A 47-year-old female visited our emergency room due to facial trauma, with no underlying disease. Blood and urine tests were normal except for the presence of anemia (hemoglobin: 9.7 g/dL). Chest radiography during routine checkup showed multiple nodules in both lungs, predominantly in the lower lung zones (Fig. 1A). However, the patient had no symptoms related to the chest radiography findings.

Contrast-enhanced chest CT was performed for further evaluation. Multiple well-defined enhancing nodules, less than 1 cm in size, were observed in both lungs and their CT attenuation value was around 50 Hounsfield unit (Fig. 1A). Based on the radiologic findings, hematogenous pulmonary metastasis was highly suspected and, therefore, abdominopelvic CT and ^{18}F-FDG PET/CT scans were ordered to identify the cancer of unknown primary origin.

An abdominopelvic CT scan revealed multiple myomas of the uterus. The ^{18}F-FDG PET/CT scan showed only the two largest nodules in the right upper lobe and in the superior segment of the right lower lobe, both were more than 1 cm in size (1.4 cm and 1.8 cm, respectively), which were observed as hypermetabolic lesions (maximum standardized uptake value, 3.9–4.4) (Fig. 1A). The possibility of a pulmonary benign metastasizing leiomyoma was suggested.

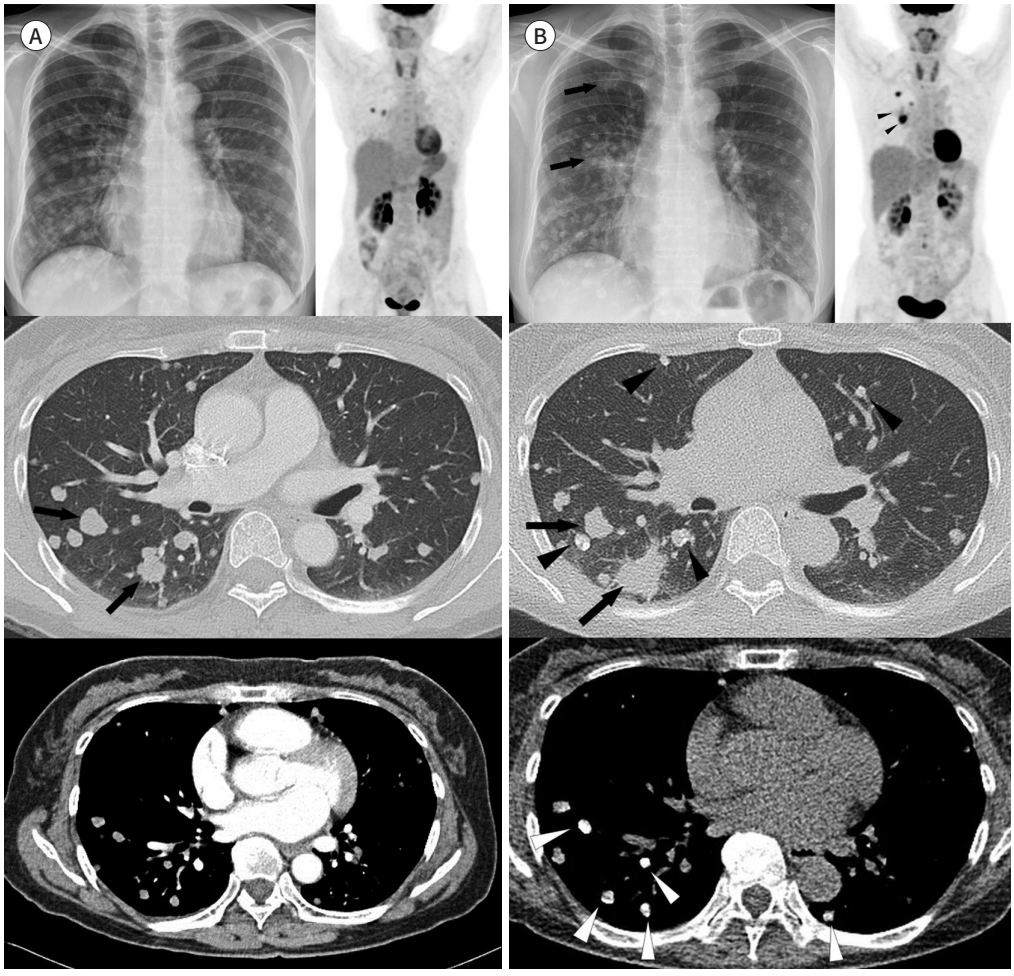
Percutaneous needle biopsy and transbronchial lung biopsy were performed on the largest nodule in the right lower lobe. Histopathological examination revealed non-specific chronic inflammation, without definite tumor cells. Close follow-up with chest radiographs and CT scans was performed for one year without any treatment, and the nodules did not show any change in size or attenuation. Subsequently, the patient stopped visiting the hospital.

After seven years, the patient revisited with a recently developed dry mouth and hand joint pain. Blood tests revealed the presence of anti-SS-A and SS-B antibodies, fluorescent antinuclear antibodies, and elevated rheumatoid factor (18.2 IU/mL, normal range: 0–18 IU/mL). The patient was diagnosed with Sjögren's syndrome. Chest radiography showed suspiciously increased sizes of some nodules in the right lung (Fig. 1B), following which non-contrast-enhanced chest CT was performed.

In comparison with the last CT scan obtained seven years earlier, four nodules in the right

upper and lower lobes increased in size (previous two largest nodules, 1.6 cm and 3.6 cm, respectively). The largest one in the right lower lobe showed an indistinct margin (Fig. 1B), and the other three demonstrated peripheral focal calcifications. Two of them, including the largest nodule, corresponded to the previous two largest nodules, which had demonstrated high

Fig. 1. A 47-year-old female with pulmonary epithelioid hemangioendothelioma with mixed progression and spontaneous regression of nodules during a 7-year follow-up.
A. An initial chest radiograph (top, left) shows multiple small nodules in both the lungs, predominantly in the lower lungs. An initial ^{18}F-FDG PET/CT (top, right) image shows high FDG uptake (maximum standardized uptake value: 3.9–4.4) in the two largest nodules in the right lung. The initial axial contrast-enhanced chest CT (middle and bottom; slice thickness, 2 mm) shows multiple small nodules in both lungs, predominantly in the lower lungs. The two largest nodules in the right upper and lower lobe superior segment (arrows) are larger than 1 cm in size, with a lobulated margin.
B. A follow-up chest radiograph acquired 7 years later demonstrates an increase in the size of some nodules in the right lung (top left, arrows). Similarly, ^{18}F-FDG PET/CT images obtained 7 years later show an increase in FDG uptake by the two previous hypermetabolic nodules (top right, arrowheads) and two new hypermetabolic nodules in the right upper lung. All of these nodules correspond to the four enlarged nodules in the right upper lobe and superior segment of the right lower lobe on follow-up CT. A follow-up chest CT image acquired 7 years later shows an increase in the size of the two largest nodules (middle and bottom, arrows); moreover, the nodule in the right lower lobe shows an indistinct margin. There are two other enlarged nodules in the right upper lobe. The other small nodules in both the lungs demonstrate no change or slightly decreased sizes with peripheral rim or nodular calcification (arrowheads).
FDG = fluorodeoxyglucose



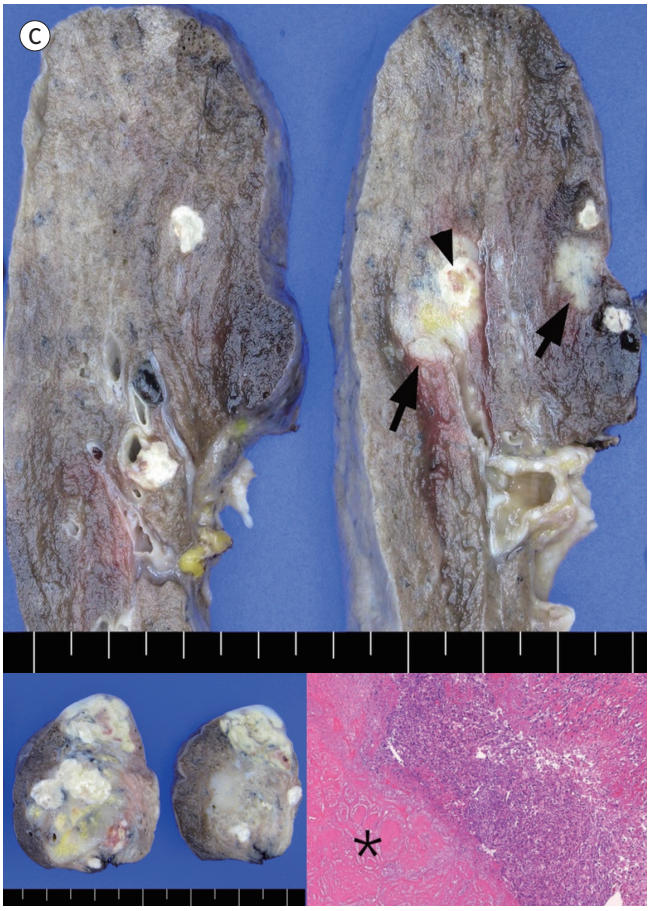


Fig. 1. A 47-year-old female with pulmonary epithelioid hemangioendothelioma with mixed progression and spontaneous regression of nodules during a 7-year follow-up.
C. Gross finding of the right upper lobe lobectomy specimen (top) and right lower lobe wedge resection specimen (bottom). The cut section shows several dominant masses (top, arrows) and multiple small, whitish nodules. The largest nodule in the right upper lobe, relevant to the growing nodule on CT, shows a well-defined whitish area in the center (top, arrowhead) and a gray area in the periphery. An ill-defined 3.5-cm mass and several small white nodules are found in the right lower lobe. The dominant mass has a solid white area, gray area, and admixed yellowish area. Pathological analysis of the yellowish area of the tumor with hematoxylin-eosin stain (× 100) shows necrotizing granulomatous inflammation associated with degenerated tumor tissue (bottom right, asterisk).

FDG uptake, while the other two nodules were small (less than 1 cm) nodules that showed no FDG uptake on the last ^{18}F-FDG PET/CT scan. Other small nodules in both lungs showed no growth or slightly decreased sizes with peripheral rim or nodular calcification (Fig. 1B). An ^{18}F-FDG PET/CT scan was performed and revealed increased FDG uptake in four nodules in right upper lobe and right lower lobe but previously hypermetabolic RUL nodule decreased metabolism (Fig. 1B).

Percutaneous needle biopsy was performed on the largest nodule in the right lower lobe and was diagnosed PEH. Right upper lobectomy and right lower lobe superior segmentectomy with mediastinal lymph node dissection were subsequently performed.

Macroscopic examination of the right upper lobe specimen revealed several dominant masses and multiple small nodules (Fig. 1C, top). In the largest nodule of the right upper lobe, relevant to the growing nodule on CT, the cut surface showed a well-defined whitish area in the center (Fig. 1C, top arrowhead) and a gray area in the periphery. Microscopically, the nodules consisted of epithelioid cells with occasional intracytoplasmic vacuoles forming anastomosing cords, strands, and single cells in a hyaline stroma, which are typical features of epithelioid hemangioendothelioma. The tumor cells were positive for CD31 and CD34 immunohistochemical staining, confirming the pathological diagnosis.

This study was approved by the Institutional Review Board of Ewha Womans University

Mokdong Hospital assigned IRB No. 2020-12-043 and the requirement for informed consent was waived.

DISCUSSION

Epithelioid hemangioendothelioma is a malignant vascular neoplasm with full-spectrum clinical behavior, albeit with less aggressive behavior than conventional angiosarcoma (2). It can be found in many organ systems such as bones, lungs, liver, and somatic soft tissues.

PEH follows a slow progressive clinical course. The reported mortality associated with EH, after a minimum of 4 years of follow-up, is 13%, 35%, and 65% in soft tissue, liver, and lung EH, respectively (3). Many PEH patients are asymptomatic, but some are accompanied by chest pain, sputum, and cough, which are non-specific symptoms. Metastatic disease occurs in nearly 20% of the patients with soft tissue disease, 15% of those with lung disease, and 25% of those with liver disease (3).

Various treatment options have been used to either stop or slow the progression of PEH. Corticosteroids, azathioprine, multiple wedge resections, or simple surveillance are the other PEH management options (4). One report showed that extensive lung resection did not improve long-term survival compared with wedge resection (5).

Due to its vascular origin, inhibition of angiogenesis may be helpful for metastatic PEH (1). However, because of the rarity of PEH, there is no established precise treatment.

There are three different patterns of CT findings in thoracic EH: multiple pulmonary nodules, multiple pulmonary reticulonodular opacities, and diffuse infiltrative pleural thickening (6).

The most common radiologic feature of PEH is the presence of multiple perivascular nodules in both lungs. Their borders are well-circumscribed or slightly ill-defined and may be less than 2 cm in size, but most are less than 1cm and predominant in the lower parts of the lungs with punctate calcification (6). A review by Bagan et al. found that lesions without distinct borders, such as pulmonary infiltrates, pleural effusions, and ascites, were the main factors indicating poor prognosis (5).

In some cases, PET/CT is considered a significant tool for PEH diagnosis. FDG uptake may show activated PEH tumor cells, which means a worse prognosis. However, a negative PET scan cannot completely exclude PEH (1).

One case report described a 47-year-old male with a lung mass in the left lower lung, which was diagnosed as EH, and 4–5 months later it spontaneously regressed without any medical or surgical intervention (7).

In the present case, chest CT showed multiple, small, well-defined, and non-calcified nodules and a few large ill-defined nodules in both lungs, predominantly in the lower lungs as shown on the initial CT scan. Rim or nodular calcification was noted in the spontaneously regressing nodules observed on the follow-up CT scans, while indistinct margins and punctate calcifications were observed in the large progressing nodules. The most likely diagnosis was pulmonary benign metastasizing leiomyoma, but the patient had no associated symptoms and showed no abnormalities in tumor markers.

Differential diagnoses included chronic granulomatous disease, hamartoma, and primary and metastatic lung cancers (6). In addition, growing nodules spotted on the follow-up CT

scans were noted as hypermetabolic lesions on the ^{18}F-FDG PET/CT scan, while the other nodules that were stable or shrunk with calcification did not demonstrate high FDG uptake. Multinodular PEH demonstrated a combination of spontaneous regression and progression in our patient during the 7-year follow-up.

Unlike angiosarcoma, PEH does not have features of necrosis, cytological atypia, or a high mitotic index (8). Recently, risk stratification of EH in somatic soft tissue was based on tumor size and mitotic activity. Tumors larger than 3 cm with greater than 3 mitoses per 50 high-power fields have shown a worse prognosis (9).

In the present case, Multiple small nodules were predominantly composed of hyaline stroma with occasional tumor cells. In the right lower lobe of the lung, a 3.5-cm ill-defined mass and several small nodules were identified (Fig. 1C, bottom). The histopathological features of the central white and gray peripheral areas were similar to those of the right upper lobe nodules. However, the yellowish area of the tumor showed necrotizing granulomatous inflammation, which was associated with degenerated tumor tissue (Fig. 1C, bottom right, asterisk). Ziehl Neelsen staining and tuberculosis polymerase chain reaction were negative for microorganisms.

The growing mass of the right upper lobe on CT showed higher tumor cellularity compared to the nodules without interval changes. However, the growing mass in the right lower lobe showed chronic granulomatous inflammation associated with tumor degeneration. Since no causative microorganism was detected, the inflammatory change might be related to the tissue response to tumor necrosis and exposure of the tumor matrix.

In conclusion, multinodular PEH may have mixed progression and spontaneous regression in the same individual. Nodules with large size (more than 1 cm), indistinct margins, and high FDG uptake are more prone to progression; therefore, close surveillance/early surgical resection could be warranted. Increasing nodule size may not indicate tumor progression but an inflammatory response associated with tumor degeneration.

Small (less than 1 cm) and non-hypermetabolic nodules usually undergo spontaneous regression (CT findings: peripheral rim/nodular calcification) but may also have the potential to progress to large hypermetabolic lesions; therefore, long-term imaging follow-up could be needed.

Author Contributions

Conceptualization, K.Y.K.; resources, all authors; supervision, K.Y.K.; writing—original draft, Y.G.Y.; and writing—review & editing, Y.G.Y., K.Y.K., P.H.S.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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7년간 추적관찰에서 진행과 자발적 퇴행을 함께 보인 폐의 다결절성 상피양 혈관내피종: 증례 보고 및 영상 소견 고찰

이가영[1] · 김유경[1*] · 김관창[2] · 박혜성[3]

폐 상피양 혈관 내피종은 경계성 또는 저등급 악성의 드문 혈관성 종양이며 그 예후를 예측하기는 어렵다. 이 논문에서는 다발성 폐결절이 있는 47세 무증상 여성에서 7년의 추적 기간 동안, 초기 검사에서 크기가 크고 높은 ^{18}F-fluorodeoxyglucose 흡수를 보이는 결절은 크기가 증가하는 진행을 보였고, 1 cm 미만의 대부분의 작은 결절은 말초 가장자리 석회화 또는 결절 석회화와 함께 자발적인 퇴행을 보여주었다. 환자는 폐 상피양 혈관내피종으로 진단되었으며 크기가 커진 결절에 대해 수술적 절제술을 받았다. 이 사례는 한 개인에서 질병의 진행과 퇴행이 동시에 나타난 혼합적인 반응을 보여준다는 점에서 주목할 만하며 이 논문을 통해 예후를 예측하는 데 도움이 될 수 있겠다.

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