

[ CASE REPORT ]

## CT-guided Biopsy for the Diagnosis of Pulmonary Epithelioid Hemangioendothelioma Mimicking Metastatic Lung Cancer

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### Abstract:

A 69-year-old male patient presented with multiple lung nodules revealed by chest-computed tomography (CT) during a preoperative examination for an appendiceal tumor. The nodule diameters ranged from 2-10 mm without either pleural thickening or effusions. A fluorine-18-labeled fluorodeoxyglucose (<sup>18</sup>F-FDG)-positron emission tomography (PET)/CT scan showed a high FDG uptake in the appendiceal tumor, but almost normal standardized uptake values in the bilateral lung nodules. A CT-guided biopsy led to a diagnosis of pulmonary epithelioid hemangioendothelioma, a rare vascular tumor with a radiological presentation similar to that of a metastatic lung tumor. The present case is the first to describe successful treatment using a CT-guided biopsy instead of more conventional methods.

**Key words:** thoracoscopic biopsy, multiple lung nodules, vascular tumor, minimally invasive procedure

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### Introduction

Pulmonary epithelioid hemangioendothelioma (PEH) is a rare vascular neoplasm of low-grade malignancy. It is often diagnosed asymptotically in middle-aged patients and tends to be more common in women (1), 50% of whom are less than 40 years of age (2). The typical findings of chest radiography and computed tomography (CT) scans are multiple bilateral perivascular lung nodules, generally measuring less than 2 cm in diameter (3). However, these imaging methods are not sufficient to make a diagnosis because the results are difficult to differentiate from those for metastatic cancer and other benign diseases. A histopathological analysis is usually conducted via a surgical biopsy because the peripheral nodules are difficult to reach with bronchoscopy. We herein report the first case of PEH that was successfully

diagnosed by CT-guided biopsy instead of more conventional surgical methods. This minimally invasive procedure allowed for accurate detection of the peripheral lung nodules and helped in selecting the most appropriate treatment.

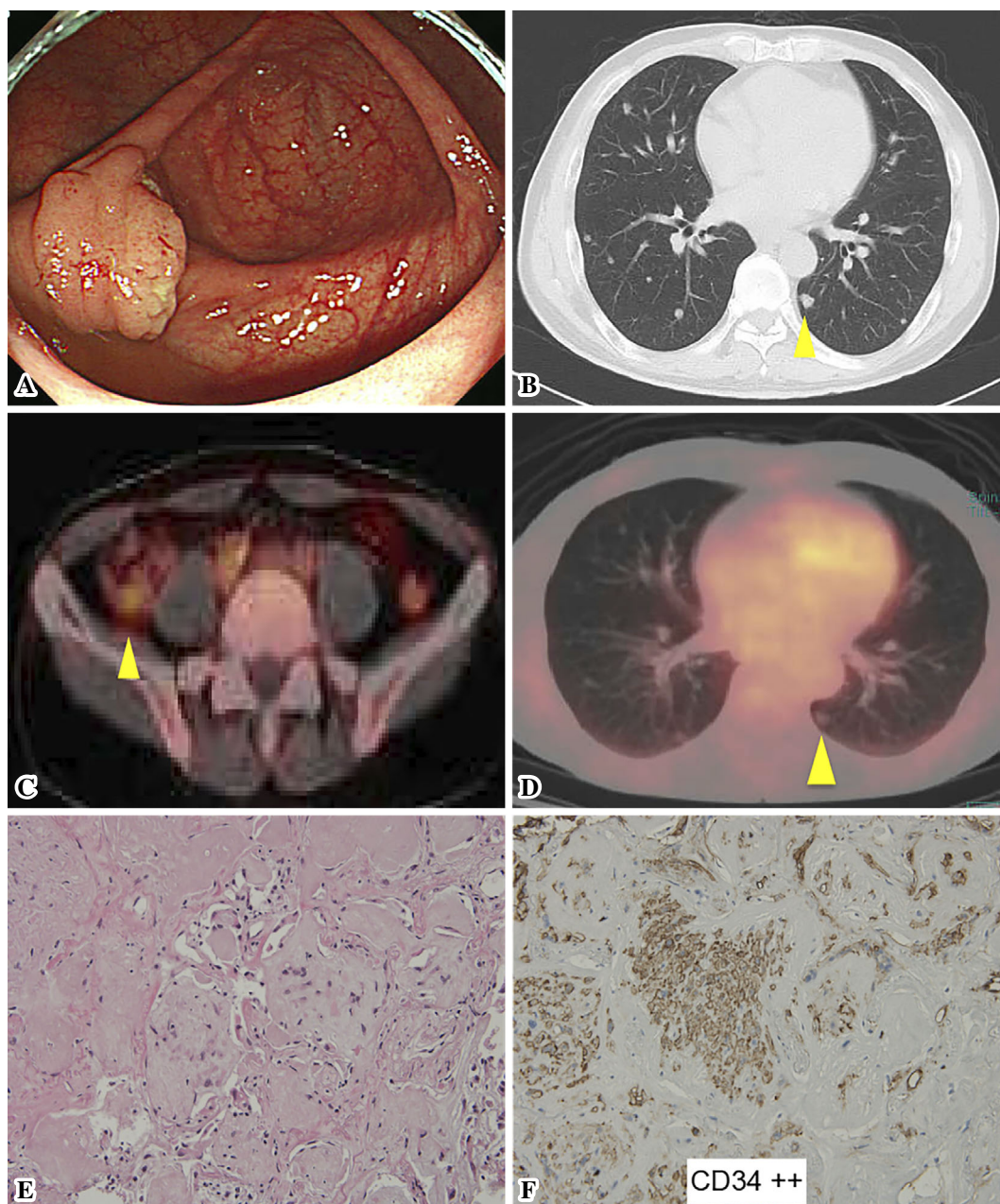
### Case Report

This study was approved by the Shonan Kamakura General Hospital Institutional Review Board and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from the patient for the publication of this case report and the accompanying images. A previously healthy 69-year-old Japanese man visited our hospital with chief complaints of diarrhea and lower abdominal discomfort. The results of a physical examination were unremarkable, and a digital exam did not reveal any tumor. Laboratory investigations revealed a hemoglobin level of 14.5 mg/

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**Figure.** Imaging of the appendiceal tumor and PEH. (A) Colonoscopy revealed a 15-mm Paris class 0-IIa lesion located in the appendiceal orifice. (B) Computed tomography (CT) scan revealed multiple bilateral lung nodules. The nodule diameters ranged from 2 to 10 mm (yellow arrow head points to a 10-mm lesion). (C)  $^{18}\text{F}$ -FDG-PET/CT revealed an appendiceal tumor with a maximum SUV of 2.4 (yellow arrow head). (D) Bilateral lung nodules showed normal SUVs, and the largest nodule (10 mm) showed an SUV of 1.0 (yellow arrow head). (E) A specimen composed of pale eosinophilic nonstructural substances, which contained epithelioid spindle and cubic mid-sized tumor cells (100 HPF). (F) Immunohistopathologic staining showed the tumor cells to be endothelial in origin and immunoreactive for CD34 (100 HPF).

dL, normal liver and kidney profiles, and a positive fecal occult blood test. Colonoscopy revealed a 15-mm Paris class 0-IIa lesion located in the appendiceal orifice (Figure A). We suspected the lesion to either be tubular adenoma or intramucosal cancer extending into the appendiceal orifice. We thought that removing the lesion by colonoscopy would be difficult because of the lesion's location. The histopathological findings showed an atypical epithelium with focally sus-

pected adenocarcinoma, and surgical treatment was thus planned for the patient. During a preoperative examination for the surgery, multiple bilateral lung nodules were revealed by chest CT (Figure B). The nodule diameters ranged from 2 to 10 mm in size, and there was no pleural thickening or pleural effusions. The serum levels of the tumor markers, including carcinoembryonic antigen (CEA) and CA19-9, were within the normal ranges. The appendiceal tumor itself

could not be detected by CT imaging, and no other signs of metastasis, such as lymph node swelling or liver nodules, were observed. The initial diagnosis was appendiceal cancer with lung metastasis. However, the diagnosis of lung metastasis was uncertain because it seemed unlikely that the small appendiceal tumor would cause metastasis.

Fluorine-18-labeled fluorodeoxyglucose ( $^{18}\text{F}$ -FDG)-positron emission tomography (PET)/CT revealed the appendiceal tumor to have a maximum standardized uptake value (SUV) of 2.4 and the bilateral lung nodules had normal SUVs. The largest nodule was 10 mm in size and showed an SUV of 1.0 (Figure C and D). A CT-guided biopsy of the nodules was performed to assess the presence of metastatic lung cancer. The biopsy was performed using an 18-gauge co-axial core needle (SuperCore Argon Medical Devices, Texas, USA) and the target lesion was the biggest nodule. This lesion was located in the subpleural left S10. Immediately after the procedure, the patient suffered a mild pneumothorax, but recovered under conservative treatment within a short time frame. The specimen was composed of pale eosinophilic nonstructural substances containing epithelioid spindle cells and cubic, mid-sized tumor cells (Figure E). The tumor cells showed a low degree of atypia and low cell density. Immunohistopathologic staining revealed that the tumor cells were endothelial in origin, were immunoreactive for CD34 (Figure F) and vimentin, and were negative for cytokeratin AE1/AE3, thyroid transcription factor (TTF-1), and CD68. The nonstructural substances were negative for Periodic acid-Schiff stain and CEA stain. Therefore, the final diagnosis was PEH. After making this diagnosis, the appendiceal lesion was removed by laparoscopic surgery and it was thereafter diagnosed to be high-grade tubular adenoma. The patient's lung nodules did not show any progression without treatment for a follow-up period of 24 months.

## Discussion

The present case is the first report of a successful diagnosis of PEH using CT-guided biopsy. This made it possible to perform a minimally invasive procedure to successfully treat a relatively low-grade tumor instead of performing a conventional surgical biopsy. Upon searching PubMed, we were unable to find any results using the search terms "PEH" or "IVBAT" (intravascular sclerosing bronchioalveolar tumor) with "CT guided biopsy."

The term epithelioid hemangioendothelioma (EH) was first proposed by Weiss and Enzinger in 1982 to describe a unique tumor consisting of an endothelial vascular neoplasm in soft tissue, with an intermediate course between hemangioma and conventional angiosarcoma (4). EH can arise from several origins, including the lung, liver, and soft tissue. When EH arises from the lung, it is termed pulmonary EH (PEH), which was originally described as an IVBAT by Dail and Liebow in 1975 (5). PEH has been described as being a low- to intermediate-grade vascular neoplasm by the

2004 World Health Organization Classification of Tumors (6).

Approximately 120 cases of PEH have been reported worldwide, and 53 of these have been reported in Japan (7, 8). Of the cases in Japan, 71.1% of patients were asymptomatic, while only 35.4% of cases worldwide were asymptomatic. The symptoms include cough, hemoptysis, tightness of breath, chest pain, and others (9).

Chest radiography and CT results for PEH are mainly characterized by bilateral multiple perivascular nodules measuring less than 10 mm in diameter with well-defined margins. In Japan, 39.5% of patients showed unilateral nodules, while 21.4% of patients outside of Japan have shown unilateral nodules (9).

The radiologic differential diagnoses for pulmonary nodules include metastases, primary lung cancer, lymphoid tumors, benign and malignant vascular tumors, infections, sarcoidosis, and others (10). In cases of metastatic lung tumor, the nodules usually show random distribution and size. Further, the margins can be smooth or irregular, and can be either well- or ill-defined (11). In the present case, diffuse multiple nodules were revealed bilaterally in the lungs on a CT scan, which suggested metastatic cancer. However, this diagnosis was uncertain because the appendiceal tumor was too small to suspect metastasis.

$^{18}\text{F}$ -FDG-PET/CT is considered to be more useful for differentiating between malignant and benign diseases compared with CT. Malignant tumor cells usually demonstrate an increased FDG uptake, and an SUV $\geq$ 2.5 has been reported to be a criterion for malignancy, with a sensitivity and specificity of 94% and 71%, respectively (12). Okamura et al. (13) speculated that the FDG uptake reflects the activation of PEH tumor cells, and Watanabe et al. (2) reported that the  $^{18}\text{F}$ -FDG-PET/CT results might be a useful indicator for determining whether PEH resection is necessary. False positives can occur in cases of tuberculosis, aspergillosis, histoplasmosis, and inflammatory disorders, while false negatives can occur in cases of well-differentiated adenocarcinomas or small nodules measuring less than 15 mm in diameter (12). There have been 10 published reports describing the  $^{18}\text{F}$ -FDG-PET/CT findings of 11 cases of PEH. Among the 11 cases, 8 cases showed an increased FDG uptake. The maximum SUVs ranged from 3.5 to 9.4, and the known tumor sizes ranged from 10 mm to 35 mm. The remaining 3 cases showed a negative SUV uptake, and the tumor size was under 10 mm in 2 cases and 30 mm in the other case (Supplementary material) (2, 7, 10, 13-19). In the present case,  $^{18}\text{F}$ -FDG-PET/CT revealed an appendiceal tumor with a maximum SUV of 2.4, and the largest lung nodule, which had a 10-mm diameter, showed an SUV of 1.0. This result suggests that lung nodules are not necessarily metastases from the appendiceal tumor, and a negative  $^{18}\text{F}$ -FDG-PET/CT could not completely exclude the possibility of metastasis and PEH because of the size and malignancy potential of the appendiceal tumor.

Most clinicians agree that imaging methods, including  $^{18}\text{F}$ -

FDG-PET/CT, are limited in their ability to make a correct diagnosis of cancers and that a final diagnosis should be determined by a histopathological study. A biopsy of PEH by bronchoscopy is usually difficult because of the location of the lesion, and therefore, it is common for clinicians to perform a surgical lung biopsy using mediastinoscopy and thoracoscopy along with video-assisted thoracic surgery (VATS). This method achieves almost 100% sensitivity and specificity for diagnosing peripheral lesions; however, it requires general anesthesia, and the mortality rate from the operation is reported to be as high as 0.5%. Furthermore, side effects can include atelectasis, pneumonia, and pneumothorax, and have been reported to occur in 3-9.6% of patients (20-22). In contrast, CT-guided lung biopsy is less invasive and has a high diagnostic accuracy, with a sensitivity of 90% and a specificity of 97% (23, 24). Yoshimura et al. (25) reported that the diagnostic accuracy is 91% in nodules over 8 mm in size and 64% in those under 8 mm in size. However, the diagnostic accuracy for nodules under 1 cm has been reported to be 70% with CT-guided biopsy, compared with just 44% for transbronchial lung biopsy (26, 27). Unfortunately, pneumothorax can occur in 15-25% of the cases undergoing CT-guided biopsy, whereas hemoptysis can occur in 2-6% (28, 29). Dissemination and air embolism are extremely rare, but life-threatening complications, occurring in less than 0.1% and 0.061% of cases, respectively (28, 30). Air embolism has been reported to be the most common cause of acute death associated with CT-guided biopsy (4 of 7 cases in 9,783 evaluated patients) (30). However, hyperbaric oxygen therapy has been reported to be effective for resolving this complication (31). Pneumothorax tends to occur in small lesions that are under 2 cm in size. Indeed, 28.4% of lesions under 2 cm lead to pneumothorax, and 2.5% require chest drainage as a result. Further, 62% of the lesions under 1 cm lead to pneumothorax, and 31% require chest drainage as a result (29, 32). In the present case, the patient suffered mild pneumothorax after undergoing a CT-guided biopsy, but the successfully recovered under conservative treatment. Although pneumothorax is a serious complication associated with CT-guided biopsy, the procedure has the great advantage of being minimally invasive and it is especially favorable for benign lesions and end-stage patients.

In conclusion, a CT-guided biopsy made it possible to successfully diagnose multiple lung nodules as PEH. Negative <sup>18</sup>F-FDG-PET/CT results cannot rule out the presence of PEH, and depending on the size and biological malignancy state of the nodules, PEH can be one of several differential diagnoses. If there is no appropriate origin for lung metastasis, then CT-guided biopsy might be a good option as a minimally invasive histopathological approach to make an accurate diagnosis.

**The authors state that they have no Conflict of Interest (COI).**

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