Case Report

A Case of Pulmonary Epithelioid Hemangioendothelioma Surviving 10 Years without Treatment

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A 19-year-old woman was referred to our hospital because of bilateral multiple nodular shadows on the chest radiograph. She complained of no symptoms. The pulmonary lesions were diagnosed pathologically as epithelioid hemangioendothelioma. She has been followed without treatment for more than 10 years. Among all lesions, only two pulmonary nodules enlarged slightly, and it is interesting that one showed significant uptake in a fluorodeoxyglucose positron emission tomography (FDG-PET) scan. The current case suggests the clinical usefulness of an FDG-PET scan in a pulmonary epithelioid hemangioendothelioma (PEH) patient. (Ann Thorac Cardiovasc Surg 2010; 16: 432–435)

Key words: pulmonary epithelioid hemangioendothelioma, flourodeoxyglucose positron emission tomography, intravascular bronchioloalveolar tumor, multiple nodular shadows

Introduction

Pulmonary epithelioid hemangioendothelioma (PEH) is a rare vascular tumor categorized into a borderline or low-grade malignancy. There have been only a few reports of long-term survival in patients with PEH. The disease was originally reported by Dail and Liebow in 1975 as an intravascular bronchioloalveolar tumor (IVBAT).[1)] Immunohistochemical and electron microscopic studies revealed that IVBAT is of endothelial origin, and the tumor was renamed epithelioid hemangioendothelioma.[2–5)] PEH is also of multicentric origin, and extrapulmonary lesions arise from liver, bone, soft tissue, and skin.[6)] PEH is often detected incidentally because patients are usually asymptomatic or they present minor symptoms at the time of diagnosis. We report a case of PEH surviving 10 years without treatment.

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Case report

A 19-year-old woman was admitted to our hospital in 1997 because of a chest radiograph abnormality that appeared during a medical checkup at her school. Although she complained of no symptoms, the chest radiograph showed multiple nodular shadows in both lungs. She was a never-smoker and had no particular past history of disease. In a physical examination, she appeared to be well without any rash or superficial lymph node swelling. Most of the laboratory data were normal, but a microcytic hypochromic anemia suggesting iron deficiency anemia was detected. The computed tomography (CT) scan of the chest showed multiple nodules, ranging 3 to 10 mm in diameter, scattered throughout both lungs without hilar and mediastinal lymphadenopathy or pleural effusion (Fig. 1). Examinations of abdominal organs, pelvic organs, thyroid gland, and bone were also normal. Therefore the lesions were determined as primary lung tumors or metastatic tumors from other lung tumors. At first, a bronchofiberscopic examination was performed, but not enough samples

for pathological examination were obtained from a transbronchial lung biopsy. A video-assisted thoracoscopic lung biopsy was then performed. The pathological examination of the biopsied specimen showed that the center of the pulmonary nodule was sclerotic and hypocellular with hyalinization and calcification. A few spindle cells were seen in the center region. The peripheral zone of the nodule consisted of proliferating tumor cells growing polypoid tufts into alveolar spaces in hematoxylin-eosin staining (Fig. 2a, 2b). In the immunohistochemical analysis, the tumor cells were positive for the endothelial markers, factor-VIII-related antigen, and CD 34 (Fig. 2c, 2d). Based on these pathological findings, the nodules were diagnosed as PEH. There was no established standard therapy for PEH with multiple lesions, and the patient was observed without treatment. The pulmonary lesions were checked by CT scan every year. Ten years have passed since diagnosis, and the patient is still asymptomatic. Most of the nodules have not changed in size except for only two, one in the left upper lobe and the other in right middle lobe (Fig. 3a, 3b). So a fluorodeoxyglucose positron emission tomography (FDG-PET) scan was performed to examine the progression of PEH. The results of the PET scan showed a significant FDG uptake only in the nodule in the left upper lobe, with a standardized uptake value (SUV) of 4.7 at maximum (Fig. 3c). No significant uptakes in other known nodules were found, and no new metastatic lesions were seen.

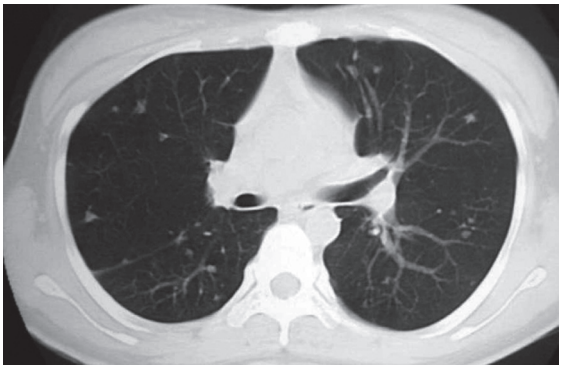

Fig. 1. Chest CT scan showing multiple pulmonary nodules in both lungs.

Discussion

PEH is a rare vascular tumor of borderline or low-grade malignancy whose clinical course is between that of epithelioid hemangioma and angiosarcoma. Initially, it was believed to be an aggressive form of bronchioloalveolar cell carcinoma that invaded adjacent blood vessels; therefore it was called an intravascular bronchioloalveolar tumor.[1] After immunohistochemical techniques were employed, the tumor cells were found to be from a lineage capable of differentiation along endothelial lines.[2–5] It can arise simultaneously or sequentially from many organ systems, including liver, bone, and soft tissues. When this occurs, it may be difficult to determine if the tumor is multicentric or a primary lesion with metastases to other tissues. Among only 93 cases of PEH reported in the current literature, the lungs are rarely involved.[7] Pathologically, the tumor shows nodules ranging in shape from round to oval, and they typically have a central sclerotic, hypocellular zone and a cellular peripheral zone. The tumor cells are round with abundant eosinophilic cytoplasm and intracytoplasmic vacuolization having a signet ringlike appearance. Spindle-shaped tumor cells are occasionally seen, and the presence of tumor cells with a high mitotic activity has been reported to be an even worse prognostic factor.[4,8] Immunohistochemically, these cells exhibit positive staining for endothelial markers, such as factor-VIII-related antigen, CD31, and CD34. Factor-VIII-related antigen has been reported to be positive staining in 42 out of 51 cases.[7] CD31 and CD34 are more sensitive and more reliable markers than factor-VIII-related antigen, being positive in about 90% of cases.[9] In the present case, we could diagnose PEH from typical pathological findings, including immunohistochemical analysis, though a metastatic tumor and granulomatous disease are initially suspected.

The 5-year survival probability was 60% (range 47%–71%),[10] and only a few cases with long-term follow-up over 10 years were reported.[11] Most patients die from respiratory failure as a result of an increasing size and number of tumor nodules. Previous papers reported that loss of weight, anemia, pulmonary symptoms, and pleural hemorrhagic effusion were the independent risk factors of poor prognoses.[7,10] In the present case, our patient also had neither respiratory symptoms nor pleural effusion and has been followed asymptomatically without treatment for more than 10 years.

Because of PEH rarity, there is little consensus regarding its treatment. However, unilateral single or multiple nodules may require that surgical lung resection be proposed. On the other hand, no standard therapy is established for a case with bilateral multiple nodules.[10,12] A few case reports show an antitumor effect with interferon[13,14] or chemotherapy using carboplatin and etoposide.[15] The

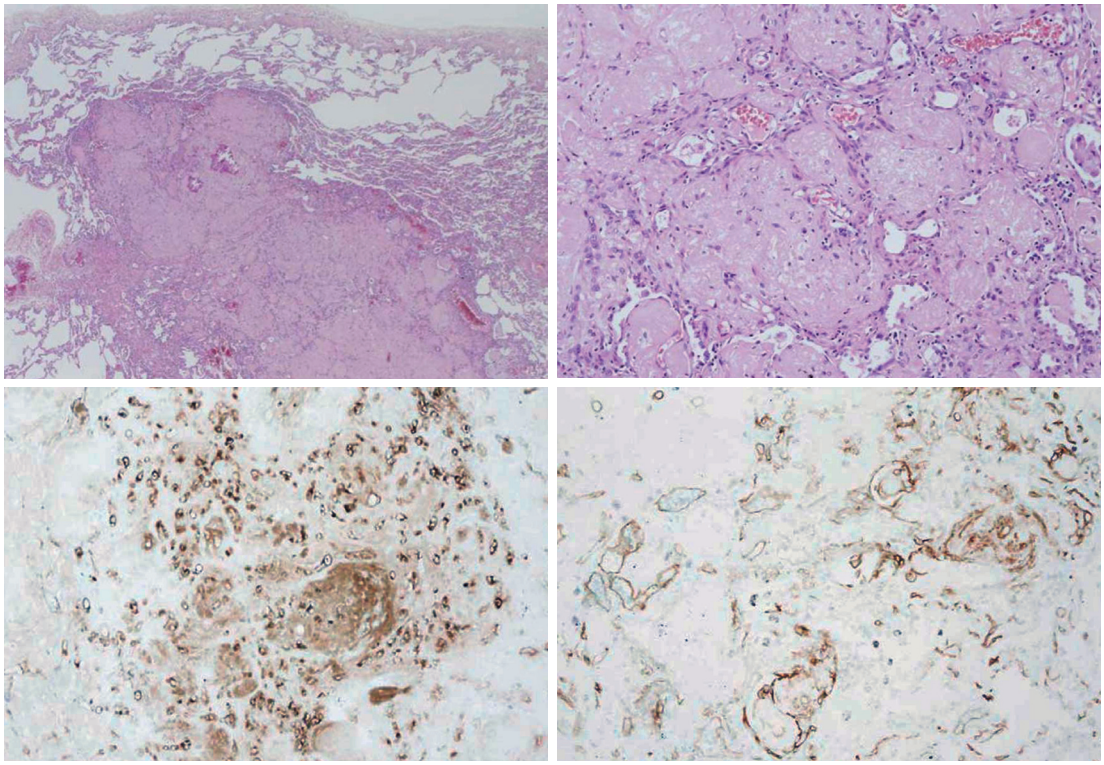

Fig. 2. Hematoxylin-eosin staining of lung biopsy specimen. (**a**) The tumor grows in a polypoid manner and fills the alveolar space (× 20). (**b**) The tumor consists of a peripheral cellular lesion and a hypocellular hyalinized center (× 200). In the immunohistochemical staining of the same specimen, tumor cells show positive staining for factor-VIII-related antigen (**c**) and CD 34 (**d**) (× 200).

a	b
c	d

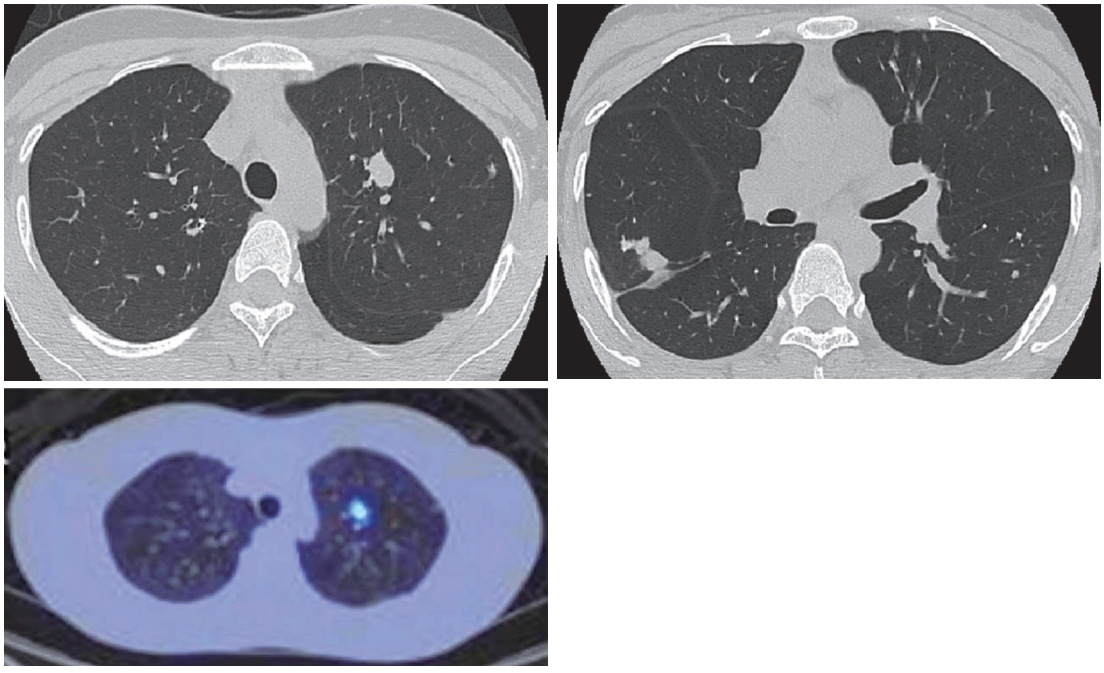

Fig. 3. (**a**) and (**b**) Conventional CT scan 10 years after diagnosis. (**c**) FDG-PET scan overlapped with conventional CT scan. Although most of the lung nodules have not changed in size, the two shown here are enlarged. One nodule located in the left upper lobe showed a significant FDG uptake at the maximum of SUV 4.7.

a	b
c	

behavior of each nodule in the current is different. Two nodules grow, and the remaining nodules are stable. Such a different behavior of each lesion makes it more complex to establish a treatment strategy. An FDG-PET scan may provide useful information concerning the malignant potential of each nodule. As shown in Fig. 3c, a significant FDG uptake is detected in only one of the two nodules growing in size. Two explanations for this discrepancy between FDG uptake in the two nodules are possible. One is the difference in size between the two. The larger one tends to show a higher FDG uptake. Conversely, a PET scan sometimes fails to detect a malignant lesion of less than 6 mm in diameter. As shown in Fig. 3b, the nodule in the left upper lobe is bigger than the one in the right middle lobe, which results a higher uptake of FDG. A second reason could be because the nodule in the left upper lobe has a more clinically malignant potential, though the precise mechanism is unclear. Other nodules show negative study in PET scans, perhaps being evidence of a more benign character. Among all legions, an FDG-PET scan may be useful to select the more clinically malignant nodule, which worsens prognosis. In the previous reports comparing the PET scan with the pathological findings, the FDG uptake portion coincided with the cellular portion in the periphery of the PEH nodule.[16,17] Although the obvious malignant transformation of these cells was not detected pathologically, increased glucose metabolizing activity is clear. Taken these data together with the clinical course in this case, we speculate that the FDG uptake reflects the activation of PEH tumor cells, resulting in progression of the disease. Watanabe et al. reported that an FDG-PET scan finding might be an indicator to decide on PEH resection.[16] If this is correct, surgical resection or stereotactic radiotherapy for only the PET-positive lesions may improve the prognosis. More study data should be accumulated to confirm the clinical usefulness of an FDG-PET scan in a PEH patient.

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