

Case Report

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Role of FDG-PET scan in staging of pulmonary epithelioid hemangioendothelioma

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Abstract: In this report we describe a case of pulmonary epithelioid hemangioendothelioma (PEH) in a young woman. The neoplasm manifested with dry cough, chest pain, finger clubbing, and multiple bilateral pulmonary nodules on chest x-ray and computed tomographic (CT) scan. She underwent thoracoscopy, and the histological features of the lung biopsies were initially interpreted as consistent with a not-well-defined interstitial lung disease. Our patient was clinically and radiologically stable over a period of four years, after which the disease progressed to involve not only the lung but also mediastinal lymph nodes, liver and bone. Fiberoptic bronchoscopy showed subtotal occlusion of the right middle and lower lobe bronchi. The histologic examination of bronchial biopsies revealed a poorly differentiated neoplasm immunohistochemically positive for vimentin and vascular markers CD31, CD34 and Factor VIII. A diagnosis of malignant hemangioendothelioma was made. Positron emission tomography (PET) is more sensitive than CT scan and bone scintigraphy in detecting PEH metastases. Furthermore, 18-fluorodeoxyglucose (FDG) uptake seems to be related to the grade of malignancy of PEH lesions. Therefore, we suggest that FDG-PET should be included in the staging system and follow-up of PEH.

1 Introduction

Pulmonary epithelioid hemangioendothelioma (PEH) is a rare malignant vascular tumor. It represents pulmonary involvement of epithelioid hemangioendothelioma (EHE), and it occupies an intermediate position on the spectrum of epithelioid vascular tumours between benign hemangioma and aggressive epithelioid angiosarcoma.

2 Case report

A non-smoking 20-year-old woman was admitted to our hospital for fever, pleuritic pain and a one-year history of dry cough. At the time of the hospitalization, clinical ultrasound examination of the neck showed a 15-mm lymph node and a 20-mm thyroid nodule. Cytologic examination of an ultrasound-guided fine-needle aspiration specimen revealed a benign reactive hyperplasia and a nodular goiter. Technical procedures and diagnostic criteria have been extensively described elsewhere (1-8).

Physical examination was normal, except for finger clubbing. Spirometry showed a mild restrictive ventilatory defect associated with a normal gas transfer. Chest radiograph and computed tomography (CT) scanning demonstrated multiple, bilateral, centimetric, non-calcified nodules (Figure 1, A). The patient underwent thoracoscopy, and the histological features of the lung biopsies were initially interpreted as consistent with a not-well-defined interstitial lung disease. A nine-month course of corticosteroid therapy resulted in improvement in the cough, without modifying either digital clubbing or CT scan images. The patient remained clinically and radiologically stable during the next four years, after which she

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was again admitted to our hospital for fever, dry cough, and pleuritic pain. Physical examination showed dullness and decreased breath sounds over the right lung base. Thoracic CT scanning revealed extensive areas of consolidation in the right middle and lower lobes, a mild homolateral pleural effusion, and the previously described nodules (Fig.1B). Fiberoptic bronchoscopy showed a sub-total occlusion of the right middle and lower lobe bronchi. The histologic examination of bronchial biopsies revealed a poorly differentiated neoplasm immunohistochemically positive for vimentin and vascular markers CD31, CD34 and Factor VIII (Figure 2, *top* A and B). A diagnosis of malignant hemangioendothelioma was made. A total body CT scan did not reveal any other organ involvement. Bone scintigraphic findings were suggestive of hypertrophic pulmonary osteoarthropathy. In contrast, fluorodeoxyglucose-positron emission tomography (FDG-PET) revealed abnormal accumulation of FDG throughout the right middle and lower lobes, in the superior mediastinal lymph nodes, in the left iliac crest and in a left rib (Figure 3). After three cycles of chemotherapy with paclitaxel, CT scan showed a progression of the disease, with an involvement of mediastinal lymph nodes, two liver nodules, and lytic lesions in the cortical bone structure of the ilium. The patient died seven months after the diagnosis.

A histologic review of the first lung specimens was made. The demonstration of rare nodules with a fibrotic core and a micropolypoid structure at their periphery associated with the immunoreactivity for CD34 led to a diagnosis of PEH (Figure 2, *bottom* C and D).

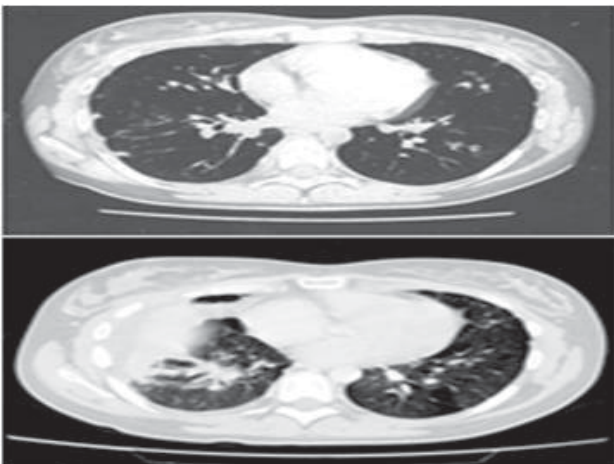


Figure 1: CT scan of the thorax. A: multiple bilateral centimetric and sub-centimetric pulmonary. B: extensive areas of consolidation in the right middle and lower lobes, and bilateral centimetric pulmonary nodular opacities.

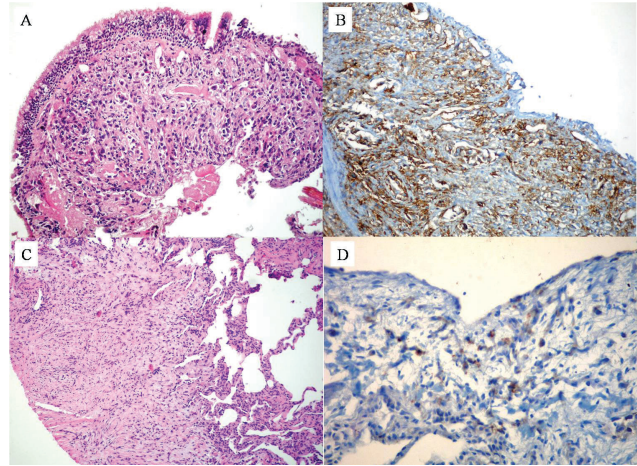


Figure 2: . Top: Bronchial biopsy showing PPA. A: Diffuse submucosal infiltration by anaplastic, large cells (hematoxylin-eosin, original x 25); B: Neoplastic cells stained positively for CD31 (original x 25). Bottom: Lung biopsy showing PEH; C: nodule with a fibrotic core and a micropolypoid structure at their periphery (hematoxylin-eosin, original x 250); D: Rare CD34 positive cells (original x 400).

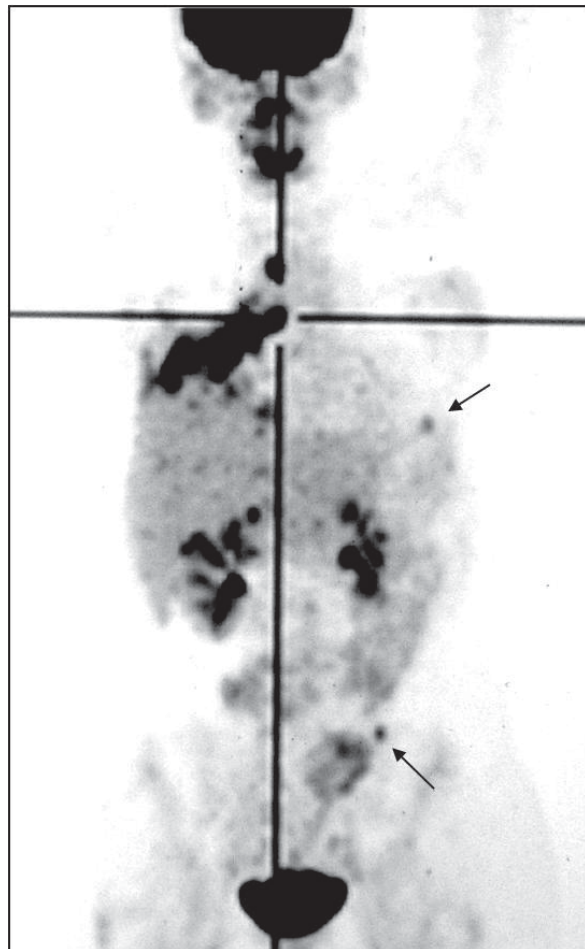


Figure 3: 18-FDG-PET showing abnormal accumulation throughout the right middle and lower lobe, and in mediastinal lymph nodes, in the left iliac crest (arrow) and in a left rib (arrow).

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Informed consent: Informed consent has been obtained from all individuals included in this study.

3 Discussion

PEH is a rare low-to-intermediate grade malignant vascular tumor. It was originally considered a form of bronchoalveolar tumor with a high rate of intravascular spread and hence named “intravascular sclerosing bronchoalveolar tumor (IVBAT)” [9]. The endothelial origin of the tumor was later demonstrated by immunohistochemical and ultrastructural studies. Weiss and Enzinger named it “epithelioid hemangioendothelioma” to emphasize its distinctively epithelioid (or histiocytoid) cytological features [10].

PEH represents a relatively rare localization of EHE. The involvement of the lung alone was reported in 12% of cases in a large series involving 206 patients, although it was more frequently observed in association with other organs such as liver and bone [11,12]. PEH affects young people and is two times more common in women. Patients are often asymptomatic or have no specific respiratory symptoms such as shortness of breath, pleuritic chest pain, dry cough, or hemoptysis. Hypertrophic pulmonary osteoarthropathy manifested in this case has been rarely reported in association with PEH [13-15]. Radiologically, PEH is characterized by multiple bilateral nodular opacities less than 2 cm in diameter. Occasionally, solitary nodules as well as “ground glass” opacities with interlobular septal thickening or pleural effusions have been described. The pathologic diagnosis of PEH is usually made on open lung biopsies and, occasionally, on transbronchial biopsies [13]. Microscopically, PEH is characterized by multiple, oval or round nodules with a hypocellular sclerotic centre and a hypercellular periphery with clusters of neoplastic cells showing a variable degree of cytological atypia. Usually, they demonstrate few morphological signs of malignancy and growth such as polypoid tufts into alveolar spaces. Sometimes, they show a greater degree of nuclear atypia and mitotic activity. The neoplastic cells are positive for markers of endothelial

differentiation such as anti-factor VIII, anti-CD31 and anti-CD34. Recently, Gill *et al* showed that nuclear FLI-1, a protein expressed in endothelial cells, T cells and megakaryocytes, represents a new useful marker for the diagnosis of EHE that is more sensitive than CD34 and more specific than CD31 [16,17].

PEH has a very unpredictable prognosis. The neoplasm usually leads to death from progressive restrictive respiratory failure due to the spread of the tumor through the airspaces. However, aggressive forms with pleural involvement and/or distant metastases, as well as rare cases with spontaneous partial regression, have been described [18]. Recently, it has been proposed to categorize EHE as discrete/confined (pattern A) or diffuse/uncontained (pattern B) [11]. In the chest, pattern A corresponds to multiple, distinct nodules, whereas pattern B includes pulmonary infiltrates, pleural effusion, extrapulmonary thoracic disease, and the symptom of hemoptysis. Patients with pattern A have significantly better survival rates than those with pattern B. In our patient the progression of the disease probably corresponds to a transition of the disease from pattern A to pattern B. It can be hypothesized that areas with different degrees of atypia coexist in some PEH nodules and those with more cytological atypia and pleomorphism have prevailed during the evolution of the disease. The literature also documents a case of epithelioid hemangioendothelioma in the cervical spine showing epithelioid angiosarcomatous areas [19].

Although there is no single effective treatment in cases of bilateral multiple PEH nodules, a recent study suggests that surgery can be an option in patients with unilateral single or multiple nodules [20].

A strict follow-up of patients with PEH is mandatory. In our case we outline the role of FDG-PET in PEH staging. In fact, it is more sensitive than CT scan and bone scintigraphy in detecting PEH metastases. The literature documents several studies demonstrating FDG-uptake in PEH lesions [21-24], although there are few reports of PET-negative pulmonary nodules [25-30]. It can be speculated that FDG uptake is related to the grade of malignancy of PEH nodules and the lack of tracer uptake can be an expression of a more benign character, taking into account that PET scan fails to detect nodules smaller than 6 mm in diameter. In conclusion, we suggest that FDG-PET should be included in the staging system and follow-up of PEH.

Conflict of interest statement: Authors state no conflict of interest.

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