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Epithelioid Hemangioendothelioma: A Case with Large Solitary Pulmonary Mass and Hypertrophic Osteoarthropathy

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ABSTRACT

We describe a case of pulmonary epithelioid hemangioendothelioma (PEH), previously known as intravascular bronchoalveolar tumor, in a 48- year-old woman with an initial diagnosis made by CT-guided transthoracic needle biopsy. This is a rare disease, with approximately 50 cases described in the literature. To our knowledge, this has not been previously described in the English-language literature. This tumor can affect multiple organs. PEH is usually multifocal or small sized; hypertrophic osteoarthropathy is uncommon. This patient presented with hypertrophic osteoarthropathy and large solitary pulmonary mass, rare presentations of this uncommon tumor. ***(Tanaffos 2005; 4(16): 73-78)***

Key words*: Epithelioid hemangioendothelioma, Hypertrophic osteoarthropathy, Intravascular bronchoalveolar tumor*

INTRODUCTION

Pulmonary epithelioid hemangioendothelioma (PEH) is the currently preferred term for the neoplastic process, originally described in the lung as intravascular bronchoalveolar tumor by Dail et al. (1). PEH typically occurs as bilateral multiple nodules in young women. Only in rare cases PEH develops as a solitary lung nodule (2-4). Moreover large mass is exceptional.

On the other hand, hypertrophic osteoarthropathy (HOA) is a syndrome characterized by periosteal new bone formation, clubbing and joint effusion. It develops as a primary disease or secondary to intrathoracic malignancy, suppurative lung disease, cyanotic heart disease, inflammatory bowel disease, or chronic liver disease (5).

We describe an unusual case of PEH presented with HOA and a single large mass. We diagnosed the case with CT guided transthoracic needle lung biopsy, which has not been reported already.

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CASE HISTORY

A 48-year-old woman presented to our clinic in Urmia, Iran with a one-year history of pain and swelling in her wrists and ankles; and cough for six

months duration. She had never smoked. On examination, there were dullness on percussion with decreased breath sounds over upper two third of right hemithorax. Fingers and toes were clubbed and her wrists and ankles were swollen and tender. Chest x-ray (Fig. 1A) and computerized tomography (Fig. 1B) revealed a large right hemithorax mass without bone destruction. Radiography of radius (Fig. 2) showed subperiosteal formation of new bone consisting in HOA. In Fiberoptic bronchoscopy, there was an external compression on trachea and right main and upper lobe bronchi without any endobronchial tumor.

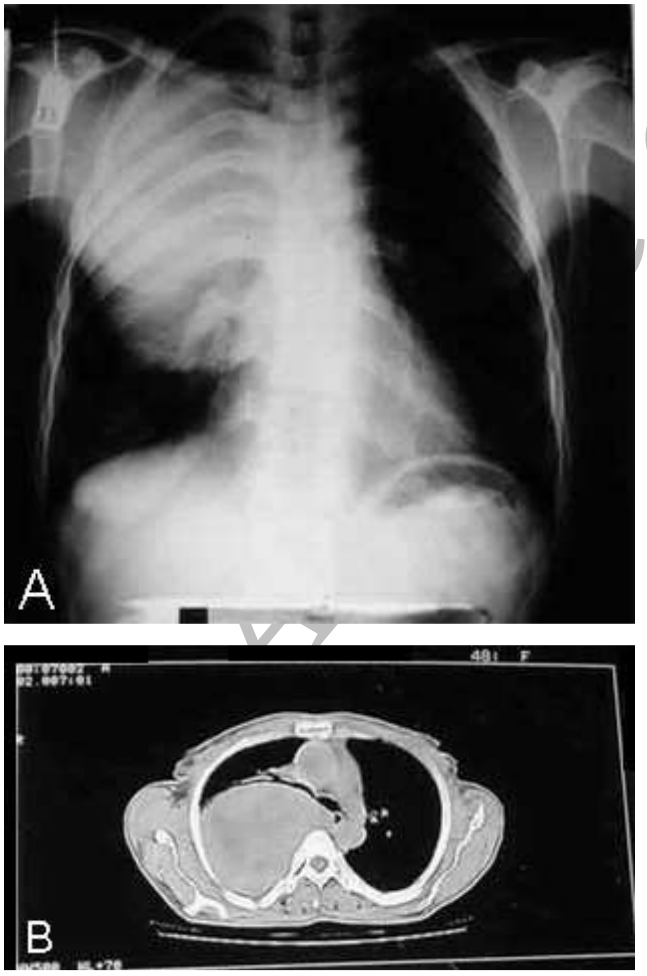

Figure 1. Plain chest radiography (A) and CT scan (B) show a large mass on right side of chest.

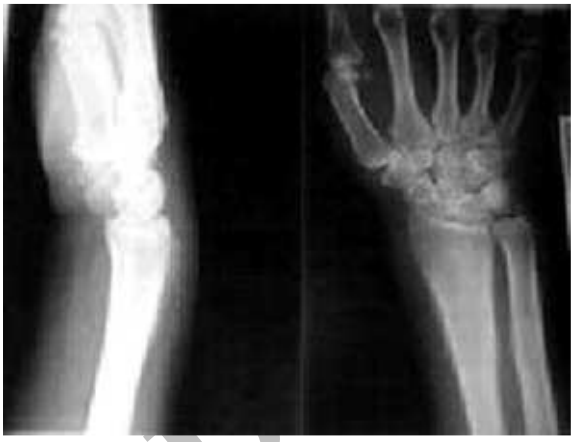

Figure 2. Plain radiograph of radius showing periosteal reaction on the medial and lateral aspects

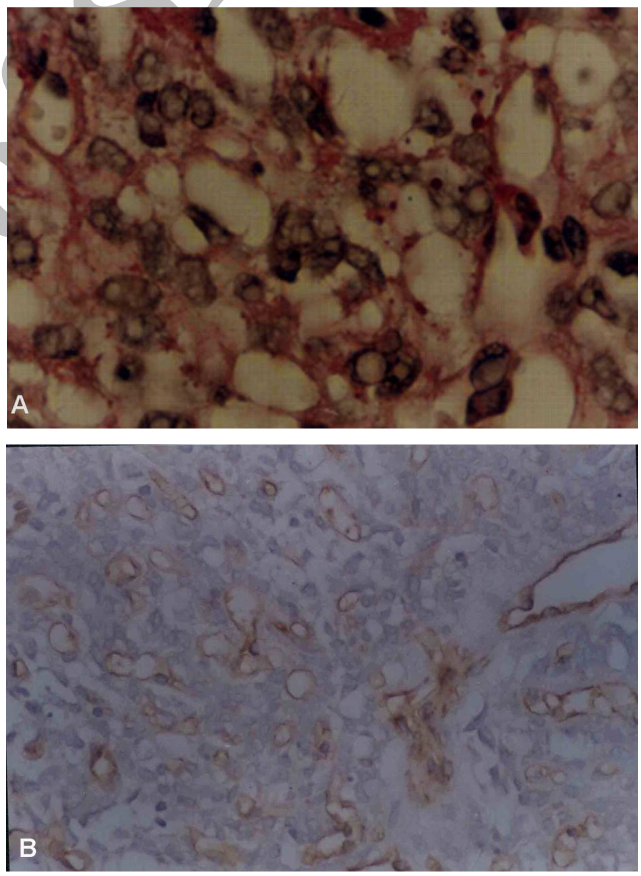

Figure 3. Specimen from a lung biopsy. (A) Pleomorphic polygonal cells with intracellular vascular lumina containing red blood cells (H&E, ×400). (B) endothelial cells are strongly immunostained (brown color) with antibody to von Willebrand (factor VIII) (×400).

CT guided transthoracic cutting needle biopsy of tumor was performed. Sections showed a solid hypercellular tumor containing a few vessels in low power filed. In high power field, there was micro vascular background containing red blood cells in many capillary vessels (Fig. 3A). The tumor cells have round to oval nuclei and some vacuoles have given a "blistering" appearance to the majority of those cells in their cytoplasms. No mitotic activity was seen. Immunohistochemistry staining was strongly positive for factor VIII (von Willebrand) (Fig 3B) and negative for carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA), and leukocyte common antigen (LCA) markers.

Immunohistochemistry staining was performed for CD31 but was no helpful because the specimen was scant. The patient refused the treatment and died 6 months later as the result of respiratory failure.

DISCUSSION

Dail et al. (1) first described epithelioid hemangioendothelioma (EHE) in 1983. Initially, this was believed to be an aggressive form of bronchoalveolar cell carcinoma that invaded adjacent blood vessels; hence, was named as "intravascular bronchoalveolar tumor". Corrin and coworkers employed immunohistochemical techniques to demonstrate that the tumor cells were from a lineage capable of differentiation along endothelial lines. Weldon-Linne et al. confirmed this using electron microscopy and applied immunohistochemistry. Electron microscopic features, and immunochemistry showing diffuse cytoplasmic staining of the malignant cells with factor VIII-related antigen confirmed the endothelial lineage of tumor cells.

Weiss et al. were the first to offer the term "epithelioid hemangioendothelioma". It is a rare vascular tumor of borderline or low-grade malignancy. It can arise from many organ systems, including liver, bone, and soft tissues simultaneously or sequentially. When this occurs, it may be difficult to determine if the tumor is multicentric or is a primary lesion with metastases to other tissues. Rarely, the lungs are involved, with only 50 cases of pulmonary EHE described in the literature (1, 6).

The majority of patients affected by pulmonary epithelioid hemangioendothelioma (PEH) are females with the age of first examination ranging from 7 to 76 yrs (2, 3, 7). Half the patients are asymptomatic and are discovered on incidental chest radiography. Symptoms are uncommon and are usually mild and including shortness of breath, mild pleuritic chest pain, and cough, although hemoptysis has been reported as well (8).

The case described in this report was presented with HOA based on findings of clubbed fingers, arthritis, and periosteal reactions, which were confirmed by typical radiographic changes (Fig 2). To the best of our knowledge, five case reports of PEH complicated by HOA have been reported. In one report, HOA was found in a 17-year-old boy, concurrently with hepatic and pulmonary epithelioid hemangioendothelioma. In the other, HOA was diagnosed in a 24-year-old woman concurrently with PEH. Kim et al. (9) report a case in which the tumor was first found in the liver and HOA developed after pulmonary metastasis. Ledson et al. (10) have reported HOA in a 24-year old woman with multiple pulmonary nodules with diagnosis of PEH and Chartier et al. (11) in a 15-year old girl with PEH. This case is the sixth one with HOA in a patient with PEH.

The pathologic findings of hypertrophic osteoarthropathy are known to show vascular hyperplasia and activated endothelial cells in clubbed fingers, and vascular hyperplasia and periosteal proliferation in affected bones. In cases of cyanotic heart disease, the activation of cytokine-producing endothelial cells by macrothrombocytes is found, which might be a mechanism of hypertrophic

osteoarthropathy (12). Plasma levels of the von Willebrand factor antigen, which is a marker of endothelial cells, is known to be elevated in hypertrophic osteoarthropathy (13).

These findings suggest that the activation of endothelial cells and platelets plays an important role in the pathogenesis of hypertrophic osteoarthropathy. The endothelial origin of epithelioid hemangioendothelioma suggests a link between the tumor and hypertrophic osteoarthropathy.

The most common feature of PEH on chest radiograph or CT-scan is the presence of multiple perivascular nodules with well-or ill-defined margins in both lungs. The nodules size ranges up to 2 cm, but most are<1 cm in diameter. They are usually found in relation to small and medium-sized vessels and bronchi. In a review of 20 cases, Dail et al. showed 20% of patients had <10 nodules, 25% had ≥ 20 nodules, and the rest were somewhere in-between. This presentation is often mistaken for metsatatic carcinoma, which is the initial radiologic interpretation in nearly all cases (14). However, PEH rarely develops as a solitary lung nodule. The frequency of this presentation lies between 10% and 19% of PEH cases (2, 3). Jang et al (4). reported a case with single cavitary lung mass. Our case revealed a single large mass, a rare finding for this rare neoplasm.

Strangely the CT-guided transthoracic needle lung biopsy specimen of this patient showed histological features of PEH. To our knowledge, this has not been previously described in the English-language literature. All previously reported cases of PEH in the literature were diagnosed using open-lung or thoracoscopic biopsy specimens. Recently for the first time Cronin et al. (14) described a case which was diagnosed by transbronchial lung biopsy specimen and Mhoyan et al. (15) reported the first case of PEH diagnosed by ultrasound-guided fine needle aspiration of hilar mass. But there is no report of diagnosing this tumor by transthoracic needle biopsy.

Macroscopically in PEH, there are solarity or multiple pulmonary nodules measuring several millimeters, up to 5 cm in diameter. Their consistency is rubbery or cartilage-like. The cut surface is gray-white to yellow-brown, with semitranslucency or non-translucency. Calcifications are rarely seen (3).

Histologically, the periphery of the neoplasm is hyoercellular, while the center is hypocellular with coagulative necrosis, hyalinization, calcification or even ossification. The tumor cells are round with an abundant cytoplasm, while the nucleus is round or oval, with low-grade atypia, evenly distributed chromatin and scarce mitosis. Spindle-shaped tumor cells are occasionally seen. The cell growth may form lumens of various sizes, which may contain red blood cells (Fig 3.A). At the periphery of the nodule, tumor cells extend to adjacent alveoli through the pores of Kohn, in the form of a micropolypoid growth into the lumen of respiratory and membranous bronchioles. However, the alveolar elastic framework is essentially preserved. The neoplastic tissues may invade the walls and lumens of small pulmonary arteries, venis and lymphatics. Inflammatory cellular infiltration and congestion in the adjacent lung parenchyma as well as fibrin thrombosis are not usually seen (3).

In this case, the immunohistochemical study was pivotal for the correct diagnosis, being negative for epithelial markers, such as EMA, CEA and lymphoma marker i.e. LCA, and being strongly positive for factor VIII, a vascular marker. This tumor is positive for antibodies directed against CD31 and CD34. Our specimen was insufficient for staining; however, it was strongly positive for factor VIII.

Histologically, our case should be distinguished from epithelioid angiosarcoma, sclerosing

hemangioma and carcinoma. However, angiosarcoma and carcinomas display far more nuclear atypia and mitotic activity than PEH. Although immunohistochemical technology makes the differentiation from carcinoma easy, differentiation from angiosarcoma and sclerosing hemangioma can pose more problems. Unlike angiosarcoma, PEH does not show necrosis, significant cytonuclear atypia or a high mitotic index. Sclerosing hemangioma, on the other hand, is a benign tumor without cytonuclear atypia and mitotic figures. Therefore, some researchers stress the fact that hemangioendotheliomas are in a continuum between hemangioma and epithelioid angiosarcoma (16).

Our patient refused any treatment and died 6 months after diagnosis. In the original cases described by Dail et al. the mean survival of PEH was 4.6 yrs, with range of 6 months to 15 yrs. Cronin et al. (14) described a 35 year-old woman died 9 months after her initial diagnosis despite the treatment with interferon-α2b and chemotherapy. The shortest survival was eight weeks in a patient who succumbed to gross hemoptysis. The patient with the longest survival was treated surgically, undergoing 11 separate resections over 24 years, finally succumbing to pneumonia superimposed on a decreasing repiratory function (10).

Distant metastases are seen in less than a quarter of cases, the sites involved included the liver, lymph nodes, bowel, retroperitoneal soft tissues, skin and central nervous system (17).

Treatment can vary from observation in asymptomatic patients, surgery in a few patients with resectable tumor or chemotherapy in cases with widely disseminated disease, these options should be discussed with the patient. However, the chemotherapy to be used is still a matter of debate. The notion of PEH as a chemoresistant disease is probably still true. There is a report regarding a case of complete remission of a pleural EHE after treatment with chemotherapy (carboplatin and etoposide) and a partial remission of a widely disseminated EHE with a year of treatment with α-2A interferon, suggesting a possible role of immunotherapy (3, 17).

In conclusion, we describe a case of pulmonary EHE diagnosed by transthoracic needle biopsy. It is concluded that this diagnosis can be made by transthoracic biopsy, and open-lung or thoracoscopic biopsy is not necessarily required, potentially sparing the patients from the morbidity and mortality associated with surgical lung biopsy. We also described clinical and imaging features and concluded that PEH may present with HOA and single large mass.

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