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Case Report

Pulmonary Epithelioid Hemangioendothelioma

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Abstract

Epithelioid hemangioendothelioma is a rare vascular tumor with a clinical course between hemangioma and angiosarcoma. Until 2008 there were approximately 50 cases reported in the literature. The tumor may affect any organ, and in the lung it may grow extensively. Distant metastases and multiorgan involvement may occur as well. Surgical resection is the primary treatment for localized disease, and there is no consensus about the best treatment for systemic disease.

Keywords: Neoplasms,Vascular Tissue Neoplasms,Hemangioma,hemangioendothelioma,Epithelioid hemangioendothelioma.

Introduction

Epithelioid hemangioendothelioma (EHE), previously known as intravascular bronchioalveolar tumor (IVBAT), is a rare vascular tumor with a clinical course intermediate between hemangioma and conventional angiosarcoma. It is classified as a malignant vascular tumor according to the 2002 World Health Organization (WHO) classification.[1]

The prognosis of this tumor is unpredictable, with life expectancy ranging from one to 15 years, but about 40% of patients survive less than five years. Normally, this tumor arises from a variety of sites, more commonly soft tissues (especially in the extremities), bones, spleen, brain, heart, meninges, gastrointestinal tract, lymph nodes, liver and lung. In the lung, this tumor is often multifocal, bilateral, and usually affects young people, with age ranging from 12 to 61 years (mean 39), with a predominance for women (female/male ratio of 2:1).

Most patients are asymptomatic, but in the lung, this tumor may arise extensively and systemic metastases, mainly to the liver, have been documented.

We present a case of pulmonary EHE with liver metastases, with a review of treatment options and prognosis of these patients according to the literature.

Case Report

A 20-year-old female presented in another medical service a one-month history of dry cough and dyspnea after medium efforts. The patient was not immunocompromised and had no history of smoking or intravenous drug abuse.

The chest computerized tomography (CT) scan showed bilateral ground-glass opacities in both lungs, without pleural effusion or enlarged regional lymph nodes. The patient underwent a right thoracotomy for an open lung biopsy. The frozen section revealed a sclerosing hemangioma. Immunohistochemical stains led to the diagnosis of EHE.

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The patient was referred to the Department of Thoracic Surgery of Hospital A.C. Camargo, five months after lung biopsy, with no further treatment done. A new chest and upper abdominal CT scan was performed, showing several lung and liver nodules and masses (Figures 1A and 1B). No hilar or mediastinal lymphadenopathy, and no pleural effusion was observed. The brain magnetic resonance imaging was normal.

The pathology report review was performed by the Department of Pathology and confirmed the EHE

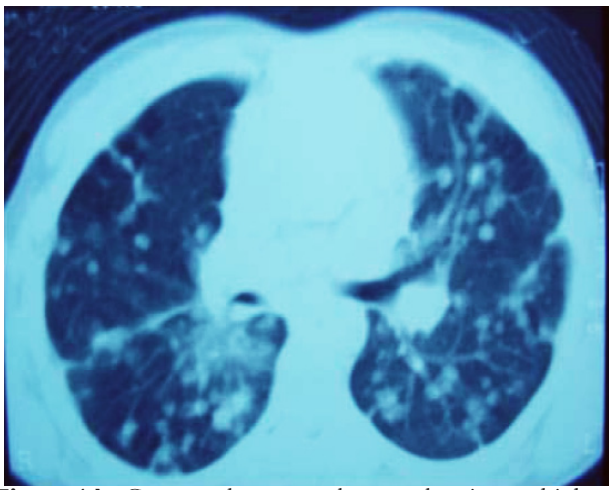

Figure 1A- Computed tomography scan showing multiple nodules

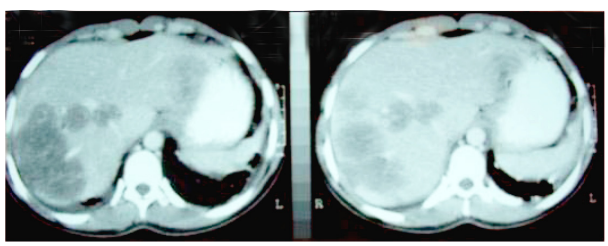

Figure 1B - Computed tomography scan showing liver nodules and masses

diagnosis. At microscopy, the tumor was composed of round and spindle eosinophilic epithelioid cells, embedded in a myxoid to hyaline matrix (Figure 2A and 2B). Some cells showed intracytoplasmatic lumina, containing erythrocytes. There was only bland nuclear atypia and the mitotic index was low.

Immunohistochemistry was performed using the Advance Detection Kit from Dako®. A wide panel of antibodies was performed including CD31, CD34, desmin, smooth muscle actin, factor VIII, S100 protein, EMA, pan keratin, vimentin and TTF1. Neoplastic cells were positive for CD31 (Figure 2C) and CD34 (Figure 2D) and were negative for all other antibodies tested.

Due to the multifocal presentation of the disease, the patient was referred to the Department of Clinical Oncology. She was started on a chemotherapy regimen with paclitaxel 80mg/m^2, given on day 1 and 8, and repeated every 21 days. After two months, a new radiologic evaluation of both lung and liver showed stable disease.

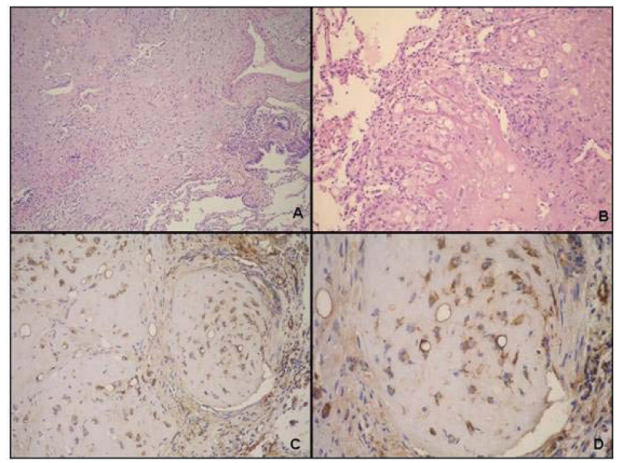

Figure 2 - A) Solid fusocellular neoplasia with mixoid-hyaline stroma, within the pulmonary parenchyma (hemotoxilyn and eosin, HE 40x) B) Eosinophilic epithelioid cells, embedded in a myxoid to hyaline matrix (HE 200x) C and D) Same area showing epithelioid cells positive for CD 34 (100x) and CD31 (400x)

Discussion

The IVBAT tumor was first described as pulmonary EHE by Dail et al.,[1] reporting on 20 cases. They described EHE as an unusual tumor of the lung that presented with multiple small, slowly growing pulmonary nodules. According to Cronin, Arenberg,[2] there were approximately 50 cases described in the literature. There are only three papers reporting on EHE in Brazil, but none referred to pulmonary disease.[3-5]

EHE is not specific to the soft tissues and the biological behavior shows great variance depending upon its site of origin. Concurrent multiorgan involvement of EHE, most commonly the liver and lung, occurs occasionally and may represent metastatic disease or the multicentric origin of the tumor.[6-7] Most patients die from pulmonary insufficiency as a result of increasing size and number of tumor nodules. A small group succumbs because of extrapulmonary spread of the tumor.[8]

The diagnosis of EHE is often incidental, as patients are usually asymptomatic or have minor respiratory symptoms at the time of diagnosis.[1-2,9] Patients with multifocal EHE may present pain, occasional swelling or headache.[9]

The most characteristic feature of EHE in chest CT is the presence of multiple nodules with well defined margins in both lungs. The literature also describes enlarged lymph nodes and pleural effusion and thickening, and areas of ground glass opacity diffusely in

both lungs.[2,6-7]

There are several differential diagnosis diseases that can result in bilateral nodules such as sarcoidosis, Wegener's granulomatosis, idiopathic bronchiolitis obliterans, eosinophilic granuloma, lymphomatoid granulomatosis, pulmonary lymphomas, lung metastases and bronchioloalveolar carcinoma.[7,10]

Celikel et al.[6] described the difficulties for the diagnosis of EHE, since EHE may mimic other neoplastic and also non-neoplastic lesions. Literature shows that most cases have been diagnosed after open lung biopsy, although transbronchial lung biopsy may also be an alternative for diffuse lesions.[2] It is suggested that the expression of CD31, CD34, factor VIII and vimentin support the diagnoses of EHE,[2,6-7] as reported in our case.

The biological behavior of EHE is often indolent, but it is highly variable. Factors associated with poor prognosis were reported by Celikel et al.[6] and Van Kasteren et al.[11] as being multiple nodules, peripheral lymphadenopathy, extensive intravascular involvement, distant metastases and especially anemia, pleural effusion and alveolar hemorrhagic symptoms.

Overall survival in exclusive pulmonary disease is 4.6 years.[7] Cronin, Arenberg[2] have found partial spontaneous regression described in three patients, between 5 and 15 years after detection.

Although there is currently no consensus about whether patients with solitary pulmonary nodules have a better prognosis than those with multinodular disease, surgical resection is the primary treatment for localized disease. There may be a role for hormonal therapy in patients with diffuse pulmonary disease since the tumor express estrogen and progesterone receptors.[12]

Therapeutic options for EHE are limited and there is no consensus in the literature about the best one. Kradin e Mark used combination chemotherapy with doxorubicin, ifosfamide and dacarbazine. They have achieved control of hemoptysis and satisfactory clinical response. The patient was enrolled in a clinical trial of high dose chemotherapy and autologous stem-cell rescue and a few months later developed recurrent nodules and pleural effusion and died approximately ten months after the diagnosis.[7]

Cronin, Arenberg[2] used interferon alpha-2b and also had progression of the disease. Chemotherapy with gemcitabine and docetaxel was started but it has been changed to oral regimen including cyclophosfamide and etoposide. The patient died nine months after the initial diagnosis.[2] Celikel et al.[6] report a patient treated with doxorubicin, cisplatin and cyclophosphamide that had stable disease through the follow-up.

Conclusion

We conclude that EHE, despite being a rare disease, must be considered in the differential diagnosis of multiple lung nodules. CT findings should lead to lung biopsy and immunohistochemistry should confirm the correct diagnosis. The prognosis depends on vascular markers or presence of hemorrhagic symptoms. There is no single effective treatment in cases of bilateral multiple nodules. As there is no standardized therapy, more studies are needed.

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