ORIGINAL ARTICLE

THORACIC EPITHELIOID HEMANGIOENDOTHELIOMA: CLINICAL DEMONSTRATION AND THERAPEUTIC PROCEDURES

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Abstract

Epithelioid hemangioendotheliomais a low to intermediate grade malignant vascular tumors that can involve any organ.About 60-80%of patients are women, patient ages range 7 to 81 years, with a median age of 38 years. Four cases of thoracic epithelioid hemangioendotheliomas with different clinical presentation and disease progression are reported. Cases 1 and 2 are pulmonary epithelioid hemangioendotheliomas diagnosed at different advanced stages and patients died after 6 and 2,5 months of medical treatment, respectively. Case 3 corresponds to pleural epithelioid hemangioendothelioma, submitted to left lung decortication and pleuro-pericardial window; patient is free either from symptoms and radiographic manifestations for 10 months of follow-up. Case 4, of mediastinal epithelioid hemangioendothelioma, represented by a mass in the upper left mediastinum adherent to the aortic arch; patient underwent block excision of the mass followed by chemotherapy; subsequent recurrence 41 months later and the patient died 8 months after. The reported 4 cases reveal the heterogeneous clinical presentation of epithelioid hemangioendotheliomas with behavior in between benign and high-grade tumors, raising difficulty in either differentiating from other vascular tumors and previewing clinical outcome.

INTRODUCTION

Weiss and Enzinger first reported Epithelioid hemangioendothelioma (EHE) in 1982 as a rare tumor with a prevalence of one in one million, and described its intermediate clinical behavior between hemangiomas and angiosarcomas.[1, 2] Mainly considered lowto intermediate grade malignant vascular tumors involving any organ, including lung, liver, bone, soft tissue, skin, gastrointestinal tract, and breast,it develops from vascular endothelial cells and is characterized by a translocation between chromosomes 1 and 3 resulting in a fusion protein of the WW domain-containing transcription regulator 1 (WWTR1) and the calmodulin-binding transcription activator 1 (CAMTA1), leading to constitutive activation and neoplastic transformation.[1, 3, 4] World Health Organization (WHO) - 2020 classification of sarcomas distinguishes EHE from other vascular tumors by the pathognomonic WWTR1-CAMTA1 fusion as t(1;3)(p36.3;q25) translocation, as well as the less common YAP1-TFE3 fusion, with unique clinical features.[5]

As a result of its rarity, the current reported literature is limited to case reports, with a handful of retrospective descriptive case series to better characterize the clinical, pathologic, and molecular characteristics as well as treatment approaches.[6]

A group of 4 thoracic cases diagnosed through histopathology and immunohistochemistry, raised concern due to different clinical presentation and follow-up.

MATERIALS AND METHODS

Between 1990 and 2020, 4 cases of EHE were diagnosed at Centro Hospitalar e Universitário de Coimbra (CHUC), serving as reference to 3 million inhabitants in the center of Portugal. We describe these 4 rare cases of EHE associated with cardiothoracic manifestations.

CASE REPORTS

Case 1

A 69-years-old female, housekeeper, presenting anemia of unknown cause, asthenia, diffuse abdominal pain and weight loss of 20 Kg in 8 months, underwent abdominal and chest Computed Tomography (CT). A large pulmonary mass on the left lower lobe without cleavage plane to the left diaphragmatic dome and spleen measuring 8 x 5.3 cm, heterogeneously enhanced for intravenous contrast was certified (figure 1A,1B). There were enlarged lymph nodes next to corresponding segmental bronchus, infra-hilar on the left, the largest measuring 2.6 cm, and at the esophageal hiatus where the largest measured 3.2 cm. Serological CEA and CA 19.9 biomarkers were negative. Surgical biopsy of the left lower lobe mass was concordant with malignant EHE, characterized by solidnests of round endothelial cells with clear cytoplasmwhere erythrocytes were occasionally seen; there were also extensive areas of necrosis; neoplastic cells expressed FactorVIIIand vimentin and other connective tissue markers were negative (figure 2).

Subsequent medical oncology treatment and follow-up was performed and the patient died 6 months after the diagnosis.

Case 2

An ex-smoker (40 pack-year), 54-years-old male, professional of mechanics, presented with 1-month right pleuritic chest pain irradiating to the back and productive hemoptoic cough.

The chest x-ray showed a right para-hilar mass and diffuse hypotransparency on the right hemithorax, that in the chest CT measured 5.3 x 5.8 cm, encompassing the emergence of the right main bronchus and upper lobar bronchus, without cleavage plane with the right pulmonary artery. Bronchogram in the right upper lobe, peri-centimetric dense subpleural nodules in the right upper lobe, and pre-tracheal and pre-carinal enlarged lymph nodes were also observed. Magnetic Resonance Imaging (MRI) scan confirmed the pulmonary mass on the right side, centered on the hilar region with 5.7 x 59 cm of axes and 8.2 cm of cranial-caudal dimension, with extension to the mediastinum, circumscribing the right pulmonary artery and the right main and intermediate bronchi, narrowing the lumen of the superior vena cava. Positron Emitting Tomography (PET) scan showed adrenal, hepatic and latero-cervical supposed lymph node metastasis. The patient underwent

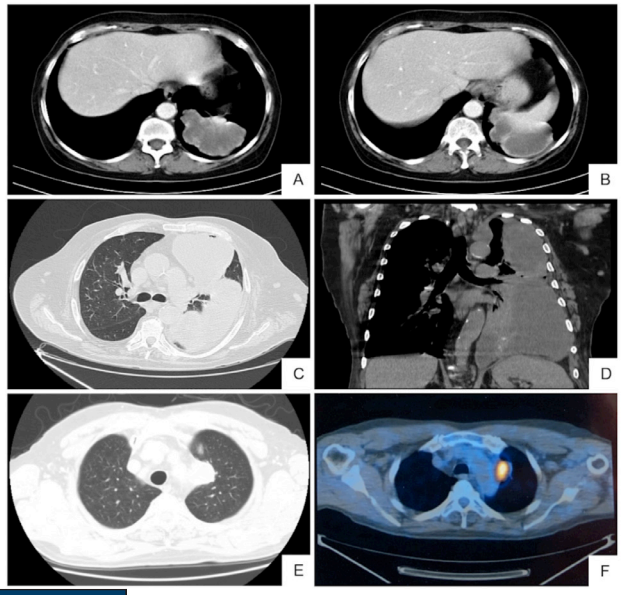

Figure 1

Case 1 – Abdominal computed tomography (CT) scan showing a left lower lobe mass without cleavage plane to the left diaphragmatic dome and spleen (A, B). Case 3 – Chest CT scan showing an extensive, organized left pleural effusion, defining several loci - Axial plane (C); coronal plane (D). Case 4 – Upper left mediastinal mass, adherent to the aortic arch - Chest CT scan (E); PET scan (F).

surgical biopsy by mediastinotomy with extensive tumoral tissue sampling. One fragment corresponded to a vascular pathway in the wall of which there was proliferation of spindle and polygonal cells, with cytoplasmic vacuole and expressing FactorVIII, CD31 and CD34. No characteristics of epithelial neoplasia were observed. It was diagnosed as EHE.

Treatment and follow-up lasted for 2.5 months after the biopsy.

Case 3

A 75-year-old male, administrative professional, presented with pleuritic thoracic pain. Thoracic x-ray revealed left pleural effusion and CT scan (figure 1) defined extensive, organized left pleural effusion, with several loci, some of them with gas levels, and on pleural leaflets there were areas of thickening with nodular aspect. Multiple mediastinal enlarged lymph nodes were present: paratracheal, pre-vascular, hilar, and in the aortopulmonary and infracarinal window. On left lung decortication tissue, pathology reported individual cell proliferation with no defined cytoplasmic delimitation, nuclear atypicalhyaline matrix and CD31expressing, corresponding to EHE (figure 2).

The patient has been in clinical follow-up for 10 months and, so far, free either from symptoms and radiographic manifestations.

Case 4

A 60-year-old male, smoker (20 pack-year), present-

ed with nonspecific chest pain which worsened in supine position and improved in orthostatism, persistent and irritative non-productive cough and dysphonia. Chest CT (figure 1) revealed a 3.4 cm diameter mass in the upper left mediastinum, adherent to the aortic arch. Pulmonary function tests were normal. PET scan (figure 1) showed an anterior 3.1 x 2.1 cm mass, next to the aortic arch, of high metabolic index, compatible with lung or upper mediastinaltumor. Surgical biopsy followed by pathology analysis revealed cells with marked nuclear atypia and cytoplasmic occasional vacuole. Factor VIII and CD31 expression concurred for the diagnosis of malignant EHE.

Chemotherapy was followed by substantial tumor regression, until 2 cm diameter 3 months later, seen in the chest CT, and PET scan, without other hyperuptaking lesions. Block excision of the aortic arch mass and adjacent tissues was evaluated as post-therapeutic healing scar-like tissue without neoplastic cells, as observed in the previous surgical biopsy.

Adjuvant chemotherapy was prescribed for 3 months. In the three years after, follow-up chest CT revealed 6 small pulmonary nodules suggestive of secondary lesions. Surgical biopsy was performed and pathology reported biphasic pattern with nests of neoplastic cells with marked nuclear atypia, some mitoses and focally the presence of cytoplasmic vacuoles and spindle cells with moderate nuclear atypia,also with some cytoplasmic vacuoles in hyalinizing stroma were seen in the periphery of malignant epithelial cells; Factor VIII, CD31, vimentin and actin immunoexpression was revealed.

The actual morphological changes were similar to previous histological analysis.

The patient presented with pain in the left supraclavicular region, left shoulder and arm, associated with motor impairment of the left arm. A chest CT showed a 4.3 x 4.5 cm adenopathic conglomerate, exerting a compressive effect on the ipsilateral subclavian artery, which remained permeable. Surgical biopsy confirmed extension of the malignant EHE.

The patient died 4 years after the first diagnostic biopsy.

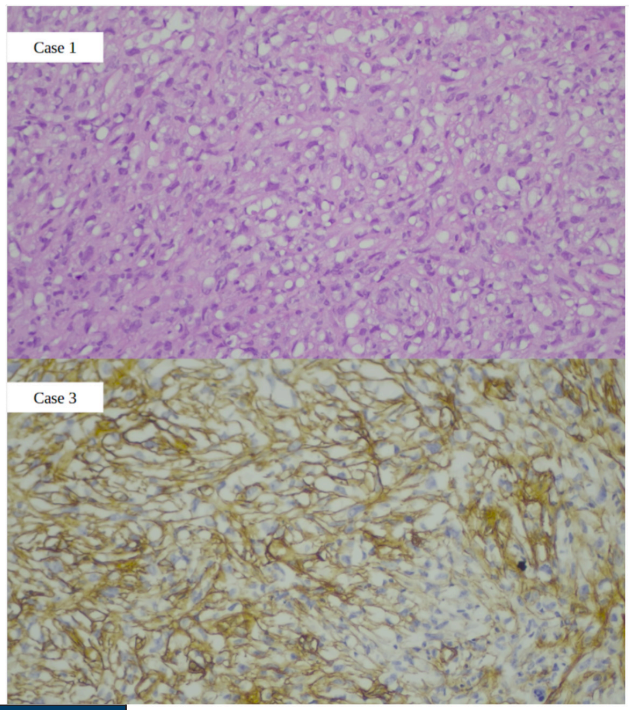

Figure 2 *Case 1 – hyaline matrix involving malignant epithelioid vascular cells with anisocariosis and clear cytoplasm; HE x200. Case 3 – CD31 expression in epithelioidmalignant vascular cells; x400.*

DISCUSSION

The median age of diagnosis of EHE is usually 36 years, however it may range from childhood to elderly. It is more common in women than in men with a 4:1 ratio.[6]

The clinical presentation and nature of EHE is heterogeneous. The reported sites of involvement include the lungs (30%), liver (21%), liver plus lung (18%), lung alone (12%), and bone alone (14%).[6,10] Most patients are asymptomatic and are diagnosed incidentally. However, they may present with respiratory symptoms such as pleuritic chest pain, pleural effusion, or hemoptysis and systemic manifestations such as weight loss and anemia have also been reported.[6,7,8]

Pulmonary EHE can appear as perivascular nodules 1 to 2 cm in size throughout both lungs, with lower lobe predominance.[6] Other intrathoracic presentations such as reticulonodular, diffuse pleural involvement, or pleural thickening have also been reported.[6,11]

Pleural EHE is reported to have a less common and more aggressive behavior.[15, 17] A case series described 32 cases, revealing pleural effusions (96.9%) and pleural thickening (31.2%).[12] In a few cases pericardial effusion, ascites, and pulmonary embolism causing pulmonary hypertension have also been described.[12-15, 18] The differential diagnosis of pleural EHE from a diffuse pleural carcinomatosis or mesothelioma should be given careful consideration due to their similar radiologic appearance.15Apparently there is no significant correlation with smoking but may be related to genetic disorders, asbestos or radiation exposure.[15,16] Reade et al. found that 8 in 22 patients diagnosed with pleural EHE had a history of asbestos exposure.[18]

Anterior mediastinal EHE is rare. In 25 cases reported in literature, 16 (64%) patients were males aged 19–79 years (median, 47 years). The sizes of the tumors ranged from 3 to 13.5 cm (mean, 7.6 cm) in the greatest diameter. Furthermore, 13 (52 %) patients were asymptomatic, whereas the remaining patients had symptoms including chest pain, coughing, dyspnea, superior vena cava syndrome, and dysphagia.[20]

According to Ishibashi et al., tumor sites of anterior mediastinal EHE were described in 11 patients: 3 tumors

arose from the SVC/right brachiocephalic vein; 2 from the SVC, azygos vein, and left brachiocephalic vein, respectively. One tumor arose from the SVC and bilateral brachiocephalic veins.[20]

It is important to distinguish EHE and morphologic mimics, as epithelioid angiosarcoma and other epithelioid tumors. Desmoplastic reaction, a morphologic characteristic, may obscure vascular tumoral cells in tumoral tissue.[1, 24] Other stromal changes such as chondroid, myxoid, or hyalinized stroma, are useful morphologic features for this task.[25] EHE cytologic characteristics include moderate to large amounts of clear cytoplasm, pleomorphic nuclei with nuclear grooves, intranuclear pseudoinclusions and intracytoplasmic lumina.[26]

Immunohistochemical staining may determine the origin of tumor cells by identifying vascular endothelial cell markers, including CD31, CD34, Factor VIII, Friend leukemia integration 1 transcription factor (FLI-1), the h and y epitopes of blood group antigen (BNH9), UEA-1 (Ulex-1), and tumor cell vimentin (vimentin).[6, 12] Among these markers, CD34 is expressed by more than 90% of vascular tumors, so, although relatively sensitive, it has a low specificity for EHE. On the other hand, CD31 is a more specific marker, therefore, the combination of Fli-1 and CD31 has been suggested to identify EHE immunohistochemically.[6,29] On the other hand, positive tests for factor VIII-related antigen and CD34, were also considered suggestive of EHE in several studies.[21,23]Moreover, some patients also have focal expression of epithelium-derived antigens, such as CK, and CEA, while myogenic or neurogenic antigens are negative.[12]

The EHE prognosis is variable from an indolent clinical course to metastization. Risk factors for worse outcomes include constitutional symptoms such as weight loss, as well as pulmonary symptoms such as hemoptysis and hemorrhagic pleural effusions.[9]

In a review of 93 patients with pulmonary EHE by Amin et al.,[9] distant metastases were confirmed in 47 patients (50.5%). Among these, the most common were hepatic (22.6%), pleural (20.4%) and lymph node metastases (10.8%). Although pulmonary EHE is capable of producing regional and distant metastases, it does so far less frequently than conventional angiosarcoma.[9] Regarding treatment, in that review, tumor resection was performed in 40 patients (43%) and was the most common treatment undertaken. Among these, 28 patients (70%) were followed-up without adjuvant therapy. Twenty-two patients lived from 2 to 20 years; eight patients showed no tumor progression; and 1 patient showed tumor regression. On the other hand, 4 patients showed tumor progression resulting in death after 2, 20 and 41 months. Adjuvant treatment was tried in 12 patients, among which, 10 demonstrated no effect on tumor growth.[9]

In general, the standard therapy for EHE is resection with free surgical margins, and, although they are radio- and chemo-resistant tumors, additional chemotherapy or radiotherapy might be beneficial in cases of angiosarcoma-like behavior.[12,15,22] However, in asymptomatic patients with diffuse lesions, watchful waiting may be a reasonable strategy.[12] There may be a role for multimodality in certain clinical scenarios with surgery, radiotherapy, chemotherapy, immunotherapy, and targeted therapies.[30]

An effective treatment for pleural EHE has not yet been established. For patients with local pleural involvement, complete surgical resection is the first choice of treatment, with a recurrence rate of 10% to 20%. Lesions in the lung, chest wall, or diaphragm are surgical contraindications.[15,19]Chemotherapy may be a treatment option, however, there are currently no known effective or recommended chemotherapy regimens for this disease.[12]

Suster et al. reported that after surgical excision as a single treatment, 7 patients among 9 were asymptomatic after a mean follow-up of 8 years; there was 1 recurrence, and 1 death of unknown origin.[23]

Deyrup et al. categorized their patients into low-risk and high-risk (tumor with >3 mitoses/50 HPFs or with size >3 cm) groups and reported 5-year disease-specific survival rates of 81% and 59%, respectively, and metastatic rates of 15% and 32%, respectively.[22]

The EHE heterogeneity is evident in the presented cases. Cases 1 and 2 report pulmonary EHE, case 3 appears to be a pleural EHE, and an anterior mediastinal EHE is reported in case 4. In this small series, 3 patients are male and 1 female, with ages ranging from 54 to 75 years, above the median age of diagnosis reported in literature.

In case 1, we describe a mass on the left lower lobe with invasion of the diaphragm, spleen and enlarged local lymph nodes. The presentation symptoms were anemia, asthenia, diffuse abdominal pain and significant weight loss. In case 2, the patient presented with right pleuritic chest pain and productive hemoptoic cough, and the pulmonary mass was present on the right hilar region, with extension to the mediastinum, circumscribing the right pulmonary artery, main and intermediate bronchi, superior vena cava, and contacting the ascending aorta and left auricle. Moreover, it was diagnosed together with subpleural nodules in the right upper lobe, and adrenal, hepatic and latero-cervical ganglion metastases. According to the literature, most patients with EHE are asymptomatic, however, these symptoms have also been reported.

In case 1, pathology analysis revealed nests of endothelial cells with clear cytoplasm, and, in case 2, proliferation of spindle and polygonal cells, with cytoplasmic vacuole, which are EHE cytologic characteristic. The immunohistochemical analysis of these two cases revealed, in case 1, positivity for Factor VIII and Vimentin, and, in case 2, expression of Factor VIII, CD31 and CD34, which, as described in the literature, point towards the suspected diagnosis.

In case 3, the patient presented with pleuritic thoracic pain, extensive pleural effusion, and pleural nodular thickening, which is in accordance with the literature. On

the other hand, this patient had no history of asbestos or radiation exposure. Pathology reported cell proliferation with no defined cytoplasmic delimitation and nuclear atypia in hyaline matrix, which, together with the expression of CD31, favors the diagnosis of EHE. A similar case of diffuse thickening of the pleura with pleural effusion and compression atelectasis in a pulmonary lobe was reported by Fan et al., with a similar immunohistochemistry analysis (positive for CD31 and negative for CD34 and factor VIII).[12]

In case 4, the presentation symptoms were chest pain and coughing, which is in line with reported literature. Some studies report tumor sites of anterior mediastinal EHE, however,in our case, it was not possible to determine the specific origin of the tumor. Pathology analysis revealed, once again, cells with marked nuclear atypia and cytoplasmic vacuole. Furthermore, neoplastic cells expressed Factor VIII and CD31, together with focal smooth muscle markers, concurring for the diagnosis of EHE.

Regarding treatment, in contrast to the data presented by Amin et al.[9]in their review of 93 patients with pulmonary EHE, where tumor resection followed by adjuvant therapy was the most common treatment undertaken, in the presented cases 1 and 2, tumor resection was not performed and both patients underwent medical treatment after the diagnosis of pulmonary EHE. The patients died after a follow-up of 6 months and 2.5 months, respectively, which may be explained by the advanced stage of the disease at the time of diagnosis.

Even though an effective treatment for pleural EHE has not yet been established, complete surgical resection is the first choice of treatment for patients with local pleural involvement. However, in case 3, the patient had an extensive pleural effusion, pleural leaflets and areas of thickening and nodular aspect, therefore the treatment of choice was lung decortication.

In the presented case 4, the patient died after 48 months of follow-up. Considering the block excision was performed with free margins, we may hypothesize about the tumor aggressiveness or the effectiveness of the chosen chemotherapy agent to justify the progression of the disease. If our patient was considered "high-risk" by the Deyrup et al. criteria (tumor with >3 mitoses/50 HPFs or with size >3 cm), it would be in accordance with the literature. Unfortunately, mitoses rate was not accessed but tumor size makes the patient fall in the "high-risk" category.[22]

A common feature in these 3 presented cases is the presence of regional enlarged lymph nodes at presentation, a poor prognostic factor.[9]

Although outside the scope of this work, which did not encompass molecular characterization, it is important to note that molecular characterization has identified a gene fusion of WWTR1 (WW domain-containing transcription regulator 1) on 3q25.1 with CAMTA1 (calmodulin-binding transcription activator 1) on 1p36.23, leading to WWTR1-CAMTA1 fusion protein, which has been reported to differentiate EHE from its morphologic mimics such as epithelioid hemangioma and epithelioid angiosarcoma.[27]A small subset of EHE demonstrates a YAP1 (Yes associated protein 1)-TFE3 (transcription factor E3) fusion gene leading to overexpression of TFE3.[28] A recent series of 18 cases of EHE demonstrated that these rearrangements can coexist, and that TFE3 positive compared with TFE3 negative cases, demonstrated larger tumoral masses, increase in intra-tumoral well-formed vessels and increased high grade nuclear atypia and hypercellularity.[29]

CONCLUSIONS

EHE keeps being a rare vascular tumor, with indolent clinical activity but with metastatic potential and, sometimes, aggressive clinical behavior. The reported 4 cases reveal the heterogeneous clinical presentation contributing to the difficult differentiation from other vascular tumors.

In the 2 reported cases of pulmonary EHE, the patient's survival was inferior to that reported in literature, while in the pleural EHE case, the disease-free survival reached the higher end of the mean survival in literature.

The presented mediastinal EHE may be considered "high risk" and therefore its survival is in accordance with the literature.

Treatment can range from watchful waiting to surgical resection in asymptomatic or localized disease, while metastatic disease should be treated with systemic therapies.

Increasing awareness of clinical features, diagnosis, and treatment options for EHE is important to increase early diagnostic rate for adequate treatment and prognosis improvement.

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