CASE REPORT

Pleural epithelioid hemangioendothelioma*

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Epithelioid hemangioendothelioma (EHE), a very uncommon pleural tumor, was diagnosed in a 61-year-old man who had suffered work-related exposure to asbestos. The patient complained of chest pain and weight loss and was diagnosed with pleural effusion, in which there was a predominance of lymphocytes but no malignant cells. Pleural needle biopsy disclosed only a non-specific inflammatory process, with areas of myxoid tissue. Video thoracoscopy revealed diffuse nodules in the parietal and visceral pleura. The nodule biopsy revealed a mesenchymal neoplasm and focal areas similar to those seen in the first biopsy. The immunohistochemical study showed the presence of the vascular markers CD 31, CD 34 and VIII factor, characteristic of tumors of vascular origin. The tumor was not responsive to cisplatin or etoposide, and the patient died 3 months after being diagnosed.

Key words: **Hemangioendothelioma, epithelioid. Pleural neoplasm. Asbestos. Pleural effusion. Mesothelioma.**

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Abbreviations used in this paper:

EHE – Epithelioid hemangioendothelioma

CEA – Carcinoembryonic antigen

CA – Cancer antigen

PSA – Prostate-specific antigen

INTRODUCTION

Pleural effusion is a condition commonly seen by pulmonologists, and its appearance is frequently due to lung disease or to diseases in other organs. However, it is uncommon for pleural disease to be the primary cause of such effusion. Heart failure, metastatic carcinoma, tuberculosis, pneumonia, pulmonary embolism/infarction are responsible for 80% of cases. There are more than 50 causes that are, collectively, responsible for approximately 10% of cases. These include some very rare diseases such as ovarian hyperstimulation syndrome, cavity-based AIDS-related lymphoma, and hypereosinophilic syndrome. The remaining 10% of cases are of unknown etiology.

Clinical, radiological, and laboratory test results are used to determine the etiology of the disease. Generally speaking, identification of the cause is not difficult. Occasionally, special methods, such as the characterization of the exact nature of a neoplasia within the pleural space, must be used in order to define the etiology more precisely.

Most of these neoplasias are metastatic. Therefore, primary pleural tumors, such as fibrous tumors of the pleura and mesothelioma, rarely occur.

Epithelioid hemangioendothelioma (EHE) is a rare malignant tumor of vascular origin (epithelial/endothelial cells) that may occur in soft tissues, lungs, heart, liver, bones or (rarely) in the thyroid or pleura.[1] Less than 20 cases of pleural EHE have been reported.

The objective of this report is to present the case of a 61-year-old man with a history of exposure to asbestos who was diagnosed with pleural EHE.

CASE REPORT

We report the case of a 61-year-old caucasian male. He was originally from Osasco, São Paulo (SP) and was living in Carapicuíba (SP). He was a retired assistant TV technician and carpenter. His last job, which he held for 10 years, consisted of frequent scraping of amianthus tiles. It had been an additional 10 years since he was last been exposed to this substance.

The patient reported severe, progressive chest pain on his left side. He had had that pain, which worsened with movement or palpation, for a month. Concomitantly, he had lost 4 kg. The patient reported having *diabetes mellitus,* which he controlled through diet, and systemic arterial hypertension, controlled with captopril and chlorthalidone. He used to smoke (80 pack years) and had quit smoking 2 years prior.

The patient presented with a good general condition in the physical examination, with normal respiration and a blood pressure of 160 x 110 mmHg. He had pain when the area between the fifth and sixth intercostal spaces was compressed. Decreased vesicular breath sounds were detected in the lower third of the left hemithorax. The liver was palpable to 4 cm from right costal margin, with a thin and pain-free border. There was no digital clubbing or peripheral adenoid enlargement. Digital rectal examination revealed a slightly enlarged prostate, with smooth borders. No other abnormalities were detected during the physical examination.

Lab tests were performed. The complete blood count included hematocrit of 39%; hemoglobin of 14.2g/dL; leukocyte count of 8510/μL (segmented: 65%; lymphocytes: 28%; monocytes: 5.4%; eosinophils: 0%; basophils: 1.1%); platelet count: of 262,000/μL; blood glucose of 220 mg/dL. The total protein was 7.5g/dL (albumin: 4.3g/dL). Test results for sodium, potassium, urea, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase were normal. Sputum culture for acid-fast bacilli was negative. Serology tests for hepatitis B and C and for the HIV antibody were also negative. Test results for the tumor markers carcinoembryonic antigen (CEA), alpha-fetoprotein and carbohydrate antigen 19-9 were normal, whereas cancer antigen (CA) 125 was at 153 U/mL (normal limit, 33U/mL). Prostate-specific antigen (PSA) was at 11 ng/mL (normal limit, 4 ng/mL). Chest radiography revealed small pleural effusion on the left side. Chest tomography showed, in addition to the left pleural effusion, pleural thickening and a small pleural nodule, also on the left side (Figure 1). Cancerous cells were not found in the prostate biopsy. Abdominal ultrasound only revealed that the liver had enlarged proportions. An echocardiogram showed moderate concentric left ventricular hypertrophy. The bronchoscopy results were normal. A computed tomography (CT) scan of the head indicated alterations consistent with nonspecific microangiopathy. Radiocontrast images of the bone were normal, and the bone biopsy showed no cancerous cells.

A punch biopsy was performed in the pleura and approximately 500 mL of fluid was collected. The analysis revealed a pH of 7.13, glucose of 156 mg/dL, total protein of 5.6 g/dL (albumen: 3.3g/dL), HDL of 1155 μ/L, adenosine deaminase of 19.3 U/L and CEA of 1.1 μ/L. The cytological examination revealed 1,106 erythrocytes and 44,000 cells/mm^3 (64% lymphocytes; 20% neutrophils; 16% histiocytes). No cancerous cells were found. Pleural biopsy indicated chronic pleuritis, with mesothelial hyperplasia and proliferation of young fibroblasts, and areas with myxoid aspects.

Since a definite diagnosis was not made, video thoracoscopy was performed and various hardened pleural nodules were identified, especially in the parietal pleura. Frozen biopsy of the nodules indicated malignancy. Subsequently, the usual procedures for talc pleurodesis were performed.

The anatomopathological examination showed that the neoplasm formed nodular arrays and that there was a proliferation of cells with minimal pleomorphism and elongated nuclei amid vascularized myxoid tissue (Figure 2), which appeared similar to the focal areas seen in the first biopsy. Due to the immunohistochemical profile, a diagnosis of mesenchymal neoplasm was made. Further immunohistochemical investigation detected the presence of the vascular markers CD-31, CD-34 and factor VIII (figure 3), which indicated that the neoplasia was vascular in origin, allowing us to arrive at a diagnosis of pleural EHE.

The chest tomography performed 3 months after the beginning of the investigation (Figure 4) clearly showed the extent of the pleural effusion and of the lesion, which had spread throughout the entire left hemithorax.

The patient was treated with cisplatin (100 mg) and etoposide (300 mg) for 3 consecutive days. There was no response and the patient died 3 months after the diagnosis.

DISCUSSION

The patient presented with pleural effusion. Clinical examinations and laboratory tests showed no evidence of lung disease or generalized disease, including neoplasia. Since it is a routine procedure in such cases, a parietal punch biopsy of the pleura was performed. The biochemical analysis showed an exudate, but cytological investigation and the biopsy were inconclusive. Considering the age of the patient and the appearance of the exudate, there was a high probability of pleural neoplasm (a normal concentration of CEA does not rule out the disease)[2].

When we relate the chest pain and previous exposure to asbestos to the tomographic results, the presumptive diagnosis of mesothelioma was understandable, although the latency period is typically longer than 15 years.[3] Clinical exams, laboratory tests and radiographs provided no evidence for other possible etiologies (such as tuberculosis or pulmonary embolism/infarction) of the pleural effusion. The repetition of the pleural biopsy (by the needle rather the punch method) and a second cytological examination of the pleural liquid could have led to the definite diagnosis but, if negative, would not have ruled out the possibility of mesothelioma.

Thoracoscopy was chosen because of its high diagnostic yield and low morbidity. Macroscopic findings suggested metastatic malignancy in the visceral and parietal pleura. Frozen biopsy confirmed the malignancy of the lesions, which were classified as EHE of the pleura after the positive results for vascular markers in the anatomopathological and immunohistochemical examinations. The standard procedures for pleurodesis were performed, since they are routinely used in such cases.

The most interesting aspects of this case are the relationship between the pleural tumor and pulmonary symptoms, the differential diagnostic between EHE and mesothelioma, and the previous exposure to asbestos.

Initially, EHE initially received various denominations, such as sclerotic interstitial vascular sarcoma, sclerotic intravascular bronchioloalveolar tumor, sclerotic angiogenic tumor, sclerotic endothelial tumor, and pulmonary deciduosis [5]. Daiel and Liebow introduced the name intravascular bronchioloalveolar tumor because they interpreted it as a particular manifestation of a bronchioloalveolar tumor with vascular involvement. Its vascular origin was only later recognized.[6]

This is a rare tumor and, although it may affect various organs, the primary site is more often in the lungs. Two review studies established the most significant aspects of the disease. The first was carried out in the United States and involved 20 cases submitted to anatomopathological examination,[6] and the second reviewed 21 cases studied in various countries in Asia.[4]

These studies provided evidence of a higher incidence of the disease in women. It generally affects patients younger than 40 years of age, and is rare in patients older than 50. The tumor is usually detected in routine radiographs, although symptoms such as dyspnea, weight loss, hemoptysis, peripheral adenopathies and digital clubbing may be present. Only two patients, one of who worked with roofing materials, were found to have a history of environmental exposure to potentially hazardous substances. Chest radiographs revealed disseminated bilateral pulmonary nodules, mainly in the lower lobes. This distribution and simultaneity of bilateral lesions suggest that the disease might be hypothetically related to inhalation. Some important anatomopathological aspects are the precise delimitation of the nodules, the extension through the pores of Kohn, calcification, chondrification or even ossification. The evolution of the disease is variable. The patient may be cured (which can occur spontaneously, through surgery or through chemotherapy) or there may be a gradual (or, in rare cases, acute) worsening of the disease. In one case, estrogen and progesterone receptors were found, which might explain why most patients are women. This knowledge may have some therapeutic use in the future.[7] In another study, a patient with pericardial effusion presented high serum levels of CA-125, as did our patient, although that patient was not submitted to puncture.[8] These findings suggest that tumor markers may even be present.

Tumors that are exclusively pleural are very rare. However, extensive pleural involvement, with pulmonary entrapment and fissure infiltration, has been observed in radiographs and autopsies of cases which originated in the lungs.[4,6,9] Pleural involvement is very similar to mesothelioma, and macroscopic distinction is often impossible. Exclusive pleural involvement is usually unilateral but can be bilateral and even extend to the pericardium or peritoneum.[7]

Pleural tumors usually occur in men over 60. The main symptoms are chest pain, dyspnea, and weight loss. Other symptoms are cough, hemoptysis, fever, asthenia, fatigue, and anorexia. The most common radiological aspects are pleural effusion, pleural thickening, nodules, and a reduced volume on the affected side.[1,4] Chest tomography can reveal pleural effusion (usually locular), nodular or smooth pleural thickening, pleural or pulmonary masses or nodules, or diffuse mediastinal lymph node enlargement (as was seen in our case). The diaphragm, chest wall, mediastinum or pericardium may also be invaded.

Diagnosis is generally made through surgical biopsy, video thoracoscopy or pleural biopsy. The tumor forms a carapace around the lung that may extend to the pulmonary parenchyma along interlobular fissures and septa. Firm pleural nodules may also be also present.[1] Under electron microscopy, polygonal and oval cells can be seen, along with cytoplasmic factors and varying quantities of organelles, which conform to the characteristics of endothelial differentiation, including pinocytosis vesicles in the periphery and Weibel-Palade bodies of human endothelial cells.[1,9]

Our patient presented with clinical and radiological features, and his evolution and prior exposure to asbestos made his case similar to those described above.

Attanos et al.[10] reported 3 cases of EHE which were sent to them for legal analysis under medical law. In all 3 cases, the initial diagnosis was mesothelioma. Exposure to asbestos ranged from 18 months to 5 years and latency period from 17 to 42 years. The authors compared the findings in the 3 EHE patients to 92 archived cases of mesothelioma and highlighted as a fundamental difference the absence of CD-31, CD-34, and factor VIII markers in the cases of mesothelioma. This finding allows for definitive differential diagnosis between these tumors and should be routinely used when mesothelioma is suspected. On the other hand, the absence of these markers in mesothelioma invalidates the hypothesis that those tumors could present with vascular differentiation. The authors also reported abnormally high concentrations of crocidolite found in the histological examination of the pleura of one patient. Its absence in the other patients was explained by the short period in which the mineral remains in the form of chrysotile, which was the type of mineral to which the patients had been exposed. Sex, age, and clinical and radiological findings were very similar to those of our patient. However, in those patients, the exposure to asbestos was more prolonged and the latency period was much shorter. Since it was impossible to quantify exposure to asbestos in our patient, it is acceptable to believe that the intensity and the duration of exposure are very important, just as they are in cases of silicosis.

Relationships between pleural and pulmonary tumors are hard to establish. On the one hand, the evolution of various pulmonary tumors to pleural forms suggests that the pleural involvement is just an uncommon manifestation of the same disease. On the other hand, the general evolution and the clinical profile are quite different.

Surgical resection is considered the treatment of choice when possible. Chemotherapy and radiotherapy are not usually beneficial.[1,4] The prognosis is poor, with a median survival of 10 months. Indications of poor prognosis include initial symptoms such as lymphangitis, liver metastasis, and peripheral lymphadenopathy.[1,6,9] However, therapeutic success has been reported. A patient with multiple involvement of serous membranes presented complete remission after chemotherapy (6 rounds with carboplatin and etoposide).[7] Partial remission was observed in a patient with EHE involving the skin, bones, lungs and liver after a one-year course of alpha-interferon.[11]

Our patient did not benefit from therapy, and there was a rapid progression of the lesions. The patient died 3 months later. An autopsy was not performed.

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Figure 1 – Pleural effusion and a single pleural nodule, without mediastinal pleura involvement

Figure 2 – Fusocellular neoplasm (EHE) with nodular arrays and myxoid-like areas (left; x40) and with some atypical cells and proliferation of small blood vessels (right; 100x)

Figure 3 – Immunohistochemical markers CD 34 (x100) and Factor VIII (x100), confirming the vascular histogenesis of the neoplasia

Figure 4 – Irregular pleural masses and extensive pleural thickening with mediastinal pleura involvement, which caused reduced volume in the left hemithorax