Caso Clínico
Clinical Case

Sandra Saleiro[1]
Miguel Barbosa[2]
Conceição Souto Moura[3]
João Almeida[4]
Silva Ferreira[5]

Hemangioendotelioma epitelióide – Um tumor pulmonar raro

Epithelioid hemangioendothelioma – A rare pulmonary tumor

Recebido para publicação/*received for publication*: 07.12.14
Aceite para publicação/*accepted for publication*: 08.01.30

Resumo

Os autores descrevem um caso de uma neoplasia pulmonar rara – hemangioendotelioma epitelióide – numa doente do sexo feminino, de 39 anos, assintomática até Dezembro de 2003, altura em que apresentou toracalgia direita de características pleuríticas. A doente era portadora de uma radiografia torácica antiga, efectuada há 13 anos, que revelava múltiplos pequenos nódulos pulmonares bilaterais, atribuídos a sequelas de tuberculose pulmonar. O diagnóstico histológico definitivo foi efectuado através de biópsia pulmonar por toracotomia. Dado

Abstract

The authors report a case of a rare pulmonary neoplasm – epithelioid hemangioendothelioma, in a 39 year-old woman, asymptomatic until December 2003, when she developed pleuritic and right-sided chest pain. The patient presented a previous chest radiograph, performed 13 years before, which showed multiple small bilateral pulmonary nodules attributed to tuberculous sequelae. The definitive histological diagnosis was made by lung biopsy through thoracotomy. The patient developed a clinical and

[1] Interna Complementar de Pneumologia
[2] Interno Complementar de Oncologia Médica
[3] Assistente Hospitalar de Anatomia Patológica
[4] Chefe de Serviço de Pneumologia
[5] Chefe de Serviço de Medicina Interna

Serviço de Pneumologia
Director de Serviço: Professor Doutor Venceslau Hespanhol

Serviço de Anatomia Patológica
Directora de Serviço: Professora Doutora Fátima Carneiro

Serviço de Oncologia Médica
Director de Serviço: Dra. Margarida Damasceno

Hospital de São João, Faculdade de Medicina da Universidade do Porto – Porto

Correspondência:
Sandra Saleiro
Serviço de Pneumologia - Hospital de São João
Alameda Prof. Hernâni Monteiro
4202-451 – Porto – Portugal
E-mail: sandrasaleiro@portugalmail.pt

a doente ter apresentado agravamento clínico e imagiológico foi iniciada terapêutica com interferão α-2a. Apesar da estabilidade imagiológica das lesões pulmonares, a doente manteve-se sintomática e faleceu nove meses depois do diagnóstico ter sido estabelecido.
Os autores realçam a raridade deste tipo de neoplasia pulmonar e discutem a sua apresentação clínica, características histológicas, tratamento e prognóstico.

Rev Port Pneumol 2008; XIV (3): 421-425

Palavras-chave: Hemangioendotelioma epitelióide, pulmão, interferão α.

imagiological worsening and then therapy with interferon α-2a was started. Even with imagiological stability of pulmonary lesions the patient remained symptomatic and died nine months after the diagnosis had been established.
The authors emphasise the rarity of this type of pulmonary neoplasm and discuss its clinical presentation, histological features, treatment and prognosis.

Rev Port Pneumol 2008; XIV (3): 421-425

Key-words: Epithelioid hemangioendothelioma, lung, interferon α.

Introduction

Epithelioid hemangioendothelioma (EHE) is a rare pulmonary neoplasm, which was originally described in 1975 as intravascular bronchioloalveolar tumor (IVBAT). It is considered a low-grade sclerosing angiosarcoma, can be multifocal as multiorganic and has metastic potential.
Clinical course is uncertain: sometimes there is slow growing of the lesions, but a rapid course can also occur with death within few months after the diagnosis.

Case report

A 39-year-old nonsmoker woman, with a good global health status, developed pleuritic, right-sided postero-inferior chest pain in December 2003, with no other complaints. She took anti-inflammatory medication with no clinical improvement. The patient had no history of occupational or ambiental exposure to dusts, pets or birds, nor exposure to tuberculosis or recent travel outside the country. Her past medical history was unremarkable and she only took a contraceptive regularly. On physical examination, she had no cyanosis, clubbing, nor peripherical lymphadenopathy. Respiratory sounds were diminished at the right pulmonary base and inspiratory crackles were audible diffusely. A previous chest radiograph (1991) showed multiple bilateral pulmonary nodules, attributed to tuberculous sequelae, because of the high incidence of tuberculosis in Portugal, although she had no known history of this disease. Actual chest radiograph showed increased number and size of the nodules and right pleural effusion.
Pulmonary function tests showed a restrictive pattern – vital capacity: 2.13 L (59% of predicted); total lung capacity: 3.63 L (68% of predicted); residual volume: 1.50 L (90% of predicted); forced expiratory volume in one second (FEV1): 1.86 L (61% of predicted); forced vital capacity (FVC): 2.13 L (60% of predicted); FEV1/FVC: 87% – with decreased diffusion capacity of the

lung for carbon monoxide (16.4 mL/mmHg/min; 60% of predicted). Full blood count, urea and electrolytes, liver function tests and calcium level were all normal. The erythrocyte sedimentation rate was 73 mm in the first hour and reactive C protein was 2.2 mg/dl (normal value: < 0,8 mg/dl). Autoantibodies screen, including rheumatoid factor and antinuclear factor were negative. Tumor markers were normal, namely, carcino-embryonic antigen (CEA) – 1,7 ηg/ml (reference value: 0-3 ηg/ml) and cancer antigen 125 (CA 125) – 14 U/ml (reference value: 0-35 U/ml).

Thoracic computed tomography (CT) scan confirmed multiple bilateral pulmonary nodules, approximately 1 cm or less in diameter, ill-defined, non-calcified, with low-density, scattered through the lungs, predominantly in the peripherical region and right-sided pleural effusion. There were also subpleural and peripherical linear opacities, suggesting interstitial component; neither hilar nor mediastinal lymphadenopathy were seen (Fig. 1).

Right-sided thoracentesis revealed an exudate, with normal ADA (33 U/L), reactive mesothelial cells, some neutrophils and eosinophils and no malignant cells. Fluid culture was negative. No endobronchial lesions were found at fiberoptic bronchoscopy and transbronchial lung biopsy revealed only inflammatory infiltrate in the interstitium. The bronchoalveolar lavage had a large number of macrophages (99%) and was negative for malignant cells and so was the microbiological analysis for *Mycobacterium tuberculosis* and fungi.

The patient underwent a diagnostic thoracotomy in order to obtain a definitive histological diagnosis.

Fig. 1 – Thoracic computed tomography scan: presence of multiple bilateral pulmonary nodules, approximately 1 cm or less in diameter, ill-defined, non-calcified, with low-density, scattered throughout the lungs, predominantly in the peripherical region, and a right-sided pleural effusion; no hilar or mediastinal lymphadenopathy were seen.

Histologically the nodules had central fibrimixoid stroma, sometimes with a chondroid phenotype. The periphery of the nodules was more cellular with moderate nuclear atypia and low mitotic index. The cells had prominent cytoplasmatic vacuoles or intracytoplasmatic lumina. Multifocal pleural involvement was documented and foci of vasculitis lesions were seen (Figs. 2 and 3). Immunohistochemical stains revealed positivity in the tumor cells for endothelial markers (CD31 and CD34) and negativity for S100 and CAM5.2, supporting the diagnosis of EHE (Fig. 4).

There were no complications detected in post-operative period, and discharge happenend 3 days after thoracotomy. The patient maintained pleuritic right-sided chest pain which was relieved by non-opiate central analgesics.

Seven months after the onset of pulmonary symptoms she presented clinical deteriora-

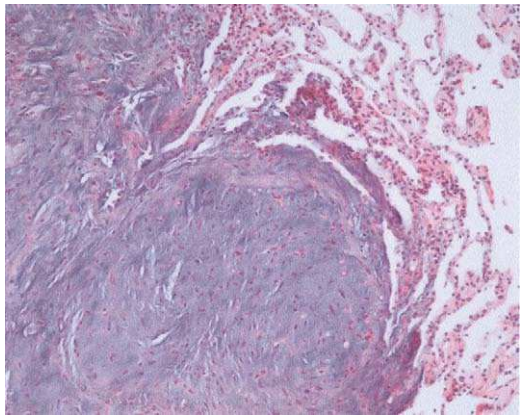

Fig. 2 – Tumor nodules showing increased cellularity and fibrimixoid stroma

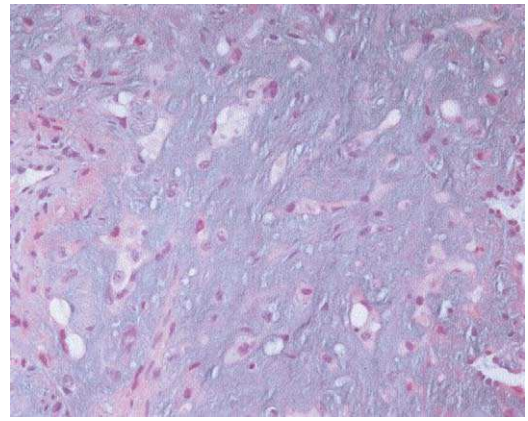

Fig. 3 – The cells have prominent cytoplasmatic vacuoles or intracytoplasmatic lumina

tion with increasing chest pain, requiring opiate analgesics and intercostal neural block. A simultaneous imagiological worsening was documented, with right-sided pleural effusion of greater volume. So therapy with interferon α-2a, 3 million units three times weekly was started. During four months under this treatment and with analgesic therapeutic, the patient remained clinically stable. Nevertheless, besides all these therapeutic strategies, there was clinical worsening with uncontrolled chest pain, while thoracic CT scan did not show disease's progression. Neither distant metastasis nor respiratory failure were documented. Oral steroid (prednisolone 20 mg, per day) was empirically added, but the patient's condition deteriorated further and occured sudden death at home, approximately thirteen months after the onset of symptoms. Since the patient had a diagnosis of malignancy, which was under these circumstances the possible cause of death, autopsy was not requested and the exact cause of death was not determined.

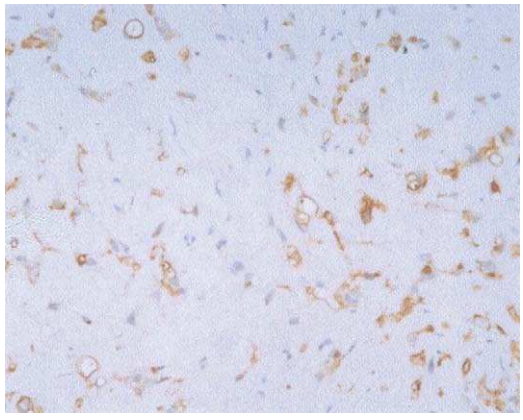

Fig. 4 – CD 34 stain: tumor cells stain positively

Discussion

EHE is a low-to-intermediate grade vascular tumor[1]. Involvement of the lungs is rare with only 50 cases described in the literature to the best of our knowledge[2].

Most of patients are females, about 40% of them under 30 years.

The most common presentation is bilateral multiple nodular opacities on chest radiograph, up to 2 cm in diameter but most are less than 1 cm. In some cases there is exten-

sive calcification of the nodules and variable interstitial involvement. Patients are usually asymptomatic or have minor symptoms at the time of diagnosis. Chest pain, cough and sputum are common non-specific symptoms. About 10% of patients have pleural effusions.

The tumour nodules are round to oval shaped with a typically hypocellular core with coagulative necrosis, hyalinization and calcification while the periphery is hypercellular. The cytoplasm is abundant and intracellular vacuoles are common, sometimes creating a signet-ring appearance, which suggests an attempt to form unicellular vascular channels. The disease may invade the wall and lumen of small pulmonary arteries, veins and lymphatics. The immunohistochemical study of our patient showed immunoreactivity of the neoplastic cells for CD31 and CD34, confirming its vascular nature, as currently described.

Diagnosis is usually made by open lung biopsy although there is one case in the literature in which transbronchial lung biopsy was sufficient to make the diagnosis[2].

Because of the small number of patients with confirmed epithelioid hemangioendothelioma, it is difficult to establish prognostic factors. The manifestation of respiratory symptoms at presentation, liver involvement, peripheral lymphadenopathy, spindle tumour cells at histology, fibrous pleuritis with extrapleural proliferation and pleural effusion on chest radiograph are associated with an unfavourable prognosis[3].

Because of its rarity, there is no standard treatment. Surgery remains the preferable choice whenever there is a solitary nodule or a limited number of lesions. Three spontaneous partial regressions and a complete response to carboplatin plus etoposide chemotherapy have been described[3,4].

The use of interferonα is a reliable possibility as it can induce partial remission[5]. EHE has a vascular origin with endothelial cell migration and proliferation induced by the fibroblast growth factor (FGF). Interferon α-2a is a potent angiogenesis inhibitor and it is believed that acts by blocking the action of FGF. However, the role of immunotherapy is not established[2]. The exact role of steroid in the tumor's pathogenesis is not known.

Bibliography

1. Díaz R, Segura Á, Calderero V *et al.* Central nervous system metastases of a pulmonary epithelioid hemangioendothelioma. Eur Respir J 2004; 23: 483-6.

2. Cronin P, Arenberg D. Pulmonary epithelioid hemangioendothelioma – an unusual case and a review of the literature. Chest 2004; 125: 789-92.

3. Kitaichi M, Nagai S, Nishimura K *et al.* Pulmonary epithelioid hemangioendothelioma in 21 patients, including three with partial spontaneous regression. Eur Respir J 1998; 12: 89-96.

4. Pinet C, Magnan A, Garbe L *et al.* Aggressive form of pleural epithelioid hemangioendothelioma: complete response after chemotherapy. Eur Respir J 1999; 14(1): 237-8.

5. Kumar Pankaj, Judson I, Nicholson AG *et al.* Mediastinal hemangioma: successful treatment by alpha–2a interferon and postchemotherapy resection. J Thorac Cardiovasc Surg 2002; 124: 404-6.