CASE REPORTS

Persistent Hemoptysis Secondary to Extensive Epithelioid Angiosarcoma

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Pulmonary angiosarcoma is an unusual cause of diffuse pulmonary hemorrhage. Angiosarcomas are rare malignant vascular tumors accounting for 1% to 2% of all sarcomas. Angiosarcomas have been detected in nearly all organs, but lung involvement is unusual, accounting for less than 7%. The literature describes approximately 10 isolated cases of primary pulmonary angiosarcoma as opposed to the more common metastatic type. Given that primary and metastatic types are clinicopathologically similar, the presence of a distant primary sarcoma must be ruled out before a diagnosis of primary pulmonary angiosarcoma can be made. A pathological diagnosis requires a finding of polygonal or oval cells with atypical irregular nuclei and vascular spaces lined with such cells surrounded by hemorrhagic phenomena. Immunohistochemical analysis is positive for specific endothelial cell markers such as CD31 and factor VIII, and coexpression of keratin is a frequent finding.

Key words: *Angioendotheliomatosis. Epithelioid angiosarcoma. Lung sarcoma. Hemoptysis.*

Hemoptisis de repetición secundarias a un angiosarcoma epitelioide generalizado

Una causa excepcional de hemorragia pulmonar difusa es la presencia de un angiosarcoma pulmonar. Éste es un tumor vascular maligno que representa del 1-2% del total de sarcomas. Los angiosarcomas se han descrito en casi todos los órganos, siendo la afección pulmonar rara, de alrededor del 7%. En la bibliografía se describen aproximadamente 10 casos aislados de tumores primarios y es más frecuente la afección metastásica pulmonar. Desde el punto de vista clinicopatológico son superponibles las formas primarias y las metastásicas, por lo cual, ante la presencia de un angiosarcoma pulmonar primario, hay que descartar la existencia de un posible tumor primario a distancia. El diagnóstico anatomopatológico se caracteriza por células poligonales u ovoides de núcleos atípicos irregulares, y espacios vasculares tapizados por dichas células tumorales con fenómenos hemorrágicos alrededor. Las técnicas de inmunohistoquímica que demuestran la naturaleza endotelial del tumor son la positividad del CD-31 y factor antiproteína VIII, así como la positividad de la queratina, coexpresión frecuente del angiosarcoma epitelioide.

Palabras clave: *Hemangioendotelioma. Sarcomas pulmonares. Hemoptisis.*

Introduction

Hemoptysis is defined as the presence of blood in sputum. When it presents, the source of bleeding must be located and differential diagnoses taken into consideration. Hemoptysis is usually secondary to infectious disease, neoplasms, cardiovascular disease, immunodeficiency, trauma, or pharmaceuticals, and other causes appear sporadically.

We report an exceptional case of persistent hemoptysis secondary to an extensive malignant vascular tumor confirmed by autopsy. In the literature we have found only 10 cases of primary pulmonary angiosarcoma,[1-7] the most frequent manifestation being pulmonary metastasis,[8-10] and only a single case of extensive angiosarcoma.[11]

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Case Description

A 68-year-old woman who denied any use of tobacco, alcohol, or street drugs, who had no medical or surgical history of relevance but who was allergic to metamizol was admitted to our unit in February 2001 describing a 2-month history of asthenia, dyspnea with moderate exercise, and slight hemoptysis daily. On examination, pale skin and mucosa were noted and bilateral basal crackles were heard. Blood cell counts showed normochromic and normocytic anemia with hemoglobin level, 9 g/dL; hematocrit, 25%; mean corpuscular volume, 84 fL; mean corpuscular hemoglobin, 28 pg; and erythrocyte sedimentation rate, 30 mm/h. Biochemical parameters were normal in blood and urine tests. Immunological tests were also normal. A chest x-ray showed a predominately basal heterogeneous alveolar pattern (Figure 1). A chest computed tomography scan revealed patchy images of alveolar infiltration, multiple bilateral diffuse pseudonodules, and focal splenic lesions of 1 cm, all of which was indicative of hemangioma (Figure 2). Bronchoscopy revealed red blood in both bronchial trees and reddened mucosa that bled easily but no visible points of active bleeding. Cytology and sputum

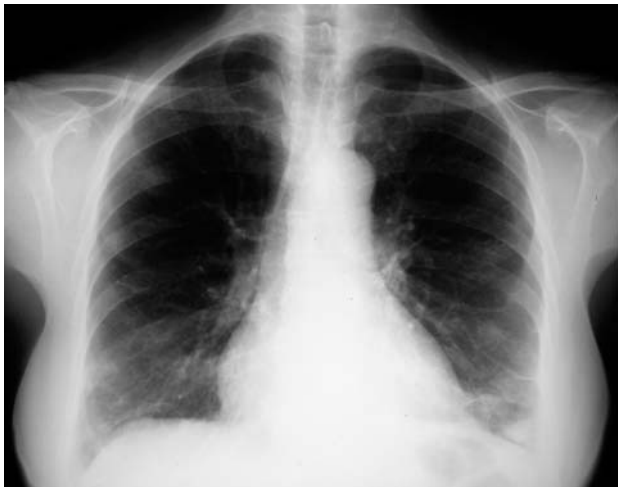

Figure 1. Chest x-ray: alveolointerstitial pattern.

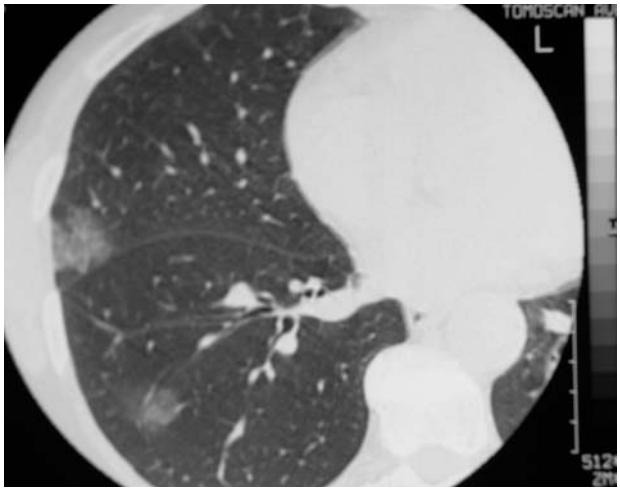

Figure 2. Chest computed tomography scan: bilateral patchy images and pseudonodules.

smear test of bronchial washings were negative. Bronchoalveolar washings showed 117 000 cells per mL with frequent siderophores, neutrophils 18%, lymphocytes 4% (endothelial markers: CD3, 23%; CD4, 8%; CD8, 8%), and histiocytes 78%. Lung function tests were normal. A pulmonary biopsy by thoracotomy found hemorrhagic microfoci in resolution and mesothelial hyperplasia with no presence of granuloma or indication of vasculitis. We interpreted the case as one of pulmonary hemorrhage, probably due to idiopathic pulmonary hemosiderosis. Corticosteroid treatment (methylprednisolone 1 mg/kg/d) was initiated.

The patient was readmitted 2 months later owing to slight hemoptysis that was persistent and daily. Evidence of wasting syndrome, with 4 kg loss in weight, was noted along with fever and severe asthenia. Admission tests showed anemia (hemoglobin, 6.5 g/dL), thrombocytosis (platelet count, 717 000/µl); and leukocytosis (white cell count, 13 900/µl). Analytic, radiologic, and bronchoscopic findings were similar to those of the previous admission. Tests for anemia and a bone marrow aspiration revealed nonspecific myelopathy and anemia secondary to a chronic process. While hospitalized the patient suffered digestive track bleeding with resulting bloody stools and hematemesis; gastroscopy revealed bleeding in the duodenal submucosa. Arteriography of the celiac trunk following radiopaque enema was performed and yielded no anomalous findings. The patient´s general state deteriorated, with episodes of hemoptysis, hematemesis, and regular bloody stools such that multiple blood transfusions were required. Suspecting polyarteritis nodosa microvasculitis with pulmonary and digestive involvement—despite repeatedly negative anticytoplasmic antibody tests—we initiated treatment with 1-gram bolus doses of methylprednisolone and 5 mg/kg of cyclophosphamide. Deterioration continued and the patient died. Autopsy led to a diagnosis of epithelioid angiosarcoma (malignant hemangioendothelioma) affecting the lungs, lymph nodes, liver, spleen, kidneys, and digestive tract. We found microscopic evidence of a high grade malignant infiltrating neoformation that formed anastomotic vascular channels lined with atypical anaplastic cells. This description was consistent with a diagnosis of angiosarcoma affecting mainly the lungs and lymph nodes, with focal involvement of the liver, spleen, kidneys, and submucosa of the digestive tract. Immunohistochemical analysis showed positivity for CD31, factor VIII, and keratin, demonstrating the endothelial nature of the tumor cells.

Discussion

Diffuse pulmonary hemorrhage is characterized by the clinical triad of hemoptysis, anemia, and diffuse radiologic infiltrations. The most common causes of such hemorrhaging are Goodpasture syndrome, angiitis (such as Wegener granulomatosis and microscopic polyangiitis), and various connective tissue diseases (such as systemic lupus erythematosus). Idiopathic pulmonary hemosiderosis is a rare cause but a candidate diagnosis if others are ruled out. Neoplastic disease, an exceptional diagnosis in this context, should also be considered in the differential diagnosis of diffuse alveolar hemorrhage.[8]

Diffuse pulmonary hemorrhage is rare as the presenting sign of angiosarcoma, which is itself a rare malignant vascular tumor accounting for only 1% to 2% of all sarcomas.[1] No consensus has been reached in the literature regarding the incidence of the disease in men and women. In the opinion of some authors the disease is more common in males,[8] but in a larger series (15 cases) no predilection for men or women was evident.[1] The disease affects a wide age range with a higher incidence among people 40 years of age and older.[1,8]

Angiosarcoma may occur in almost any organ but is found most often in the skin (33%) and deep soft tissues (24%). It also occurs in breasts (8%); liver (8%); bones (6%); spleen (4%); heart, large vessels, and the pericardium (3%); eye sockets (3%); the ear, nose, and throat (4%); and other organs, including the lungs (7%).[2]

Lung involvement is unusual: the literature describes approximately 10 isolated cases of such primary lung angiosarcomas.[1-7] Pulmonary metastatic involvement is more common.[8-10] Since primary and metastatic forms are pathologically similar,[2] however, the existence of a

possible distant primary tumor must be ruled out before primary pulmonary angiosarcoma is diagnosed.

Angiosarcoma presents clinically as hemoptysis, be it episodic or massive. Frequent symptoms are weight loss, cough, thoracic pain, and dyspnea. If pleural involvement exists, pneumothorax or pleural infiltration may be noted. Another form of presentation is diffuse pulmonary hemorrhage. As many as 20% of cases are asymptomatic and are found by chance at autopsy.[1,2,8]

Bilateral pulmonary nodules are observed on images in 70% of cases although the disease can also manifest as a single nodular lesion. Diffuse alveolar infiltration secondary to the alveolar hemorrhages may be noted.[1,8]

Pathologic diagnosis is characterized by polygonal or oval cells with atypical irregular nuclei and vascular spaces lined with such cells surrounded by hemorrhagic phenomena. Immunohistochemical findings that demonstrate the endothelial nature of the tumor are positivity for CD31, factor VII antibodies, and keratin, whose coexpression is frequent in epithelioid angiosarcoma.[1,2,8] These immunohistochemical findings were present in the case we report.

Since angiosarcoma is characteristically a metastasizing tumor, it is always described in the literature as simultaneously involving 2 to 3 organs. In many cases the primary focus cannot be identified.[1,8-10] Cardiopulmonary involvement is common. However, what is exceptional is a finding of diffuse involvement of lungs, digestive tract, spleen, liver, and kidney—as in the case we describe. We found only a single instance in the literature of another such case.[11]

In general, pulmonary angiosarcoma has a poor prognosis with a mean survival of 9 months.[1,2,8]

In summary, this report presents a case of angiosarcoma as a rare cause of hemoptysis. Even more unusual, the angiosarcoma was epithelioid and diffuse. We bring this case to the literature as an exceptional cause of persistent hemoptysis.

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