

Pulmonary Sclerosing Hemangioma in a Patient With Cowden Syndrome

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We describe the case of an 18-year-old female with Cowden syndrome in whom a simple x-ray detected a solitary pulmonary nodule that was identified as a sclerosing hemangioma. Pulmonary sclerosing hemangioma is an unusual lung neoplasm which typically presents as a solitary peripheral nodule in asymptomatic women. Although the histology of this entity is well defined, its origin and treatment is debated. One of the main diagnostic problems is to histologically differentiate a pulmonary sclerosing hemangioma from a papillary lung carcinoma.

Hemangioma esclerosante pulmonar en un paciente con síndrome de Cowden

Describimos el caso de una paciente de 18 años con síndrome de Cowden, en quien una radiografía simple objetivó un nódulo pulmonar solitario que resultó ser un hemangioma esclerosante. El hemangioma esclerosante de pulmón es una neoplasia pulmonar poco frecuente, que suele presentarse como un nódulo solitario periférico en mujeres asintomáticas. En la actualidad, aunque la histología del hemangioma esclerosante está bien definida, son objeto de discusión la histiogénesis de esta entidad y su tratamiento. Uno de los principales problemas diagnósticos es diferenciar histológicamente el hemangioma esclerosante del adenocarcinoma pulmonar con patrón papilar.

Key words: *Sclerosing hemangioma. Lung tumor. Cowden syndrome.*

Palabras clave: *Hemangioma esclerosante. Tumores de pulmón. Síndrome de Cowden.*

Introduction

Cowden syndrome is a rare disease with an autosomal dominant inheritance pattern that usually manifests as benign hamartomas—mainly colonic polyps. It is therefore classified as a form of colonic polyposis. It is associated with germline mutations in the *PTEN* gene, which lead to the development of both malignant and benign skin, thyroid, breast, and brain tumors.

Pulmonary sclerosing hemangioma is an unusual neoplasm that was first described by Liebow and Hubble¹ in 1983. Although its histology is well defined, its histogenesis and treatment are the subject of debate. Four histological patterns are recognized: papillary, solid, sclerotic, and haemorrhagic.²⁻⁴ One of the main diagnostic problems is to differentiate a pulmonary sclerosing hemangioma from a papillary lung carcinoma.⁵

The pathophysiology of the association between Cowden syndrome and sclerosing hemangioma is unclear; the literature describes cases of lung sclerosing hemangioma co-occurring with other polyposes, and this could indicate that sclerosing hemangioma is yet another of the malformations that might be present in Cowden syndrome.

Case Description

We report the case of an 18-year-old woman who was referred to our department with a solitary pulmonary nodule that had been detected by chance in a routine x-ray. The medical history included multiple nodular hyperplasia of the thyroids, high-flow venous vascular malformations in the distal third of the right thigh and back that had been removed surgically, and perirenal, retroauricular and supraclavicular lipomas that had also been treated surgically. She had also been diagnosed with an ovarian cyst and breast fibroadenomas. A simple chest x-ray performed as part of regular follow-up ordered by an endocrinologist revealed a solitary pulmonary nodule—approximately 2 cm in diameter—in the right upper lobe; the patient was consequently referred to the pneumology department.

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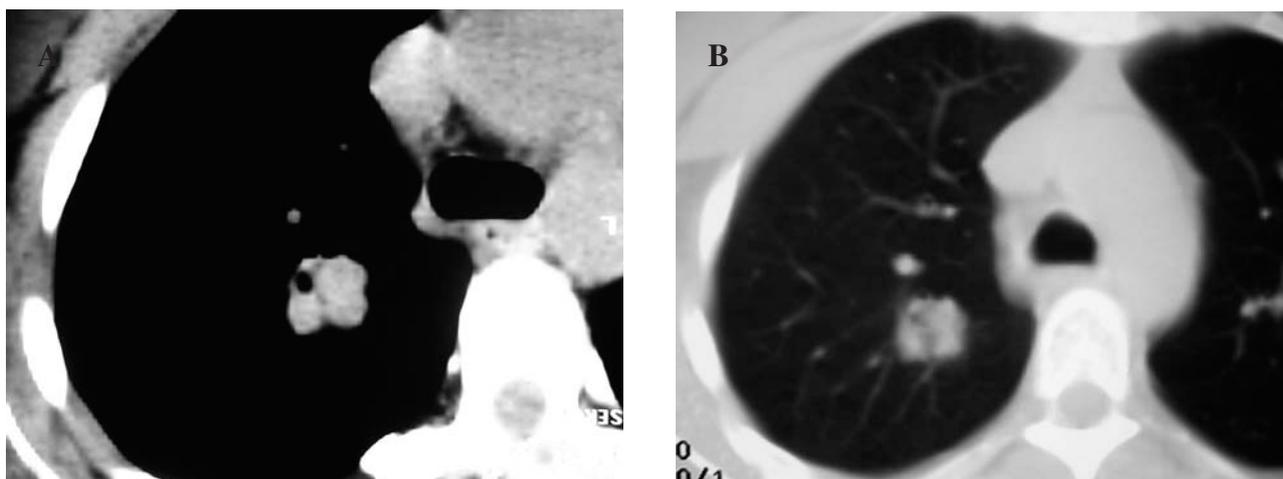


Figure 1. Contrast-enhanced computed tomography of the right upper lobe in the area of the aortic arch. **A:** mediastinal window, showing a solid, polylobulated lesion that has not absorbed the contrast medium, with dense soft tissue and a cavitated appearance. **B:** lung parenchyma window, showing a well-defined and more homogeneous lesion.

She had no history of substance abuse or allergies to medication, and had no fever, cough, expectoration, asthenia, anorexia, or weight loss. A physical examination revealed no enlargement of the adrenal glands. Cardiopulmonary auscultation was normal and analytical data (blood count, biochemistry, and coagulation factors) were normal except for signs of anemia. Immunological and tumor markers were within normal limits. Given the presence of the solitary pulmonary nodule, fiberoptic bronchoscopy was performed with bronchial aspiration and bronchoalveolar lavage, both of which were negative for tumor and inflammatory cells. Computed tomography (CT) revealed a solid nodule in the right upper lobe, approximately 2 cm in diameter and with lobulated edges; there also appeared to be cavitation around the edges, although no uptake of the intravenous contrast could be observed. Nor was lymph node involvement evident within a relevant distance from the nodule. A routine scan 3 months later confirmed no change in nodule size or shape (Figure 1).

CT-guided fine-needle aspiration was performed on the lung nodule; although results indicated epithelial proliferation with papillary formations and isolated atypia, there were no signs of

malignancy. Given these inconclusive results, a right thoracotomy was performed to biopsy the nodule (Figure 2); the diagnosis was sclerosing hemangioma. Given the patient's age and multiple malformations, a genetic study was ordered and Cowden syndrome was diagnosed. The patient was referred to the digestive system department in order to rule out colonic hamartomatous polyps.

No specific treatment was prescribed. The patient is currently being monitored and has presented no further complications related to her underlying disease.

Discussion

Sclerosing hemangioma—which is also referred to as benign sclerosing pneumocytoma, benign pulmonary histiocytoma, sclerosing angioma or xanthomatous pseudotumor⁶—is a rare disease. Although it was initially described as a vascular tumor with cellular infiltration and sclerotic and hemorrhaging areas,^{1,7} its histogenesis

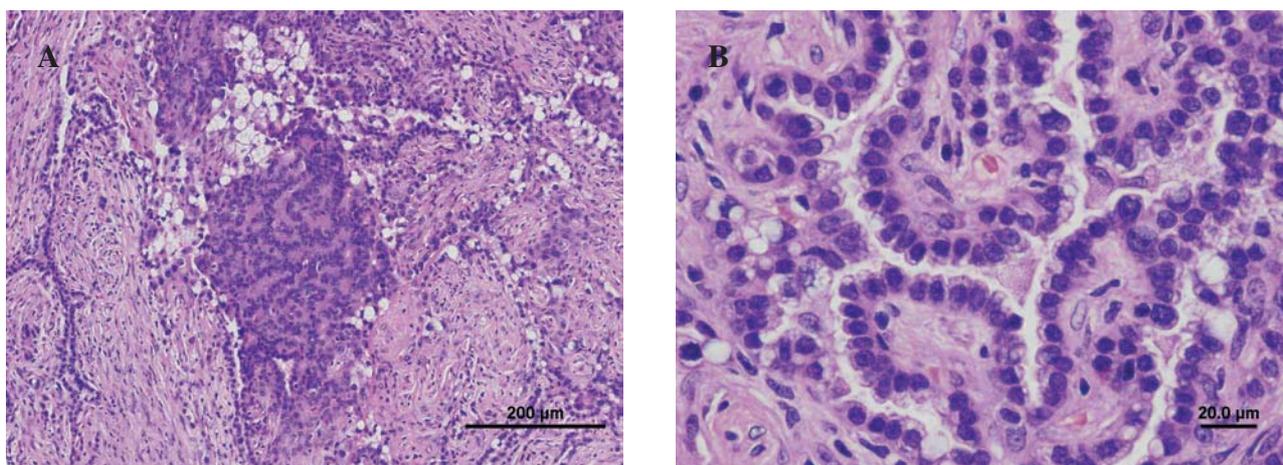


Figure 2. Pathology. **A:** a poorly defined nodular structure, of a predominantly papillary pattern, with intermixed solid areas and few sclerotic ones. **B:** a polygonal arrangement of a proliferation of monomorphous cells, with large nuclei with irregular edges and grumous chromatin. The cells, many of which have apical vacuoles, have dense, eosinophilic cytoplasm. The appearance is syncytial in the solid areas. In the papillary zones, the cells are arranged in a single layer along thick connective axes of abundant fibroblastic cells.

continues to be debated. The mesothelial origin of sclerosing hemangioma has been attributed to undifferentiated mesenchymal and epithelial alveolar cells; however, immunohistochemical and electron microscopy studies have indicated that the most likely histogenesis is type 2 pneumocytes.^{2,4,8} Sclerosing hemangioma is characterized immunohistochemically by the presence of thyroid transcription factor 1 and the epithelial membrane antigen in both round and surface cells.

Over 95% of patients are women (ratio of women to men, 5 to 1), ranging in age from 6 to 83 years (mean, 46 years), although cases have been reported in children aged under 6 years. In most cases (70%-80%) the hemangioma is detected by chance—as was the case with our patient.

In chest x-rays the lesion appears as a well-defined solitary nodule with a diameter ranging from 0.3 to 7 cm (mean, 2.6 cm), although 73% of lesions measure less than 3 cm (which was the case with our patient). The location is usually subpleural—typically the lower lobes—and there is a slight preference for the right lung. In our patient the nodule was located in the central part of the right upper lobe (Figure 1). Contrast-enhanced CT generally reveals a well-defined subpleural mass; in our patient, however, the solitary solid nodule—with well-defined edges, a diameter of approximately 2 cm, and a central location in the right upper lobe—was difficult to detect in the mediastinal window without uptake of the contrast medium. No changes were evident in a subsequent check-up at 3 months.

The macroscopic study revealed a nonencapsulated lesion ranging in color from whitish-grey to dark red-yellow, with well-defined edges, and a solid, cystic consistency with spongy areas. Histologically it was composed of round cells, with papillary and tubular structures intermixed with sclerotic and angiomatous areas. Sclerosing hemangiomas often have a papillary pattern; in a study of 51 patients Katzenstein et al⁵ reported a solid pattern in all of them, a hemorrhagic pattern in 37, and a papillary pattern in 38 patients; the sclerotic pattern was very evident in 50 of these patients. A diagnosis of metastatic papillary carcinoma, mesothelioma, and bronchioloalveolar adenocarcinoma should be considered whenever a papillary pattern is predominant.

Cowden syndrome is an autosomal dominant disease, characterized by multiple hamartomas deriving from the endoderm, mesoderm, and ectoderm. It is caused by germline mutations at 10q23 in the *PTEN* gene, which appears to be associated with signaling and cell adherence processes. However, there are other diseases in which this gene mutates, such as the Bannayan-Ruvalcaba-Riley syndrome (recently described as a variation of Cowden syndrome), Lhermitte-Duclos disease and a subgroup of familial juvenile polyposis,^{9,10} and also multiple sporadic tumors.

Cowden syndrome has traditionally been classified as a hamartomatous intestinal polyposis disorder. It is associated with wartlike skin lesions, tricholemmomas, cerebellar gangliocytomas, thyroid adenomas, skin hemangiomas, visceral arteriovenous malformations, fibrocystic disease, and breast cancer.^{9,10} Our patient had many of these conditions.

Although pulmonary sclerosing hemangioma has not been previously associated with Cowden syndrome, cases

of this lesion associated with familial adenomatous polyposis have been reported in the literature. That association probably results from aberrant expression of β -catenin, an oncogene that activates transcription of the *Wnt* pathway, which is regulated by the adenomatous polyposis coli protein.¹¹ Pulmonary sclerosing hemangioma has also been found in association with myomas and with thyroid and kidney cysts.¹²

This is the first reported case of pulmonary sclerosing hemangioma in Cowden syndrome, and it would seem that sclerosing hemangioma should be added to the list of the many lesions associated with this entity. Nonetheless, the low prevalence of both diseases has meant that it has not been possible to explore the association between them in depth. This case highlights the fact that the lesions associated with Cowden syndrome tend to be quite similar. Even though some of these lesions—for example, pulmonary sclerosing hemangioma—may have a low prevalence, they should be included in the differential diagnosis of solitary lung nodules.

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