

Benign Clear Cell Tumor of the Lung

To the Editor: Benign clear cell tumor of the lung (CCTL) is an extremely rare neoplasm of uncertain histogenesis.¹ First described in 1963 by Liebow and Castleman,² it has been given the name "sugar tumor" due to the presence of high levels of glycogen in cytoplasm. It mainly affects adults between 40 and 50 years of age who are asymptomatic and in whom a peripheral pulmonary nodule is found in the course of a radiographic examination performed for other reasons. By 1998, 40 cases had been described in the English language medical literature. While some cases of malignancy have been reported,^{3,5} such tumors generally exhibit the usual behavior of benign tumors: nuclear pleomorphism and necrosis are absent and mitoses are scarce. Diagnosis should be made with caution, as these tumors present histologic features that are similar to those of clear cell pulmonary carcinoma and metastatic renal cell carcinoma.

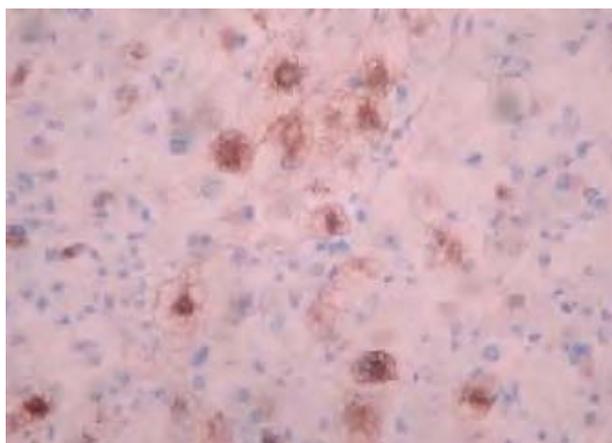
We report the case of a 54-year-old man, an ex-smoker of 40 cigarettes per day. A routine chest x-ray showed a peripheral nodule in the right upper lobe. No relevant medical or surgical history was reported and the physical examination and laboratory test results were normal. Computed tomography showed a solid, well-circumscribed pulmonary nodule in the anterior segment of the lobe, with a diameter of approximately 2.5 cm and no internal calcification. Examination of the liver, kidneys, and suprarenal glands showed no focal lesions. Bronchoscopic exploration was normal and showed no alterations.

On the basis of fine-needle aspiration (FNA) performed in another hospital, the diagnosis was clear cell carcinoma suggesting metastasis of renal or adrenal origin and the patient underwent surgery after routine preoperative evaluation. During surgery a frozen-section study was done and the presence of some "signet ring" cells consistent with mucus-secreting carcinoma (probably of gastric origin) was noted. The lesion was believed to be of metastatic origin, and atypical pulmonary resection was performed.

Postoperative study of the excised tissue confirmed the diagnosis of clear cell tumor. The tumor appeared to be benign and to have originated in the lung; the possibility of its being a metastasis was considered remote. In view of this result, we decided to monitor the patient periodically and give no adjuvant therapy, as the surgery was presumed to have been curative. The patient has remained disease free for 4 years.

CCTL usually presents as a small, peripheral, solitary pulmonary nodule.^{1,4} FNA harvests cells with pale or vacuolar cytoplasm, and differential diagnosis must distinguish between CCTL and renal carcinoma metastases.^{3,4} A lesion may also be a variant of certain tumors that have clear cell areas, such as melanoma, carcinoid tumor, or soft tissue clear cell sarcoma, among others, although these are less frequent diagnoses.³

Figure. Positive immunoreactivity for HMB-45 in the cytoplasm of many of the tumor cells (200).



Macroscopically, CCTL presents as a pink nodule of about 2 cm (range, 1-6.5 cm) that is well demarcated from the lung parenchyma, but not encapsulated, with no necrosis or bleeding. Evident under an optical microscope are typical large cells with clear abundant cytoplasm and neither atypia or mitoses, consistent with the usual behavior of a benign tumor; a few cells have the appearance of spider cells because of round granules radiating from the nucleus to the periphery. In the case we describe, the presence of widespread recent necrosis was noteworthy and might have been suggestive of a poorer prognosis, despite the absence of other factors.¹ It should be remembered, however, that in some cases necrosis may appear after FNA in lesions or tumors in various locations, especially in the thyroid gland.

CCTL is characterized immunohistochemically by immunoreactivity for HMB-45,^{1,3,4} and nonreactivity for cytokeratin or epithelial membrane antigen (EMA) (Figure). Neuroendocrine differentiation has been documented in some cases^{1,3,4} and a case of nonreactivity for HMB-45 has recently been described.⁵

The finding of a clear cell tumor calls for differential diagnosis between a benign tumor and clear cell pulmonary carcinoma, which is characterized by nuclear pleomorphism, abundant mitosis, necrosis, positivity for p-aminosalicylic acid, the presence of diastase-resistant intracytoplasmic granules, immunohistochemical reactivity for cytokeratin and EMA, and the ultrastructural presence of zymogen granules.⁴ A second differential diagnosis to consider is renal carcinoma metastasis, which presents intracytoplasmic accumulations of glycogen and lipids, as well as immunohistochemical reactivity for cytokeratin and EMA.¹

While the histogenesis of CCTL is unclear, the hypothesis that has been most extensively investigated is that, like lymphangiomyomatosis and angiolioma, it originates from perivascular epithelioid cells. These tumors show HMB-45 reactivity, antibodies to perivascular myoid cell proliferation, and melanosomes, all of which are suggestive of pericytic origin.⁶

Such tumors, traditionally considered benign, require periodic monitoring, given the possibility of metastasis.^{3,4} In our review of the literature, we found that certain clinicopathologic features, such as a diameter greater than 2.5 cm, the presence of symptoms, and extensive necrosis or abundant mitoses visible under an optical microscope, have been associated with more aggressive behavior. When present, such features indicate that closer monitoring is necessary.^{1,6}

Thus, the differential diagnosis is quite difficult. Cytologic study of the lesion following FNA shows an inflammatory pseudotumor, with a reduced number of disorganized cells without the characteristic arrangement of the tissue to which they belong. This does not allow a diagnosis of metastatic or primary carcinoma to be ruled out. Relying on a suspected diagnosis based on FNA findings can lead to error, and surgical excision of the nodule is needed to confirm a diagnosis.

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