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CASE REPORT

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INCIDENTAL PULMONARY CARCINOID TUMORLET ASSOCIATED WITH LUNG CANCER

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Abstract Lung tumorlets are rare neuroendocrine neoplasms of 0.5 cm or less in diameter that extend beyond the basement membrane. Although they are associated with bronchiectasis and fibrosis they tend to be asymptomatic and behave in a benign way, usually being diagnosed as incidental microscopic nests of neuroendocrine cells in lung tissue. We present a case of a pulmonary tumorlet finding after right upper lobectomy for lung cancer.

Key words: tumorlet, neuroendocrine tumor, lung cancer

Resumen ***Tumorlet carcinoide pulmonar incidental asociado a cáncer de pulmón.*** Los *tumorlets* pulmonares son neoplasias neuroendocrinas poco frecuentes, que se extienden más allá de la membrana basal y miden 0.5 cm o menos de diámetro. Aunque suelen asociarse a bronquiectasias y fibrosis pulmonar, suelen ser asintomáticas comportándose de una manera indolente, siendo usualmente diagnosticadas de forma incidental en el estudio microscópico de una pieza pulmonar. Presentamos el caso de un *tumorlet* pulmonar incidental luego de una lobectomía superior derecha por cáncer de pulmón.

Palabras clave: *tumorlet*, tumor neuroendocrino, cáncer de pulmón

Nikolai Kulchitsky first identified the enterochromaffin cell in 1897 in the intestinal mucosa of cats and dogs, nevertheless lung neuroendocrine cells (LNC) were first discovered by Feyrter in 1938[1, 2]. Normal lung tissue contains neuroendocrine cells along the bronchial and bronchiolar epitelium. LNC can be divided into isolated cells along the tracheal mucosa, accounting for 0.41% of the epithelial cells or clusters, also called neuroendocrine bodies, composed of 4 to 10 cells[3].

Lung tissue inflammation, injury and exposure to toxic products are associated with reactive hyperplasia of LNC with subsequent regenerative repair, fibrosis and chronic inflammation. However, LNC hyperplasia can occur without underlying disease. This proliferation of neuroendocrine cells is the so called phenomenon diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH). DIPNECH is a rare idiopathic disease, associated with occlusive bronchitis, first reported by Aguayo in 1992[4].

In the World Health Organization classification of tumors of the lungs, published in 2015, all neuroendocrine tumors are grouped together in the same category. Nevertheless, high grade small cell lung cancer and large cell neuroendocrine carcinoma are differentiated from atypical carcinoids, low grade typical carcinoids and DIPNECH[5].

A 5.7% of patients with carcinoids have DIPNECH as a comorbidity and 47.4% of patients with DIPNECH have typical carcinoids, whereas 15.8% have atypical carcinoids, suggesting that DIPNECH develops into a tumorlet and eventually a carcinoid tumor. Nowadays DIPNECH is considered a pre-invasive lesion[6].

Case report

A 64-year-old woman with smoking history of 20 years discovered a painless nodule in her right axillary region. Axillary ultrasound revealed enlarged lymph nodes with irregular margins and loss of the usual cortico-medullary differentiation.

Mammography and mammary ultrasound showed grouped coarse heterogeneous calcifications on the upper outer quadrant of the right breast and two poorly circumscribed and defined nodular formations with deposits of calcium, respectively. The patient underwent a core biopsy of the breast nodule. The histopathological result was concordant with breast invasive ductal carcinoma of no special type (NST), negative for hormonal receptors (estrogen and progesterone) and HER2 positive, Ki67 of 40%.

A thoracoabdominal staging CT showed a 2.27 cm part-solid nodule (solid part < 5mm) with air bronchogram in the upper segment of the superior right lobe and a soft tissue

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formation in the upper outer quadrant of the right breast of 2.3 × 3cm and a 2 × 1.7cm axillary lymph node (Fig. 1).

Breast cancer metastases tend to be solid, well circumscribed, rounded lesions, more often in the periphery of the lung. Because of the imagenological characteristics (ground glass opacity), the lung nodule was interpreted as inflammatory vs. a primary lung cancer (adenocarcinoma). The breast cancer was staged as T2cN2cM0 according to the TNM system. The patient underwent neoadjuvant chemotherapy with cyclophosphamide, doxorubicin and paclitaxel prior toaxillary lymphadenectomy with quadrantectomy, followed bylocoregional radiotherapy to the right breast area and the right supraclavicular fossa and monoclonal therapy with trastuzumab and pertuzumab.

Within a year, anew thoracic CT scan showed persistence of the lung nodule with no changes according to maximum diameter, but with solid portion of 6mm. Due to persistence in time and enlargement of the solid portion, the nodule was interpreted as a lung primary tumor. We decided to perform an excisional biopsy with intraoperative pathological analysis, which informed positive for neoplastic cells, possible adenocarcinoma. Due to the nodule characteristics and its location, the decision was toper form a right upper lobectomy with systematic nodal sampling after confirmation of the malignancy of the nodular lesion.

At cross section, macroscopic observation showed a consolidated area of grayish white. The diameters were 2cm and 1.3 cm respectively. At 4cm of the previous mentioned lesion, a 0.4cm area of increased consistency was found.

Microscopic observation revealed acinar adenocarcinoma in the bigger lesion. Absence of mediastinal nodal metastasis. The small lesion was on the basis of chronic inflammation and fibrosis. Immunohistochemical staining was positive for synaptophys in and chromogranin. (Fig. 2).The lung adenocarcinoma was staged as T1N0M0.

Discussion

Proliferation of LNC may be confined to the mucosa of the airway or invade it locally, beyond the basement membrane to form tumorlets, benign neoplasms (lesions ≤ 0.5cm) or develop into carcinoid tumors (lesions >0.5cm).

Tumorlets are prevalent among middle aged women, between 50 and 70 years old, often diagnosed with a previously diagnosed cancer, particularly breast carcinoma. Regarding clinical significance, tumorlets are usually asymptomatic and lack evidence of severely restrictive or obstructive lung disease, despite they are surrounded by inflammatory and reactive tissue with fibrosis, even when they are multiple[7].

These lesions are usually seen as small, smooth and spherical nodules on CT scan, with surrounded areas of scarring and bronchiectasis. They are usually informed

Fig. 1.– Pre-operative Chest CT. A: Axial view. 0.46cm ground glass nodule in the apical segment of the right upper lobe. B: Axial view. 2.27 cm subsolid nodular opacity with air bronchogram in the upper segment of the superior right lobe. C: Coronal view

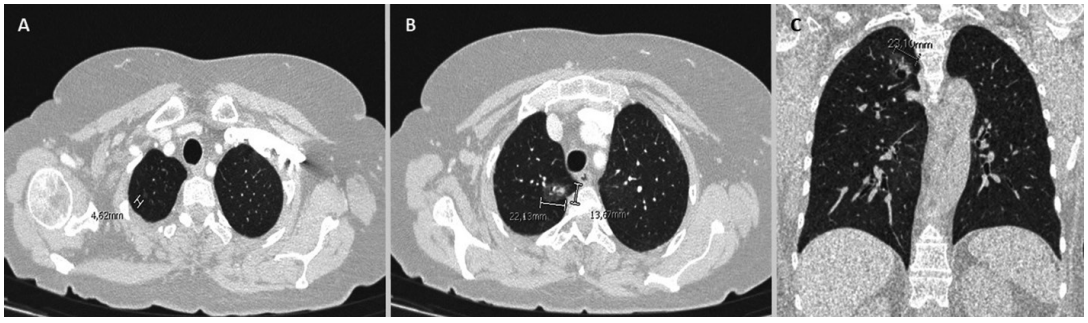
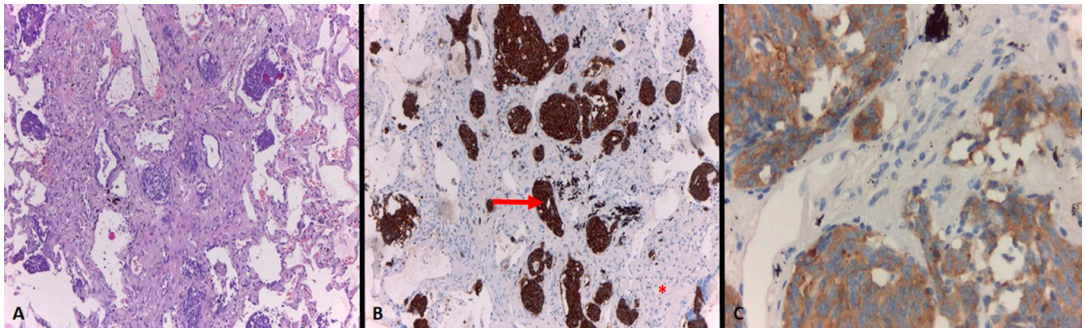


Fig. 2.– Histological examination of resected lung tissue. A: Adenocarcinoma. Well differentiated glandular epithelial proliferation with stromal invasion. H&E staining x10. B: Arrow indicated oval and short fusiform cell hyperplasia displayed in nodular arrangement, on the basis of chronic inflammation and fibrosis (asterisk). Neuroendocrine cells strongly positive for chromogranin immunohistochemical staining, x10. C: Tumorlet positive for synaptophys inimmunohistochemical staining, x40



as indeterminate because of the size and morphology[8]. As said before, tumorlets are often seen in patients with a previously diagnosed cancer. In case of a patient with multiple pulmonary nodules and a previous diagnosed malignancy, a misdiagnosis of metastatic disease can occur if lung biopsies are not performed.

In our case, the combination of the pathology report mentioning the lung nodule and the tumorlet in the resection specimen with the CT showing a tiny ground glass nodule in the same region, constitute evidence that they are the same entity (Fig 1). Retrospectively, we believe that is highly likely that the nodular ground glass opacity seen on the CT scan is actually the tumorlet found at the histopathologic examination.

Tumorlets share morphologic and immunohistochemical features with other neuroendocrine tumors. LNC have round, oval, or spindle nuclei with salt-and-pepper chromatin and clear or eosinophilic cytoplasm. Hyperplastic LNC spread thru the basement membrane of the peribronchiolar tissues forming tumorlets with nesting pattern and desmoplastic stromal reaction. Diagnosis of NLC should be performed by immunostaining with chromogranin, synaptophysin and CD56[9].

The relationship between pulmonary tumorlets and carcinoid tumors has not been definitively established. As previously mentioned, it is suggested that DIPNECH develops into tumorlets and eventually into carcinoid tumors. The mechanism for any such progression may involve critical genetic alterations, such as allelic imbalance of the int-2 gene, causing progressive growth deregulation[10].

Since isolated tumorlets are incidental finding at histopathologic examination of lung parenchyma after surgery, no further treatment is necessary, not being the case when associated with DIPNECH. Although they tend to be benign and indolent, there are reports of tumorlets with cellular atypia, progression into invasive neuroendocrine tumors and lymph node metastases[11, 12]. Surveillance imaging with CT scan should be performed according the base pathology, as tumorlets are usually findings after lung resection for other reasons.

This case report reveals the importance of considering carcinoid tumorlets as differential diagnosis of small pulmonary nodules visible on CT, as they usually manifest as a sub centimeter pulmonary nodules, tending to be misdiagnosed as primary lung tumors or metastases.

The presence of these lesions in association with other tumors are rare, most cases being breast or lung cancer[13]. Although they tend to be benign and indolent neoplasms, some lesions may progress into invasive neuroendocrine tumors.

The patient is in good condition, still receiving trastuzumab/pertuzumab therapy, currently under surveillance without any signs of tumor recurrence.

Conflict of interest: None to declare

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