documented metastatic cancer, the most common tumor being gastric adenocarcinoma followed by lung cancer, but on occasions (as in our case) it can occur in patients with no diagnosis of metastatic disease.[2] In a recent review, none of the 30 cases scrutinized was due to disseminated prostate cancer.[3] Unfortunately, most PTTMs are diagnosed *post mortem* on autopsy, and only some isolated cases have been described in surgical biopsies *ante mortem*. Only a high clinical suspicion and consistent radiological findings will prompt the physician to make a clinical diagnosis of PTTM and to plan the appropriate treatment, which is generally based on a combination of chemotherapy, anti-coagulants and corticosteroids.[4] Significant radiological signs of PTTM described on CT include the "tree-in-bud" pattern. This is practically the only vascular cause of this radiological pattern, and should be distinguished from the bronchial presentation that is generally observed in patients with infectious bronchiolitis.[5]

PTTM should be suspected in oncological patients with worsening respiratory function and/or who develop acute/subacute *cor pulmonale*, particularly in the absence of pulmonary artery embolisms on chest CT angiogram. Detection of a "tree-in-bud" pattern without clinical signs of respiratory infection should also alert to this diagnosis.

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Luis Gorospe Sarasúa,* Almudena Ureña-Vacas, Ernesto García-Santana

Servicio de Radiodiagnóstico, Hospital Universitario Ramón y Cajal, Madrid, Spain

* Corresponding author.
E-mail address: luisgorospe@yahoo.com (L. Gorospe Sarasúa).

Efficacy of Double Bronchodilation (LABA+LAMA) in Patients with Chronic Obstructive Pulmonary Disease (COPD) and Lung Cancer☆

Análisis de la eficacia de la doble broncodilatación (LABA+LAMA) en pacientes con enfermedad pulmonar obstructiva crónica (EPOC) y cáncer de pulmón

Dear Editor,

The prevalence of chronic obstructive pulmonary disease (COPD) among patients with a new diagnosis of lung cancer (LC) is 40%–70%. Both underdiagnosis of COPD and absence of treatment are common in these patients,[1–3] and in curable cases these factors influence the choice of surgery or radiation therapy to treat LC, and affect tolerance to chemotherapy and radiation therapy.[1,3] International LC guidelines recommend smoking cessation and respiratory rehabilitation, but do not make any explicit statements on intensive, short-term COPD treatment other than those given in the specific COPD guidelines.

Our aim was to study functional improvement of COPD in patients with LC after treatment with double bronchodilation (DBD) with a long-acting beta-adrenergic agent (LABA) and a long-acting muscarinic antagonist (LAMA). We conducted this prospective study in a population of outpatients seen in a lung cancer rapid diagnosis unit with spirometry performed on their first day in this unit showing forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio <70% and a post-bronchodilator predicted FEV_1 <80%. Patients who were already receiving DBD treatment and those with an alternative diagnosis of bronchial asthma were excluded. The effect of DBD on lung function was evaluated at 4 weeks. The choice of the LAMA and the LABA were selected according to medical criteria and the ability and capacity of the patient to follow the treatment. Participants receiving inhaled corticosteroids before inclusion continued to receive this therapy. During this period, all other laboratory, endoscopic and imaging tests required for diagnosis, staging, and multidisciplinary therapeutic decision-making were also performed. At 4 weeks, before LC treatment in all cases, spirometry was repeated to evaluate the impact of DBD on FEV_1 and FVC.

Results

Thirty-seven patients with LC and COPD were included; patient characteristics are shown in Table 1. Six had a previous diagnosis of COPD and were receiving bronchodilator treatment, none of which was DBD-based; 4 of these were fluticasone combined with salmeterol. The most commonly used LABA was indacaterol (83.8%), followed by salmeterol, vilanterol, and olodaterol. The most commonly used LAMA was glycopyrronium (51.4%), followed by aclidinium and tiotropium. After 4 weeks of DBD treatment, FEV_1 increased by 200 ml (interquartile range [IQR] 40–320) and 8% (IQR 9–11) and FVC by 290 ml (IQR 75–665) and 6.5% (IQR 1.5–14) on average with respect to baseline values. In 40% of patients, FEV_1 and/or FVC increased by 400 ml or more, although no response predictors or differences in LC staging were detected on a multivariate analysis. In 5 of the 10 potentially resectable patients who initially presented poor lung function, improvements in FEV_1 and FVC after DBD permitted surgical resection for LC to be performed without the need for an oxygen consumption test.

In this pilot study, we observed a notable improvement in lung function among patients with a diagnosis of COPD and LC who received DBD, allowing curative surgical interventions in a high percentage of patients.

In a study with a similar objective to ours that also explored postoperative pulmonary complications in 2 intervention groups who received DBD (formoterol+tiotropium) alone vs DBD+budesonide found comparable improvements to those described in our series in both groups, while the group that received budesonide had significantly better outcomes, including fewer postoperative complications.[4] A lower incidence of postoperative

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Table 1
Epidemiological and Clinical Characteristics.

Mean age in years (IQR)	67 (58–67)
Sex (men), n (%)	34 (92)
Smoking habit, n (%)	37 (100)
Active smokers, n (%)	23 (62.2)
Smoking index[a], mean (IQR)	40 (35–60)
LC histology, n (%)	
Adenocarcinoma	21 (56.8)
Squamous	11 (29.7)
TNM staging, n (%)	
I-IIIA	24 (65)
IIIB-IV	13 (35)
No COPD treatment, n (%)	31 (84)
BODEX, mean (SD)	1 (0–3)
CAT>10, n (%)	6 (16)
Exacerbators[b], *n (%)*	4 (11)
GOLD 2011 classification, n (%)	
A	22 (59.5)
B	7 (19)
C	4 (10.8)
D	3 (8.1)
FEV_1, mean (IQR)	2150 (1760–2430)
FEV_1%, mean (IQR)	72 (58.5–79)
FEV_1 ml, mean (IQR)	3730 (3220–4120)
FVC%, mean (IQR)	88 (75.5–96.5)

CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IQR: interquartile range; LC: lung cancer.

[a] Smoking index: pack-years=(number of cigarettes/day×total years smoking)/20.

[b] Pack-years index=(number of cigarettes/day×total years smoking)/20.

complications was observed in another study of patients treated with tiotropium.[5] In our study, we also found significant improvements in patients with severe COPD, in whom a small improvement in lung function can be decisive in the choice of a treatment, making surgery possible in half of the initially inoperable cases. Despite the obvious benefits of intensive bronchodilator therapy in patients with LC and COPD, no specific evidence-based recommendations are available. If we take into account the limitations of this study, namely, small sample size, lack of a control group and adjustment for the possible benefit of other treatments, our results may justify the conduct of other larger studies to clarify the benefit of DBD in the treatment and prognosis of these patients.

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Virginia Leiro-Fernández,* Ana Priegue Carrera, Alberto Fernández-Villar

Servicio de Neumología, Hospital Álvaro Cunqueiro, EOXI Vigo, Instituto de Investigación Biomédica de Vigo, Vigo, Pontevedra, Spain

* Corresponding author.
E-mail address: virginia.leiro.fernandez@sergas.es (V. Leiro-Fernández).

Diffuse Idiopathic Neuroendocrine Cell Hyperplasia, Tumorlets and Typical Carcinoid Tumors☆

Hiperplasia idiopática difusa de células neuroendocrinas, tumorlets y carcinoides típicos

Dear Editor:

The World Health Organization classification of lung cancer categorizes diffuse idiopathic neuroendocrine cell hyperplasia as a premalignant lesion. This entity presents with clinical and radiological manifestations, such as cough and pulmonary nodules, that are so non-specific that they present a diagnostic challenge for clinicians. We report 2 cases of this disease and describe our diagnostic experience.

Case 1: A 66-year-old woman with ductal carcinoma in situ of the breast with positive hormonal receptors, treated with lumpectomy, radiation therapy and adjuvant hormone therapy. She developed chronic pericardial effusion associated with radiation therapy requiring evacuation. In a follow-up computed tomography (CT), pulmonary nodules were observed that were subsequently evaluated.

She had a history of chronic cough for many years. Lung function tests showed forced vital capacity of 1820 cm^3 (80.5%) and a forced expiratory volume in 1 second of 1120 cm^3 (59.6%), ratio 61.33%. CT revealed multiple nodules of different sizes distributed throughout both lung fields. Six months later, the number and size of the nodules had increased (Fig. 1).

Positron emission tomography (PET)-CT revealed solid nodules measuring between 8 and 14 mm, with maximum SUV of 3.88. Others showed no uptake. Three enlarged lymph nodes were also observed with maximum SUV of 6.8–8.0 mm in the right cervical and retromandibular region. Bronchoscopy provided no significant information, with the exception of *Aspergillus fumigatus* growth in the bronchial aspirate which subsequently became negative. Two months later, a video-assisted thoracoscopy with wedge resections of the middle and lower right lobe showed diffuse idiopathic neuroendocrine cell hyperplasia associated with tumorlets and peripheral typical carcinoid tumors (Fig. 2).

Case 2: A 29-year-old woman with bilateral breast prostheses, with a diagnosis of extrinsic bronchial asthma presented with a complaint of chronic cough. Spirometry, chest radiograph, and paranasal sinuses were normal. Bilateral pulmonary micronodules with a residual appearance were seen on chest CT. Nine months later, multiple pulmonary nodules were detected in the patient's

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