documented metastatic cancer, the most common tumor being gastro-
adic adenocarcinoma followed by lung cancer, but on occasions (as
in our case) it can occur in patients with no diagnosis of metastatic
disease. In a recent review, none of the 30 cases scrutinized was
due to disseminated prostate cancer. Unfortunately, most PTMs
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 PTM and to plan the
appropriate treatment, which is generally based on a combination
of chemotherapy, anti-coagulants and corticosteroids. Significant
radiological signs of PTM described on CT include the “tree-in-
bud” pattern. This is practically the only vascular cause of this radi-
ological pattern, and should be distinguished from the bronchial
presentation that is generally observed in patients with infectious
bronchiolitis.

PTM should be suspected in oncological patients with wors-
ening respiratory function and/or who develop acute/subacute
cor pulmonale, particularly in the absence of pulmonary artery
embolism on chest CT angiogram. Detection of a “tree-in-bud” pat-
tern 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 Interna-
tional LC guidelines recommend smoking cessation and respiratory
rehabilitation, but do not make any explicit statements on inten-
sive, 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 (FEV1/FVC) ratio <70% and a post-
bronchodilator predicted FEV1 <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 func-
tion 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 receiv-
ing inhaled corticosteroids before inclusion continued to receive
this therapy. During this period, all other laboratory, endoscopic
and imaging tests required for diagnosis, staging, and multidisci-
plinary 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 FEV1 and FVC.

Results

Thirty-seven patients with LC and COPD were included; patient
characteristics are shown in Table 1. Six had a previous diagno-
sis 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
(83.5%), 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, FEV1
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, FEV1
and/or FVC increased by 400 ml or more, although no response pre-
dictors 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 FEV1 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 interven-
tion 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.

<table>
<thead>
<tr>
<th>Trait</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (IQR)</td>
<td>67 (58-67)</td>
</tr>
<tr>
<td>Sex (men), n (%)</td>
<td>34 (92)</td>
</tr>
<tr>
<td>Smoking habit, n (%)</td>
<td>37 (100)</td>
</tr>
<tr>
<td>Active smokers, n (%)</td>
<td>23 (62.2)</td>
</tr>
<tr>
<td>Smoking index*, mean (IQR)</td>
<td>40 (35-60)</td>
</tr>
<tr>
<td>LC histology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>21 (56.8)</td>
</tr>
<tr>
<td>Squamous</td>
<td>11 (29.7)</td>
</tr>
<tr>
<td>TNM staging, n (%)</td>
<td></td>
</tr>
<tr>
<td>I-IIIA</td>
<td>24 (66)</td>
</tr>
<tr>
<td>IIIB-IV</td>
<td>13 (35)</td>
</tr>
<tr>
<td>No COPD treatment, n (%)</td>
<td>31 (84)</td>
</tr>
<tr>
<td>BODEX; mean (SD)</td>
<td>1 (0-3)</td>
</tr>
<tr>
<td>CAT&gt;10, n (%)</td>
<td>6 (16)</td>
</tr>
<tr>
<td>Exacerbatorsb, n (%)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>GOLD 2011 classification, n (%)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>22 (59.5)</td>
</tr>
<tr>
<td>B</td>
<td>7 (19)</td>
</tr>
<tr>
<td>C</td>
<td>4 (10.8)</td>
</tr>
<tr>
<td>D</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>FEV1, mean (IQR)</td>
<td>2150 (1760–2430)</td>
</tr>
<tr>
<td>FEV1/FVC, mean (IQR)</td>
<td>72 (58.5–79)</td>
</tr>
<tr>
<td>FEV1 ml, mean (IQR)</td>
<td>3730 (3220–4120)</td>
</tr>
<tr>
<td>FVC% (IQR)</td>
<td>88 (75.5–96.5)</td>
</tr>
</tbody>
</table>

CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IQR: interquartile range; LC: lung cancer.

Complications were 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 ducal 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 cm³ (80.5%) and a forced expiratory volume in 1 second of 1120 cm³ (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 prosthesis, with a diagnosis of extrinsic bronchial asthma presented with a complaint of chronic cough. Spirometry, chest radiograph, and parasanal 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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