Arch Bronconeumol. 2014;50(9):392–396

ARCHIVOS DE BRONCONEUMOLOGIA

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Review

Diagnosis and Treatment of Neuroendocrine Lung Tumors☆

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ARTICLE INFO

Article history:
Received 7 January 2014
Accepted 3 February 2014
Available online 15 July 2014

Keywords:
Pulmonary neuroendocrine tumors
Diagnosis
Treatment
Classification

ABSTRACT

Pulmonary neuroendocrine tumors (PNT) encompass a broad spectrum of tumors including typical carcinoid (TC) and atypical (AC) tumors, large-cell neuroendocrine carcinoma (LCNEC) and small-cell lung cancer (SCLC). Although no variety can be considered benign, AC and TC have a much lower metastatic potential, are usually diagnosed in early stages, and most are candidates for surgical treatment. Several chemotherapy (CT) regimens are available in the case of recurrence or in advanced stages, although scientific evidence is insufficient. LCNEC, which is currently classified alongside large-cell carcinomas, have molecular features, biological behavior and CT sensitivity profile closely resembling SCLC. Pathological diagnosis is often difficult, despite the availability of immunohistochemical techniques, and surgical specimens may be necessary. The diagnostic tests used are similar to those used in other lung tumors, with some differences in the optimal tracer in positron emission tomography. The new TNM classification is useful for staging these tumors. Carcinoid syndrome, very rare in PNT, may cause symptoms that are difficult to control and requires special therapy with somatostatin analogs and other drugs. Overall, with the exception of SCLC, new trials are needed to provide a response to the many questions arising with regard to the best treatment in each lineage and each stage.

Diagnóstico y tratamiento de los tumores pulmonares neuroendocrinos

Palabras clave:
Tumores pulmonares neuroendocrinos
Diagnóstico
Tratamiento
Clasificación

RESUMEN

Los tumores neuroendocrinos pulmonares (TNP) abarcan un amplio espectro de tumores que incluyen los carcinoides típicos (CT) y atípicos (CA), el carcinoma neuroendocrino de células grandes (CNCG) y el carcinoma microcítico de pulmón (CMP). Aunque ninguna variedad puede considerarse benigna, los CA y CT tienen un potencial metastásico mucho menor, habitualmente se diagnostican en estadios tempranos y la mayoría son subsidiarios de tratamiento quirúrgico. Se dispone de varias pautas de quimioterapia (QT) en caso de recidiva o en estadios avanzados, aunque la evidencia científica es insuficiente. Los CNCG, encuadrados en la clasificación actual junto a los carcinomas de células grandes, tienen rasgos moleculares, conducta biológica y perfil de sensibilidad a la QT que los asemejan más a los CMP. Con frecuencia su diagnóstico anatomopatológico es difícil, pese al uso de técnicas de inmunohistoquímica, y pueden ser necesarias muestras quirúrgicas. Las pruebas diagnósticas a utilizar son similares a las empleadas en otros tumores de pulmón, con algunas diferencias en cuanto al trazador óptimo que se usa en la tomografía de emisión de positrones. La nueva clasificación TNM es de utilidad en la estadificación de estos tumores. El síndrome carcinoide, muy infrecuente en los TNP, puede dar síntomas de difícil control que requieren medicación especial con análogos de la somatostatina y otros fármacos. En general, y con la excepción del CMP, se necesitan nuevos ensayos que den respuesta a numerosos interrogantes sobre el mejor tratamiento a aplicar en cada estirpe y cada estadio.

Introduction

Neuroendocrine cells are derived from primitive pluripotent cells and are characterized by production of neurotransmitters and lack of axons and synapses. The tumors they produce in various organs are classified into 3 groups, anterior, middle and posterior, according to their embryonic origin in the gastrointestinal tract.

☆ Please cite this article as: Sánchez de Cos Escuín J. Diagnóstico y tratamiento de los tumores pulmonares neuroendocrinos. Arch Bronconeumol. 2014;50:392–396.

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1579-2129/$ – see front matter

Table 1
Characteristics of Pulmonary Neuroendocrine Tumors.

	Typical carcinoid	Atypical carcinoid	Large cell neuroendocrine carcinoma	Small cell lung cancer
% Of primitive pulmonary tumors	1%–2%	0.1%–0.2%	2%–3%	15%–20%
Differentiation grade	Low	Intermediate	High	High
Mitotic count per 2 mm^2 field	<2	2–10	>10 (media: 70)	>10 (media: 80)
Necrosis	Absent	Present. Focal	Extensive	Extensive
Lymphatic metastases at diagnosis	5%–15%	40%–50%	60%–80%	60%–80%
Distant metastases at diagnosis	3%–5%	20%–25%	40%	60%–70%

These tumors may arise not only from the lung but from various regions of the digestive system.[1,2] Pulmonary neuroendocrine tumors (PNT) represent approximately 25%–30% of primitive lung cancers (LC). Of these, 80% are anaplastic small cell lung cancers (SCLC), 12% are large cell neuroendocrine carcinomas (LCNEC) and the remaining 8% are typical carcinoid (TC) and atypical carcinoid (AC) tumors, the latter being the most uncommon.[3–5] As discussed below, the prognosis for these tumors is very variable and although some, such as TCs, are associated with good life expectancy, they should not be described as "benign" as they all have metastatic potential.[3] At present, these tumors are classified according to their grade of malignancy as: low grade (TC), intermediate grade (AC) and high grade (LCNEC and SCLC) (Table 1). The latest World Health Organization lung tumor classification (2004) also includes other entities, such as diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) and tumorlets.[6–8] The latter are accumulations of neuroendocrine cells generally found in the airways that invade the basement membrane. Their appearance is similar to that of carcinoid tumors but they measure less than 0.5 cm. They are usually found by chance and do not cause symptoms.[7] Although the significance and natural history of DIPNECHs has not been well determined, they are considered by many as the earliest manifestation of neuroendocrine disease and classed as precancerous lesions.[8] They are often associated with chronic bronchopulmonary lesions, such as bronchiectasis and fibrosis, so in this setting they are considered reactive lesions. They rarely occur in previously normal lungs, and if they do, they may develop into carcinoid tumors.[3]

With regard to the histological classification of these tumors, some criteria for the definition of the various types are shown in Table 1. Surgical specimens often have to be examined to determine diagnosis, particularly in the case of LCNEC. When only small biopsy specimens from fiberoptic bronchoscopy are available, it may be very difficult to establish a precise diagnosis. In addition to the mitotic index, the presence or absence of necrosis and the structure of the tumor, the immunohistochemical detection of various neuroendocrine markers, such as chromogranin A, synaptophysin or CD56 and other molecular changes may be an aid to identification.[3,7,9] LCNEC does not always display all the features that characterize this lineage; therefore, in terms of the overall group of large cell carcinomas, the possible spectrum of neuroendocrine differentiation varies widely[6,7] (Table 2). Moreover, the Ki-67 proliferation marker has recently been identified as possibly useful for distinguishing between low and high grade tumors, particularly when only small biopsies or cytological specimens are available.[3,8] Despite the availability of these techniques, differential diagnosis of the disease is often complicated and careful evaluation by experienced pathologists is required.[8] Recent studies suggest that as LCNEC is relatively rare and difficult to diagnose, it may be underdiagnosed, and although it frequently resembles conventional non-small cell lung cancer (NSCLC) both clinically and morphologically, its biological characteristics and prognosis are different, and more importantly, its sensitivity to various chemotherapy (CT) regimens appears to be closer to that of SCLC.[9]

Clinical Presentation and Diagnosis

Low grade PNTs appear at an earlier age (mean 40–50 years) than most LCs and are not clearly associated with tobacco smoking or gender, while high grade PNTs are mainly diagnosed in men over 60 years of age and are closely related with smoking. Carcinoid tumors are central in 75% of the cases and initial symptoms are cough, hemoptysis, wheezing, recurrent pneumonia or chest pain.[2,5] Paraneoplastic syndromes are uncommon: carcinoid syndrome, considered characteristic, is more common in the gastrointestinal presentation of the disease and only appears in 1%–3% of tumors of pulmonary origin. Others, including Cushing's syndrome (1%–2% of cases), acromegaly, etc., are even less common. However, when a thorough endocrine evaluation is performed, hypersecretion may be found in up to 15% of patients, the majority of whom do not have clinical symptoms.[5]

Peripheral pulmonary carcinoid tumors are usually detected by chance. The biological behavior of LCNEC and SCLC is more aggressive, so they are more likely to produce metastasis and are often advanced when diagnosed. SCLC commonly occurs with paraneoplastic syndromes of various types (endocrine, neuromuscular, hematological, etc.), the most common of which is insufficient antidiuretic hormone secretion that may occur in up to 40% of cases.[10]

Diagnosis and Staging

Like other more common LCs, the starting point for suspected diagnosis is generally an abnormal image on chest X-ray. Other imaging tests to be performed for defining the anatomical characteristics of the tumor and possible distant metastases, including chest computed tomography (CT), magnetic resonance, scintigraphy, etc., are also similar, so the guidelines for the diagnosis and staging of LC in general[11–13] are also applicable in these patients. Since most tumors are central, a biopsy specimen is usually obtained by fiberoptic bronchoscopy. If the tumor is peripheral, transthoracic biopsy or aspiration may be the first option, although the small size of cytological specimens and biopsies can be a limiting factor for precise diagnosis, as has been mentioned previously. Thus, after the specimen has been examined, a larger specimen may have to be obtained in a second intervention.

For staging, carcinoid tumors show some specific biological features that limit the efficacy of tests such as positron emission tomography (PET). These slow-growing tumors have low glucose uptake, so ^{18}F-fluordeoxyglucose PET is of little use, particularly in TCs.[2] However, new radiotracers, such as ^{111}In-octreotide or ^{68}Ga-DOTATATE, have been developed that, given their special affinity for the somatostatin receptors often present in low grade tumors, are of great utility in diagnosis and staging.[5] The usefulness of both ^{18}F-fluordeoxyglucose and ^{68}Ga-DOTATATE was recently evaluated with PET/CT in a group of neuroendocrine tumors of different grades. The authors found an inverse infinity for both radiotracers for low and high grade tumors. High grade tumors showed great avidity for ^{18}F-fluordeoxyglucose and low avidity for ^{68}Ga-DOTATATE, while the opposite was true in low grade tumors.[14]