Clinical Presentation and Evaluation of Neuroendocrine Tumors of the Lung

Frank C. Detterbeck, MD

KEYWORDS

• Carcinoid tumors • Bronchopulmonary carcinoid tumors • Neuroendocrine tumors of the lung
• Clinical presentation

KEY POINTS

- Carcinoid tumors can usually be reliably clinically diagnosed (ie, either a smooth endobronchial lesion or an asymptomatic round parenchymal nodule).
- Biopsy confirmation of a carcinoid tumor is usually unnecessary and distinction of typical versus atypical carcinoid tumor by biopsy is usually unreliable.
- Clinical distinction of typical versus atypical carcinoid tumors can be predicted based on age, tumor location, and nodal size, which guide further staging tests.
- Large cell neuroendocrine lung cancer presents similarly to non-small cell lung cancer and the clinical evaluation is the same.
- Small cell lung cancer is strongly predicted by rapid progression of symptoms and a bulky central mediastinal tumor.

INTRODUCTION

Neuroendocrine tumors (NETs) of the lung all display neuroendocrine granules on microscopic examination; however, these tumors cover a wide spectrum. This includes demographic features, epidemiologic aspects, the clinical and radiographic presentations, as well as the prognosis and treatment. In keeping with this, the approach to these cases is varied. This article focuses on the clinical and radiographic presentation and uses these to build a clinical approach to the evaluation of patients.

CLINICAL PRESENTATION

Epidemiology

Patients with bronchopulmonary carcinoid tumors are younger than patients with non-small cell lung cancer (NSCLC), with median ages of 48 and 70, respectively.[1–3] There is a broad age distribution and a relatively equal gender distribution.[3] Patients with an atypical carcinoid (AC) tumor are older than those with a typical carcinoid (TC) tumor (<10% of carcinoid tumors are AC in patients <30 years old, gradually increasing to ~25% in those older than age 60).[3–6] These tumors seem to not be related to smoking.[3,7]

In general, patients with small cell lung cancer (SCLC) and large cell neuroendocrine lung cancer (LCNEC) have the demographic distribution of SCLC and NSCLC patients. The median age is around 70 and the gender distribution is relatively equal in North America.[8,9] LCNEC is rare, accounting for less than 1% of pulmonary NETs.[9] Smoking is so strongly associated with SCLC that the diagnosis must be questioned in a nonsmoker.[10–12]

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Yale Thoracic Surgery, Yale University, PO Box 208062, New Haven, CT 06520-8062, USA
E-mail address: frank.detterbeck@yale.edu

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Abbreviations

AC	Atypical carcinoid
CT	Computed tomography imaging
LCNEC	Large cell neuroendocrine lung cancer
MET	Mucoepidermoid tumor
MRI	Magnetic resonance imaging
NET	Neuroendocrine tumor
NSCLC	Non-small cell lung cancer
PET	Positron emission tomography
SCLC	Small cell lung cancer
TC	Typical carcinoid
TTNA	Transthoracic-needle aspiration
5-HIAA	5-hydroxyindoleacetic acid

LCNEC also seems to be strongly correlated with smoking, although not as exclusively as SCLC.[13–15]

Symptoms

Central carcinoid tumors often present with symptoms related to airway obstruction (cough, recurrent pneumonia, wheezing, and hemoptysis) and many patients are treated for prolonged periods for asthma or infection.[1,3,16,17] On the other hand, peripheral carcinoid tumors are usually discovered incidentally in patients without symptoms.

Patients with SCLC are almost always symptomatic, typically with rapid progression of symptoms consistent with the rapid growth of these tumors. Common symptoms include systemic complaints (weight loss and fatigue) as well as those due to bulky central disease (cough dyspnea, chest pain, hemoptysis, and hoarseness).[18] The clinical presentation of LCNEC is less well defined but, in general, parallels that of NSCLC. Although patients with NSCLC may be asymptomatic, cough, hemoptysis, dyspnea, persistent pneumonia, chest pain, weight loss, and fatigue are common.[19] The progression of symptoms with LCNEC generally lasts months, instead of weeks as in SCLC.

Endocrine Syndromes

Carcinoid tumors

Carcinoid syndrome (episodic flushing and diarrhea) is distinctly rare in patients with bronchopulmonary carcinoid tumors, occurring in less than 1% of patients at presentation and in less than 5% during the subsequent course.[2–4,9,20–28] However, studies suggest that mild complaints of diarrhea or flushing may be elicited in approximately 10% of patients.[16,29] True carcinoid syndrome is almost exclusively seen in patients with liver metastases.[24,30] These data clearly refute the frequently cited speculation that carcinoid syndrome is seen when carcinoid tumors drain into the systemic, as opposed to the portal, circulation. Instead, development of carcinoid syndrome may be related to tumor burden.

Although mild elevation of serotonin or its urinary metabolite, 5-hydroxyindoleacetic acid (5-HIAA), have been reported by some investigators,[16] others have found these only rarely abnormal.[7,29] Routine assessment of these laboratory tests does not seem to be useful and is not recommended.[3,7]

Nevertheless, rare cases of therapeutic interventions have been reported, including initiation of chemotherapy precipitating carcinoid crisis (a life-threatening condition involving flushing, confusion, coma, and either hypotension or hypertension).[31] This is treated by administration of somatostatin.[31–34]

A more frequent endocrine syndrome seen in patients with bronchopulmonary carcinoid tumors is Cushing syndrome, occurring in approximately 4% of patients.[2,16,31,35–38] Bronchial carcinoids account for the most common source of ectopic Cushing syndrome and a search for such a tumor is warranted.[31] Most of these patients have small localized tumors, often only visible on CT.[38] These are usually peripheral tumors. About 80% are TC tumors.[2,39,40] In most patients the syndrome resolves after resection.[36,38,41]

Other endocrine syndromes are rarely reported.[31] These include several cases of acromegaly, which resolved after resection.[2,31,42–44] A case of a patient with elevated parathyroid hormone resulting from a metastatic pulmonary carcinoid tumor was reported.[45] Cardiac valvular disease attributed to a carcinoid tumor has been extremely rarely reported and these involved the right (not left) heart valves.[30]

SCLC or LCNEC

There is a well-known association of SCLC with various paraneoplastic syndromes, which are described in more detail by Ferone.[46] These include the syndrome of inappropriate antidiuretic hormone, hyponatremia, ectopic corticotropin production, and Eaton-Lambert syndrome. LCNECs are not generally associated with paraneoplastic syndromes, although owing to the rarity of these tumors this is less well defined.

RADIOGRAPHIC PRESENTATION

Central Carcinoid Tumors

Approximately 70% of carcinoid tumors present as central tumors.[2–5,16,25,27,28,35,37,41,47,48] Central is not precisely defined but usually means that it is visible by bronchoscopy. Most are located in segmental bronchi (**Fig. 1**), with a predilection for the right middle lobe and the lingula.[3] Carcinoid