Pathology and Diagnosis of Neuroendocrine Tumors: Lung Neuroendocrine

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KEYWORDS

• Carcinoid • Typical carcinoid • Atypical carcinoid • Large cell neuroendocrine carcinoma
• Small cell carcinoma • Neuroendocrine • Lung • Neuroendocrine cell hyperplasia

KEY POINTS

- Neuroendocrine tumors of the lung represent a spectrum of low-grade typical carcinoid (TC), intermediate-grade atypical carcinoid (AC), and high-grade large cell neuroendocrine carcinoma (LCNEC) and small cell lung carcinoma (SCLC).
- The most important histologic feature used to distinguish the grade of lung NE tumors is the mitotic count.
- Unlike in the gastrointestinal tract, Ki-67 is not established as a way to distinguish TC from AC. However, it is very useful for the separation of carcinoid tumors from the high-grade LCNEC and SCLC, particularly in small biopsies with crush artifact.

INTRODUCTION: NATURE OF THE PROBLEM

Neuroendocrine (NE) tumors of the lung range from the low-grade typical carcinoid (TC) and intermediate-grade atypical carcinoid (AC) to the high-grade large cell neuroendocrine carcinoma (LCNEC) and small cell lung carcinoma (SCLC) (**Box 1**).[1,2] SCLC is the most common NE lung tumor, representing approximately 14% of invasive lung cancers.[3] LCNEC represents about 3% of lung cancers in surgical series. Carcinoid tumors account for 1% to 2% of invasive lung malignancies. AC are the rarest of the lung NE tumors. Comprising approximately 10% of all carcinoids, they account for only about 0.1% to 0.2% of lung cancers.[4] Diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH) is a very rare condition, characterized by widespread tumorlets and NE cell hyperplasia, which represents a preinvasive lesion for carcinoid tumors (**Fig. 1**). The pathologic diagnosis of TC and SCLC is straightforward in most cases, and can be made based on light microscopy. However, it is difficult to diagnose AC and LCNEC in small biopsies or cytology, and a definitive diagnosis usually requires a surgical specimen. Therapy for TC and SCLC is primarily surgery and chemotherapy, respectively. However, the best therapy for AC and LCNEC is not established.[4]

In this article, basic principles of diagnostic pathology of pulmonary NE tumors are presented, with emphasis on the pathology, diagnostic criteria (**Box 2**), and their implications for treatment.

RELEVANT ANATOMY AND PATHOPHYSIOLOGY

Molecular Changes in Pulmonary Neuroendocrine Tumors

Recent molecular studies by the Clinical Lung Cancer Genome Project (CLCGP) clearly show that carcinoids show relatively few genetic changes when compared with the high-grade SCLC and LCNEC, supporting the concept in the 2004 World Health Organization (WHO)

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Box 1
Spectrum of neuroendocrine (NE) lung tumors

I. Tumors with NE morphology
  A. Small cell carcinoma
    Combined small cell carcinoma[a]
  B. Large cell neuroendocrine carcinoma
    Combined large cell neuroendocrine carcinoma[a]
  C. Typical carcinoid (≥0.5 cm)
  D. Atypical carcinoid
II. Non–small cell carcinomas with NE differentiation
II. Other tumors with NE properties
  A. Pulmonary blastoma
  B. Primitive neuroectodermal tumor
  C. Desmoplastic round cell tumor
  D. Carcinomas with rhabdoid phenotype
  E. Paraganglioma

[a] The histologic type of the other component of non–small cell carcinoma should be specified.

Adapted from Travis WD, Brambilla E, Miller-Hermelink HK, et al. Pathology and genetics: tumors of the lung, pleura, thymus and heart. Lyon (France): IARC; 2004; with permission.

classification that these are 2 very different groups of tumors.[5] Both SCLC and LCNEC frequently show mutations in TP53, RB1, and EP300. Additional genetic changes, such as copy number, can be found in some LCNEC that are characteristic of adenocarcinoma or squamous cell carcinoma,[5] which is compatible with the known existence of combined LCNEC where components of these other histologies are also present.

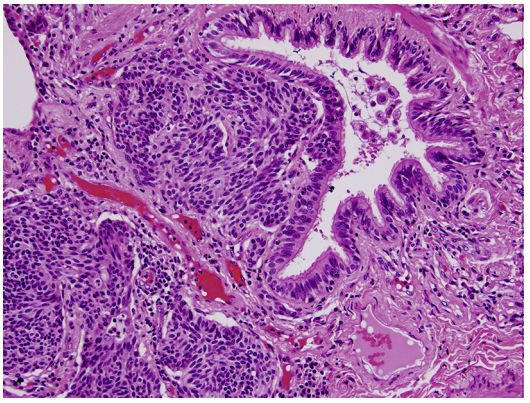

Fig. 1. Diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH). This tumorlet from a patient with DIPNECH consists of nodular clusters of neuroendocrine cells in a peribronchiolar location, causing compression of the bronchiolar lumen (Hematoxylin and eosin ×20).

Box 2
Criteria for diagnosis of neuroendocrine tumors

Small cell carcinoma

Small size (generally less than the diameter of 3 small resting lymphocytes)

Scant cytoplasm

Nuclei: finely granular nuclear chromatin, absent or faint nucleoli

High mitotic rate (≥11 per 2 mm^2, median of 80 per 2 mm^2)[a]

Frequent necrosis often in large zones

Large cell neuroendocrine carcinoma

A tumor with a neuroendocrine morphology (organoid nesting, palisading, rosettes, trabeculae)

High mitotic rate: 11 or greater per 2 mm^2 (10 HPF[a]), median of 70 per 2 mm^2 (10 HPF[a])

Necrosis (often large zones)

Cytologic features of a non–small cell lung carcinoma (NSCLC): large cell size, low nuclear to cytoplasmic ratio, vesicular or fine chromatin, and/or frequent nucleoli. Some tumors have fine nuclear chromatin and lack nucleoli, but qualify as NSCLC because of large cell size and abundant cytoplasm

Positive immunohistochemical staining for 1 or more NE markers (other than neuron-specific enolase) and/or NE granules by electron microscopy

Typical carcinoid

A tumor with carcinoid morphology and less than 2 mitoses per 2 mm^2 (10 HPF[a]), lacking necrosis and 0.5 cm or larger

Atypical carcinoid

A tumor with carcinoid morphology with 2 to 10 mitoses per 2 mm^2 (10 HPF[a]), or necrosis (often punctate)

[a] 10 high-power fields (HPF) in a microscope with field of view of 0.2 mm^2; however, the number of HPF to reach 2 mm^2 varies depending on the field of view in different microscope models; see Ref.[32]

Data from Travis WD, Brambilla E, Miller-Hermelink HK, et al. Pathology and genetics: tumors of the lung, pleura, thymus and heart. Lyon (France): IARC; 2004.

Fernandez-Cuesta and colleagues[6] recently showed that carcinoid tumors show frequent mutations in chromatin remodeling genes. Mutations were found in covalent histone modifiers in 40%