Seminars in Diagnostic Pathology 32 (2015) 445–455

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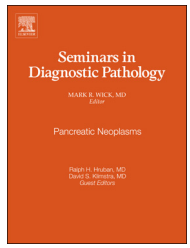

Neuroendocrine neoplasms of the lung: Concepts and terminology

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ARTICLE INFO

Keywords:
Neuroendocrine neoplasms
Small-cell carcinoma
Large-cell neuroendocrine carcinoma
Carcinoid tumors
Tumor classification

ABSTRACT

Neuroendocrine neoplasms of the lung continue to undergo scrutiny, with respect to the diagnostic terminology recommended for them and details of their clinicopathologic profiles. This overview considers the nosological evolution of such lesions and presents current views on classification schemes that pertain to them.

Feyrter[1] developed the concept of a "diffuse neuroendocrine system" (DNS) in 1938,[2] in an attempt to interrelate tumors in several anatomic locations with potentially secretory function and comparable morphologic features. Pearse[3] again addressed the same group of lesions over three decades later and developed the acronym "APUD" (for amine precursor uptake and decarboxylation) to describe its biochemical characteristics. He presumed that "APUD" cells and neoplasms (i.e., "APUDomas") originated from vestiges of the neural crest.

The term APUDOma did not gain widespread acceptance, because of considerable prior literature that used the term "carcinoid" to designate low-grade neoplasms derived from "APUD" cells. The issue became even more complex as it was recognized that not all "carcinoid" tumors behaved as low-grade neoplasms; conversely, high-grade neoplasms such as small-cell carcinoma of the lung also were found to exhibit neuroendocrine differentiation. Thus, classification schemes were modified to include additional categories such as "atypical carcinoid," "neuroendocrine carcinoma grades I–III," "low-grade, intermediate grade, and high-grade neuroendocrine carcinomas," and "large-cell neuroendocrine carcinoma." These different terms have been used variably in different anatomic sites. For example, the terms "typical carcinoid" and "atypical carcinoid" are recommended by the World Health Organization (WHO) with regard to lung neoplasms, but they are not used for gastrointestinal tumors. Moreover, differing diagnostic criteria have been used to define tumor entities with the same name but in dissimilar locations.

Because of a desire for greater standardization of diagnosis and terminology in this area, many investigators have become dissatisfied with such traditional terms as "carcinoid" and others, in reference to potentially malignant but indolent lesions of the neuroendocrine system. In like manner, the categorization of high-grade neuroendocrine tumors also has been reconsidered.[4] This presentation shall summarize the major existing nosological systems for neuroendocrine lesions of the lung, with the goal of providing a practical current approach to this confusing area of oncology.

Terminology pertaining to neuroendocrine neoplasms

There is no question that the nomenclature and diagnostic criteria that have been applied to pulmonary neuroendocrine

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http://dx.doi.org/10.1053/j.semdp.2015.09.012
0740-2570/

tumors through the years have been inconsistent and controversial. Designations such as "bronchial adenoma," "carcinoid," "atypical carcinoid," "Kulschitsky cell carcinoma," "argentaffinoma," "APUDoma," "atypical endocrine carcinoma," and "oat-cell carcinoma" have all been used at one time or another.[5,6]

An important concept underlying the classification of neuroendocrine neoplasms is that all of them are at least potentially malignant. Furthermore, the prognosis of some lesions, such as classical "carcinoid" tumor, cannot always be reliably predicted using macroscopic or microscopic observations. Hence, it is the authors' opinion that the modifier "benign" should never be employed in descriptions of any neuroendocrine neoplasm.

Modern terminological preferences differ from those that have been used in the past. That fact will no doubt threaten the mental comfort of some practitioners who have grown accustomed to using traditional, albeit confusing, designations. *Neuroendocrine carcinoma* has been proposed as a replacement for all of the historical terms attached to neuroendocrine epithelial tumors, with modifiers of "well differentiated" (grade I/III); "moderately differentiated" (grade II/III); and "poorly differentiated" (grade III/III) being appended as appropriate.[4,7]

Distribution and pathogenesis of neuroendocrine neoplasia

A common theme that applies to virtually all anatomic locations—including the lung—is that of a neuroendocrine or neuroectodermal phase of organogenesis.[8,9] Because it is believed that oncogenesis partially reproduces normal embryologic development, this information is key to our understanding of why neuroendocrine and neuroectodermal neoplasms have been observed so widely in a topographical sense. It is true that some tissue locations much more commonly serve as hosts to such tumors. For example, the lung is the most frequently encountered site of neuroendocrine carcinogenesis, and, in that organ, many tumors of this lineage are clearly related etiologically to cigarette smoking and demonstrate a relatively consistent set of cytogenetic and molecular-genetic aberrations.[10] Loss of heterozygosity at one or more regions on chromosome 3p is a common finding, and the multiple endocrine neoplasia-type 1 (MEN1) gene on chromosome 11q also shows similar abnormalities, with deletions in the entire spectrum of pulmonary neuroendocrine neoplasms. Both gains and losses of chromosomes 5q, 5p, and 13q are also commonly observed in such tumors.[11–15] It is interesting that morphologically identical sporadic primary neuroendocrine carcinomas in *other* organs have not, as yet, been linked with any definitive pathogenetic factors, and they often demonstate dissimilar cytogenetic changes as well.[16] Selected neuroendocrine neoplasms of the lung may develop in hereditary (autosomal dominant) patterns, as in multiple endocrine neoplasia, type I, together with pancreatic, pituitary, parathyroid, and thymic lesions.[17,18]

Other aspects of pulmonary neuroendocrine neoplasia

Increasingly, documentation has accrued to support the premise that human malignancies often show "divergent" differentiation. Hence, oncologists are being confronted with such pathologic interpretations as "adenocarcinoma/squamous carcinoma/transitional cell carcinoma with neuroendocrine features" or "mixed adenocarcinoma–small-cell neuroendocrine carcinoma." In the first scenario, the pathologist wishes to convey the concept that the tumor in question has the microscopic image of conventional squamous carcinoma, adenocarcinoma, or transitional cell carcinoma, but that additional studies have demonstrated the presence of submicroscopic neuroendocrine differentiation.[19,20] One may alternatively see a truly mixed-pattern carcinoma at a light microscopic level, in which there is a juxtaposition or admixture of two distinct histologic patterns such as adenocarcinoma and small-cell neuroendocrine carcinoma.[21–24] It might be expected that the biological nature of such mixed lesions would also be a hybrid of the characteristics of each component in pure form, but validation of that premise and the definition of optimal therapies for these "amalgamated" tumors are still being studied.

Pulmonary neuroendocrine proliferations: A model of terminological evolution

Selected pulmonary neoplasms can be used to construct a representative paradigm for tracing the evolution of terminology pertaining to neuroendocrine tumors. Travis et al.[25] have recently published a classification scheme for neoplasms of the lung in general, through the auspices of the World Health Organization (WHO).

2015 WHO classification of pulmonary neuroendocrine lesions

(1) Preinvasive pulmonary neuroendocrine lesions
  – Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
(2) Typical carcinoid tumor
(3) Atypical carcinoid tumor
(4) Small-cell carcinoma—pure and combined
(5) Large-cell neuroendocrine carcinoma—pure and combined

As others have done previously,[7,26,27] we would like to discuss the following scheme[33] as a modification of the WHO model in the categorization of neuroendocrine lesions.

Alternative classification for lesions of the lung that exhibit neuroendocrine differentiation

(1) Neuroendocrine hyperplasias—microscopic tumorlets
(2) "Type I" neoplastic lesions (Neuroendocrine carcinomas [NECs])
  – Grade I NEC (formerly called "classic carcinoid")
  – Grade II NEC (formerly called "atypical carcinoid" or "well differentiated neuroendocrine carcinoma")