Pathologic Classification of Neuroendocrine Neoplasms

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KEYWORDS

• Pathological classification • Neuroendocrine • Lung • Thymus • Pancreas
• Intestines

KEY POINTS

- Neuroendocrine neoplasms arise throughout the body. They are recognized pathologically based on characteristic morphologic patterns and immunoexpression of neuroendocrine differentiation markers.
- The pathologic classification of neuroendocrine neoplasms has evolved over the past decades, as new understanding of the biological behavior, histologic characteristics, and genetic features of these neoplasms has emerged.
- Many aspects of the classification systems remain confusing or controversial. The reasons for the lack of uniformity in approach include the diversity of neuroendocrine neoplasms, the functional status of some neuroendocrine neoplasms, and the organ-specific differences.
- Recent efforts to standardize the classification of gastroenteropancreatic neuroendocrine neoplasms have been reasonably successful; but other organ systems, such as the lung and thymus, use different terminology and classification criteria.
- Genetic findings have not only helped establish relationships among different types of neuroendocrine neoplasms but they have also revealed potential therapeutic targets. Thus, the pathologic approach to neuroendocrine neoplasms is becoming more consistent and clinically relevant.

INTRODUCTION

Neuroendocrine neoplasms arise throughout the body. They are recognized pathologically based on characteristic morphologic patterns and immunoexpression of neuroendocrine differentiation markers. The pathologic classification of neuroendocrine neoplasms has evolved over the past decades, as new understanding of the biological behavior, histologic characteristics, and genetic features of these neoplasms has

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Hematol Oncol Clin N Am 30 (2016) 1–19
http://dx.doi.org/10.1016/j.hoc.2015.08.005 **hemonc.theclinics.com**
0889-8588/16/$ – see front matter

emerged. Nonetheless, many aspects of the classification systems remain confusing or controversial. The reasons for the lack of uniformity in approach include the diversity of neuroendocrine neoplasms. Although their shared neuroendocrine differentiation suggests a closely related family, it is now clear that several distinct types of neuroendocrine neoplasms exist. Most importantly, the well-differentiated neuroendocrine tumor (WD-NET) and poorly-differentiated neuroendocrine carcinoma (PD-NEC) families are increasingly recognized to be very different and, in all likelihood, not closely related. Other variables include the functional status of some neuroendocrine neoplasms, which can drive their clinical manifestations and treatment, relative to the nonfunctional counterparts. Finally, there are organ-specific differences.

Recent efforts to standardize the classification of gastroenteropancreatic neuroendocrine neoplasms, first proposed by the European Neuroendocrine Tumor Society (ENETS) and then adopted by the World Health Organization (WHO), have been reasonably successful; but other organ systems, such as the lung and thymus, use different terminology and classification criteria; even within the gastroenteropancreatic group there exists biological heterogeneity that is partially obscured by the standardization of classification criteria. Despite these difficulties, much progress has been made in determining the features predicting behavior. In particular, recently implemented grading schemes can effectively stratify the indolent, moderately aggressive, and highly aggressive groups of neuroendocrine neoplasms. Genetic findings have not only helped establish relationships among different types of neuroendocrine neoplasms but they have also revealed potential therapeutic targets. Thus, the pathologic approach to neuroendocrine neoplasms is becoming more consistent and clinically relevant. This review summarizes the current approach to the diagnosis, classification, grading, and therapeutic stratification of neuroendocrine neoplasms, with a focus on those arising in the lung and thymus, pancreas, and intestines. The array of rare neuroendocrine neoplasms affecting other epithelial organs and the skin (Merkel cell carcinoma) is beyond the scope of this review.

GENERAL FEATURES OF NEUROENDOCRINE NEOPLASMS

Neuroendocrine differentiation in tumors is conceptually defined as the secretion by the neoplastic cells of bioactive substances, usually bioamines or peptide hormones, into the bloodstream. Non-neoplastic neuroendocrine cells, which are dispersed within the epithelium of most organs and clustered in islets of Langerhans in the pancreas, produce similar substances; their morphologic appearance is shared by the cells of neuroendocrine neoplasms, WD-NETs in particular. The origin of neuroendocrine neoplasms from normal neuroendocrine cells has, thus, been postulated, although the concept that neoplasms arise from their mature non-neoplastic cellular counterparts is likely overly simplistic. Potentially, it is more primitive cells with stem cell features that give rise to these neoplasms, and it is the differentiation, rather than the cell of origin, of the neoplasm that allows its classification. Pathologically, neuroendocrine differentiation is defined as architectural and cytologic patterns reminiscent of non-neoplastic neuroendocrine cells (such as a nesting or trabecular growth pattern and coarsely stippled nuclear chromatin (**Fig. 1**)) and the production of characteristic neurosecretory proteins that can be detected by immunohistochemistry. A wide array of peptide hormones and bioamines can be produced as well; but for the purposes of pathologic diagnosis, it is the so-called general neuroendocrine markers that are detected. The most specific general neuroendocrine markers in wide use are chromogranin A and synaptophysin. Staining for one or both of these can be detected in essentially all WD-NETs. Other general neuroendocrine markers