

## Chapter 2

# Pathology

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**Abstract** Neuroendocrine tumors are ubiquitous neoplasms that may occur anywhere in the human body. Although these tumors have been recognized for more than 100 years, a unifying concept regarding classification has been controversial, and concepts introduced a century ago are still kept in use in today's nomenclature. In addition, some of the current entities encompassed in the rubric of neuroendocrine carcinomas still require better definition and proper study. Interestingly, even though it is known that the great majority of neuroendocrine neoplasms occur in the gastrointestinal tract, most of the current concepts regarding classification and nomenclature are being driven by studies in thoracic tumors. Nevertheless, one of the issues that has been put forward to keep separate nomenclatures for these tumors in different organ systems is the supposed different clinical behavior of these neoplasms in the different systems.

The emphasis in this chapter will be the morphological approach with the idea of unifying histological criteria for the diagnosis of the spectrum of these tumors whether they are in the genitourinary, gynecological, thoracic, or gastrointestinal system. The use of ancillary methods such as immunohistochemistry or electron microscopy although important will be included as a manner to refine the diagnosis.

**Keywords** Carcinoid • Atypical carcinoid • Neuroendocrine carcinoma • Gastrointestinal tract • Thoracic tumors • Classification of tumors

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## Introduction

Neuroendocrine tumors are ubiquitous neoplasms that may occur anywhere in the human body. Although these tumors have been recognized for more than 100 years, a unifying concept regarding classification has been controversial, and concepts introduced a century ago are still kept in use in today's nomenclature. In addition, some of the current entities encompassed in the rubric of neuroendocrine carcinomas still require better definition and proper study. Interestingly, even though it is known that the great majority of neuroendocrine neoplasms occur in the gastrointestinal tract, most of the current concepts regarding classification and nomenclature are being driven by studies in thoracic tumors. Nevertheless, one of the issues that has been put forward to keep separate nomenclatures for these tumors in different organ systems is the supposed different clinical behavior of these neoplasms in the different systems. All the same, it is important to note that whether a conventional schema or a new classification is used in the definition of these tumors, it is likely that there is still going to be some controversy about the best way to classify neuroendocrine neoplasms. The most important aspect regarding this group of tumors is the fact that they should be considered neoplasms capable of local recurrence and distant metastasis. Close clinical correlation and appropriate treatment is important in order to improve survival rate in this group of patients. Because of the wide spectrum of tumors that can be categorized as "neuroendocrine," the emphasis in this chapter will be predominantly with the spectrum of epithelial neoplasms that correspond to the low, intermediate, and high-grade neuroendocrine carcinomas (so-called carcinoid, atypical carcinoid, and small and large cell neuroendocrine carcinoma). We will keep in the differential diagnosis other neuroendocrine tumors that may pose a problem in the differential diagnosis, thus contrasting when appropriate such other tumoral conditions.

As stated before, the ubiquitous distribution of these tumors in the human body is a well-known fact, and tumors with similar histological features as those seen in the gastrointestinal tract or in the thoracic area have also been described in other anatomic areas, including the male and female genitourinary system [1, 2]. Although "carcinoids" in some anatomic areas are believed to represent "benign tumors," the experience with these neoplasms in general does not reflect such consideration. Unfortunately, the use of different nomenclature and classifications has obscured the fact that "carcinoids" and "atypical carcinoids" metastasize in approximately 15% of the cases for the former while the survival rate for the latter has been estimated to be 56 and 35% at 5 and 10 years, respectively [3–18]. On the other hand, the distribution of these neoplasms is of importance as primary thymic neuroendocrine carcinomas (carcinoids), although not very common tumors representing no more than 5% of all mediastinal tumors appear to behave more aggressively in approximately 80% of the cases [19–21] while the opposite may be true for the incidental appendiceal "carcinoid tumor." In addition, depending on the anatomic location, some of these tumors may be associated with clinical conditions that may

play a role in the survival of these patients. For instance, when these neoplasms occur in the mediastinal region, they may be associated with the multiple endocrine neoplasia (MEN) syndrome. Because of these clinical associations they have been the subject to numerous reports, some emphasizing clinical aspects while others emphasizing more histopathological aspects [22–76]. The diverse clinical conditions as well as classification schema for primary thymic neuroendocrine tumors have been reported in only a few large series in the literature, with the largest series comprising 80 thymic primary neuroendocrine carcinomas (carcinoid and atypical carcinoid) [77, 78]. On the contrary, similar tumors with almost identical histopathological features occurring in the gastrointestinal tract are divided differently assuming that some of them are benign. In addition, their classification involves not only the morphology of the neoplasm but also the endocrine activity of the tumor as well as the use of immunohistochemistry, namely Ki-67, which is a proliferating marker [79]. Needless to say, the emphasis in this chapter will be the morphological approach with the idea of unifying histological criteria for the diagnosis of the spectrum of these tumors whether they are in the genitourinary, gynecological, thoracic, or gastrointestinal system. The use of ancillary methods such as immunohistochemistry or electron microscopy although important will be included as a manner to refine the diagnosis.

## Clinical Aspects

The clinical features of neuroendocrine tumors are wide and to some extent will depend on the anatomic area in which these tumors may be located. For instance, thymic neuroendocrine tumors are more commonly associated to the MEN, type I endocrinopathy [21], which in some authors view, may alter the prognosis of these tumors [19]. In that regard, it is possible that previous cases of thymomas associated with endocrinopathies such as Cushing's syndrome may in fact represent thymic neuroendocrine carcinomas as has been reported in other occasions [36, 38, 47, 80–82]. Nevertheless, thymic neuroendocrine carcinomas may also be associated to other conditions including polyarthropathy, proximal myopathy, and peripheral neuropathy [24]; hyperparathyroidism [30, 39]; incomplete Sipple syndrome (MEN-II) [31]; ADH secretion; Eaton–Lambert syndrome; hypertrophic osteoarthropathy [83]; secretion of ACTH [36]; and secretion of parathyroid hormone, calcitonin, beta-lipoprotein, and serotonin [84]. It has been estimated that about half of all neuroendocrine carcinomas in the thymus are functionally active or associated to MEN while about 30% are malignant on the basis of local invasion, metastasis, or both [33]. Interestingly thymic carcinoids have not been associated with myasthenia gravis, carcinoid syndrome, or hypogammaglobulinemia. On the other hand, it is exactly the concept of hormonal functionality that has been the driving force for the classification of these tumors, when they occur in the gastrointestinal tract [79].

## Gross Features

Regardless of the anatomic location, these tumors may be well circumscribed or may be infiltrative including extension into adjacent organs. Those occurring primarily within the lung may have a central location, namely endobronchial location, or may be peripheral tumors. Primary pulmonary neuroendocrine tumors regardless of their histological grade may present with lymph node involvement or extra-thoracic spread. Those occurring in the gastrointestinal area may show similar features regarding well circumscription or infiltrative pattern similarly to those in the genitourinary system. Also, the size of these tumors may vary, as some tumors may be as small as 0.5 cm in diameters while other tumors may show a larger size of more than 10 cm in greatest dimension. It is important to mention that the size of these tumors plays an important role in the current nomenclature as those tumors under 0.5 cm in diameter are coined as “carcinoid tumorlet” when they occur in the lung parenchyma. This so-called carcinoid tumorlet may be analogous to the small incidental “carcinoid tumor” found in the appendix.

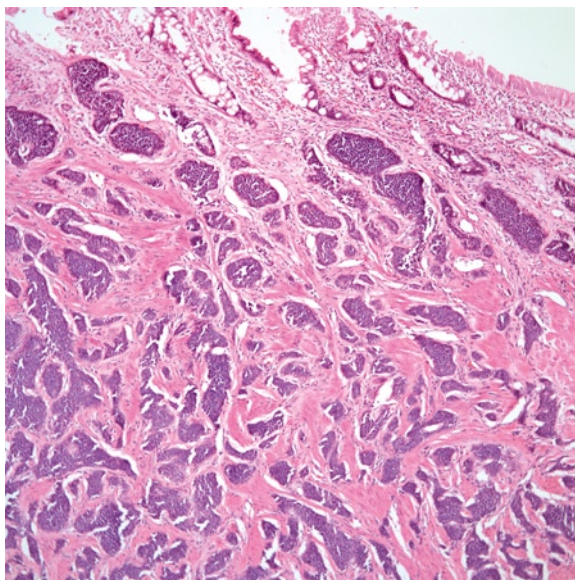
At cut surface they may show a tan color with a homogeneous surface while other tumors may show areas of hemorrhage and/or necrosis. These latter features are commonly used in the grading and classification of these tumors and its presence or absence may upgrade or downgrade a particular tumor.

## Histopathological Features

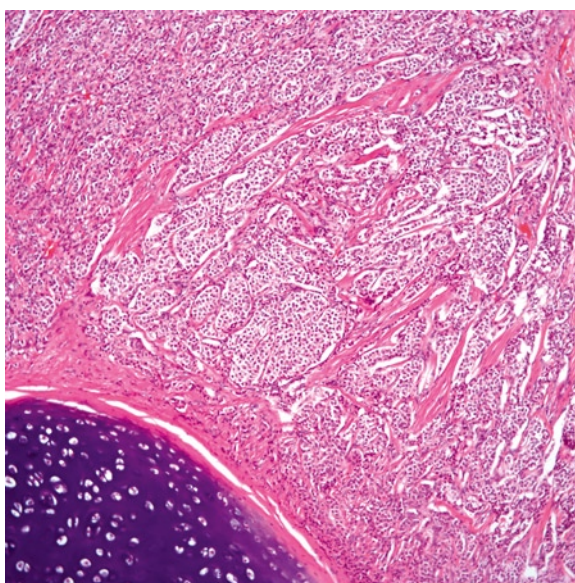
Neuroendocrine carcinomas (carcinoids, atypical carcinoids, small or large cell neuroendocrine carcinoma) share similar histopathological features regardless of the anatomic site (Figs. 2.1–2.3). More recently, a more expanded view of the different histopathologic growth patterns that may be observed in these tumors has been presented [85–89]. Nevertheless, the basic concept of cell morphology is applicable to these tumors regardless of the anatomic distribution. In some cases, certain growth patterns may be seen more often in some anatomic areas but in general the basic histopathology is similar.

These tumors are characterized at low magnification view by a prominent nesting and a homogenous growth pattern. The nests are separated by thin fibrocollagenous tissue while in other areas the growth pattern is that of ribbons of cells exhibiting similar cytological features. The characteristic cytology is that of small or medium size cells with moderate amounts of light eosinophilic or pale cytoplasm, round to oval nuclei, and inconspicuous nucleoli. The tumors in occasions may show a prominent oncocytic differentiation in which the tumor cells appear slightly larger than those of the conventional growth pattern. In this setting, the cells show moderate amounts of eosinophilic cytoplasm and the nuclei appears to be more prominent. However, the nucleoli are still inconspicuous. Tumors with prominent spindle cell features also may be seen and in these cases the cells adopt a fusiform shape mimicking a mesenchymal tumor. In some cases, melanin pigment may be observed

**Fig. 2.1** Well-differentiated neuroendocrine carcinoma (low grade, Grade I) involving the colonic mucosa. Note the well-organized nesting pattern

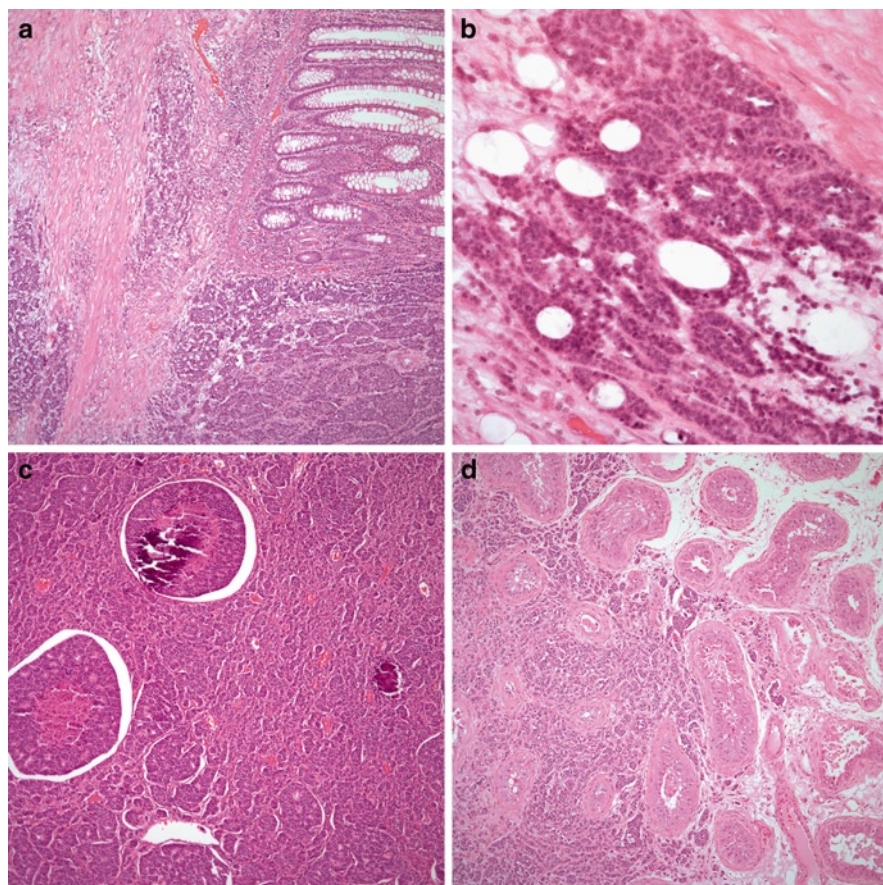


**Fig. 2.2** Similar type of tumor involving the lung. Once again, note the well-organized nested pattern. A portion of the bronchial cartilage is also present



in any of the growth patterns and these tumors are regarded as pigmented neuroendocrine carcinomas (carcinoids). In very unusual circumstances, the tumor may display a characteristic angiectatic growth pattern similar to that observed in vascular tumors. In these tumors, the presence of large ectatic areas filled with red cells may

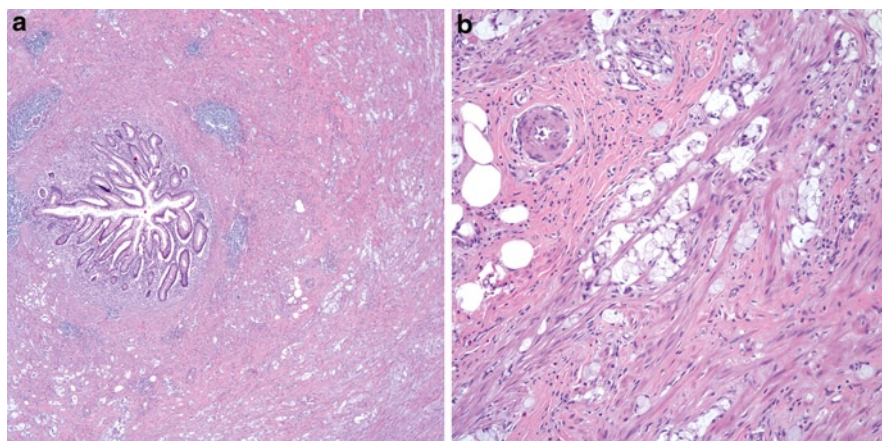




**Fig. 2.3** Moderately differentiated neuroendocrine carcinoma (intermediate grade, Grade II) displaying similar characteristics in different anatomic areas. **(a)** Moderately differentiated neuroendocrine carcinoma involving the mucosa and muscular layer of the colon; **(b)** same tumor infiltrating deeply and involving the serosa and adipose tissue; **(c)** similar tumor in the mediastinal compartment showing the classical come-like necrosis; **(d)** similar tumor involving the testis, note the presence of seminiferous tubules

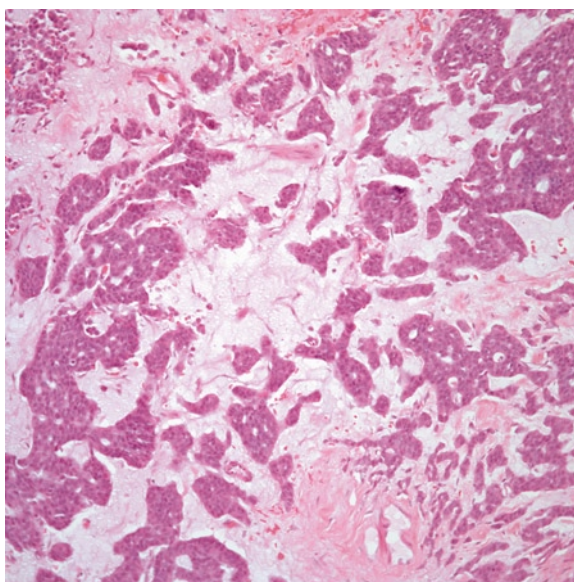
be confused with a vascular tumor. However, the areas in which these ectatic areas are seen show the typical cytological features of a neuroendocrine tumor. Also important to note is the presence of tumors in which the neoplastic cells are embedded in an acellular eosinophilic amyloid-like stroma. Tumors showing this type of growth pattern may be confused with tumors of different origin such as thyroid medullary carcinoma.

Other unusual variants that are important to be recognized include mucinous neuroendocrine carcinoma (carcinoid) [90], signet ring cell, goblet cell (Figs. 2.4 and 2.5), and tumors that share combined features of low- and high-grade differentiation [85]. In the mucinous variant, the tumor cells may be scant and embedded in



**Fig. 2.4** (a) So-called Goblet cell carcinoid tumor involving the appendix; (b) higher magnification showing the presence of “goblet-like cells” splitting fibromuscular fibers

**Fig. 2.5** Mediastinal mucinous neuroendocrine carcinoma, note the presence of clusters of neoplastic cells embedded in a mucinous stroma. This type of tumors is more commonly seen in the gastrointestinal area



large pools of mucin, which may be confused with a primary mucinous adenocarcinoma. Similar problem may arise when the morphology of the tumor is that of goblet cells or signet ring cells in which the tumor may be confused with a conventional adenocarcinoma. On the other hand, there are some tumors that may show alternating areas of conventional “carcinoid” admixed with other areas more in keeping with conventional “small cell carcinoma.” It is important to keep these histopathological growth patterns in mind, namely in the setting of limited mediastinoscopic biopsies.

In this context, it is also important to mention that neuroendocrine carcinomas (carcinoids) may also be associated or admixed with other neoplasms such as thymic carcinoma or mesenchymal tumors [60, 90].

Since most of these histopathological growth patterns are recognized in complete surgical resection, a practical approach to the diagnosis of these tumors has been put forward when dealing with small limited biopsy material [91]. Although not a complete full proof schema, it provides important information for the treating physician to outline a treatment approach.

## **Immunohistochemistry and Ultrastructure**

In general, the use of neuroendocrine markers including chromogranin, synaptophysin, and Leu-7 are important markers in the evaluation of neuroendocrine neoplasms. More recently, a study of 40 cases of primary thymic neuroendocrine carcinomas [76] using a panel of antibodies including CAM 5.2 low molecular weight keratin, broad spectrum keratin cocktail, chromogranin, synaptophysin, and Leu-7 was performed showing strong positive reaction for CAM 5.2 in all cases while broad-spectrum keratin was positive in approximately 88% of the cases studied. Of the neuroendocrine markers tested, chromogranin was seen positive in 75%; synaptophysin in 73%, and Leu-7 in 68%. In only 60% of the cases a dual staining with chromogranin and synaptophysin was observed. Interestingly, in our experience, p53 was seen only focally positive in less than 5% of the cases studied. More recently, a new antibody CD56 has become available as a new neuroendocrine marker. This panel of immunohistochemical markers is commonly used for the diagnostic evaluation of neuroendocrine carcinomas. Nevertheless, when these tumors occur in the gastrointestinal tract, other immunohistochemical antibodies directed against hormonal antigens are also used. In addition, in gastrointestinal tumors, the use of Ki-67 has been used to measure the proliferating index of these tumors. Assessments of more than or less than 2% have been drawn to determine whether the tumor is benign or of low-grade malignancy. Interestingly, it is not clear whether that 2% is assessed in a biopsy material or in a resected tumor. Obviously, that percentage will fluctuate depending on the size of the material studied. Also of questionable value will be the use of a proliferative marker Ki-67 in a resected specimen in which the pathologist is able to determine the presence of mitotic activity, nuclear atypia, and the presence of necrosis by light microscopy alone.

Ultrastructurally, the finding of neurosecretory granules in tumor cells is the most important feature. However, the presence of neurosecretory granules is more readily seen in better-differentiated neoplasms.

## **Classification**

Since the original description by Oberndorfer and Frankfurt [92] of carcinoid tumor, there have been numerous attempts to correlate specific features of these tumors with clinical behavior, which in due process have given rise to the several classification



schemas presented over the last decades. Although none of those schemas has been universally accepted, numerous important contributions to our understanding of these tumors have been presented. For instance, the introduction of the term “atypical carcinoid” by Arrigoni et al. [8] who separated tumors which today are considered to behave more aggressively than the conventional “carcinoid tumor.” However, it is important to recognize that because of this terminology, some authors have considered that the conventional “carcinoid tumor” represents a benign neoplasm. Other authors have advanced the field by highlighting the necessity for a more expanded classification system. This expanded view of neuroendocrine tumor has generated some gain but also some confusion as the histopathological evaluation of these tumors has been joined with the immunohistochemical results; thus, the reluctance of some authors to completely endorse those schemas. Nevertheless, important issues including recognition of the Kultchitsky cell as the origin of these tumors, expanding the classification system from three to four different categories, and proposing that these tumors are part of a spectrum of differentiation ranging from low- to high-grade neoplasms are among the important gains and contributions to our understanding of these tumors [3–18]. However, each one of those systems has brought some controversy. Table 2.1 depicts the conventional, modern/practical, and World Health Organization (WHO) histopathological classification of neuroendocrine tumors [93]. However, it is important to also note that the American Joint Committee on Cancer (AJCC) [94] also has established a staging system for these tumors, which for the most part uses the conventional TNM. That system applies mainly to tumors of the gastrointestinal tract and also subdivides tumors into well-differentiated neuroendocrine tumor and well-differentiated neuroendocrine carcinoma, making an exact correlation with other nomenclatures difficult. In addition, it is important to note that even in the last publication of the WHO for thoracic tumors, which includes lung and mediastinum, there is still some inconsistency in the approach for primary lung tumors as opposed to mediastinal neoplasms. While mediastinal tumors that have been proved to be more aggressive depending on their histological grade, according to the WHO, these tumors are separated into well and poorly differentiated tumors. On the contrary, similar pulmonary tumors that are considered less aggressive than their mediastinal counterparts are separated into four different categories. Needless to say, this very exact issue denotes the obscurity that different authors and classifications systems have embedded in the literature. On the other hand, there are some other issues that remain unsolved, such as the diagnostic criteria for the so-called large cell neuroendocrine carcinoma. The diagnostic criteria for the latter tumor does not depend on light microscopic diagnosis but one that requires positive immunohistochemical neuroendocrine markers or presence of neurosecretory granules by electron microscopy in addition to the “neuroendocrine pattern.” As currently defined, the diagnosis cannot be made on a small biopsy due to the possible lack of “neuroendocrine pattern.” Additionally, any given nonsmall cell carcinoma may show neuroendocrine differentiation by immunohistochemistry, thus, creating a problem on when to separate large cell neuroendocrine carcinoma from the nonsmall cell carcinoma with neuroendocrine differentiation. Furthermore, the controversy deepens when one encounters a tumor that has a “reasonable neuroendocrine pattern” but yet the

**Table 2.1** Different classifications schemas for neuroendocrine carcinomas

Conventional	Moran and Suster	WHO (thymus)	WHO (lung)	WHO (gastrointestinal)
Carcinoid tumor	Low grade neuroendocrine Ca	Well-differentiated neuroendocrine Ca	Carcinoid	Well-differentiated tumor
Atypical carcinoid	Intermediate grade neuroendocrine Ca	Well-differentiated neuroendocrine Ca	Atypical carcinoid	Well-differentiated neuroendocrine Ca
Small cell carcinoma	High grade neuroendocrine Ca <sup>a</sup> Small cell type	Poorly differentiated neuroendocrine Ca	Small cell carcinoma	Poorly differentiated neuroendocrine Ca
	High grade neuroendocrine Ca <sup>a</sup> Large cell type	Poorly differentiated neuroendocrine Ca	Large cell neuroendocrine Ca	Poorly differentiated neuroendocrine Ca

<sup>a</sup> In the Moran and Suster approach both small and large cell neuroendocrine carcinomas belong to the high-grade category

immunohistochemical neuroendocrine markers are negative. Then the diagnosis of large cell neuroendocrine carcinoma (LCNECa) cannot be made, leaving the diagnosis of large cell carcinoma with neuroendocrine pattern. In this regard, the pathologist is left with three possibilities to assess such problem:

- *Large Cell Neuroendocrine Carcinoma*: neuroendocrine pattern plus positive neuroendocrine markers.
- *Large Cell Carcinoma with Neuroendocrine Pattern*: neuroendocrine pattern is present but immunohistochemical markers are negative.
- *Large Cell Carcinoma with Neuroendocrine differentiation*: positive neuroendocrine markers by immunohistochemistry in a tumor that does not show neuroendocrine histological growth pattern.

Although histologically speaking thoracic neuroendocrine carcinomas are similar to those seen in other areas such as the gastrointestinal tract, great care must be exercised in their classification since the prognosis for these tumors in the thymus appears to be different than those in the lung or gastrointestinal tract. Thus, a modified approach and nomenclature of these tumors when they occur in the thymus has been argued [76, 77] following the notion already presented by others [61, 82] that these tumors represent a spectrum of differentiation. In addition, we currently use similar histological criteria for those tumors occurring in the lung parenchyma [95], and consider that similar histopathological approach should also be extended to similar tumors regardless of their anatomic location. Nevertheless, it must be understood that the classification scheme takes into account not only the presence of necrosis, cellular atypia, and mitotic count but also takes into account that in order to provide a more precise classification, a surgical resection of the tumor must take place. The use of this classification based on limited biopsies may prove limited.

The working schema that has been proposed in the evaluation of neuroendocrine carcinomas is as follows:

#### Biopsy Material

- Low or intermediate grade neuroendocrine carcinoma – for those tumors that follow in the range of low or intermediate grade tumors (carcinoid or atypical carcinoid) and the tumor is more than 5 mm in greatest diameter (the pathologist must specify the possibilities of this diagnosis).
- Small cell carcinoma.
- Other types of conventional carcinomas, nonneuroendocrine or possibly a large cell neuroendocrine carcinoma.

#### Surgical Resections

1. Well-differentiated (low grade, Grade I) neuroendocrine carcinoma (conventional carcinoid)
  - Mild cellular atypia
  - 0–3 mitotic figures/10 hpf
  - Small focus of punctuate comedonecrosis may be allowed

2. Moderately differentiated (intermediate grade, Grade II) neuroendocrine carcinoma (atypical carcinoid)
  - Moderate cellular atypia
  - 4–10 mitotic figures/10 hpf
  - More extensive foci of necrosis
3. Poorly differentiated (high grade, Grade III) neuroendocrine carcinoma (small cell carcinoma or large cell neuroendocrine carcinoma – because of the restricted diagnostic parameters imposed on the diagnosis of large cell neuroendocrine carcinoma, it has been considered that such designation may be given for those tumor that show the conventional light microscopic features with or without positive immunohistochemical markers.)
  - Severe or prominent cellular atypia
  - More than 10 mitotic figures/10 hpf
  - Extensive areas of necrosis

It is important to note that some of these tumors may show overlap of features and mix histologies [66]. Therefore, careful interpretation of the different histological grades is necessary.

## Differential Diagnosis

The most important consideration regarding primary neuroendocrine carcinomas is to establish the site of origin. Since all these tumors share similar histopathological features, the diagnosis of primary tumor will depend largely on clinical evaluation and proper exclusion of the most common sites, i.e., gastrointestinal and lung. In this particular setting, the use of TTF-1 and CDX2 immunohistochemical studies may provide help as tumors of lung origin will likely express TTF-1 and not CDX2 while those of gastrointestinal origin would do the opposite. Other tumors that may be easily confused with neuroendocrine carcinomas include paragangliomas and/or ectopic parathyroid adenoma. Both of these tumors may pose considerable difficulty since both tumors are by definition neuroendocrine in nature. In paragangliomas, the histopathologic characteristic is that these tumors will show a similar growth pattern as neuroendocrine carcinomas. However, they are also characterized by the presence of large “megalic” cell with bizarre forms and shapes but very few mitotic figures if any. In addition, paragangliomas will display negative staining for keratin while neuroendocrine carcinomas show for the most part positive staining [96]. In cases of ectopic parathyroid adenomas, the presence of prominent clear cells (chief cells) admixed with oncocytic cells may lead in the correct interpretation. In addition, the use of periodic acid-Schiff to determine the presence of glycogen and the use of immunohistochemical studies for parathyroid hormone will also be helpful in this setting. In the gastrointestinal tract, one other tumor that may pose a problem in diagnosis mainly with limited biopsy material is glomus tumor. However, the use of immunohistochemical studies will show glomus tumor positive for smooth muscle actin and negative for neuroendocrine markers, leading to a more accurate interpretation.



## Prognosis

Based on our experience, we consider that the prognosis of neuroendocrine tumors is linked to the size of the tumor, degree of differentiation, and proliferative activity [76]. For instance, in tumors occurring in the thymus and showing better-differentiated features, it is expected that the survival rate be around 50% at 5 years; those showing moderately differentiated features 20% at 5 years; and those showing poorly differentiated features 0% at 5 years. On the other hand, “carcinoid” of lung origin has 15% rate of lymph node metastasis and 90% 5-year survival, while the rates for “atypical carcinoid” are 25 and 56%, respectively [16]. Therefore, we consider that every attempt should be made to properly classify these tumors according to the degree of differentiation and extent of infiltration. However, it is also important to mention that those tumors that have been coined as “carcinoid tumorlets,” which by definition measure less than 5 mm in diameter, may observe a much better survival rate of possible 100% at 5 years. Similar analogy may be seen with the incidental microscopic “carcinoid tumor” of the appendix.

## Conclusion

It has been more 100 years since the term “carcinoid” was introduced in the literature [92] in order to separate a group of tumors in the small intestine that behave better than conventional carcinomas. Currently, similar tumors have also been described in other anatomic areas and in some of them time has proven that the behavior is not necessarily of a benign tumor. Thus, we have proposed to abandon the term “carcinoid” for a more appropriate term, neuroendocrine carcinoma. It is hoped that by providing this “more meaningful” approach, more research can be done in terms of better therapeutic panels to improve the life expectancy of these patients. We also consider that the term neuroendocrine carcinoma with their different grades of differentiation denotes the spectrum of differentiation that these tumors may show.

## References

1. Conner MG, Richter H, Moran CA, et al. Small cell carcinoma of the cervix: a clinicopathologic and immunohistochemical study of 23 cases. *Ann Diagn Pathol.* 2002;6(6):345–8.
2. Reyes A, Moran CA, Suster S, et al. Neuroendocrine carcinomas (carcinoid tumor) of the testis: a clinicopathologic and immunohistochemical study of 10 cases. *Am J Clin Pathol.* 2003;120(2):182–7.
3. Reyes A, Moran CA. Low-grade neuroendocrine carcinoma (carcinoid) of the prostate. *Arch Pathol Lab Med.* 2004;128(12):166–8.
4. Gosset A, Masson P. Tumeurs endocrines de l’appendice. *Presse Med.* 1914;22:37–40.
5. Goodner JT, Berg JW, Watson WL. The non-benign nature of bronchial carcinoids and cylindromas. *Cancer.* 1961;14:539–45.

6. Markel SE, Abell MR, Haight C, et al. Neoplasms of bronchus commonly designated as adenomas. *Cancer*. 1964;17:590–605.
7. Smith RA. Bronchial carcinoid tumors. *Thorax*. 1969;24:43–7.
8. Arrighi MG, Woolner LB, Bernatz PE. Atypical carcinoid tumors of the lung. *J Thorac Cardiovasc Surg*. 1972;64:413–21.
9. Mills SE, Walker AN, Cooper PH, et al. Atypical carcinoid tumor of the lung: a clinicopathologic study of 17 cases. *Am J Surg Pathol*. 1982;6:643–54.
10. Gould VE, Linnoila RI, Memoli VA, et al. Neuroendocrine cells and neuroendocrine neoplasms of the lung. *Pathol Annu*. 1983;18:287–330.
11. Warren WH, Gould VE, Faber PL, et al. Neuroendocrine neoplasms of the bronchopulmonary tract. *J Thorac Cardiovasc Surg*. 1985;89:819–25.
12. Paladugu RR, Benfield JR, Pak HY, et al. Bronchopulmonary Kultchitsky cell carcinoma: a new classification scheme for typical and atypical carcinoids. *Cancer*. 1985;55:1303–11.
13. Grote TH, Macon WR, Davis B, et al. Atypical carcinoid of the lung: a distinct clinicopathologic entity. *Chest*. 1988;93:370–5.
14. Valli M, Fabris GA, Dewart A, et al. Atypical carcinoid tumour of the lung: a study of 33 cases with prognostic features. *Histopathology*. 1994;24:363–9.
15. Dressler CM, Ritter JH, Patterson GA, Wick M. Clinical-pathologic analysis of 40 patients with large cell neuroendocrine carcinoma of the lung. *Ann Thorac Surg*. 1997;63:180–5.
16. Travis WD, Rush W, Flieder DB, et al. Survival analysis of 200 pulmonary neuroendocrine tumors with classification of criteria of atypical carcinoid and its separation from typical carcinoid. *Am J Surg Pathol*. 1998;22:934–44.
17. Huang Q, Muzitansky A, Mark EJ. Pulmonary neuroendocrine carcinomas: a review of 234 cases and a statistical analysis of 50 cases treated at one institution using a simple clinicopathologic classification. *Arch Pathol Lab Med*. 2002;126:545–53.
18. Schreurs JM, Westermann JJ, van den Bosch JMM, et al. A twenty-five year follow-up of ninety-three resected typical carcinoid tumors of the lung. *J Thorac Cardiovasc Surg*. 1992;104:1470–5.
19. Duh QY, Hybarger CP, Geist R, Gamsu G, Goodman PC, Gooding GAW, et al. Carcinoids associated with multiple endocrine neoplasia syndromes. *Am J Surg*. 1987;154:142–8.
20. Rosai J, Higa E. Mediastinal endocrine neoplasm of probable thymic origin related to carcinoid tumor. *Cancer*. 1972;29:1061–74.
21. Rosai J, Higa E, Davie J. Mediastinal endocrine neoplasm in patients with multiple endocrine adenomatosis: a previously unrecognized association. *Cancer*. 1972;29:1075–83.
22. Manes JL, Taylor HB. Thymic carcinoid in familial multiple endocrine adenomatosis. *Arch Pathol*. 1973;95:252–5.
23. Tanaka T, Tanaka S, Kimura H, Ito J. Mediastinal tumor of thymic origin and related to carcinoid tumor. *Acta Pathol Jpn*. 1974;24:413–26.
24. Lowenthal RM, Gumpel JM, Kreel L, McLaughlin JE, Skeggs BL. Carcinoid tumour of the thymus with systemic manifestations: a radiological and pathological study. *Thorax*. 1974;92:553–8.
25. Hughes JP, Ancalmo N, Leonard GL, Ochsner JL. Carcinoid tumour of the thymus gland: report of a case. *Thorax*. 1975;30:470–5.
26. Sundstrom C, Wilander E. Thymic carcinoid: a case report. *Acta Pathol Microbiol Scand*. 1976;84:311–6.
27. DeLellis RA, Wolfe HJ. Calcitonin in spindle cell thymic carcinoid tumors. *Arch Pathol Lab Med*. 1976;100:340.
28. Chalk S, Donald KJ. Carcinoid tumour of the thymus. *Virchows Arch A*. 1977;377:91–6.
29. Ho FCS, Ho JCI. Pigmented carcinoid tumour of the thymus. *Histopathology*. 1977;1:363–9.
30. Lokich JJ, Li F. Carcinoid of the thymus with hereditary hyperparathyroidism. *Ann Intern Med*. 1978;89:364–5.
31. Marchevsky AM, Dikman SH. Mediastinal carcinoid with an incomplete Sipple's syndrome. *Cancer*. 1979;43:2497–501.
32. Stewart CA, Kingston CW. Carcinoid tumour of the thymus with Cushing's syndrome. *Pathology*. 1980;12:487–94.

33. Wick MR, Scott RE, Li YC, Carney JA. Carcinoid tumor of the thymus: a clinicopathologic report of seven cases with a review of the literature. *Mayo Clin Proc.* 1980;55:246–54.
34. Gelfand ET, Basualdo CA, Callaghan JC. Carcinoid tumor of the thymus associated with recurrent pericarditis. *Chest.* 1981;79:350–1.
35. Floros D, Dosios T, Tsourdis A, Yiatromanolakis N. Carcinoid tumor of the thymus with multiple endocrine adenomatosis. *Pathol Res Pract.* 1982;175:404–9.
36. Brown LR, Aughenbaugh GL, Wick MR, Baker BA, Salassa RM. Roentgenologic diagnosis of primary corticotropin-producing carcinoid tumors of the mediastinum. *Radiology.* 1982;142:143–8.
37. Fetissof F, Boivin F. Microfilamentous carcinoid of the thymus: correlation of ultrastructural study with Grimelius stain. *Ultrastruct Pathol.* 1982;3:9–15.
38. Thorner MO, Martin WH, Ragan GE, MacLeod RM, Feldman PS, Bruni C, et al. A case of ectopic ACTH syndrome: diagnostic difficulties caused by intermittent secretion. *Acta Endocrinol.* 1982;99:364–70.
39. Birnberg FA, Webb WR, Selch MT, Gamsu G, Goodman PC. Thymic carcinoid tumors with hyperparathyroidism. *Am J Radiol.* 1982;139:1001–4.
40. Vener JD, Zuckerbraun L, Goodman D. Carcinoid tumor of the thymus associated with a parathyroid adenoma. *Arch Otolaryngol.* 1982;108:324–6.
41. Blom P, Johannessen JV. Mediastinal mass in a young man. *Ultrastruct Pathol.* 1983;4:391–5.
42. Miettinen M, Partanen S, Lehto VP, Virtanen I. Mediastinal tumors: ultrastructural and immunohistochemical evaluation of intermediate filaments as diagnostic aids. *Ultrastruct Pathol.* 1983;4:337–47.
43. Wick MR, Scheithauer BW, Kovacs K. Neuron-specific enolase in neuroendocrine tumors of the thymus, bronchus, and skin. *Am J Clin Pathol.* 1983;79:703–7.
44. Adkins RB, Maples MD, Haisworth JD. Primary malignant mediastinal tumors. *Ann Thorac Surg.* 1984;38:648–59.
45. Kogan J. Carcinoid tumor of the thymus. *Postgrad Med.* 1984;75:291–6.
46. Wick MR, Scheithauer BW. Thymic carcinoid. *Cancer.* 1984;53:475–84.
47. Huntrakoon M, Lin F, Heitz PU, Tomita T. Thymic carcinoid tumor with Cushing's syndrome: report of a case with electron microscopic and immunoperoxidase studies for neuron-specific enolase and corticotropin. *Arch Pathol Lab Med.* 1984;108:551–4.
48. Lieske TR, Kincaid J, Sunderrajan JV. Thymic carcinoid with cutaneous hyperpigmentation. *Arch Intern Med.* 1985;145:361–3.
49. Otto HF. Letters to the case. *Pathol Res Pract.* 1985;180:448–9.
50. Herbst WM, Kummer W, Hofmann W, Otto H, Heym C. Carcinoid tumors of the thymus: an immunohistochemical study. *Cancer.* 1987;60:2465–70.
51. Lagrange W, Dham HH, Karstens J, Feichtinger J, Mittermayer C. Melanocytic neuroendocrine carcinoma of the thymus. *Cancer.* 1987;59:484–8.
52. Economopoulos GC, Lewis JW, Lee MW, Silverman NA. Carcinoid tumors of the thymus. *Ann Thorac Surg.* 1990;50:58–61.
53. Steen RE, Kapelrud H, Haug E, Frey H. In vivo and in vitro inhibition by ketoconazole of ACTH secretion from a human thymic carcinoid tumour. *Acta Endocrinol.* 1991;125:331–4.
54. Paties C, Zangrandi A, Vasallo G, Rindi G, Solcia E. Multidirectional carcinoma of the thymus with neuroendocrine and sarcomatoid components and carcinoid syndrome. *Pathol Res Pract.* 1991;187:170–7.
55. Miura K, Sasaki C, Katsushima I, Ohtomo T, Sato S, Demura H, et al. Pituitary-adrenocortical studies in a patient with Cushing's syndrome induced by thymoma. *J Clin Endocrinol Metab.* 1967;27:631–7.
56. Gartner LA, Voorhess ML. Adrenocorticotropin hormone-producing thymic carcinoid in a teenager. *Cancer.* 1993;71:106–11.
57. Valli M, Fabris GA, Dewar A, Chikte S, Fisher C, Corrin B, et al. Atypical carcinoid tumour of the thymus: a study of eight cases. *Histopathology.* 1994;24:371–5.
58. Wang DY, Chang DB, Kuo SH, Yang PC, Lee YC, Hsu HC, et al. Carcinoid tumours of the thymus. *Thorax.* 1994;49:357–60.

59. Llaverias S, Valls C, Picas E. Carcinoid tumor of the thymus. *Am J Roentgenol.* 1994;163:478.
60. Kuo TT. Carcinoid tumor of the thymus with divergent sarcomatoid differentiation: report of a case with histogenetic consideration. *Hum Pathol.* 1994;25:319–23.
61. Montpreville VT, Macchiarini P, Dulmet E. Thymic neuroendocrine carcinoma (carcinoid): a clinicopathologic study of fourteen cases. *J Thorac Cardiovasc Surg.* 1996;111:134–41.
62. Kimura N, Ishikawa T, Sasaki Y, Sasano N, Onodera K, Shimizu Y, et al. Expression of pro-hormone convertase, PC2, in adrenocorticotropin-producing thymic carcinoid with elevated plasma corticotropin-releasing hormone. *J Clin Endocrinol Metab.* 1996;81:390–5.
63. Rao U, Takita H. Carcinoid tumour of possible thymic origin: a case report. *Thorax.* 1977;32:771–6.
64. Salyer WR, Salyer DC, Eggleston JC. Carcinoid tumors of the thymus. *Cancer.* 1976;37:958–73.
65. Fishman ML, Rosenthal S. Optic nerve metastasis from a mediastinal carcinoid tumour. *Br J Ophthalmol.* 1976;60:583–8.
66. Wick MR, Carney JA, Bernatz PE, Brown LR. Primary mediastinal carcinoid tumors. *Am J Surg Pathol.* 1982;6:195–205.
67. Baker J, Holdaway IM, Jagush M, Kerr AR, Donald RA, Pullan PT. Ectopic secretion of ACTH and met-enkephalin from a thymic carcinoid. *J Endocrinol Invest.* 1982;5:33–8.
68. Yamaji I, Iimura O, Mito T, Yoshida S, Shimamoto K, Minase T. An ectopic ACTH producing oncocytic carcinoid tumor of the thymus: report of a case. *Jpn J Med.* 1984;23:62–6.
69. Loon G, Schiby G, Milo S. Lesions of the thymus. A study of 53 cases. *Isr J Med Sci.* 1980;16:433–9.
70. Asbun HJ, Calabria RP, Calmes S, Lang AG, Bloch JH. Thymic carcinoid. *Am Surg.* 1991;57:442–5.
71. Zeiger MA, Swartz SE, MacGillivray DC, Linnoila I, Shakir M. Thymic carcinoid in association with MEN syndromes. *Am Surg.* 1992;58:430–4.
72. Wollensak G, Herbst EW, Beck A, Schaefer HE. Primary thymic carcinoid with Cushing's syndrome. *Virchows Arch A Pathol Anat.* 1992;420:191–5.
73. John LC, Hornick P, Lang S, Wallis J, Edmonson SJ. Giant thymic carcinoid. *Postgrad Med.* 1991;67:462–5.
74. Dusmet ME, McKneally MF. Pulmonary and thymic carcinoid tumors. *World J Surg.* 1996;20:189–95.
75. Zahner J, Borchard F, Schmitz U, Scheneider W. Thymus carcinoid in multiple endocrine neoplasms type I. *Dtsch Med Wochenschr.* 1994;119:135–40.
76. Moran CA, Suster S. Neuroendocrine carcinomas (carcinoid tumor) of the thymus: a clinicopathological analysis of 80 cases. *Am J Clin Pathol.* 2000;113(1):100–10.
77. Klemm KM, Moran CA. Primary neuroendocrine carcinomas of the thymus. *Semin Diagn Pathol.* 1999;16:32–41.
78. Kay S, Willson MA. Ultrastructural studies of an ACTH-secreting thymic tumor. *Cancer.* 1970;26:445–52.
79. Kloppel G, Perren A, Heitz PU. The gastroenteropancreatic neuroendocrine cell system and its tumors. The WHO classification. *Ann N Y Acad Sci.* 2004;1014:13–27.
80. Duguid JB, Kennedy AM. Oat-cell tumours of mediastinal glands. *J Pathol.* 1932;23:93–9.
81. Pimstone BL, Uys CJ, Vogelpoel L. Studies in a case of Cushing's syndrome due to an ACTH-producing thymic tumour. *Am J Med.* 1972;53:521–8.
82. Wick MR, Rosai J. Neuroendocrine neoplasms of the thymus. *Pathol Res Pract.* 1988;183:188–99.
83. Viebahn R, Hiddemann W, Klinke F, Bassewitz DB. Thymus carcinoid. *Pathol Res Pract.* 1985;180:445–8.
84. Moran CA, Suster S. Thymic neuroendocrine carcinomas with combined features ranging from well-differentiated (carcinoid) to small cell carcinoma. *Am J Clin Pathol.* 2000;113:345–50.
85. Moran CA, Suster S. Spindle cell neuroendocrine carcinomas of the thymus (spindle-cell thymic carcinoid): a clinicopathologic and immunohistochemical study of seven cases. *Mod Pathol.* 1999;12:587–91.



86. Moran CA, Suster S. Angiomatoid neuroendocrine carcinoma of the thymus: report of a distinctive morphological variant of neuroendocrine tumor of the thymus resembling a vascular neoplasm. *Hum Pathol.* 1999;30:635–9.
87. Moran CA, Suster S. Primary neuroendocrine Carcinoma (thymic carcinoid) of the thymus with prominent oncocytic features: a clinicopathological study of 22 cases. *Mod Pathol.* 2000;13(5):489–94.
88. Klemm KM, Moran CA, Suster S. Pigmented thymic carcinoids: a clinicopathological and immunohistochemical study of two cases. *Mod Pathol.* 1999;12:946–8.
89. Suster S, Moran CA. Thymic carcinoid with prominent mucinous stroma: report of a distinctive morphologic variant of thymic neuroendocrine neoplasm. *Am J Surg Pathol.* 1995;19:1277–85.
90. Sensaki K, Aida S, Takagi K, Shibata H, Ogata T, Tanaka S, et al. Coexisting undifferentiated thymic carcinoma and thymic carcinoid tumor. *Respiration.* 1993;60:247–9.
91. Moran CA, Suster S, Coppola D, Wick MR. Neuroendocrine carcinomas of the lung: a critical review. *Am J Clin Pathol.* 2009;131:206–21.
92. Oberndorfer S, Frankfurt Z. Karzinoide tumoren des Duenndarms. *Pathology.* 1907;1:426–30.
93. Travis WD, Brambilla E, Muller-Hermelink K, Harris CC, editors. World Health Organization (WHO). Pathology and genetics of tumours of the lung, pleura, thymus, and heart. Lyon: IARC Press; 2004.
94. American Joint Committee on Cancer (AJCC). AJCC cancer staging manual. Neuroendocrine tumors. 7th ed. New York: Springer; 2010. p. 181–5.
95. Moran CA, Suster S. Tumors of the lung/pleura. In: Fletcher CD, editor. *Diagnostic histopathology of tumors.* 2nd ed. Philadelphia: Churchill Livingstone; 2000.
96. Moran CA, Suster S, Fishback N, Koss MN. Mediastinal paragangliomas: a clinicopathologic and immunohistochemical study of 16 cases. *Cancer.* 1993;72:2358–64.



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Neuroendocrine Tumors

Yao, J.C.; Hoff, P.M.; Hoff, A.O. (Eds.)

2011, XII, 268 p., Hardcover

ISBN: 978-1-60327-996-3

A product of Humana Press