Neuroendocrine carcinomas (carcinoids) of the thymus

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Primary thymic neuroendocrine carcinomas (carcinoids) are unusual. It has been estimated that they account for no more than 5% of all mediastinal tumors and that they also behave more aggressively in approximately 80% of the cases. Rosai and Higa are credited for the first description of these tumors in the thymic region after their description of 8 cases. Also Rosai et al are credited for highlighting the association of these tumor with the multiple endocrine neoplasia (MEN) syndrome. The authors stated that this association might prove to follow a more aggressive behavior than tumors not associated to this syndrome.

Since those initial descriptions of thymic neuroendocrine carcinomas (carcinoids), numerous other descriptions of similar tumors have followed, some emphasizing clinical aspects while other emphasizing more histopathological aspects. More recently, a larger study comprising 80 primary neuroendocrine carcinomas has been presented highlighting a new classification scheme when these tumors occur in the thymic region as well as the diverse clinical conditions that may be associated to these tumors.

Clinical Aspects

Thymic neuroendocrine carcinomas are a group of tumors more commonly associated to the MEN, type I endocrinopathy, which in some authors view, may alter the prognosis of these tumors. 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. Nevertheless, thymic neuroendocrine carcinomas may also be associated to other conditions including polyarthropathy, proximal myopathy, and peripheral neuropathy, hyperparathyroidism, incomplete Sipple syndrome (MEN-II), ADH secretion, Eaton-Lambert syndrome, hypertrophic osteoarthropathy, secretion of ACTH, and secretion of parathormone, calcitonin, beta-lipoprotein, and serotonin. Some authors have 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. Interestingly carcinoids have not been associated with myasthenia gravis, carcinoid syndrome, or hypogammaglobulinemia.

Gross Features

The tumors may be well circumscribed and limited to the anterior mediastinum or may infiltrate the pleura, pericardium, and lung. At cut surface they may show a tan color with a homogeneous surface while other tumors may show areas of hemorrhage and/or necrosis.

Histopathological Features

Thymic neuroendocrine carcinomas (carcinoids) recapitulate similar features as those in other anatomic areas such as the lung or gastrointestinal tract. More recently, a more expanded view of
the different histopathologic growth patterns that may be observed in these tumors has been presented.

These tumors are characterized at the low power view by a prominent nesting pattern and a homogenous growth. 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 pale eosinophilic of 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 a little larger than the conventional growth patter. In this setting the cells show moderate amounts of prominent eosinophilic cytoplasm and the nuclei appears to be more prominent. However, the nucleoli are still inconspicuous. Thymic neuroendocrine carcinomas with prominent spindle cell features also may be seen. In these cases the cells adopt a fusiform shape mimicking a mesenchymal tumor. In some cases melanin pigment may be observed 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 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 tumor in which the neoplastic cells are embedded in an acellular eosinophilic amyloid-like stroma. Tumors showing this type of growth pattern may be confuse with tumors of different origin such as thyroid medullary carcinoma.

Two additional unusual variants that are important to recognized include the mucinous thymic neuroendocrine carcinoma (carcinoid) and tumors that shared combined features of low and high-grade differentiation. In the former, the tumor cell population may be scant and embedded in large pools of mucin which may be confused with a primary mucinous carcinoma of lung origin while in the latter, the tumor shows alternating areas of conventional “carcinoid” admixed with other areas more in keeping with conventional “small cell carcinoma.” It is important to keep these two histopathological growth pattern in mind, namely when 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.

**Immunohistochemistry and Ultrastructure**

We were able to analyzed 40 cases of primary thymic neuroendocrine carcinomas using a panel of antibodies which included CAM 5.2 low molecular weight keratin, broad spectrum keratin cocktail, chromogranin, synaptophysin, and Leu-7. In our experience, all our cases showed strong positive reaction for CAM5.2 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 studied 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.

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

**Classification**

Although histologically speaking thymic neuroendocrine carcinomas are similar to those seen in other areas such as lung, great care must be exercise in their classification since the prognosis for these tumors in the thymus is different than those in the lung or gastrointestinal tract. Thus, we have
modified the approach and nomenclature of these tumors when they occur in the thymus following
the notion already presented by others that these tumors represent a spectrum of differentiation.
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 mediastinal tumor must take place.
The use of this classification based on mediastinoscopic biopsies may prove inaccurate.
1. Well-differentiated (low grade) neuroendocrine carcinoma (conventional carcinoid)
   • Mild cellular atypia
   • Fewer than 3 mitotic figures x 10hpf
   • Small foci of comedonecrosis
2. Moderately-differentiated (intermediate grade) neuroendocrine carcinoma (Atypical carcinoid):
   • Moderate cellular atypia
   • 3-9 mitotic figures x 10hpf
   • More extensive foci of necrosis
3. Poorly differentiated (high grade) neuroendocrine carcinoma (small cell carcinoma)
   • Severe or prominent cellular atypia
   • More than 10 mitotic figures x 10hpf
   • Extensive areas of necrosis

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

**Differential Diagnosis**

The most important considerations regarding primary neuroendocrine carcinomas of the
thymus include metastatic neuroendocrine carcinoma from other source such as lung, mediastinal
paraganglioma, and ectopic parathyroid adenoma. In cases of metastatic tumors from the lung, a
precise interpretation of thoracic radiographs play an important role in properly assess the origin of
the tumor. Paraganglioma and parathyroid adenomas pose a more difficult problem since both
tumors are for 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. In cases of
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.

**Prognosis**

Based on our experience, we consider that the prognosis is linked to the degree of
differentiation of these tumors. Those tumors showing better differentiated features, it is expected
that the survival rate be around 50% at five years; those showing moderately differentiated features
20% at five years; and those showing poorly differentiated features 0% at five years. Therefore, we
consider that every attempt should be made to properly classify these tumors accordingly to the
degree of differentiation.

**Analysis**

It has been more than 90 years since the term “carcinoid” was introduced in the literature in
order to separate a group of tumors in the small intestine that behave better than conventional
carcinomas. In time, the same tumor was also described in other anatomic areas and in some of them, time has proven that the behavior is not as innocuous as once was thought. 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 believe that the term neuroendocrine carcinoma with their different grades of differentiation denotes the spectrum of differentiation that these tumors may show when they occur in the thymic region.

**Selected References**


