Neuroendocrine Carcinomas (Carcinoid Tumor) of the Thymus

A Clinicopathologic Analysis of 80 Cases

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Key Words: Carcinoid; Thymus; Neuroendocrine carcinoma; Mediastinum; Atypical carcinoid

Abstract

We studied 80 cases of primary thymic neuroendocrine carcinomas. Most patients had symptoms; approximately one third were asymptomatic. All cases were treated by surgical excision. The tumors were divided according to histopathologic features into low-(n = 29), intermediate- (n = 36), and high-grade (n = 15) types. The tumors displayed a variegated histologic appearance and unusual cytologic features. Some cases showed transition from low to high grade within the same tumor mass. Mitotic activity ranged from fewer than 3 to more than 10 mitotic figures per 10 high-power fields, and most tumors displayed marked cellular atypia and areas of necrosis. In 73 patients, the tumor was confined to the anterior mediastinum. Positive immunohistochemical reaction was observed using antibodies for CAM 5.2 low-molecular-weight cytokeratins, broad-spectrum keratin, chromogranin, synaptophysin, and Leu-7. The clinical follow-up obtained in 50 patients correlated well with tumor differentiation. Therefore, the behavior of these tumors seems to correlate with histologic grade, which seems directly proportional to degree of differentiation. We propose replacing the term thymic carcinoid with thymic neuroendocrine carcinoma, which better reflects the aggressive biologic behavior of these tumors in the mediastinal location.

Materials and Methods

The files of the Department of Pulmonary and Mediastinal Pathology, Armed Forces Institute of Pathology,
Washington, DC, and the Department of Pathology, Mount Sinai Medical Center, Greater Miami, FL, were searched for cases of primary (thymic) carcinoids and neuroendocrine tumors of the anterior mediastinum. For a 35-year period (1960-1995), 144 cases of primary mediastinal tumors with the diagnosis of thymic carcinoid or neuroendocrine carcinoma were identified. In 29 cases, adequate material for examination could not be obtained (incomplete or absent blocks or slides), a primary site of origin could not be determined with certainty in 25 cases (ie, patients with concomitant bulky mediastinal mass and large lung mass), and in 10 cases, the diagnosis had to be revised after immunohistochemical studies (ie, thymomas, lymphomas, and other tumors); these cases were eliminated from the study. A total of 80 cases that had adequate baseline information and histologic material for examination formed the basis of the present study.

H&E-stained sections were available for review in all cases studied. The tumors were separated into 3 groups according to the following morphologic criteria: (1) low-grade (well-differentiated neuroendocrine carcinoma): mitotic figures, fewer than 3 per 10 high-power fields (HPF); small (<0.5 mm) areas of necrosis; and mild cellular atypia, including nuclear enlargement with prominent nucleoli; (2) intermediate-grade (moderately differentiated neuroendocrine carcinoma): mitotic figures, 3 to 10 per 10 HPF; more extensive areas of necrosis (1-2 cm); and moderate cellular atypia, including nuclear enlargement with nucleolar prominence and increased nuclear/cytoplasmic ratio; and (3) high-grade (poorly differentiated neuroendocrine carcinoma): mitotic figures, more than 10 per 10 HPF; prominent cellular atypia; and extensive areas of necrosis.

For immunohistochemical studies, representative formalin-fixed paraffin-embedded tissue sections were available for 40 cases. Thin sections were incubated with antibodies against CAM 5.2 low-molecular-weight keratin (Becton Dickinson, Mountain View, CA), broad-spectrum keratin cocktail (DAKO, Carpinteria, CA), chromogranin (Enzo, New York, NY), synaptophysin (DAKO), and Leu-7 (CD57) (DAKO) by the avidin-biotin peroxidase complex technique. Nonimmune rabbit and mouse serum was substituted for negative controls. Appropriate positive controls were run concurrently for every antibody tested.

For clinical follow-up, a questionnaire was developed and mailed to the respective contributing physician or tumor registry during a period of 24 months. Information requested included sex, age, initial symptoms and signs, previous important history (mainly of the existence of a similar tumor within the lung or in extrathoracic areas), gross findings, treatment, and follow-up. Adequate responses were obtained for 50 cases. Survival analysis graphs were produced using NCSS Statistical Software (Kaysville, Utah).

Results

Clinical Features

The patients were 21 females and 59 males between the ages of 16 and 100 years (mean, 58 years). A distribution of tumor by age group is shown in Figure 1. None of the patients had a history of carcinoid tumor elsewhere. A summary of the diversity of clinical symptoms encountered is shown in Figure 2. Of the patients, 22 (28%) were completely asymptomatic, and their tumors were discovered on routine chest radiographs. No clinical information could be obtained for 12 (15%) of the patients. All patients were treated by complete surgical excision of the tumor.

Gross Features

In 43 cases for which this information was obtained, the tumors were described as large, soft, tan-brown infiltrative masses that ranged from 2 to 20 cm in greatest diameter. On the cut surface, the tumors showed homogeneous rubbery tissue with focal areas of hemorrhage, necrosis, or both.

Histopathologic Features

The tumors were divided according to their histopathologic features into 3 categories: low-grade (well-differentiated), intermediate grade (moderately differentiated), and high-grade (poorly differentiated).
Low-Grade (Well-Differentiated) Neuroendocrine Carcinoma

In 29 cases, the tumors most closely resembled conventional foregut carcinoids. They were characterized by their prominent “organoid” growth pattern composed of rounded nests of tumor cells (Zellballen) surrounded by thin fibrovascular septa, or elongated cords or ribbons of tumor cells with little intervening stroma. These tumors, however, differed from other conventional carcinoids in that the tumor cells, although retaining the characteristic features of carcinoid tumors (ie, small round nuclei with coarse clumping of chromatin surrounded by abundant cytoplasm), also displayed subtle cytologic features of atypia, such as nuclear enlargement, occasional prominent nucleoli, and scattered mitotic figures (<3 mitotic figures per 10 HPF). Another feature found in all of these cases was discrete foci of necrosis that closely resembled the pattern of comedonecrosis seen in breast carcinoma. The foci of necrosis usually were centered within large “nests” of tumor cells, imparting the lesion with a characteristic low-power appearance. Foci of dystrophic calcification were another feature often encountered in the center of the large tumor nests. Foci of vascular invasion in the periphery of the lesion could be observed in 20% of these cases.

Intermediate-Grade (Moderately Differentiated) Neuroendocrine Carcinoma

In 36 cases, the tumors were characterized by more pronounced cytologic features of atypia as evidenced by increased nuclear size with large prominent nucleoli, coarsening of chromatin pattern, increased nuclear/cytoplasmic ratio, and more frequent mitotic figures (>3 but <10 mitotic figures per 10 HPF). The architectural growth patterns were similar to those of the previous group, but these tumors showed a marked tendency to form sheets of monotonous tumor cells resulting in a diffuse growth pattern. Occasionally, the solid areas

Table 1
Pathologic Features in 80 Cases of Primary Thymic Neuroendocrine Carcinomas by Tumor Grade

<table>
<thead>
<tr>
<th>Histologic Grade</th>
<th>Growth Pattern</th>
<th>Cytologic Atypia</th>
<th>Mitotic Activity (per 10 HPF)</th>
<th>Necrosis</th>
<th>Vascular Invasion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade (well differentiated) (n = 29)</td>
<td>Predominantly organoid; focally diffuse</td>
<td>Mild</td>
<td>&lt;3</td>
<td>Small foci of comedonecrosis</td>
<td>20</td>
</tr>
<tr>
<td>Intermediate (moderately differentiated) (n = 36)</td>
<td>Organoid with diffuse sheet-like areas</td>
<td>Moderate</td>
<td>4-9</td>
<td>More extensive foci of comedonecrosis</td>
<td>50</td>
</tr>
<tr>
<td>High-grade (poorly differentiated) (n = 15)</td>
<td>Diffuse with loss of organoid pattern</td>
<td>Severe</td>
<td>&gt;10</td>
<td>Extensive areas of necrosis</td>
<td>&gt;75</td>
</tr>
</tbody>
</table>

HPF, high-power fields.
merged with areas displaying prominent rosette-like structures composed of tumor cells arranged concentrically around an empty central lumen Image 4D. A few tumors were characterized by prominent deposition of extracellular mucinous matrix closely simulating a metastasis from a mucin-secreting carcinoma. Other tumors showed abundant deposition of dense eosinophilic material reminiscent of amyloid, thus closely simulating the growth pattern of medullary carcinoma of the thyroid. Other unusual histologic appearances included prominent spindling of the tumor cells, tumors containing scattered melanin pigment, and tumors characterized by abundant oncocytic, densely eosinophilic cytoplasm.

Irrespective of the growth pattern or cytologic features, all of these tumors contained frequent areas of necrosis. The areas of necrosis were mostly focal, comedo type, and centered within large nests of tumor cells, but they also showed a more confluent quality involving solid areas. Clear-cut areas of vascular invasion by tumor cells were much more prominent in these tumors than in the well-differentiated tumors and were present in up to 18 cases (50%).

High-Grade (Poorly Differentiated) Neuroendocrine Carcinoma

Fifteen cases were characterized by sheets and cords of highly atypical tumor cells with loss of the organoid pattern
of growth, extensive areas of necrosis (ie, occupying more than 1 low-power field), marked cytologic atypia and hyperchromatism, and high mitotic activity (>10 mitotic figures per 10 HPF). The tumor cells in 4 cases were large and showed high nuclear/cytoplasmic ratios, with nuclear condensation of chromatin and frequent atypical mitotic figures. Focally, the tumor cells appeared smaller and more uniform and were reminiscent of undifferentiated small cell carcinoma of the lung. In 11 cases, areas of transition between foci showing the features of well-differentiated neuroendocrine carcinoma and areas showing the features of poorly differentiated neuroendocrine carcinoma of small cell type also were present. Vascular invasion was a common finding (>75%) in these cases.

Overall, the most frequent histologic growth pattern in these tumors was the nested or organoid pattern (52 [65%] of 80 cases) followed by diffuse growth pattern (28 [35%] of 80 cases). Trabecular and microacinar (rosette-like) areas frequently were present in association with these tumors but more often were focal and did not represent a dominant feature.

A predominant trabecular or ribbon-like growth pattern was present in only 10 (12%) of 80 cases. The nested growth pattern in these tumors differed somewhat from the nested organoid pattern seen in the more conventional foregut carcinoids because many of the nests in these tumors were larger, with central areas of necrosis and/or dystrophic calcification, and frequently showed a distinctive “retraction” artifact from the surrounding stroma. Mitotic activity was more concentrated around the larger nests. In general, tumors with a predominant nesting growth pattern showed an average of 4 mitotic figures per 10 HPF, whereas mitotic activity tended to be slightly higher in areas showing a diffuse growth pattern (average, 6 per 10 HPF).

Another interesting feature observed in these tumors was the presence of numerous apoptotic cells. Apoptotic activity was more prominent in the intermediate- and high-grade tumors than in the low-grade tumors.

**Immunohistochemical Features**

Forty cases were studied using a panel of antibodies on formalin-fixed paraffin-embedded tissues, including CAM 5.2 low-molecular weight cytokeratin, broad-spectrum keratin cocktail, chromogranin, synaptophysin, and Leu-7. All cases (40/40 [100%]) showed strong positive staining of tumor cells for CAM 5.2; broad spectrum keratin was positive in 35 (88%) cases; chromogranin in 30 (75%); synaptophysin in 29 (72%); and Leu-7 in 27 (68%). Only 24 (60%) of the cases showed chromogranin and synaptophysin positivity. The positive reaction in these tumors varied from focal and weak (<25% of tumor cells) to strong diffuse positivity (>70% of tumor cells).

**Clinical Follow-Up**

Follow-up information ranging from 1 month to 17 years was obtained for 50 patients (mean follow-up, 8.6 years). Overall survival rate for these patients was 28% (12/42) at 5 years, and 10% (4/42) at 10 years. When stratified according to histologic grade, 7 (32%) of 22 patients with low-grade neoplasms died of tumor
between 0.5 and 11 years, 12 (48%) of 25 patients with intermediate-grade neoplasms died of tumor between 1 month and 11 years, and 10 (91%) of 11 patients with high-grade neoplasms died of tumor between 1 and 7 years.

**Figure 4.** Recurrences were documented in 18 patients and metastases in 20; the most frequent metastatic sites were lymph nodes (16 cases), lung (11 cases), bone (3 cases), and esophagus, chest wall, and liver (1 case each). Adequate information about postoperative adjuvant therapy could not be obtained in a sufficient number of cases to draw meaningful conclusions about the role of chemotherapy or radiation therapy in the treatment of these lesions.

**Discussion**

Primary neuroendocrine carcinomas (carcinoid tumors) of the thymus are unusual neoplasms. They have been estimated to account for approximately 2% to 4% of all anterior mediastinal neoplasms. Rosai and Higa were the first to point out the existence of primary neuroendocrine neoplasms in the thymus showing features analogous to those of carcinoid tumors in other locations. They also called attention to the fact that previous reports on thymomas associated with endocrine abnormalities most likely corresponded to cases of primary neuroendocrine tumors of the thymus. The existence of primary thymic neuroendocrine neoplasms is
Poorly differentiated neuroendocrine carcinoma of the thymus. A, Large tumor cells with marked cytologic atypia and hyperchromatism are seen associated with extensive areas of necrosis (H&E, x40). B, Transitions between well-differentiated neuroendocrine carcinoma of the thymus (left) and poorly differentiated neuroendocrine carcinoma of small cell type (right) (H&E, x40).

Clinical Follow-Up for 50 Patients With Primary Thymic Neuroendocrine Carcinomas

<table>
<thead>
<tr>
<th>Tumor Grade</th>
<th>Alive and Well*</th>
<th>Alive With Disease*</th>
<th>Dead of Tumor*</th>
<th>Disease-Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade (well-differentiated)</td>
<td>11/22 (50)</td>
<td>4/22 (18)</td>
<td>7/22 (32)</td>
<td>50% at 5 y; 9% at 10 y</td>
</tr>
<tr>
<td>Intermediate-grade (moderately differentiated)</td>
<td>4/25 (16)</td>
<td>9/25 (36)</td>
<td>12/25 (48)</td>
<td>20% at 5 y; 0% at 10 y</td>
</tr>
<tr>
<td>High-grade (poorly differentiated)</td>
<td>0/11 (0)</td>
<td>1/11 (9)</td>
<td>10/11 (91)</td>
<td>0% at 5 y</td>
</tr>
</tbody>
</table>

* Data are given as number/total number (percentage).

Overall survival in years for patients with neuroendocrine carcinoma of the thymus.

Survival curves for neuroendocrine carcinoma of the thymus according to tumor grade. Solid line, well-differentiated neuroendocrine carcinoma; hatched line, moderately differentiated neuroendocrine carcinoma; dotted line, poorly differentiated neuroendocrine carcinoma.
well-recognized, and many studies dealing with this topic have been published in the literature, mainly in the form of case reports or small series of cases.4-41

Despite the suggestion of benign behavior implied by their name, thymic carcinoids have been noted to follow a more aggressive behavior than their counterparts in other locations. Duh et al5 stated that thymic carcinoids were malignant in about 80% of cases, while bronchial carcinoids exhibited malignant behavior in only about 26% of cases. Valli et al,31 in a study on thymic carcinoids, concluded that when such tumors are located in the mediastinum, they essentially represent the equivalent of “atypical carcinoids” of the lung, a morphologic variant of pulmonary carcinoid originally described by Arrigoni et al43 that is characterized by more atypical histologic features and more aggressive behavior than conventional carcinoid tumor of the lung.

Because of the apparent variability in the histologic and biologic spectrum of these lesions, a new nomenclature was proposed by Rosai et al44 in 1976 for mediastinal carcinoids that included carcinoid grade I, for the well differentiated tumors (the term considered equivalent to conventional carcinoids); carcinoid grade II, for the moderately differentiated lesions (the term considered equivalent to atypical carcinoid); and carcinoid grade III for poorly differentiated lesions (the term considered equivalent to oat cell carcinoma). Wick and Rosai45 later suggested that the terms carcinoid and atypical carcinoid were outmoded and that such tumors should be regarded as part of the spectrum of neuroendocrine carcinomas. Gould46 suggested use of the term neuroendocrinoma for these tumors when they occurred in the thymus.

In practice, none of these proposed terms has been adopted fully, and the term thymic carcinoid remains the one most commonly used. The present study indicates that these tumors indeed form part of a family of closely related neuroendocrine neoplasms that can display a variable spectrum of differentiation and that have a tendency to follow a more aggressive biologic behavior than their counterparts in other foregut locations. Accordingly, we propose the designation thymic neuroendocrine carcinoma for this family of tumors. Furthermore, we agree with Rosai et al44 that these tumors can be separated adequately based on their histopathologic features into well-differentiated, moderately differentiated, and poorly differentiated neoplasms. We also concur with the opinion expressed by Wick and Rosai45 that the term carcinoid for these tumors is outmoded and that they all should be regarded as cases of neuroendocrine carcinomas. For this reason, we favor using the term neuroendocrine carcinoma of the thymus of well-, moderately, or poorly differentiated type instead of the previous terms.

In the present study, 18 patients (22%) had endocrine manifestations, while 20 patients (25%) were completely asymptomatic. Acute clinical symptoms, such as the superior vena cava syndrome were present in fewer than 5% of patients, and general constitutional symptoms were present in fewer than 10%. The tumors occurred in all age groups (16-100 years), but they seemed to show a predilection for adults between 40 and 60 years of age. Our study supports the male predilection noted in previous studies in a ratio of 3:1.

Histologically, the tumors showed a wide spectrum of features that correlated with their degree of differentiation and biologic behavior. Twenty-nine cases had features of well-differentiated neuroendocrine carcinoma, including mild cytologic atypia, scattered mitotic figures (<3 per 10 HPF), and small foci of necrosis; 36 cases had features of moderately differentiated neuroendocrine carcinoma, including more pronounced cytologic atypia, increased mitotic activity (approximately 3-10 mitotic figures per 10 HPF), more frequent and extensive areas of necrosis, and vascular invasion; and 15 cases showed features of poorly differentiated neuroendocrine carcinoma, including marked cytologic atypia, high mitotic activity (>10 mitotic figures per 10 HPF), extensive areas of necrosis, and frequent foci of vascular invasion.

Clinical behavior closely correlated with the histologic degree of differentiation; disease-free survival was 50% at 5 years and 9% at 10 years for the well-differentiated tumors, 20% at 5 years and 0% at 10 years for the moderately differentiated tumors, and 0% at 5 years for the poorly differentiated tumors. Other features, such as sex, age, size of the lesion, and associated clinical manifestations, did not seem to correlate with prognosis.

The present study also underscores the varied histopathologic appearances that these tumors are able to display in the mediastinum. Although the classic organoid (nested or trabecular) pattern of growth was the most commonly observed, a number of unusual appearances were encountered frequently, including diffuse (lymphoma-like) growth pattern, tumors with prominent mucinous stroma, amyloid-like stroma, and tumors with pigmented or spindle cells, or composed of cells with prominent oncocytic cytoplasm. However, none of these morphologic variants showed any meaningful independent correlation with the behavior of the tumor; clinical behavior was dependent on histologic grading as in the more conventional histologic types.

Another interesting finding observed in the high-grade lesions in our study was the presence of areas showing features of well-differentiated neuroendocrine carcinoma of the thymus (classic thymic carcinoid) in direct transition with areas of poorly differentiated neuroendocrine carcinoma indistinguishable from those of small cell (oat cell) carcinoma of the lung.47 The existence of such cases supports the notion that these tumors represent part of a continuous spectrum of differentiation that ranges from well-differentiated
through poorly differentiated neuroendocrine neoplasms. Rare cases also have been reported in the literature of thymic carcinoids displaying different lines of differentiation, including sarcomatous components. None of the cases in our study, however, displayed such features.

The differential diagnosis for these lesions includes other primary mediastinal tumors, mainly thymoma, paraganglioma, lymphoma, parathyroid adenoma or carcinoma, and medullary carcinoma of the thyroid arising in mediastinal location. The most difficult and important differential diagnosis in this setting is with thymoma, particularly of the spindle cell type. Spindle cell thymomas often can show areas displaying a prominent neuroendocrine appearance, with abundant epithelial pseudosettes composed of plump oval to spindle epithelial cells disposed radially around an empty space closely simulating the microacinar growth pattern sometimes seen in carcinoid tumors. Application of immunohistochemical stains can be helpful in such instances; although both lesions share strong CAM 5.2 positivity, thymomas will be negative for neuroendocrine markers such as chromogranin or synaptophysin.

Mediastinal paragangliomas also may pose difficulties for diagnosis because of their prominent organoid or neuroendocrine growth pattern and positive staining for neuroendocrine markers. Subtle distinguishing features between the 2 include lack of significant cytologic atypia, mitotic activity, necrosis, or vascular invasion in paraganglioma. It should be noted, however, that paragangliomas often may be characterized by prominent cytomegaly with enlarged, hyperchromatic, and atypical nuclei. However, despite the nuclear atypia, mitotic activity and other signs of malignancy, such as vascular invasion and necrosis, will be lacking in such lesions. In some instances, particularly in small mediastinoscopic biopsy specimens, the morphologic overlap between the 2 can be such that it may be impossible to distinguish them based on morphologic features alone. Immunohistochemical stains may be of aid in such instances; although both lesions share positivity for neuroendocrine markers such as synaptophysin and chromogranin, mediastinal paragangliomas are usually negative for CAM 5.2 cytokeratins, a finding in contrast with the results of the present study, which showed 100% positivity for this marker in thymic neuroendocrine carcinoma.

Other neuroendocrine neoplasms that may enter the differential diagnosis are ectopic mediastinal parathyroid tumors, including ectopic parathyroid adenomas and carcinomas. Histochemical studies for periodic acid–Schiff will demonstrate the presence of intracellular glycogen in parathyroid lesions, while results generally are negative in neuroendocrine carcinomas. Immunohistochemical stains for parathyroid hormones also may be helpful for identifying these tumors in equivocal cases.

Finally, medullary thyroid carcinoma arising in ectopic mediastinal location also could be confused with a thymic neuroendocrine carcinoma. Positivity for calcitonin and carcinoembryonic antigen will help distinguish these lesions from primary mediastinal neuroendocrine carcinomas.

Primary mediastinal neuroendocrine carcinomas predominantly composed of diffuse sheets of cells also can be confused with diffuse large cell lymphomas. The “salt-and-pepper” distribution of the nuclear chromatin and identification of areas displaying the more conventional nesting or organoid pattern will help make this distinction. Inclusion of lymphoid markers, such as leukocyte common antigen (LCA), L26, and UCHL-1, however, may be justified in the panel of immunostains used in cases showing the diffuse growth pattern to rule out the possibility of a lymphoid malignant neoplasm.

The present study supports previous observations suggesting that primary mediastinal neuroendocrine carcinomas represent a different biologic entity than foregut carcinoids arising at other locations. A study of a large series of patients with pulmonary neuroendocrine tumors that used morphologic criteria and a grading system similar to those used in our study found that the pulmonary tumors observed a distinctively better prognosis, stage for stage, than did their mediastinal counterparts. Thus, low-grade tumors (ie, typical pulmonary carcinoids) showed 5- and 10-year survivals of 87%, compared with a 50% 5-year survival and a 9% 10-year survival for low-grade neuroendocrine carcinomas of the thymus in the present study; intermediate-grade lung tumors (ie, atypical carcinoids) showed a 56% 5-year survival and 35% 10-year survival compared with intermediate grade neuroendocrine thymic tumors that showed a 20% 5-year survival and a 0% 10-year survival in the present study; and high-grade lung tumors (ie, small cell and large cell neuroendocrine carcinoma) showed 9% to 27% 5-year and 5% to 9% 10-year survival rates compared with 0% 5-year survival for high-grade neuroendocrine carcinoma of the thymus in the present study.

The present study also highlights the broad spectrum of histologic appearances of primary thymic neuroendocrine carcinomas and confirms the generally more aggressive nature of these tumors when arising in mediastinal location. Also, we documented cases in which we observed transitions of well- to moderately differentiated neuroendocrine carcinoma of the thymus to poorly differentiated neuroendocrine carcinoma of the small cell type. This latter feature lends support to the notion that low-grade tumors (ie, carcinoids) may evolve into high-grade malignant neoplasms (small cell carcinomas). Because of the generally more aggressive clinical behavior of these lesions and their more pronounced cytologic atypia, we believe the term carcinoid...
should be abandoned for these tumors and replaced by the term thymic neuroendocrine carcinoma.

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