

# Thymic Neuroendocrine Carcinomas With Combined Features Ranging From Well-Differentiated (Carcinoid) to Small Cell Carcinoma

## A Clinicopathologic and Immunohistochemical Study of 11 Cases

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**Key Words:** Thymic neoplasms; Carcinoid; Carcinoma; Small cell carcinoma; Neuroendocrine

### Abstract

We reviewed 11 cases of primary thymic neuroendocrine carcinomas with combined features ranging from well-differentiated to poorly differentiated neuroendocrine carcinoma. For 3 asymptomatic patients, tumors were discovered during routine examination. Presentation in the other patients was as follows: Cushing syndrome, 2 patients; chest pain, 3 patients; superior vena cava syndrome, 1 patient; and hypercalcemia and hypophosphatemia, 1 patient. No clinical data were available for the 11th patient. All tumors were located in the anterior mediastinum and treated by surgical excision. The lesions were large and well-circumscribed with areas of hemorrhage and necrosis. They were characterized by areas showing a proliferation of monotonous, round tumor cells adopting a prominent organoid pattern admixed with areas showing sheets of atypical cells with hyperchromatic nuclei, frequent mitoses, and extensive areas of hemorrhage and necrosis.

Immunohistochemical studies performed in 6 cases showed strong CAM 5.2 low-molecular-weight cytokeratin positivity in all cases, chromogranin and synaptophysin positivity in 4, Leu-7 in 3, and focal positivity for p53 in 2. Follow-up information for 9 cases showed that all patients died of their tumors between 1 and 4 years after diagnosis. The present cases highlight the heterogeneity of neuroendocrine neoplasms and reinforce the notion that these tumors form part of a continuous spectrum of differentiation.

The term *carcinoid* was first introduced by Oberndorfer<sup>1</sup> to identify a group of tumors in the small intestine that despite their epithelial morphologic features followed a better clinical behavior than conventional carcinomas. Since then, numerous publications dealing with this type of neoplasm have been reported in the literature with conflicting viewpoints expressed about their classification and malignant potential.<sup>2,3</sup> However, no single classification has been accepted completely, and currently the term *carcinoid* is still used to designate these neuroendocrine tumors irrespective of their location.

In 1972, Arrigoni et al<sup>4</sup> identified a distinctive type of neuroendocrine neoplasm that shared many of the cytoarchitectural features of carcinoid tumors yet displayed markedly atypical features, such as increased mitotic activity, nuclear pleomorphism, and areas of necrosis; the authors proposed the designation of *atypical* carcinoid for such tumors. Subsequent studies identified cases showing combinations and transitions between typical and atypical carcinoid, as well as between typical carcinoid and areas bearing the light microscopic features of small cell carcinoma. Such observations led to the proposal that all of these tumors belong in a single family of neoplasms showing varying degrees of neuroendocrine differentiation.<sup>5-7</sup>

We present a study of 11 cases of primary thymic neuroendocrine carcinomas that were characterized by the admixture of areas ranging from well-differentiated to moderately differentiated (carcinoid or atypical carcinoid) to poorly differentiated neuroendocrine carcinoma (small cell carcinoma) within the same tumor mass. The present cases highlight the variability in the spectrum of differentiation of primary thymic neuroendocrine carcinomas and support the

hypothesis that all such tumors form part of a single spectrum of lesions that are capable of showing varying degrees of differentiation.

## Materials and Methods

Eleven cases of primary thymic neuroendocrine carcinomas showing the features described herein were identified from the files of the Department of Pulmonary and Mediastinal Pathology, Armed Forces Institute of Pathology, Washington DC, and the personal consultation files of one of us (S.S.) from 1960 through 1995. Hematoxylin-eosin (H&E)-stained sections were available for review in all cases.

For immunohistochemical studies, representative formalin-fixed paraffin-embedded tissue sections were available for 6 cases. The 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, NY), synaptophysin (Dako), and p53 (Biogenex, San Ramon, CA) by the avidin-biotin complex peroxidase technique. Nonimmune rabbit and mouse serum was substituted for negative controls. Appropriate positive controls were run concurrently for every antibody tested.

For clinical information, a questionnaire was developed and mailed to the respective contributing physicians or tumor registries during a period of 24 months. Information requested included sex, age, presenting signs and symptoms, relevant history (mainly of the existence of similar tumor within the lung or extrathoracic area), gross findings, treatment, and follow-up.

## Results

### Clinical Features

The patients were 10 men and a woman aged 19 to 72 years (median, 45 years). Two patients presented with Cushing syndrome and 1 with hypercalcemia and hypophosphatemia. In 3 patients, the presenting symptom was chest pain; 1 patient presented with the superior vena cava syndrome. The tumors were discovered incidentally in 3 patients on routine physical examination. For 1 patient, no clinical information could be obtained. All the tumors were located in the anterior mediastinum and were treated by complete surgical excision. Clinical follow-up information was obtained for 9 patients; all patients were dead of tumor within a period of 1 to 4 years after diagnosis. No clinical follow-up information could be obtained for 2 patients.

### Gross Features

In cases for which this information was available, the tumors were described as large, well-circumscribed masses that measured between 10 and 13 cm in greatest diameter. The tumors showed a tan-white to brown soft cut surface with areas of necrosis and hemorrhage.

### Histologic Features

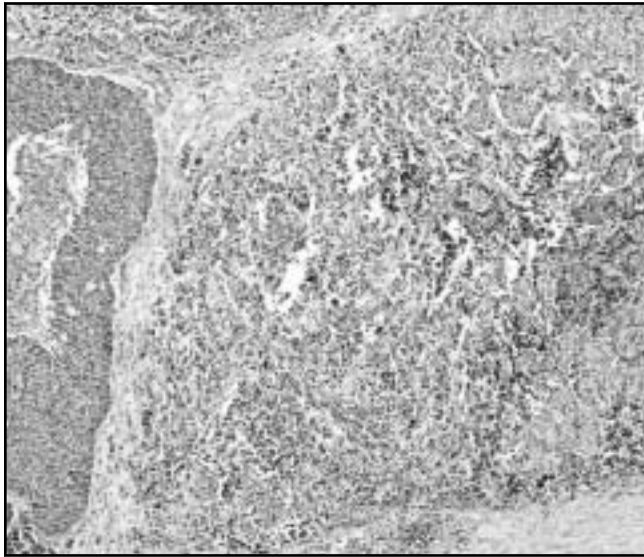
On scanning magnification, 2 different growth patterns were seen admixed in various proportions. The better differentiated areas were composed of round medium-sized cells with indistinct cell borders, moderate amounts of pale eosinophilic cytoplasm, mild to moderate nuclear atypia, and low mitotic activity (<3 per 10 high-power fields). Transitions to areas characterized by an organoid pattern composed of nests of monotonous round tumor cells with central areas of necrosis showing solid sheets of highly atypical cells with extensive areas of necrosis and increased mitotic activity were observed **Image 1** and **Image 2**. The high-grade areas were composed of a solid proliferation of smaller cells showing more pronounced nuclear atypia, with dark, hyperchromatic nuclei with inconspicuous nucleoli, increased mitotic activity (>10 per 10 high-power fields), and extensive confluent areas of necrosis **Image 3** and **Image 4**. Foci displaying extensive crush artifact also could be observed in these areas. In some areas, remnants of thymic tissue in the form of entrapped Hassall corpuscles were admixed with tumor cells **Image 5**. In other areas, more subtle transitions between the better and the poorly differentiated areas could be observed **Image 6**.

### Immunohistochemical Features

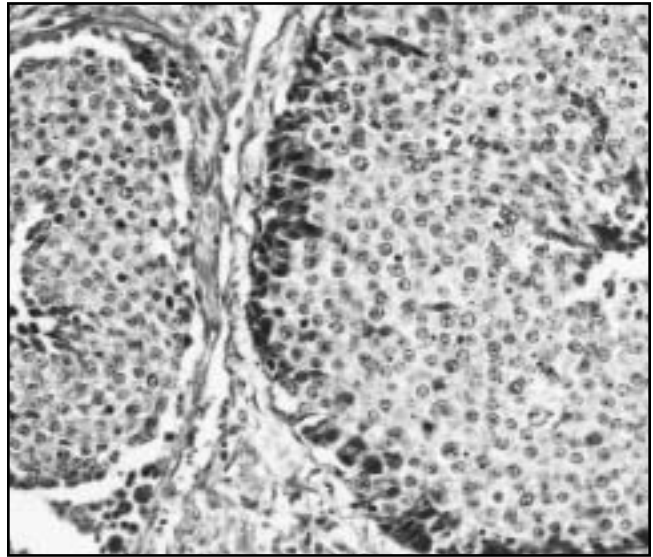
Immunohistochemical studies were performed in 6 cases using antibodies for CAM 5.2 low-molecular-weight cytokeratin, broad-spectrum keratin cocktail, chromogranin, synaptophysin, Leu-7, and p53. All cases stained strongly positive for CAM 5.2 keratin antibodies in the better differentiated areas and focally for broad-spectrum keratin, while the poorly differentiated areas showed weak and focal (dot-like) positivity for CAM 5.2 only. Stains for chromogranin and synaptophysin were positive in 4 cases and for Leu-7 in 3. Two cases showed focal p53 staining in the poorly differentiated areas.

## Discussion

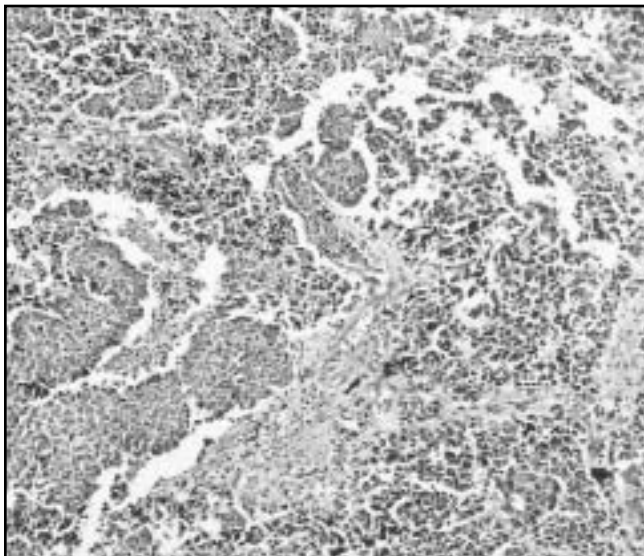
Primary thymic neuroendocrine carcinomas are relatively rare neoplasms. They may account for approximately 2% to 4% of all anterior mediastinal neoplasms. These tumors seem to show a male predilection in a proportion of 3:1; approximately 65% of cases are discovered incidentally during



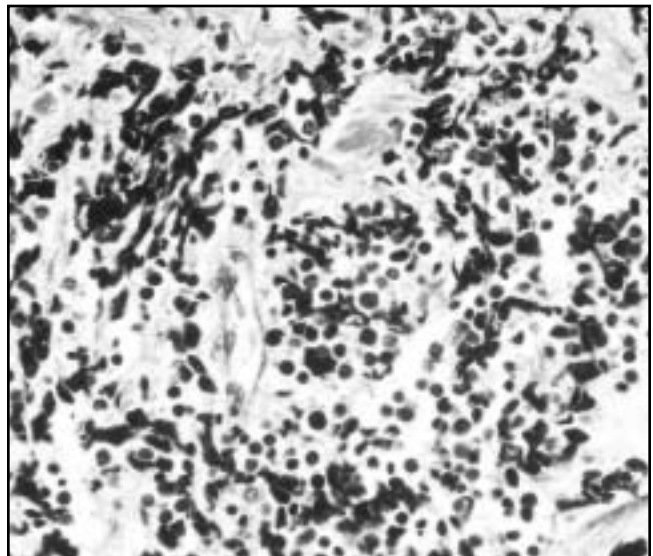
**Image 1** Combined neuroendocrine neoplasm showing 2 distinct growth patterns (H&E,  $\times 20$ ).



**Image 2** High-power view of a better differentiated neuroendocrine neoplasm conserving a nesting pattern (H&E,  $\times 40$ ).



**Image 3** Poorly differentiated neoplasm with haphazard distribution of neoplastic cells (H&E,  $\times 20$ ).

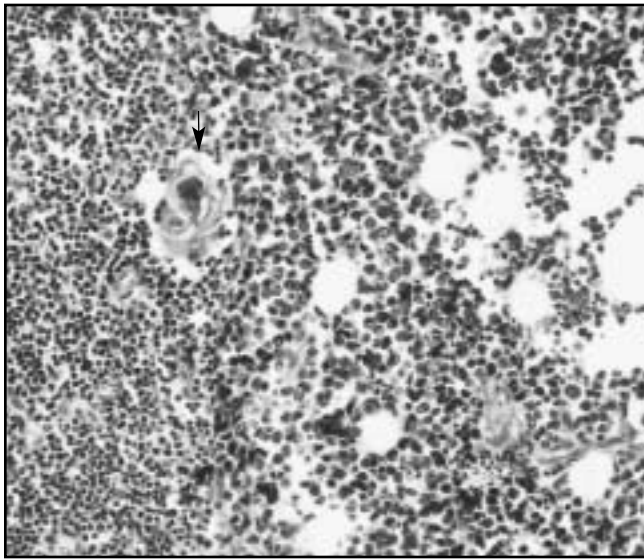


**Image 4** Higher power view of a poorly differentiated area showing crush artifact and a better preserved cell population with features of small cell carcinoma (H&E,  $\times 75$ ).

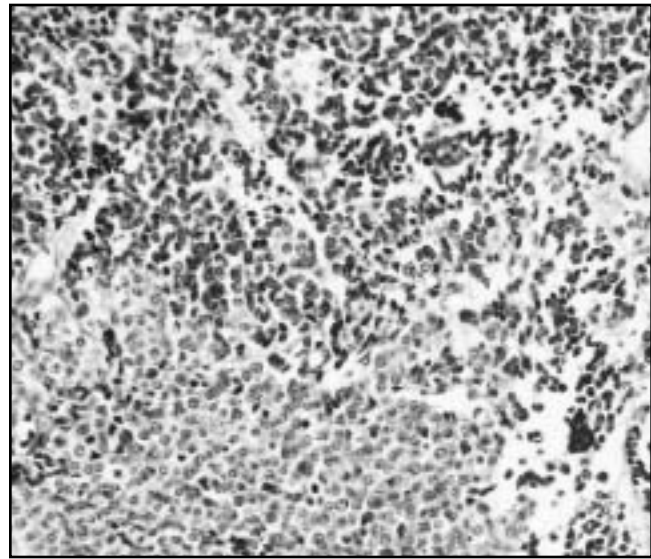
routine physical examination, while approximately 35% of these lesions may be associated with endocrinopathies.<sup>6</sup> Rosai and Higa were the first to identify these neoplasms in the thymic region<sup>8</sup> and to highlight their association with the multiple endocrine neoplasia syndrome.<sup>9</sup> Since these descriptions, many other cases have been reported in the literature highlighting such an association or describing unusual histopathologic or clinical features of these tumors.<sup>10-54</sup>

Although most primary thymic neuroendocrine carcinomas (thymic carcinoids) histologically resemble those

arising at other anatomic locations, such as the intestine or the lung, there seems to be a marked difference in the clinical behavior of these tumors when they arise in the mediastinum. For instance, a higher degree of aggressive behavior has been noted for thymic carcinoids compared with bronchial carcinoids, particularly those associated with the multiple endocrine neoplasia syndrome.<sup>5,55</sup> Moreover, recent studies seem to indicate that primary thymic carcinoids may indeed display a broader range of cytologic features of atypia than other conventional foregut carcinoids,



**Image 5** Remnants of thymic tissue (Hassall corpuscles, arrow) involved by tumor (H&E, x30).



**Image 6** Subtle transition between well-differentiated and poorly differentiated areas in a combined neuroendocrine neoplasm (H&E, x60).

thereby justifying their inclusion within the broad category of neuroendocrine carcinomas.

In addition to their more aggressive clinical behavior and marked histologic features of atypia, thymic neuroendocrine carcinomas also are characterized by their capability to display a number of unusual histopathologic appearances. Thus, tumors showing spindle cell features, abundant oncocyctic cytoplasm, mucin-rich stroma, or microfilamentous inclusions on light and electron microscopy have been described.<sup>18,32,56-58</sup> Even more unusual morphologic variants, such as tumors showing combinations of different lines of differentiation, also have been reported.<sup>37,59</sup> Paties et al<sup>37</sup> described a thymic tumor in a 62-year-old man that showed a combination of carcinoma, sarcoma, and carcinoid tumor. Another report of a similar occurrence has been documented in a 54-year-old man who had paraneoplastic symptoms and an anterior mediastinal mass that histologically showed a carcinoid tumor with areas of chondroid and osseous differentiation.<sup>59</sup> At the other end of the spectrum, tumors associated with other types of poorly differentiated carcinoma have been described.<sup>7,60</sup> Sensaki et al<sup>60</sup> described a case of thymic carcinoid in association with undifferentiated carcinoma. Scholz and Bahn,<sup>61</sup> in a review of 11 cases of thymic tumors associated with Cushing syndrome, found 3 cases that contained small cell carcinoma. Wick and Scheithauer<sup>7</sup> also reported a case of small cell carcinoma arising in association with a carcinoid tumor of the thymus. The authors<sup>7</sup> stated that since small cell carcinomas are located at the far end of the spectrum of neuroendocrine tumors, it is expected that such an association could occur at any site at which better differentiated neuroendocrine tumors occur.

The cases presented herein support the concept that neuroendocrine neoplasms form part of a spectrum of differentiation that ranges from well-differentiated to moderately differentiated (carcinoid and atypical carcinoid), to poorly differentiated neuroendocrine carcinomas (small cell carcinoma).<sup>62,63</sup> The presence of areas of transition between the better differentiated elements and the poorly differentiated components observed in our cases further supports the notion that, in some instances, the well-differentiated elements may undergo progressive malignant transformation to give rise to a poorly differentiated neuroendocrine carcinoma. It is of interest that this type of combination has not been reported more often at other sites at which poorly differentiated neuroendocrine carcinomas are more common, such as the lung. A likely explanation for this may be the rapid doubling times of small cell carcinoma of the lung, which could lead to the poorly differentiated elements overrunning the better differentiated components early in the evolution of the process. Although the findings we describe may be ascribed to a chance occurrence or a “collision” of 2 different unrelated neoplastic processes, we believe these cases support the existence of a continuum of differentiation in thymic neuroendocrine neoplasms, which as a result of tumor progression, may lead to the development of poorly differentiated neuroendocrine carcinoma arising from thymic carcinoid.

The existence of these combined tumors may pose a problem for differential diagnosis under certain circumstances, particularly when dealing with limited mediastinoscopic biopsy material. In small thoracoscopic

biopsy specimens, only 1 line of differentiation may be apparent in the tissues available for examination. If the material sampled represents small cell carcinoma, it is most likely that the patient will undergo treatment with chemotherapy without surgical resection of the mass. However, if the material sampled is the well-differentiated area, then the most likely possibility is that surgical resection of the tumor mass will be elected as the treatment of choice. Adequate and extensive sampling of the resected specimens are, therefore, important in cases of thymic carcinoids to rule out the possibility of the emergence of a small cell carcinoma component in these lesions.

We have documented 11 cases of thymic tumors showing transitions ranging from well-differentiated to moderately differentiated (carcinoid or atypical carcinoid) to poorly differentiated neuroendocrine carcinoma (small cell carcinoma). Such a phenomenon, although unusual, is important to recognize so that adequate treatment may be instituted for these patients.

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