

# Cystic Well-Differentiated Neuroendocrine Carcinoma (Carcinoid Tumor)

## A Clinicopathologic and Immunohistochemical Study of Two Cases

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### Abstract

*Two cases of primary neuroendocrine carcinoma (carcinoid tumor) arising in the walls of a multilocular thymic cyst (MTC) are described. The patients were 2 men, ages 36 and 44 years. Clinically, the patients had chest pain, cough, and dyspnea. Radiographic evaluation demonstrated the presence of anterior mediastinal tumor in both patients, and complete surgical resection of the tumor mass was performed. The tumors measured approximately 6 and 8 cm in greatest dimension and were cystic with solid areas but did not show areas of necrosis or hemorrhage. Histologic examination revealed a cystic tumor with features similar to those previously described for MTCs. In addition, in the walls of the cystic structures, there was cellular proliferation arranged in a nesting growth pattern, similar to the more solid areas of the tumor. The tumor was characterized by a homogeneous cellular proliferation with mild cellular atypia and no more than 2 mitotic figures per 10 high-power fields. Immunohistochemically, the tumor cells showed strong positive reactions for keratin and neuroendocrine markers, ie, chromogranin and synaptophysin. Both patients were alive after periods of 12 and 18 months.*

Primary thymic neuroendocrine carcinomas are uncommon neoplasms that recapitulate the histologic features of the tumors that occur in other areas of intrathoracic or extrathoracic origin. When they occur in the anterior mediastinum, they may be associated with other endocrine syndromes such as the multiple endocrine neoplasia syndrome and other endocrinologic abnormalities. However, such association is present in no more than 25% of the cases. Different growth patterns and a classification system have been recorded in the literature.<sup>1-29</sup>

It is interesting that the presence of tumors growing in association with or developing from the walls of multilocular thymic cysts (MTCs) has not been described properly in the literature thus far. The present cases highlight the importance of proper evaluation and proper sectioning of tumors that are predominantly cystic.

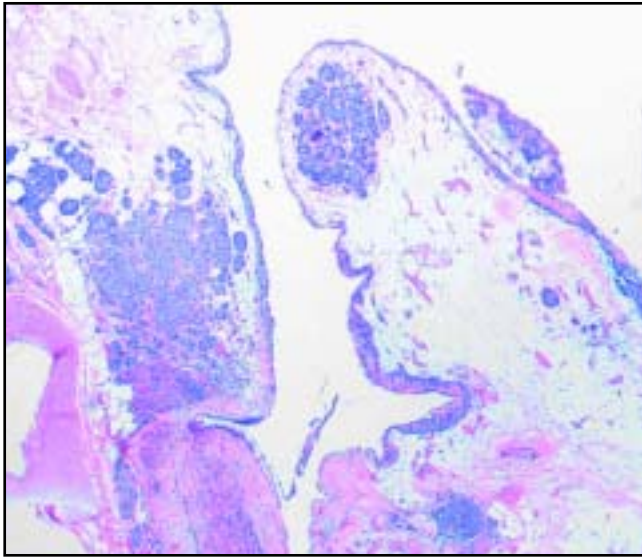
### Case Description

#### Clinical Features

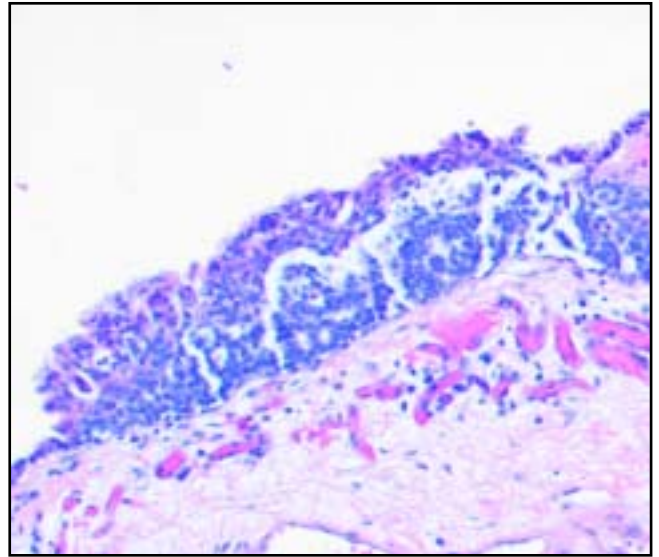
The 2 patients were men, ages 36 and 44 years. Neither of the patients had any history of tumor elsewhere. Both had chest pain, cough, and dyspnea. Radiologic evaluation in both patients disclosed the presence of an anterior mediastinal mass, and complete surgical resection of the anterior mediastinal mass was performed.

#### Gross Features

The tumors measured approximately 6 and 8 cm in greatest dimension. Both were described as cystic with solid areas. The cysts varied in size and contained clear fluid. Neither necrosis nor hemorrhage was present in either of the tumors.



**Image 1** Cystic anterior mediastinal tumor with features of multilocular thymic cyst and areas of well-differentiated neuroendocrine carcinoma growing in the cystic walls (H&E,  $\times 10$ ).



**Image 2** Well-differentiated neuroendocrine carcinoma growing under the epithelial lining of the thymic cyst (H&E,  $\times 20$ ).

### Histologic Features

The tumors were characterized by a predominant cystic appearance, similar to that described in MTCs. The cysts were lined by squamous or flattened epithelium, areas of lymphoid hyperplasia, and thymic remnants. Within the wall of the cysts, a tumor growing in a nesting pattern was identified **Image 1**. In addition, under the epithelium lining the cystic structures, nests of tumor cells growing alongside also were identified **Image 2**. Higher magnification of the tumor cells showed a homogeneous cellular proliferation composed of round to polygonal cells with round nuclei and inconspicuous nucleoli. The cellular proliferation showed mild cellular atypia with a mitotic count of 1 to 2 mitoses per 10 high-power fields **Image 3**. Neither necrosis nor hemorrhage was present.

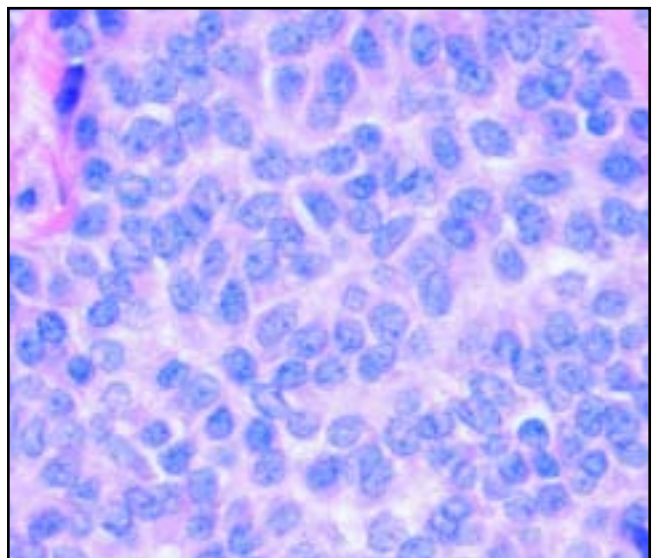
Immunohistochemical studies performed in both cases showed tumor cells positive for keratin, chromogranin, and synaptophysin.

Clinical follow-up disclosed that both patients were alive at 12 and 18 months after surgical resection of the neoplasms.

### Discussion

Neuroendocrine tumors in the anterior mediastinum encompass a group of tumors that can be categorized as benign and low-, intermediate-, and high-grade malignant potential. A classification system and the different growth patterns that these tumors can have when in the anterior mediastinum have been described.<sup>23-29</sup> On the other hand, MTC,

which represents an unusual benign lesion in the anterior mediastinum, has been reported to be associated with numerous tumors, including germ cell tumors, mucoepidermoid carcinomas, and metastatic carcinomas.<sup>30-36</sup> However, despite the different growth patterns that neuroendocrine tumors might have in the thymic region and despite the different associations of MTC with other tumors, the existence of neuroendocrine carcinomas arising within the walls of an MTC has not been recorded properly in the literature.



**Image 3** Higher magnification of the well-differentiated neuroendocrine carcinoma. Note the absence of necrosis and mitotic activity (H&E,  $\times 40$ ).

Clinically, neuroendocrine carcinomas may be associated with endocrine syndromes such as the multiple endocrine neoplasia syndrome. Nevertheless, these cases represent a small percentage of cases, whereas the majority of neuroendocrine carcinomas have nonspecific symptomatology. In addition, from the radiologic viewpoint, the presence of a cystic anterior mediastinal tumor should raise the suspicion of an MTC or another neoplasm with cystic degeneration. From the histopathologic viewpoint, the histologic features are such that they should not present a problem in interpretation. However, the problem may be in the proper sampling of these cystic mediastinal lesions. As documented in the past, MTC is well known to represent an unusual benign lesion that most likely is an acquired lesion probably secondary to an inflammatory insult.<sup>37,38</sup> The existence of different types of neoplasms arising in the walls of an otherwise “classical” example of MTC is well documented. The gamut of the neoplasms is wide and encompasses epithelial neoplasms, germ cell tumors, and tumors of lymphoid origin. In addition, in more unusual circumstances, metastatic neoplasms may mimic the histologic features of MTC. Therefore, it is of utmost importance to amply sample any mediastinal cystic tumor in which the features are those of MTC before identifying the lesion as a bona fide MTC. In a recent review of cystic lesions of the mediastinum, Wick<sup>39</sup> illustrated the presence of a similar phenomenon of neuroendocrine carcinoma with prominent cystic changes, comparable to the cases described herein.

Regarding the clinical significance of this type of association (neuroendocrine carcinoma and MTC), it is difficult with 2 cases to predict the clinical behavior that these tumors will exhibit. However, it is likely that the potential behavior will be predicted by the extent of disease. In cases in which the tumor is found only focally in the wall of a cyst, the tumor may follow a more indolent course, whereas in cases in which there is extensive tumor, the behavior will be similar to that ascribed to similar tumors in the mediastinum. One important histologic characteristic that was observed in one of our cases was the presence of tumor growing under the lining epithelium of the cyst. That feature suggests the possibility that some cells lining the epithelium in cystic structures may undergo neuroendocrine differentiation or that the epithelium itself may have neuroendocrine cells that, in some circumstances, can trigger the development of neuroendocrine tumors. Similar observation has been made in cystic mucoepidermoid carcinomas of the thymus in which the epithelium lining the cysts had areas of transition between neoplastic and nonneoplastic epithelium. Nevertheless, in one of the cases described herein, we found only focal nested areas under the lining epithelium and not a definite “pagetoid” appearance or an “in situ” neuroendocrine component.

In short, neuroendocrine neoplasms should be added to the list of tumors that also might grow along the walls of an

otherwise MTC. Careful sectioning becomes crucial before identifying a lesion as a classical MTC.

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