



# Thymic carcinoma: update of current diagnostic criteria and histologic types

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## KEYWORDS

Thymic carcinoma;  
 Histologic  
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Thymic carcinomas are rare tumors thought to derive from thymic epithelium. Because of the complex embryological origin of the thymus, whose development includes contributions from the third and, to a lesser extent, the fourth pharyngeal pouches, thymic carcinomas are endowed with great morphologic heterogeneity. A large number of histologic types have been described that resemble tumors arising in other organs. Unfortunately, no definitive pathognomonic histological features or immunohistochemical markers are associated with these tumors, making them a real challenge for diagnosis. Because of their close similarity with tumors arising at other organs, the diagnosis of thymic carcinoma must be regarded, for the most part, as a diagnosis of exclusion. This review will focus on current criteria for diagnosis of these tumors, with a review of the various histopathologic appearances that they can adopt. © 2005 Elsevier Inc. All rights reserved.

Thymic carcinomas have attracted much attention in the recent literature because of their morphologic heterogeneity and difficulties for precise diagnosis. Because of their lack of organotypical features of thymic differentiation, these tumors were for many years considered as a manifestation of metastatic disease from an occult primary. The first recognition of such tumors as a primary neoplasm of thymic epithelium was in the study in 1977 by Shimosato and coworkers of squamous cell carcinoma of the thymus.<sup>1</sup> This was followed by a study by Snover and coworkers<sup>2</sup> in 1982 in which several additional histologic variants of this tumor were delineated. Since then, numerous articles have appeared in the literature addressing this topic. The largest study on these tumors was published in 1991 by Suster and Rosai.<sup>3</sup> In this study of 60 cases, various histologic subtypes were identified, the majority of which could be assigned to either a high- or low-grade histologic category, with clinical behavior paralleling their morphology. Despite the many

advances in our understanding of these tumors, thymic carcinoma remains an elusive diagnosis. With very few exceptions, it continues to be a diagnosis of exclusion, since the possibility of a late metastasis or of spread from an occult primary to the mediastinum must always be first ruled out before making this diagnosis. Herein we will review the current status on these tumors along with an evaluation of the role of special stains and other techniques for diagnosis and of the most recently described morphologic variants.

## Clinical features and diagnostic criteria

Thymic carcinomas are, in general terms, highly aggressive neoplasms. In the largest study published by Suster and Rosai,<sup>3</sup> two distinct clinical groups were identified: one associated with a favorable clinical behavior with long survival, and one associated with a rapidly fatal clinical course. These two clinical groups directly correlated with the histologic grade of the lesions, with the group exhibiting favorable prognosis being associated with low-grade histol-

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ogy, and the cases with a poor prognosis being associated with high-grade histology. At the time that paper was published, criteria for the morphologic classification of thymic epithelial neoplasms were not yet very well developed and, in retrospect, many of the tumors included in the low-grade, favorable prognostic clinical category most likely would be reclassified today as atypical thymomas (WHO type B3 thymoma). The majority of cases that would qualify under current criteria for a diagnosis of thymic carcinoma are therefore more likely to correspond to high-grade tumors with highly aggressive behavior.<sup>4-6</sup>

Thymic carcinoma can occur in all age groups but is most frequent in adults between 30 and 60 years of age.<sup>3</sup> In the study by Suster and Rosai, a slight male predilection was noted (1.5:1 male-to-female).<sup>3</sup> The majority of patients present with symptoms directly attributable to the anterior mediastinal location of the mass, including chest pain, shortness of breath, and the superior vena cava syndrome. Other symptoms include weight loss, fatigue, fever, and anorexia, and less commonly hypertrophic pulmonary osteoarthropathy. In a small percentage of patients, the lesions can be asymptomatic and incidentally discovered on routine chest X-rays.<sup>3</sup> Cases associated with a history of myasthenia gravis before the development of the tumor have been described<sup>3,7,8</sup>; in two cases, development of a thymic carcinoma from a preexisting thymoma in patients with long-standing myasthenia gravis could be histologically demonstrated.<sup>7</sup> The tumors often present in advanced stages; however, examples of well-circumscribed and even encapsulated lesions can be observed.

Thymic carcinoma is histologically defined as a primary thymic epithelial neoplasm showing overt cytologic features of malignancy with absence of the organotypical features of differentiation of the thymus.<sup>4-6,9,10</sup> Because of the highly nonspecific histology of thymic carcinoma, the criteria for making this diagnosis should be, in the majority of instances, based on a combination of clinical and morphologic data. The diagnosis of thymic carcinoma, with the exception of select cases, cannot be established in a vacuum based solely on histopathologic examination. The role of histologic examination is mainly to confirm a diagnosis of malignancy (ie, establish the presence of overt cytological atypia) and to specify the morphologic type of the lesion (ie, squamous, basaloid, lymphoepithelioma-like, sarcomatoid, etc). It cannot be over-emphasized that *there is nothing distinctive or pathognomonic* about the histology of thymic carcinoma that can help establish a definitive diagnosis based solely on histologic examination of a biopsy or resected specimen. Thorough clinical and radiological studies are needed to demonstrate the absence of an occult tumor elsewhere or to elicit a history of a remote primary. In many cases, the answer to this question may only be determined by means of a postmortem examination.<sup>3</sup> Exceptions to this rule include cases in which obvious transitions with preexisting thymic epithelium<sup>9</sup> or with well-differentiated areas displaying the conventional organotypical features of a pre-

**Table 1** Histologic types of thymic carcinoma

Squamous cell carcinoma
- Well-differentiated, keratinizing
- Moderately differentiated
- Poorly-differentiated, non-keratinizing (lymphoepithelioma-like)
Neuroendocrine carcinoma
Mucoepidermoid carcinoma
Clear cell carcinoma
Basaloid carcinoma
Carcinosarcoma
Spindle cell (sarcomatoid) carcinoma
Papillary carcinoma
Adenocarcinoma
- Mucinous
- Non-mucinous
Adenosquamous carcinoma
Desmoplastic carcinoma
Anaplastic carcinoma
Rhabdoid carcinoma
Other rare types
- Hepatoid carcinoma
- Rhabdomyomatous carcinoma

existing thymoma are demonstrated,<sup>7</sup> or when dealing with some variants of thymic carcinoma whose features are so highly distinctive that origin from an alternate source other than the thymus would be highly unlikely, such as basaloid carcinoma of the thymus with cystic changes or carcinoma of the thymus with rhabdomyomatous cells.

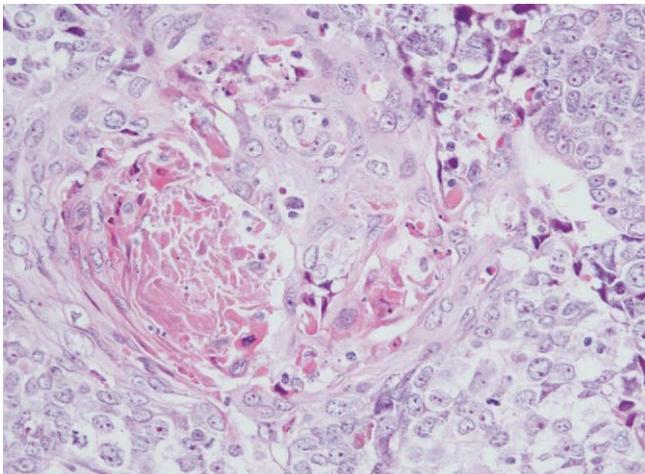
## Histopathologic types

Thymic carcinoma can show a wide spectrum of morphologic features. A large number of histologic types of thymic carcinoma have been described, the majority of which seem to have their counterpart in similar tumors arising in other organs (Table 1). The morphologic spectrum of these tumors ranges from that of low-grade, well-differentiated neoplasms, to high-grade poorly differentiated malignancies. A common feature of all thymic carcinomas is the fact that they lack any of the organotypical features of thymic differentiation (ie, lobulation separated by broad fibrous bands originating from the capsule, perivascular spaces, areas of “medullary” differentiation, and a dual cell population composed of immature T-lymphocytes and thymic epithelial cells). When present, the lymphoid component in these tumors is made up of either mature T-cells or B-lymphocytes/plasma cells. The most common type of thymic carcinoma in Western patients is poorly differentiated, nonkeratinizing squamous cell carcinoma. Primary neuroendocrine carcinomas of the thymus are a special category that, although belonging in the same family of tumors, share several common features that merit special attention. These will be discussed in a separate article in this issue (see neuroendocrine carcinoma of the thymus).

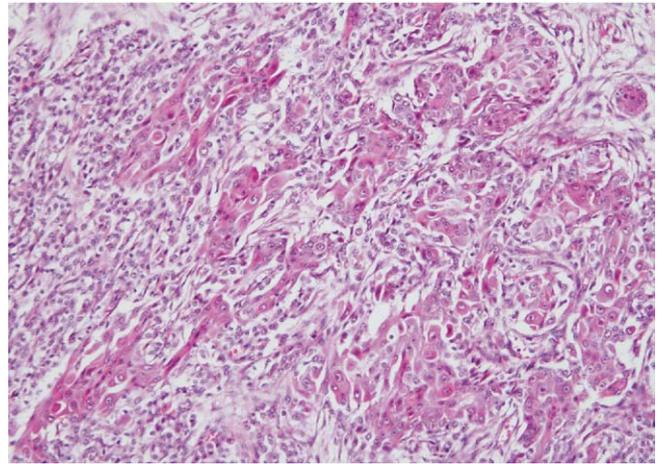
## Squamous cell carcinoma of the thymus

Shimosato and coworkers<sup>1</sup> were the first to recognize tumors with features of squamous differentiation as examples of primary carcinoma of the thymus. Additional examples were subsequently identified.<sup>3,11–14</sup> Primary squamous cell carcinoma of the thymus can manifest in three forms depending on their degrees of differentiation: well-differentiated (keratinizing) squamous cell carcinoma, moderately differentiated squamous cell carcinoma, and poorly differentiated (nonkeratinizing) squamous cell carcinoma. The latter often shows a distinctive syncytial growth pattern accompanied by a heavy lymphoplasmacellular stromal infiltrate, reason why it was dubbed “lymphoepithelioma-like” carcinoma of the thymus to acknowledge the close similarity with its counterpart in the nasopharynx.<sup>2</sup> Squamous cell carcinoma is the most common type of thymic carcinoma.<sup>6,8</sup> Most cases occur in middle aged adults with a slightly increased female ratio. The tumor presents as an anterior mediastinal mass, usually invading adjacent structures, with frequent lymph node metastases.

*Well-differentiated, keratinizing squamous cell carcinoma* shows identical features to its common counterpart in other organs. It is composed of nests or cords of large, polygonal tumor cells showing a pavement-like, epidermoid arrangement. The tumor cells display overt evidence of cytologic atypia manifested by large, vesicular nuclei with prominent eosinophilic nucleoli and mitoses. The cells usually have thick cell membranes and often show intercellular bridges. Foci of keratinization and squamous pearl formation are usually easily identified (Figure 1). Focal areas of necrosis may be present. The tumors are widely invasive and often display a desmoplastic stroma, with accompanying neutrophilic, eosinophilic, or lymphocytic infiltration. Some cases can show transitions with areas bearing the features of organotypical or atypical thymoma<sup>1,7</sup> (Figure 2). Rare cases have been described in association with multilocular thymic cysts.<sup>15,16</sup> The main differential diagnoses



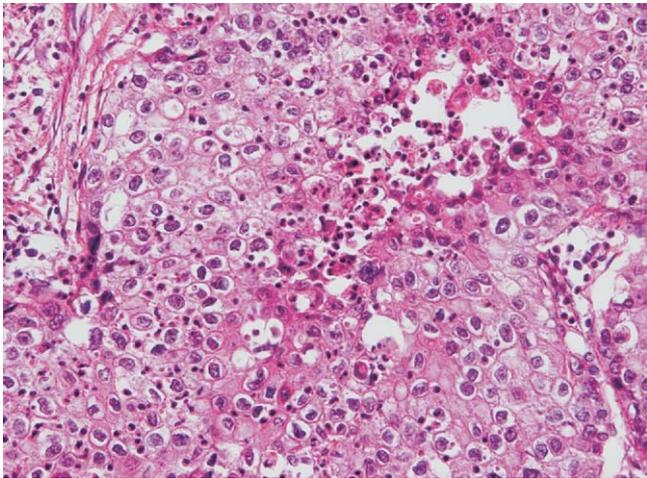
**Figure 1** Well-differentiated squamous cell carcinoma of the thymus with focus of keratin pearl formation.



**Figure 2** Epithelial-rich thymoma showing transitions with foci of well-differentiated squamous cell carcinoma of the thymus.

include a metastasis of squamous cell carcinoma to mediastinal lymph nodes and atypical thymoma (WHO type B3 thymoma). Distinction of these tumors from atypical thymoma can be sometimes difficult. In fact, it is likely that many of the cases reported as well-differentiated squamous cell carcinoma of the thymus in the literature actually correspond to atypical thymomas.<sup>1,3,6</sup> The main distinguishing features between these two entities include the extensive, as opposed to focal nature of the keratinizing areas in squamous cell carcinoma, and the demonstration of immature T-lymphocytes intimately admixed with the epithelial tumor cells in atypical thymoma. The possibility that well-differentiated squamous cell carcinoma of the thymus arises as a result of tumor progression from atypical thymoma is supported by the frequent areas of transition observed between these two neoplasms and the overlap in histologic features that both can display.<sup>7</sup> This could also explain the much more favorable prognosis of well-differentiated thymic carcinoma, which closely parallels that of atypical thymoma.<sup>1,6</sup>

*Moderately differentiated squamous cell carcinoma* is characterized by more pronounced cytologic atypia and less clear-cut evidence of squamous differentiation. The cells generally display a higher nuclear-to-cytoplasmic ratio, with more frequent mitoses and loss of clear-cut intercellular bridges. Keratinization is usually very focal and inconspicuous and keratin pearls are generally absent (Figure 3). Many of the tumor cells display single cell keratinization, with deeply eosinophilic cytoplasm surrounding small piknotic or degenerating nuclei. Areas of necrosis are more prominent than in the well-differentiated tumors and may be often confluent. Lymphovascular invasion is also commonly seen. Some tumors can show prominent peripheral palisading of tumor cells around small tumor islands. The most important differential diagnosis is with a metastasis from a squamous cell carcinoma of the lung. This distinction is of clinical importance since primary squamous cell carcinoma of the thymus follows a better prognosis than a comparable primary squamous cell carcinoma of the lung with extensive mediastinal lymph node involvement. In the

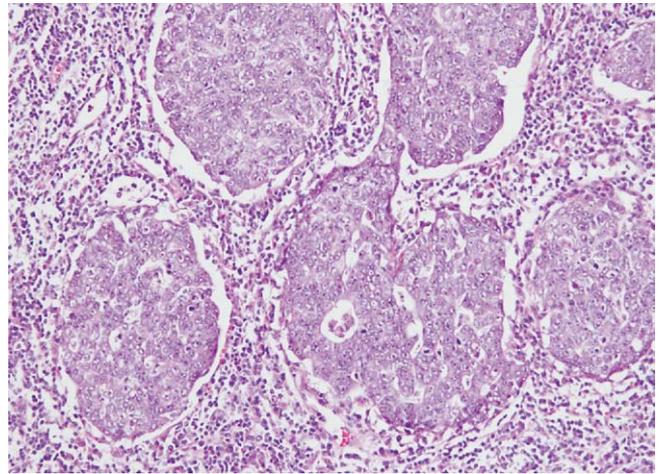


**Figure 3** Moderately differentiated squamous cell carcinoma showing more pronounced cytologic atypia, single cell keratinization, and incipient focus of necrosis.

study by Shimosato and coworkers,<sup>1</sup> in all cases in which the primary thymic tumors could be successfully excised and treated with postoperative radiation, the patients were alive and well from 1 to 12 years after diagnosis. Endoscopic examination and detailed radiographic studies are necessary to demonstrate absence of bronchial compromise in such tumors and to rule out the possibility of massive mediastinal extension from a bronchogenic primary lesion.

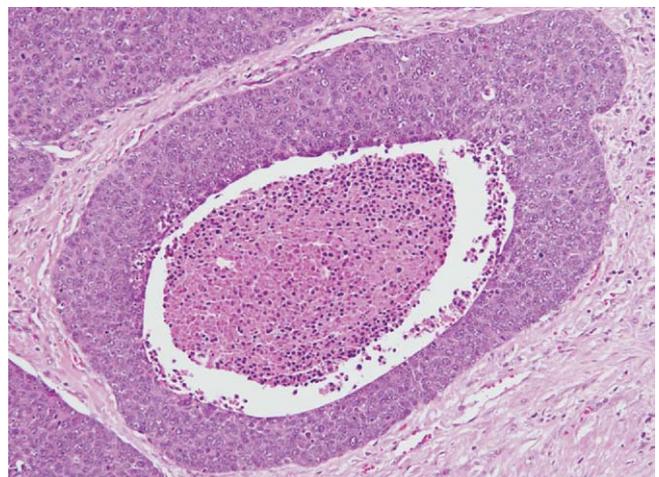
*Poorly differentiated (nonkeratinizing) squamous cell carcinoma* is characterized by sheets and islands of primitive-appearing round to oval tumor cells with large, vesicular nuclei, prominent, often centrally placed eosinophilic nucleoli, and scant rim of pale cytoplasm with indistinct cell borders. Foci of keratinization are rarely seen and intercellular bridges are always absent. The tumors often grow in a syncytial pattern separated by a dense lymphoid stroma closely reminiscent of their counterparts in the nasopharynx (Figure 4). Snover and coworkers<sup>2</sup> were the first to point out the resemblance of these tumors with their nasopharyngeal counterpart; the term “*lymphoepithelioma-like carcinoma*” has since been employed for these lesions to stress their close resemblance to the nasopharyngeal tumors of similar name. The latter term, however, is an anachronism and is no longer used to refer to the nasopharyngeal tumors<sup>17</sup>; it is therefore probably best abandoned.

A striking and distinctive feature of these tumors is foci of central, comedo-like areas of necrosis within the tumor cell islands (Figure 5). On higher magnification, the tumor cells often display high mitotic activity ( $>10$  mitoses  $\times$  10 high power fields) (Figure 6). Although the intervening stroma often displays a heavy lymphoplasmacellular infiltrate, many tumors show instead a desmoplastic stroma devoid of lymphoid elements. The clue to the diagnosis lies in the identification of the characteristic nuclear morphology featuring large vesicular nuclei with scant chromatin and centrally placed round eosinophilic nucleoli. Cases arising in association with preexisting thymoma have also been

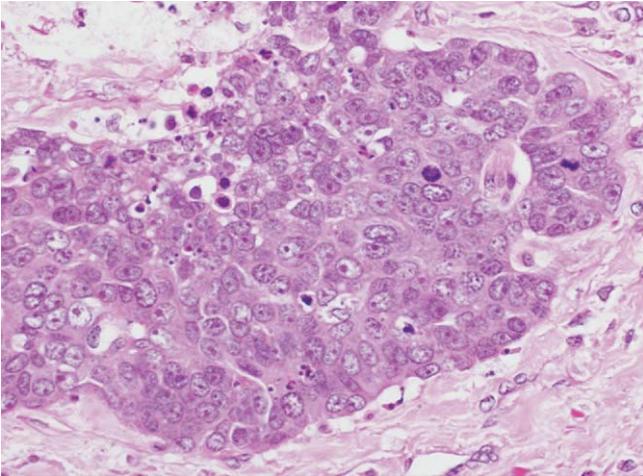


**Figure 4** Poorly differentiated, nonkeratinizing squamous cell carcinoma (“lymphoepithelioma-like” carcinoma) of the thymus showing syncytial growth with dense lymphoid stroma.

well-documented.<sup>7</sup> In particular, a close relationship with spindle cell thymoma (WHO type A thymoma) has been observed for these tumors. It is possible that some cases may arise from transformation of spindle cell thymoma.<sup>7,9</sup> Another association observed for these tumors is with Epstein–Barr viral (EBV) infection. A number of cases have been demonstrated to harbor EBV by EBER in situ hybridization or DNA analysis.<sup>18–21</sup> The majority of the EBV-positive cases have occurred in children or young adults. The significance of this association is still unclear. A comprehensive study from Denmark in a large series of cases of thymic carcinoma, including lymphoepithelioma-like carcinoma, was not able to identify a single case of EBV-positive tumor.<sup>22</sup> The author concluded that since most reported cases of EBV-associated tumors occur in young people, at an age when patients are most susceptible to EBV infection, the EBV may simply be an innocent bystander rather than



**Figure 5** Poorly differentiated, nonkeratinizing squamous cell carcinoma of the thymus showing characteristic comedolike areas of necrosis.



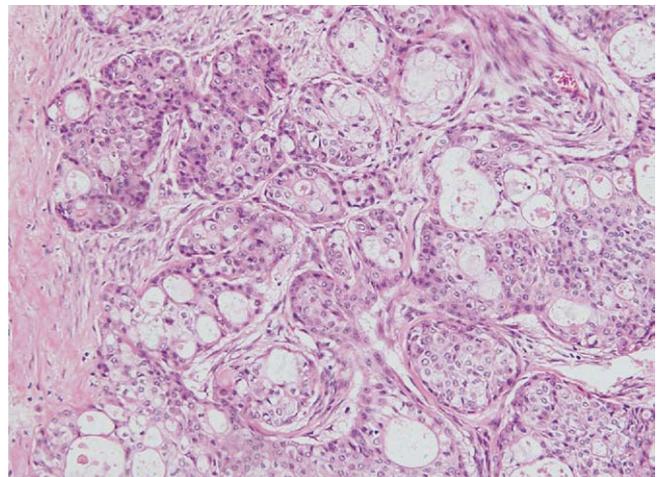
**Figure 6** Higher magnification of poorly differentiated, nonkeratinizing squamous cell carcinoma of the thymus showing primitive nuclear morphology, with large, round to oval nuclei with dispersed chromatin, small eosinophilic nucleoli, and frequent mitoses. Note absence of lymphoplasmacellular stromal infiltrates in this particular example.

having any pathogenetic implications. There is also an unusual case reported in the literature of lymphoepithelioma-like carcinoma of the thymus with focal neuroblastomatous differentiation demonstrated by ultrastructural examination.<sup>23</sup> Poorly differentiated nonkeratinizing squamous cell carcinoma is a highly aggressive tumor with a mean survival time of approximately 18 months.<sup>3</sup>

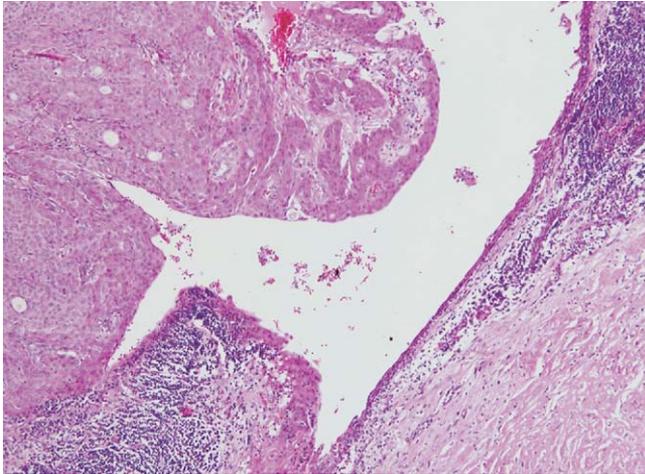
### Mucoepidermoid carcinoma

Mucoepidermoid carcinoma is a rare form of thymic carcinoma characterized by the intimate admixture of squamous and mucinous components within the same tumor. The tumors are histologically indistinguishable from their counterparts in the salivary glands and other organs. Although these tumors were initially believed to represent low-grade carcinomas of the thymus,<sup>3,24,25</sup> poorly differentiated and widely invasive cases with a much more aggressive behavior have now been documented.<sup>26,27</sup> Approximately 20 cases have been reported so far in the literature.<sup>3,14,24–27</sup> The tumors can present over a broad age range, but occur with most frequency in middle aged adults, without any sex predilection. The patients can present clinically with symptoms related to compression of adjacent structures due to an expanding anterior mediastinal mass; approximately 50% of cases are asymptomatic. Secondary cystic changes can be observed in association with these tumors in up to 40% of cases,<sup>26,27</sup> and will manifest radiographically as multicystic masses on chest CT scans. The lesions are grossly characterized by relatively well-circumscribed, lobulated, rubbery to firm masses showing focal infiltration into adjacent structures. The tumors associated with a cystic component display on cut surface multiple mul-

tilocular cystic structures of varying sizes filled with mucinous material. Histologically the tumors can display either a well-differentiated, low-grade morphology or features of high-grade, poorly differentiated mucoepidermoid carcinoma. The well-differentiated neoplasms are characterized by sheets and lobules of squamous cells with minimal atypia displaying intercellular bridges, admixed with singly scattered or small focal collections of mucocytes or goblet cells and small cystically dilated spaces filled with mucin (**Figure 7**). PAS or mucicarmine stains will highlight the cytoplasmic mucin in individual scattered mucocytes, and will also strongly stain the secretions within the cystic spaces. The squamous tumor cells usually do not display marked cytologic atypia and are characterized by large, polygonal cells with round nuclei and small nucleoli; mitoses are generally scarce and no areas of necrosis are observed. So-called “intermediate” cells, characterized by a squamoid appearance but without intercellular bridges are commonly present in various proportions. Areas of keratinization are rare and keratin pearl formation is almost never seen. Clear cytoplasmic changes can be observed focally in some tumors in the squamous component. Cases associated with cystic changes similar to those observed in acquired multilocular thymic cysts can show transitions between the lining of the cysts and the tumor (**Figure 8**), suggesting that the tumor might have arisen from the cyst lining. The poorly differentiated variants are characterized by sheets of round or polygonal tumor cells with occasional small cystic spaces filled with mucinous material. Intermediate cells and mucocytes are very scarce and difficult to identify. The cells show enlarged nuclei with increase in chromatin pattern, prominent nucleoli and frequent mitoses. Foci of necrosis can be identified. The most helpful stain for diagnosis is a mucicarmine, which will highlight foci of intracytoplasmic mucin in scattered tumor cells. Transitions with foci of well-differentiated mucoepider-



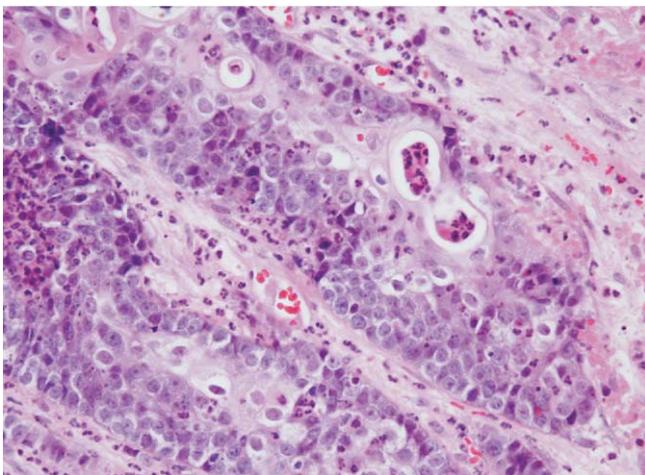
**Figure 7** Well-differentiated mucoepidermoid carcinoma of the thymus showing islands of polygonal squamous cells containing multiple cystlike spaces filled with mucin.



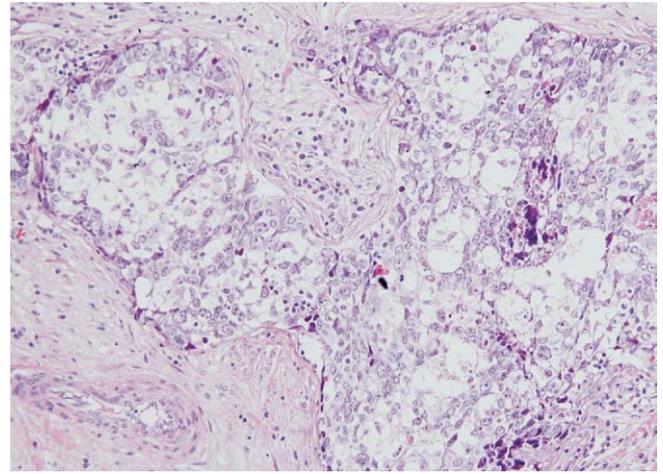
**Figure 8** Well-differentiated mucoepidermoid carcinoma of the thymus (left) showing transitions with the flat cuboidal epithelium lining the cystic cavity.

moid carcinoma can also be occasionally seen in well-sampled specimens (Figure 9).<sup>26</sup>

The clinical behavior of these tumors will depend on the staging and degree of differentiation of the lesion. Tumors presenting in high stages and with poorly differentiated histology behave in a much more aggressive manner than well-circumscribed and well-differentiated tumors. There have been seven tumor-related deaths reported so far for these lesions<sup>25–27</sup>; they all occurred in tumors with advanced stage or with poorly differentiated histology. The differential diagnosis for these lesions involves mainly a late metastasis from a mucoepidermoid carcinoma in the head and neck region or another site. A thorough clinical history and physical and radiological examination is necessary before making a diagnosis of primary thymic mucoepidermoid carcinoma.



**Figure 9** Poorly differentiated mucoepidermoid carcinoma of the thymus showing islands of poorly differentiated tumor cells admixed with residual well-differentiated squamoid areas.



**Figure 10** Clear cell carcinoma of the thymus. Notice abundant cells with optically clear cytoplasm. Other areas of this tumor showed areas of keratinization.

### Clear cell carcinoma of the thymus

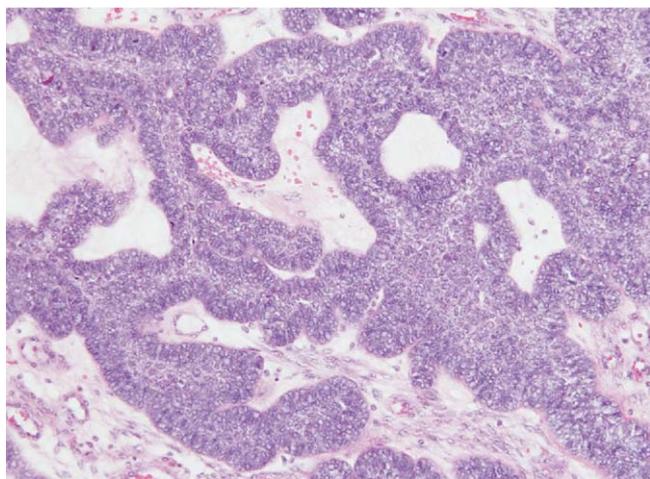
Clear cell thymic carcinoma is a rare variant of thymic epithelial neoplasm characterized by cells with abundant optically clear cytoplasm (Figure 10). Fewer than 15 cases have been reported so far in the literature.<sup>2,3,12–14,28–30</sup> These tumors are generally regarded as a high-grade variant of thymic carcinoma with aggressive behavior including massive local recurrence with infiltration of adjacent organs and distant metastases. The largest study by Hasserjian and coworkers<sup>30</sup> reported 8 cases of this rare tumor. The tumors affected middle aged adults (mean: 52 years) with no sex predilection. Six patients presented with symptoms of chest pain and dyspnea and two were asymptomatic. Tumor size ranged from 4 to 12 cm, and 2 tumors were grossly cystic. The majority of the tumors were widely invasive. In their study, the tumors showed a broad range of cytologic features from uniform clear cells with minimal atypia, to large, pleomorphic tumor cells with prominent nucleoli. In some cases, transitions of the clear cells with areas of conventional squamous cell carcinoma could be observed. In the majority of cases, cytoplasmic glycogen was demonstrated whereas mucin stains were uniformly negative. There was a striking disparity observed between the rather bland cellular features and the aggressive clinical behavior.

Most of the cases of clear cell tumors of the thymus that we have encountered actually have corresponded to examples of well or moderately differentiated squamous cell carcinomas with prominent clear cell change.<sup>9</sup> In our cases, transitions with areas displaying unequivocal features of squamous differentiation were frequently encountered. The tumors were also often associated with a lobular growth pattern and prominent desmoplastic stromal response. The main differential diagnosis is with metastatic renal cell carcinoma or a metastasis from other clear cell tumors of internal organs. Clinical and radiological correlation is important for establishing the correct diagnosis. Another pitfall for diagnosis is distinction from an as yet underrecog-

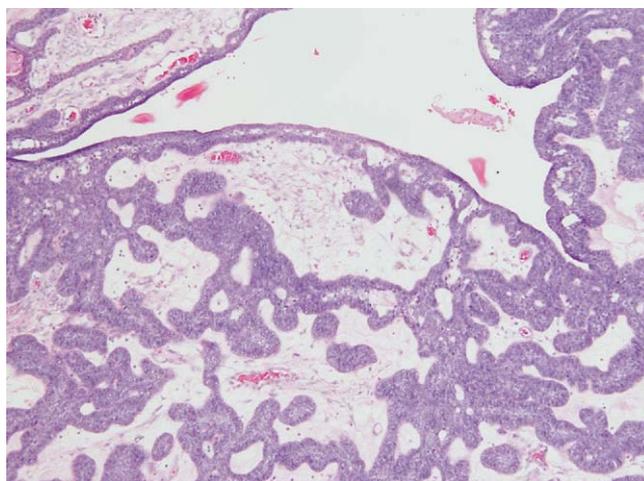
nized variant of thymoma characterized by prominent clear cell changes. These tumors retain the organotypical features of thymic differentiation (ie, lobular growth pattern, dual cell population with immature T-lymphocytes, perivascular spaces), except that the epithelial tumor cells display abundant optically clear cytoplasm. The prognosis for the latter tumors is essentially the same as for conventional thymomas; ie, it will depend on the status of capsular integrity. Tumors showing extensive invasion at the time of diagnosis will behave in an aggressive fashion similar to thymic carcinoma, and well-circumscribed and encapsulated tumors will behave in an indolent fashion.<sup>30</sup> It is possible that many of these cases may have been misdiagnosed for the clear cell variant of thymic carcinoma in the past. It is therefore imperative that strict criteria be adhered to in making the diagnosis of clear cell carcinoma of the thymus, and that cytologic and/or architectural features of malignancy (ie, nucleolar prominence, mitotic activity, infiltration, lymphovascular invasion) and absence of the organotypical features of the thymus be demonstrated before making this diagnosis. A rare tumor showing combined features of thymoma and thymic carcinoma with clear cell, squamous cell and undifferentiated carcinoma components has also been described, underscoring the close relationship between thymoma and the different variants of thymic carcinoma.<sup>31</sup>

### Basaloid carcinoma

Basaloid carcinoma of the thymus is another rare histological variant characterized by anastomosing cords and islands of small, round, or oval tumor cells showing prominent peripheral palisading of nuclei reminiscent of basal cell carcinomas of the skin (Figure 11). These tumors are frequently associated with cystic changes. The cystic changes may result from neoplastic transformation of the lining in an acquired multilocular thymic cyst or they may



**Figure 11** Basaloid carcinoma of the thymus showing anastomosing cords of tumor cells with prominent peripheral palisading of nuclei.



**Figure 12** Basaloid carcinoma of the thymus showing transitions between the tumor and the lining of cystic cavity (top).

be secondary to cystic degeneration within the tumor itself. In the latter circumstance, the cells lining the cyst walls will show similar cytological features as in the tumor cells. There have been ten cases reported in the literature.<sup>2,3,32–36</sup> All tumors were described as large, well circumscribed masses with either focal or extensive cystic changes (Figure 12). The tumor cells in basaloid carcinoma can show a range of features from bland-appearing oval to spindle shaped cells closely reminiscent of the cells in spindle cell thymoma, to primitive-appearing cells with hyperchromatic nuclei and prominent nucleoli reminiscent of poorly differentiated nonkeratinizing squamous cell carcinoma. The overriding characteristic is the basaloid arrangement of nuclei at the periphery of the tumor cell islands. Mitotic figures are numerous and apoptotic cells can frequently be seen scattered throughout. Areas of necrosis are rare. Foci of squamous differentiation can also be occasionally identified. We have observed cases displaying areas of transition with conventional spindle cell thymoma. A rare feature is the presence of focal collections of thymic myoid cells within the tumor.<sup>9</sup> By immunohistochemical analysis, the tumor cells are reactive for keratin and EMA, and cytoplasmic tonofilaments and desmosomes have been demonstrated on ultrastructural examination.<sup>33</sup> The differential diagnosis includes a mediastinal metastasis from a basaloid squamous cell carcinoma of the lung or upper aerodigestive tract. Basaloid carcinoma is regarded as a low-grade variant of thymic carcinoma<sup>3,33</sup>; however, cases with aggressive behavior, including metastases to lung and liver have been reported in 30% of cases.<sup>2,35,36</sup>

### Carcinosarcoma

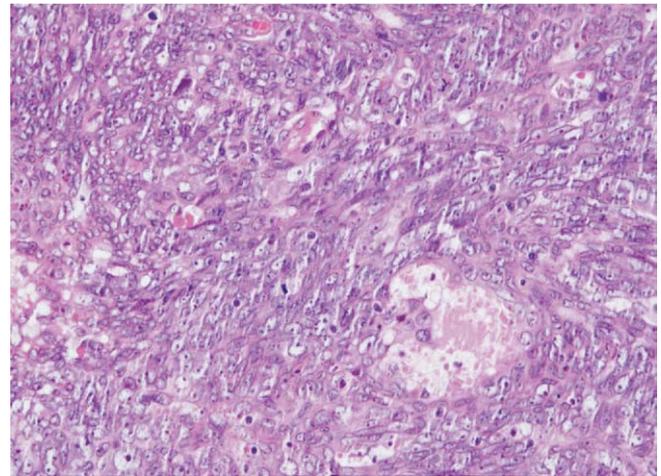
Carcinosarcoma is a rare type of biphasic thymic neoplasm characterized by areas displaying easily identifiable features of epithelial differentiation (ie, carcinoma) and areas composed of truly sarcomatous elements. The epithe-

lial component can be squamoid, adenocarcinomatous, or poorly differentiated large cell or anaplastic. The sarcomatous elements can be composed of poorly differentiated spindle cells without demonstrable evidence of any specific type of differentiation, or may show features of other well-developed conventional soft tissue sarcomas such as rhabdomyosarcoma, chondrosarcoma or osteosarcoma. The term “sarcomatoid carcinoma” applied to these tumors in the past is a misnomer since they do not simply resemble a sarcoma, but actually contain true sarcomatous areas as part of their cellular constituents. Fewer than 20 well-documented cases have been reported in the literature.<sup>2,3,11,14,37–40</sup> In the majority of instances, the sarcomatoid component consisted of embryonal rhabdomyosarcoma. By immunohistochemistry, the epithelial components express cytokeratin and EMA; the sarcomatoid components are most often only positive for vimentin, but cases with rhabdomyoblastic differentiation will show positivity for desmin and other muscle markers.<sup>2,37–40</sup>

Thymic carcinosarcoma is a highly aggressive malignancy with a mean survival of three years. The differential diagnosis involves other biphasic neoplasms of the anterior mediastinum. An important pitfall to avoid in this setting is mistaking the rare variant of thymoma with pseudosarcomatous stroma for a true carcinosarcoma. Thymoma with pseudosarcomatous stroma is a recently described variant of thymoma characterized by a biphasic cell population composed of islands and cords of mildly atypical oval to polygonal thymic epithelial cells surrounded by a florid reactive stromal spindle cell proliferation composed mainly of fibroblasts.<sup>41</sup> The stromal spindle cell proliferation may be quite cellular and display a storiform pattern of growth closely reminiscent of a spindle cell sarcoma. The spindle cells in the stromal component, however, are totally devoid of cytologic atypia or mitotic activity. It is important to properly identify this lesion because, unlike carcinosarcoma, it is associated with an indolent behavior with long tumor-free survival following simple excision.<sup>41</sup> Another important differential diagnosis is with synovial sarcoma of the anterior mediastinum.<sup>42</sup> These tumors can be composed of a monotonous spindle cell proliferation admixed with scattered glandular elements. Unlike carcinosarcoma, both the spindle cell elements as well as the glandular component will show positivity for cytokeratin and EMA. In questionable cases, demonstration of the fusion product for the X:18 translocation will be of help in establishing the diagnosis of synovial sarcoma.

### Spindle cell (sarcomatoid) carcinoma

Spindle cell carcinoma of the thymus is a novel variant of thymic carcinoma that until recently was regarded as synonymous with thymic carcinosarcoma.<sup>43</sup> In fact, this tumor is still regarded by the WHO as equivalent with carcinosarcoma, a biphasic neoplasm with an entirely different cellular composition.<sup>6</sup> We make a distinction between spindle cell (sarcomatoid) carcinoma and carcinosarcoma,



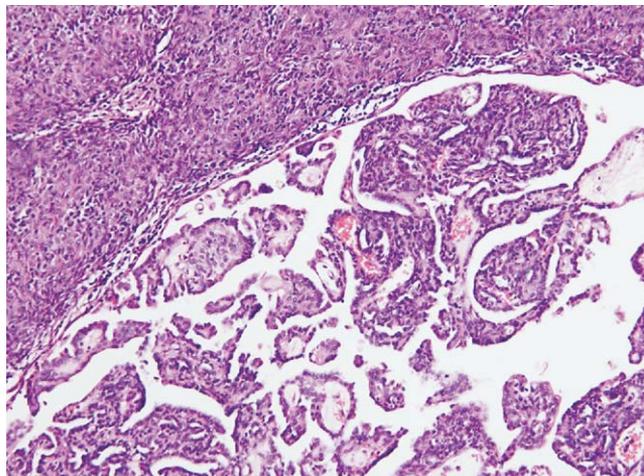
**Figure 13** Spindle cell carcinoma of the thymus showing population of atypical spindle cells with prominent nucleoli and frequent mitoses.

in that the latter is a neoplasm composed of two distinct and separate components within the same tumor (carcinoma plus sarcoma), whereas spindle cell carcinoma is exclusively composed of carcinomatous (epithelial cell) elements that happen to resemble a sarcoma by virtue of their spindle cell morphology. (Figure 13). Similar cases have been previously reported in the literature and interpreted as spindling squamous cell carcinomas of the thymus.<sup>11</sup> The study by Suster and Moran<sup>43</sup> reported 16 cases of this tumor in adult patients who presented with large, infiltrating mediastinal lesions. Histologically the tumors were characterized by a spindle cell proliferation showing varying degrees of cytologic atypia and mitotic activity. In 12 of the 16 cases, transitions could be seen with areas that showed the features of conventional spindle cell thymoma. In 2 cases, areas showing features of poorly differentiated nonkeratinizing squamous cell carcinoma and anaplastic carcinoma were also present. Immunohistochemical stains showed strong positivity of the spindle tumor cells for low-molecular weight cytokeratin and negative results for an extensive panel of other differentiation markers. Clinical follow-up was available in 8 patients and showed an aggressive behavior with recurrence, metastasis and death by tumor. The differential diagnosis includes invasion or metastasis from a spindle cell (sarcomatoid) carcinoma of the lung, thyroid, kidney, or other organs or a metastasis of spindle cell melanoma. Good clinical correlation is indispensable to make this distinction. Another important differential diagnosis is with a monophasic synovial sarcoma.<sup>42</sup> Although both conditions share positivity for cytokeratin, unlike spindle cell carcinoma of the thymus, monophasic synovial sarcoma shows a more uniform cell population devoid of significant nuclear pleomorphism. Identification of areas of transition with conventional spindle cell thymoma can be of help in establishing the primary thymic nature of the neoplasm. In equivocal cases, molecular studies for detecting the fusion product of the X:18 translocation may be of help.

## Papillary carcinoma

Papillary adenocarcinoma of the thymus is an extremely rare variant of thymic carcinoma that is very closely associated with spindle cell thymoma. Only 5 cases have been described of this type of tumor.<sup>44,45</sup> Matsuno and coworkers<sup>44</sup> presented a study of 2 men and 2 women between 57 and 70 years of age with encapsulated, focally infiltrative anterior mediastinal masses that ranged in size between 3.5 to 10 cm in greatest diameter. One case showed prominent cystic changes. Three of the cases showed remarkably similar histologic features. They were composed of a proliferation of tubulopapillary structures lined by monotonous cuboidal to polygonal tumor cells with round to oval nuclei with condensed chromatin and occasional prominent nucleoli. The papillary structures showed well-formed fibrovascular cores and, in one case, were associated with numerous psammoma bodies. Mitotic activity ranged from 1 to 7 mitoses per 10 high-power fields. All tumors were microscopically invasive and accompanied by extensive lymphatic permeation. In all three cases, a second component could be identified within the lesion that showed the features of conventional spindle cell thymoma. Focal areas of transition showing an intimate admixture between the papillary and spindle cell component could be identified. The case reported by Choi and coworkers<sup>45</sup> also resembled these three cases and showed well-developed papillary structures associated with numerous psammoma bodies but with the absence of a spindle cell thymoma component. The fourth case in the study by Matsuno and coworkers<sup>44</sup> was described as a “high-grade variant” of this tumor and showed completely different features; it was neither associated with spindle cell thymoma, nor did it show true papillary structures centered by fibrovascular cores. The papillary areas illustrated appear rather as pseudopapillary structures resulting from artifactual disruption of the tumor cells in the central portions of the tumor lobules. The high-grade morphology of the tumor, marked nuclear pleomorphism, high mitotic rate (45 mitoses per 10 high power fields), absence of any “precursor” lesion, and lack of true papillary architecture make it unlikely that the 2 types are related and correspond to the same entity. One of the patients with papillary carcinoma in their study died of the tumor after 7 months, 1 was alive and well after 1 year and a third one was lost to follow-up. Paradoxically, the fourth patient with the high-grade tumor was alive and well, with no evidence of disease after 5 years.

There is no question that the first three cases in the study by Matsuno and coworkers<sup>44</sup> and the case reported by Choi and coworkers<sup>45</sup> represent a distinct type of primary thymic epithelial neoplasm. Moreover, the degree of cytologic atypia, mitotic activity, and extensive lymphovascular invasion in all cases qualify for the designation of thymic carcinoma. Care must be taken, however, not to over-interpret focal areas displaying a similar papillary architecture for evidence of malignancy in an otherwise conventional



**Figure 14** Spindle cell thymoma (top left) showing areas with papillary structures indistinguishable from those seen in papillary thymic carcinoma.

spindle cell thymoma. We have observed several cases of encapsulated, well-circumscribed thymomas of spindle cell type in which focal to extensive areas displaying identical papillary architecture could be observed (Figure 14). The papillary component, however, did not display any overt evidence of cytologic atypia, mitotic activity, necrosis or lymphovascular invasion, and the tumors behaved in accordance with their well-circumscribed and encapsulated nature in an appropriately indolent fashion. The differential diagnosis for papillary carcinoma of the thymus is quite limited, particularly when the classical areas of spindle cell thymoma can be easily identified. However, on small biopsy specimens in which only the papillary component is sampled, the possibility of a metastasis from a papillary thyroid carcinoma, papillary carcinoma from another organ, or malignant mesothelioma should be considered. Clinical correlation and caution are indicated in making this diagnosis under such circumstances; a definitive diagnosis may need to await thorough examination of a completely resected specimen.

## Adenocarcinoma of the thymus, mucinous and nonmucinous subtypes

Primary malignant neoplasms of the thymus composed of glandular epithelial elements are extremely rare with very few cases documented in the literature.<sup>45–49</sup> Moriyama and coworkers<sup>46</sup> were the first to report a case of adenocarcinoma with features reminiscent of biliary tract or intestinal adenocarcinoma presumably arising from a thymic cyst in a 51-year-old woman. A case of nonmucinous thymic carcinoma with glandular differentiation arising in a congenital thymic cyst in a 50-year-old man has also been described.<sup>47</sup> The tumor showed focally a well-developed glandular pattern in association with areas that were said to resemble spindle cell thymoma. Intracellular mucin or goblet cells could not be demonstrated. The case reported by Makino

and coworkers<sup>48</sup> in a 39-year-old man presented as a solid mass and was unassociated with a cyst; the illustrations provided also depict an adenocarcinoma with intestinal or biliary tract-type of features. Choi and coworkers<sup>45</sup> were the first to report an example of thymic carcinoma that showed the features of a mucinous (so-called “colloid”) carcinoma. The tumor occurred in a 15-year-old boy and was composed of islands and small clusters of tumor cells floating in large pools of extracellular mucin. Transitions between the carcinomatous elements and the lining of a residual thymic cyst could be observed. The tumor followed an aggressive behavior with multiple bone metastases and death after 26 months. A similar case of mucinous adenocarcinoma was reported more recently by Takahashi and coworkers<sup>49</sup> in a 59-year-old man. The tumor presented as a 10-cm solid, unencapsulated anterior mediastinal mass unassociated with a cyst. Following an open chest biopsy, the patient was treated with radiation therapy with poor success and died 2 months after surgery. It thus appears that the mucinous (“colloid”) variety of primary adenocarcinoma of the thymus may be associated with a more aggressive behavior than the nonmucinous types.

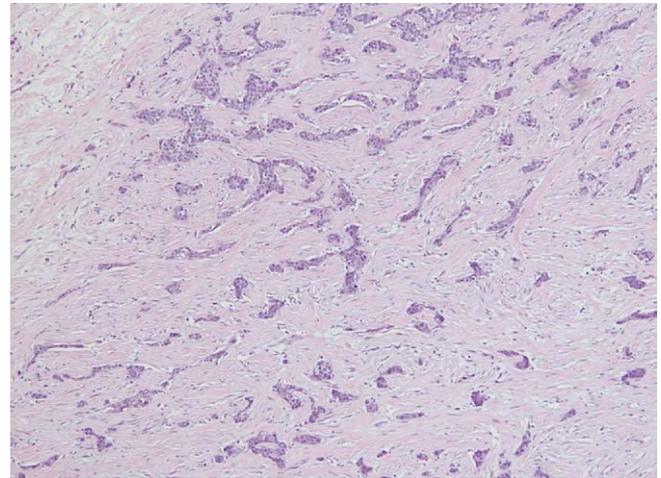
The differential diagnosis includes a metastasis of an adenocarcinoma from internal organs. This possibility needs to always be ruled out by careful clinical and radiographic studies before labeling a tumor as a primary adenocarcinoma of the thymus. Another condition that needs to be excluded in the differential diagnosis is a carcinoma arising from an enteric or foregut cyst.<sup>51</sup> For the mucinous tumors that resemble so-called “colloid” carcinoma, an important differential diagnosis is with the rare variant of neuroendocrine carcinoma of the thymus with prominent mucinous stroma.<sup>52</sup> The latter condition can closely resemble mucinous carcinoma with islands and small clusters of epithelial cells floating in large pools of mucin. Immunohistochemical demonstration of positivity for neuroendocrine markers or ultrastructural demonstration of dense-core neurosecretory granules will help establish the correct diagnosis.<sup>52</sup>

### Adenosquamous carcinoma

Adenosquamous carcinoma is defined as a primary thymic epithelial neoplasm in which well-developed glandular carcinomatous and clearly malignant squamous epithelial areas are admixed within the same lesion.<sup>12,13,50</sup> Some tumors can also show a small cell carcinoma component admixed with the adenosquamous elements.<sup>13</sup> The tumors do not differ significantly in clinical presentation and behavior from otherwise comparable squamous cell carcinomas of the thymus.

### Desmoplastic carcinoma

We have observed several examples of an unusual form of thymic carcinoma that is remarkable for the presence of

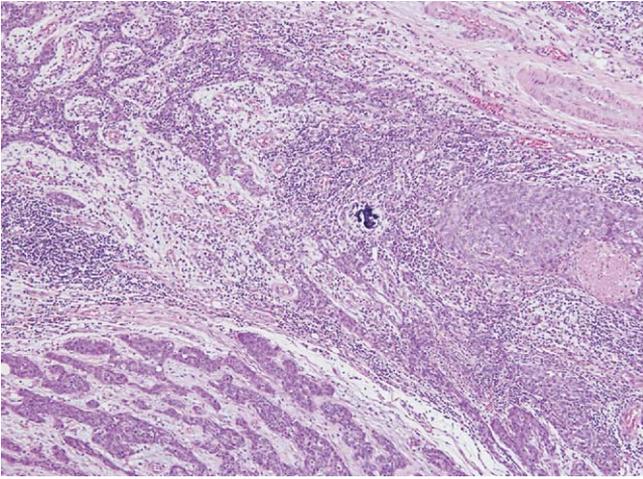


**Figure 15** Desmoplastic carcinoma of the thymus showing irregular small islands of tumor cells surrounded by abundant desmoplastic stroma.

prominent areas of stromal desmoplasia encircling poorly-differentiated carcinomatous elements (Figure 15). The carcinomatous component in these tumors is characterized by small islands or irregular clusters of small round to polygonal epithelial cells with large nuclei showing prominent nucleoli and scattered mitoses. Some of the carcinomatous elements can display a vaguely squamoid appearance, and in some instances palisading of tumor cells around the tumor islands similar to that seen in poorly differentiated examples of squamous cell carcinoma of the lung can also be seen. Transitions between the carcinomatous islands and residual normal thymic epithelium in the periphery of the lesion can sometimes be observed (Figure 16). The cells can sometimes show prominent clearing of the cytoplasm, or may adopt an oval to spindle configuration. The overriding characteristic of these tumors, however, is the striking fibrotic stroma that surrounds the tumor cell islands. The tumors are usually widely invasive at the time of diagnosis. The behavior is variable and most likely depends on the stage of the tumor at the time of initial diagnosis.

### Anaplastic (“undifferentiated”) carcinoma

Anaplastic or “undifferentiated” carcinoma is a vaguely defined tumor that essentially serves as a “wastebasket” category for tumors presenting in the anterior mediastinum in which an epithelial nature can be established by immunohistochemical or ultrastructural studies and a primary tumor elsewhere cannot be identified.<sup>3</sup> The majority of such tumors probably correspond to poorly-differentiated variants of squamous cell carcinoma.<sup>9</sup> Areas of anaplastic carcinoma can often be identified as a focal component in otherwise well-defined types of thymic carcinoma. Transitions with thymoma, in particular spindle cell thymoma have also been documented.<sup>7</sup> The term anaplastic carcinoma is favored for such lesions over that of “undifferentiated” carcinoma. The latter term has been often abused in the



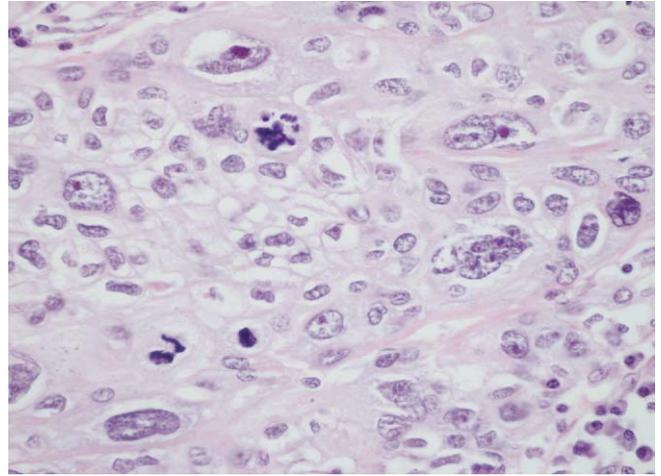
**Figure 16** Area of transition between residual thymic epithelium at the periphery of the lesion (top left) and desmoplastic carcinoma of the thymus (bottom and right).

literature and applied indiscriminately to a variety of unrelated neoplasms, including small cell neuroendocrine carcinomas. It is also contradictory to speak of an “undifferentiated” carcinoma as the term carcinoma already implies an epithelial line of differentiation, whereas the term “undifferentiated” designates a tumor without differentiation. The tumors are histologically characterized by marked cellular pleomorphism with bizarre nuclear features and atypical mitoses (Figure 17). The differential diagnosis for these tumors includes pleomorphic sarcomas, metastases of malignant melanoma or anaplastic carcinoma from other organs, choriocarcinoma and pleomorphic large cell lymphomas of the mediastinum.<sup>53,54</sup> Careful clinical correlation and application of selected immunohistochemical stains may be of help in separating anaplastic carcinoma of the thymus from these conditions.

Anaplastic carcinomas of the thymus are associated with a highly aggressive behavior with poor prognosis.<sup>3,14,55</sup> There is a recent report, however, of an unusual variant of undifferentiated large cell carcinoma of the thymus associated with a Castleman disease-like stromal reaction that showed an indolent behavior despite the high-grade histology.<sup>56</sup> It was postulated that the Castleman-like stromal response may be related to the indolent behavior of these lesions.

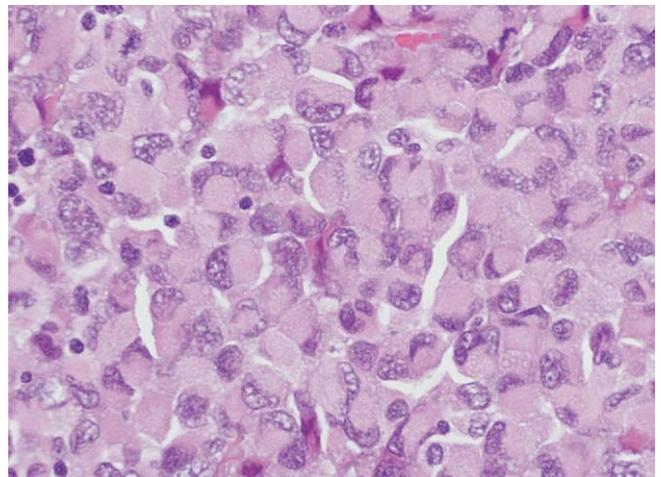
### Rhabdoid carcinoma

Two cases of mediastinal tumors bearing morphologic features similar to that of rhabdoid tumors of the kidney have been recently described by Falconieri and coworkers.<sup>57</sup> The cases occurred in male patients aged 40 and 46 years of age. The tumors measured from 1.3 to 4 cm in diameter and were located in the upper and anterior mediastinum. They were histologically characterized by a diffuse proliferation of round to polygonal cells with large glassy, eosinophilic cytoplasmic inclusions that displaced the nu-



**Figure 17** Anaplastic carcinoma of the thymus showing striking nuclear pleomorphism and bizarre mitotic figures.

clei toward the periphery (Figure 18). The tumor cells showed positivity for keratin and EMA and electron microscopy showed abundant intracytoplasmic collections of intermediate filaments corresponding to the rhabdoid inclusions. One of the patients on whom follow-up was available died of tumor 8 months after initial diagnosis. The most important differential diagnosis is with a rhabdoid carcinoma of the lung secondarily invading the mediastinum.<sup>57</sup> This can only be established through detailed imaging and endoscopic studies. Another more remote possibility is that of a metastasis of malignant melanoma with rhabdoid features; the latter tumors are generally reactive for melanocytic-associated markers such as S-100 protein and HMB45. The exact origin of these tumors is still uncertain and deserve further study; however, the anterior mediastinal location, positivity for epithelial markers, and absence of tumor elsewhere support this being a novel variant of thymic carcinoma.



**Figure 18** “Rhabdoid” carcinoma of the thymus showing distinctive globular cytoplasmic inclusions that push the nuclei toward the periphery.

## Other rare types of thymic carcinoma

Other highly unusual morphologic variants of thymic carcinoma have been also described, mostly as single case reports. A case of thymic carcinoma showing striking "hepatoid" features was reported by Franke and coworkers.<sup>58</sup> The tumor occurred in a 70-year-old woman as an encapsulated anterior mediastinal mass 18 cm in greatest diameter. Histologically it was composed of sheets of polygonal tumor cells or as trabeculae and single cells that resembled hepatocytes. The tumor cells were immunoreactive for cytokeratin and the hepatocyte-specific antigen hep-Par-1, and were negative for a large battery of differentiation markers tested, including AFP, HCG, and PLAP. Local recurrence was noted at 6 months after surgery; the patient was free of disease following radiation and chemotherapy after 26 months. An unusual case of thymic carcinoma characterized by a prominent component of benign rhabdoid cells has been described by Moreira de Queiroga and coworkers.<sup>59</sup> The tumor occurred in a 70-year-old woman as a large posterior mediastinal mass. Histologically it contained poorly-differentiated adenosquamous carcinoma; interspersed among the carcinomatous elements were also numerous large cells containing brightly eosinophilic cytoplasm and small, round eccentrically placed nuclei that stained strongly positive for desmin and myogenin.

## Role of special stains and other techniques

The potential use of immunohistochemical stains and of some of the more novel molecular techniques has been intensively studied in recent years in the hope that they may contribute to facilitate the diagnosis and provide predictive data for clinical outcome in these tumors. Unfortunately, little actual progress has been made in this regard and much of the available data has been contradictory or inconclusive.

A large number of markers have been analyzed in thymic carcinomas. The common minimum denominator for these tumors is the universal expression of cytoplasmic cytokeratin intermediate filaments in the tumor cells. Some studies have also shown increased expression of EMA in thymic carcinoma as opposed to thymoma. An interesting finding has been the demonstration of lymphoid markers in the tumor cells of thymic carcinoma, including CD5, CD70, and CD74.<sup>60-62</sup> Initial studies seemed very promising and it was proposed that detection of CD5 in the tumor cells could serve as positive proof to support the diagnosis of primary thymic carcinoma.<sup>60,63,64</sup> In the study by Kornstein and Rosai,<sup>65</sup> the authors found that there were significant differences in the staining results between two commercially available CD5 antibodies; clone CD5/54/B4 identified only 30% of thymic carcinomas but did not stain other types of carcinoma, whereas clone 4C7 identified 62% of cases of thymic carcinoma but also labeled other neoplasms, including thymomas, and carcinomas of the stomach, thyroid,

endometrium and salivary glands. The diagnostic sensitivity for clone CD5/54/B4 was 29% with 100% specificity; whereas the sensitivity of clone 4C7 was found to be 62% with 96% specificity and a predictive value of 48%. It was concluded that clone 4C7 was not sufficiently specific for routine use, and that strong positive staining with clone C5/54/B4 could be used to support a diagnosis of primary thymic carcinoma. More recent studies have also plainly demonstrated lack of specificity of CD5 for thymic carcinoma. The study by Tateyama and coworkers<sup>66</sup> using the 4C7 clone showed broad expression of this marker in a wide variety of tumors, including atypical thymomas, malignant mesothelioma, lung adenocarcinoma, bladder urothelial carcinoma, and adenocarcinoma of stomach, colon, and breast. Moreover, it should be pointed out that not all variants of thymic carcinoma are associated with CD5 staining. CD5 positivity is most frequently observed in squamous cell carcinoma of the thymus and has been reported only occasionally in poorly differentiated (lymphoepitheliomalike) carcinoma, clear cell carcinoma and papillary carcinoma.<sup>60,63,64</sup> Small cell neuroendocrine carcinomas are universally unreactive for this antigen. Because the diagnosis of thymic carcinoma is a diagnosis of exclusion that requires demonstration of absence of a primary tumor elsewhere, extreme caution should be used in over interpreting the results of CD5 staining. Additional studies are still needed to reliably map the spectrum of immunoreactivity of this antibody in nonthymic carcinomas.

CD70, a protein that mediates the interaction between B and T-lymphocytes has also been studied in thymic tumors. Hishima and coworkers<sup>61</sup> in a study of 27 thymic epithelial tumors found that 7/8 thymic carcinomas and 1/5 atypical thymoma were positive for CD70, whereas the rest of the cases, including 13 thymomas, 1 thymic carcinoid and 24 intrathoracic malignancies of nonthymic origin were negative for this marker. The number of cases in this study, however, was quite limited, and the results of this study still require additional validation. Similar observations have been made for CD74, a major histocompatibility complex (MHC) class II-associated protein.<sup>62</sup> This marker was preferentially expressed in thymic carcinoma but also marked conventional and atypical thymomas. The study did not include an assessment of the expression of this marker in nonthymic tumors, thus severely limiting the utility of this finding for differential diagnosis.

Another aspect of thymic carcinomas that has been studied by immunohistochemistry is the focal expression of neuroendocrine markers in the tumor cells.<sup>67,68</sup> Focal immunoreactivity for chromogranin, synaptophysin, neuron specific enolase (NSE), and a variety of peptides including HCG and ACTH could be detected in scattered tumor cells in cases of thymic carcinoma of various types and in a few cases of atypical thymoma. This finding was supported by demonstration of dense-core neurosecretory granules in scattered cells by electron microscopy in both studies.<sup>67,68</sup> This finding has been interpreted as a manifestation of

aberrant differentiation in these neoplasms. Awareness of this phenomenon is only of importance to avoid making a misdiagnosis of neuroendocrine carcinoma in such tumors.

A series of markers have been studied in an attempt to separate thymic carcinoma from thymoma, including p53, c-kit (CD117), and Ki-67.<sup>69-72</sup> Overexpression of p53 and Ki-67 was observed more often in thymic carcinoma than thymoma.<sup>69,72</sup> There appears to be, however, some degree of overlap in the expression of these markers between these tumors that mirrors the complexities encountered on conventional microscopy, therefore limiting their utility. Expression of c-kit (CD117) has shown considerable promise,<sup>70,71</sup> since strong staining has been noted in squamous cell carcinoma of the thymus and this marker has been, for the most part, negative in the majority of the cases studied of thymoma and squamous cell carcinomas at other sites. Additional studies are needed to validate these results. Other markers that have been applied with variable success to the differential diagnosis of these tumors include TTF1, calretinin and other mesothelioma markers.<sup>73,74</sup> TTF1 was found in one study to stain 3/10 cases of large cell undifferentiated carcinomas of the lung but none of the thymic carcinomas.<sup>73</sup> Primary squamous cell carcinomas of the lung, however, were also negative for this marker. In another study, about one third of thymic carcinomas were found to be positive for calretinin, mesothelin, HBME-1 and CK5/6, and were negative for TTF1.<sup>74</sup> This information is of importance for the interpretation of small mediastinoscopic biopsies so as not to over interpret the finding of positive mesothelioma-associated markers in a mediastinal neoplasm as positive proof of malignant mesothelioma.

The role of cytogenetics has also been recently addressed in thymic carcinoma. Trisomy 8 and der(16)t(1;16) have been reported in a single case of squamous cell carcinoma of the thymus.<sup>75</sup> A study using comparative genomic hybridization has shown loss of chromosome 16q,6,3p and 17p, and gains of 1q,17q and chromosome 18 in thymic carcinoma.<sup>76</sup> A single case of carcinosarcoma of the thymus has been studied by cytogenetics, which identified complex chromosomal abnormalities including der(16)t(1;16)(q12;q12.1).<sup>40</sup> Interestingly, this chromosomal translocation is similar to that previously encountered in a thymic squamous cell carcinoma.<sup>75</sup> The cytogenetics of the other histologic types of thymic carcinoma has not yet been properly studied.

Several cases have been reported in the literature of intrathoracic malignancies involving the lung and/or mediastinum that share in common a distinctive t(15;19) chromosomal translocation.<sup>77-81</sup> These cases have been listed as a distinctive variant of thymic carcinoma in the new WHO classification of thymic epithelial neoplasms.<sup>6</sup> The tumors show a predilection for children or young adults, and occur in supra-diaphragmatic midline organs. They are locally invasive and present with pleural effusion and superior vena cava syndrome. The tumors appear to be morphologically heterogeneous but most often manifest as poorly differen-

tiated carcinomas similar to nonkeratinizing poorly differentiated (lymphoepitheliomalike) squamous cell carcinoma of the thymus. Foci of squamous differentiation are frequently present. All reported cases have shown an extremely aggressive behavior with an average survival of 18 weeks. Given the uncertainty as to the exact origin and pathogenesis of these tumors, I believe it is still premature to regard them as a separate or distinctive form of thymic carcinoma. Not all cases appear to arise in the mediastinum, and origin from the thymus has not been demonstrated. Moreover, since cytogenetic studies have not yet been undertaken for the lymphoepitheliomalike variant of thymic carcinoma which shares many of the histologic features and aggressive clinical behavior with these tumors, the possibility that the two may be the same condition cannot be discounted. Further delineation of this tumor and additional studies are necessary to clarify some of these points. For the time being, demonstration of the characteristic 15;19 translocation, or the fusion protein BDR4 by FISH in poorly differentiated carcinomas arising in the chest cavity is of importance to identify this highly aggressive subset of tumors, particularly in children and young adults.<sup>18</sup>

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