Clinical history:
A 58 year old woman with a history of myasthenia gravis (MG) diagnosed 16 years ago was seen for shortness of breath and chest pain of recent onset. Ten years ago, an anterior mediastinal mass had been discovered in the course of routine evaluation for MG. A mediastinoscopic biopsy was diagnosed as a benign thymoma. The patient refused surgery at that time and was followed with periodic CT scans. It was noted at the time of her present examination that the mass had increased in size twofold since the last CT scan done one year ago. The patient underwent median sternotomy and surgical resection of the mass.

Pathologic findings:
The resected specimen consisted of a gray white, lobulated, rubbery to firm tissue mass that measured 12 x 10 x 5 cm. The outer surface was irregular and focally hemorrhagic. The cut surface showed gray white, homogeneous firm to rubbery tissue with focal areas of necrosis. On histologic examination, the tumor was composed of lobules of monotonous round to oval cells showing large nuclei with peripheral margination of chromatin and single prominent nucleoli, and surrounded by abundant amphophilic cytoplasm with indistinct cell borders. In some areas, the cells showed prominent spindling, with elongated vesicular nuclei. The tumor lobules contained scattered small lymphocytes, and the epithelial cells showed occasional mitotic figures. Also present in the same mass were areas that were characterized by more striking cytologic atypia. These areas showed diminution in the size of the tumor lobules, which became more irregular in shape and were separated by abundant densely hyalinized fibrous connective tissue. The tumor lobules in these areas were characterized by extensive central areas of necrosis, and showed increased nuclear pleomorphism with an average of 10 mitoses per 10 HPF's. There was extensive infiltration of the capsule and foci of vascular invasion by tumor.

Immunohistochemical findings:
The tumor cells strongly labeled with CAM 5.2 low-molecular weight keratin and with broad-spectrum keratin antibodies. Scattered cells were positive for EMA. Stains for CEA, PLAP and AFP were negative. Southern blot analysis from a portion of the tumor failed to demonstrate Epstein-Barr virus (EBV) genome using an EBV-specific probe for the long internal repeat and terminal repeat regions of the EBNA-1 gene.

Diagnosis: **THYMIC CARCINOMA ARISING IN PREEXISTING THYMOMA.**

Discussion:
Thymic carcinomas are defined as primary thymic epithelial neoplasms displaying overt cytologic features of malignancy which have already lost all of the organotypical features characteristic of the thymus (1-7). These tumors had until recently been a highly controversial entity, primarily due to the lack of agreement regarding their definition and the proper criteria for diagnosis. Another problem for the study of these tumors stemmed from the fact that they can show extreme morphologic diversity, with a wide variety of histologic growth patterns and types having been described (1,2).

The largest series of thymic carcinoma published in 1991 studied 60 patients who had been followed for at least 3 years or until their time of death (2). Two clinically distinct...
groups of patients were identified: 1) one that followed a relatively favorable clinical course with long survival, and 2) one that followed a rapidly fatal outcome. The tumors in the first group were composed of carcinomas of low-grade histology characterized by good gross circumscription, partial preservation of lobular growth pattern on histologic examination, absence or minimal nuclear atypia and necrosis, and low mitotic activity, whereas those in the second group showed the opposite features, namely extensive infiltration of adjacent structures, marked nuclear atypia, frequent areas of necrosis, increased mitotic activity and high-grade histology.

On the basis of the above observations, thymic carcinomas were classified into low-grade and high-grade histology groups. The tumors in the low-grade histology group included well-differentiated squamous carcinoma, mucoepidermoid carcinoma, and basaloid carcinoma. The tumors in the high-grade histology group included poorly-differentiated squamous cell (lymphoepithelioma-like) carcinoma, small cell/neuroendocrine carcinoma, clear cell carcinoma, sarcomatoid carcinoma, and anaplastic/undifferentiated carcinoma (2).

**Thymic Carcinoma - Histologic Variants**

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<tr>
<th>Low-Grade Histology:</th>
<th>High-Grade Histology:</th>
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<tr>
<td>- Well-differentiated squamous cell</td>
<td>- Poorly-differentiated (lymphoepithelioma-like)</td>
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<td>carcinoma</td>
<td>non-keratinizing squamous carcinoma</td>
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<td>- Well-differentiated mucoepidermoid</td>
<td>- Poorly-differentiated mucoepidermoid</td>
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<td>- Basaloid carcinoma</td>
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<td>- Anaplastic/undifferentiated carcinoma</td>
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The relationship of thymic carcinoma with thymoma has been for many years poorly understood. In a recent study, we identified 22 patients in whom a thymic carcinoma was seen to develop in close association with a morphologically conventional thymoma (8). Several instances of this phenomenon have also been previously reported in the literature (9-11). Shimosato et al, in their series of squamous cell carcinoma of the thymus described one case in which transitions were found between the squamous elements and areas of benign thymoma (9). Wick et al later documented a case of sarcomatoid thymic carcinoma complicating an epithelial-rich thymoma. More recently, Kuo et al described two cases among 13 thymic carcinomas in which a lymphoepithelioma-like carcinoma and a squamous carcinoma were seen to arise from a preexisting thymoma (5). The present case represents another example of this phenomenon, whereby a high-grade malignancy supervenes on a long-standing thymoma.

The original mediastinoscopic biopsy in this patient showed a tumor with the features of a conventional lymphocyte-rich thymoma. The present resection specimen, however, shows areas of predominantly epithelial-rich thymoma admixed with spindle cell thymoma, in addition to areas of high-grade poorly-differentiated squamous cell carcinoma. Interestingly, Southern blot analysis performed for the detection of Epstein-Barr viral genome was negative. Although it was initially thought that these tumors, like their counterparts in the nasopharynx, were invariably associated with EBV infection, a recent study has shown that not all cases of lymphoepithelioma-like carcinoma of the thymus will test positive for EBV genomic sequences (12).
The present case suggests the existence of a continuous spectrum of differentiation between thymoma and thymic carcinoma. Such evidence would support the notion that the process of tumorigenesis in thymoma and thymic carcinoma obeys a multistep process, such as has been demonstrated for many other types of malignancy. Demonstration of a multistep process of carcinogenesis in this setting would support the notion that the different morphologic types of thymic epithelial neoplasms are histogenetically very closely related. This information is of more than academic interest, since it would force us to acknowledge the fact that some of the sharp divisions and criteria we have devised for the classification of these tumors may be more arbitrary than real.

References: