

Case No. 1
Presented by:
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Clinical history:

A 45 year old man with no significant past history was seen for chest pain and cough. On CT scan, a large anterior mediastinal mass was identified showing areas of attenuation suggestive of a cystic lesion. A sternotomy was performed, and a 15x6x5 cm. rubbery tissue mass was removed. The surgeon noted at the time of the operation that the mass was firmly adhering to the pleura and pericardium and appeared to infiltrate these structures causing great difficulty for surgical removal. A separate small piece of tissue was also submitted by the surgeon from the site at which the tumor was felt to be infiltrating the pericardium.

Pathologic findings:

Grossly, the tumor showed a shaggy, tan-purple outer surface. On cut section, it was multicystic alternating with solid areas. The solid areas were gray white and rubbery and showed foci filled with red-brown, soft gelatinous material. The cystic areas were filled with reddish-brown fluid; the largest cyst measured approximately 6 cm. in greatest dimension. Histologic examination from the solid areas showed lobules composed of a dual population of cells typical of thymoma, including small lymphocytes and larger epithelioid cells with round to oval nuclei and occasional prominent nucleoli surrounded by abundant lightly eosinophilic cytoplasm. There was no evidence of nuclear pleomorphism or mitotic activity in the epithelioid cell component.

Adjacent to the viable tumor areas there were also well-circumscribed areas of necrosis. The necrosis in these areas was massive, without any residual or preserved normal elements, and was associated in some areas with vascular thrombosis. Examination of the cystic areas revealed distended cysts lined by a single layer of flat cuboidal or squamous epithelium. In some areas, the lining could be traced to hyperplastic thymic epithelial elements found in the walls of the cyst; in other areas, they could be observed in continuity with distended Hassall's corpuscles. The walls of the cysts showed severe acute and chronic inflammation and hemorrhage, cholesterol clefts, and occasional hyperplastic lymphoid follicles. Examination of multiple sections did not reveal any evidence of invasion through the capsule. The capsule, however, was thickened and fibrotic, and showed severe inflammatory changes. The separately submitted piece of tissue from the pericardium also showed severe inflammatory changes but no evidence of tumor.

Immunohistochemical findings:

Immunohistochemical stains in the viable portions of the tumor showed positive staining of the small lymphocytes with LCA and CD3. The epithelial cells strongly labeled with keratin antibodies (Dako broad-spectrum and AE1/AE3); some of the cells also showed weak, focal reactivity for EMA.

Diagnosis: ENCAPSULATED THYMOMA WITH SECONDARY CYSTIC CHANGES AND NECROSIS.

Discussion:

Thymomas are primary malignant thymic epithelial neoplasms that may show a broad spectrum of differentiation and histopathologic features (1-3). Much controversy has existed in the literature regarding the classification of thymoma. The most recent
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proposal by the WHO Committee for the International Histological Classification of Tumors is a formula that assigns a combination of letters and numbers to the various histologic types of thymoma from the current existing classifications (Table I). According to the authors, this proposal was not meant to represent a new histologic classification, nor was it intended to replace any previous terminology, but was rather devised as a means for facilitating comparison among the currently existing classifications (4).

Table I: Comparison of Current Histological Classifications of Thymoma

<i>Bernatz et al (1961)</i>	<i>Muller-Hermelink (1989)</i>	<i>Suster & Moran (1999)</i>	<i>WHO (1999)</i>
Spindle cell thymoma	Medullary thymoma	Thymoma, well-differentiated	Type A
-----	Mixed thymoma	“ “ “	Type AB
Lymphocyte-rich	Predominantly cortical	“ “ “	Type B1
Mixed lymphoepithelial	Cortical	“ “ “	Type B2
Epithelial-rich	Well-differentiated thymic carcinoma	Atypical thymoma	Type B3
-----	Other thymic carcinoma	Thymic carcinoma	Type C

We recently introduced a simplified classification scheme for primary thymic epithelial neoplasms based on different stages of differentiation according to the presence or absence of organotypical features of the normal thymus (1). Our proposal is essentially a three-tiered classification that is patterned after standard classifications for epithelial tumors in other systems. This classification follows the rationale that thymomas, as with other malignant epithelial neoplasms, can be reliably divided according to their degrees of differentiation into 3 types: well-differentiated, moderately differentiated, and poorly-differentiated. The well-differentiated tumors are those that retain all of the organotypical features of the parent tissue and are designated by convention as thymoma. The poorly-differentiated tumors are those in which the organotypical features of differentiation are absent and the tumor cells already display conventional cytologic features associated with malignancy; such tumors have been labeled as thymic carcinomas in the literature. The third group of lesions corresponds to tumors located in-between the latter two groups and that are characterized by partial preservation of the organotypical features of the thymus but which already display cytological features of atypia; we have designated these lesions as “atypical thymoma”. The present tumor, because of its preservation of organotypical features of thymic differentiation and absence of cytologic features of malignant would correspond to a well-differentiated thymoma in our classification, or to a thymoma type B-1 in the WHO schema and lymphocyte-rich thymoma in the traditional classification.

The prognosis of thymoma remains a subject of debate. Despite the numerous reports in the recent literature, it is still generally accepted that morphology of thymoma is in general a poor predictor of prognosis. So far, the only parameter that has consistently correlated with clinical outcome in tumors displaying a well-differentiated histology has been staging at the time of initial diagnosis. The most widely accepted staging system for thymoma in use today is the one proposed by Masaoka et al (5), in which Stage I corresponds to grossly well-encapsulated tumors without microscopic evidence of capsular invasion; Stage IIa are tumors showing gross invasion into surrounding adipose tissue or mediastinal pleura, or IIb tumors showing microscopic invasion into the capsule; Stage III, tumors displaying gross invasion into adjacent organs such as

pericardium, great vessels, or lung; and Stage IVa, tumors with pleural or pericardial implants, and IVb lymph-borne or blood-borne distant metastases. Kornstein et al have also noted that microscopic invasion *through* the capsule is associated with a significant propensity for recurrence, as opposed to invasion *into* the capsule, which appears not to carry the same clinical and prognostic connotation.

The current case was felt to be malignant by the surgeon at the time of the operation because of its attachment to the pleura and apparent infiltration into the pericardium. Extensive sampling of the capsule for histologic examination, however, demonstrated no evidence of capsular invasion, but showed instead fibrosis and severe inflammation which resulted in firm adhesions to the adjacent structures. This case illustrates a secondary event that may supervene in thymoma and which can occasionally obscure the main underlying pathologic process, that of secondary inflammatory changes with cystic degeneration of residual thymic parenchyma (6).

Cystic change in the thymus is a well-known phenomenon that has been said to occur in up to 40% of thymomas as a focal event. Occasionally, the process may proceed to the extent that most, or all of the lesion becomes cystic (7). In the majority of such instances, the cystic changes result from extreme dilatation and coalescence of perivascular spaces. In contrast with other types of thymic cysts, the walls of the cavities in such cases are generally devoid of an epithelial lining, and inflammatory changes or lymphoid hyperplasia are not seen as part of the process.

More rarely, thymomas may be associated with secondary cystic changes of an inflammatory nature that will result in the creation of a multilocular thymic cyst (8,9). The cysts in such instances are characterized by a lining made up of squamous, cuboidal, and less frequently, ciliated columnar epithelium which is seen to merge with residual normal or atrophic thymic epithelial elements within the walls of the cyst or in continuity with dilated Hassall's corpuscles. It may be impossible to determine whether the cystic changes supervened in a preexisting thymoma or whether the thymoma developed secondarily and represents an incidental finding in cases in which the inflammatory/cystic changes predominate and the thymoma is found incidentally as a small mural nodule attached to the wall of a cyst.

In the present case, viable foci of thymoma were present throughout most of the sections examined, and the cystic changes were only seen to affect residual normal thymic parenchyma. The cystic changes with accompanying severe inflammatory changes accounted for the firm adhesions to the surrounding structures, which led the surgeon to regard the lesion as grossly invasive. Another feature observed in the present case, which also served to confound the diagnosis was the presence of extensive areas of infarction on histologic examination. Infarct-like areas of necrosis can be frequently observed in otherwise benign, encapsulated thymomas with associated inflammatory and cystic changes, and are not an indication of high-grade malignancy or a prognostic parameter for more aggressive behavior. Absence of atypia and mitotic activity in the areas of necrosis as well as in the better-preserved tumor islands in the vicinity coupled with the presence of surrounding inflammatory/cystic changes should help avert a misdiagnosis of malignancy in such instances.

Differential diagnosis:

On occasion, tumors with a lymphocyte-rich histology may be extremely difficult to differentiate from a malignant lymphoma on frozen section examination and one may have to defer to permanents. Inking and extensive sampling of the capsule on the gross specimen is of prime importance in the microscopic assessment of thymomas, and the

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pathologist should never rely on the surgeon's operative impression regarding invasiveness for the staging of these tumors.

Much has been made about the cytokeratin patterns of expression in thymoma, and the lymphoid cell immunophenotype for the diagnosis of thymoma (10,11). The fact is that the diagnosis of thymoma remains an H&E diagnosis. Immunohistochemical stains, electron microscopy, and other special techniques remain of limited value in these tumors. Moreover, more important than specific subtyping of well-differentiated variants of thymoma is making the correct diagnosis and not mistaking this tumor for other types of lesions that may present in a similar anterior mediastinal location. The most important prognostic factor for the clinical evaluation and prognostication of these tumors remains the status of capsular integrity. Tumors that are completely encapsulated at the time of initial diagnosis are practically cured by complete surgical excision; whereas invasive or incompletely excised lesions tend to recur and can occasionally metastasize. Adequate inking of the outer surface of the specimen and extensive sampling of the capsule are therefore of primary importance for the evaluation of these tumors.

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