

Primary Pleural Thymomas

Clinical presentation

Thymomas are uncommon and represent 0.2-1.5% of all malignancies. Patients are usually aged between 40-60 years at the time of diagnosis. A third to half of patients will be asymptomatic and thymoma discovered as an incidental mediastinal mass. According to some studies, as much as 70% will present with an auto-immune disease, the most common being myasthenia gravis, followed by a variety of rheumatoid diseases, and less commonly pure red cell aplasia and hypogammaglobulinemia. Other symptoms include cough, dyspnea, chest pain and superior vena cava syndrome. Thymomas usually arise in the mediastinum, anterior and/or upper. However, as in our patient, they can occur in the thoracic cavity, arising from the pleura or lung. Their occurrence has also been reported in extra-thoracic locations, including thyroid, para-thyroid, and soft tissue of the neck.

Pleural thymomas are uncommon, with less than 20 cases reported in the literature. Usually, pleural thymomas represent extensive metastases from a primary mediastinal tumor. In these cases, a mediastinal mass is identified radiologically or at surgical exploration, and this poses no diagnostic problem. However, there are cases where a pleural biopsy or resection is performed without knowledge or identification of an existing mediastinal mass and diagnostic difficulties might then ensue. True primary pleural thymomas without mediastinal involvement are rare and thought to arise from ectopic thymic tissue. These cases can be truly challenging for the pathologists who need to be aware of occurrence of thymoma in the pleura and recognize the typical histologic features of this tumor.

Table 1: Summary of clinical, radiologic and histologic features of pleural thymomas

Gender	7M:8W	
Age	47 yo mean (range 27-71)	
Symptoms	SOB	5
	Chest pain	4
	Weight loss	2
	SVC	1
	Autoimmune	1
	Unknown	4
	More than 1	2
Radiologic features	Discrete mass	7
	Pleural thickening	7
	Pleural effusion	4
	More than 1	3
Histologic subtypes	Lymphocytic	6
	Predominantly epithelial	5
	Mixed epithelial/lymphocytic	5
	Unknown	1
Treatment	Surgery	10
	Chemotherapy	5
	Radiation	3
	More than 1	3
Follow-up and survival	Alive	1-10 years
	WNED	2
	WED	4
	Dead	1mo-4yrs
	DOD	2
	DOC	2
Unknown	5	

SOB= shortness of breath, SVC= superior vena cava, WNED= with no evidence of disease, WED= with evidence of disease, DOD= dead of disease, DOC= dead other cause

Pathology

Grossly, thymomas are largely solid, yellowish, lobulated tumors. They are commonly encapsulated with cases noted to be infiltrative at surgery. Cystic degeneration, particularly in large tumors, is not uncommon.

Classic histologic features of thymomas usually recapitulate the appearance of the normal thymus in children and adolescents and include:

- Well-developed lobular architecture with lobules separated by broad bands of fibrosis.
- Presence of a dual population comprised of a mixture of neoplastic thymic cells and thymic lymphocytes in various proportions.
- Dilated perivascular spaces.
- Bland appearance of neoplastic thymic cells.

Thymomas can be very heterogeneous and show morphologic variability. Multiple morphologic patterns and unusual appearances of thymomas have been described complicating, not only all potential classification, but also the diagnosis (Table 2). The only importance in knowing and recognizing these different patterns is to avoid mis-diagnosis with other entities, especially when the thymoma is located in an unusual location such as the pleura. Despite unusual features, these thymomas usually retain the classic characteristics of thymoma, such as lobulated pattern, perivascular spaces, admixed lymphocytes, and usually more conventional thymoma can also be found within the tumor.

The epithelial cells of thymomas strongly express different types of keratins, including AE1/AE3 and CAM 5.2, and more specifically cytokeratins 8, 13, 16 and 19. Some studies have reported the spindle cells to express CD20. The lymphocytes are generally CD 4 positive T cells and in all subtypes the T cells usually have an immature phenotype, expressing CD1 and TdT. In the spindled/medullary/Type A, T cells are often mature, showing no expression of CD1 or TdT and CD20 positive B lymphocytes can also be identified. CD5 and CD70 are usually expressed in thymic carcinomas but half of cases of atypical thymomas/WHO B3 can show similar expression. Also C5 expression can be seen in other types of carcinomas. Therefore CD5 as a diagnostic marker or in determining a primary site is not entirely specific.

Table 2: Morphologic patterns of thymoma (from Sem Diagn Pathol 1999)

Polygonal cell type	Spindle cell type
Starry-sky appearance	Prominent storiform pattern
Adenoid pattern	Pseudosarcomatous stroma
Microcystic pattern	Hemangiopericytic growth pattern
Cystic changes	Rosette-like structure
Cribriform pattern	Cystic, glandular, papillary structures
Clear-cell thymoma	Micronodular growth pattern
Plasma-cell rich thymoma	Basaloid features
Rhabdomyomatous thymoma	

Differential diagnosis of pleural thymoma

The differential diagnosis will vary according to the histologic subtype of the thymoma. For our present case of spindle cell/medullary/ type A, the differential includes malignant mesothelioma, sarcomatoid type, sarcomatoid carcinoma and sarcoma. Thymoma can be distinguished from these based on differences in histologic and immunohistochemical features (Table 4).

Table 3: Differential diagnosis of pleural thymomas

- 1- Predominantly epithelial:
 - Malignant mesothelioma, epithelial type
 - Carcinoma
 - Malignant melanoma
- 2- Predominantly lymphocytic:
 - Lymphoma
- 3- Spindled cell:
 - Malignant mesothelioma, sarcomatoid
 - Sarcomatoid carcinoma
 - Localized fibrous tumor/ Sarcoma
 - Malignant melanoma
 - Histiocytic malignancies

Classification, staging and prognosis

The current WHO classification merges different historical classifications, trying to correlate morphologically similar thymomas amongst the classifications, and referring to these using letters and numbers. This was in attempt to unify sometimes opposing views on the clinical significance of histologic classification of thymomas (Table 5).

Table 5: WHO classification

WHO type	Clinicopathologic	Histogenetic	Traditional
A	Benign thymoma	Medullary	Spindled
AB		Mixed	
B1	Malignant thymoma type I	Predominantly cortical	Lymphocytic
B2		Cortical	Mixed lympho/epithelial
B3		Well-differentiated thymic carcinoma	Predominant epithelial
C	Malignant thymoma type II	Epidermoid keratinizing ca	
		Epidermoid non-keratinizing ca	
		Lymphoepithelioma-like ca	
		Sarcomatoid ca	
		Clear cell ca	
		Mucoepidermoid ca	
		Basaloid ca	
		Papillary ca	
		Undifferentiated ca	
		Neuroendocrine tumors	
Combined			

Although several studies have shown that the WHO classification has prognostic significance, two facts are usually uniformly highlighted. One is that, although there are 6 histologic types, grouping of these types which have meaningful clinical use could be done. Two is that there is a strong correlation between the histologic classification and tumor invasiveness and in metanalyses, staging remains the strongest prognostic marker. Similarly, there is no standardized staging system. The one proposed by Masaoka et al has undergone some modification and is usually employed (Table 6). A recent surgical study suggested lumping Stage I and II together since no significance in survival was identified between both groups.

Table 6: Modified Masaoka staging system of thymoma

I	Totally encapsulated (gross and micro)
II	A- Capsular invasion B- Invasion into surrounding fat or adherence to mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring organs (pericardium, lung and great vessels) A- Without invasion of great vessels B- With invasion of great vessels
IV	A- Pleural or pericardial implants B- Lymphatic and hematogenous metastases

Overall 5-year survival for thymomas varies between 67-77% and 10-year survival between 50-55%. Using the Masaoka staging system, 5-year survival rate for stages I and II is 90-100% and for stage III and IV, 41-70%.

Treatment

Surgery remains the mainstay in the treatment of thymomas. Thymomas are sensitive to chemotherapy and radiation, thus both are being used in adjuvant or neo-adjuvant settings, determined by the stage of the disease. For stage I and II tumor, surgery alone is usually the treatment of choice without adjuvant therapy. However, some studies are recommending adjuvant radiation for stage II thymomas, even after complete surgical resection, since the rate of recurrence is not negligible. For completely resected stage I and II, there is no role for chemotherapy. For potentially resectable stage III and IVA, neo-adjuvant chemotherapy alone or chemo-radiation, followed by surgery is usually performed. For unresectable stage III and IV, combination chemotherapy and radiation is usually the treatment of choice.

References

1. Begg CB, Cramer LD, Venkatraman ES, Rosai J. Comparing tumour staging and grading systems: a case study and a review of the issues, using thymoma as a model. *Stat Med.* 2000;19:1997-2014.
2. Chalabreysse L, Etienne-Mastroianni B, Adeleine P, Cordier JF, Greenland T, Thivolet-Bejui F. Thymic carcinoma: a clinicopathological and immunohistological study of 19 cases. *Histopathology.* 2004;44:367-74.
3. Chong VF, Fan YF. Invasive thymoma presenting as pleural thickening. *AJR. American Journal of Roentgenology.* 1997;168:568-9.
4. Eng TY, Thomas CR, Jr. Radiation therapy in the management of thymic tumors. *Seminars in Thoracic & Cardiovascular Surgery.* 2005;17:32-40.
5. Evans TL, Lynch TJ. Role of chemotherapy in the management of advanced thymic tumors. *Seminars in Thoracic & Cardiovascular Surgery.* 2005;17:41-50.
6. Fukayama M, Maeda Y, Funata N et al. Pulmonary and pleural thymoma. Diagnostic application of lymphocyte markers to the thymoma of unusual site. *American Journal of Clinical Pathology.* 1988;89:617-21.
7. Fushimi H, Tanio Y, Kotoh K. Ectopic thymoma mimicking diffuse pleural mesothelioma: a case report. *Human Pathology.* 1998;29:409-10.
8. Honma K, Shimada K. Metastasizing ectopic thymoma arising in the right thoracic cavity and mimicking diffuse pleural mesothelioma--an autopsy study of a case with review of literature. *Wiener Klinische Wochenschrift.* 1986;98:14-20.
9. Lewis JE, Wick MR, Scheithauer BW, Bernatz PE, Taylor WF. Thymoma. A clinicopathologic review. *Cancer.* 1987;60:2727-43.
10. Marchevisky AM. Lung tumors derived from ectopic tissues. *Seminars in Diagnostic Pathology.* 1995;12:172-84.
11. Marino M, Muller-Hermelink HK. Thymoma and thymic carcinoma. Relation of thymoma epithelial cells to the cortical and medullary differentiation of thymus. *Virchows Arch A Pathol Anat Histopathol.* 1985;407:119-49.
12. Moran CA, Travis WD, Rosado-de-Christenson M, Koss MN, Rosai J. Thymomas presenting as pleural tumors. Report of eight cases. *Am J Surg Pathol.* 1992;16:138-44.
13. Nakagawa K, Asamura H, Matsuno Y et al. Thymoma: a clinicopathologic study based on the new World Health Organization classification. *Journal of Thoracic & Cardiovascular Surgery.* 2003;126:1134-40.
14. Pan CC, Chen PC, Chou TY, Chiang H. Expression of calretinin and other mesothelioma-related markers in thymic carcinoma and thymoma. *Human Pathology.* 2003;34:1155-62.
15. Payne CB, Jr., Morningstar WA, Chester EH. Thymoma of the pleura masquerading as diffuse mesothelioma. *American Review of Respiratory Disease.* 1966;94:441-6.
16. Rena O, Papalia E, Maggi G et al. World Health Organization histologic classification: an independent prognostic factor in resected thymomas. *Lung Cancer.* 2005;50:59-66.
17. Ritter JH, Wick MR. Primary carcinomas of the thymus gland. *Semin Diagn Pathol.* 1999;16:18-31.
18. Shih DF, Wang JS, Tseng HH, Tiao WM. Primary pleural thymoma. *Arch Pathol Lab Med.* 1997;121:79-82.
19. Suster S, Moran CA. Thymoma, atypical thymoma, and thymic carcinoma. A novel conceptual approach to the classification of thymic epithelial neoplasms. *Am J Clin Pathol.* 1999;111:826-33.
20. Tateyama H, Eimoto T, Tada T, Hattori H, Murase T, Takino H. Immunoreactivity of a new CD5 antibody with normal epithelium and malignant tumors including thymic carcinoma. *American Journal of Clinical Pathology.* 1999;111:235-40.
21. Wright CD, Kessler KA. Surgical treatment of thymic tumors. *Seminars in Thoracic & Cardiovascular Surgery.* 2005;17:20-6.
22. Wright CD, Wain JC, Wong DR et al. Predictors of recurrence in thymic tumors: importance of invasion, World Health Organization histology, and size. *Journal of Thoracic & Cardiovascular Surgery.* 2005;130:1413-21.

Table 4: Differential diagnosis of pleural thymoma, spindled/medullary/Type A

Tumor	Clinical features	Histologic features	Immunohistochemical features	Molecular
Thymoma	Mean age 47 years, Diffuse pleural thickening or discrete mass	Lobules separated by fibrous bands, Perivascular spaces, Small spindle cell, no atypia Lymphoid component	Keratin + diffusely CK5/6 + Calretinin - CD34- SMA - S100 - Lymphocytes immature T cells Keratin + diffuse CD99+ CD34 - Calretinin + CK5/6 + Keratin + focal EMA + focal to diffuse	-6p, -6q, -12p, -16q
Malignant mesothelioma, sarcomatous	Mean age 60 years, Diffuse pleural thickening, Rarely localized mass	Short blunt fascicles, Poorly formed fascicles, Abundant eosinophilic cytoplasm Lymphocytes occ abundant		-1p, -3p, -22
Sarcomatoid carcinoma	Average age 60 years, Prominent lung involvement	Infiltrative growth pattern, Prominent pleomorphism, Marked nuclear atypia		-3p, 15q, -22q, -17p
Synovial sarcoma of pleura Monophasic	Mean age 47 years, Pleural based mass	Densely packed fascicles, Fibrosarcomatous or hemangiopericytomatous pattern, Oval to round nuclei	Keratin + focal EMA + focal CD34- Desmin - S-100 + rare, focal Keratin - EMA - CD34 +	t(X,18) SYT/SSX
Localized fibrous tumor	Fifth-sixth decade, Asymptomatic, solitary pleural-based mass	Variety of patterns, Deposition of collagen between cells		Complex chromosomal aberration
Fibrosarcoma	No primary fibrosarcoma of the pleura described in the English literature, Metastatic disease	Herringbone pattern, Slender spindle nuclei, Interwoven collagen fibers	Keratin - EMA-	
Smooth muscle tumor	Rare primary, benign or malignant, Mean age 45 years, Solitary pleural-based mass	Abundant eosinophilic cytoplasm, "cigar shaped" nuclei	Keratin + rare focal SMA +	-1p