CHAPTER

11 Tumors of the Mediastinum

Anatomy of Mediastinum

The mediastinum (also known as the interpleural space) extends from the thoracic inlet to the diaphragm. It is divided into two major divisions (superior and inferior) by a horizontal line between the sternal angle and T 4-5 intervertebral disc (Fig 11-1). The inferior mediastinum is further subdivided into three parts: anterior, middle (containing the heart) and posterior parts. Mediastinal tumors have a characteristic location in the different parts of mediastinum (Fig 11-1). Mediastinal cysts are also site specific. Thus thymic cysts are usually located at the anterior mediastinum and the mesothelial pleuro-pericardial cysts are also located anteriorly at the costophrenic area. Conversely, cysts derived from the foregut (bronchial, esophageal and enteric) are commonly encountered in the posterior mediastinum.

Histology of Thymus

The two lobes of thymus are incompletely divided into lobules by septa that extend inward from its fibrous capsule. Each lobule consists of an outer cortex and inner medulla. The most notable cells in the thymus are the epithelial cells and T-lymphocytes, previously named thymocytes (Fig 11-2). Lymphocytes are more numerous in the cortex than the medulla.

The thymus contains four distinct types of epithelial cell: (1) the subcapsular epithelium which is adherent to the capsule, (2) cortical epithelium with rounded vesicular nuclei, prominent central nucleoli, and a stellate shaped cytoplasm forming a loose network around the lymphocytes, (3) medullary epithelial cells are spindle shaped with fusiform nuclei and dense chromatin, and finally, (4) Hassall's corpuscles, which are concentric structures of keratinizing squamous epithelium, though occasionally, there is evidence of glandular differentiation.

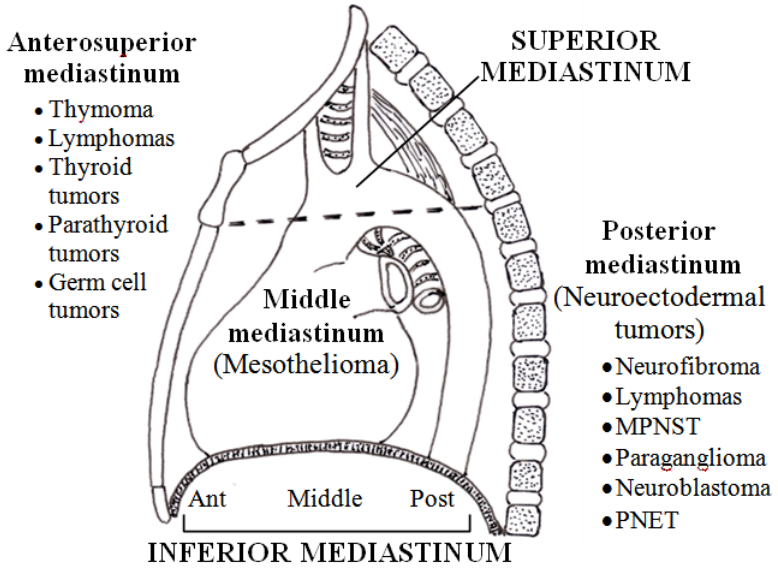

Fig 11-1 *Anatomic landmarks and site distribution of mediastinal tumors. Mediastinal cysts are also site specific, thymic and pleuropericardial cysts are located anteriorly, whereas, bronchial, esophageal cysts are posterior.*

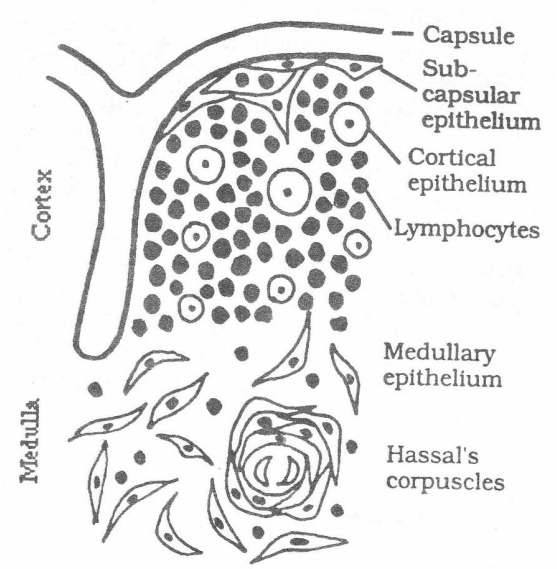

Fig 11-2 *Histologic structure of normal thymus. Cortical thymic epithelium is rounded, whereas, medullary epithelium is spindle in shape. Thymic lymphocytes are T phenotype (CD3+), immature in cortex (TdT+, CD1a+ and CD99+), but more mature in medulla (TdT-).*

In addition, the thymus contains six other cell inclusions from which tumors may arise, including: B-cells, Langerhans cells, neuroendocrine cells, melanocytes, myoid cells (skeletal muscle) and ectopic germ cells.

GENERAL CONSIDERATIONS

The mediastinum may be the site of a variety of primary and metastatic tumors. The majority of the primary tumors (75%) are benign. Malignant tumors are more commonly metastatic, and most frequently originating from lymphomas, lung, breast, intestinal tract or testes. In some cases, the primary tumor may be occult.

The frequency of most common mediastinal tumors are presented in (Table 11-1). The most common tumor in adults is thymoma, whereas, in children neurogenic tumors predominate.

With regard to the compartment of origin (Fig 11-1), thymomas and endocrine tumors arise from the anterosuperior mediastinum, whereas, neurogenic tumors are located in the posterior compartment, and pericardial mesothelioma in the middle compartment. Some tumors, as lymphomas and soft tissue tumors, arise from all compartments, hence, widening the differential diagnosis. Moreover, particular difficulty is encountered with masses arising at the anterior cardiophrenic junction (angle of sorrow), where the anterior and middle compartments converge with the diaphragm. Masses in this area may arise from either compartments of mediastinum, the dia -phragm or from below the diaphragm.

The pathologic effects and manifestations of mediastinal tumors may be local or general. Specific compression symptoms may arise when tumors impinge on the trachea, superior vena cava, or invade nerves resulting in hoarseness of voice, intercostal neuralgia or Horner syndrome. The main systemic manifestations of mediastinal tumors are presented in (Table 11-2).

TUMOR-LIKE LESIONS

A variety of non-neoplastic swellings in the mediastinum may simulate tumors on CT scanning. Examples include: diaphragmatic hernias, esophageal diverticula, aortic aneurysm, retrosternal goiter, reactive lymphadenopathy and mediastinal cysts. The latter may be true cysts of developmental origin (e.g. bronchogenic, esophageal, gastroenteric, pericardial, or mesothelial), or inflammatory such as hydatid cyst.

The thymus may also be the seat of tumor-like lesions. Four main lesions are described: (1) thymic cysts, which may be congenital (unilocular) or acquired (multilocular), (2) lympho-follicular hyperplasia which may be associated with myasthenia gravis, (3) true thymic hyperplasia (P 11-1) and (4) thymolipoma.

Table 11-1 Primary Mediastinal Neoplasms

Neurogenic	**25%**
Thymoma	**23%**
Lymphoma	**15%**
Germ cell tumors	**12%**
Endocrine	**8%**
Soft tissue sarcomas	**7%**
Others	**9%**

(Davis, 1987)

Table 11-2 Systemic Manifestations Of Mediastinal Tumors

Thymoma	Myasthenia, anemia
Pheochromocytoma	Hypertension
Neuroendocrine	Cushing, SIADH
Thyroid	Thyrotoxicosis
Parathyroid	Hypercalcemia
Germ cell tumor	Gynecomastia
S.T. sarcoma	Hypoglycemia
Neuroblastoma (VIP)	Diarrhea

THYMIC TUMORS

These may either be primary tumors arising from thymic epithelium (thymomas), or from a variety of cell inclusions within the thymus, or they may be secondary tumors affecting the thymus gland.

THYMOMAS

A thymoma is a tumor, benign or malignant, derived from the thymic epithelium. The lymphocytes present in tumor stroma are normal T lymphocytes, with a normal 2:1 helper to suppressor ratio, and play no role in neoplastic proliferation. The epithelial nature of thymomas is confirmed by histochemistry which demonstrates cytokeratin positivity of tumor cells.

The macroscopy of a thymoma is characterized by its gray white color and mean size of 7 cm (up to 20 cm). The cut section appears lobulated with demarcation by fibrous septa (P 11-2). The majority appear well encapsulated, but in 25% of cases, there is penetration of the capsule and infiltration of perithymic tissues and structures. This feature is of great prognostic importance.

The classification of thymomas had been a subject of much debate, but three useful schemes ultimately emerged. Rosai and Levine (1976) divided thymomas into three categories on the basis of their invasiveness and metastatic potential : (1) benign or completely encapsulated tumors with spindle cell structure, (2) malignant thymoma category I which is only locally invasive, and (3) malignant thymoma category II or thymic carcinoma which is a more aggressive tumor capable of distant metastases.

Muller-Hermelink (1994) classified thymomas on the basis of similarity of the tumor to the normal thymic compartments. The diagnostic criteria are restricted to the neoplastic epithelial cells rather than lymphocytes (Table 11-3). Quantitation of the lymphocytes, however, helps to identify the histologic type since they are abundant in cortical thymomas, scanty in medullary thymomas and absent in thymic carcinoma category II, as well as, metastatic tumors in thymus.

Medullary thymoma, is a benign tumor composed of spindle shaped epithelial cells with uniform nuclei and dense chromatin. The cells are often arranged in a storiform pattern. Only few lymphocytes are present, but no evidence of mitotic activity or squamous differentiation.

Mixed thymoma, also a benign tumor, is composed of two distinct cell components; one of which is spindle shaped identical to medullary thymoma, and the second consists of lymphocyte rich rounded epithelial cells with vesicular nuclei and prominent nucleoli as in cortical thymoma.

Predominantly cortical thymoma, a category I malignant tumor, is composed mainly of the lymphocyte-rich cortical thymoma, but there are focal areas of medullary differentiation in which lymphocytes are less densely packed, epithelial cells spindle and Hassall corpuscles may be evident.

Cortical thymoma is composed of large rounded epithelial cells, with vesicular nuclei and prominent central nucleoli. The tumor is rich in lymphocytes and their number is more than the number of thymic epithelial cells. These features are similar to the histology of the outer cortex of the normal thymus.

Well-differentiated thymic carcinoma shows a marked predominance of epithelial cells with only few lymphocytes. Cytologically, the tumor cells are smaller than in cortical thymoma with oval folded nuclei and inconspicuous nucleoli A characteristic feature of this subtype is the lobular pattern, marked fibrosis and a palisading pattern of the epithelial cells around perivascular spaces and along the fibrous tissue bands. The presence of a few interepithelial lymphoid cells is a typical and constant feature of this subtype and helps to distinguish it from primary or secondary squamous cell carcinoma of the thymus.

Malignant thymoma category II (thymic carcinomas) represent a variety of malignant

tumors capable of both local invasion, as well as, producing metastases, and are generally classified into low and high grade variants (Table 11-3).

THE WHO Classification

The WHO histologic classification (1999) of primary thymic tumors adopted the thymoma categories recognized in the Muller-Hermelink classification (1985), only replacing them with alphanumeric terms (Table 11-3). The new terminology (A, B, C) thus avoids the histogenetic implications (cortical versus medullary) and the misleading term (well-differentiated thymic carcinoma) which is an invasive tumor of borderline malignancy (type B3) distinct from the frankly malignant type C or thymic carcinoma (Fig 11-3). The following is a description of the individual WHO subtypes:

Type A thymoma: it is a benign tumor composed of spindle cells with few lymphocytes.

Type AB or mixed thymoma: a benign tumor composed of spindle cell, as well as, lymphocyte rich rounded cells.

Type Bl thymoma: a tumor of borderline malignancy, composed predominantly of lymphocyte-rich rounded cells with few spindle cells. Hassall corpuscles may be evident.

Type B2 thymoma: a tumor of borderline malignancy composed entirely of lymphocyte rich rounded cells with vasicular nuclei and prominent nucleolus.

Type B3 thymoma: a tumor of borderline malignancy composed of polygonal cells with squamoid differentiation or clear cytoplasm (Koilocytes). The nuclei are small with distinct nucleoli. Few lymphocytes are evident.

Type C or thymic carcinoma: a malignant tumor composed of pleomorphic anaplastic cells which may be of low or high grade (Table 11-3). This tumor type lacks lymphocyte component in the stroma (except lymphoepithelioma).

In practice, it is important to distinguish thymoma (type A and B) from thymic carcinoma (type C), because the former group includes favorable tumors, whereas, the latter group is malignant capable of producing metastases (Table 11-4). The thymoma group is recognized by presence of *organotypic feature* characteristic of thymic differentiation and include the following:

1. lobular pattern with sharp angles separated by fibrous stroma (P 11-8 A)
2. Presence of thymic epithelial component, positive for cytokeratin (rounded or spindle cells).
3. Perivascular spaces or serum lakes, (P 11-8 A and B) which are rarely filled with blood (Peliosis thymomis).

Table 11-3 Classification of Primary Thymic Tumors

Category	Frequency (%)	Muller-Hermelink (1996)	WHO 2004	10-year survival (%)
Benign	26	Medullary thymoma	A	100
		Mixed thymoma	AB	
Borderline	66	Predominantly cortical	B1	90
		Cortical thymoma	B2	75
		Well-differentiated thymic carcinoma	B3	60
Malignant	8	**Low grade:**	C	33
		Squamous carcinoma		
		Bassaloid carcinoma		
		Mucoepidermoid carcinoma		
		High grade:		
		Lymphoepithelioma		
		Clear cell carcinoma		
		Sarcomatoid carcinoma		

(Travis et al, 2004)

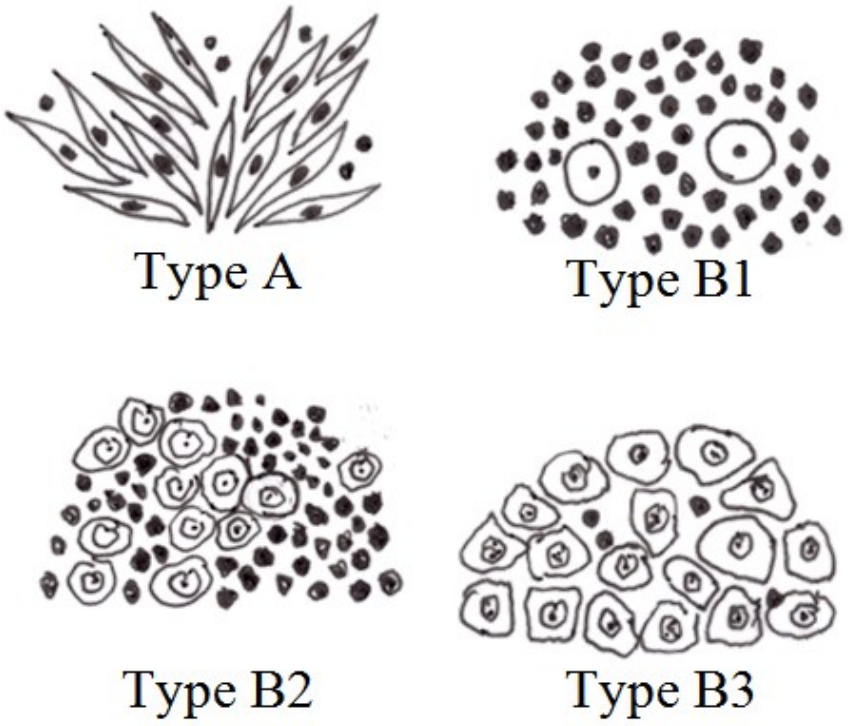

Fig 11-3 *The WHO classification of thymomas (Travis et al, 2004). It is based on shape of thymic epithelium, quantity of associated lymphocytes and the degree of epithelial atypia-Type A: spindle cells, associated few lymphocytes and no epithelial atypia, Type B1: rounded cells with abundant cytoplasm, abundant lymphocytes and minimal atypia, type B2: rounded atypical epilhelial cells, lymphocytes which are immature and type B3: epithelium rich, composed of polygonal cells with sharp cell borders and moderate atypia, associated few lymphocytes. Type AB: is a combination of spindle and round cells. Type C: is a diverse subtypes of frankly malignant anaplastic cells, laking lymphocyte association. Lymphocytes are mature in type A and immature in other types.*

Table 11-4 Comparison of Thymomas and Thymic Carcinomas

Feature	Thymoma (A, AB, B)	Thymic carcinoma (C)
Organotypic	Present	Absent
T lymphocytes	Present	Absent
EMA, CEA, Chromogranin	Absent	Frequent
Invasion	Minimal	Marked
Myasthenia	May be present	Absent
Prognosis	Favorable	Unfavorable

4. Reactive lymphoid component. The lymphocytes are normal polyclonal T-phenotype. They are mature (TdT-) in type A and immature (TdT+) in type B.

5. Hassall corpuscles which represent squamous differentiation of thymic epithelium and appear as concentric keratotic cell nests (P 11-8 C).

Differential Diagnosis

1. Benign round cell lesions: these include thymic hyperplasia (presence of germinal centers or preserved thymic cortical and medullary patterns) and Castleman disease (presence of fibrovascular septa and cytokeratin negativity).

2. Malignant round cells: including non-Hodgkin lymphoma and Hodgkin nodular sclerosis (both are cytokeratin negative). Mediastinal seminoma is PLAP positive and cytokeratin negative.

3. Malignant spindle cell sarcomas are cytokeratin negative and lack a lymphocyte component.

Immunophenotyping

Immunohistochemistry is helpful in typing thymic tumors (Table 11-5). Thus, the neoplastic thymic epithelium expresses different cytokeratin profile according to tumor subtype. Moreover, some thymic tumors (type A, B3 and C) exhibit characteristic other markers of their own. Finally, the T-lymphocytes associated with the tumor are mature in type A thymoma (TdT-, CD99- and CD1a-), but, immature in B and C subtypes (TdT+, CD99+ and CD1a+).

Paraneoplastic syndromes

Paraneoplastic syndromes may be associated with thymomas, the most common is myasthenia gravis in 30% of cases. This association is high with cortical thymoma (B2) and the related well differentiated thymic carcinoma (B3), as well as, follicular lymphoid hyperplasia of thymus. The associated myasthenia is a paraneoplastic syndrome with immunologic basis. Myasthenic patients with thymoma tend to be at an older age. Thus, a young woman with myasthenia is likely to have a thymus with lymphoid hyperplasia, whereas, an older patient is more likely to harbor a thymoma. About 25% of thymectomies are successful in the treatment of myasthenia, but the start of benefit may be delayed for up to two years. Other paraneoplastic syndromes that may be associated with thymomas include: red cell aplasia and hypogammaglobulinemia but, this is most commonly associated with medullary thymomas.

Prognosis

Prognostic factors of major importance are the gross findings at operation (stage of the disease), histologic type and the presence or absence of myasthenia gravis. The staging system of thymomas according to Masaoka (1981) is presented in (Table 11-6). Stage I or encapsulated thymoma contributes about 75% of cases, and if not associat-ed with myasthenia gravis, surgical excision is almost curable with a recurrence rate of only 2%. Conversely, the prognosis of invasive

Table 11-5 Immunophenotyping of Primary Thymic Tumors

WHO type	Cytokeratin (CK)	Other markers
A	Pan-CK	CD20
B1	CK7, CK14, CK18	-
B2	CK19, CK5/6, CK7	-
B3	CK19, CK5/6, CK7	CD5, C-kit, Glut-1
C	Pan-CK	CD5, EMA, CEA Chromogranin

(Travis et al, 2004 and Rosai, 2011)

Table 11-6 Masaoka Staging of Thymomas and its Corresponding TNM Classification

	(Masaoka et al, 1981)	(Travis et al, 2004)
I	Encapsulated, noninvasive	T1 N0 M0
II	Invasion of capsule or mediastinal tissue	T2 N0 M0
III	Invasion of pericardium, great vessels or pleura	T3 N1 M0
IVa	Dissemination in pericardium or pleura	T4 N0 M0
IVb	Nodal or distant metastases	Any T, N2, N3, M1

N1= anterior mediastinal nodes
N2= other intrathoracic lymph nodes
N3= Positive scalene or supraclavicular

N.B. Study of surgical margin is necessary to guide postsurgical adjuvant therapy.

thymomas are less favorable and depends on the histologic category (Table 11-3).

The presence of myasthenia gravis is associated with unfavorable outcome. Thus, the 10-year survival is 67% for thymomas without myasthenia gravis and only 32% for thymomas with myasthenia gravis. The subtyping of thymomas according to its lymphocyte content into predominantly lymphocytic, mixed and predominantly epithelial, has no prognostic significance.

Tumors of Cell-Inclusions in Thymus

This group of thymic tumors include: germ cell tumors, carcinoid, Langerhans cell disease and malignant lymphomas. The latter fall into three main groups: (1) *Large cell B-cell lymphoma* of adults, a high grade tumor, (2) *Small cell B-cell lymphoma* of MALT type, low grade, and (3) *Hodgkin lymphoma*, usually of the nodular sclerosing type and more common in females. In addition, lymphoblastic lymphoma (T-phenotype) which is common in children is a fourth type arising from T-thymocytes.

Neurogenic Tumors

Neural tumors are most commonly located in the posterior mediastinum near the paravertebral gutter. They are the most common mediastinal tumors in children. Such tumors may arise from peripheral nerves, sympathetic ganglia or from the paraganglia (Table 11-7).

Germ Cell Tumors

The mediastinum is the most common site of extragonadal germ cell tumors. Primary mediastinal seminoma constitutes about one half of all cases and is more common (95%) in men. Teratomas are benign in 77% of cases, and are most common in the anterior mediastinum accounting for about 20% of tumors of this compartment. It equally affects both sexes. Benign teratomas are classically multicystic, but unilocular dermoid cyst may also occur. The histology reveals tissues arising from all three germ cell layers. About 65% of patients have elevated beta HCG and / or AFP. Areas of calcification are present in 75% of tumors and may be seen on radiographs. Malignant change to teratocarcinoma occurs in 15% of cases.

Table 11-7 Neurogenic Tumors

I. From Peripheral Nerves
Neurofibroma
Neurosarcoma
II. From Sympathetic Ganglia
Ganglioneuroma
Ganglioneuroblastoma
Neuroblastoma
III. From Paraganglia
Pheochromocytoma
Chemodectoma

TUMORS OF THE HEART

Cardiac tumors are exceedingly rare (only 0.02% in autopsy series), but, because of their location are important since even benign tumors may have serious clinical complications. Tumors of the heart are classified into three main groups, namely: benign, primary malignant and secondary tumors (Table 11-8).

Myxoma is by far the most common cardiac tumor contributing about 60% of all neoplasms. It affects adults and the left atrium is the most common site. The tumors may be sporadic (solitary) or familial (multiple). The latter is usually a component of Carney syndrome (associated skin pigmentation and endocrine tumors). Myxoma is a true neoplasm (not an organized thrombus) and its histogenesis is related to a stem cell (vasoformative of cardiomyocyte progenitor). Histologically, the tumor is composed of stellate cells in a vascular myxoid stroma. Rarely, it may show glands or calcification.

Secondary tumors of the heart are 30 times more common than primary ones. Malignant tumors may reach the heart through one of three pathways, namely: (1) translymphatic spread from nearby malignancy in lung or breast, (2) transarterial metastases from distant primaries such as melanoma and lymphoma/leukemia, and (3) transvenacaval spread from liver of renal malignancies.

Complications of heart tumors may be cardiac or systemic. (1) The local cardiac complications include: ischemia, heart block, heart failure or

Table 11-8 Classification of Cardiac And Pericardiac Tumors

Benign Tumors
Myxoma, Rhabdomyoma, lipoma, hemangioma, fibroma
Papillary fibroelastoma and
Solitary fibrous tumor of pericardium
Primary Malignant
Endothelioma, angiosarcoma,
Malignant fibrous histiocytoma,
Rhabdomyosarcoma,
Pericardial mesothelioma
Secondary tumors
From: lung, breast, melanoma,
NHL / Leukemia, kidney and liver

(Travis et al, 2004)

cardiac tamponade from pressure effect of malignant pericardial effusion. (2) The systemic complications include: embolic phenomenon, and paraneoplastic syndromes (e.g. myxoma may secrete IL-6 causing systemic symptoms as fever, weight loss and weakness.

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