Mediastinum

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Objectives:

1. Discuss the compartments of the mediastinum
2. Discuss diagnostic evaluation of mediastinal lesions
3. Describe common mediastinal disorders

Key words: goiter; mediastinitis; mediastinum; neurogenic tumors; teratoma; thymoma

Anatomy

Definitions

The mediastinum is the intrathoracic compartment (extrapleural) located between the two pleural cavities. Its superior boundary is the thoracic outlet and the inferior boundary the diaphragm. Anterior extent is the sternum and its posterior border is the anterior surface of the vertebral bodies but also includes the paravertebral zones (posterior gutters). Anatomically, mediastinum can be divided into three compartments: anterior, middle, and posterior. The anterior mediastinum includes thymus, adipose tissue, aorta, brachiocephalic vessels, and lymph nodes. The middle mediastinum comprises the heart, pericardium, all major vessels entering and leaving the heart, trachea, main bronchi, paratracheal and tracheobronchial lymph nodes, phrenic and upper vagus nerves. The posterior mediastinum includes descending aorta, esophagus, thoracic duct, posterior mediastinal lymph nodes, and paravertebral tissues. The superior mediastinum lies above the aortic arch and is usually subdivided into anterior, middle, and posterior mediastinum. A substernal goiter is the most common mass in the superior mediastinum. Anatomic structures and tumors of the mediastinum are shown in Table 1.

Mediastinal Tumors

Majority (>75%) of mediastinal masses in adults are benign, where as 50% are malignant in children. Over 90% of malignant lesions are symptomatic but almost all benign lesions are asymptomatic. Symptoms vary, depending on the organ involved in the mediastinum. Paraneoplastic syndromes occur with many mediastinal tumors.

Table 1 — *Anatomic Structures and Tumors of the Mediastinum*

Superior
Thyroid 90+%
Neurogenic
Vascular
Adipose tissue

Anterior
Hodgkin's
Thymoma
Germ cell
- Teratoma (10% teratocarcinoma)
- Seminoma
- Choriocarcinoma (HCG elevated)
- Embryonal cell carcinoma (alpha fetoprotein, CEA elevated)

Castleman's disease
Primary bronchogenic carcinoma (origin?—not lung)
Mesenchymal sarcomas
Ascending aortic aneurysm

Middle
Lymph nodes
Cysts
Neurogenic
- Vagus
- Phrenic
- Sympathetic

Heart; Pericardium
Trachea; Main stem bronchi
Lymph nodes: paratracheal and tracheobronchial
Aorta
- Aneurysm
- Coarctation—1/3 have poststenotic aneurysm
- Right-sided aortic arch

Pulmonary artery—dilation (pulmonary HTN; poststenotic; idiopathic)

Posterior
Neurogenic
Esophagus
Extramedullary hematopoiesis
Descending aorta
Thoracic duct
Posterior mediastinal lymph nodes

Thymoma is an excellent example of paraneoplastic or "parathymic" syndromes, the most common being myasthenia gravis.

Tables 2 and 3 show the incidence of mediastinal masses among 1064 patients who underwent thoracotomy over a 40-year period (pre-CT era). To summarize, nearly 60% of them had one of three common masses: neurogenic tumor (20%), thymoma (19%), or benign cyst (18%). More than 30% of the patients had either malignant lymphoma, teratoma, granuloma, or intrathoracic goiter. The least common lesions were mesenchymal tumor, primary carcinoma, benign lymph node hyperplasia, mesothelioma, and parathyroid tumor. About 8% of patients were younger than 15 years of age and among these patients, 78% of the tumors were neurogenic, teratomas, or enterogenous cysts. Thymomas are rare in children.

Diagnostic Studies

Plain chest roentgenogram (both posteroanterior and lateral are necessary) helps to localize a mass to one of the mediastinal compartments. Cystic lesions appear lobulated and often are compressed between adjacent bronchi; solid masses are usually appear smooth and rounded but tend to compress adjacent structures. A contrast esophagogram may help diagnose a primary esophageal lesion such as a leiomyoma or achalasia producing a large dilated esophagus. A barium swallow can be diagnostic in carcinoma of the esophagus and achalasia. A barium swallow is also diagnostic in substernal goiter and esophageal leiomyomas or enterogenous cyst. These lesions both move up and down with swallowing.

Computed tomography (CT) is perhaps the most important imaging procedure in the diagnosis of mediastinal tumors. CT defines the density of a mass, especially in relation to the density of nearby structures such as air (lung), soft tissue, fat, and bone. Masses with density consistent with fat, such as benign epipericardial fat pad or mediastinal lipomatosis from hypercortisonism, do not enhance intravenous contrast medium. Intrathoracic omental fat protruding through a hiatal hernia or the foramen of Morgagni will appear as a very-low-density tissue.

Cystic lesions, such as bronchogenic and pericardial cysts, have densities close to that of water. They also have clearly defined outlines. Transthoracic or bronchoscopic needle aspiration may help solidify the diagnosis. Solid masses have higher attenuation values and frequently enhance with contrast medium. Solid masses may be benign or malignant. Benign masses usually do not obliterate the interface between surrounding tissues, whereas malignant masses more often have irregular margins and the suggestion of infiltration into adjacent tissues.

CT remains the procedure of choice in suspected malignant lesions because it can detect pulmonary parenchymal metastasis better than MRI, even though MRI is a little better than CT for chest wall invasion. Neither can separate benign from malignant tissue unless, of course, invasion or metastasis is evident. With uncommon exceptions, it is not necessary to do both.

MR imaging is useful to confirm cystic structure of mediastinal lesions that look solid on CT.

Table 2—*Types of Mediastinal Tumors in 1,064 Patients Who Underwent Thoracotomy at Mayo Clinic, Rochester, Minnesota**

Type of Tumor	Patients	%
Neurogenic tumor	19.9	
Thymoma	19.4	57.7
Benign cyst	18.4	
Malignant lymphoma	10.1	
Teratoma	9.3	
Granuloma	6.3	31.0
Intrathoracic goiter	5.3	
Mesenchymal tumor	5.6	
Primary carcinoma	2.3	11.3
Miscellaneous	3.4	
Total	1,100.0	100.0

* From J Thorac Cardiovasc Surg 1971; 62:379-391.

Table 3—*Histologic Diagnosis of Mediastinal Tumors in 1,064 Patients Who Underwent Thoracotomy at Mayo Clinic, Rochester, Minnesota**

Diagnosis	Patients, %
Malignant	23
Lymphoma	44
Thymoma	21
Mesenchymal tumor	14
Primary carcinoma	10
Neurogenic tumor	6
Teratoma	5
Benign	77
Total	100

* From J Thorac Cardiovasc Surg 1971; 62:379-391.

Detection of small amounts of intralesional fat can indicate hemangioma, teratoma, or extramedullary hematopoesis. MRI is preferred by many to assess neurogenic tumors, intraspinal extension, and craniocaudad extent. MRI is indicated imaging in patients who are allergic to iodinated contrast material. MRI is recommended as a first imaging study in the initial evaluation of superior sulcus tumors, suspected brachial plexus lesions, paraspinal masses that appear to be consistent with neurogenic tumors.

Calcification does not guarantee benignancy. It can be found in the following lesions: thymoma, goiter, treated Hodgkin's and rarely untreated Hodgkin's, mediastinal granuloma and fibrosing mediastinitis, teratoma and rarely other germ cell tumors, Castleman's, walls of aortic aneurysms, and neurogenic lesions

Transesophageal echocardiography is especially valuable in diagnosing mediastinal hematomas and dissecting aortic hematomas in the emergency room where the patient may be too sick and unstable to go to an MRI unit. It is also helpful in identification of cardiac myxomas, cardiac tamponade, differentiating vascular from nonvascular mid-mediastinal lesions, superior vena cava flow, and degree of infiltration or compression of vascular and cardiac structures.

Bronchoscopy is useful if there is suspicion of airway compression from mediastinal masses or suspicion of direct airway invasion by the tumor. Bronchogenic cysts compressing the main stem bronchi have been drained via bronchoscopic needle aspiration.

CT-guided needle aspiration/biopsy is being done more frequently to diagnose mediastinal tumors.

Thymoma

Thymoma is the most common neoplasm of the anterior mediastinum. About 20% of all mediastinal tumors are thymomas. The peak incidence is between 40 and 60 years of age. Male to female ratio is 1:1 to 1.2 to 1. Thymomas are benign in 65% of cases (encapsulated and fully resectable). About 40% of the tumors are associated with one or more of the 30 or so "parathymic" syndromes, most commonly myasthenia gravis and less commonly adult-onset acquired hypogammaglobulinemia and pure red cell aplasia (PRCA). A review of thymomas in 960 patients noted the following: malignant 35%, myasthenia gravis in 35%, parathymic syndromes in 40%, invasive in 35%, and extrathoracic metastasis in <5%. Five-year survival: noninvasive 80%, and invasive 25%.

Roentgenographically, thymomas are round, smooth, lobulated densities that occur near the junction of the heart and great vessels. They measure between 5 and 15 cm in diameter. Large thymomas can mimic cardiomegaly. Calcification is evident in about 20% of cases; however, this finding does not denote benignancy. Histologically, thymomas are predominantly lymphocytic or predominantly epithelial cells or a mixture of the two. There is also a spindle cell variety. Another classification divides thymomas into cortical (organoid), medullary, and mixed types. Histologic analysis of tissue may not separate benign from malignant thymoma. Presence of invasion detected by imaging or during surgery determines if a thymoma is benign or not. Treatment of thymoma is surgical excision. In invasive disease, surgical debulking is usually indicated. Many malignant thymomas respond to radiotherapy. Tumor recurrence rate and mortality ate higher with cortical types. Thymolipoma constitutes <8% of all thymic tumors. It tends to be large and CT shows fat tissue attached to thymus.

Thymopathies

These denote clinical manifestations not caused by the anatomic location or metastatic spread of thymomas. In some ways, they are akin to paraneoplastic syndromes seen with lung cancer. For instance, thymic carcinoid may be associated with Cushing's syndrome (never Carcinoid syndrome). A small thymic carcinoid may remain hidden for long periods. A CT or an MRI of the mediastinum should be considered in such cases. About 35% of patients with thymoma have myasthenia gravis, where as 15% of those with myasthenia gravis will have thymoma. MG is more common in the cortical form of thymoma. Anti-ChR-binding antibodies are present in 80% of patients with MG. If thymoma is present, striated muscle antibody will usually be positive and can serve as an indicator for recurrence of the (malignant) thymoma. Thymectomy for thymoma with MG has been reported to provide remission from MG in over 65% of patients. The remission rate is lower with older patients, advanced Osserman stage, high doses of pyridostigmine, use

of steroids before surgery, the total duration of the disease, previous thymectomy, and plasmapheresis after surgery. While only 5% with thymoma have PRCA, 50% of patients with PRCA will have thymoma (usually spindle cell or medullary type). Thymectomy leads to resolution of PRCA in 35% of patients. Hypogammaglobulinemia is present in 10% with thymoma and <5% of patients with hypogammaglobulinemia will have thymoma.

Thymic Hyperplasia

Normal thickness of thymus in those <20 years is 1.8 cm, and in those >20 years, it is <1.3 cm. Thymic hyperplasia denotes increase in size of the thymus with normal architecture and histology. This is usually seen in children and young adults. Usual causes include rebound phenomenon due to chemotherapy or hypercortisonism, hyperthyroidism, and less commonly due to "stress" such as sepsis or massive burn. Thymic lymphoid hyperplasia is more likely to be associated with myasthenia gravis.

Table 4—*The Definitions of World Health Organization Classification of Thymic Epithelial Tumors*

Type	Definition
A	A tumor comprised of a homogenous population of neoplastic epithelial cells with spindle/oval shape, lacking nuclear atypia, and accompanied by few or no nonneoplastic lymphocytes
AB	A tumor in which foci with the features of type A thymoma are admixed with foci rich in lymphocytes: the segregation of two patterns can be sharp or indistinct
B1	A tumor that resembles the normal functional thymus in that it combines large expanses with an appearance practically indistinguishable from that of normal thymic cortex with areas resembling thymic medulla
B2	A tumor in which the neoplastic epithelial component appears as scattered plump cells with vesicular nuclei and distinct nucleoli among a heavy population of lymphocytes; perivascular spaces are common
B3	A tumor comprised predominantly of epithelial cells with a round or polygonal shape and exhibiting mild atypia admixed with a minor component of lymphocytes; foci of squamous metaplasia and perivascular spaces are common

Staging

The WHO staging systems and Masaoka staging are shown in Tables 4 and 5 respectively. Some use both classifications to assess prognosis.

Therapy

An aggressive surgical approach is recommended. The 5-year survival rates for patients with stage III thymomas is much higher (>75%) than in those with incomplete resections (35%). Thymomas frequently show recurrence, and many of these are late recurrences. Treatment with somatostatin analogs and prednisone has shown efficacy in patients with recurrent and metastatic malignant thymic tumors refractory to standard therapeutic options (Cancer 2002;94:1414-20). A study of completely resected thymomas has shown that whole mediastinal field with or without boost (total dose of 40 Gy) is effective in preventing mediastinal recurrence for patients with completely resected thymoma (Cancer 2002;94:1405-13). It has been noted that thymoma is associated with an increased risk of second malignancy.

Germ Cell Tumors

Germ cell tumors are histologically identical to certain testicular or ovarian neoplasms, all of which are believed to be derived from primitive germ cell elements. They include benign and malignant teratomas (teratocarcinoma in 10%), seminoma, choriocarcinoma (elevated HCG), embryonal cell carcinoma (elevated alpha fetoprotein and CEA), and endodermal sinus (yolk sac) tumors. The vast majority (>90%) are located in the anterior mediastinum. The mean age at diagnosis is between 20 and 40 years. In adults, these tumors account for 11% of mediastinal masses and for about 12% of primary mediastinal tumors in children (mostly teratomas). Benign tumors are more common

Table 5—*Masaoka Staging*

Stage I	Well-encapsulated without evidence of gross or microscopic capsular invasion
Stage II	Pericapsular growth into adjacent fat or mediastinal pleura, or microscopic invasion of the thymic capsule
Stage III	Invasion of adjacent organs
Stage IVa	Intrathoracic metastasis
Stage IVb	Extrathoracic metastasis (uncommon)

in women whereas malignant tumors are more common in men. Dermoid tumors would also be considered in this classification, but they never have any malignant propensity. Eighty percent of primary germ cell tumors in the mediastinum are teratomas.

Teratoma is the most common germ cell tumor. The vast majority are benign (>85%). They are usually unicystic or multicystic. Teratoma commonly contains calcium and other tissues such as fat, muscle tissue, dental tissue, etc. When it is large enough, it will compress mediastinal structures, producing a cough or a fullness sensation and then the diagnosis established after a chest x-ray is obtained. A dermoid contains only a single ectodermal type of tissue, whereas a teratoma has at least two and usually three germinal cell lines. Systemic symptoms or invasiveness on imaging studies imply a teratocarcinoma, which is most commonly an adenocarcinoma or squamous cell carcinoma. Excision of mature teratoma in younger patients is followed by good prognosis. Teratomas in older individuals are more aggressive.

Seminoma is the most common malignant germ cell tumor. Seminomas occur almost exclusively in men in the third or fourth decade of life. These are primary in the mediastinum and not metastatic from the testes. CT shows anterior mediastinal mass with homogeneous attenuation. Up to 30% of patients are asymptomatic. Most patients have symptoms of cough, chest pain, hoarseness, or obstruction of the superior vena cava (in 10%). The tumors may invade adjacent structures as well as produce distant metastatic lesions. A small percentage of patients will have elevated beta human chorionic gonadotropin (ß HCG). Seminomas are radiosensitive in contrast to the nonseminomatous germ cell tumors. In patients with bulky lesions or those that have metastasized, chemotherapy can produce complete remission in 80 to 90% of patients. Poor prognostic sings: age >35 years, fever, and superior vena cava syndrome.

Embryonal cell carcinoma, choriocarcinoma, and endodermal sinus tumor are rare, occurring in men between the ages of 20 and 50. They almost always have systemic symptoms as well as local symptoms. Gynecomastia develops in nearly two-thirds of patients and is associated with high levels of ß HCG and alpha fetoprotein. Cisplatin-based chemotherapy is effective in 50 to 70% of patients. Following the tumor markers is a good way of assessing response to therapy. Surgical resection when tumor markers return to normal is an option. About 20% of nonseminomatous germ cell tumors have a rapid downhill course and must be treated aggressively.

Thyroid

Most intrathoracic goiters are extensions of nodular colloid goiters and carry a vascular supply with them from the neck. Primary intrathoracic goiters are rare. Intrathoracic goiter should be suspected in a patient with a mediastinal mass with a palpable goiter in the neck or who has had a partial thyroidectomy. Extension into the anterior or posterior mediastinum occurs in 10%. Substernal goiters usually occur in middle-aged women, who are often asymptomatic, although symptoms such as cough, hoarseness, or swelling in the face and arms may arise from compression of the trachea or involvement of the recurrent laryngeal nerve, esophagus, or superior vena cava.

The chest roentgenogram shows a sharply defined, smooth, lobulated anterior superior mediastinal mass, commonly with tracheal deviation. A characteristic feature of intrathoracic thyroid is a distinct area of calcification, which is thought to be the result of bleeding into a cyst. A ^{131}I scan is generally positive and is therefore the nuclear scan of choice, if necessary. A barium swallow examination reveals that the substernal goiter moves up and down with swallowing and is quite characteristic. Colloid goiter may rarely be associated with carcinoma (1%) or thyrotoxicosis.

Bronchogenic and Enterogenous Cysts

These lesions occur in the middle mediastinum. Bronchogenic cysts have respiratory epithelium and enterogenous cysts have an enterogenous epithelium. Bronchogenic cysts are usually located near the large airways and are most often found in the subcarinal area. These cysts are commonly discovered early in life on a screening chest roentgenogram. CT scan shows that these cysts are denser than fat but less dense than soft tissue and do not enhance with intravenously administered contrast medium. They are generally homogeneous, with crisp borders. Through the bronchoscope or with CT guidance, a needle can often be directed

into such cysts and clear fluid aspirated; this technique establishes the diagnosis and is sometimes all the treatment that is needed. A few have been treated with intracystic instillation of doxycycline or minocycline or talc slurry to obliterate the space. Pleuropericardial cysts are located in the cardiophrenic angle, usually on the right side, and are lined by a single layer of mesothelial cells. The name "spring-water cysts," has been used to describe these because of the clear fluid that can be aspirated. Although pleuropericardial cysts may be quite large and contain several liters of fluid, they are usually asymptomatic. CT is usually diagnostic. Needle aspiration with ultrasonic or fluoroscopic guidance, if necessary.

Esophageal Lesions

Benign lesions that arise from the esophagus such as leiomyomas, fibromas, or lipomas may also present as posterior mediastinal masses and may be visible on a chest roentgenogram. Gross dilatation of the esophagus occurs in achalasia and should be suspected in a patient with dysphagia, odynophagia, or recurrent pneumonia due to aspiration. Presence of air fluid level is helpful in the diagnosis. A barium esophagogram shows a smooth-bordered mass in patients with a leiomyoma that moves up and down with swallowing or gross dilatation and sharp narrowing of the lower esophageal sphincter in patients with achalasia. Leiomyoma occurs only in the smooth-muscle portion of the esophagus--that is, the lower two-thirds. Most leiomyomas are asymptomatic unless huge.

Neurogenic Tumors

Eighty-five to ninety percent of posterior mediastinal masses are neurogenic in origin with 6% being malignant (higher in children). Neurogenic tumors can arise from the nerve sheath or the nerve cell itself. They include neurofibromas (they arise from endoneural tissue) or schwannomas (these arise from the protective sheath of Schwann), ganglioneuromas or neuroblastomas, and pheochromocytomas or paragangliomas. Neurogenic tumors are common in patients < 30 years. CXR usually shows a sharply circumscribed round or oval shadow in the paravertebral gutters. They are much more likely to be malignant in children (neurofibrosarcoma) and more likely to be malignant the farther away they are from the paravertebral gutter. Ten percent of neurogenic tumors arise in the intervertebral foramen and assume a dumbbell shape, causing spinal cord compression. A CT or MRI is sensitive to this and should be done in all paravertebral neurogenic lesions.

Mediastinitis

Most cases of acute mediastinitis are associated with esophageal perforation (mostly iatrogenic), esophageal or cardiac surgery (<1%), head and neck infection (retropharyngeal abscess, etc). Spontaneous perforation (Boerhaave's syndrome) can also lead to acute mediastinitis. Positive blood cultures are found in about one-third. Bacteria involved include Streptococcus, anaerobes, Pseudomonas, and Candida. Abrupt onset of severe retrosternal pain with radiation to neck and fever are common symptoms. A chest x-ray may show mediastinal widening, air within the mediastinum and soft tissues in the neck. CT is relatively sensitive and specific. Extraluminal extravasation of contrast is a helpful sign. Pneumothorax is more common on the left in distal esophageal perforation whereas it is more common on the right in mid-esophageal perforation. Aggressive therapy including surgical drainage as well as antibiotics is indicated. Prognosis is poor if the diagnosis and treatment are delayed.

Mediastinal Fibrosis/Mediastinal Granuloma

Mediastinal fibrosis may present as a well-localized form presenting as a mediastinal mass or in the form of diffuse mediastinal fibrosis with or without granulomatous changes obstructing vital structures to the point of compromise and death. In a review of 33 cases, a localized pattern was seen in 82% and a diffuse pattern in 18%. The majority of these are thought to be due to histoplasmosis. Some consider the diffuse variety to be an immune phenomenon. The diffuse variety may be associated with other conditions such as retroperitoneal fibrosis, methysergide therapy, Riedel's sclerosing thyroiditis, and orbital pseudotumors. Complications of mediastinal fibrosis include bronchial narrowing, pulmonary artery obstruction or narrowing, esophageal narrowing, and SVC obstruction. The chest roentgenogram may be normal in these pa-

tients with significant involvement of surrounding structures or with subtle changes such as widened mediastinum. Hyperlucent lung from complete occlusion of the pulmonary artery, almost always on the right side, can occur. Rarely, pulmonary veno-occlusive disease can occur. Therapies have included steroids, antifungal agents, and tamoxifen.

Pneumomediastinum

Perforation of the esophagus or traumatic rupture of the trachea or mainstem bronchi are among the etiologies (Table 6). Spontaneous pneumomediastinum can occur as a result of weightlifting, acute asthmatic attack, and even a viral respiratory illness. The vast majority of spontaneous pneumomediastinum occur in the second and third decades. Retrosternal pain, dyspnea, and dysphagia are present in almost all patients. Air may only be seen on the lateral film in a fair number of patients. Hamman's sign, that is, an auscultatory crunch with each heartbeat, is present in most but not all. However, when present, it would be a significant clue.

Table 6—*Pneumomediastinum*

Upper respiratory tract
Head, neck infection
Trauma
Dental procedures
Trauma
Major airway disruption
Via subq air
Ruptured esophagus
Surgical
Tracheostomy
Mediastinoscopy
"Spontaneous"
Valsalva
Asthma
Boerhaave
Other
Pneumoperitoneum
Mechanical ventilation

Annotated Bibliography

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This is a good review of the pathology, diagnosis, and treatment of this nearly uniformly fatal condition if not adequately recognized.

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A review of the role of MRI in the imaging of mediastinal structures.

Grosfeld JL, Skinner MA, Rescorla FJ, et al. Mediastinal tumors in children: experience wtih 196 cases. Ann Surg Oncol 1994; 1:121-127

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Wychulis AR, Payne WS, Clagett OT, et al. Surgical treatment of mediastinal tumors: a 40 year experience. J Thorac Cardiovasc Surg 1971; 62:379-392
This is a summary of over 1,000 surgically treated mediastinal masses. This was all done before the days of CT and MR in which essentially all masses including benign cysts were surgically removed, but it gives a good incidence.

Notes

Notes