Chapter 2
Clinical Approach: Recommendations for the Clinicians

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Introduction

Mediastinal masses include a wide variety of entities both neoplastic (benign or malignant, primitive or secondary) and not (infections, trauma, aneurysms, malformations). They may present a spectrum of clinical and pathological features and often pose a diagnostic challenge for clinicians.

Anatomic Distribution

Each compartment of mediastinum can be the origin of specific masses, as summarized in Table 2.1. Primary masses most often found in the anterior compartment are thymic tumors (thymoma, thymic carcinoma, thymic carcinoid tumor, and thymolipoma), thymic cysts, Hodgkin and non-Hodgkin lymphoma, germ cell tumors (seminoma, choriocarcinoma, embryonic carcinoma, teratoma), goiter, parathyroid adenomas and carcinomas, connective tissue tumors and soft tissue sarcomas (e.g., lipomas, liposarcomas, fibroma, fibrosarcoma), and lymphovascular tumors (lymphangioma, lymphangiohemangioma, hemangioma) [1].

Masses of the middle mediastinum include congenital cysts (bronchogenic cysts, pericardial cysts, and neurenteric cysts), tracheal tumors, aortopulmonary paraganglioma (chemodectoma), and lymphoma. A middle mediastinal mass may also

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Table 2.1 Differential diagnosis of mediastinal mass by compartment

Anterior	Middle	Posterior
Thymic disease	Reactive lymphadenopathy	Neurogenic tumors
Germ cell tumors	Granulomatous lymphadenopathy	Meningocele
Lymphoma	Lymphoma	Esophageal lesions
Thyroid neoplasms	Castleman's disease	Diaphragmatic hernia (Bochdalek)
Parathyroid neoplasms	Developmental cysts	
Mesenchymal tumors	Vascular enlargement	
Diaphragmatic hernia (Morgagni)	Diaphragmatic hernia (hiatal)	

represent lymphadenopathy as a result of infectious, malignant (metastatic), and idiopathic (e.g., sarcoidosis) etiologies [2].

Posterior mediastinum is the site of most neurogenic tumors, meningocele, esophageal lesions (diverticula and tumors), hiatus hernia, and neurenteric cysts [3].

Finally, suppurative acute mediastinitis is usually secondary to either perforation of the esophagus or cardiovascular and endoscopic surgical procedures. Chronic mediastinitis is more rare and may be secondary to tuberculosis infection [4].

Clinical Presentation

In about half of cases, a mediastinal mass can be an incidental finding in patients who undergo imaging studies for other reasons [5].

Local symptoms, if present, may be due to compressive or infiltrative effects of the mass, while systemic symptoms are due to release of hormones, cytokines, and antibodies. In general, malignant lesions are more likely to be symptomatic, and venous compression symptoms precede those of the esophagus or trachea because veins are more easily collapsible.

- *Symptoms of compression of superior vena cava* (SVC). Compression of the superior vena cava may result from the presence of a mass in the middle or anterior mediastinum. Severity of symptoms depends on how quickly the SVC obstruction develops and the degree of narrowing. Acute thrombosis can also occur causing sudden exacerbation of a partial obstruction.

  Increased venous pressure causes distention of jugular veins, not changing with respiratory cycle. Edema can be limited to the face or extended to the neck, upper chest, and upper limbs (mantle edema). Venous stasis symptoms (confusion, headache, dizziness) in the cerebral circulation can occur; however, cerebral edema, although rare, can be serious or fatal.

  In long-standing cases with 50% or more of SVC stenosis, various collateral channels, depending on the site of obstruction, are formed to restore venous return to the right atrium. Most of the patients with pre-azygos obstruction of the SVC remain asymptomatic for a long period of time, because in these conditions the right superior intercostal veins serve as the collateral pathway. When the

azygos vein is also obstructed, the collateral circulation establishes between the SVC and IVC via minor communicating channels, i.e., internal mammary veins; thus, signs of venous stasis are more pronounced [6].
Clinical and radiological scoring systems of SVC syndrome have been proposed. In the case of a malignancy causing SVC obstruction, management issues include surgical, medical, or radiotherapy treatment of the malignancy itself and palliative treatments for the symptoms. Traditional medical treatment such as corticosteroids and diuretics is not supported by data demonstrating benefit [7].

- *Symptoms of compression of esophagus*: dysphagia. Paraesophageal lymph node metastasis from lung cancer is a frequent cause of dysphagia.
- *Symptoms of compression of trachea*: dyspnea, inspiratory stenotic noises, and reentry of intercostal and suvraclavear spaces appear below a critical threshold of 50% of normal diameter. The worsening of the tracheal compression causes stagnation of secretions and coughs.
- *Neurological symptoms* can be caused by compression of phrenic nerves (hiccup, paralysis of hemi diaphragm), recurrent laryngeal nerve (dysphonia; the left recurrent laryngeal nerve is the most frequently affected, due to its longer course), or vague nerves (heart rhythm alterations, digestive symptoms as nausea, vomiting, and diarrhea). Sympathetic chain compression in paravertebral region leads to miosis and enophthalmus (Horner's syndrome).
- *Systemic symptoms*. Most common paraneoplastic syndrome associated with thymoma is myasthenia gravis (MG), followed by hypogammaglobulinemia and pure red cell aplasia. Autoimmune disorders such as systemic lupus erythematosus, polymyositis, and myocarditis may also be associated with thymoma. However, lack of myasthenia gravis does not rule out thymoma [8]. Clinical presentation of lymphoma can include "B" symptoms such as fever, night sweats, or weight loss. Furthermore, syndromes and symptoms caused by the production of hormones by primitive neoformations of the mediastinum (ACTH, thyroid hormones, PTH, catecholamines, etc.) can be present (Table 2.2).

Table 2.2 Syndromes and symptoms due to hormone production or paraneoplastic syndromes

Symptoms	Mediastinal mass
Hypercalcemia	Parathyroid disease, lymphoma
Thyrotoxicosis	Intrathoracic goiter
Gynecomastia	Germ cell tumors
Hypoglycemia	Mesenchymal tumors
Blood hypertension	Neurogenic tumors
Diarrhea	Neurogenic tumors
Opsomyoclonus	Neurogenic tumors
Syndromes	
Myasthenia gravis, pure red cell aplasia	Thymoma
Cushing's syndrome, multiple endocrine adenomatosis	Carcinoid, thymoma
Night sweats, fever, weight loss ("B" symptoms)	Lymphoma
Von Recklinghausen's syndrome	Neurofibroma

Presumptive Clinical Diagnosis

In most patients, a combination of demographic information, clinical presentation, and imaging features allows a presumptive diagnosis (Table 2.3). All patients should have a detailed history and physical examination before a major work-up is initiated.

- *Epidemiology*. Age and gender of the patient help predict the etiology of a mediastinal mass, as specific conditions are more common in certain demographic groups [9]. In infants and children, neurogenic tumors and enterogenous cysts are the most common mediastinal masses, while in adults thyroid goiter and thymic malignancies are most frequent encountered lesions. Since both Hodgkin's and non-Hodgkin's lymphoma and germ cell tumors are most common between the ages of 20 and 40, the likelihood of a mediastinal mass being malignant is increased among these patients. Also benign teratoma is relatively common in this age group.
- *Physical examination*. Enlarged lymph nodes in the cervical, supraclavicular, and axillary regions may be palpable. A palpable cervical mass may suggest mediastinal extension of a cervical goiter. Pleuropulmonary (pleural effusion) or abdominal (hepatomegaly and/or splenomegaly) signs may be additional findings.

Table 2.3 Diagnostic approach to mediastinal masses

Radiological exams	Chest plain X-ray CT scan MR PET Ultrasonography Esophagus X-ray
Endoscopic exams	Bronchoscopy and bronchial endoscopy Esophagogastroduodenoscopy and esophageal ecoendoscopy
Bioptic exams	Surgical excision (VATS, thoracotomy) Anterior mediastinotomy Mediastinoscopy Needle aspiration and core biopsy (transbronchial via a fiber-optic bronchoscope, percutaneous CT or US, endoscopic US guided)
Scintigraphic exams	Bone scintigraphy ^{131}I scintigraphy ^{123}I MIBG scintigraphy ^{99m}Tc scintigraphy
Laboratory exams	Tumor markers: NSE, LDH, αFP, βHCG Plasma and urinary catecholamines Urinary vanillylmandelic acid ACTH, cortisol PTH, calcemia, and phosphatemia FT3, FT4, TSH Insulin AChR antibodies

In suspecting a germ cell tumor, a testicular examination should be done in all male patients. Clinical signs of diseases such as neurofibromatosis or Klinefelter syndrome can address the diagnosis. Multiple neurogenic tumors and plexiform neurofibroma are typical findings of neurofibromatosis.

- *Laboratory tests*. Increased levels of alpha-fetoprotein (AFP) are typically found in non-seminomatous tumors (embryonal carcinoma and yolk sac). Elevated serum levels of human chorionic gonadotropin (HCG) are present in choriocarcinoma [10].
  Lactate dehydrogenase (LDH) is a less-specific marker, reflecting the growth rate and tumor burden. Increased levels of serum LDH have been reported in approximately 80% of advanced seminomas and in about 60% of non-seminomas. Serum LDH is commonly elevated also in lymphoproliferative disorders.
  Pre-chemotherapy levels of LDH, AFP, or HCG have also been integrated into the International Germ Cell Cancer Consensus Group (IGCCCG) prognostic index for non-seminoma classification.
  In approximately 85% of MG patients, circulating antibodies against the acetylcholine receptor (AChR) are not only the pathogenic effector immune molecules but also provide a diagnostic test.
- *Imaging*. Most mediastinal abnormalities are first detected by standard posteroanterior and lateral chest radiographs. It is rarely diagnostic but provides information on the mediastinum profile, any calcific or bone formations, or levels between the various components (solid, fluid, aerial) of the mass.
- Whenever a mediastinal mass is detected on plain films, a computed tomography (CT) scan of the chest is generally indicated. It allows to define seat, size, density, and relationship with anatomical structures of thorax. It also guides further biopsy diagnostic tests. Diagnosis can be suggested based on components of the mass: cystic, fatty, or solid tissue.
  Chest wall study and assessment of relationships with pericardium, spinal cord, and canal are the major indication for magnetic resonance imaging (MRI) of the mediastinum. Also, MRI provides better soft tissue differentiation than CT, useful in characterization of cysts and adenomas and differentiation of postsurgical or post-actinic fibrosis from disease relapse. MRI should be considered in patients who cannot receive iodinated intravenous contrast [11].
  18F-FDG PET is not routinely performed to evaluate or characterize a mediastinal mass but is typically used to stage lymphomas and monitor response to therapy.

Tissue Diagnosis

In a proportion of patients with a mediastinal mass, a presumptive clinical diagnosis cannot be reached, and biopsy is mandatory for diagnosis and/or treatment plain [12].

The histological diagnosis of a mediastinal tumor is always important, even in cases of inoperable disease, in order to evaluate the most appropriate therapeutic choice. Various methods can be used, which differ in the access path and picking technique, depending on location, size, and diagnostic suspect.

The cytological examination can be performed as CT-guided percutaneous fine needle aspiration, while agobiopsy remains the preferable option to obtain a tissue fragment. The access route may also be mininvasive surgical (by videothoracoscopy or mediastinoscopy). Anterior mediastinotomy or thoracotomy can be necessary in some cases.

Differential Diagnosis

Middle Mediastinal Mass

Lymphoma is one of the most common primary mediastinal tumors, representing 10–15% of mediastinal masses and presents more often as generalized disease. Only 10% of lymphomas involving mediastinum are primary, and the majority are Hodgkin lymphomas (~70%). The three most common types of mediastinal lymphoma include nodular sclerosing HD, large B-cell lymphoma, and lymphoblastic lymphoma [13].

Primary mediastinal B-cell lymphoma (PMBCL) is a diffuse large B-cell non-Hodgkin lymphoma that arises in the thymus, now identified as distinct clinicopathologic entity.

Lymphoproliferative disorders include also Castleman disease. It might be localized or multicentric and usually involves the mediastinum. Multicentric Castleman disease (MCD) involves hyperactivation of the immune system, excessive release of cytokines leading to systemic symptoms, and multiple organ system dysfunctions [14]. IL-6 is the most commonly elevated cytokine, and its release is caused in 50% of cases by infection with human herpesvirus 8 (HHV-8), whose DNA can be detected in peripheral blood by polymerase chain reaction (PCR).

Other causes of lymphadenopathy are infections, metastases, and idiopathic diseases (sarcoidosis).

Tuberculosis lymphadenopathy is another hypothesis in patients with middle mediastinal mass. Cervical region is more frequently involved, followed by mediastinal lymph nodes. In developed countries majority of patients are immigrants. Also in this case, systemic symptoms, such as fever, night sweats, and weight loss, can be present. The best diagnostic approach appears to be a combination of skin testing and FNA, since most HIV-seronegative patients are PPD-positive.

Developmental cysts account for 15% of mediastinal masses. They present as well-circumscribed masses with a smooth wall. The most common type of mediastinal cyst is foregut cysts, with enterogenous cysts (50–70%) and bronchogenic cysts (7–15%) being the most common subtypes. Pericardial cysts are part of a larger group of mesothelial cysts; the most common is at the right cardiophrenic

angle. Neurenteric cysts are characterized by the presence of both enteric and neural tissue. Most of these cysts form in the posterior mediastinum above the level of the main carina [15].

Anatomical variants as vascular anomalies (aneurysm) or masses arising from digestive tract (hiatal hernia) can be radiologically recognized.

Anterior Mediastinal Mass

The classification of **thymic neoformations** includes thymic hyperplasia, thymic cysts, thymoma, thymolipoma, and thymic carcinoid. The last two are very rare. The typical seat is the upper anterior mediastinum.

Thymic neoplasms, predominantly thymomas, constitute the 30 and 50% of anterior mediastinal masses in adults and children, respectively. No specific etiology or risk factors are known but a well-known association with myasthenia gravis does exist. Only a small part of thymoma patients is affected by myasthenia, while about 20% of myasthenic patients are affected by thymoma.

Ninety percent of thymomas occur in the anterior mediastinum, the reminder in the neck or other areas of the mediastinum. Classification is based on cell-type predominance as lymphocytic, epithelial, or spindle cell variants. Thymomas may be encapsulated or frankly invasive. A strong association between histologic subtype and invasiveness as well as prognosis is known.

Chest pain, cough, and dyspnea are the most common symptoms due to local growth. Metastatic disease is uncommon and can occur in pleural implants or pulmonary nodules.

Thymic carcinomas are aggressive malignancies. Their incidence is rare, occurring predominantly in middle-aged men. They often manifest as large, poorly defined, infiltrative mass that frequently metastasizes to regional lymph nodes and distant sites [16].

In anterior mediastinum prevascular and paratracheal lymph nodes are the most common localizations of **lymphoma**.

Primary mediastinal goiters (PMG) are very uncommon. Cervical **goiters** may descend into the thorax in 10% of cases, generally into the left anterior superior mediastinum. The most common symptoms are cervical mass, dysphagia, and dyspnea. Ten percent of patients are asymptomatic.

Germ cell tumors. Mediastinal germ cell (MGC) neoplasms account for 2–5% of germ cell tumors but constitute more than half of extragonadal tumors. They are responsible for 10–15% of mediastinal primary tumors. They can occur at any age but most commonly between the third and fifth decade of life.

Benign neoplasms include mature and mixed teratomas (with an immature component of less than 50%). Among these, benign teratomas are the most common MGC tumor; the majority of them contain variable amounts of mature ectodermal, mesodermal, and endodermal elements and exhibit a benign course. Mature teratomas have the potential in rare circumstances to undergo malignant transformation.

Malignant germ cell tumors are divided into seminomatous and non-seminomatous tumors. Primary mediastinal seminomas, although uncommon, comprise 25–50% of malignant mediastinal GCTs. On radiological imaging seminomas appear as bulky lobulated and homogeneous mass. Choriocarcinomas, yolk sac tumors, immature teratomas, and embryonal carcinomas are classified together as non-seminomatous. Radiologically they are large, irregular masses frequently with areas of low attenuation due to necrosis or hemorrhage.

Many patients with benign tumors are asymptomatic, whereas most of patients with malignant MGC have symptoms of chest pain, cough, dyspnea, and fever due to compression and invasion of surrounding structures. Gynecomastia can develop as a result of β-hCG secretion. Pulmonary metastases are present in 60–70% of patients.

Measuring AFP and β-hCG levels is important in making the diagnosis and follow-up [17]. Only 10% of **parathyroid adenomas** are ectopic, and almost half occur in the anterior mediastinum, near or within the thymus. It generally causes hyperparathyroidism, resulting in hypercalcemia. These tumors are encapsulated, round, and usually <3 cm in size. MRI or nuclear scans with 99m Tc and 201 Ti are more effective than CT scan for the diagnosis of parathyroid adenomas.

Posterior Mediastinal Mass

Neurogenic tumors represent approximately 20% of all adult mediastinal neoplasms. They can arise from neural cells in any location; however, they commonly are found in the posterior compartment of mediastinum, at costovertebral angle. About 10% of neurogenic tumors extend for contiguity in the vertebral canal through the spinal foramina.

Neurogenic tumors can be benign or malignant, with a wide array of both clinical and pathologic features; classification is based on cell type of origin. Adults have a lower rate of malignancy (5–10% in adults compared with 40–60% in children). Schwannoma and neurofibroma are the most common neurogenic tumors in adults; they arise from the nerve sheath and appear on imaging studies as well-circumscribed, spherical, lobulated paraspinous masses. A significant proportion of cases are asymptomatic and discovered incidentally. Symptomatic cases present with chest pain, cough, or compression symptoms, in particular in tumors extending through spinal foramina. Up to 45% of neurofibromas occur in patients with neurofibromatosis type I (von Recklinghausen's disease; NF1); in this setting, the tumors occur at a younger age and are often multiple. Plexiform neurofibroma is pathognomonic for NF1 and carries a risk of transformation to malignant peripheral nerve sheath tumor (MPNST). In pediatric populations the cells of origin are those involved in the development of sympathetic nervous system, ranging from benign ganglioneuromas to malignant neuroblastoma and, the intermediate form, ganglioneuroblastoma. Neuroblastoma is the most common extracranial solid tumor of infancy, and in 20% of cases, it originates in the chest. Neuroblastoma has a high propensity to produce vasoactive substances that can cause hypertension, flushing, and diarrhea; measurement of urinary metabolites of catecholamines

(vanillylmandelic acid, VMA, and homovanillic acid, HVA) can also help the diagnosis. Neuron-specific enolase (NSE)-elevated levels can be demonstrated in most patients with metastases. Metaiodobenzylguanidine (MIBG) is an analog of norepinephrine taken up specifically by catecholaminergic cells, so scintigraphy using iodine-123-marked MIBG can help to detect metastatic disease in bones as well as in soft tissue. Modern management is tailored to the risk stratification of individual patients according to International Neuroblastoma Staging System (INSS) [18].

Spinal **meningocele** is a saccular protrusion, containing cerebrospinal fluid, of the meninges through intervertebral foramina or bone defects in one or more vertebrae. Most meningoceles are associated with syndromes, such as neurofibromatosis type 1.Small meningoceles are asymptomatic, whereas larger lesions may compress the spinal cord, spinal nerves, and adjacent mediastinal structures.

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