Tumors of the Mediastinum*

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Tumors of the mediastinum represent a wide diversity of disease states. The location and composition of a mass is critical to narrowing the differential diagnosis. The most common causes of an anterior mediastinal mass include the following: thymoma; teratoma; thyroid disease; and lymphoma. Masses of the middle mediastinum are typically congenital cysts, including foregut and pericardial cysts, while those that arise in the posterior mediastinum are often neurogenic tumors. The clinical sequelae of mediastinal masses can range from being asymptomatic to producing symptoms of cough, chest pain, and dyspnea. This article will review the anatomy of the mediastinum as well as the different clinical, radiographic, and prognostic features, and therapeutic options of the most commonly encountered masses. ***(CHEST 2005; 128:2893–2909)***

Key words: bronchogenic; cysts; enterogenous; germ cell tumor; goiter; lymphoma; mediastinum; neuroblastoma; neurogenic tumor; pericardial; teratoma; thyroid; thymoma

Abbreviations: AFP = α-fetal protein; ALL = acute lymphoblastic leukemia; BMT = bone marrow transplant; GCT = germ cell tumor; hCG = human chorionic gonadotropin; HD = Hodgkin disease

The mediastinum is demarcated by the pleural cavities laterally, the thoracic inlet superiorly, and the diaphragm inferiorly. It is further compartmentalized into anterior, middle, and posterior divisions based on structural landmarks seen on the lateral radiograph. This has important implications for diagnosing suspected masses[1] (Table 1). The anterior mediastinum contains the thymus, fat, and lymph nodes. The middle mediastinum contains the heart, pericardium, ascending and transverse aorta, brachiocephalic veins, trachea, bronchi, and lymph nodes, while the posterior mediastinum consists of the descending thoracic aorta, esophagus, azygous vein, autonomic ganglia and nerves, thoracic lymph nodes, and fat.

The likelihood of malignancy is influenced primarily by the following three factors: mass location; patient age; and the presence or absence of symptoms. Although more than two thirds of mediastinal tumors are benign, masses in the anterior compartment are more likely to be malignant.[2] In the study by Davis et al[3] of 400 patients with mediastinal masses, malignancy was seen in 59%, 29%, and 16%, respectively, of anterior, middle, and posterior mediastinal masses. Age is an important predictor of malignancy as well with many of the lymphomas and germ cell tumors (GCTs) presenting between the second and fourth decade of life. Last, symptomatic patients are more likely to have a malignancy. In Davis et al,[3] 85% of patients with a malignancy were symptomatic at presentation, compared to 46% of patients with benign neoplasms.

The most common symptoms at presentation were as follows: cough (60%); chest pain (30%); fevers/chills (20%); and dyspnea (16%). Most symptoms can be categorized into the following two groups: localizing symptoms (Table 2); and systemic symptoms (Table 3). Localizing symptoms are secondary to tumor invasion. Common localizing symptoms include respiratory compromise; dysphagia; paralysis of the limbs, diaphragm, and vocal cords; Horner syndrome; and superior vena cava syndrome.[4] Systemic symptoms are typically due to the release of excess hormones, antibodies, or cytokines. A classic example is hypercalcemia, which is caused by a parathyroid adenoma.

The initial workup of a suspected mediastinal mass involves obtaining posteroanterior and lateral chest radiographs. This can provide information pertaining to the size, anatomic location, density, and composition of the mass (Table 1). CT scanning is used to further characterize mediastinal masses and their

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Table 1—*Differential Diagnosis of a Mediastinal Mass by Anatomic Location

Anterior	Middle	Posterior
Thymoma	Lymphoma	Neurogenic tumor
Teratoma, seminoma	Pericardial cyst	Bronchogenic cyst
Lymphoma	Bronchogenic cyst	Enteric cyst
Carcinoma	Metastatic cyst	Xanthogranuloma
Parathyroid adenoma	Systemic granuloma	Diaphragmatic hernia
Intrathoracic goiter		Meningocele
Lipoma		Paravertebral abscess
Lymphangioma		
Aortic aneurysm		

*From Baum and Crapo.[122]

relationship to surrounding structures as well as to identify cystic, vascular, and soft-tissue structures.[4] In rare circumstances, fluoroscopy, barium swallow, angiograph, CT angiography, and three-dimensional reconstruction may provide additional information. The role of MRI is primarily in ruling out or evaluating a neurogenic tumor.[5] MRI is also valuable to evaluate the extent of vascular invasion or cardiac involvement.

Although nuclear scans and biochemical studies can be used to further characterize a lesion, tissue diagnosis is almost always required. If a mass is likely to be benign after initial workup, it can be removed surgically without biopsy. Otherwise, a diagnostic biopsy specimen can be obtained by transthoracic or transbronchial needle aspiration, mediastinoscopy, anterior mediastinotomy, or video-assisted thoracic surgery, depending on the anatomic location and radiographic appearance of the lesion.

Tumors of the Anterior Mediastinum

Thymoma

Thymomas are the most common neoplasm of the anterior mediastinum with an incidence of 0.15 cases per 100,000.[6–9] Although rare in children, thymomas represent 20% of anterior mediastinal neoplasms in adults.[10,11]

Table 3—*Systemic Syndromes Secondary to Primary Mediastinal Tumors and Cysts

Syndrome	Tumor
Myasthenia gravis, RBC aplasia, hypogammaglobulinemia, Good syndrome, Whipple disease, megaesophagus, myocarditis	Thymoma
Multiple endocrine adenomatosis, Cushing syndrome	Carcinoid, thymoma
Hypertension	Pheochromocytoma, ganglioneuroma, chemodectoma
Diarrhea	Ganglioneuroma
Hypercalcemia	Parathyroid adenoma, lymphoma
Thyrotoxicosis	Intrathoracic goiter
Hypoglycemia	Mesothelioma, teratoma, fibrosarcoma, neurosarcoma
Osteoarthropathy	Neurofibroma, neurilemoma, mesotheioma
Vertebral abnormalities	Enteric cysts
Fever of unknown origin	Lymphoma
Alcohol-induced pain	HD
Opsomyoclonus	Neuroblastoma

*From Baum and Crapo.[122]

Thymomas as a group have a wide spectrum of histologic diversity and are classified based on cell type predominance as lymphocytic, epithelial, or spindle cell variants. There is a strong association between histologic subtype and invasiveness as well as prognosis.[12–14] As a result, the World Health Organization[15] devised a new classification system to group thymomas based on cytologic differences, which may be helpful in determining treatment regimens and predicting survival (Table 4).

Most thymomas are solid tumors, but up to one third may have components that are necrotic, hemorrhagic, or cystic.[7,16] Thirty-four percent of thymomas invade through their own capsules, extending into surrounding structures.[8,17–20] Likewise, transdiaphragmatic extension into the abdomen and metastasis into the ipsilateral pleura and pericardium

Table 2—*Localizing Symptoms Secondary to Tumor Invasion of Surrounding Structures

Involved Anatomic Structure	Localizing Symptom
Bronchi/trachea	Dsypnea, postobstructive pneumonia, atelectasis, hemoptysis
Esophagus	Dysphagia
Spinal cord/vertebral column	Paralysis
Recurrent laryngeal nerve	Hoarseness, vocal cord paralysis
Phrenic nerve	Diaphragmatic paralysis
Stellate ganglion	Horner syndrome
Superior vena cava	Superior vena cava syndrome

*From Baum and Crapo.[122]

Table 4—*World Health Organization Classification of Thymomas

Class of Thymoma	Cytologic Features
Type A	Spindle cell, medullary
Type AB	Mixed
Type B1	Lymphocyte rich, lymphocytic, predominantly cortical, organoid
Type B2	Cortical
Type B3	Epithelial, atypical, squamous, well-differentiated thymic carcinoma

From Wilkins et al.[15]

can occur,[7,9,18] although lymphogenous and hematogenous spread is rare.[16,17]

The Masaoka clinical staging system is based on the degree of invasion of the tumor through the capsule into the surrounding structures, which has important implications for prognosis[21] (Table 5). In the study by Okumura et al,[12] the Masaoka staging system was shown to be useful as an independent predictor of survival in patients with thymoma.

Typically, a thymoma is an incidental finding on a chest radiograph.[10,22,23] One third of patients manifest symptoms of chest pain, cough, or dyspnea related to tumor compression or invasion.[16] Metastasis is uncommon; however, parathymic syndromes, which include myasthenia gravis, hypogammaglobulinemia, and pure RBC aplasia, may develop.[17]

Myasthenia gravis is most frequent in women and is associated with thymoma. Symptoms include diplopia, ptosis, dysphagia, weakness, and fatigue. Thirty percent to 50% of patients with thymomas have myasthenia gravis, compared to 10 to 15% of patients with myasthenia gravis who have a thymoma.[24,25] Pathogenesis is thought to occur via myloid cell lineages derived from the thymus that recognize antigens on the neuromuscular junction producing autoantibodies.[26] These autoantibodies bind to acetylcholine receptors of the neuromuscular junction, causing muscle fatigue.[26] Thymectomy can alleviate symptoms; however, this benefit is often delayed for months after surgery. Given the association between thymoma and myasthenia gravis, the serum anti-acetylcholine receptor antibody level should be measured in all patients with a suspected thymoma to rule out myasthenia gravis before surgery.[27,28]

Hypogammaglobulinemia and pure RBC aplasia are present in 10% and 5% of patients with a thymoma, respectively.[7] Good syndrome is diagnosed in patients with a thymoma and combined B-cell/T-cell immunodeficiency.[29] Thymoma is also associated with various other autoimmune disorders, such as systemic lupus erythematosus, polymyositis, and myocarditis.[3,7,18,30]

Thymomas appear on a chest radiograph as a well-defined lobulated mass in the anterosuperior mediastinum, typically anterior to the aortic root.[7,18] Further evaluation with contrast-enhanced thoracic CT scanning usually reveals an encapsulated, well-defined, soft-tissue mass, often with hemorrhage, necrosis, or cyst formation[31] (Fig 1). They can also appear predominantly cystic with a nodular component.[32]

Surgical excision can be used for diagnosis; however, the sensitivity of ultrasonography and CT scan-guided fine-needle aspiration is increasing. Anderson and colleagues[33] reported a success rate of 95% using ultrasonographically guided fine-needle aspiration. The success of fine-needle aspiration is operator-dependent and contingent on the skill of the immunohistologist. Thus, the results in the study by Anderson et al[33] may overstate the true success of preoperative diagnosis. Tissue diagnosis may occur simultaneously with total resection of the mass if a thymoma is strongly suspected on the basis of clinical and radiologic evidence.[34]

Surgical resection remains the standard of care for both noninvasive and invasive thymomas as it provides the best prognosis. Adjunctive chemotherapy and radiation treatment is used for locally invasive or metastatic disease, or inoperable tumors. Additionally, although it is commonly accepted that resection alone is sufficient treatment for stage I disease, there is no consensus regarding the role for postoperative radiation therapy in patients with stage II disease.[35]

According to Curran et al,[36] of 117 patients, postoperative radiotherapy showed no survival benefit for those patients with stage I disease but did for patients with stage II and III disease. The 5-year mediastinal relapse rate for patients with stage II or III disease treated with surgery alone was 53%, while patients who received treatment with total resection and radiotherapy experienced no relapses. A smaller retrospective study by Eralp et al[37] of 36 patients with stage II or III disease also showed a benefit for postoperative radiation therapy. While these studies had positive results, other institutional reviews[35,38] have shown no benefit to postoperative radiotherapy. A larger randomized controlled trial would be useful to assess the benefit of postoperative radiation therapy in patients with stage II thymomas.

Thymoma is generally responsive to chemotherapy

Table 5—*Masaoka Staging System of Thymoma

Stage	Degree of Invasion	5-yr Survival Rate, %
1	Complete encapsulation macroscopically and no capsular invasion microscopically	96–100
2	Invasion into the surrounding fatty tissue or mediastinal pleura macroscopically or invasion into the capsule microscopically	86–95
3	Invasion into neighboring organs macroscopically	56–69
4a	Pleural or pericardial dissemination	11–50
4b	Lymphogenous or hematogenous metastasis	

*From Shamji et al.[21]

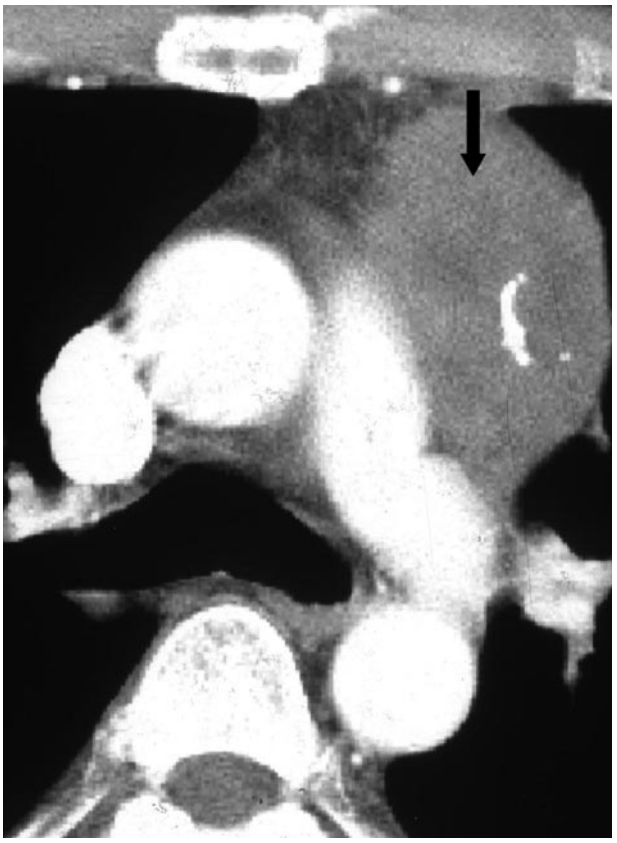

FIGURE 1. A 36-year-old man with an invasive thymoma. A contrast-enhanced CT scan shows a heterogenous high-attenuated solid upper portion (arrow) with a small calcification in the left anterior aspect of the main pulmonary artery.

as well. In locally invasive or bulky disease, preoperative cisplatin-based chemotherapy, with or without postoperative radiotherapy, may offer the best prognosis.[39] Kim et al[40] examined 23 patients with locally advanced, unresectable disease who underwent three courses of induction chemotherapy with cisplatin, doxorubicin, cyclophosphamide, and prednisone. The 7-year disease-free and overall survival rates were 77% and 79%, respectively.[40]

Other chemotherapeutic agents and regimens are less efficacious. Thus, these alternative regimens should only be used in patients who cannot tolerate cisplatin and doxorubicin or as second-line therapy in those who have relapsed.[41]

The following features are associated with poor prognosis: metastasis; large tumor size (*ie*, > 10 cm); tracheal or vascular compression; age < 30 years; epithelial or mixed histology; and the presence of a hematologic paraneoplastic syndrome.[42] As the above prognostic factors suggest, both histologic subtype and disease stage appear to be important in predicting survival. Currently, stage is used principally to guide treatment; however, controversy regarding the use of chemotherapy and radiation therapy in patients with different stages of thymoma may reflect that histologic subtype ought to play an important role in determining which treatment modalities are most appropriate. The creation of the World Health Organization classification system for thymoma in 1999 has given further insight into the potential importance of histologic subtype on prognosis; however, the Masaoka staging system is still currently used to stratify 5-year survival rates (Table 5).

Thymic Carcinoma

Thymic carcinomas are a heterogeneous group of aggressive, invasive epithelial malignancies.[3] Their incidence is rare, occurring predominantly in middle-aged men. Most patients present with cough, shortness of breath, and chest pain.[43] Fatigue, weight loss, and anorexia are common, while superior vena cava syndrome and cardiac tamponade have been described.[44–46]

Histologically, thymic carcinomas are large, firm, infiltrating masses with areas of cystic change and necrosis. They are classified as low grade or high grade, with squamous cell-like and lymphoepithelioma-like variants being the most common cell types.[47] In contrast to thymomas, thymic carcinomas are cytologically malignant, with typical features of cellular necrosis, atypia, and mitoses.[44] Radiographically, thymic carcinomas are heterogeneous with necrosis and calcifications (Fig 2) and can be associated with pleural and pericardial effusions.

Treatment and prognosis depend on the cancer stage and grade. The Masaoka staging system used for thymomas is not useful as a prognostic tool in thymic carcinoma.[48] Morphologic features that portend a poor prognosis include the following: infiltration of the tumor margin; absence of a lobular growth pattern; presence of high-grade atypia and necrosis; and > 10 mitoses per high-power field.[21] Complete surgical resection is the treatment of choice and can be curative.[49] Chemotherapy and radiation therapy have roles in treating unresectable tumors.[36,40,50]

Yoh et al[51] examined 18 patients with thymic carcinomas. Patients with unresectable disease were treated with cisplatin, vincristine, doxorubicin, and etoposide. The overall response rate was 42% with 1-year and 2-year survival rates of 80% and 56%, respectively.[51] Superior to previous chemotherapeutic regimens, the regimen of cisplatin, vincristine, doxorubicin, and etoposide warrants additional study by a randomized controlled trial for its use in the treatment of thymic carcinoma.

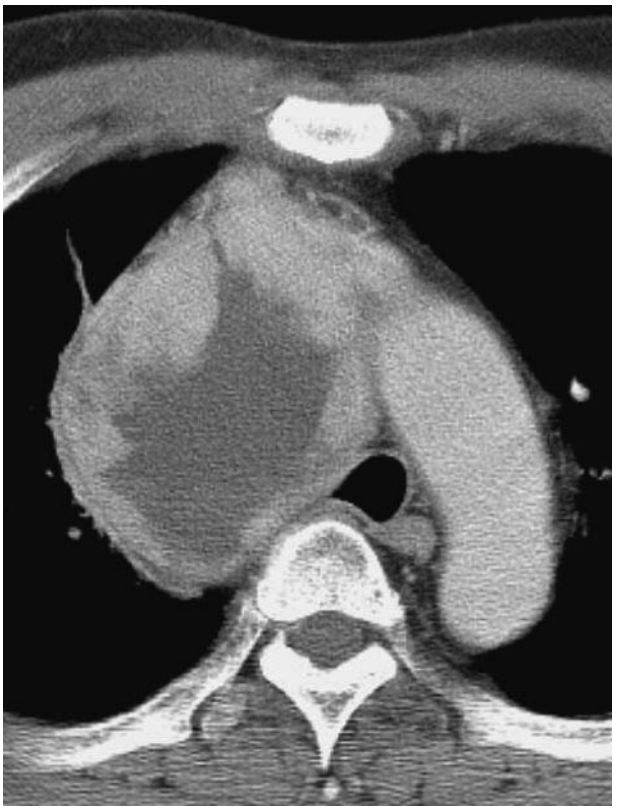

FIGURE 2. A 46-year-old man with a thymic carcinoma. A contrast-enhanced CT scan shows a necrotic mass with an irregularly shaped enhancing wall in the right anterior mediastinum.

Thymic Carcinoid

Thymic carcinoid is a malignant tumor, which is histologically similar to carcinoid tumors found at other sites. Its highest incidence is in the fourth and fifth decades of life.[44] Thymic carcinoid is associated with Cushing syndrome and multiple endocrine neoplasia syndrome.[7] According to a prospective study of patients with endocrine neoplasia syndrome type 1 by Gibil et al,[52] thymic carcinoid developed in 8% of patients.

Thymic carcinoid presents as a large, lobulated, invasive mass of the anterior mediastinum with or without hemorrhage and necrosis.[53] Metastasis is common, with spread to regional lymph nodes as well as distant metastasis developing in two thirds of patients.[53] The treatment is complete surgical resection. For a locally invasive tumor, radiotherapy and chemotherapy are used despite minimal effect.[53,54] The prognosis of these tumors is poor but difficult to assess. In a retrospective study by Tiffet et al,[55] there was no association between prognosis and histologic features.

Thymolipoma and Nonneoplastic Thymic Cysts

Thymolipoma is a rare, benign, slowly growing tumor of the thymus gland that occurs in young adults of both sexes.[2] CT scans and MRI studies show a characteristic fat density. The treatment of choice is surgical excision.

Thymic cysts are rare tumors of unclear etiology. They can be congenital or acquired, and are associated with inflammation or with an inflammatory neoplasm, such as Hodgkin disease (HD).[56] Congenital thymic cysts are remnants of the thymopharyngeal duct.[57] Inflammatory cysts probably arise from an inflamed thymic parenchyma. Radiographically, they appear as simple homogenous cysts (Fig 3). Microscopically, thymic cysts may be identical to cystic thymic neoplasms. Thus, thorough sampling and examination are essential.[58] Surgical excision is curative.

MEDIASTINAL GCTS

Mediastinal GCTs are derived from primitive germ cells that fail to migrate completely during

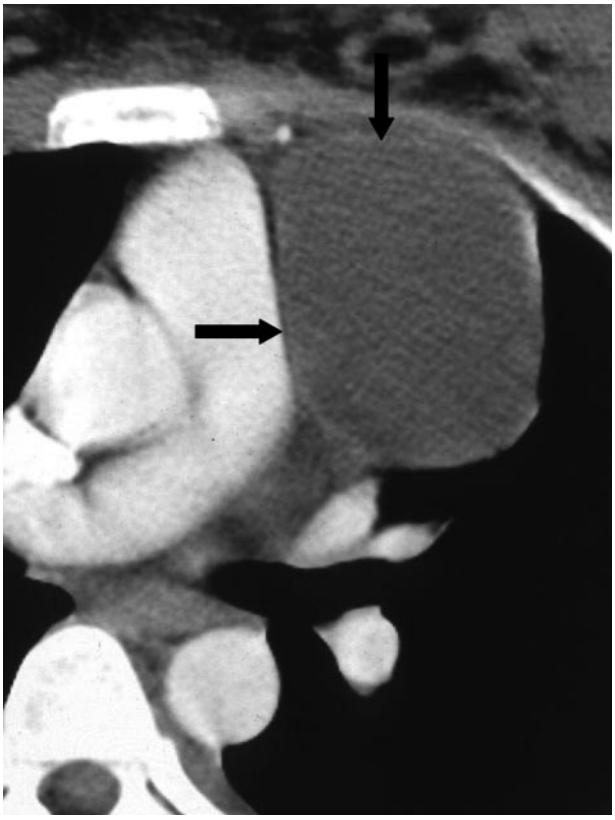

FIGURE 3. A 30-year-old woman with a unilocular thymic cyst. A contrast-enhanced CT scan shows a homogeneous cystic mass with a partially enhanced wall (arrows).

early embryonic development.[59–61] GCTs are found in young adults and represent 15% of anterior mediastinal masses found in adults.[2] Malignant GCTs are more common (> 90%) in men. A mediastinal GCT should prompt a search for a primary gonadal malignancy.

GCTs are classified into the following three groups based on cell type: benign teratomas; seminomas; and embryonal tumors. The embryonal tumors, also called *malignant teratomas* or *nonseminomatous GCTS*, are diverse and include choriocarcinomas, yolk sac carcinomas, embryonal carcinomas, and teratocarcinomas.[62] These tumors often produce serologic markers such as α-fetal protein (AFP) and human chorionic gonadotropin (hCG), which can be useful in the diagnostic evaluation.[2]

Mediastinal Teratomas (Benign)

Consisting of tissue from at least two of the three primitive germ layers, benign teratomas are the most common mediastinal GCT.[63] Ectodermal tissues, which usually predominate, include skin, hair, sweat glands, and tooth-like structures. Mesodermal tissues, such as fat, cartilage, bone, and smooth muscle are less common, as are endodermal structures like respiratory and intestinal epithelium.[64] The majority of mediastinal teratomas are mature teratomas that are histologically well-defined and benign.[63] If a teratoma contains fetal tissue or neuroendocrine tissue, it is defined as immature and malignant. In children, the prognosis is favorable, but it can often recur or metastasize.[65]

Most patients are completely asymptomatic. Like other mediastinal masses, presenting symptoms include cough, dyspnea, and chest pain. Digestive enzymes secreted by intestinal mucosa or pancreatic tissue found in the teratoma can lead to the rupture of the bronchi, pleura, pericardium, or lung.[2] A rare result of a ruptured mediastinal teratoma is the expectoration of hair or sebum.[66,67] Mature teratomas do have the potential in rare circumstances to undergo malignant transformation into a variety of malignancies. Reports[68] of rhabdomyosarcoma, adenocarcinoma, leukemia, and anaplastic small cell tumors have all been identified as arising from mature or immature teratomas.

Benign teratomas are well-defined, round, or lobulated masses when seen on a chest radiograph. Up to 26% are calcified, as they often have elements of bone or teeth.[69] CT scanning and MRI are used to assess resectability (Fig 4), and may identify sebaceous elements and fat, supporting the diagnosis.[70,71] Complete surgical resection is the treatment of choice; however, subtotal resection can relieve symptoms. Adjunctive chemotherapy may be useful after subtotal resection.[72]

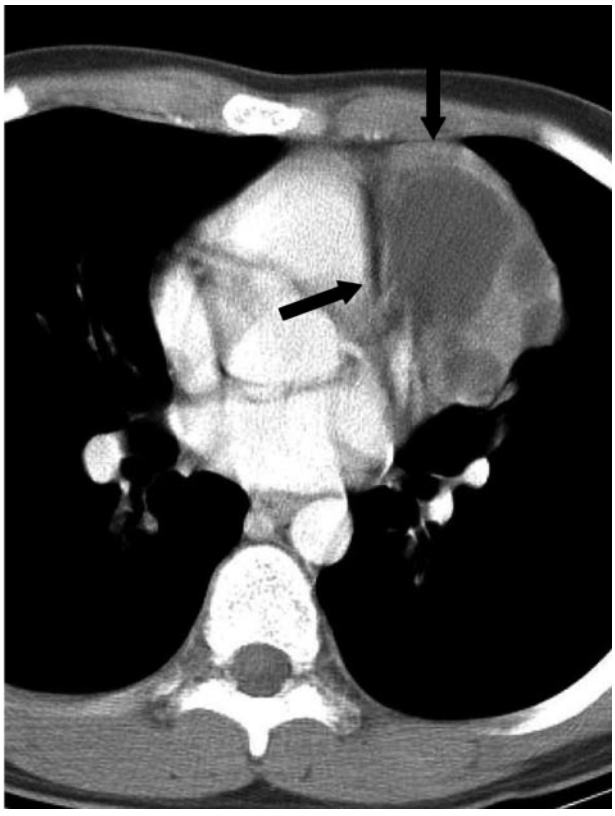

FIGURE 4. A 16-year-old male patient with a mature cystic teratoma. A contrast-enhanced CT scan shows a multilocular cystic mass in the left anterior mediastinum. Histologic examination revealed a mature cystic teratoma with foreign-body reaction and dystrophic calcification.

Mediastinal Seminoma

Primary mediastinal seminomas, although uncommon, comprise 25 to 50% of malignant mediastinal GCTs occurring most frequently in men ages 20 to 40 years. Patients present with dyspnea, substernal pain, weakness, cough, fever, gynecomastia, or weight loss. Because of the tumor location, about 10% of patients present with superior vena cava syndrome.[73] However, tumors can grow 20 to 30 cm before symptoms develop.[74]

Radiographically, seminomas are bulky, lobulated, homogenous masses. Local invasion is rare, but metastasis to lymph nodes and bone does occur.[2] CT and gallium scanning is used to evaluate the extent of disease.[75]

Seminomas are uniquely sensitive to radiation therapy. In a study by Bush et al[76] of 13 patients with localized disease who were treated with external beam radiation, the 10-year disease-free survival rate

was 54%, with an actuarial survival rate of 69%. There is, however, debate as to the role of chemotherapy and surgical resection. A retrospective study by Bokemeyer et al[77] showed that chemotherapy alone led to a 90% 5-year disease-free survival rate and that additional radiation offered only a slight survival advantage, while patients treated with just radiation initially had a much higher rate of disease recurrence. In patients with locally advanced disease, the preferred treatment includes chemotherapy followed by the surgical resection of residual disease.[78]

Mediastinal Nonseminomatous GCTs

Nonseminomatous malignant GCTs comprise a heterogeneous group of masses that includes embryonal cell carcinomas, endodermal thymus tumors, choriocarcinomas, yolk sac tumors, and mixed GCTs with multiple cellular components. These tumors are often symptomatic and malignant, and predominantly affect young men.[2] In addition, they can be associated with hematologic malignancies, and 20% of patients have Kleinfelter syndrome.[79,80]

At diagnosis, 85% of patients are symptomatic, which includes complaints of chest pain, hemoptysis, cough, fever, or weight loss. Gynecomastia can develop as a result of β-hCG secretion from certain tumor types.[62,81]

These tumors are large, irregularly shaped, with areas of central necrosis, hemorrhage, or cyst formation[82] (Fig 5). Measuring AFP and β-hCG levels is important in making the diagnosis. An elevated AFP level is suggestive of an endodermal sinus tumor or embryonal carcinoma and is sufficient, in the presence of a mediastinal mass, to establish the diagnosis.[62,81]

Chemotherapy with bleomycin, etoposide, and cisplatin is the current standard of care for patients with nonseminomatous malignant GCTs.[83] Following chemotherapy, $< 5\%$ of patients have total resolution of their malignancy with normalized serum markers. Patients with residual tumor undergo surgical resection, although studies have shown that the normalization of tumor markers prior to surgery portend a better prognosis.[83,84] In contrast to pure seminomas, nonseminomatous GCTs carry a poorer prognosis; patients with these tumors have a 5-year overall survival rate of 48%, compared to 86% in patients with seminomas.[85]

Mediastinal Goiter

In patients undergoing thyroidectomy, the incidence of mediastinal goiter is 1 to 15%.[86] Most goiters are euthyroid and are found incidentally during a physical examination. Radiographically, mediastinal goiters are encapsulated, lobulated, heterogeneous tumors.[2] A classic finding on a CT scan is continuity of the cervical and mediastinal components of the thyroid. If the goiter contains functional thyroid tissue, then scintigraphy with a radioactive isotope of iodine can be diagnostic.[2]

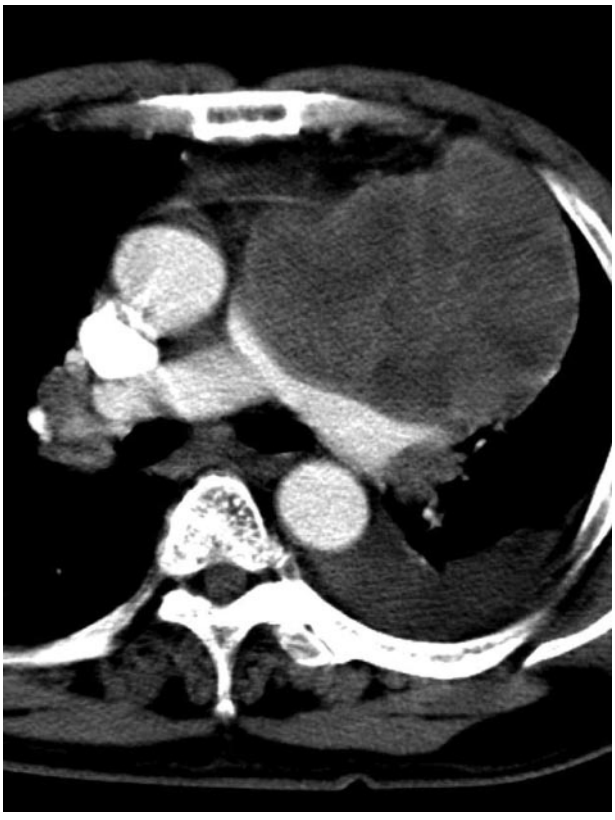

FIGURE 5. A 59-year-old man with a nonseminatous malignant GCT. A contrast-enhanced CT scan shows a heterogeneous low-attenuating anterior mediastinal mass compressing the pulmonary artery.

Surgical resection is recommended since these lesions are not usually amenable to needle biopsy, and malignancy develops in a significant number. Nearly all substernal goiters can be removed easily through a cervical incision minimizing surgical morbidity.[87]

Mediastinal Parathyroid Adenoma

The mediastinum is the most common location at which an ectopic parathyroid tumor may develop. Overall, 20% of parathyroid adenomas develop in the mediastinum, with 80% occurring in the anterior mediastinum.[88]

These tumors are encapsulated, round, and usually < 3 cm in size, so that they may not be identified on a CT scan. Thus, MRI or nuclear scans with ^{99m}Tc and ^{201}Tl are more effective for the diagnosis of parathyroid adenomas.[89] Surgical resection is curative.

Primary Mediastinal Lymphoma

Primary mediastinal lymphoma is a rare entity comprising only 10% of lymphomas in the mediastinum. Lymphoma usually occurs in the anterior mediastinum and is part of more widespread disease. HD represents approximately 50 to 70% of mediastinal lymphomas, while non-Hodgkin lymphoma comprises 15 to 25%.[90,91] The three most common types of mediastinal lymphoma include nodular sclerosing HD, large B-cell lymphoma, and lymphoblastic lymphoma.[2]

HD

HD has an incidence of approximately 2 to 4 cases per 100,000 people per year, with a bimodal distribution of incidence peaking in young adulthood and again after age 50 years.[92] For mediastinal-predominant disease, prevalence peaks in young women during the third decade of life, while it is unaffected by age in men.[93] HD is divided into four subtypes, including nodular sclerosing, lymphocyte-rich, mixed cellularity, and lymphocyte depleted HD, with the nodular sclerosing subtype representing more than two thirds of cases.[94]

Most patients experience constitutional symptoms (B symptoms), including fevers, night sweats, and weight loss. For patients with mediastinal involvement, cough, dyspnea, chest pain, pleural effusions, and superior vena cava syndrome may occur.[93]

The presence of Reed-Sternberg cells are pathognomonic of HD. These cells contain bilobed nuclei containing prominent eosinophilic nuclei. The classic immunohistochemical profile is biomarker positivity for CD15 and CD30 cells.[95]

The chest radiograph finding is abnormal in up to 76% of patients with HD, often showing enlargement of the prevascular and paratracheal nodes.[96–98] A CT scan examination is usually sufficient to identify lymphoma; however, in certain circumstances, such as after radiation treatment, MRI may be better in distinguishing scars from residual disease[96] (Fig 6). A positron emission tomography scan may also be useful in staging and following disease progression.[99]

Still widely used is the Ann Arbor staging system for HD. This system has important implications for determining prognosis and types of treatment (Table 6). In 1989, the Ann Arbor staging system was modified at a meeting in Cotswold, England, to separate out patients with bulky disease due to its prognostic significance.

The treatment of HD is separated into the treatment of early-stage disease (*ie*, stage I and II disease) and late-stage disease (*ie*, stage III and IV disease). Based on the Cotswold modifications, early-stage disease can be further subclassified into favorable and unfavorable, depending on the degree of tumor burden. For patients with favorable stage I or II disease, extended-field radiation alone used to be the standard of care. Hagenbeek et al[100] conducted a

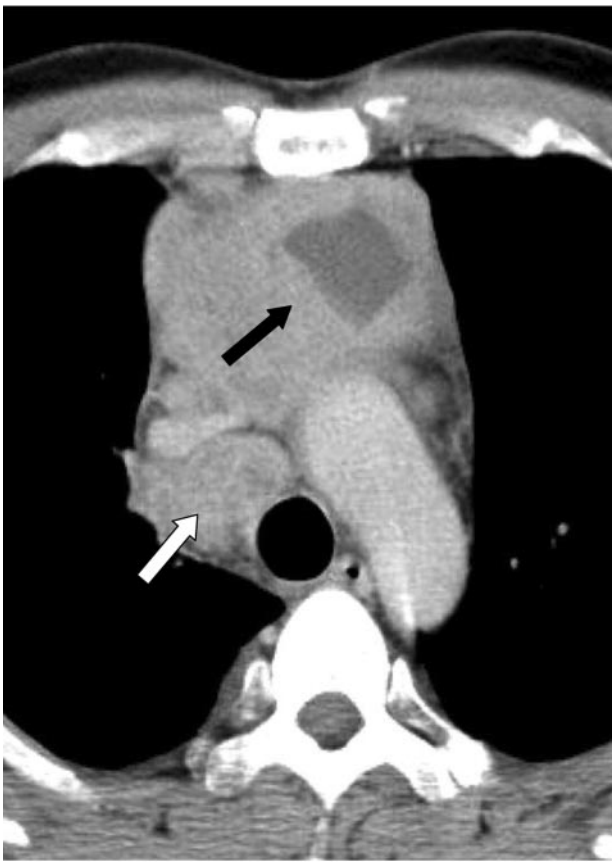

FIGURE 6. A 39-year-old man with nodular sclerosis HD. A contrast-enhanced CT scan shows an anterior mediastinal mass in which the central portion is cystic (black arrow). The right paratracheal lymph node is enlarged (white arrow).

Table 6—*Ann Arbor Staging System With Cotswold Modifications for HD**

Stage	Characteristics
1	Involvement of one lymph node region or lymphoid structure
2	Two or more lymph node regions on same side of the diaphragm
3	Lymph nodes on both sides of the diaphragm
4	Involvement of extra nodal sites
Modifications	
A	No symptoms
B	Fever, night sweats, weight loss > 10% in 6 mo
X	Bulky disease (greater than one third widening of the mediastinum or > 10 cm diameter of nodal mass
E	Involvement of single, contiguous, or extra nodal site

*From Yung and Linch.[94]

randomized controlled trial in which 762 patients with favorable stage I or II HD were randomized to receive either combination therapy with six cycles of epirubicin, bleomycin, vinblastine, and prednisone, and involved field radiation, or to receive subtotal nodal irradiation alone. The complete remission rate was similar among patients in both groups, while the relapse rate was significantly higher in the radiation-alone group.[100] Thus, the use of combined involved-field radiation and chemotherapy is quickly becoming the standard of care. For patients with stage I or II HD with bulky tumors, treatment consists of chemotherapy followed by radiation.[101] Patients with stage III or IV HD are treated primarily with chemotherapy. Canellos et al[102] showed that ABVD was superior to MOPP in preventing relapse.

Patients who relapse may benefit from a bone marrow transplant (BMT), while those who have had a good response to standard-dose second-line chemotherapy benefit the most.[103] For patients with HD, autologous BMT is superior to allogeneic BMT since the relapse rate for both is similar, and the nonrelapse mortality rate is 48% for patients who have undergone allogeneic BMT and 27% for those who have undergone autologous BMT.[104]

Patients with stage I and II HD have cure rates of $> 90\%$. Patients with stage IIIA HD have a cure rate of 30 to 90% with standard treatment. Stage IIIB HD offers a cure rate of 60 to 70%, while stage IV HD has a cure rate of 50 to 60% (2,101). Among patients with advanced disease, a prognostic index was created by the International Prognostic Factor Project on Advanced Hodgkin's Disease that was based on the total number of unfavorable features from among seven potential features found at diagnosis, as follows: serum albumin level, < 4 g/dL (or 40 g/L); hemoglobin level, < 10.5 g/dL (105 g/L); male gender; age > 45 years; stage IV disease; WBC count, $\geq 15{,}000$ cells/μL; and lymphocyte count, $< 600/\mu$L and/or $< 8\%$ of the WBC count.[105]

Non-Hodgkin Lymphoma

Although there are many classes and grades of non-Hodgkin lymphoma, lymphoblastic lymphoma and large B-cell lymphoma are the most common subtypes to affect the mediastinum.[106] The overall incidence of non-Hodgkin lymphoma is greatest in white men with a mean age of 55 years.[106] However, the mean ages of presentation for lymphoblastic lymphoma and primary large B-cell lymphoma are 28 and 30 to 35 years, respectively.[106,107]

Lymphoblastic lymphoma is highly aggressive, arising from thymic lymphocytes.[108] Common symptoms include cough, wheezing, shortness of breath, superior vena cava syndrome, cardiac tamponade, or tracheal obstruction, and can involve the mediastinum, bone marrow, CNS, skin, or gonads.[108] It is often confused with T-cell acute lymphoblastic leukemia (ALL) because bone marrow involvement with blasts is relatively common.[109,110]

Primary mediastinal B-cell lymphoma is a diffuse large B-cell lymphoma derived from the thymus. Common symptoms at presentation include chest pain, cough, dysphasia, superior vena cava syndrome, phrenic nerve palsy, and hoarseness.[107] The involvement of extrathoracic structures and bone marrow is less common at presentation than for lymphoblastic lymphoma. However, on the recurrence of disease, involvement of the liver, kidneys, and brain can occur.[111,112]

Computer tomography scanning is used to characterize the lesion and to determine the extent of invasion. The middle and posterior mediastinal nodes are involved more often than the anterior ones.[2] Tissue diagnosis should be obtained before treatment. Flow cytometry and cytogenetic analysis can be used to help render a definitive diagnosis.[113]

Treatment for mediastinal non-Hodgkin lymphoma depends on the stage, histologic subtype, and extent of the disease. For lymphomblastic lymphoma, the treatment regimens are often similar to ALL due to its propensity to involve the marrow. Treatment with intensive chemotherapy programs with maintenance-phase chemotherapy is superior to short-term chemotherapy without a maintenance phase. In a study by Kobayashi et al,[114] patients with ALL and those with lymphoblastic lymphoma who received short-term chemotherapy had a cure rate of 78% but a relapse rate of 72% with only a 7% 7-year survival rate. Intrathecal chemotherapy is also necessary to prevent CNS relapse. CNS irradiation is often part of prophylactic treatment to prevent CNS recurrence, while mediastinal irradiation has been used as well. Many patients go on to relapse even after treatment. As a result, BMT is a commonly employed treatment for patients with lymphoblastic lymphoma. Levine et al[115] demonstrated in a retrospective analysis of 204 patients with lymphoblastic lymphoma who had been treated with either allogeneic or autologous BMT that although there were fewer relapses at 5 years with allogeneic BMT (relapse rate, 46% vs 56%, respectively), the incidence of treatment-related mortality in patients who underwent allogeneic BMT made the overall survival benefit insignificant.

Patients with primary mediastinal B-cell lymphoma can be treated with conventional chemotherapy; however, there may be an additional benefit to treatment with high-dose chemotherapy and involved-field radiation.[107,116] Currently, if patients fail to have a full response to standard chemotherapy,

high-dose chemotherapy and/or radiation therapy are considered. After relapse, many patients are treated with high-dose chemotherapy and autologous BMT.[107]

Tumors of the Middle Mediastinum

Mediastinal Cysts

Mediastinal cysts comprise 12 to 20% of mediastinal masses and are found in the middle compartment of the mediastinum.[117–119] Despite a similar incidence, children are more often symptomatic at presentation due to compression on the surrounding structures.[120] The most common type of mediastinal cyst are foregut cysts, which are derived as an embryonic abnormality, with enterogenous cysts (50 to 70%) and bronchogenic cysts (7 to 15%) being the most common subtypes.[2]

Bronchogenic Cysts

Bronchogenic cysts are formed during embryonic development as an anomalous budding of the laryngotracheal groove.[121] These cysts are lined with ciliated, pseudostratified, columnar epithelium, and contain bronchial glands and cartilaginous plates.[2] Approximately 40% of bronchogenic cysts are symptomatic resulting in cough, dyspnea, or chest pain.[121]

Radiographically, bronchogenic cysts can be identified on plain radiographs (Fig 7a) but are best defined by CT scanning. These cysts are well-defined round masses with a homogenous density similar to water; however, some bronchogenic cysts are mucoid and can give the impression of being a solid mass.[120] Bronchogenic cysts are nonenhancing, and, when there is a direct communication with the tracheobronchial tree, air-fluid levels may be seen.[122] MRI can differentiate the lesion from other masses (Fig 7, *bottom*, *B*, 8).

Tissue is often required to make a definitive diagnosis of a bronchogenic cyst. This can be accomplished by tracheobronchial, endoscopic, or thoroscopic needle aspiration. Most bronchogenic cysts are removed surgically or are drained by needle aspiration. The treatment of asymptomatic cysts is controversial as surgery is not without risk, yet these cysts can grow to cause symptoms in the future.[123]

Enterogenous Cysts

Enterogenous cysts arise from the dorsal foregut and are lined by squamous or enteric (alimentary) epithelium and may contain gastric or pancreatic tissue. Esophageal duplication cysts are located in or are attached to the esophageal wall. Twelve percent

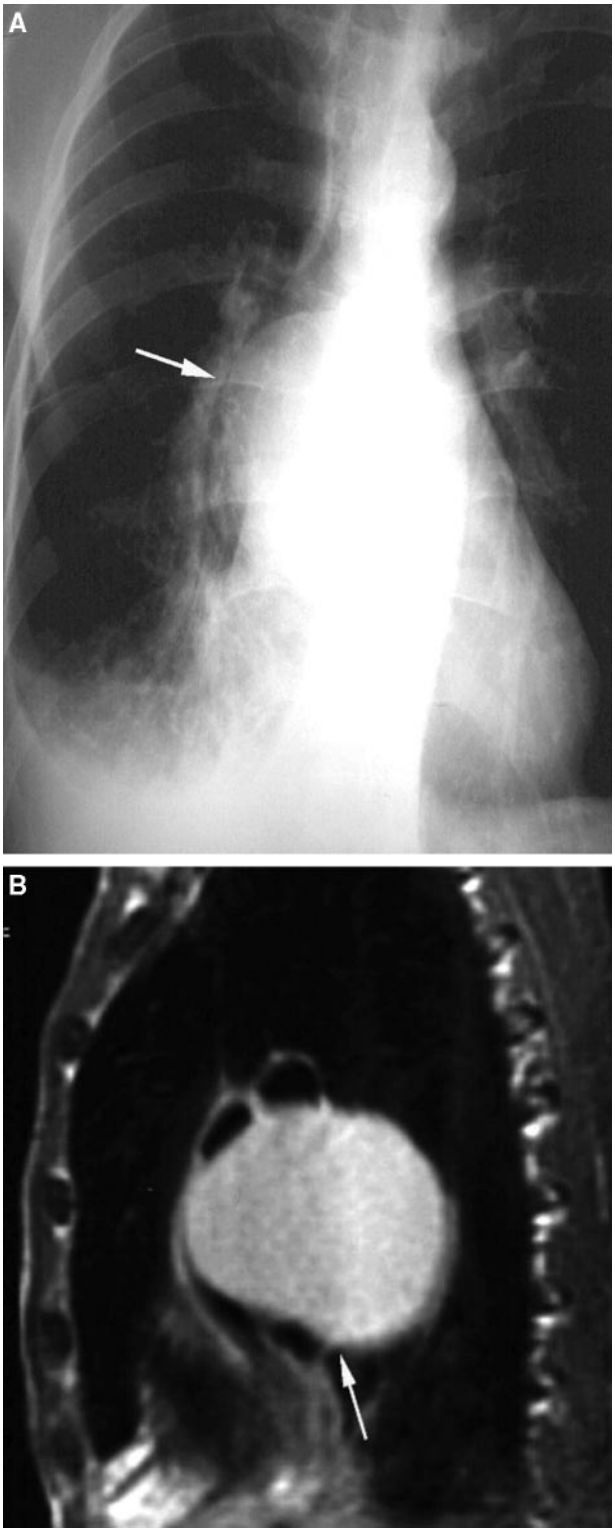

Figure 7. *Top*, *A*: a 49-year-old man with a bronchogenic cyst. A chest radiograph shows a rounded mass (arrow) that displaces the right primary bronchus superiorly. *Bottom*, *B*: a 49-year-old man with a bronchogenic cyst. A sagittal T1-weighted magnetic resonance image shows a high-signal intensity cyst with a fluid-fluid level due to infection (arrow).

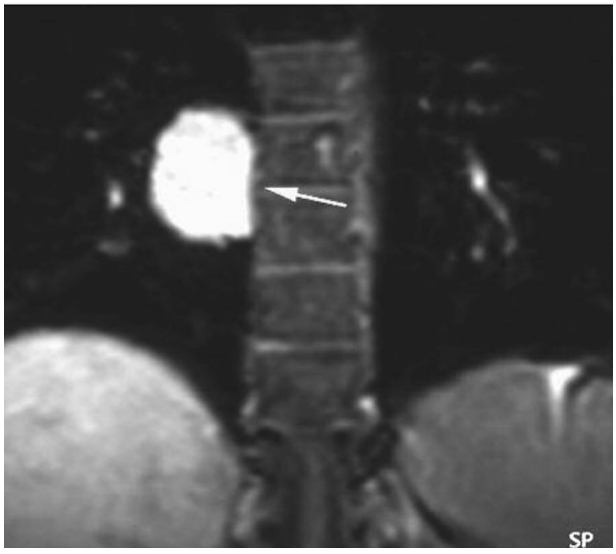

FIGURE 8. A 37-year-old woman with a bronchogenic cyst. A coronal T1-weighted magnetic resonance image shows a cyst with high-signal intensity contents (arrow).

of patients with esophageal duplication cysts have associated malformations, mostly of the GI tract.[124]

Symptoms of enterogenous cysts are similar to those of other mediastinal cysts. They are often asymptomatic, but if they contain gastric or pancreatic mucosa, there is the added risk of hemorrhage or rupture of the cyst from mucosal secretions. Radiographically, it can be difficult to distinguish these from bronchogenic cysts, although they are more often calcified (Fig 9). The presence of cartilage

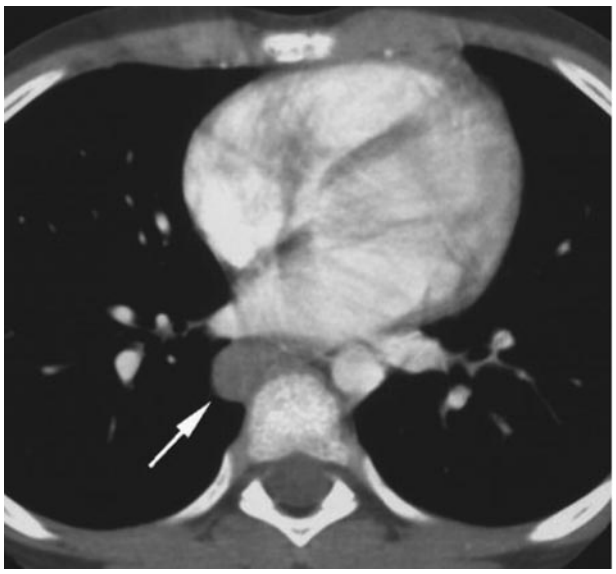

FIGURE 9. A 10-year-old female patient with a duplication cyst. A contrasted-enhanced CT scan shows a thin-walled water-attenuation cyst adjacent to the esophagus (arrow).

suggests the presence of a bronchogenic cyst.[121] Most cysts should be surgically excised, and video-assisted thoracic surgery is the treatment of choice.[125]

Neuroenteric Cysts

Neuroenteric cysts are characterized by the presence of both enteric and neural tissue in surgical specimens.[126] Most of these cysts form in the posterior mediastinum above the level of the main carina. The close association of the foregut and notochord during embryogenesis possibly explains this anatomic location. Neuroenteric cysts are associated with multiple vertebral anomalies, such as scoliosis, spina bifida, hemivertebra, and vertebral fusion. Almost all are discovered by age 1 years due to symptoms from tracheobronchial compression.[2] Neurologic symptoms may be caused by intraspinal extension. Complete surgical excision is curative.[127]

Pericardial Cysts

Pericardial cysts are part of a larger group of mesothelial cysts. They form as a result of a persistent parietal recess during embryogenesis.[121] They are estimated to occur in 1 of 100,000 people. Although most are congenital, a few cases of acquired pericardial cysts do exist. They are often asymptomatic and are identified in the fourth to fifth decade of life. Rarely, cardiac compression may occur, causing hemodynamic compromise.[95] Radiographically, pericardial cysts are well-marginated spherical or tear drop-shaped masses that characteristically abut the heart, anterior chest wall, and diaphragm.[2] The most common location of pericardial cysts is at the right cardiophrenic angle (70%), followed by the left cardiophrenic angle (22%).[128] On CT scans, these masses appear as unilocular and nonenhancing (Fig 10, 11). As with most mediastinal cysts, surgical removal is the treatment of choice, although clinically asymptomatic patients may be observed without intervention.

Lymphangiomas

Lymphangiomas are rare congenital abnormalities of the lymphatic vessels. Typically, they are isolated solitary masses, but they can be more widespread or associated with chromosomal abnormalities.[129] These lesions are benign in nature and are found in the cervical region 75% of the time. In 10% of cases, the cysts extend into the mediastinum and are associated with chylothorax and hemangiomas.[129] Although these tumors are commonly identified in children before the age of 2 years, when the mass is isolated to the mediastinum it is often not identified

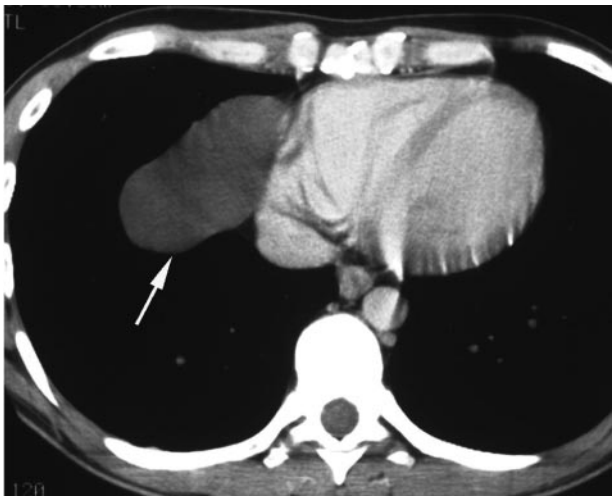

FIGURE 10. A 37-year-old man with a pericardial cyst. A contrast-enhanced CT scan shows a thin-walled water-attenuation cyst (arrow).

until it has gotten large enough to cause compressive symptoms.[130] Such symptoms include chest pain, cough, and dyspnea. Radiographically, these lesions appear cystic and can be confused with pericardial cysts, although lymphangiomas are more likely to have a loculated appearance.[130] The use of lymphangiographic contrast media combined with CT scanning can also differentiate these lesions.[129] Total resection is optimal; however, in cases complicated by chylothorax, there is some evidence suggesting that additional radiotherapy may be of some benefit.[131] Lymphangiomatosis seen in young women is typically a more progressive form of disease in which multiple tumors are found and invade multiple organ structures, including the lung, heart, and bone.[132]

TUMORS OF THE POSTERIOR MEDIASTINUM

Neurogenic Tumors

Neurogenic tumors are derived from tissue of the neural crest, including cells of the peripheral, autonomic, and paraganglionic nervous systems. Ninety-five percent of posterior mediastinal masses arise in the intercostal nerve rami or the sympathetic chain region.[133] They are classified on the basis of cell type and comprise approximately 12 to 21% of all mediastinal masses, although 95% occur in the posterior compartment.[134] Seventy percent to 80% of neurogenic tumors are benign, and nearly half are asymptomatic; however, they can occasionally cause compressive or neurologic symptoms.[133,135,136]

Nerve Sheath Tumors

These benign, slowly growing tumors comprise 40 to 65% of neurogenic mediastinal masses. Neurilemomas or schwannomas constitute 75% of this group of masses. These tumors are firm, encapsulated masses consisting of Schwann cells. Neurofibromas are nonencapsulated, soft, and friable, and are associated with Von Recklinghausen neurofibromatosis.[137,138] They are often asymptomatic and are discovered incidentally.

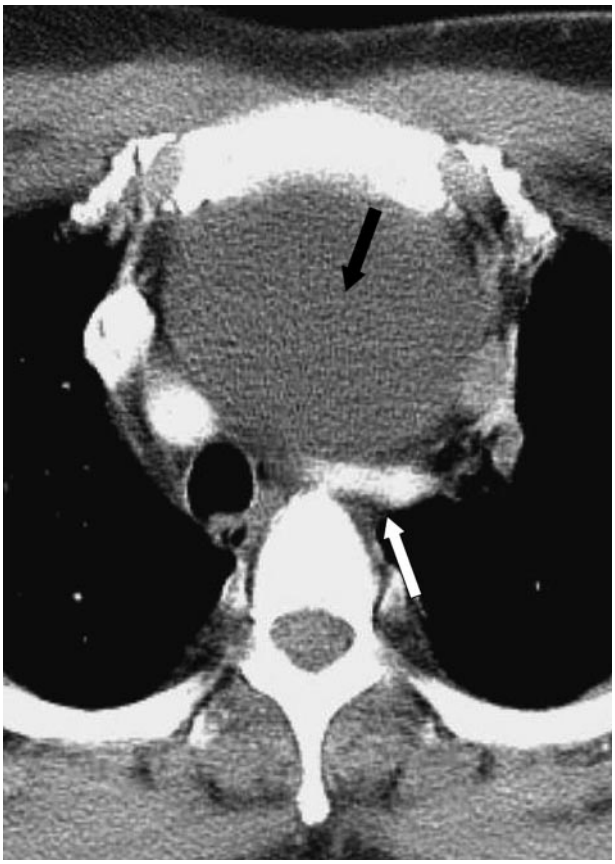

FIGURE 11. A 54-year-old woman with a pericardial cyst. A contrast-enhanced CT scan shows a large thin-walled cystic mass at the level of the aortic arch (black arrow). The innominate vein is compressed by this mass (white arrow).

Radiographically, nerve sheath tumors are sharply marginated spherical masses. Being adjacent to the spine, they can cause erosion and deformity of the ribs and ventral bodies as they increase in size. Low attenuation on CT scans can indicate hypocellularity, cystic changes, hemorrhage, or the presence of lipid within myelin.[2] Ten percent of these tumors grow through the intervertebral foramina and create a dumbbell appearance on radiographs.[139] MRI is used to rule out intraspinal extension.

The surgery of choice for removal of these tumors is thoroscopy, or thorocotomy when the former is not an option.[133,134] For tumors invading the vertebral body or foramina, *en bloc* resection can be achieved.[140] There may be a role for postoperative chemotherapy or radiation therapy when total resec-

tion is not possible. Postoperative complications include Horner syndrome, partial sympathectomy, recurrent laryngeal nerve damage, and paraplegia.[134]

Malignant Tumors of Nerve Sheath Origin

Malignant nerve sheath tumors are spindle cell sarcomas of the posterior mediastinum, and include malignant neurofibromas, malignant schwannomas, and neurogenic fibrosarcomas. They affect men and women equally in the third to fifth decade of life and are closely associated with neurofibromatosis, with a 5% risk of sarcomatous degeneration.[141] Pain and nerve deficits are common. Complete surgical resection is the optimal treatment, but, in patients with unresectable tumors, adjuvant chemotherapy and radiation are options.

Autonomic Ganglionic Tumors

Tumors of the autonomic nervous system arise from neuronal cells rather than from the nerve sheath. They form a continuum ranging from benign encapsulated ganglioneuroma to aggressive malignant nonencapsulated neuroblastoma. Derived from embryologic origins, these tumors arise in the adrenal glands or in the sympathetic ganglia. However, ganglioneuromas and ganglioneuroblastomas arise mostly in the sympathetic ganglia of the posterior mediastinum.[142] Fifty percent of neuroblastomas arise in the adrenal glands and up to 30% in the mediastinum.[142,143]

Ganglioneuroma: Ganglioneuromas are benign tumors composed of one or more mature ganglionic cells. Arising from the nerve ganglion cells, they are the most benign and differentiated of the autonomic ganglionic tumors.[144] Most patients are asymptomatic and receive diagnoses in the second or third decade of life.[145] Radiographically, the tumors are oblong and well-marginated, occurring along the anterolateral aspect of the spine and spanning three to five vertebrae[145] (Fig 12). CT scanning is not particularly helpful as the mass can be homogenous or heterogeneous. Complete surgical resection is ideal.[146]

Ganglioneuroblastoma: Ganglioneuroblastomas have histologic features of both ganglioneuromas and neuroblastomas. They are the least common type of neurogenic tumor. Prognosis depends on histologic appearance.[2] Both sexes are equally affected in the first decade of life.[147] Symptoms may arise due to large tumor size, intraspinal extension, and metastasis. Staging is similar to that for neuroblastoma, as described in the following section.

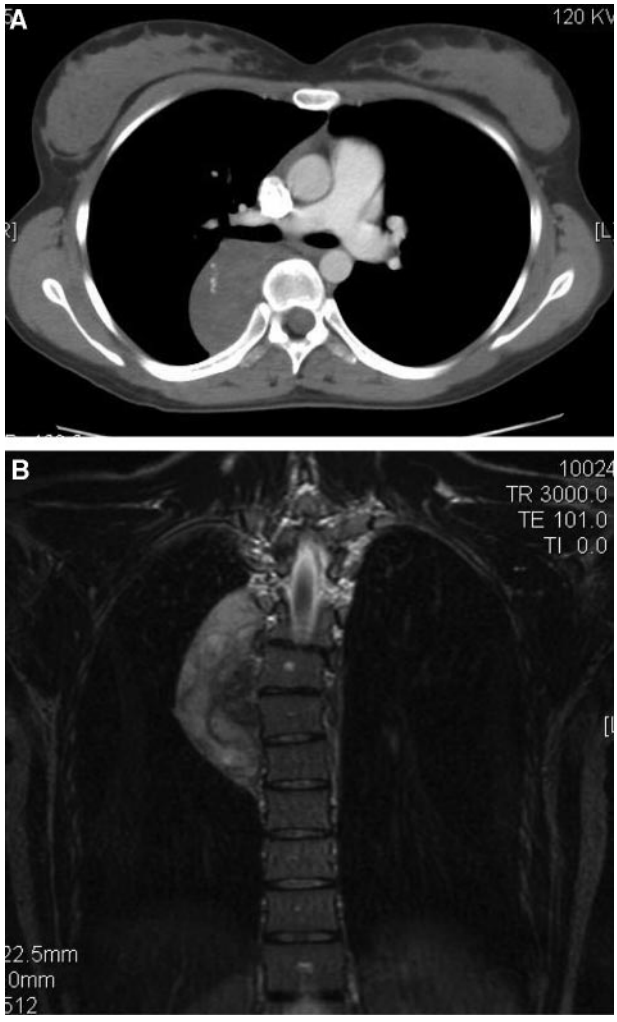

Figure 12. A 20-year-old woman with a posterior mediastinal ganglioneuroma. *Top*, *A*: a contrast-enhanced CT scan image that shows a mass with mixed attenuation and calcifications. *Bottom*, *B*: acoronal T2-weighted magnetic resonance image that shows an 8-cm mass with heterogeneous signal intensity.

Neuroblastoma: Neuroblastoma is a disease of young children, with 95% occurring in patients < 5 years of age.[143,148] Neuroblastomas are highly aggressive and readily metastasizing tumors that are composed of small round cells arranged in sheets or pseudorosettes.[149] They are nonencapsulated lesions, often exhibiting hemorrhage, necrosis, or cystic degeneration. Symptoms include pain, neurologic deficits, Horner syndrome, respiratory distress, and ataxia.[148,149] Neuroblastomas have the highest propensity of any tumors in its class to produce vasoactive substances that can cause hypertension, flushing, and diarrhea.[142]

Grossly, these tumors appear as an elongated paraspinous mass, sometimes impinging on adjacent

Table 7—*Staging of Neuroblastoma and Ganglioneuroblastomas**

Stage	Characteristics
I	Well-circumscribed, noninvasive ipsilateral tumors
II	Local invasion without extension across the midline, ipsilateral regional lymph node involvement
III	Tumor extension across the midline and involvement of bilateral regional lymph nodes
IV	Metastatic disease
IVS	Clinical stage I or II and metastatic disease limited to the liver, skin and bone marrow

*From Baum and Crapo.[122]

structures and causing skeletal damage.[150,151] On CT scans, 80% of these tumors have calcification.[151] As with all neurogenic tumors, MRI is useful to determine the extent of intraspinal involvement.[146] Radionuclide imaging with ^{123}I metaiodobenzylguanide can also be used to detect primary and metastatic disease.[152]

Treatment for neuroblastoma depends primarily on the stage of disease (Table 7). Treatment for limited-stage disease is surgical resection. For patients with stage I disease, resection is usually curative. For patients with partially resectable stage II and III disease, treatment includes postoperative chemotherapy and radiation. For patients with stage IV disease, there is much controversy over the role of surgery; however, some studies[153] have suggested that delayed surgery after initial treatment with chemotherapy and radiation results in a better outcome than initial surgical intervention. In addition, there are ongoing studies looking at the role of radioactive ^{131}I metaiodobenzylguanide therapy in combination with chemotherapy in patients with advanced-stage disease.[154] Poor prognostic factors in neuroblastoma include large tumor size, poorly differentiated cell type, advanced stage, extrathoracic origin, and presentation in an elderly patient.[138]

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