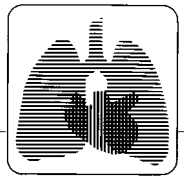

reviews

Primary Mediastinal Tumors*

Part II. Tumors of the Middle and Posterior Mediastinum

Diane C. Strollo, MD, FCCP; LtC Melissa L. Rosado-de-Christenson, MC, USAF; and James R. Jett, MD, FCCP

Lymphoma, mediastinal cysts, and neurogenic neoplasms are the most common primary middle and posterior mediastinal tumors. Lymphoma may involve the anterior, middle and/or posterior mediastinum, frequently as lymphadenopathy or as a discrete mass. Foregut cysts are common congenital mediastinal cysts and frequently arise in the middle mediastinum. Pericardial cysts are rare. Schwannoma and neurofibroma are benign peripheral nerve neoplasms, represent the most common mediastinal neurogenic tumors, and rarely degenerate into malignant tumors of nerve sheath origin. Sympathetic ganglia tumors include benign ganglioneuroma and malignant ganglioneuroblastoma and neuroblastoma. Lateral thoracic meningocele is a rare cause of a posterior mediastinal mass.

(CHEST 1997; 112:1344-57)

Key words: cyst; ganglioneuroma; lymphoma; mediastinum; meningocele; neoplasm; neuroblastoma; neurofibroma; neurogenic tumor; schwannoma

Abbreviations: HD=Hodgkin's disease; MTNSO=malignant tumors of nerve sheath origin; NHL=non-Hodgkin's lymphoma; PA=posteroanterior; REAL=revised European-American classification of lymphoid neoplasms; SVC=superior vena cava

This article will review primary middle and posterior mediastinal neoplastic and nonneoplastic tumors that comprise approximately 50% of all mediastinal masses. Lymphoma constitutes one of the most common mediastinal neoplasms and may affect any mediastinal compartment. Congenital cysts usually affect the middle mediastinum while neurogenic tumors are typical lesions of the posterior mediastinum.

Primary Mediastinal Lymphomas

Lymphoma is one of the most common mediastinal tumors[1,2] and may manifest as a primary mediastinal lesion, or more frequently, as generalized disease.[3-5] Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) are unique and separate entities[6] that may have overlapping features. Both may affect the mediastinum, although it is infrequent for either to be limited to the mediastinum at the time of diagnosis.[3,4,7] HD represents only 25 to 30%[8] of all cases of lymphoma. However, 50 to 70%[7] of patients with peripheral lymphoma and mediastinal involvement have HD while 15 to 25% have NHL.[3,9] HD is the most common mediastinal lymphoma.[10] Nodular sclerosing HD, the most common subtype, has a unique predilection for the anterior mediastinum, especially the thymus.[3,4,9] The other cell types of HD usually affect mediastinal lymph nodes rather than the thymus and typically do not manifest as a primary mediastinal mass. Two important variants of NHL, large B-cell lymphoma[3,11] and lymphoblastic lymphoma,[9] also primarily involve the anterior mediastinum and are the most frequent primary mediastinal NHLs.

Hodgkin's Lymphoma

Clinically, patients with HD exhibit a bimodal age distribution with a peak incidence in adolescence and early adulthood and a second peak after the age

*From the Department of Radiology (Dr. Strollo), University of Pittsburgh Medical Center, the University of Pittsburgh Cancer Institute (Dr. Jett), Pittsburgh, the Department of Pulmonary Pathology (Dr. Rosado de Christenson), Armed Forces Institute of Pathology, Washington, DC, and the Department of Radiology and Nuclear Medicine (Dr. Rosado de Christenson), Uniformed Services University of the Health Sciences, Bethesda, Md.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as representing the views of the Department of the Air Force or the Department of Defense.

Manuscript received May 14, 1997; accepted May 15.

of 50 years.[12] Patients with mediastinal involvement are younger (29 years) than those without mediastinal disease (38 years).[7] While men and women are equally affected with HD,[7] nodular sclerosing HD is two times more common in women,[13,14] but thymic involvement is more common in men.[4] Patients with HD typically present with cervical or supraclavicular lymphadenopathy.[3,14] Twenty to 30% present with fever, night sweats, and/or weight loss.[12] Most mediastinal lymphomas do not cause symptoms and are discovered incidentally on chest radiographs,[4] but patients may experience chest pain, cough, wheezing, and/or dysphagia[4] due to invasion of or mass effect on mediastinal structures.[2,3] Superior vena cava (SVC) syndrome and chest wall invasion are uncommon. Most patients with HD present with disease localized above the diaphragm,[5,13,14] and <5 to 10% have extranodal disease at diagnosis.[6,12]

Pathologically, HD is characterized by a large inflammatory cell reaction within a fibrotic stroma, and the diagnosis is established by the identification of Reed-Sternberg cells.[5,15] Nodular sclerosing HD exhibits dense fibrotic bands that subdivide the abnormal lymphoid tissue into circumscribed nodules.[5,13,15] Grossly, HD may manifest as a conglomerate of enlarged nodes or as a bosselated soft-tissue mass[4] and may exhibit necrosis and hemorrhage. In addition, thymic HD may produce epithelial-lined cystic areas in the thymus[4,15,16] prior to or following therapy.[17]

Sixty-seven to 76%[12,14] of patients with HD have an abnormal chest radiograph, and 90% of these have bilateral asymmetric nodal disease[13] (Fig 1) that may spread contiguously along lymph node chains[5,14,18] (Table 1). Prevascular and paratracheal nodes are most commonly affected,[19] occasionally as an isolated finding. Only 15% of patients with intrathoracic HD have enlargement of a single lymph node group[10] and only rarely are the posterior mediastinal or paracardiac lymph node groups involved.[19] Nodular sclerosing HD may manifest as a discrete, lobulated anterior superior mediastinal mass.[5] Visualization of adjacent adenopathy is useful in suggesting the correct diagnosis. In 12% of patients with HD, direct invasion of the lung may occur and is almost always associated with hilar adenopathy.[10,19] Both HD and NHL can cause bulky nodal mediastinal disease[3,18,20] that is occasionally associated with ipsilateral interstitial edema from lymphatic[12] or venous obstruction.

Seventy-one[21] to 85%[8,19] of patients with newly diagnosed HD have thoracic involvement on chest CT scans. Mediastinal HD can manifest as multiple, rounded soft-tissue masses (lymph nodes), as a dom-

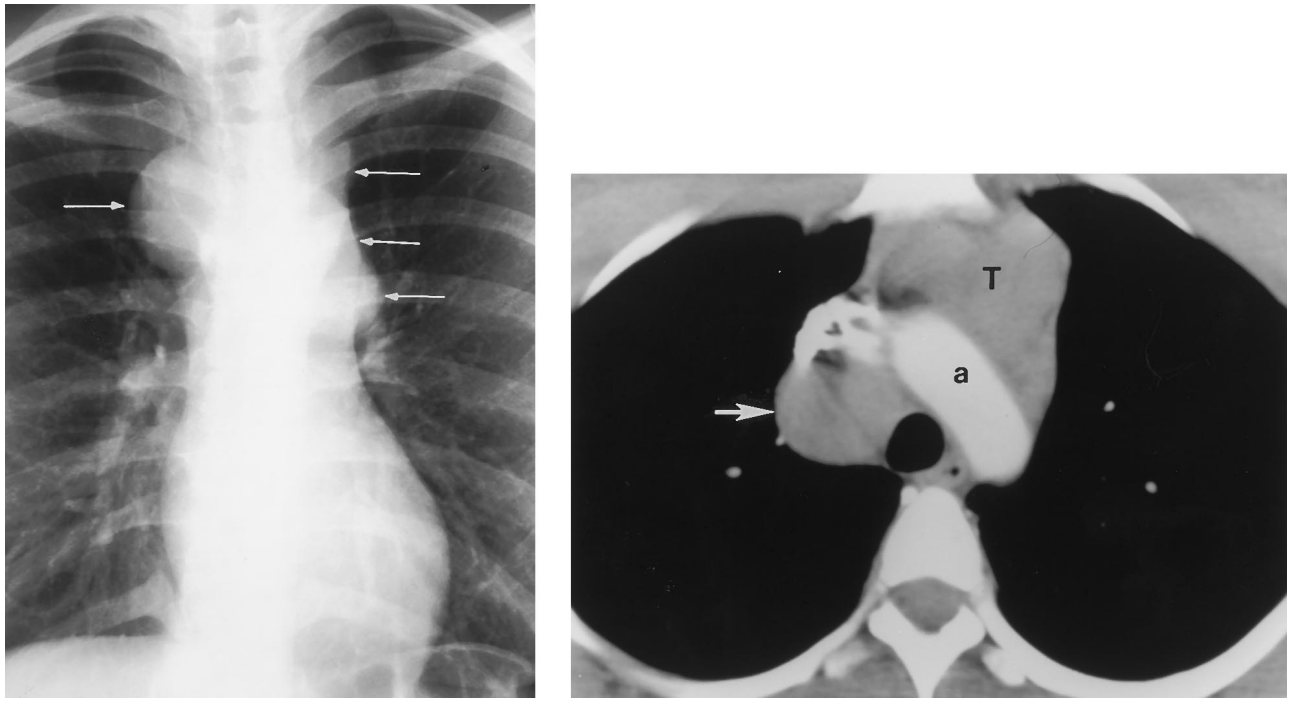

FIGURE 1. (*Left*) posteroanterior (PA) chest radiograph and (*right*) enhanced chest CT (mediastinal windows) at the level of the aortic arch in a 24-year-old man with HD diagnosed by cervical node biopsy specimen. Asymmetric, lobulated paratracheal and aorticopulmonary window lymphadenopathy (arrows) and a homogeneous, well-marginated thymic mass (T) are consistent with mediastinal involvement (a=aortic arch).

Table 1—*Radiographic Distribution of Intrathoracic Abnormalities in Untreated Lymphoma (Percentage of Patients With Positive Findings)

Site Involved	HD, % (n=164)	NHL, % (n=136)
Intrathoracic disease (any site)	67	43
Anterior mediastinum	46	13
Tracheobronchial nodes	45	13
Paratracheal nodes	40	13
Hilar nodes	21	8
Subcarinal nodes	11	4
Internal mammary nodes	7	1
Posterior mediastinum	5	11
Lung	12	5
Pleura	7	11

*Adapted with permission from reference 10.

inant bulky soft-tissue mass (nodal coalescence),[21] or as a discrete or infiltrating thymic mass.[4,22] There may be associated mediastinal infiltration and displacement, compression, or invasion of vascular structures, pericardium, heart, and/or tracheobronchial tree and/or direct invasion of pleura, lung, and chest wall. Masses typically exhibit homogenous soft-tissue attenuation, but large tumors may demonstrate heterogeneity with complex low attenuation and fluid-like areas representing necrosis, hemorrhage, and cyst formation.[16,17,21] Calcification is rare prior to therapy.[10] On MRI, HD is a relatively homogeneous[23] mass or masses with low-signal intensity on T_1-weighted images, similar to muscle, and mixed or high signal on T_2-weighted images, equal to or slightly greater than fat. On T_2-weighted sequences, HD may demonstrate high-signal intensity correlating with tumoral edema, inflammation, immature fibrosis, or granulomatous tissue. Dense fibrosis may demonstrate low-signal intensity on T_2-weighted images,[12] and bulky HD often leaves a residual fibrotic mass after therapy[20,23] that cannot be distinguished from residual tumor on CT. In these cases, T_2-weighted MRIs may demonstrate increasing signal intensity from baseline or one or more areas of high-signal intensity correlating with disease recurrence.[12] A new or enlarging mediastinal mass in a treated patient may represent recurrent disease,[24] a posttherapeutic thymic cyst,[16] or thymic hyperplasia.[24]

Anatomic staging of HD, according to the modified (Cotswold) Ann Arbor staging system[25] (Table 2), distinguishes patients benefiting from radiation therapy alone from those requiring systemic treatment. The revised European-American classification of lymphoid neoplasms (REAL)[25] classifies HD into two relatively distinct groups: (1) nodular sclerosing (66%), mixed cellularity (25%), lymphocyte depleted (5%), and diffuse lymphocyte predominant (<3%) and (2) nodular lymphocyte predominant (<3%).[12] Patients with surgically staged I or II nonbulky HD may be treated with radiation therapy alone.[25] Patients with bulky disease or disease requiring extensive radiation of normal tissue are usually treated with chemotherapy followed by radiation therapy.[12,25] Patients with stage III and IV disease receive chemotherapy, occasionally combined with radiation therapy.[25] Most authors recommend chemotherapy followed by radiation therapy for patients with a large mediastinal mass.[25]

Patients with nonbulky stage IA and IIA HD have cure rates >90% when treated with radiation therapy alone.[12,25] Eighty to 90% of patients with stage IIIA disease may be cured when treated with combined modality therapy.[12,25] Sixty to 70% of patients with stage IIIB disease are cured by chemotherapy alone or in combination with radiation therapy.[12,25] Cures have been achieved with combination chemotherapy in 50 to 60% of patients with stage IV disease.[12,25] Large mass size or direct invasion of the adjacent lung are adverse prognostic factors.[25] Half of patients with HD develop recurrent disease, typically in contiguous lymph node groups.[4,25] These patients have potentially curable disease with salvage therapy.[12,25]

Non-Hodgkin's Lymphoma

While NHL is seen in all age groups,[12] affected patients are usually older with a median age of 55

Table 2—*Modified (Cotswold) Ann Arbor Staging Classification for HD

Stage	Description
I	Single node region or a lymphoid structure (eg, spleen, thymus, Waldeyer's ring) or involvement of a single extralymphatic site (IE)
II	Two or more node regions on the same side of the diaphragm, localized contiguous involvement of only one extranodal organ or site and node region on the same side of the diaphragm (IIE); the number of anatomic sites is indicated by a subscript (eg, II_3)
III	Node regions involved on both sides of the diaphragm (III), and/or involvement of the spleen (III_s) or localized contiguous involvement of only one extranodal organ site (IIIE) or both (IIISE)
III_1	With or without involvement of splenic, hilar, celiac, or portal nodes
III_2	With involvement of para-aortic, iliac, and mesenteric nodes
IV	Diffuse or disseminated involvement of one or more extranodal organs or tissues, with or without associated node involvement

*Adapted with permission from reference 25.

years, and men are slightly more commonly affected than women (1.4:1).[8] Eighty-five percent of patients with NHL present with advanced disease and typically have constitutional symptoms, generalized lymphadenopathy, and/or extensive extranodal disease at diagnosis.[6,8] Large B-cell lymphoma primarily affects the mediastinum and occurs predominantly in young adults with a median age of 26 years[11] and occasionally in children[13] with a female predominance in both groups.[26] These patients may present subacutely, occasionally as oncologic emergencies, with signs and symptoms of a rapidly enlarging mediastinal mass[3] that often directly invades the SVC,[11,13] airway,[26] chest wall, or adjacent structures. Extrathoracic involvement at presentation is unusual. Lymphoblastic lymphomas are aggressive, high-grade lymphomas that can manifest as a rapidly enlarging primary mediastinal mass and usually occur in patients in the first to second decades of life, most often in male adolescents[6] with signs and symptoms of mediastinal invasion to include SVC syndrome.[9] Lymphoblastic lymphoma shares many clinical features with acute lymphoblastic leukemia associated with a mediastinal mass, and the two entities may represent solid and circulating phases of the same lymphoid malignancy.[26,27]

NHLs are characterized pathologically by a predominance of malignant lymphocytes and are relatively homogeneous and uniformly cellular.[23] Primary mediastinal large B-cell lymphomas are composed mainly of large clear cells within a characteristic background of compartmentalized fibrosis.[11,26] Lymphoblastic lymphomas are composed of a homogeneous population of immature lymphoblastic cells cytologically similar to acute lymphoblastic leukemia.[27] Both types manifest as bulky, unencapsulated, invasive masses that involve the thymus and may invade adjacent structures.[26]

The imaging characteristics of NHL are varied.[6] While most patients have lymph node involvement, extranodal disease is frequent.[12] Less than half of patients with NHL have an abnormal chest radiograph.[10] Almost half have intrathoracic nodal disease, typically isolated[10] and involving sites other than paratracheal or prevascular nodal groups.[8] NHL is less likely to involve the anterosuperior mediastinum (Figs 2-3) and has a greater predilection for noncontiguous and/or hematogenous spread[12] to thoracic and distant nodal and extranodal sites[8,14] as well as middle and posterior mediastinal, paracardiac, and retrocrural lymph node groups.[10,22] Isolated pulmonary, pleural, or pericardial disease also occurs.[8] Less than 5% of patients develop pulmonary involvement, typically late in the clinical course with or without associated hilar adenopathy.[10]

Chest CT may be useful in defining the extent of disease in patients with early (stage I or II) disease, in defining radiation portals in patients with abnormal radiographs but no extrathoracic disease, and in determining recurrence in treated patients with questionable radiographs.[8,28] However, chest CT has

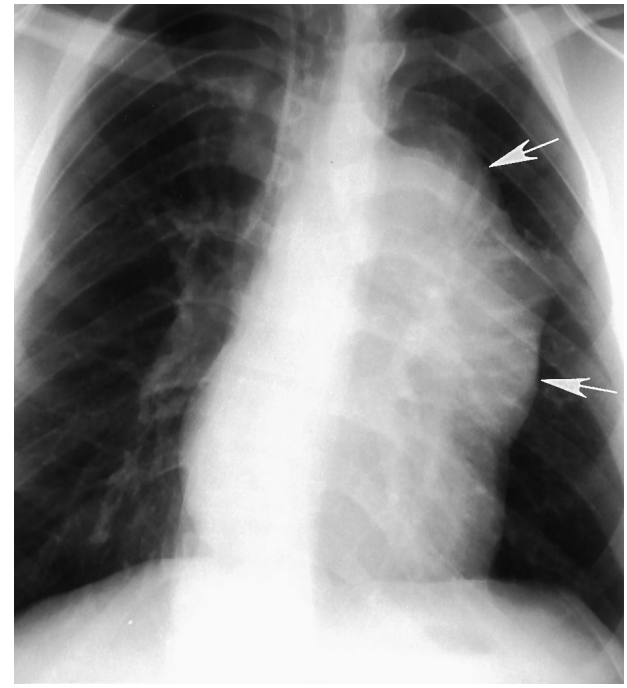

FIGURE 2. PA chest radiograph in a 19-year-old female subject with chest pain. Large B-cell NHL manifests as a 6×11-cm lobulated left anterior mediastinal mass (arrows).

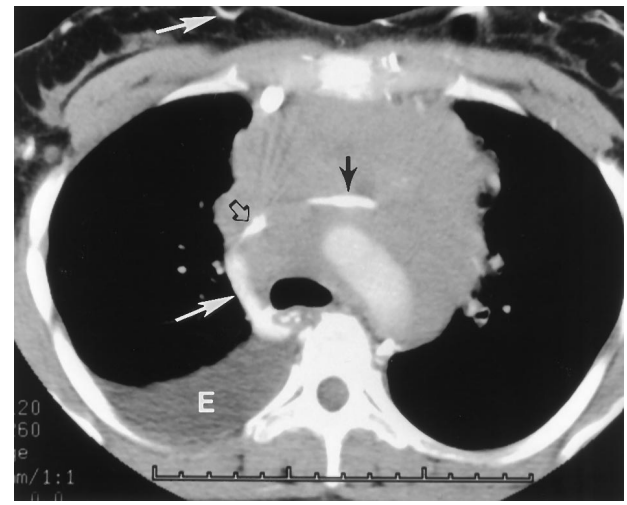

FIGURE 3. Contrast-enhanced chest CT (mediastinal windows) at the aortic arch in a 22-year-old woman with SVC syndrome. A large anterior mediastinal large B-cell NHL encases and nearly obliterates the left brachiocephalic vein (black arrow) and SVC (open arrow), with chest wall and mediastinal collateral vessels (white arrows). The mass also extends into the middle mediastinum. E=chylous effusion.

little utility in untreated patients with advanced (stage III or IV) NHL or treated patients with normal radiographs.[28] The CT and MRI features of NHL are similar to those of HD.

Because of their diversity, the NHLs are difficult to classify. While the modified Ann Arbor classification[25] may be applied, NHL is probably systemic at presentation,[9,12] and histopathologic classification is a more important predictor of behavior and outcome than anatomic extent of disease.[8,12,29] The REAL classification subdivides the B-cell NHL malignancies into indolent (with an untreated natural history measured in years) or aggressive or highly aggressive (with an untreated natural history measured in months or weeks) neoplasms.[29] Indolent NHLs have a more favorable histologic condition, tend to occur in nodal sites, and have more advanced clinical stage at presentation.[6,29] Aggressive NHLs have a less favorable histologic condition with a predilection for localized extranodal involvement[6,29] and are potentially more curable than indolent NHLs. The latter are typically inexorably fatal with a propensity to transform to higher-grade, aggressive lymphomas.[6,12,29]

Treatment of NHL varies according to histologic classification, site of presentation, and extent of disease.[6] Because patients with indolent NHL have a prolonged disease course,[12] are rarely cured, and almost always have recurrence, the goal of therapy is palliation with local radiation and/or chemotherapy when necessary.[29] Treatment of aggressive forms of NHL consists of combination chemotherapy and/or radiation therapy.[12,29] Bone marrow transplantation may improve survival.[12] Large B-cell lymphoma is potentially curable in a significant number of patients.[12,26,30] Lymphoblastic lymphoma, like acute lymphoblastic leukemia, is treated aggressively with reports of long-term disease-free survivors.[6,26] Negative prognostic factors include large tumor size at presentation, extensive extranodal disease, and slow response to treatment.[12] Relapse involves new sites in two thirds of cases.[12]

Mediastinal Cysts

Foregut Cysts

Congenital foregut cysts are the most common mediastinal cysts, accounting for approximately 20% of mediastinal masses.[31,32] Bronchogenic cysts represent 50 to 60% of all mediastinal cysts while enterogenous cysts, which include esophageal duplication and neurenteric cysts, constitute 5 to 10% and 2 to 5%, respectively. Up to 20% of mediastinal foregut cysts lack specific histologic features to permit further classification, possibly because of prior hemorrhage or infection, and are termed indeterminate or nonspecific cysts.[32-34]

Foregut cysts probably arise as a result of aberrant development of the primitive foregut. Bronchogenic cysts are thought to arise from abnormal budding of the ventral foregut, which forms the tracheobronchial tree, and enterogenous cysts are thought to arise from the dorsal foregut "destined" to become the alimentary tract.[35] Eighty-five percent of bronchogenic cysts arise in the mediastinum in close relationship to the trachea, main bronchi, and carina, and approximately 15% occur in the lungs.[34,36] Occasionally, bronchogenic cysts become "engulfed" in the growing esophagus[37,38] or can "pinch off"[39] and migrate to atypical locations such as the pericardium,[33,38] pleura, inferior pulmonary ligament,[36] neck,[38,39] diaphragm, or abdomen.[40] Esophageal duplication cysts are thought to develop during early embryogenesis when the primitive solid esophagus forms vacuoles that coalesce into a patent lumen. A persistent isolated vacuole may enlarge into an intramural or paraesophageal cyst.[33,35] Twelve percent of patients with esophageal duplication cysts have associated congenital malformations, most commonly related to the GI tract.[41] Neurenteric cysts form during early embryogenesis when the foregut and notochord are in close proximity. Although the exact mechanism is unclear, an adhesion between the two may cause the foregut to invaginate and pinch off, forming an enteric cyst that may demonstrate intraspinal extension.[33,37,42] Neurenteric cysts are associated with vertebral anomalies and less commonly bowel duplications,[43] mesenteric cysts,[37] or other anomalies.[31]

Foregut cysts are epithelial-lined cystic structures and are classified by histologic features rather than by location.[33,39] Bronchogenic cysts replicate the structure of the trachea or bronchus[42] while the enterogenous cysts recapitulate the alimentary tract. Bronchogenic cysts are lined by respiratory (ciliated pseudostratified columnar) epithelium and contain cartilaginous plates, bronchial glands, and smooth muscle bundles in their walls.[34,39,42,44] Respiratory epithelium may also persist in other congenital cysts.[42]

Enterogenous cysts are usually lined by alimentary (squamous or enteric) epithelium,[34] and 50 to 60% contain gastric mucosa[45] or pancreatic tissue. The enterogenous cyst wall is characterized by two well-developed smooth muscle layers and a myenteric plexus.[33,37] Esophageal duplication cysts are almost exclusively found within the esophageal wall or adherent to the esophagus.[45] Neurenteric cysts are pathologically identical to esophageal duplication cysts[35] and frequently contain both neural and enteric tissue, including gastric mucosa.[46] They can manifest as an isolated mediastinal cyst with no spinal connection or may have a fibrous tract at-

tached to the spine,[42] occasionally with intraspinal extension of foregut tissue. Mediastinal and intraspinal components of neurenteric cysts coexist in approximately 20% of cases,[43] and isolated intraspinal cysts have been reported.[47] Intravertebral extension of the foregut can disrupt vertebral body development and induce a sagittal cleft defect or more severe vertebral anomalies.[34] Because of the cephalic growth of the notochord and caudal growth of the foregut,[42] associated vertebral defects are typically superior to the mediastinal cyst.[34,35,37]

Foregut cysts are spherical, unilocular[42] masses with smooth, thin walls.[33] Occasionally, esophageal duplication cysts manifest as paraesophageal tubular lesions.[45] Communication with the tracheobronchial or the esophageal lumen is uncommon.[38] Cyst contents vary and include serous fluid, mucoid material, pus,[35] milk of calcium,[48] and blood.[49]

Foregut cysts occur equally in male and female subjects although a slight male predominance has been reported for neurenteric cysts.[33] While bronchogenic cysts are seen in all age groups, affected patients are frequently adults with an average age of 36 years.[38] Cysts may be discovered incidentally in asymptomatic patients. Bleeding, infection, or epithelial secretions may cause mediastinal cyst enlargement and symptomatic compression of the aerodigestive tract.[31] Two-thirds of patients eventually develop symptoms,[38] most commonly from airway or esophageal obstruction,[31] therefore "watchful waiting"[38] is discouraged.[35] Infants and children commonly present with symptoms of severe airway obstruction[31] or pneumonia.[36,44] Infection of a mediastinal bronchogenic cyst is uncommon and rupture into a bronchus,[50] the pericardium,[35] or pleura is rare.

Most esophageal duplication cysts manifest in childhood, and almost all neurenteric cysts are discovered by age 1 year, usually because of signs and symptoms of esophageal or tracheobronchial compression.[31] When the cyst lining contains gastric mucosa[43] or pancreatic tissue, digestive secretions may precipitate cyst hemorrhage or rupture.[31,35,43] Patients with neurenteric cysts with intraspinal extension can present with neurologic symptoms.[43] Malignant degeneration of foregut cysts is rare.[51]

Radiologically, foregut cysts manifest as well-marginated, homogeneous, spherical mediastinal masses ranging in size from 2 to 10 cm. Bronchogenic cysts typically occur in the paratracheal or subcarinal region[31,33,34] but may be found anywhere within the thorax. On chest CT, they are spherical nonenhancing lesions of variable attenuation.[31,48-50] Enhancement and calcification[33] of the cyst wall may occur (Fig 4). Communication with the tracheobronchial tree is rare and may manifest as a gas-fluid level within the cyst.[52] In children, compression of the tracheobronchial tree may produce air trapping,[44] atelectasis, or tracheal deviation[31] (Fig 5). Occasionally, the cyst may be occult[44,53] or may be obscured by pulmonary consolidation.[31] On MRI, cyst contents can exhibit low- or high-signal intensity on T_1-weighted images and typically have very bright-signal intensity on T_2-weighted sequences. A presumptive diagnosis can be established with bronchoscopic or thoracoscopic needle drainage of nonhemorrhagic fluid containing mucus and bronchial epithelial cells in patients with CT features indicative of foregut cyst.[2,45,52,54]

Enterogenous cysts have radiologic features nearly identical to those of bronchogenic cysts but rarely exhibit calcification. Most esophageal duplication cysts are related to the distal right aspect of the esophagus.[45,55] Ninety percent of neurenteric cysts occur in the posterior mediastinum, usually superior to the carina, on the right, and separate from the esophagus.[34] They measure from several centimeters to 12 cm, and 50% are associated with cervical and upper thoracic vertebral anomalies such as scoliosis, anterior spina bifida, hemivertebrae, butterfly vertebrae, or vertebral fusion or scoliosis.[35] MRI should be performed to exclude intraspinal extension of a posterior mediastinal cyst.

Foregut cysts are frequently treated with complete surgical excision, even when asymptomatic, to prevent complications and establish the diagnosis.[32,35,53] Partial excision with "de-epithelization" of the residua can be performed if complete excision is not possible. When a patient is not a surgical candidate, bronchoscopic or thoracoscopic needle drainage is an alternative.[52] Occasionally, incidentally discovered mediastinal bronchogenic cysts in asymptomatic adults are followed.[52] The prognosis following complete excision is excellent.[43,44]

Pericardial Cysts

Pericardial cysts are generally considered developmental abnormalities, although some may be acquired.[56] They are uncommon lesions[2] and occur almost exclusively in asymptomatic[56] adults, usually in the fourth to fifth decades of life. Complications rarely occur.

Congenital pericardial cysts are thought to arise from aberrant fusion of the anterior pericardial recesses.[42,56] They may be attached to the diaphragm or anterior pericardium[42,57] and rarely communicate with the pericardial sac. Pericardial cysts are usually unilocular[57] cystic lesions with a thin connective tissue wall and clear fluid contents,[33] thus the name "clear water" or "spring water" cyst.[42]

Radiologically, a pericardial cyst manifests as a

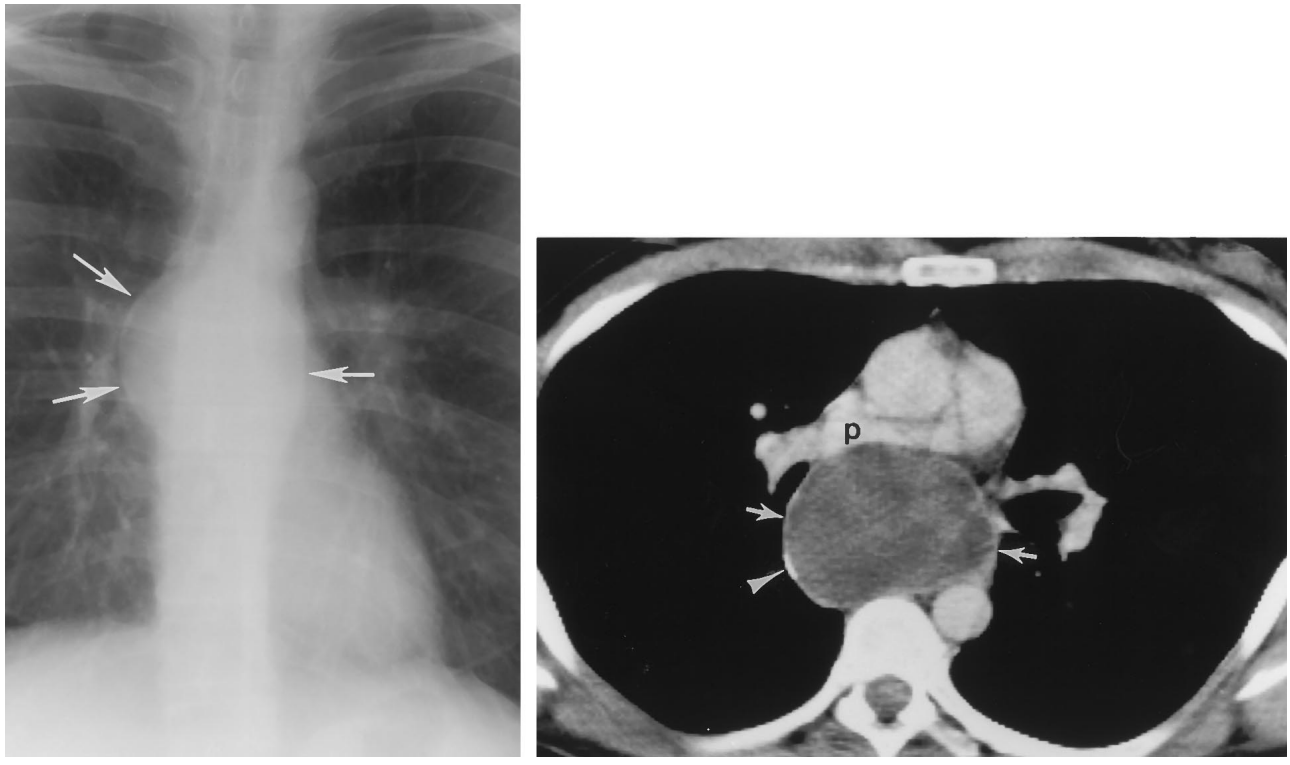

FIGURE 4. (*Left*) PA chest radiograph and (*right*) contrast-enhanced chest CT (mediastinal windows) of a 42-year-old asymptomatic man. A spherical 6-cm subcarinal bronchogenic cyst (white arrows) exhibits homogeneous water attenuation, peripheral curvilinear calcification (arrowhead), and mass effect on the right pulmonary artery (p).

well-marginated, spherical, or teardrop[57]-shaped mass that characteristically abuts the heart,[56] the anterior chest wall, and the diaphragm.[33] Most measure 5 to 8 cm,[56] but some occasionally attain larger sizes.[42] Mural calcification is rare.[57] In a surgical series of 82 cases of pericardial cysts, 70% were located in the right cardiophrenic angle, 22% in the left cardiophrenic angle, and the remaining 8% in another paracardiac location.[57] On CT, pericardial cysts are typically unilocular nonenhancing masses with water attenuation contents and an imperceptible wall (Fig 6). On MRI, they have low-signal intensity on T_1-weighted images[58] and bright-signal intensity on T_2-weighted images.

Pericardial cysts are frequently followed clinically and radiologically. If they are associated with symptoms or atypical imaging features, surgical resection should be performed to exclude a foregut cyst or cystic mediastinal neoplasm.[56]

NEUROGENIC TUMORS

Neurogenic tumors represent approximately 20% of all adult and 35% of all pediatric mediastinal neoplasms.[1,2,59,60] Neurogenic tumors are the most common cause of a posterior mediastinal mass. Approximately 90% occur in the posterior mediastinum,[59] and they comprise 75% of primary posterior mediastinal neoplasms.[61] Seventy to 80% are benign and approximately half of the patients are asymptomatic.[2] Neurogenic tumors are generally grouped into three categories: those arising from peripheral nerves, sympathetic ganglia, or rarely parasympathetic ganglia.[62] Schwannoma, neurofibroma, and malignant tumor of nerve sheath origin arise from the peripheral nerves while ganglioneuroma, ganglioneuroblastoma, and neuroblastoma arise from the sympathetic ganglia. Nerve sheath tumors are most common in adults while sympathetic ganglia tumors are more common in children.

Peripheral Nerve Tumor

Schwannoma and Neurofibroma: Schwannomas (or neurilemomas) and neurofibromas are the most common mediastinal neurogenic tumors.[2,62] They are benign, slow-growing neoplasms that frequently arise from a spinal nerve root but may involve any thoracic nerve.[63] Schwannomas arise from the nerve sheath and extrinsically compress the nerve fibers.[63] They are encapsulated neoplasms composed of

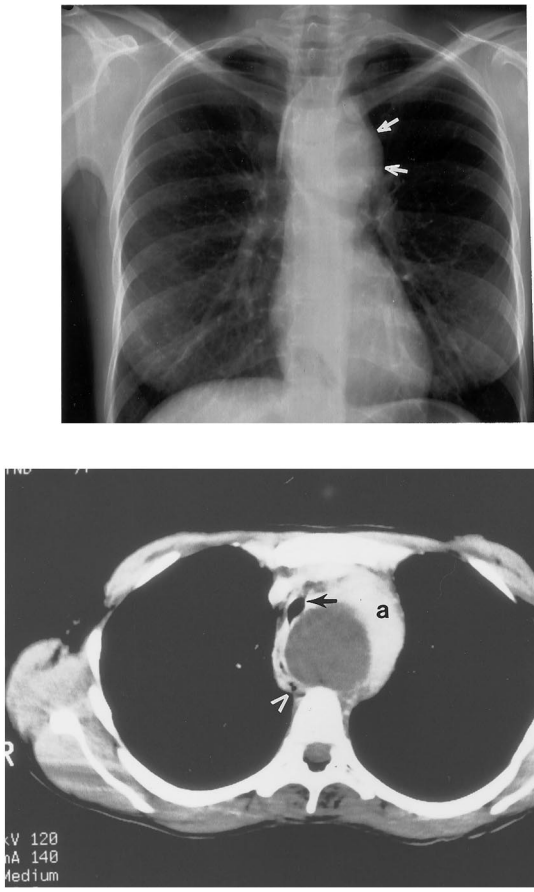

FIGURE 5. (*Top*) PA chest radiograph and (*bottom*) contrast-enhanced chest CT (mediastinal windows) at the level of the aortic arch in a 24-year-old man with acute stridor. A left paratracheal bronchogenic cyst causes mediastinal widening (white arrows) and mass effect on the airway. The nonenhancing, water attenuation cyst is interposed between the aorta (a), esophagus (arrowhead), and trachea (black arrow), with moderately severe compromise of the airway.

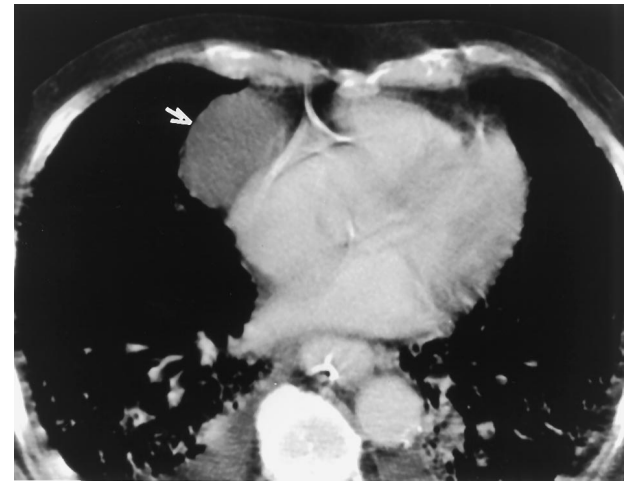

FIGURE 6. Contrast-enhanced chest CT (mediastinal windows) at the base of the heart in a 54-year-old man with complicated pneumonia. A pericardial cyst (arrow) exhibits water attenuation contents, an imperceptible wall, and contiguity with the heart and anterior chest wall.

Schwann cells within a background of loose reticular tissue without nerve fibrils or collagen.[64] Schwannomas are frequently heterogeneous, especially when large, with areas of cystic degeneration, low cellularity, hemorrhage, myelin, and small calcifications.[65] Neurofibromas are usually homogeneous, well-marginated but nonencapsulated tumors that result from a disorganized proliferation of all nerve elements, including Schwann cells, myelinated and unmyelinated nerve fibers, and fibroblasts.[62,64] Despite these differences, both tumors manifest grossly as lobulated spherical masses.[62] A plexiform neurofibroma, an important variant,[63] is a well-defined, nonencapsulated tumor that usually infiltrates along an entire nerve trunk or plexus.[64]

Schwannoma and solitary neurofibroma share many clinical features. Men and women in the third to fourth decades are equally affected. Most patients are asymptomatic,[66,67] although a small percentage experience paresthesia or pain from compression of adjacent structures or from intraspinal tumor extension.[68] Recurrence is uncommon.[69,70] Approximately 30 to 45% of neurofibromas occur in individuals with neurofibromatosis.[1,62] Multiple neurogenic tumors[70] or a single plexiform neurofibroma is pathognomonic of neurofibromatosis. Multiple schwannomas may also occur but are not pathognomonic of this disorder.[62,66] Patients with neurofibromatosis and mediastinal neurogenic tumors usually present at a younger age and are at increased risk for malignant transformation of a neurofibroma.[63,71] However, malignant transformation of a preexisting schwannoma is rare.[72]

Radiologically, schwannomas and neurofibromas are usually sharply marginated, spherical,[64] and lobulated paraspinous masses[1] that span one to two posterior rib interspaces but can attain large sizes.[62] In up to 50% of cases, they produce benign pressure erosion and/or deformity of ribs, vertebral bodies, and neural foramina. Calcification is rarely detectable on chest radiographs. On cross-sectional imaging, schwannomas and solitary neurofibromas are well-circumscribed homogeneous or heterogeneous masses.[63] On CT, punctate calcifications are occasionally detected, and low attenuation correlates with areas of hypocellularity,[65] cystic change, hemorrhage, and lipid within myelin.[64] Following IV contrast, schwannomas or neurofibromas may demonstrate mild homogeneous,[73] heterogeneous, or peripheral enhancement.[64] Ten percent of schwannomas and neurofibromas grow through the adjacent intervertebral foramen and extend into the spinal canal with a "dumbbell" or "hourglass" configura-

tion.[63] On MRI, schwannomas and neurofibromas typically have low- to intermediate-signal intensity on T_1-weighted images (Fig 7) and may have areas of intermediate- to high-signal intensity on T_2-weighted sequences.[74] MRI should be performed preoperatively in all patients with suspected neurogenic tumors to definitively exclude intraspinal tumor extension (Fig 8).

The treatment of choice is complete resection via thoracoscopic surgery[75] or thoracotomy. Tumors with dumbbell intraspinal extension are best excised with combined neurosurgical and thoracic procedures.[75]

Malignant Tumor of Nerve Sheath Origin: Malignant tumors of nerve sheath origin (MTNSO) are rare spindle cell sarcomas. They represent the malignant counterparts of schwannomas and neurofibromas and have also been termed malignant neurofibromas, malignant schwannomas, and neurogenic fibrosarcomas.[64,76] MTNSO typically arise from a simple or plexiform neurofibroma[71,76,77] but rarely, if ever, from a preexisting schwannoma.[72] They are extremely pleomorphic and cellular malignancies,[77] and patients with neurofibromatosis are more likely to have high-grade malignant tumors.[76]

Malignant tumors of nerve sheath origin affect men and women[78] in the third through fifth decades.[66] Approximately half[76] occur in individuals with neurofibromatosis, and the incidence of sarco-

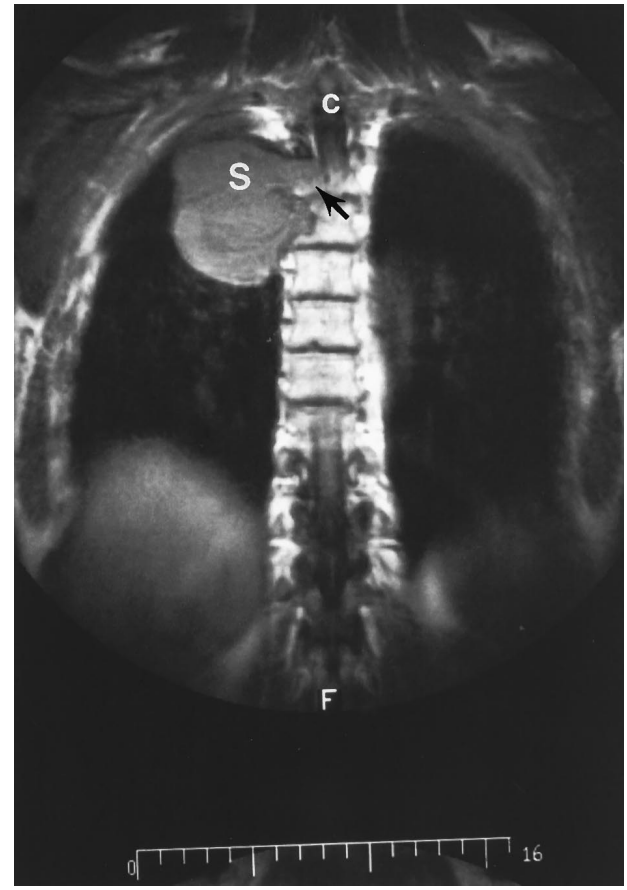

FIGURE 8. T_1-weighted unenhanced coronal MRI in a 35-year-old man with chest pain. A well-circumscribed rounded schwannoma (S) has slightly heterogeneous signal intensity and intraspinal extension (arrow) with mass effect on the spinal cord (c).

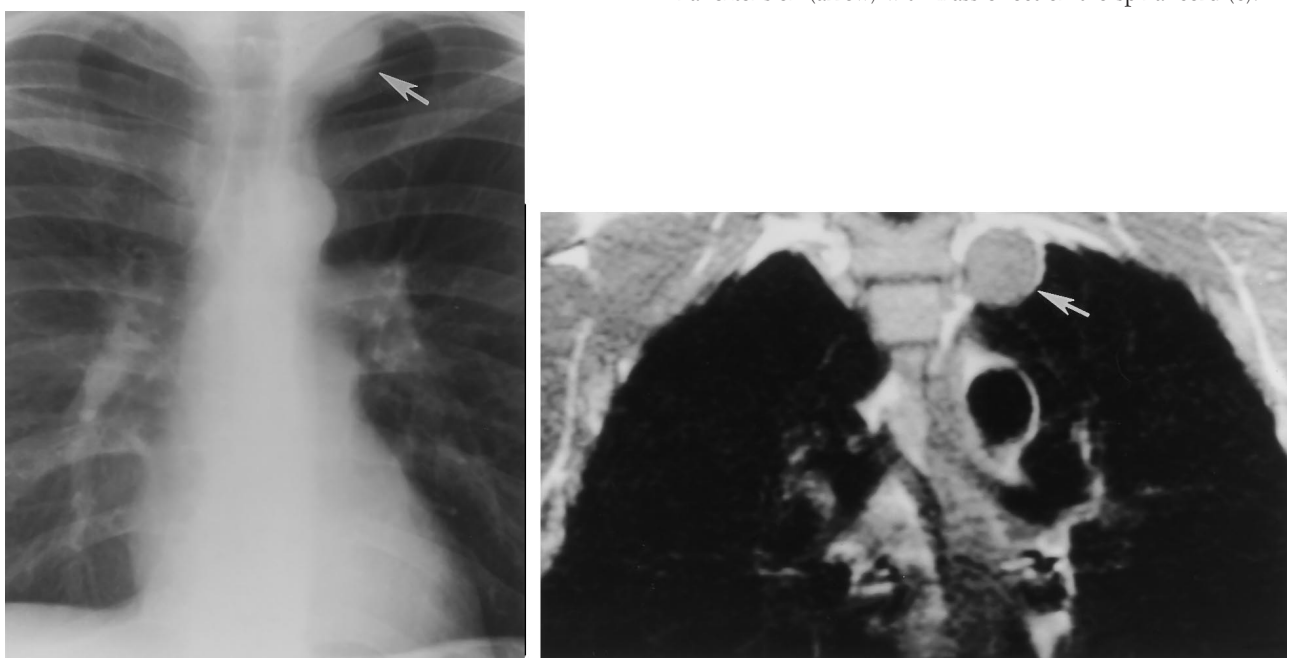

FIGURE 7. (*Left*) PA chest radiograph and (*right*) unenhanced T_1-weighted coronal MRI in an asymptomatic 24-year-old man. A schwannoma (arrow) manifests as a 3-cm spherical posterior mediastinal mass with homogeneous intermediate-signal intensity without evidence of foraminal or intraspinal tumor extension.

matous degeneration in patients with neurofibromatosis is approximately 5%.[71,73,76,78] MTNSO may also occur sporadically or may be induced by radiation exposure.[66,79] Most patients with neurofibromatosis and MTNSO are adolescents or young adults.[76,79] Pain, an enlarging mass, and/or symptoms of nerve deficit are common presentations, may persist for several months or years, and are frequently associated with a long-standing mass.[76] Local recurrence is quite common.[71]

Radiologically, MTNSO manifests as a spherical posterior mediastinal mass,[73] which usually exceeds 5 cm in diameter,[77] especially in patients with neurofibromatosis.[76] On CT, they are typically rounded well-marginated masses[73] (Fig 9) but may locally invade mediastinal structures and adjacent chest wall.[64,71] Areas of low attenuation correspond to central hemorrhage and necrosis.[72,73] Calcification may be present. Hematogenous metastases, most frequently to the lungs,[64,77] are well reported, but lymph node metastases are rare.[78]

Radical surgical excision with wide margins is the procedure of choice. When complete resection is not possible, simple excision without wide margins or subtotal excision followed by high-dose radiation therapy is an alternative.[69,76] Adjuvant radiation therapy and chemotherapy do not appear to improve survival[76] but may have utility in the treatment of metastatic disease. Local recurrence following incomplete excision is frequent. The overall survival is poor[73] and adversely affected by large tumor size, incomplete resection, and/or an association with neurofibromatosis.[66,76,77] Recurrences and metastases are more common in patients with neurofibromatosis.[76]

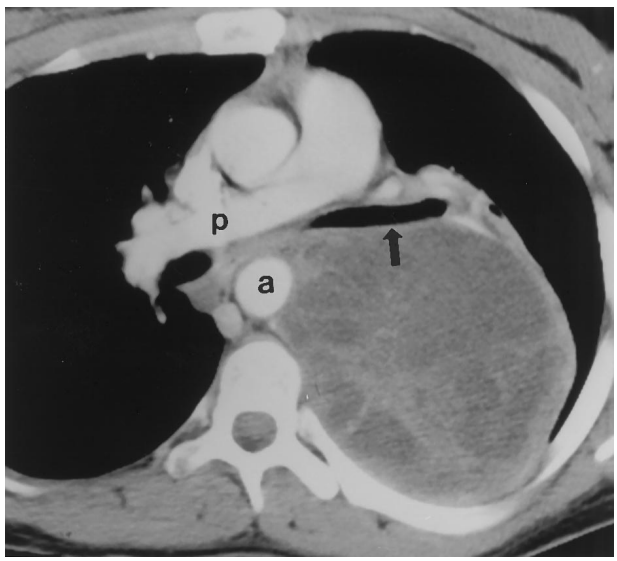

FIGURE 9. Contrast-enhanced chest CT (mediastinal windows) at the level of the right pulmonary artery (p) in a 23-year-old woman with neurofibromatosis and chest pain. A large, spherical MTNSO encases and displaces the descending aorta (a), produces mass effect on the left upper lobe bronchus (arrow), and demonstrates heterogeneous low attenuation with variable enhancement.

Sympathetic Ganglia Tumors

The sympathetic ganglia tumors are rare neoplasms that probably represent a "biological continuum"[80] from benign ganglioneuroma to malignant ganglioneuroblastoma to highly malignant neuroblastoma.[67] They originate from the nerve cells rather than the nerve sheath and can occur in sympathetic ganglia and adrenal glands. Ganglioneuroma and ganglioneuroblastoma arise most commonly from the sympathetic ganglia in the posterior mediastinum.[67] Fifty percent of neuroblastomas originate in the adrenal gland[81] and up to 30% arise in the mediastinum,[62,66,67] the most common extra-abdominal location.

Ganglioneuroma: Ganglioneuromas are composed of single or clustered mature ganglion cells[69] in a dense stroma and manifest grossly as encapsulated, elongated, and homogeneous tumors,[82] occasionally with a dumbbell intraspinal component. They typically affect male and female children older than 3 years of age,[83] adolescents, and young adults,[1] half of whom are asymptomatic[59,62] despite large tumor sizes. When present, symptoms are usually referable to mass effect or intraspinal tumor extension.[69]

Radiologically, the sympathetic ganglia tumors collectively manifest as well-marginated,[83] oblong masses with a broad base along the anterolateral aspect of the spine.[1] They typically span three to five vertebrae although larger sizes may be attained.[59] Ganglioneuroma may produce scoliosis and displacement and benign pressure erosion of adjacent skeletal structures.[66] Stippled calcification may be detectable on radiographs.[67,83] On CT, ganglioneuroma may manifest as a homogeneous or heterogeneous elongated mass. MRI usually demonstrates homogeneous, intermediate-signal intensity on all sequences[84] (Fig 10), occasionally with a "whorled" appearance on T_1-weighted images and heterogeneous high-signal intensity on T_2-weighted sequences.[74] MRI can accurately define the presence and extent of intraspinal tumor.[84]

Ganglioneuroma is cured by complete surgical excision.[67,69] Tumors with intraspinal extension should be resected with combined neurosurgical and thoracic procedures.

Ganglioneuroblastoma: Ganglioneuroblastomas are "composite" tumors that exhibit histologic features of ganglioneuroma and neuroblastoma.[82] Varying degrees of malignancy ranging from mature

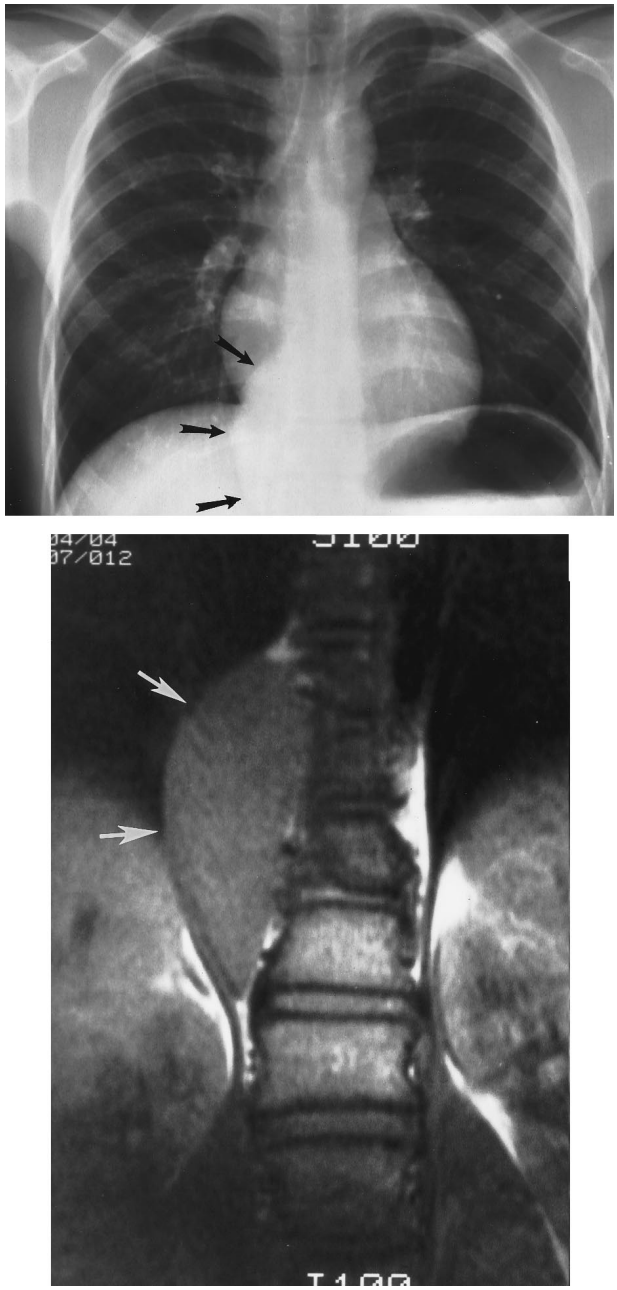

FIGURE 10. (*Top*) PA chest radiograph and (*bottom*) unenhanced T_1-weighted coronal MRI in an asymptomatic 14-year-old male subject. A well-circumscribed, oblong posterior mediastinal ganglioneuroma (arrows) has homogeneous low- to intermediate-signal intensity without intraspinal extension.

ganglion cells to immature neuroblasts[82] may make classification difficult.[69,85] Grossly, ganglioneuroblastoma may be partially encapsulated, well marginated, and homogeneous or exhibit areas of nodularity, hemorrhage, and necrosis similar to neuroblastoma.[82]

Ganglioneuroblastomas affect male and female subjects equally, and patients are usually younger than 10 years old.[85] Symptoms, when present, are typically related to large tumor size, intraspinal extension, extensive local invasion, and/or widespread metastases, similar to neuroblastoma.[82] Radiologically, ganglioneuroblastoma may manifest as a sharply marginated oblong paraspinous mass or may be irregular, locally invasive, and widely metastatic.[85] The staging, treatment, and prognosis of ganglioneuroblastoma are discussed in the next section.

Neuroblastoma: Neuroblastoma is composed of small round cells frequently arranged in sheets or pseudorosettes.[69,82] Neuroblastoma is nonencapsulated, frequently contains extensive areas of hemorrhage, necrosis, and cystic degeneration,[82] and may be locally invasive and widely metastatic.[69]

Neuroblastoma is a malignancy of young children. Approximately 60% of cases occur in children younger than 2 years and 70 to 90% afflict children younger than 5 years.[81,86] Neuroblastoma may be congenital and is uncommon in adults.[62] In children younger than 5 years, neuroblastoma is 1.3 to 2 times more common in male subjects,[81,87] but in older patients, both sexes are affected equally. Two-thirds of children with neuroblastoma are symptomatic, typically from distant metastases. Patients may have pain, constitutional symptoms,[82] neurologic deficits, Horner's syndrome, respiratory distress,[86] and ataxia.[69] Neuroblastoma, and less frequently ganglioneuroblastoma[82] and ganglioneuroma,[69] can be metabolically active with elevation of plasma catecholamine levels and vasoactive intestinal peptides that can cause hypertension, flushing, and an intractable watery diarrhea syndrome.[67,87] Patients often excrete urinary catecholamine byproducts (homovanillic acid and vanillylmandelic acid) that are helpful in establishing the preoperative diagnosis and in monitoring tumor recurrence.[67]

Neuroblastoma manifests as an elongated paraspinous mass with a propensity to displace and invade adjacent structures, cross the midline, and produce extensive skeletal erosion.[69,83] Calcification can be detected on radiographs in approximately 30% of cases.[88] On cross-sectional imaging, tumor margins may be smooth or irregular, and tumor heterogeneity correlates with large areas of necrosis and hemorrhage. Approximately 80% of neuroblastomas have various types of calcification on CT, including "cloud-like," stippled, "ring-shaped," and solid.[88] MRI typically demonstrates tumors with homogeneous or heterogeneous signal intensity on all sequences[84] and enhancement following gadolinium administration. Various degrees of intraspinal tumor extension, invasion of adjacent structures, and encasement of vessels may be demonstrated.[84] Radionuclide imaging with 123 iodine MIBG (meta-iodobenzyl-guanidine), an epinephrine precursor that is

relatively specific for neoplasms of sympathetic origin, is used in the detection of primary and metastatic neuroblastoma in young children.[89]

Staging of neuroblastoma[90] (and ganglioneuroblastoma) is based on local extension, lymph node involvement, and the presence of metastases.[69,85] Stage I represents well-circumscribed, noninvasive ipsilateral tumor. Stage II represents tumor with local invasion into adjacent soft tissues, bone, or spinal canal without extension across midline and/or ipsilateral regional lymph node involvement. Stage III represents tumor extension across the midline and involvement of bilateral regional lymph nodes. Stage IV represents widespread metastatic disease. Stage IVS includes patients with clinical stage I or II disease and metastatic disease limited to the liver, skin, and/or bone marrow.

The treatment of choice for sympathetic ganglia tumors is complete surgical resection.[67,69] Complete resection of stage I neuroblastoma and ganglioneuroblastoma is considered curative in all age groups.[91] Stage II and III neuroblastoma and ganglioneuroblastoma should be completely excised,[91] when possible. Following surgery for stage II disease, some oncologists recommend adjuvant radiation coupled with chemotherapy for treatment of residual tumor.[91] Chemotherapy can induce complete or partial response in 70% of patients with stage III disease. Reduction in size of initially inoperable lesions is frequently followed by complete excision of residual tumor.[86] Chemotherapy and radiation therapy[87] are important modalities in the treatment of advanced neuroblastoma; however, radiation therapy can have delayed complications (scoliosis and paraplegia[85]) in young children.[87] Negative prognostic factors for neuroblastoma and ganglioneuroblastoma include older age at diagnosis, large tumor size, poorly differentiated cell type, advanced tumor (stage III and IV),[86,91] and extrathoracic primary site.[69] Intraspinal tumor extension does not worsen the prognosis.[91]

Lateral Thoracic Meningocele

Lateral thoracic meningoceles are rare posterior mediastinal cystic lesions characterized by redundant meninges (dura and arachnoid with small amounts of neural tissue within the wall[42]) that balloon through the spinal foramen and are filled with cerebrospinal fluid. Male and female subjects are equally afflicted, usually asymptomatic, and frequently in the fourth to fifth decades of life. Seventy-five percent of affected patients have neurofibromatosis, and lateral thoracic meningoceles represent the most common cause of a posterior mediastinal mass in this population.[42,63] Radiologically, lateral thoracic meningocele manifests as a sharply marginated paraspinous mass frequently associated with osseous abnormalities such as pressure erosion of the posterior vertebral body, widening of neural foramina, and kyphoscoliosis. The lesions typically measure 2 to 3 cm but may attain large sizes. CT and MRI can demonstrate continuity between the cerebrospinal fluid in the meningocele and that contained in the thecal sac as well as water attenuation or signal characteristics consistent with fluid. Most lateral thoracic meningoceles may be followed up clinically and radiologically. If symptoms develop, surgical resection may be indicated.[75]

Conclusion

Middle and posterior mediastinal masses include lesions of many etiologies. Lymphoma is a lymphoproliferative malignancy that may affect any mediastinal compartment and that classically manifests as nodal enlargement. The diagnosis is frequently made by biopsy of a palpable peripheral node, and mediastinal involvement is determined by cross-sectional imaging studies. Diagnostic problems may arise when lymphoma manifests with primary mediastinal lymphadenopathy or focal mass. Mediastinal cysts typically are congenital in etiology, classically affect the middle mediastinal compartment, and often lead to symptoms and complications that warrant surgical resection. Morphologic features, location, and imaging characteristics are very helpful in suggesting the correct diagnosis. Neurogenic tumors are common masses of the posterior mediastinum. Lesions of peripheral nerve origin typically affect asymptomatic adults, have spherical morphologic features, and are cured by excision. Multiplicity of lesions suggests the diagnosis of neurofibromatosis. Neoplasms of sympathetic ganglia origin usually affect children and young adults, and have an elongated morphologic condition and a variable prognosis due to the higher frequency of malignant histologic types. Imaging and demographic features are helpful in determining patient management.

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