Chapter 1

The mediastinum

Alberto M. Marchevsky, MD, and Mark R. Wick, MD

The mediastinum is the chest cavity region located as a "septum" between the two pleural cavities [1–5]. It is an area of great interest to internists, pulmonologists, imaging specialists, thoracic surgeons, and pathologists because it can be the site of origin of numerous pathologic processes [6]. Indeed, the mediastinum has been compared to a "Pandora's box" full of surprises for physicians concerned with chest diseases.

Many interesting clinical problems associated with mediastinal lesions have become apparent in the last few decades with the development of very sensitive new radiologic techniques such as computerized tomography (CT scan), magnetic resonance imaging (MRI), and the extensive use of invasive diagnostic procedures such as mediastinoscopy, limited thoracotomy, transthoracic fine needle aspiration biopsy, ultrasound guided transesophageal fine needle aspiration biopsy (EUS), and ultrasound guided transbronchial fine needle aspiration biopsy [7–10]. These techniques enable the detection, localization and biopsy of mediastinal lesions hitherto located in "blind spots" of chest X-rays. However, the diagnosis of most mediastinal lesions is often rendered pathologically, a task that is often not simple, as the mediastinum contains numerous organs such as the thymus, lymph nodes, ganglia, ectopic thyroid and parathyroid tissues, soft tissues, and others that can become involved in various pathologic processes [6].

The aim of this volume is to review the clinicopathologic aspects of all mediastinal lesions of interest to the surgical pathologist, with the exception of pathologic processes in the esophagus. Although the esophagus is located in the mediastinum, a detailed description of its pathology is generally included in books dealing with the gastrointestinal tract.

Anatomy of the mediastinum

The mediastinum extends anteroposteriorly from the sternum to the spine and sagitally from the thoracic inlet to the diaphragm (Fig. 1.1) [1,2,5,9,11,12]. Its boundaries include the sternum anteriorly, the thoracic vertebra posteriorly, the first thoracic rib, first thoracic vertebra, and manubrium superiorly, and the diaphragm inferiorly. It contains the thymus, the heart and other structures shown in Figs 1.1 and 1.2.

Anatomic classifications of the mediastinum

It has become customary in clinical practice to divide the mediastinum into anatomic compartments separated by arbitrary lines. There are several anatomic classifications of the area, but the most widely used scheme is a simple one that divides the mediastinum into four compartments: superior, anterior, middle, and posterior (Fig. 1.3) [1–3]. This classification is useful in that certain pathologic lesions are most frequently located in particular compartments [3–5,11]. For example, thymic and thyroid tumors are usually in the anterior mediastinum, whereas most neurogenic lesions are found in the posterior compartment [3]. This scheme, however, has several drawbacks such as the fact that there is no agreement in the literature on whether the posterior mediastinum should extend backward only to the anterior margins of the vertebral bodies or more posteriorly into what some authors term the paraspinal area.

Heitzman tried to overcome the limitations of this oversimplified view of the mediastinum by proposing a much more detailed classification of the area based on anatomic landmarks that can be recognized on chest roentgenograms. In his scheme, the mediastinum can be divided into thoracic inlet, anterior mediastinum, supraaortic area, infraaortic area, supraazygous area, infraazygous area, and hila [7].

The *thoracic inlet* marks the cervicothoracic junction and is the area above and below a plane drawn transversely through the first rib. The *anterior mediastinum* is the region extending from the thoracic inlet to the diaphragm in front of the pericardium, ascending aorta, and superior vena cava. The *supraaortic area* is the region located behind the left side of the anterior mediastinum. It extends from the aortic arch to the thoracic inlet. The *infraaortic area* is the region located behind the left side of the anterior mediastinum. It extends from below the aortic arch to the diaphragm. The *supraazygous area* is the region located behind the right side of the anterior mediastinum. It extends from the arch of the azygous vein to the thoracic inlet. The *infraazygous area* is the region extending behind the right side of the anterior mediastinum from below the arch of the azygous vein to the diaphragm. The

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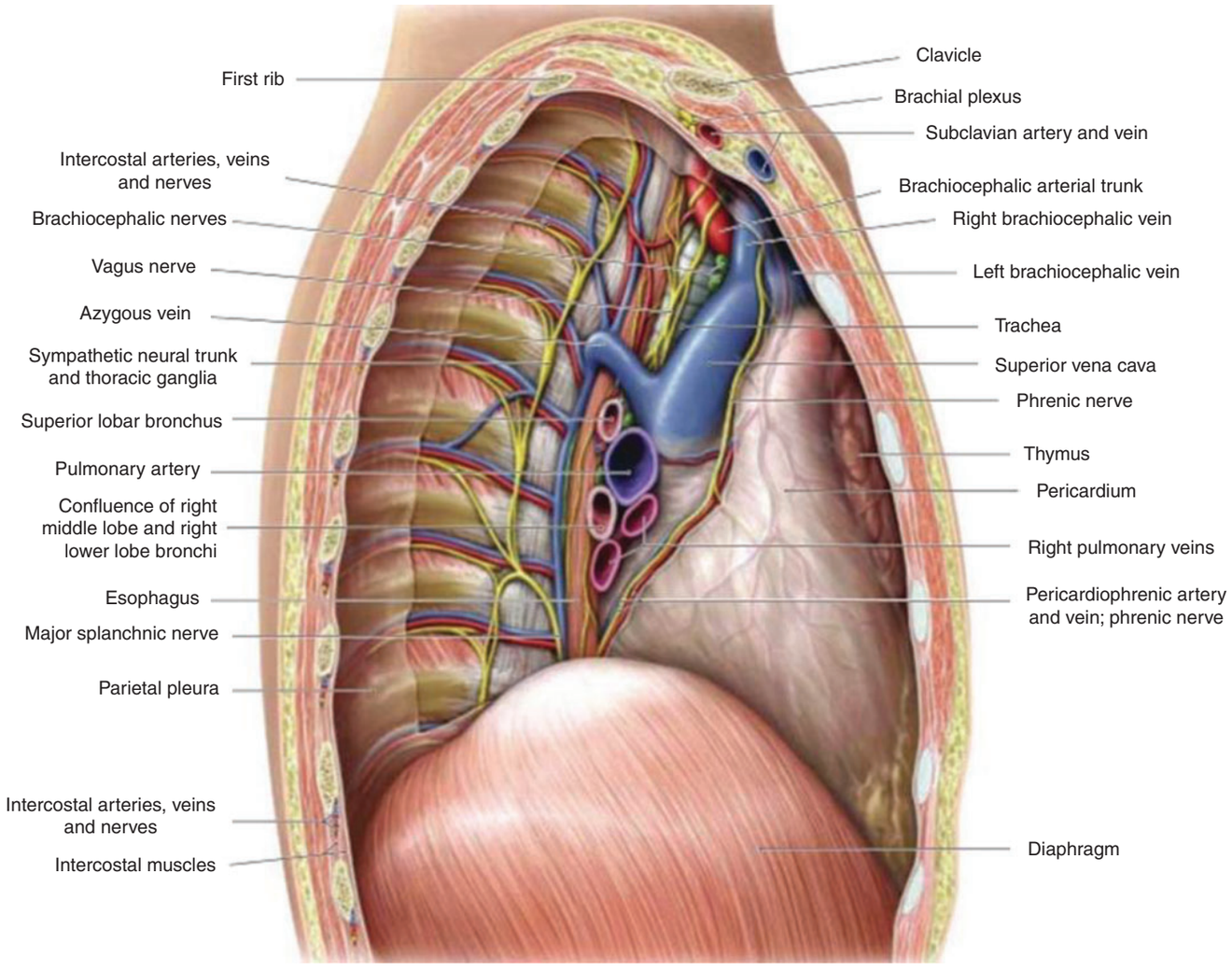

Fig. 1.1 Diagram of the mediastinum showing different structures.

- Heart (H)
- Trachea (T)
- Great vessels (GV)
- Thymus gland (G)
- Sympathetic nerves and ganglia
- Thoracic duct, lymphatic ducts, and lymph nodes

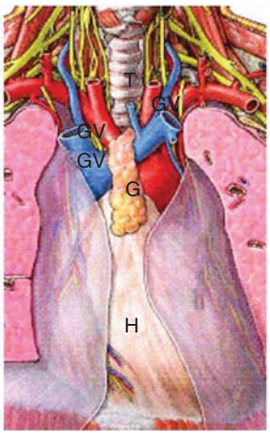

Fig. 1.2 Diagram of the mediastinum showing the heart and other mediastinal structures of interest.

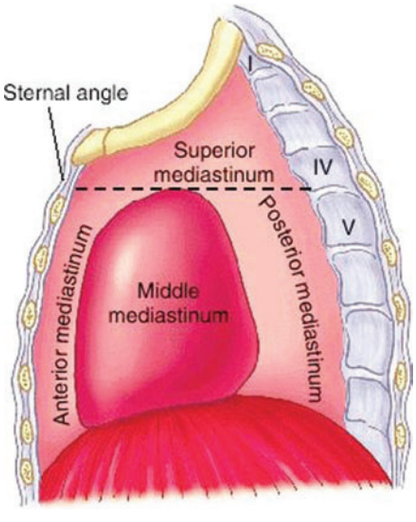

Fig. 1.3 Diagram of the mediastinum illustrating the various mediastinal compartments.

hila include both major bronchi and surrounding bronchopulmonary structures.

This classification is useful from the imaging point of view because it enables imaging specialists to localize lesions with accuracy and aids in suggesting differential diagnosis, but is of relatively little value to a surgical pathologist faced with the task of establishing the pathologic diagnosis of a particular mediastinal lesion that could arise in more than one area. Therefore, throughout this volume we utilize the simpler and more widely used classification of the mediastinum into four compartments: superior, anterior, middle, and posterior.

Anatomic compartments

The *superior mediastinum* extends above a line drawn from the manubrium of the sternum through the lower edge of the fourth thoracic vertebral body (Fig. 1.3) [5,12]. The *anterior mediastinum* lies below the superior compartment, between the sternum and the pericardium. The *posterior mediastinum* extends behind a coronal plane through the posterior aspect of the pericardium. The *middle compartment* lies between the anterior and posterior divisions of the mediastinum.

The superior mediastinum contains the phrenic nerves and the superficial and deep cardiac plexuses (Fig. 1.1). In addition, the superior and middle mediastina contain a large number of structures that can be explored with the mediastinoscope and are usually classified according to their relationship to the trachea, as the mediastinoscopist follows its pathway in order to explore the paratracheal areas [8,9,13–16]. They include (a) the soft tissues anterior to the trachea, thyroid isthmus and blood vessels (superior vena cava, pulmonary artery, aortic arch, anterior communicating jugular vein, thyroid veins, and thyroidea ima artery and vein); (b) to the right of the trachea, blood vessels (right carotid artery, right subclavian artery, azygous vein, pulmonary artery, and superior division of the right pulmonary artery), nerves (right recurrent laryngeal nerve, vagus nerve), and bronchi (right main bronchus and right upper lobe bronchus); (c) to the left of the trachea, blood vessels (thoracic duct, aortic arch, bronchial artery, pulmonary arteries), left recurrent laryngeal nerve, esophagus, and left main bronchus; and (d) inferior to the trachea, carinal lymph nodes, esophagus, and tracheal bifurcation.

The middle mediastinum strictly should include only the pericardium and its contents. For convenience, however, most anatomy textbooks describe the hila of the lungs in this compartment and include in the middle mediastinum important bronchopulmonary lymph nodes classified by Nagaishi as follows: bronchopulmonary, pulmonary ligament, Botallo's ligament, tracheal bifurcation, tracheobronchial, paratracheal, pretracheal, aortic arch, and innominate vein angle nodes [1–3].

The anterior mediastinum merges at its upper end with the superior compartment and reaches inferiorly to the diaphragm. It contains the thymus gland, blood vessels (e.g., the internal mammary artery and vein), lymph nodes (internal mammary and diaphragmatic lymph nodes), connective tissue, and fat. Occasionally it can contain thyroid and parathyroid tissue.

The posterior mediastinum is the space located behind the pericardium and above the diaphragm. It merges directly with the superior mediastinum and includes important structures such as the descending portion of the thoracic aorta, esophagus, veins of the azygous system (azygous and superior and inferior hemiazygous veins), thoracic duct, lymph nodes (preaortic, paraaortic, posterior intercostal, middle diaphragmatic, and descending intercostal nodes), and ganglia and nerves of the thoracic sympathetic trunk.

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Chapter 2

Imaging of the mediastinum

Xiaoqin Wang, MD, and Ajay Singh, MD

Introduction

Chest radiography is widely used as the initial imaging study in patients with suspected thoracic disease. Mediastinal abnormality is often manifested as unexpected findings on plain radiography performed for unrelated indications. Computed tomography (CT) is the imaging modality of choice for further characterization of suspected mediastinal masses because it can define the anatomy and characterize the tissues. CT is also a popular imaging modality for the evaluation of the mediastinum because of its wide availability and rapid image acquisition ability. Magnetic resonance imaging (MRI) can allow further soft tissue characterization and functional studies. MRI is often used to evaluate soft tissue pathologies, cardiovascular function, and spinal abnormalities.

Although there is no physical boundary to separate the compartments, the mediastinum is often arbitrarily divided into compartments to develop a differential diagnosis. Disease processes can easily spread across contiguous compartments [1]. There are many ways of dividing the mediastinal compartments on images, which have been attempted by radiologists Felson, Zylak, and Heitzman [2–4]. Felson's approach divides the mediastinum into anterior, middle, and posterior compartments, based on two imaginary lines drawn on a lateral chest radiograph. The first line is drawn from the thoracic inlet to the diaphragm along the posterior heart border and anterior tracheal wall, dividing the anterior and middle mediastinum. The second line is drawn 1cm posterior to the anterior margin of the dorsal vertebrae, and separates the middle and posterior mediastinum (Fig. 2.1) [2].

Anterior mediastinal mass

The anterior mediastinum mainly contains the thymus gland, fatty tissues, anterior mediastinal lymph nodes, and pericardium. The differential diagnosis of the anterior mediastinal mass includes thymic, thyroid, lymphoid, and germ cell tumors.

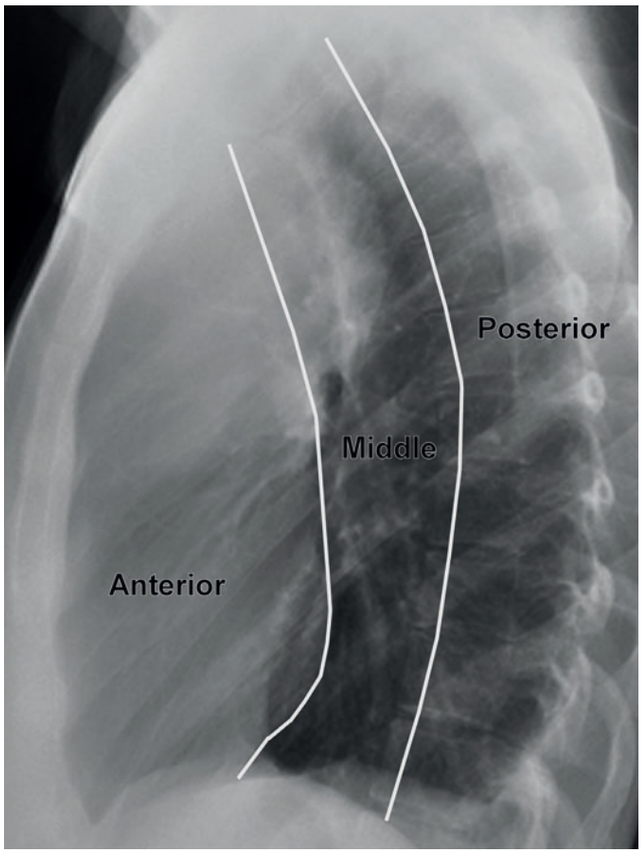

Fig. 2.1 Felson's division of the mediastinum.
The anterior line drawn posterior to the pericardium and anterior to the trachea divides the anterior from the middle mediastinum. The posterior line drawn 1 cm posterior to the anterior margin of the vertebral bodies separates the middle and posterior mediastinum.

Thymic abnormalities

Both composition and configuration of a normal thymus gland changes with age. The thymus is mainly composed of lymphocytes and epithelial cells at birth, but is replaced by fat by the age of 40 years [5]. The thymus appears largest in size in

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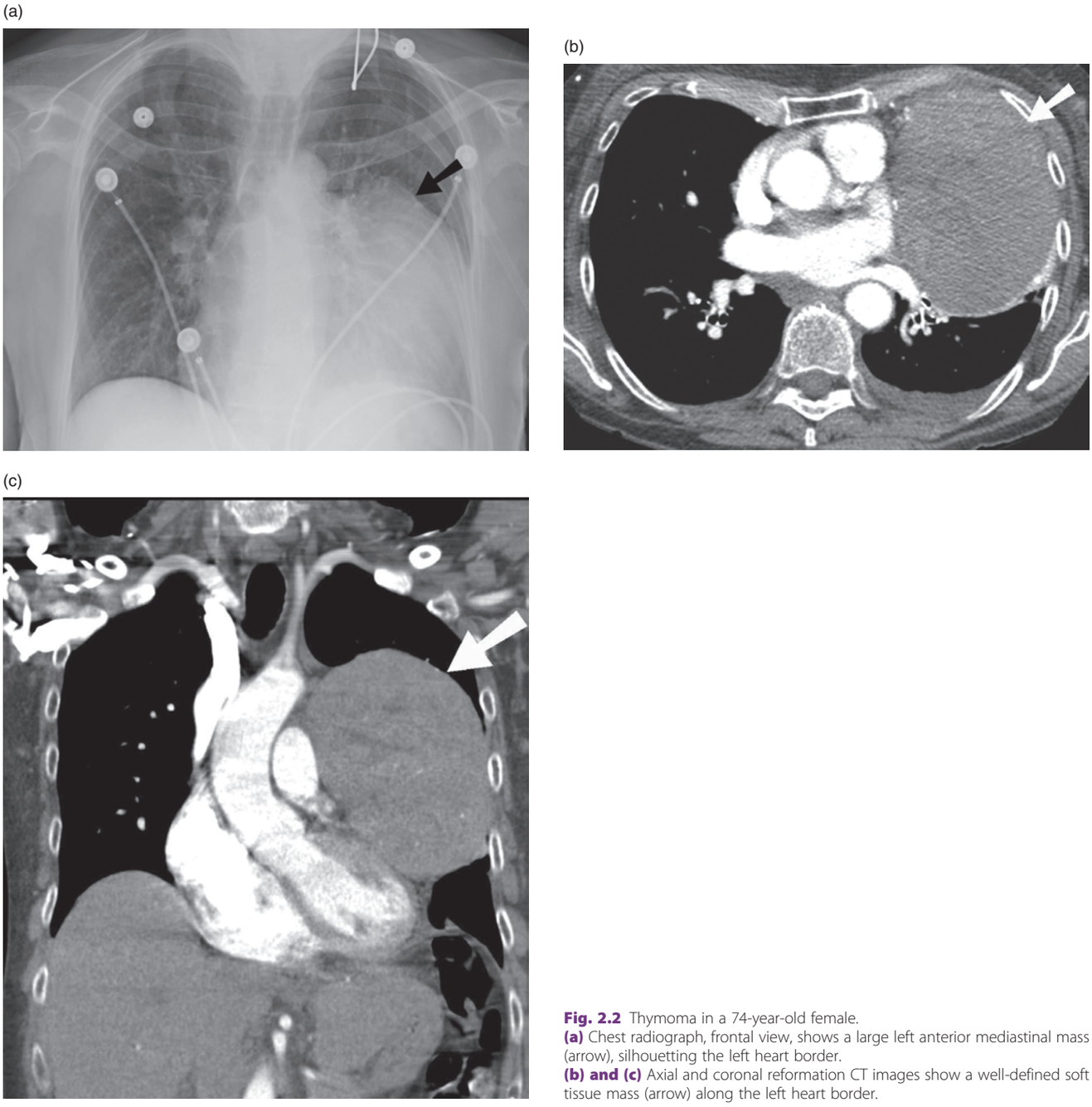


Fig. 2.2 Thymoma in a 74-year-old female.
(a) Chest radiograph, frontal view, shows a large left anterior mediastinal mass (arrow), silhouetting the left heart border.
(b) and (c) Axial and coronal reformation CT images show a well-defined soft tissue mass (arrow) along the left heart border.

proportion to the chest at birth, and starts to decrease in size after puberty, progressively undergoing fatty infiltration [6]. The thymus is not commonly visualized on CT in healthy adults.

A variety of pathologic conditions arise from cells of thymic origin, including thymoma, thymic carcinoma, thymolipoma, and thymic hyperplasia. Both thymoma and thymic carcinoma are tumors arising from the thymic epithelial cells and therefore located in the anterior mediastinum. Thymoma is a low-grade malignant thymic tumor which can be invasive or non-invasive. On CT scans a thymoma is seen as a homogeneous enhancing lobulated soft-tissue mass in the anterior mediastinum (Fig. 2.2). There is frequent association between thymoma and myasthenia gravis [7].

Thymic carcinoma is a malignant thymic tumor, which is almost indistinguishable in CT appearance from thymoma. It can invade the mediastinal fat and adjacent structures or pleura (Fig. 2.3). The relatively new World Health Organization classification scheme for thymic epithelial tumors

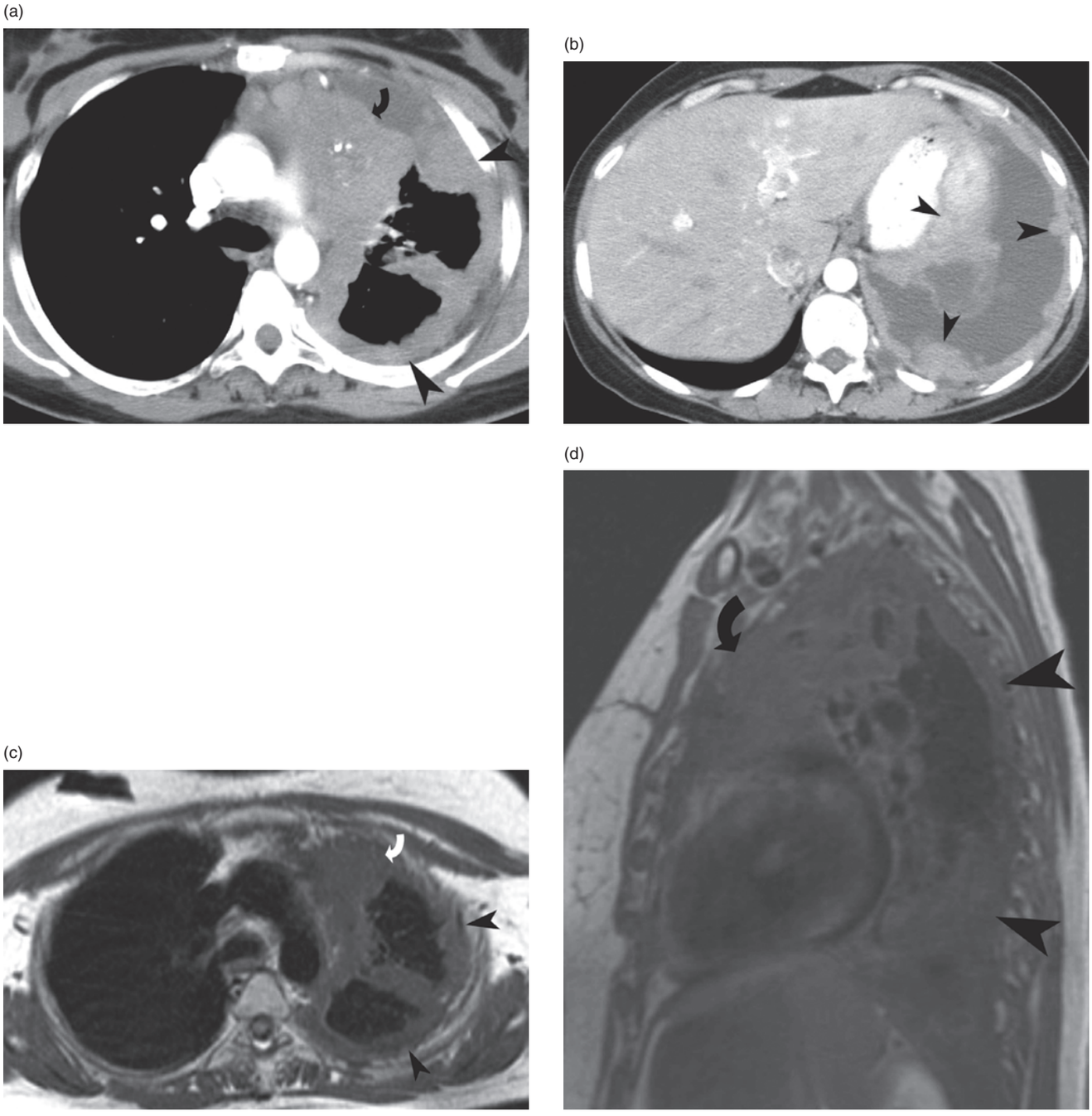


Fig. 2.3 Thymoma with pleural extension in a 36-year-old female.
Contrast-enhanced CT **(a–b)** and T1-weighted MR **(c–d)** shows a soft tissue mass (curved arrows) with calcifications in the anterior mediastinal, extending lateral to the aortic arch and aortopulmonary window. There is direct extension in to the pleural, indicated by nodular enhancing pleural thickening (arrowheads).

correlates with the invasiveness and clinical behavior of the tumors [8]. Although this classification is based on histology, familiarity with the correlation between this classification and CT findings will help the radiologist with the diagnosis.

Thymic hyperplasia is the abnormal diffuse enlargement of thymus due to either true thymic hyperplasia or lymphoid hyperplasia. Lymphoid hyperplasia is caused by chronic inflammation and proliferation of lymphoid follicles [9]. Lymphoid hyperplasia can be seen in patients with autoimmune diseases or endocrine diseases such as systemic lupus erythematosus, Addison's disease, and myasthenia gravis. Mendelson *et al.* reported that lymphoid hyperplasia is seen in up to two

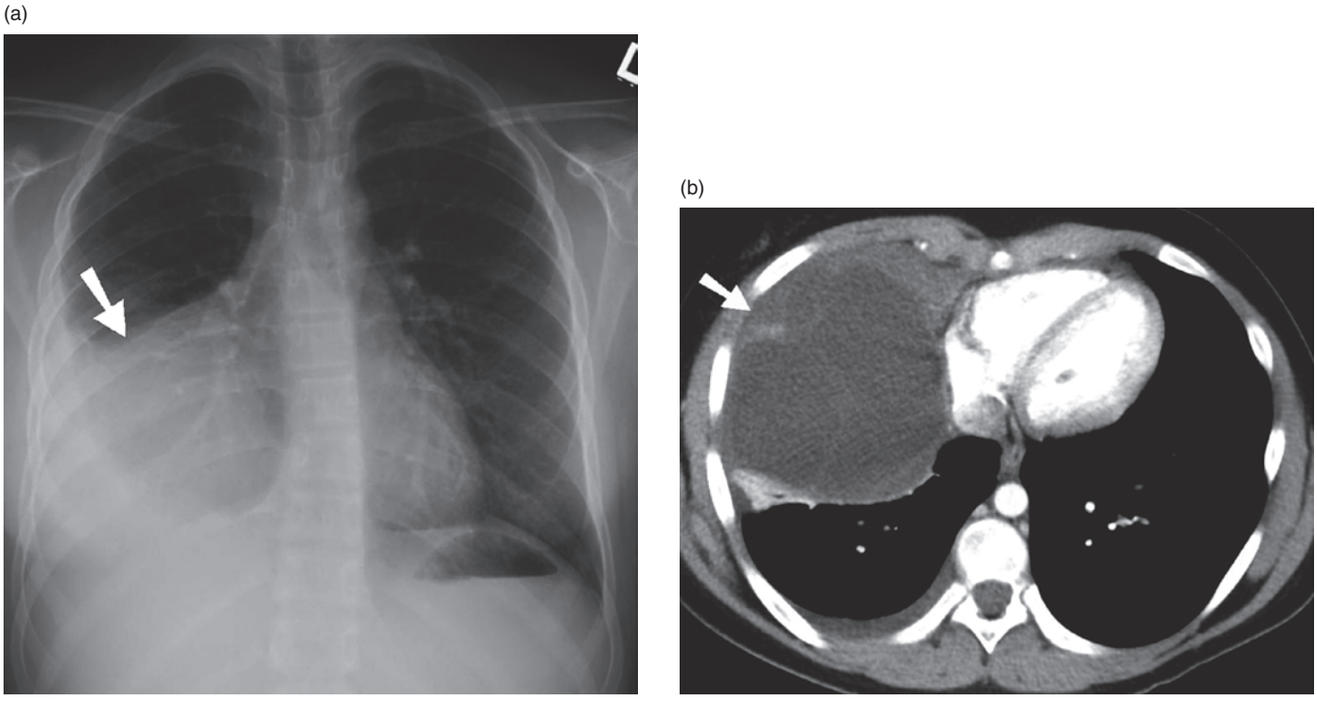


Fig. 2.4 Mature cystic teratoma in an 11-year-old female.
(a) Chest radiograph shows a large right anterior medistinal mass (arrow), silhouetting the right heart border with right pleural effusion.
(b) Contrast-enhanced CT demonstrates a septated cystic mass (arrow) with soft tissue component along the right heart border.

thirds of patients with myasthenia gravis disease [10]. True thymic hyperplasia is often seen in young patients after resolution of severe illness, steroid treatment, chemotherapy, thyrotoxicosis, and Graves' disease [10]. It is not possible to distinguish between the two types solely on the basis of imaging findings. On imaging studies, both types of thymic hyperplasia show diffuse homogeneous thymic enlargement with normal thymic tissue and shape. Awareness of the imaging features of thymic hyperplasia can help the radiologist to distinguish them from thymic neoplasm, which presents with focal mass on CT or MRI.

Thymolipoma is a rare, slow-growing, benign thymic tumor composed of mature adipose tissue and thymic tissue. It often affects young adults asymptomatically. Thymolipoma is often seen incidentally on chest radiograph as mediastinal widening. CT and MR imaging shows a large fatty mass anterior to the heart, with fibrous septa. The recurrence after surgical resection is rare [11].

Germ cell tumor

Germ cell tumors account for a fifth of all mediastinal tumors, most commonly located in the anterior mediastinum [12]. In general, germ cell tumors most often occur in the gonads, with the thorax being a rare site. It often affects children and young adults without sex predilection. Although benign germ cell tumors affect male and female patients with equal frequency, malignant germ cell tumors have predilection for male patients. Based on the cell types, germ cell tumors are usually categorized into teratomas, seminomas and non-seminomatous germ cell tumors [13].

Mediastinal teratoma is the most common mediastinal germ cell neoplasm. It is a slow-growing benign tumor that often occurs in children and young adults (less than 40 years). It is most often asymptomatic and has no sex predilection. Radiographically, the teratoma appears as a loculated cystic or solid mass with variable wall thickness in the anterior mediastinum near or within the thymus (Fig. 2.4). It may contain fluid, soft tissue, calcium, or fat attenuation, which are features of mature hematoma. Mature teratoma often has excellent prognosis and recurrence after surgical resection is rare [13].

Mediastinal seminoma is the second most common mediastinal germ cell tumor and the most common malignant mediastinal germ cell tumor. It often affects young white males and may be associated with elevated β human chorionic gonadotropin (β-HCG). CT typically shows large bulky homogeneous soft tissue attenuation mass in the anterior mediastinum, which may locally invade adjacent structures or metastasize to the lungs. Seminoma is highly sensitive to both radiotherapy and Cisplatin-based chemotherapy, with good long-term survival rate [13].

Mediastinal non-seminomatous germ cell tumors are malignant and include yolk sack tumor, embryonal carcinoma, and choriocarcinoma, as well as mixed germ cell neoplasm.

These tumors typically affect young adult men and are usually symptomatic. They often secrete the tumor markers, such as lactate dehydrogenase, alpha fetoprotein, and β-HCG, which can be used for diagnosis or follow up. On CT, non-seminomatous malignant germ cell tumors are often seen as large irregular heterogeneous density soft tissue mass with necrosis, hemorrhage, cyst formation, and peripheral contrast enhancement. They may show local invasion, lymph nodal or hematogenous metastasis [14]. The non-seminomatous germ cell tumors have poor prognosis and can be treated with Cisplatin-based chemotherapy or surgery [13].

Thyroid abnormalities

Goiter accounts for the majority of mediastinal thyroid mass. It almost always presents as a unilateral anterior mediastinal mass with glandular or fibrous continuity with the thyroid gland [15]. An ectopic primary intrathoracic thyroid mass is extremely rare. It is often an incidental finding in a female patient. However, large mediastinal goiter may have mass effects upon the adjacent structures causing tracheal or esophageal deviation or compression [15]. On CT without intravenous iodinated contrast, thyroid mass is seen as a homogeneous, smoothly marginated, space-occupying lesion with high attenuation, due to the iodine content. It shows intense and prolonged contrast enhancement with intravenous contrast [16]. Goiter may contain cystic or calcific foci. Radionuclide scintigraphy is important in confirming the diagnosis. A CT scan of the neck is often obtained to define the extent of disease [15]. Please be aware that iodinated contrast can delay the radionuclide imaging.

Mediastinal lymphoma

Mediastinal lymphoma mainly arises from the lymph node or thymus with anterior and middle mediastinal predilection. Although both Hodgkin's and non-Hodgkin's lymphoma can cause mediastinal masses, Hodgkin's lymphoma more commonly involves the mediastinum than the non-Hodgkin's lymphoma [17]. The patients with lymphoma often have hilar adenopathy and splenomegaly.

The typical CT appearance for Hodgkin's lymphoma is multiple smooth rounded homogenous or heterogeneous soft tissue density mass in the anterior mediastinum (Fig. 2.5) [18]. It tends to spread contiguously along lymph node chains, commonly affecting the prevascular and paratracheal nodes. It can cause mass effect on the adjacent mediastinal structures. Pleural or pulmonary involvement is not very common [17]. Calcifications in Hodgkin's lymphoma are rare but may be seen after therapy.

Non-Hodgkin's lymphoma is a diverse group of disease with variable histology, clinical course, and radiographic appearance. Compared with Hodgkin's disease, non-Hodgkin's disease is more likely to spread to the extranodal sites and often skip the lymph node groups [19]. Isolated pulmonary, pleural, or pericardial diseases are sometimes seen with non-Hodgkin's lymphoma. Although thoracic CT is often used as the initial imaging modality to evaluate the lymphoma, it is not an ideal imaging tool in assessing treatment response because not all effectively treated lymphoma decrease in size. It has been reported that positron emission tomography with 2-[fluorine-18]fluoro-2-deoxy-D-glucose can detect tumor viability following treatment [20].

Middle mediastinal masses

The most common abnormalities of the middle mediastinum are lymphadenopathy, cystic lesions, esophageal disease, tracheal abnormalities, diaphragmatic hernia, and vascular abnormalities.

Lymphadenopathy

The common causes of enlarged mediastinal lymph nodes are lymphoma, leukemia, metastasis, infection, sarcoidosis, and Castleman's disease.

On CT, normal lymph nodes manifest as discrete elliptical soft tissue with central hilar fat. Morphology, calcification, and contrast enhancement are used to characterize the lymph node, but lymph node size is the most important measurement to assess the lymph node. Lymph nodes with short axis diameter greater than 10 mm are generally considered to be pathologically enlarged [21,22]. The size criteria for normal lymph nodes also depends on the location. Some lymph nodes, such as the subcarinal lymph node with short axis measurement of up to 15 mm, can be normal. Internal mammary nodes, paracardiac nodes, and paravertebral nodes are not often visible on CT in a healthy subject [23].

Calcified lymph nodes are most often due to prior granulomatous disease, including histoplasmosis, tuberculosis, and sarcoidosis. Less commonly they may also be seen in silicosis, coal workers' pneumoconiosis, mucinous adenocarcinoma, treated lymphoma, or metastatic osteosarcoma.

Low attenuation in lymph nodes often reflects necrosis and can be seen in active tuberculosis, fungal infections, lymphoma, and neoplasm. Marked enhancement of an enlarged lymph node can indicate Castleman's disease, papillary thyroid disease, or hypervascular metastasis [24,25].

Other than the characteristics of the lymph node, the differential considerations in radiology are also based on the patient's clinical presentation, age, and immune status. For example, in a young African American female adult without symptoms, the presence of symmetric bilateral hilar and mediastinal lymphadenopathy favors the diagnosis of sarcoidosis. In a patient with pulmonary infection, the hilar and mediastinal masses are likely reactive lymphadenopathy. Enlarged mediastinal lymph nodes in a patient with a known history of cancer will be concerning for metastasis. Leukemia and chronic lymphocytic lymphoma patients often present with middle mediastinal and hilar lymphadenopathy.

Metastatic cancers, especially from the lung, head, neck, breast, and upper gastrointestinal tract are the major causes of

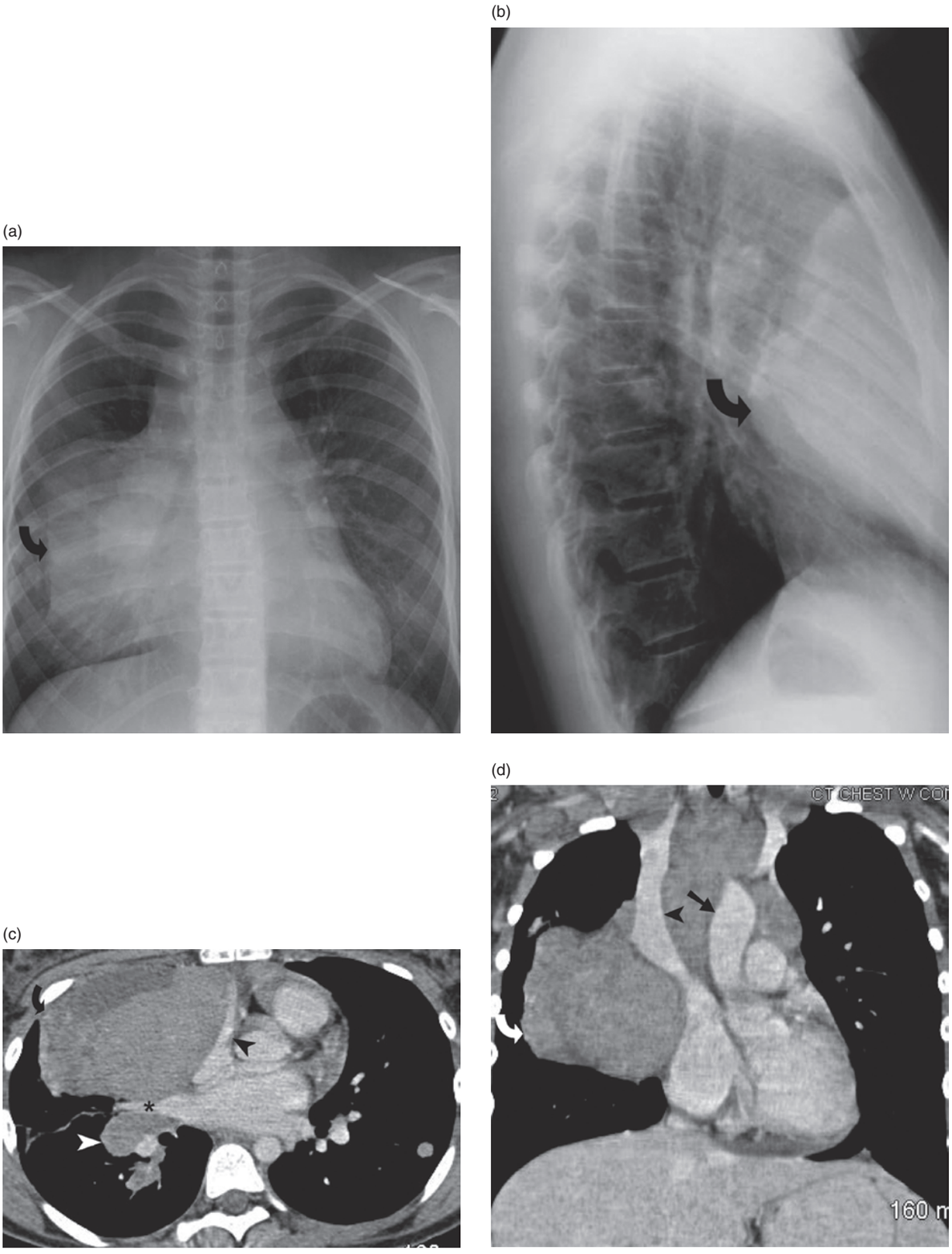


Fig. 2.5 Hodgkin's lymphoma
(a) and (b) Chest radiograph, frontal and lateral views, show a large anterior mediastinal mass (curved arrow) with right-sided extension anterior to the right lung. The bilobed density projecting through the center of the mass represents the right hilar lymphadenopathy.
(c) and (d) Axial CT image and coronal reformat shows a large heterogeneous mass (curved arrow) in the anterior mediastinal compressing the superior vena cava (black arrowhead), right pulmonary vein (asterisk), and main pulmonary artery (straight arrow). There is right hilar lymphadenopathy (white arrowhead).

mediastinal lymphadenopathy [12,26]. The revised Response Evaluation Criteria in Solid Tumor (RECIST), version 1.1 provides standards about how to measure and assess lymph nodes. Lymph nodes with a short axis of more than 15 mm are considered measurable and assessable as target lesions whereas lymph nodes with a short axis more than 10 mm but less than 15 mm are considered as non-target but assessable lesions [22].

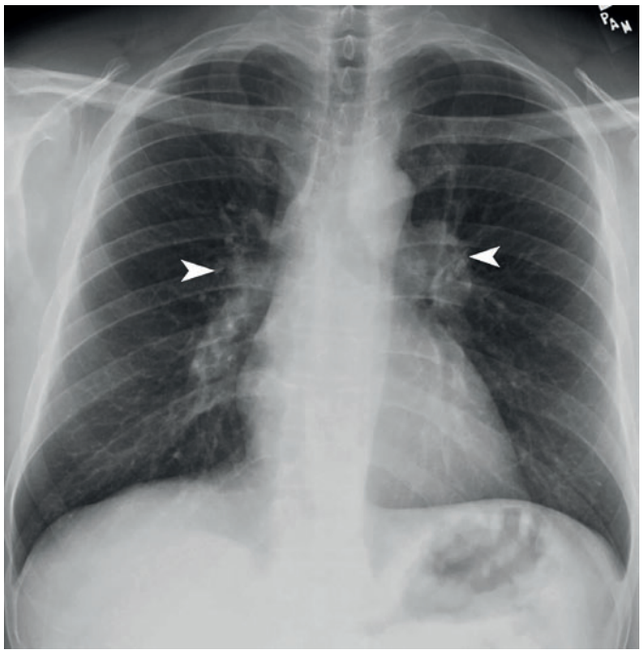


Fig. 2.6 Sarcoidosis in a 45-year-old male.
Chest radiograph, frontal view, shows bilateral hilar masses (arrowheads) proven to be sarcoidosis.

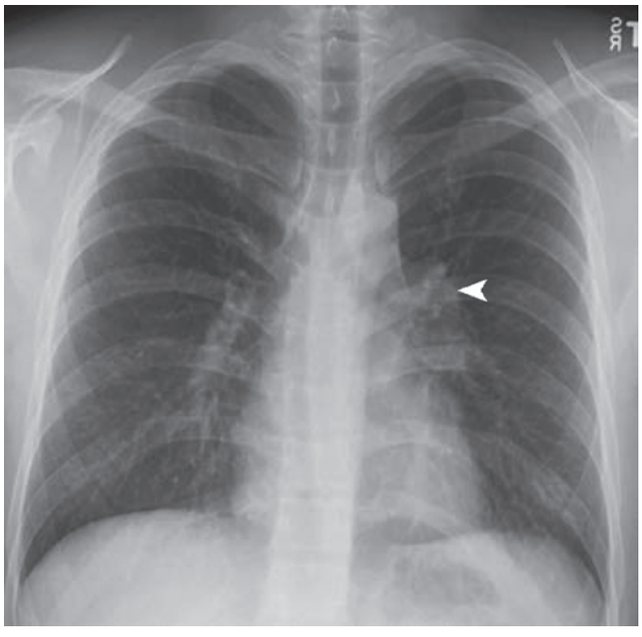
Sarcoidosis is a systemic non-caseating granulomatous disease of unknown cause that affects almost any organ in the body. It has predilection for young African American females. The most common CT findings are bilaterally symmetric hilar lymphadenopathy and pulmonary infiltrates in characteristic perivascular distribution (Fig. 2.6) [27]. Mediastinal adenopathy without hilar involvement is rare [28].

Acute or chronic infection including viral, bacterial, or fungal infection is another important cause of middle mediastinal lymphadenopathy. There is often associated cough, fever, chills, or elevated white blood count. In patients with tuberculosis, enlarged lymph nodes often show rim enhancement and central necrosis (Fig. 2.7). In patients with chronic fungal or tuberculous infections, the lymph nodes are often calcified [29].

Histoplasma capsulatum is a well-recognized cause of mediastinal and hilar disease, particularly in the endemic central United States. It has a broad spectrum of imaging findings, ranging from clinically insignificant adenopathy to fibrosing mediastinitis. The adenopathy caused by histoplasma often calcifies during the healing phase of the disease (Fig. 2.7) [30].

Castleman's disease, also known as angiofollicular lymph node hyperplasia, is a lymphoproliferative disorder of unknown etiology [31]. It can present as a benign localized form with single mediastinal mass, or a progressive diffuse form with generalized lymphadenopathy. Due to its highly vascular nature, Castleman's disease is typically manifested as

(a)



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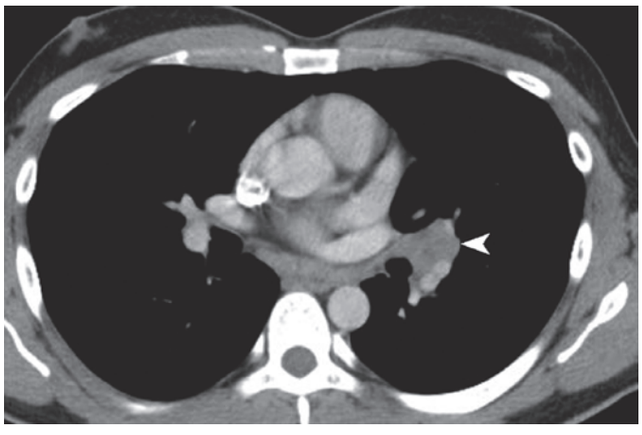

Fig. 2.7 Lymphadenopathy in a patient with tuberculosis.
(a) Chest radiograph, frontal and lateral views, show left hilar mass (arrowheads) proven to be lymphadenopathy.
(b) Axial contrast-enhanced CT confirms the left hilar lymphadenopathy (arrowhead).