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The Mediastinal Mass

A Multidisciplinary Approach

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Antonio Giordano
Editors

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Preface

The mediastinum, the anatomic district located between the lungs, can host a wide variety of neoplastic and non-neoplastic masses. The mediastinal masses can originate from structures of the mediastinum itself, from developmental tissues, or from metastases of malignant extra-mediastinal tumors. Thus, considering the wide spectrum of pathological entities that can affect this area, a correct diagnostic and therapeutic approach requires the intervention of different specialists.

This book focuses on the main approaches for mediastinal mass diagnosis and treatment, whose different aspects have been thoroughly treated by a multidisciplinary team of experts from different clinical fields.

The book includes a brief introductory section describing the anatomic sites of mediastinal masses and the epidemiological evidence for each different clinical-pathological entity.

The first part of the book describes general approaches for managing mediastinal masses from the point of view of the oncologist, the radiologist, the surgeon, and the pathologist and provides specific recommendations.

The second part of the book focuses on the most common pathological entities of the mediastinum, underlining the diagnostic difficulties. In particular, specific chapters are dedicated to thymic tumors, lymphomas, thyroid and parathyroid masses, and germ cell tumors of the anterior mediastinum. Finally, masses of the middle and posterior mediastinum are grouped and discussed in the final two chapters.

In summary, this book aims to provide an updated overview of the management of mediastinal masses through a multidisciplinary approach. Hopefully, it will be a useful tool for clinicians, surgeons, radiologists, and pathologists, dealing with this very heterogeneous group of diseases.

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Part I
Mediastinum Masses

Chapter 1
Introduction (Epidemiology, Mediastinal Anatomy, Mediastinal Masses)

Gerardo Botti and Federica Zito Marino

Introduction

Mediastinal masses include a wide variety of tumors occurring in patients of all ages. Tumors of the mediastinum are relatively uncommon and often have overlapping histologic features, therefore representing an interesting diagnostic and therapeutic challenge. The clinical presentation of mediastinal masses can range from being asymptomatic to symptoms due to compression or direct invasion of surrounding structures. The main symptoms associated with the mediastinal tumors include cough, chest pain, and dyspnea.

Mediastinal masses represent a broad and heterogeneous histological group including neoplastic or benign, congenital or acquired, and primary or secondary lesions. Primary tumors most frequently arise from thymic, neurogenic, lymphatic, germinal, and mesenchymal tissue. Secondary mediastinal tumors are more frequent than primary, and they generally represent metastasis from primary tumors such as lung, pancreatic, gastroesophageal, and testicular cancer. The location of mediastinal tumors is critical in the differential diagnosis, since specific lesions are commonly associated to mediastinal topography [1].

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Mediastinal tumors encompass a wide range of several neoplasms including thymomas, neurogenic tumors, lymphomas, germ cell neoplasms, endocrine tumors, mesenchymal tumor, and mediastinal cysts.

The broad variety of different entities demonstrates a heterogeneous spectrum of clinical and pathologic features, suggesting that a uniform "standard" management of these patients is not appropriate. The handle of these tumors requires a multidisciplinary approach due to the complex anatomy of the mediastinum as well as the different clinical, radiographic, and prognostic features. This book will provide an overview of the anatomy of the mediastinum as well as the different clinical, radiographic, and prognostic features and therapeutic options of the most commonly encountered masses.

Mediastinal Anatomy

The mediastinum is an anatomic space in the thoracic cavity bounded by the pleural cavities laterally, by the thoracic inlet superiorly, by the diaphragm inferiorly, by the sternum anteriorly, and by the chest wall posteriorly [2].

Historically, several different anatomic classifications of the mediastinum based upon anatomic boundaries have been proposed; to date the most used is Fraser's scheme that subdivides into anterior, middle, and posterior compartments [2].

The anterior mediastinal compartment is bounded between the sternum and the pericardium and contains the thymus, the internal mammary vessels, the inferior sternopericardial ligament, and variable amount of fat [3].

The middle mediastinal compartment lies between the anterior and posterior compartments and includes the heart and pericardium, the ascending aorta and the aortic arch, the superior and inferior vena cava, the phrenic and the vagus nerves, and the pulmonary arteries and veins [3].

The posterior mediastinal compartment is bounded anteriorly by the pericardium and the diaphragm, posteriorly by the thoracic vertebrae, and laterally by the mediastinal pleura. It includes the esophagus, the descending thoracic aorta, the thoracic duct, the azygos venous system, the autonomic nerves, the lymph nodes, and fat [3].

The location of the masses according to different mediastinal compartment represents crucial parameters in the differential diagnosis since each tumor type has a predilection for a specific compartment.

Mediastinal Masses

Mediastinal tumors represent approximately 3% of all lesions that occur within the chest [4]. The incidence of primary mediastinal tumors are widely variable, in order of decreasing frequency neurogenic tumors (25.3%), thymomas (23.3%), followed

by lymphomas (15.3%), germ cell neoplasms (12.2%), endocrine tumors (7.8%), and mesenchymal tumor (7.3%) [5].

Mediastinal tumors occur at any age; however they are most frequent in young and middle-aged adults. The frequency of primary mediastinal tumors varies with the site as well as the age; particularly in adults the most frequent are thymomas, thymic cysts, neurogenic tumors, and lymphomas, followed by germ cell tumors, enterogenous cysts, and pleuropericardial cysts. In children, the neurogenic tumors account for approximately 47% of primary mediastinal tumors; the remaining of resected masses include thymic tumors, germ cell tumors, lymphomas, enterogenous cysts, angiomas, stem cell tumors, and pleuropericardial cysts [6].

The mass location represents a critical issue in the differential diagnosis, since generally each variety of mediastinal tumor is associated with a specific compartment of recurrence (Fig. 1.1).

Masses in the anterior mediastinum are commonly thymomas, lymphomas, pheochromocytomas, germ cell tumors, and parathyroid lesions. Thymic tumors represent the most frequent primary tumors of the anterior mediastinum, accounting 30–50% of all lesions in this compartment [7]. Germ cell tumors account for 15% of anterior mediastinal masses in adult and 24% in children; these compartment represents the most common extragonadal primary site of occurrence of germ cell tumors [7].

Although parathyroid adenomas are infrequently ectopic, the mediastinum is the most frequent anatomical site at which these masses may develop, particularly 80% of cases occurring in the anterior compartment [7, 8].

Lymphoma represents one of the most common tumors in mediastinum approximately 10–15% of all masses, occurring generally both in anterior and in middle compartments. Lymphomas with mediastinal involvement account for 50–70% Hodgkin's disease and 15–25% non-Hodgkin's [9].

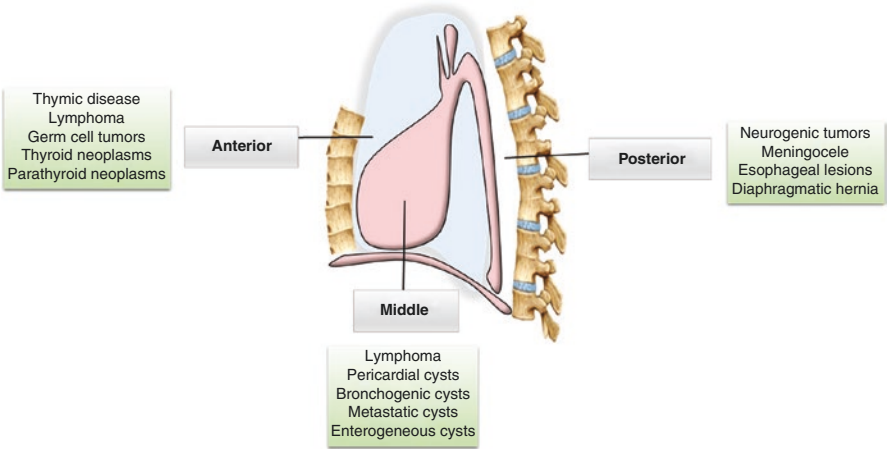

Fig. 1.1 Mediastinal tumors associated to anatomic site of the mediastinum.

Tumors of the middle mediastinum comprise predominantly mediastinal cysts, granulomatous disease, and tracheal tumors. Mediastinal cysts comprise 12–20% of all masses, including enterogenous, bronchogenic, pericardial, and metastatic cysts [8].

Masses in the posterior mediastinum are generally neurogenic tumors, esophageal tumors, and neurenteric cyst. Neurogenic tumors represent 95% of posterior mediastinal tumors; they are classified according to cell type [10].

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Chapter 2
Clinical Approach: Recommendations for the Clinicians

Fortunato Ciardiello, Floriana Morgillo, and Giuseppe Viscardi

Introduction

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

Anatomic Distribution

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

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

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Table 2.1 Differential diagnosis of mediastinal mass by compartment

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

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

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

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

Clinical Presentation

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

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

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

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

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

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

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

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

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

Presumptive Clinical Diagnosis

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

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

Table 2.3 Diagnostic approach to mediastinal masses

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

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

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

Tissue Diagnosis

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

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

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

Differential Diagnosis

Middle Mediastinal Mass

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

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

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

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

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

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

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

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

Anterior Mediastinal Mass

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

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

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

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

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

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

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

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

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

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

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

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

Posterior Mediastinal Mass

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

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

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

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

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Chapter 3
Mediastinal Masses: Radiological Point of View

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Introduction

Mediastinal masses are relatively uncommon [1]. Because such a wide variety of other pathologic entities can occur in this region, radiologists and clinicians will encounter many of these specific lesions only infrequently. Imaging is a critical part of establishing a presumptive diagnosis, which is used to guide whether and what type of confirmatory testing is needed. When classic features are present, a presumptive diagnosis can be made with a high degree of confidence based on imaging alone. Developing an appropriate differential diagnosis for a particular patient can be very useful in avoiding unnecessary and sometimes misleading biopsies or additional tests. The mediastinum contains vital vascular and nonvascular structures and organs [2, 3]. In many instances, localization and characterization of a mediastinal abnormality using multidetector CT are enough to make a diagnosis. In other cases, correlation between imaging findings and clinical context, as well as additional

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imaging examinations (such as MR imaging and fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT and histologic sampling through image guided or surgical biopsy), is necessary to make a definitive diagnosis and guide further management. Employing the existing nomenclature of the mediastinal compartments, slightly more than half of all mediastinal masses are located in the anterior compartment, whereas one fourth are identified in the middle and posterior mediastinal compartments. Division of the mediastinum into specific compartments has traditionally been valuable in the identification, characterization, and management of various mediastinal abnormalities [4].

The existing schemes used in radiologic practice represent arbitrary non-anatomic divisions of the chest, primarily based on the lateral chest radiograph. Division of the mediastinum into specific compartments is favorable for a number of reasons, including the generation of a focused differential diagnosis, assistance in planning for biopsies and surgical procedures, and the facilitation of communication between clinicians in a multidisciplinary setting. Several classification schemes for the mediastinum have been created and used. Most radiologic classifications have been based on arbitrary landmarks outlined on the lateral chest radiograph. A new scheme, based on cross-sectional imaging (principally multidetector computed tomography), has been developed by the International Thymic Malignancy Interest Group (ITMIG) and accepted as the new standard. This clinical division scheme defines unique prevascular, visceral, and paravertebral compartments based on boundaries delineated by specific anatomic structures at multidetector CT [4]. This new definition plays an important role in the identification and characterization of mediastinal abnormalities, which can often be diagnosed with confidence, based on their location and imaging features alone. In other cases, a diagnosis maybe suggested when radiologic features are combined with specific clinical information. This new definition plays an important role in the identification and characterization of mediastinal abnormalities, which, although uncommon and encompassing a wide variety of entities, can often be diagnosed with confidence based on location and imaging features alone. The three compartment cross-sectional imaging model developed by ITMIG includes prevascular (anterior), visceral (middle), and paravertebral (posterior) sections. Specific compartment boundaries and the anatomic structures contained can be readily identified at multidetector CT.

Radiological Anatomy

Prevascular Compartment

The following boundaries of the prevascular compartment are defined as (a) superiorly, the thoracic inlet; (b) inferiorly, the diaphragm; (c) anteriorly, the posterior border/cortex of the sternum; (d) laterally, the parietal mediastinal pleura; and (e) posteriorly, the anterior aspect of the pericardium as it wraps around the heart in a curvilinear shape. The major contents of the prevascular compartment include the thymus, fat, lymph nodes, and the left brachiocephalic vein [5–10]. Therefore, the

most common abnormalities encountered in the prevascular compartment include thymic lesions (cysts, hyperplasia, and malignancies such as thymomas, thymic carcinomas, and neuroendocrine neoplasms), germ cell neoplasms (which derive from germ cell rest remnants in the mediastinum), lymphomas, metastatic lymphadenopathies, and intrathoracic goiters.

Visceral Compartment

The following boundaries of the visceral compartment are defined: (a) superiorly, the thoracic inlet; (b) inferiorly, the diaphragm; (c) anteriorly, the posterior boundaries of the prevascular compartment; and (d) posteriorly, a vertical line connecting a point on the thoracic vertebral bodies 1 cm posterior to the anterior margin of the spine (referred to as the visceral paravertebral compartment boundary line). The major contents of the visceral compartment can be divided into two main categories: (a) vascular structures including the heart, superior vena cava, ascending thoracic aorta, aortic arch, descending thoracic aorta, intrapericardial pulmonary arteries, and thoracic duct and (b) nonvascular structures including the trachea, carina, esophagus, and lymph nodes. The most common abnormalities in the visceral compartment include lymphadenopathies (related to lymphomas or metastatic disease), duplication cysts, tracheal lesions, and esophageal neoplasms. Additionally, vascular lesions deriving from the heart, pericardium, and great vessels may also be present.

Paravertebral Compartment

The following boundaries of the paravertebral compartment are defined: (a) superiorly, the thoracic inlet; (b) inferiorly, the diaphragm; (c) anteriorly, the posterior boundaries of the visceral compartment; and (d) posterolaterally, a vertical line along the posterior margin of the chest wall at the lateral side of the transverse processes. The major contents of the paravertebral compartment include the thoracic spine and paravertebral soft tissues; therefore, most abnormalities in this region are neurogenic neoplasms that arise from the dorsal root ganglia/neurons adjacent to the intervertebral foramina [8–11]. Other potential lesions in this compartment may have infective (discitis/osteomyelitis) or traumatic (hematoma) origin or may be related to other underlying conditions (such as extramedullary hematopoiesis). Although localization of mediastinal lesions in a specific compartment is an important component of characterization, this may be difficult in some instances as in the case of large mediastinal lesions that may involve multiple compartments or extend from one compartment to another, making identification of the precise site of origin challenging, for example. Two tools have been described by ITMIG and are recommended to help identify the compartments of origin. One of these tools is known as the “center method” and states that the center of a mediastinal lesion (defined as the

center point of the lesion on the axial CT image that demonstrates the largest size of the abnormality) localizes the lesion to a specific mediastinal compartment [11, 12]. The JART study used this method, and the result was an accurate localization of all 445 mediastinal masses. The second tool is known as the "structure displacement tool" and is useful in scenarios in which very large mediastinal lesions displace organs from other mediastinal compartments, typically those that abut the compartment from which the lesion originated [12]. For instance, a very large prevascular mediastinal mass may displace organs of the visceral mediastinal compartment, such as the trachea, esophagus, or the heart posteriorly.

Role of Diagnostic Imaging

ITMIG uses multidetector CT as the gold standard modality for defining the mediastinal compartments. Specific imaging characteristics that should be noted at multidetector CT include (a) location, size, and configuration of mediastinal lesions; (b) descriptive features such as attenuation, heterogeneity, and enhancement; (c) presence of intralesional fat, cystic components, soft tissue, and calcification; and (d) any connection or invasion of adjacent structures. Some of these findings are more important than others; for instance, the presence of fat in a prevascular mediastinal lesion is highly suggestive of a smaller group of specific diseases, whereas punctate, coarse, or curvilinear calcifications are nonspecific and can't be used to discriminate benign from malignant prevascular mediastinal masses, because they may be associated with malignant neoplasms such as thymomas or treated lymphomas, as well as benign lesions such as mature teratomas [13, 14].

It is important to consider findings suggestive of a mediastinal abnormality at chest radiography, as it remains the most common imaging examination performed. Although small lesions may not be visible or may produce only subtle findings, large mediastinal abnormalities may manifest in a variety of ways, such as a soft-tissue masses, often accompanied by loss of the normal mediastinal contours or interfaces or thickening of specific lines or stripes. The lateral chest radiograph can be especially useful in detecting lesions that may not be visible on the posteroanterior radiograph, since mediastinal lesions may be only visible in the retrosternal space or when overlying the upper thoracic spine.

The "silhouette sign," which describes the loss of normal borders of intrathoracic structures, aids in the detection of mediastinal abnormalities. A lesion in the right aspect of the anterior mediastinum may obscure cardiovascular structures, such as the superior vena cava or right heart border. While a mass in the posterior mediastinum may result in the loss of the normal paraspinal stripes. The "hilum overlay" sign may help differentiate a mediastinal mass from cardiomegaly or enlarged pulmonary vessels.

The "cervicothoracic sign," described by Felson [8], is useful in localizing mediastinal abnormalities identified at radiography and making a focused differential diagnosis. In these cases, obscuration of the lateral borders of an upper mediastinal

mass as it extends above the clavicles into the neck implies that the lesion has both intrathoracic and cervical components. Although often misinterpreted as a manifestation of the cervicothoracic sign, an upper paravertebral (or posterior mediastinal) mass with visible edges above the clavicles is entirely located within the chest, but does not exhibit the cervicothoracic sign.

While MR imaging is not the first used exam for the evaluation of all mediastinal abnormalities, it is the most useful imaging modality to distinguish cystic from solid lesions (e.g., thymic cysts from solid neoplasms), discern cystic and/or necrotic components within solid masses, distinguish cystic neoplasms from benign cysts, and identify septa and/or soft tissue within cystic lesions. The role of fluorine-18-FDG PET/CT in the evaluation of many mediastinal abnormalities remains controversial. It has been observed that thymic epithelial neoplasms tend to demonstrate variable, often only low-grade FDG uptake, making the histologic differentiation between the various types of neoplasms unreliable. A significant factor limiting the ability of PET/CT to accurately characterize mediastinal lesions is the potential for false-positive and false-negative examinations. Some benign processes, such as thymic hyperplasia and inflammatory diseases (such as fibrosing mediastinitis), may demonstrate increased FDG uptake and mimic malignancy. In these cases, a combination of clinical history, focality of FDG uptake at PET/CT, and morphologic features at multidetector CT is necessary to determine whether the lesion is benign or malignant [15–19].

Masses of Prevascular Compartment

The true incidence of prevascular mediastinal masses is difficult to detect for multiple reasons: the most significant one is the use of different classification schemes [20]. Additionally, there is variability in the inclusion of nonneoplastic lesions such as thymic hyperplasia, thymic and pericardial cysts, and other neoplastic lesions such as lymphomas [20]. The most common neoplasms of the prevascular mediastinum include thymic epithelial neoplasms (thymomas, thymic carcinomas, and thymic neuroendocrine tumors) and lymphomas. Other neoplasms that may arise in the prevascular compartment include mature teratomas, nonteratomatous germ cell malignancies (such as seminomas), nonseminomatous germ cell neoplasms, and metastatic disease. Nonneoplastic lesions of the prevascular mediastinum include substernal extensions of thyroid goiters, thymic hyperplasia, cystic lesions such as thymic and pericardial cysts, and vascular lymphatic abnormalities [21–25].

Thyroid Goiter: A heterogeneous prevascular mediastinal mass that demonstrates continuity with the cervical thyroid gland, intrinsically hyperattenuates (HU 70–85 due to the presence of iodine), and shows a sustained and intense enhancement after administration of intravenous contrast material, can dependably be diagnosed as a mediastinal goiter. Cystic changes which manifest as internal foci of low attenuation and calcifications may also be present. In cases where a definitive connection with the cervical thyroid gland cannot be identified, the use of multidetector CT

should strongly suggest the diagnosis. When additional findings, such as the loss of mediastinal tissue planes or associated cervical or mediastinal lymphadenopathy, accompany a mediastinal goiter, then thyroid malignancy should be suspected, and further evaluation should be performed [26, 27] (Figs. 3.1 and 3.2).

Fat-containing Lesions: The presence of visible regions of intralesional fat (measuring between −40 and −120 HU at multidetector CT) within a heterogeneous prevascular mediastinal mass is highly suggestive of a mature teratoma. Patients may have symptoms related to local mass effect or be asymptomatic (Figs. 3.3 and 3.4). Moreover, associations between thymolipoma and myasthenia gravis have been reported. Graves' disease and hematologic disorders have also been reported [26, 27].

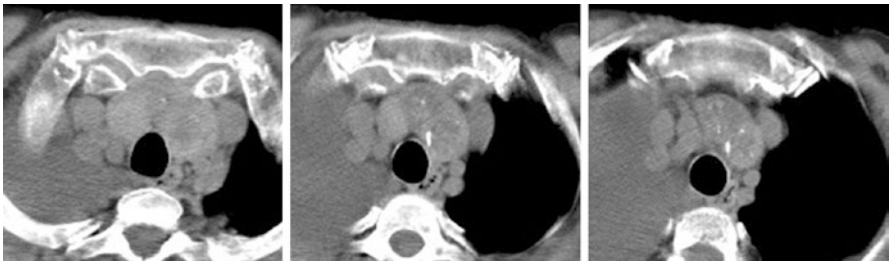

Fig. 3.1 Chest CT without contrast. Immersed thyroid goiter. Hypodense nodules with contextual calcifications

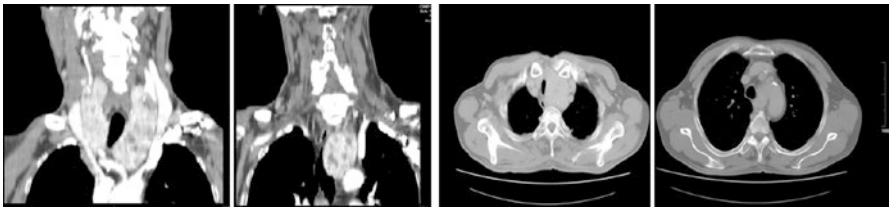

Fig. 3.2 Neck and chest CT with and without contrast: cervico-mediastinal goiter. It is observed inhomogeneous and enlarged thyroid gland that takes advantage in the mediastinum with lateral deviation of the trachea to the right which is partly compressed

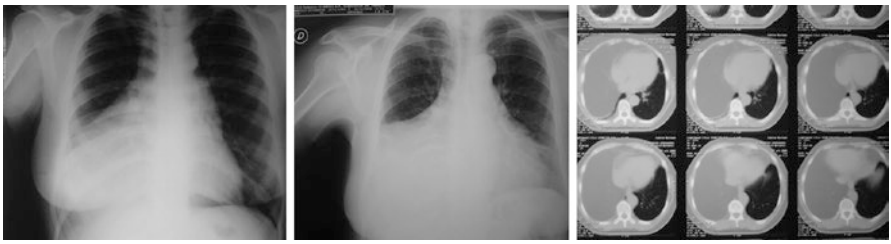

Fig. 3.3 Chest X-ray/chest CT without contrast: lipomatosis. In X-ray, presence of x-opacity in the right basal hemithorax with obliteration of the homolateral costophrenic sinus. At CT, non-ca

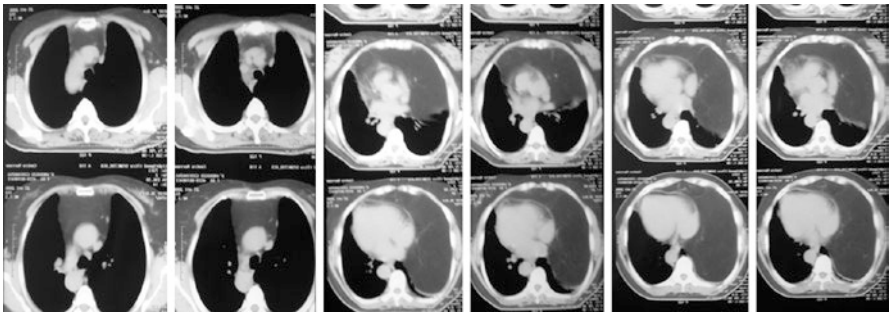

Fig. 3.4 Chest CT without contrast: lipomatosis. Increase of non-capsulated adipose tissue in the anterior mediastinum extending in left hemithorax and with contralateral dislocation of medial structures

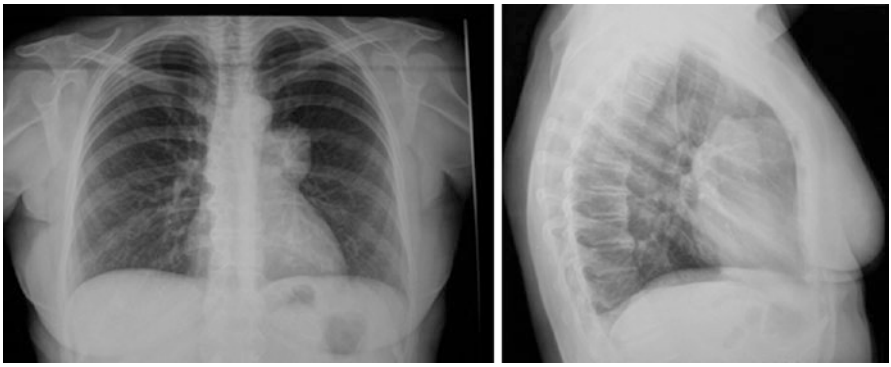

Fig. 3.5 Chest X-ray: thymic cyst. Radiopaque nodular formation is observed at the level of the II aortic arch

Cystic Lesions: Cystic lesions of the mediastinum are those that have water or fluid attenuation at multidetector CT, with Hounsfield unit values between 0 and 20. A well-circumscribed homogeneous lesion in the prevascular mediastinum, near the thymic bed that is rounded, oval, or saccular, likely represents a thymic cyst (Fig. 3.5). Most of these lesions are acquired and caused by inflammation; iatrogenic processes such as surgery, radiation therapy, or chemotherapy; or malignant neoplasms. Prevascular masses that are purely cystic with no soft-tissue components or internal septa can reliably be diagnosed as unilocular thymic cysts [28]. However, when cystic lesions contain internal soft-tissue components and/or internal septa, the differential diagnosis should include multilocular thymic cysts, cystic teratomas, lymphangiomas, and cystic thymomas.

Thymic Hyperplasia: Normal prevascular thymic tissue is seen in young individuals and decreases in prominence with advancing age, with complete fatty replacement, usually achieved by 40 years of age. Two distinct histologic types of thymic hyperplasia have been described: true and thymic lymphoid (follicular)

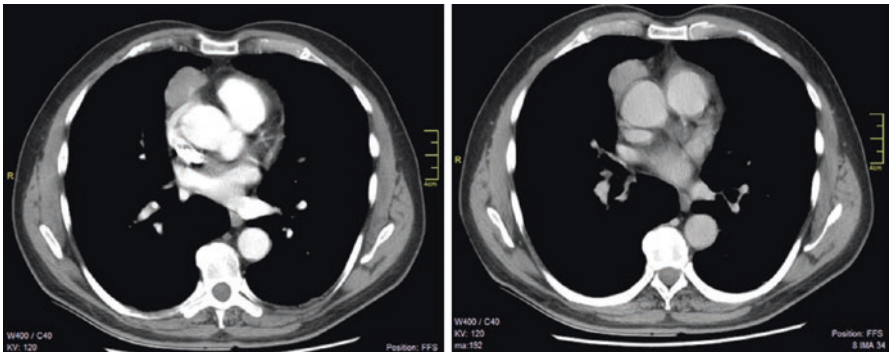

Fig. 3.6 Chest CT with contrast: infiltrating thymoma. Presence of hypodense tissue that seems to infiltrate the pericardium

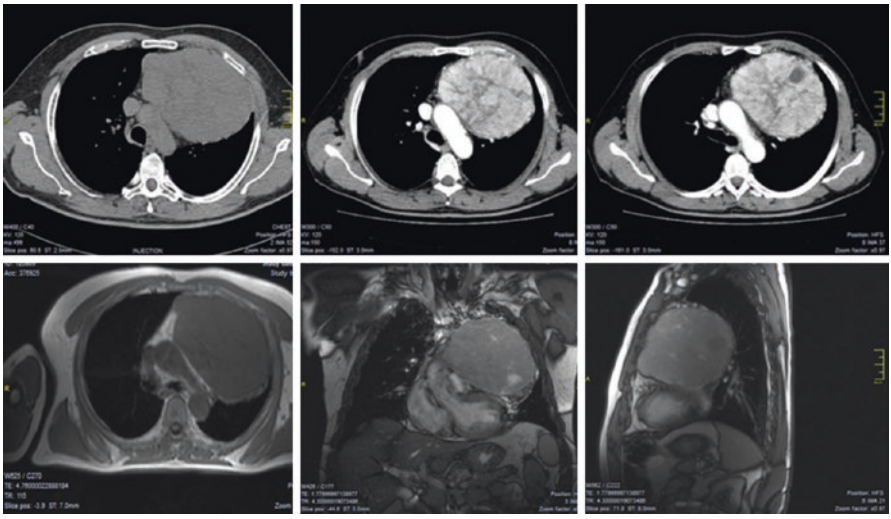

Fig. 3.7 Chest CT scan without and with mdc/chest MRI with T1w and T2w sequences: thymoma. Voluminous and inhomogeneous mass, occupying space: hypodense in sequences without contrast and it becomes hyperdense after contrast medium. At the MRI, it appears hypointense in both T1w and T2w sequences with some hyperintense spots in the T2w sequences to refer to probable colliquation phenomena

hyperplasia. True thymic hyperplasia is also known (Figs. 3.6 and 3.7) as "rebound hyperplasia" and is characterized by an increase in thymic volume that becomes greater than 50% over baseline after a causative stressor; approximately 10–25% of patients undergoing chemotherapy may develop rebound hyperplasia [29]. Thymic lymphoid (follicular) hyperplasia is a histologic diagnosis defined as the presence of an increased number of lymphoid follicles, which may be associated with an increase in the size of the gland and is typically associated with immunologic

diseases, such as myasthenia gravis, hyperthyroidism, collagen vascular diseases, or human immunodeficiency virus infection [10].

Lymphomas: A mildly enhancing lobular soft-tissue mass or group of enlarged lymph nodes in the prevascular mediastinum at multidetector CT, especially in the setting of lymphadenopathy in the neck, axilla, or elsewhere in the body, may represent a lymphoma (Figs. 3.8, 3.9, 3.10, and 3.11). Although it may be difficult to distinguish lymphomas from other soft-tissue mediastinal masses, the infiltrative nature of some types of lymphomas enables differentiation from thymic epithelial neoplasms and germ cell tumors.

Nonteratomatous Germ Cell Neoplasms: Nonteratomatous germ cell neoplasms include a wide variety of lesions, the most common of which include seminomatous and nonseminomatous germ cell tumors (NSGCTs). These lesions typically manifest as large soft-tissue masses in the prevascular mediastinum and can be difficult to distinguish from lymphomas.

Ectopic Parathyroid Adenomas: In patients with a clinical history of primary hyperparathyroidism, elevated serum calcium levels, and/or elevated serum

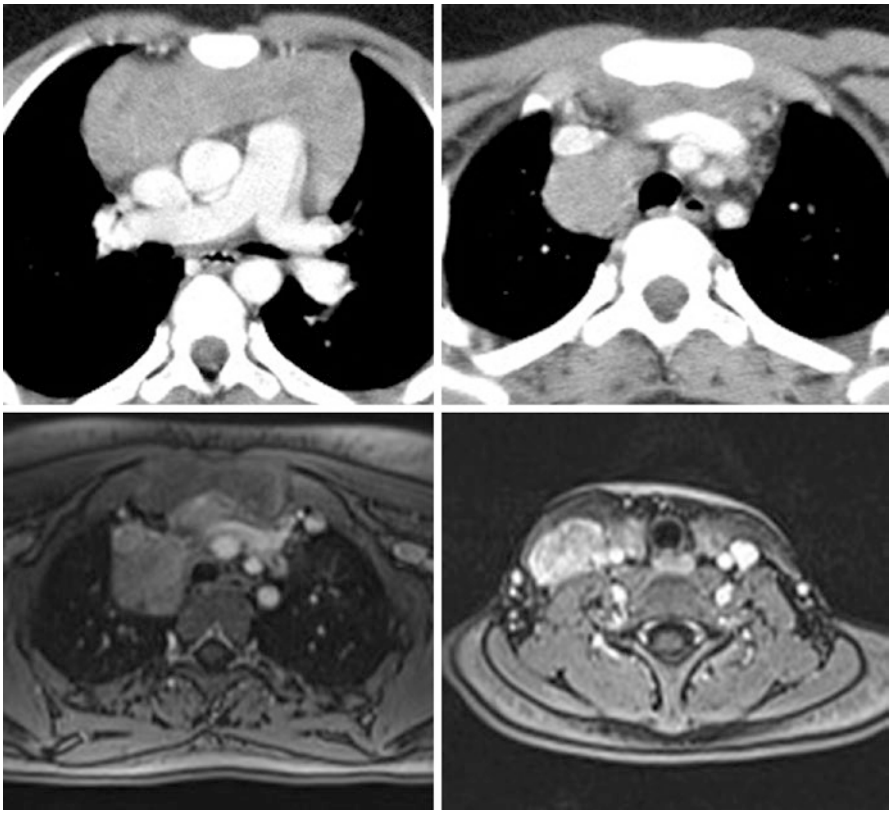

Fig. 3.8 Chest and neck CT/MRI with contrast. Recurrence of mediastinal lymphoma with involvement of the supraclavicular region

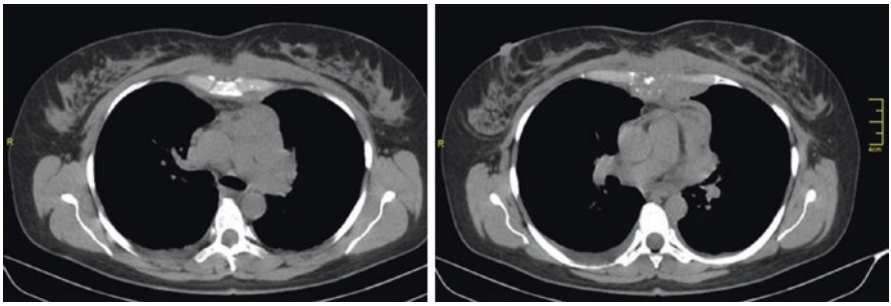

Fig. 3.9 Chest CT without contrast: Hodgkin's lymphoma infiltrating the breastbone

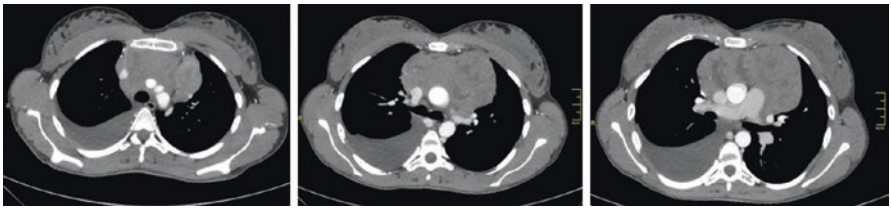

Fig. 3.10 Chest CT with contrast: non-Hodgkin lymphoma B cells of the thymus. There is an inhomogeneous, partly colliquated mass located in the anterior mediastinum. AR: right pleural effusion is observed

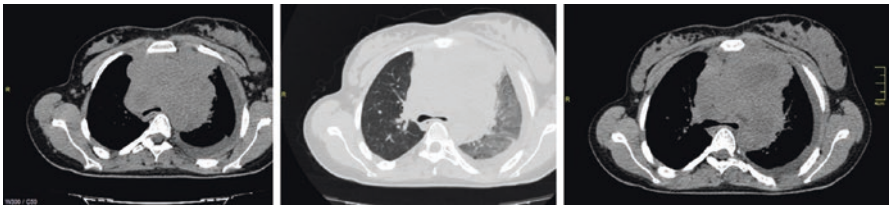

Fig. 3.11 Chest CT without contrast: non-Hodgkin lymphoma B-cell. It is observed hypodense and inhomogeneous mass occupying the mediastinum

parathyroid hormone levels, a soft-tissue nodule in the prevascular mediastinum at multidetector CT should be suspected as ectopic parathyroid adenoma. Although most parathyroid adenomas are juxtathyroid in location, they may occur in an ectopic location, with the mediastinum being the most common such site [30]. Many different imaging modalities can assist in the diagnosis of these lesions, including high-resolution ultrasonography (US) with color Doppler, technetium-99m (99mTc) sestamibi single photon emission CT (SPECT), multidetector CT, and MR imaging.

Morgagni Hernias: The major entity in the differential diagnosis of a thymolipoma is a Morgagni hernia. These hernias contain omental fat that has herniated from the abdomen into the thorax via the foramen of Morgagni [31]; the fat locates in a retrosternal or parasternal location, usually on the right side. Occasionally,

Morgagni hernias can also contain small or large bowel or portions of the liver. On CT, a Morgagni hernia appears as a fat-containing mass in the lower, anterior mediastinum that is usually large in size.

Masses of Visceral Compartment

The most common abnormalities in the visceral compartment include lymphadenopathy (related to lymphoma or metastatic disease), duplication cysts, tracheal lesions, and esophageal neoplasms. Additionally, vascular lesions arising from the heart, pericardium, and great vessels may also be present.

Cystic Lesions: A well-circumscribed, homogeneous, fluid attenuation lesion measuring 0–20 HU at multidetector CT in the visceral mediastinal compartment is compatible with benign duplication cysts, the most common of which include bronchogenic and esophageal duplication cysts. At multidetector CT, bronchogenic cysts manifest as a single, smooth, round, or ovoid masses with internal low attenuation (Fig. 3.12). The wall has variable perceptibility and may enhance or demonstrate intrinsic calcifications. Esophageal duplication cysts are uncommon developmental anomalies that manifest as well-circumscribed, homogeneous, fluid attenuation lesions adjacent to the esophagus or associated with the esophageal wall at multidetector CT. On CXR, esophageal cysts appear as solitary, rounded, well-defined mediastinal lesions, similar to other foregut cysts [8]. On CT they appear as single homogeneous masses with regular and well-defined borders and low-to-high attenuation values, due to their fluid or proteinaceous content, respectively [25, 26]. They are located in the lower right part of the posterior mediastinum within the esophageal wall or closely adjacent to it [3]. A thick wall and calcification may help in distinguishing an esophageal duplication cyst from other foregut cysts [3, 25]. On MRI, esophageal duplication cysts have high signal intensity on T2-weighted images and are usually of low signal intensity on T1-weighted sequences [12]. Contrast administration is recommended on both CT and MRI, as the complete absence of enhancement within the cyst is characteristic of benignity [25]. 99mTechnetium-pertechnetate scans can help in the identification of esophageal cysts containing ectopic gastric mucosa, which are at higher risk of developing cyst rupture and hemorrhage [32, 33].

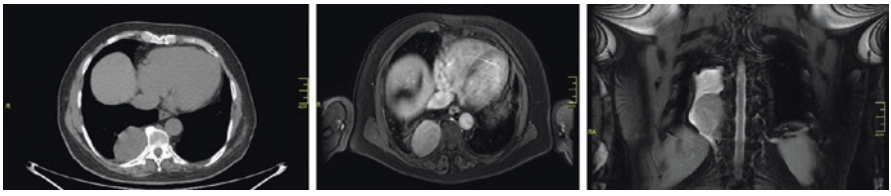

Fig. 3.12 Chest MRI T2w sequence/chest TC without contrast: neuroma type A. In CT hypodense nodular formation in right paravertebral site and hypointense in MRI

Esophageal Varices: These typically occur in the distal esophagus as a result of portal hypertension ("uphill varices") and bleed in a third of cases, representing a life-threatening complication in cirrhotic patients [34]. Less commonly they can be caused by superior vena cava obstruction ("downhill varices") and are usually located in the upper esophagus [35]. The reference standard for the diagnosis of esophageal varices is upper gastrointestinal endoscopy [36]. However, CT is a valuable tool for evaluating the cirrhotic liver and generally provides adequate coverage of the distal esophagus, where almost all varices develop.

Esophageal Neoplasms: These can be malignant (80%) or benign (20%). Malignant esophageal neoplasms are mainly squamous cell carcinomas and adenocarcinomas [37]. Once the histologic diagnosis is confirmed, CT of the chest and abdomen is recommended to assess local and distant spread of disease [37]. Oral and intravenous contrast material should be used to improve visualization of the esophageal lumen and mediastinal structures [38]. MRI does not substantially improve nodal staging, and its overall diagnostic performance does not exceed the abovementioned techniques [34, 39]. Malignant esophageal tumors usually produce intermediate signal intensity on T2-weighted images, unless they contain a high amount of extracellular mucin, which characteristically causes them to become hyperintense on these sequences.18F-FDG-PET scanning is recommended to improve the accuracy of staging of distant disease in patients who are potential candidates for curative therapy, whereas the value of 18F-FDG-PET as a predictive marker of response to neoadjuvant therapy remains uncertain [40].

Cardiac Masses: When a mass involving the heart or pericardium is identified at multidetector CT, a wide variety of malignant and benign lesions should be considered. One of the most important features is the location of the abnormality, as masses can be categorized as intracavitary, valvular, intramural, or epicardial/pericardial. Other significant features include composition (soft tissue, fat, calcium, and attenuation), behavior (well-defined or infiltrative), and enhancement characteristics after administration of intravenous contrast material.

Thoracic Aortic Aneurysms: An aortic aneurysm is defined as a permanent localized dilatation of the aorta, having at least a 50% increase in the expected normal diameter [41]. Rupture of a descending aortic aneurysm usually occurs in the mediastinum and the left pleural space, producing a periaortic soft-tissue hematoma, hemothorax, pleural or pericardial effusion, or even a contrast blush of active extravasation at the site of rupture [42]. Dissection is the most common aortic emergency and has a poor prognosis. It results from a tear in the intimal layer of aortic wall, allowing inflow of blood through the medial layer. This creates a "false lumen" that is separated from the "true lumen" by an intimal flap. According to the Stanford classification, dissections of the ascending aorta are categorized as type A and account for 62% of cases, whereas dissections of the descending aorta are categorized as type B and account for 38% of cases [43]. Type A dissections require urgent surgical repair, as they have a mortality rate over 50% within 48 h if untreated [44]. Conversely, type B dissections are generally managed conservatively, with follow-up examinations every 3–6 months [36]. Contrast-enhanced CT rapidly determines the type of dissection. It demonstrates the intimal flap in 70% of cases, the entry and

reentry points, signs of rupture, alterations of organ perfusion, dilation of the false lumen, and extension of the process into the aortic valve [43].

Masses of Paravertebral Compartment

As the paravertebral compartment includes the thoracic spine and paravertebral soft tissues, most lesions originating in this region are neoplasms of neurogenic origin. Other less common neoplastic conditions in this compartment include lymphomas, primary osseous tumors, and metastases. Nonneoplastic causes include thoracic spinal infections due to bacterial and mycobacterial agents, cystic lesions such as thoracic meningoceles and neurenteric cysts, and extramedullary hematopoiesis.

Neurogenic Tumors: Up to 95% of neurogenic tumors occur in the posterior mediastinum and are the most common posterior mediastinal masses [2, 3]. According to the cell of origin, neurogenic tumors are divided into three groups: nerve sheath tumors, sympathetic ganglion cell tumors, and paraganglionic cell tumors. Nerve sheath tumors are the most common type of neurogenic tumors in adults [45]. They include benign schwannomas and neurofibromas, as well as malignant peripheral nerve sheath tumors. Sympathetic ganglion tumors, the most common type in children [3, 4], have various histologic grades of aggressiveness. Ganglioneuromas are considered benign, despite their potential to metastasize. Ganglioneuroblastomas have intermediate aggressiveness, and neuroblastomas are the most aggressive form. Paraganglionic cell tumors in the posterior mediastinum are rare and arise along the sympathetic chain, in the so-called aortosympathetic paraganglia [46]. On CXR, the smoothly rounded or oval opacities caused by neurogenic tumors obliterate the paraspinal lines and can be associated with scalloping of the adjacent bones [5]. On CT, the sharply defined soft-tissue masses in the paravertebral area have a variable appearance, ranging from an iso- or hypoattenuating mass to heterogeneous lesions containing hemorrhage, necrosis, cystic degeneration, calcifications, and areas of patchy fat [45]. CT is superior to CXR in demonstrating erosion or scalloping of adjacent ribs and vertebral bodies. In tumors extending through the intervertebral foramina, CT also shows the typical "dumbbell" appearance. After contrast injection, small paragangliomas show avid and homogeneous enhancement, whereas ganglioneuromas show subtle enhancement in the arterial phase and mild enhancement in the delayed phase [46]. No typical enhancement characteristics have been reported for other types of neurogenic tumors. Rapid growth, necrosis, and hemorrhage are CT findings suggestive of malignancy. Finally, CT is the imaging modality used for assessing distant metastases to the bones, lungs, and liver, which are common sites of metastasis for neuroblastomas. MRI helps to differentiate between individual neurogenic tumors. Paragangliomas show a characteristic "salt-and-pepper" appearance on T1-weighted images, due to the presence of multiple curvilinear and punctate signal voids that correspond to high-velocity flow in intratumoral vessels [9]. Conversely, on T2-weighted images, ganglioneuromas may present a "whorled" appearance [6,

10], while neurofibromas may show a "target" pattern, defined as a central portion with lower signal intensity than the peripheral zone. MRI accurately demonstrates the presence and extent of intraspinal tumors, invasion of adjacent neural structures, and encasement of vessels, which all influence surgical treatment and management. Metaiodobenzylguanidine scintigraphy is highly sensitive for determining the extent of disease in catecholamine-producing neuroblastomas and paragangliomas. 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) scanning has reasonable accuracy (82%) in distinguishing malignant forms from benign forms.

Infectious Spondylitis: Infectious spondylitis is usually caused by pyogenic or tuberculous infections with the latter being known as Pott's disease [47]. Hematogenous spread is the most common pathway of infectious spondylitis, but direct inoculation, contiguous extension, or lymphatic drainage from adjacent affected areas may also occur. Infection of a vertebral body may extend into the prevertebral and paravertebral soft tissues, spreading via the anterior or posterior longitudinal ligaments [48, 49]. Early stages of paravertebral abscesses and bone destruction may be difficult to detect on CXR. Conversely, CT and MRI have a high sensitivity for detecting early osteolytic destruction of the vertebrae, accompanying focal or diffuse paraspinal soft-tissue abscesses, intervertebral disc involvement, and epidural granulation tissue [48]. Osteolytic destruction of the vertebrae may cause collapse, more commonly in the anterior part, leading to the characteristic gibbus deformity in Pott's disease. Paravertebral soft-tissue abscesses typically appear as a "horseshoe" mass surrounding an affected vertebral body. They may extend over several vertebral segments above and below the site of bone destruction. On CT, theses abscesses have soft-tissue density. On MRI, they have decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images [48]. Contrast material improves the detection of paraspinal abscesses on both CT and MRI. Pyogenic abscess usually has a thick and irregular enhancement wall, in contrast to the thin and smooth enhancement of the wall of tuberculous abscesses. Other helpful features in the differential diagnosis between tuberculous and pyogenic abscesses include calcifications in tuberculous infections and hypodensities or complete destruction of the intervertebral disc in pyogenic infections, which are best visualized on CT [49]. In addition, MRI allows for the assessment of epidural masses with nerve root or spinal cord compression. More than 80% of patients with extramedullary hematopoiesis are asymptomatic, with the condition being incidentally detected at imaging [48]. Rarely, there may also be pleural effusions, hemothoraces, or respiratory failure. Cord compression can cause back pain, lower extremity weakness, numbness, and even paraplegia. CXR shows smooth, well-delineated paraspinal masses, which may be associated with trabeculated and widened ribs in patients with chronic anemia. CT and MRI show well-defined, usually bilateral, paraspinal masses, most commonly in the lower thoracic area. CT attenuation values and MRI signal intensity vary, according to the grade of hematologic activity of the lesion. Active lesions usually have soft-tissue density on CT and intermediate signal intensity on both T1- and T2-weighted MRI. Inactive lesions may have low or high attenuation values on CT, depending on the presence

of fat and iron content of the masses. For the same reason, inactive lesions have high signal intensity on both T1- and T2-weighted images if there is fatty replacement or low signal intensity with iron deposition. Mild homogeneous enhancement on both CT and MRI is usually seen in active lesions, whereas a heterogeneous enhancing pattern is more common in inactive lesions because of iron deposition or fatty replacement [48].

Intrathoracic Meningoceles: Spinal meningoceles are saccular protrusions of the meninges through intervertebral foramina or bone defects in one or more vertebrae. Meningoceles contain cerebrospinal fluid and usually occur in the thoracic spine, especially between T3 and T7 [50]. The protrusion can be anterior, lateral, anterolateral, or posterior to the vertebral body. Posterior meningoceles are the most common type, but they are not discussed in this review because they do not affect the posterior mediastinum. Most meningoceles are associated with syndromes, such as neurofibromatosis type 1. Small meningoceles are asymptomatic and can be discovered incidentally on a routine CXR, whereas larger lesions may compress the spinal cord, spinal nerves, and adjacent mediastinal structures. On CXR, meningoceles appear as paravertebral opacities with well-defined, smooth or lobulated borders. CT confirms a sharply defined, homogeneous, low-attenuation lesion up to 15 cm in diameter [50]. The lesion protrudes from the spinal canal into the posterior mediastinum and has a predominance for the right side, which might be related to the presence of the aorta on the left side. CT also reveals abnormalities in adjacent vertebrae and enlargement of intervertebral foramina. On MRI, meningoceles are cystic masses with the signal intensity of cerebrospinal fluid.

Mediastinal Abscesses: Mediastinal abscesses should be considered when a low-attenuation mass is identified at multidetector CT in a patient after surgery or esophageal perforation, or in the setting of infection in the adjacent thorax.

Pancreatic Pseudocysts: A cystic mass in the paravertebral mediastinum that develops over a short period of time in the clinical setting of pancreatitis may represent intrathoracic extension of a pancreatic pseudocyst [51]. These uncommon lesions contain pancreatic secretions, blood, and necrotic material and spread through the esophageal or aortic hiatus [52]. At multidetector CT, these lesions typically manifest as thin-walled masses that may be isoattenuating or hyperattenuating, depending on the presence of hemorrhage or infection. Separate intra-abdominal pseudocysts may or may not be present.

Conclusions

A wide variety of disorders can arise from the anatomical structures of the mediastinum. Each imaging modality plays a fundamental role in the detection and characterization of these disorders and in answering different morphologic questions to provide definite diagnostic information. The new mediastinal division scheme developed by ITMIG is designed to enable the precise identification of mediastinal abnormalities at cross-sectional imaging by radiologists and consistent

communication between healthcare providers. This system will improve lesion localization, help generate a focused differential diagnosis, and assist in tailoring biopsy and treatment plans.

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Chapter 4
Radiotherapy in Anterior Mediastinum Cancers

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Radiotherapy treatment in anterior mediastinum cancers can be performed with curative, adjuvant, palliative/symptomatic intent.

The mediastinal tumors of radiotherapy interest are represented by:

1. *Thymic tumors*: Thymoma and thymic carcinoma
2. *Mediastinal localization of lymphomas*: Hodgkin's lymphoma and non-Hodgkin's lymphoma
3. *Germinal tumors: Seminoma and non-seminomatous germ cell tumors (NSGCT)*
4. *Superior vena cava obstruction (SVCO)*

Thymic Tumors

Over 90% of thymic cancers are located in the anterior mediastinum; these are relatively rare tumors that represent 0.2–1.5% of all primitive tumors and 20% of mediastinal tumors.

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Thymus tumors are classified in:

- Thymoma (90%)
- Thymic carcinoma (5–10%)

Establishing a staging system for thymic epithelial tumors (TETs) has been difficult due to the rarity of these tumors. Staging has most commonly been performed using the Masaoka-Koga staging system [1–3].

The system has been modified over the years, so the following staging for thymomas and thymic carcinomas is generally:

- *Stage I*: Grossly and microscopically encapsulated, it is also called a noninvasive thymoma. That is, it has not spread beyond the thymus.
- *Stage II*: The thymoma invades beyond the capsule (outer boundary of the thymus) and into the nearby fatty tissue or to the pleura (outer covering of the lung). Sometimes divided into:
- *Stage IIa*: Microscopic transcapsular invasion
- *Stage IIb*: Macroscopic capsular invasion
- *Stage III*: Macroscopic invasion of neighboring organs. The thymoma extends into the neighboring tissues or organs of the lower neck or upper chest area, including the pericardium (covering of the heart), the lungs, or the main blood vessels leading into or exiting from the heart.
- *Stage IVA*: Pleural or pericardial dissemination. The thymoma has spread widely throughout the pleura and/or pericardium.
- *Stage IVB*: Hematogenous or lymphatic dissemination. The thymoma has spread to distant organs.

Surgery is the elective treatment at almost all stages of the disease, while chemo-radiation therapy can be used as adjuvant or as exclusive treatment (neo-adjuvant radiotherapy has lost meaning today).

For patients with resectable cancers (almost all stage I and II thymus cancers, most stage III cancers, and small number of stage IV cancers), surgery offers the best chance for long-term survival if it can be tolerated. This typically includes removal of the entire thymus and, depending on the disease extension, maybe parts of nearby organs or blood vessels as well.

Stage I/IIA sec. Masaoka: After full resection (R0), the risk of intrathoracic relapse is <5%; therefore, there is no indication of adjuvant radiant treatment; in the case of incomplete resection (R1 or R2), adjuvant radiotherapy is indicated to reduce the local recurrence rate from 60–80% to 21–45%.

Stage IIB sec. Masaoka: After full resection (R0), the adjuvant radiotherapy approach is today's debate. Evaluation of prognostic factors such as histological features of the disease (tumor size, capsule invasion, age, performance status, comorbidity) can guide the radiotherapist in this decision.

Stage III sec. Masaoka: The indication for radiotherapy is certain, confirmed by some retrospective studies.

Adjuvant radiation treatment involves delivering a dose of 45–50 Gy with conventional fractionation (2 Gy per day five times a week) in full resection R0, 54 Gy for positive margins, and 60–66 Gy in case of macroscopic residual disease.

Exclusive radiant treatment is used for radical and curative purpose when surgery cannot be performed (low-performing status, presence of comorbidity of refusal to surgery) and for palliative-symptomatic purpose in advanced disease. In the exclusive treatment, the dose administrated is 60–70 Gy [4].

Mediastinal Localization Lymphomas: Hodgkin's Lymphoma (LH) and Non-Hodgkin's Lymphoma (LNH)

The elective treatment of mediastinal lymphomas is chemotherapy. The role of radiotherapy is mainly consolidation after chemotherapy treatment at the sites of disease involvement. Currently radiotherapy should be performed in involved nodes (IN) or involved sites (IS) shown at the pre-chemotherapy 18-FDG PET/CT, using advanced irradiation techniques (IMRT, VMAT, IGRT) and breath control systems such as breath-hold deep inspiration to limit toxicity at the heart and lungs (4D-RT) [5–7].

Hodgkin's Lymphoma

Radiotherapy treatment of mediastinal Hodgkin's lymphoma has an important role in multimodal treatment. The mediastinal site and the large initial tumor volume (bulky mass) represent risk factor in terms of local-regional recurrence. Radiation therapy after chemotherapy (usually ABWD schedule) represents the standard therapeutic reference. Target delineation is based on pre-chemotherapy sites of involvement, and since disease is expected to regress following chemotherapy, improved image registration with the pre-chemotherapy staging scans will allow for reduced size in target volume.

In early stage (I–IIA) non-bulky disease and with a complete response after two ABWD cycles, patients may do well with two more ABWD cycles without radiotherapy. If radiotherapy is performed, involved site will be irradiated at 20 Gy [8, 9].

In stages IIB–IV, consolidation radiotherapy after chemotherapy is indicated in patients who received a complete remission, with or without bulky disease at onset at 30–36 Gy doses in involved site [10]. In case of residual PET-avid disease, patients should receive higher doses of radiation to 39.6–45 Gy [11]. The percentage of disease response to chemo-immunotherapy treatment is assessed through Deauville score which assigns a score based on the response to 18-FDG PET [12].

Non-Hodgkin's Lymphoma

In the heterogeneous group of non-Hodgkin's lymphomas, the one that most frequently localizes in the mediastinum is the diffuse large B-cell lymphoma (DLBCL). According to the pathological stage of the disease, patients undergo several chemo-immunotherapy cycles (R-CHOP or R-CHOP like, 3–4 cycles in stages I and II, 6–8 cycles in the most advanced stages). In favorable I and II stages, after 3–4 R-CHOP cycles, consolidation radiotherapy is indicated with dose 30–36 Gy at involved site. For unfavorable I and II stages, advanced stages, and in presence of bulky disease, after 6–8 cycles of R-CHOP, radiotherapy is indicated at the site of the bulky disease or at the site of partial response with doses of 30–40 Gy [13, 14]. Radiation treatment is indicated except in selected cases (large volumes of irradiation, high risk of toxicity, poor compliance of patient).

Germinal Tumors: Seminoma and Non-seminomatous Germ Cell Tumors (NSGCT)

Seminoma

Chemotherapy is the elective treatment; moreover this histotype has high radiosensitivity, and the complementary/adjuvant radiotherapy is indicated in selected cases.

The dose to be delivered is 30 Gy/15# or 30Gy + 10 Gy-boost/20# for bulky lesion.

Non-seminomatous Germ Cell Tumors (NSGCT)

Radiotherapy in non-seminomatous forms has a secondary role only in residual disease after systemic therapy.

Superior Vena Cava Obstruction (SVCO)

Superior vena cava syndrome (SVCS) consists of a set of signs (dilation of the veins of the neck, facial plethora, edema of the upper limbs, and cyanosis) and symptoms (headache, dyspnea, cough, orthopnea, dysphagia, etc.) resulting from obstruction of the blood flow through the superior vena cava to the right atrium.

The obstruction of the vena cava can be caused by extrinsic compression, tumor invasion, thrombosis, or insufficient venous return secondary to intra-atrial or intraluminal diseases. Approximately 73–97% of SVCS cases occur dur-

ing the evolution and expansion of intrathoracic tumors as a result of compression of the superior vena cava by the tumor itself or by the affected mediastinal lymph nodes [15, 16].

The type of cancer that most frequently causes SVCS (75% of all cases) is bronchogenic cancer, and 3–5% of patients with lung cancer develop SVCS over the course of the disease [16, 17]. Lymphomas are the second leading neoplastic cause of the syndrome (15% of all cases), and 17% of lymphomas presenting mediastinal involvement result in SVCS [17]. Metastatic cancers account for 7% of all cases of SVCS [18].

The use of radiotherapy in patients with SVCS prior to receiving the histological diagnosis is currently considered inappropriate. The presence of SVCS does not impede the adoption of appropriate curative treatment when possible. Before radiotherapy is started, general therapeutic measures, such as raising the head of the bed and administering corticosteroids and diuretics, can be taken. In patients with SVCS and small cell lung cancer, although radiotherapy has been used in some studies, the most appropriate therapeutic approach is combined chemotherapy. In such cases, there are no differences between the two approaches in terms of the time to resolution or in terms of results. However, chemotherapy offers the advantage of treating the disease systemically, as well as that of avoiding high radiation loads on the heart and lungs [19]. In 43–100% of cases, resolution of the syndrome is achieved in 7–10 days.

Based on somewhat limited evidence of a more rapid response [20], initial treatment with two to four fractions of 300–400 Gy has been recommended [19]. However, the timing, dose, and fractioning of the radiotherapy applications for SVCS have not been definitively established, and there is no evidence indicating the size of the final dose required to obtain the best clinical response. In general terms, in non-small cell lung cancer, the total dose used is 60 Gy, whereas doses of 20–40 Gy have been used in lymphomas and neoplasms that are more radiosensitive.

Radiation Therapy-Related Toxicity

During radiant treatment, healthy tissues included in the treatment fields may be exposed to radiation, from which the risk of onset of side effects depends on factors related to the treatment and to the patient.

- Treatment-related factors include total dose, fractionation, and irradiation technique used.
- Normal tissue volume receiving high doses of radiation, functional reserve and structural organization of healthy tissue, association with systemic therapy, and presence of complications surgical post.
- Patient-related factors include comorbidity (diabetes, hypertension, altered lipid metabolism, cardiomyopathy, collagen diseases), lifestyle habits (smoking, alcohol intake), age and body mass index, previous traumas from surgical interventions, and individual susceptibility on a genetic basis.

- The side effects of radiant treatment are classically divided into acute (occurring during or immediately after radiating) and late (after 6–9 months after the end of therapy). They only occur in the tissues included in the irradiation fields.
- The earliest effets, usually well controlled by medical and reversible therapy, are responsible for high cellular susceptibility to radiation (skin and mucous epithelium).
- Late effects occur as a result of radio-induced alterations at the microvascular and local connective stroma level. These are the most significant disturbances for the patient as they are often permanent and therefore can significantly compromise their quality of life, especially in younger subjects such as those with mediastinic neoplasms.
- Modern radiotherapy techniques (3D-CRT) allow to significantly reduce the risk of developing important side effects with a high degree of toxicity (G3–G4) <5–10%.

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Chapter 5
Surgery: Recommendations for Surgeons

Mario Santini and Alfonso Fiorelli

Introduction

The mediastinum is a Pandora's box since it contains different and complex structures such as the esophagus, the trachea and main bronchi, the heart and great vessels, and major portions of the lymphatic system (including tracheobronchial and periesophageal lymph nodes, the thoracic duct, and the thymus gland). The vagus and phrenic nerves also run through the mediastinum. Since each of these structures can be subject to disease, the diagnosis and treatment of a mediastinal mass is a challenging task for the physician. Many arbitrary divisions of the mediastinum have been proposed over the years. The simplest and most commonly used description divides the mediastinum into three compartments, such as anterior mediastinum, middle mediastinum, and posterior mediastinum [1]. The anterior mediastinum is defined by the sternum anteriorly and pericardium posteriorly. It contains the thymus, innominate vein, aortic arch vessels, internal thoracic vessels, associated lymph nodes, connective tissue, and occasionally thyroid. The middle mediastinum is bounded anteriorly and posteriorly by the pericardium and includes: the pericardium, heart, great vessels, trachea and hilar bronchi, superior vena cava and proximal azygos vein, proximal esophagus, phrenic nerve, distal thoracic duct, paratracheal/subcarinal lymph nodes, and connective tissue. The posterior mediastinum is delimited anteriorly by the posterior pericardium and posteriorly by the spine. It contains the sympathetic chain, proximal intercostal nerves and vessels, distal esophagus, posterior paraesophageal lymph nodes, proximal thoracic duct, distal azygos vein, and connective tissue. This division could guide the diagnosis since specific lesions

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have a predilection compartment (Table 5.1) and the surgical approach. Clinical assessment and imaging are of paramount importance to define the characteristics of the mass, its location, and extension, but they do not allow to have a definitive diagnosis. Thus, a cytopathology diagnosis is required to plan the prompt therapy.

In the following chapter, the authors describe the techniques to access to the mediastinum in order to obtain a diagnostic tissue and the surgical strategies for the treatment of mediastinal mass.

Transcutaneous Biopsy

Transcutaneous biopsy through parasternal, paravertebral, and suprasternal approaches allows access to lesions in virtually all mediastinal locations [2–9]. They are performed under computed tomographic (Fig. 5.1) or ultrasonographic (Fig. 5.2) guidance in radiology room and generally do not require any type of anesthesia. The parasternal approach is used for biopsy of anterior or middle mediastinal lesions when the lesion extends to the anterior chest wall, lateral to the sternum. The paravertebral approach is used for biopsy of subcarinal and other posterior

Table 5.1 Classification of mediastinal mass according to the compartments of the mediastinum

Anterior	Middle	Posterior
Thymoma	Lymph nodes metastasis	Neurogenic tumor
Germ cell tumor	Lymphoma	Bony osteophyte
Lymphoma	Granuloma	Enteric cyst
Intrathoracic goiter	Bronchogenic cyst	Meningocele
Thymic cyst	Enteric cyst	Esophageal leiomyoma
Carcinoma	Pericardial cyst	
Parathyroid gland	Saccular aneurism	
Lipoma		
Lymphangioma		
Vascular masses		

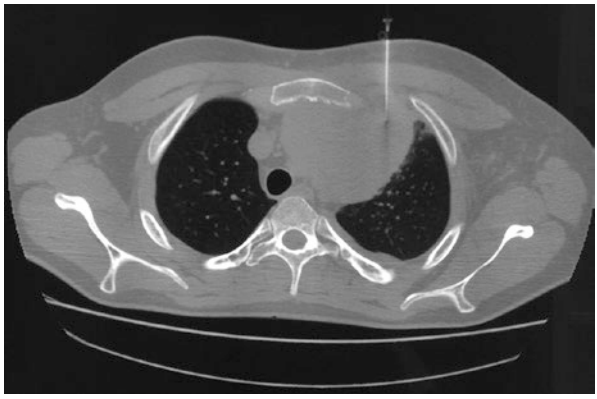

Fig. 5.1 A 29-year-old man presented a large anterior mediastinal mass. Computerized tomography-guided fine-needle aspiration biopsy was performed with a diagnosis of non-Hodgkin's lymphoma

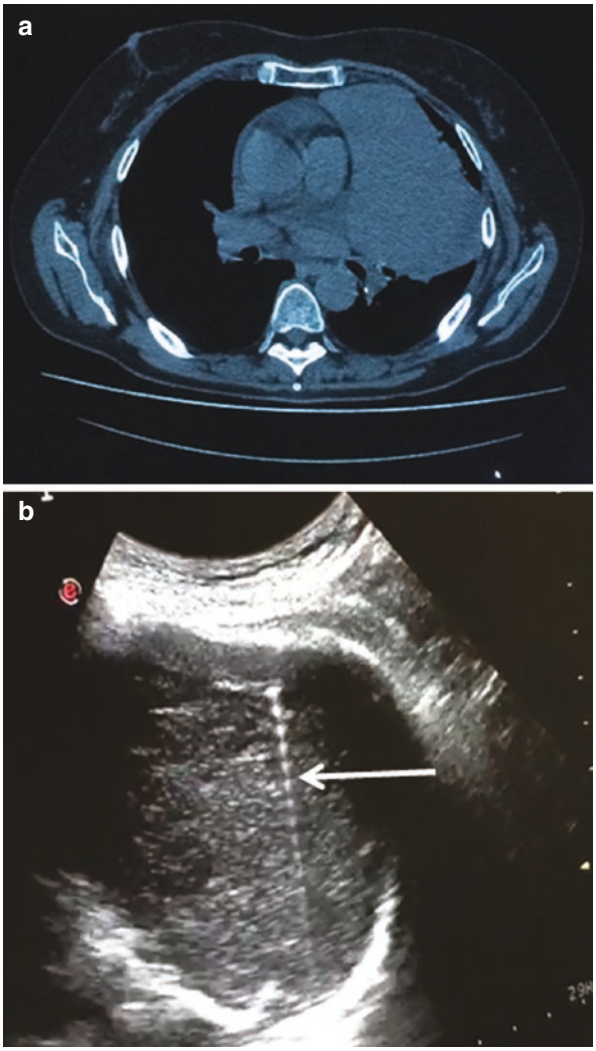

Fig. 5.2 A 47-year-old woman presented a large anterior mediastinal mass. Ultrasound-guided fine-needle aspiration biopsy was performed with a diagnosis of non-Hodgkin's lymphoma

mediastinal lesions. Biopsy of superior mediastinal lesions can be performed with a suprasternal approach. The choice of the caliber of the needle depends on the characteristics of the mass and its location, the suspicion of clinical diagnosis, the physician's experience, and the estimated amount of tissue needed for diagnosis. Generally, fine needle having a caliber of 20–25 gauge provides specimens suitable for cytologic evaluation, while cutting needle having a caliber of 14–19 gauge allows obtaining specimen for histologic evaluation. However, fine-needle aspiration biopsy (FNAB) could be a diagnostic and therapeutic procedure as in the case of the aspiration of fluid from cystic lesions. The diagnostic yield of percutaneous biopsy depends on the nature of the lesion. In fact, for the diagnosis of epithelial

metastatic disease, the sensitivity of FNAB ranges from 84 to 100% but it decreases from 42 to 82% in the case of lymphoma [2–6]. Thus, in patients with suspicion of lymphoma or other types of tumors such as thymoma, germ cell tumors, neurogenic tumors, and benign tumors, a core needle biopsy (CNB) rather than FNAB should be performed since its sensitivity is up to 91% [7, 8]. In the series of Nasit et al. [9], CNB was inadequate in only 1 of 50 (2%) patients for diagnosing anterior mediastinal mass, while other series [9] reported an unsuccessful rate of 11%. Thus, in the case of an inconclusive diagnosis after transcutaneous biopsy, surgical biopsy should be performed to obtain a diagnostic tissue especially for tumors requiring an immunologic classification. The main advantages of transcutaneous biopsy over surgical biopsy are the low cost, the minimal pain, and the possibility of performing it in radiology unit and without anesthesia. Another advantage is the possibility of starting immediately chemotherapy and radiotherapy since there is no surgical wound. The procedure is safe. The most common complication is pneumothorax ranging from 4.6 to 46% in the most of series, while the lesion of the internal mammary artery and the implantation of the tumor cells through the needle are exceptional events [10].

Ultrasound-Guided Endoscopic Biopsy

In recent years, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endoscopic bronchial ultrasound-guided fine-needle aspiration (EBUS-FNA) have assumed a central role in diagnosing and staging pulmonary malignancies and mediastinal disease [11, 12]. EUS can accurately explore middle and posterior mediastinal lesions surrounding the esophagus, while EBUS is indicated in the diagnosis of anterior mediastinal mass. The two methods target different areas of the mediastinum; thus, to explore all mediastinal compartments, a combined EUS and EBUS approach is needed.

EUS has an access to the posterior and inferior lymph nodes (stations 4L, 5, 7, 8, and 9). Its ability in diagnosing and staging lung cancer is well defined by several studies with a sensitivity ranges between 77 and 100%. In addition, in 49–70% of patients with various mediastinal masses [13–18], EUS allows to obtain a definitive diagnosis and avoids the execution of surgical biopsy. Lee et al. [19] studied 125 consecutive patients with various mediastinal and pulmonary lesions; malignancy was confirmed in 62 (50%) of patients and excluded in 42 (34%). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of EUS-FNA were 75%, 100%, 100%, 67%, and 83%, respectively. Ardengh et al. [20] performed EUS-FNA in 51 patients with different mediastinal masses with a diameter ranging from 1.1 to 9.8 cm (mean, 3.9 cm). EUS-FNA did not allow a definitive diagnosis in 5 (10%) cases. Manucha et al. [21] evaluated 281 EUS results in 269 patients with various mediastinal diseases, and a definitive diagnosis was obtained in 259 (96%) cases. Zeppa et al. [22] carried out EUS-FNA on 57 mediastinal lymph nodes and 8 mediastinal and 2 subdiaphragmatic masses. Comparison with samples obtained by surgical biopsy showed a sensitivity of 96%, a specificity of 89%, a PPV of 98%, and a NPV of 95%. Yasuda et al. [13] evaluated

the yield of EUS-FNAB in patients with idiopathic mediastinal lymphadenopathy in relation to lymphoma subclassification. Overall accuracy of EUS-FNAB for idiopathic lymphadenopathy was 98%, and lymphomas could be classified in accordance with World Health Organization classifications in 88% of cases.

EBUS-TBNA has access to anterior and superior mediastinal lymph nodes (stations 2, 3, 4, 7, 10, and 11), which are traditionally approached by mediastinoscopy, while it cannot explore the prevascular (station 3a), aortopulmonary window (APW) (station 5), para-aortic (station 6), paraesophageal (station 8), and pulmonary ligament (station 9) nodes. A meta-analysis by Dong et al. [23] and a recent review of Silvestri et al. [24] including 2756 patients with mediastinal adenopathies demonstrated a median sensitivity of 89% and a NPV of 91%. EBUS has been shown to be useful also for diagnosing other diseases that affect the mediastinum such as sarcoidosis and lymphoma [25–27]. Yasufuku et al. [28] reviewed a total of 140 patients with mediastinal masses of unknown origin without the presence of lung cancer or other pulmonary malignancies. Of these, 40 (28%) were diagnosed as malignant and 100 (72%) as benign lesions by means of EBUS-TBNA, surgery, mediastinoscopy, or long-term follow-up. The EBUS-TBNA was diagnostic in 131 of 140 patients (93.6%) for all disease categories (malignant 87.5%, benign 96.0%). Examples of EBUS-TBNA are reported in Figs. 5.3, 5.4, and 5.5.

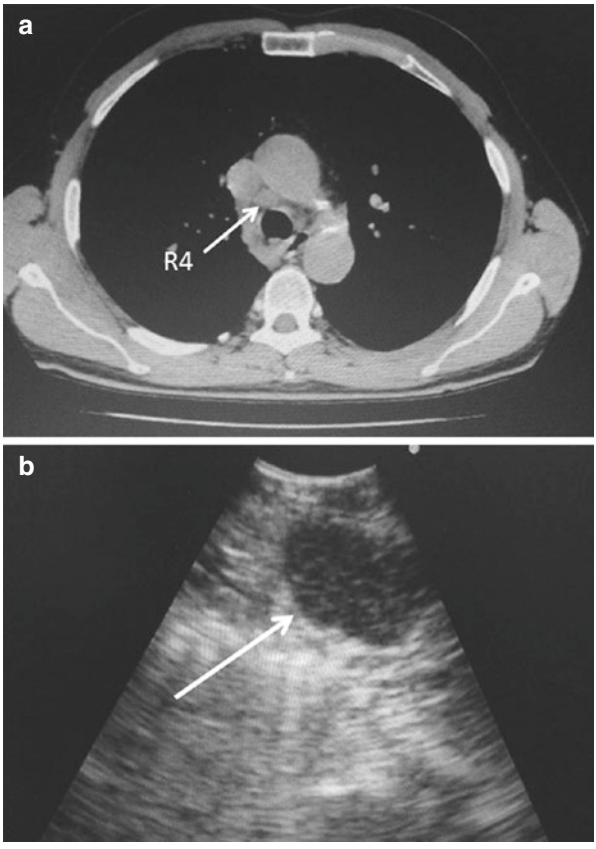

Fig. 5.3 A 47-year-old man with an adenocarcinoma of the right lower lobe presented an enlargement of the paratracheal lymph node (station R4) on computed tomography scan (**a**). EBUS-TBNA (**b**) resulted to be positive for metastasis. Photo courtesy of Mario Polverino, MD, and Carlo Santoriello, MD of Pneumology Unit of Scafati Hospital, Scafati, Italy

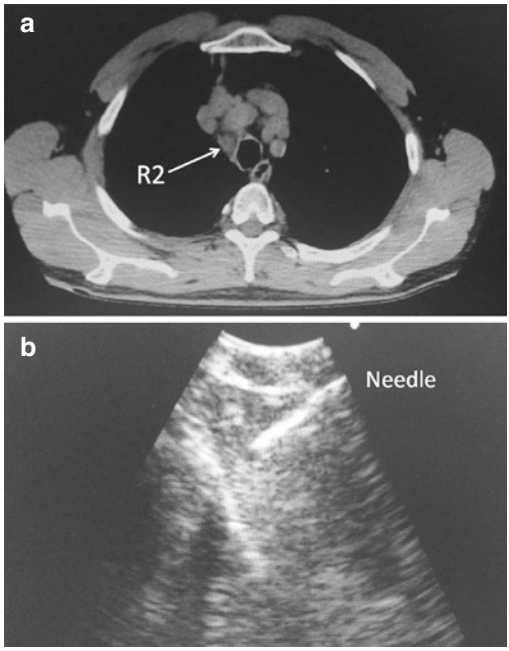

Fig. 5.4 A 59-year-old man with a squamous cell carcinoma of the left lower lobe presented an enlargement of the paratracheal lymph node (station R2) on computed tomography scan (**a**). EBUS-TBNA (**b**) resulted to be positive for metastasis. Photo courtesy of Mario Polverino, MD, and Carlo Santoriello, MD of Pneumology Unit of Scafati Hospital, Scafati, Italy

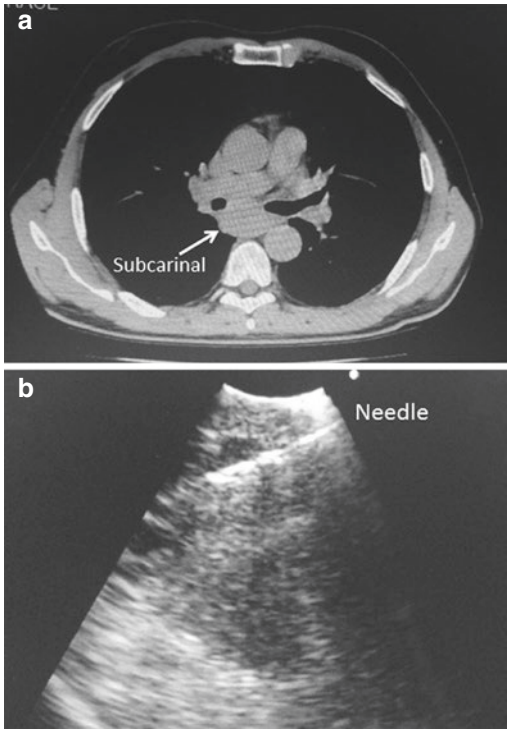

Fig. 5.5 A 71-year-old man with a squamous cell carcinoma of the right lower lobe presented an enlargement of the subcarinal lymph node (station 7) on computed tomography scan (**a**). EBUS-TBNA (**b**) resulted to be positive for metastasis. Photo courtesy of Mario Polverino, MD, and Carlo Santoriello, MD of Pneumology Unit of Scafati Hospital, Scafati, Italy

Combination of EBUS and EUS allows a complete access to all the lymph nodes and masses of the mediastinum with a median sensitivity of 91% and NPV of 86% [24, 29, 30]. Published studies consistently demonstrated a higher sensitivity and NPV when combined EBUS and EUS are compared with either modality alone [29], although this may simply be a result of more needle passes performed rather than a true complementary value of each technique. Thus, the real usefulness of combined endoscopic approaches with EBUS and EUS is unclear considering the increase in costs and procedure times and the need for additional training and equipment [29].

Several trials have then compared the diagnostic accuracy of endoscopy versus surgical biopsy. Gelberg et al. [31] prospectively enrolled 159 patients with confirmed or suspected lung cancer and performed EBUS immediately followed by cervical mediastinoscopy in all patients. They found no significant differences in sensitivity (81% versus 79%), NPV (91% versus 90%), or accuracy (93% versus 93%) between the two procedures. Annema et al. [32], in a prospective multicenter study, randomly assigned 241 patients to EBUS and EUS followed by mediastinoscopy if no nodal metastasis was identified versus mediastinoscopy alone. The authors [32] found no difference in sensitivity and NPV between mediastinoscopy and combined EBUS and EUS. The main advantages of endoscopy over surgical biopsy are the less invasiveness, the not needing of general anesthesia and of operative room, the less procedural cost, and the possibility of discharging patient few hours later. Despite all, surgical biopsy remains the standard strategy for mediastinal staging of lung cancer, and it should be carried out in patients with negative E(B)US results but having a high clinical suspicion of mediastinal involvement according to the last guidelines of the American College of Chest Physician (ACCP) [33] and European Society of Thoracic Surgeons (ESTS) [34].

Anterior Mediastinotomy (Chamberlain's Approach)

Anterior mediastinotomy, also known as Chamberlain procedure [35], is a surgical technique for sampling masses in contact with the sternum or parasternal chest wall or arising from the APW. It is performed in operative room under general anesthesia or in selected cases with local anesthesia. The patient is placed in supine position, and the level of incision is based on computed tomography scan or ultrasound findings. A vertical or horizontal 3–4 cm incision is performed over the lateral sternal border. Generally, the removal of the costal cartilage is not necessary, and the integrity of the pleura should be preserved to avoid the dissemination of tumor cells. After identification of the target mass, diagnostic tissue is excised using scalpel or forceps. An example is reported in Fig. 5.6. In the case of sampling station 5 and station 6 adenopathies, the incision is made on the left side in the second intercostal space at the anterior level, and the access to the APW is achieved by laterally pushing aside pleura. The diagnostic accuracy of anterior mediastinotomy is higher than 90% [36]. Complications including pneumothorax and injury of the mammary vessels are reported in 1–4% of cases [37]. Despite simple to perform and safe, anterior

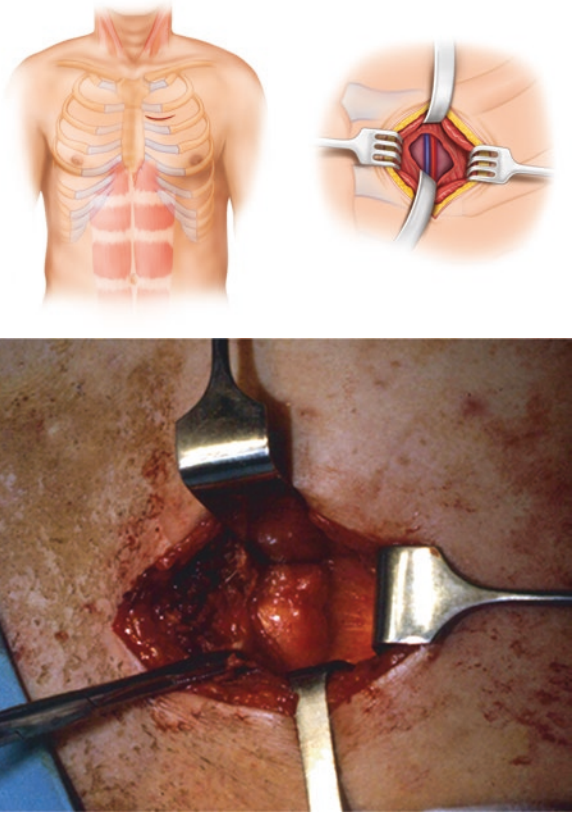

Fig. 5.6 A 67-year-old man presented a mediastinal mass that was biopsied using anterior mediastinotomy

mediastinotomy is an invasive technique that requires general anesthesia and can biopsy only masses of the anterior mediastinum. There is the risk of opening the pleura with possible tumor seeding, and the cosmetic results are poor.

Cervical Mediastinoscopy (Standard and Extended)

Standard cervical mediastinoscopy (SCM), first described by Harken et al. [38], involves a suprasternal incision through that is inserted the mediastinoscopy. It is performed in operative room under general anesthesia and without needing single-lung ventilation. An example is reported in Fig. 5.7. Mediastinoscopy remains the gold standard for preoperative mediastinal staging of lung cancer especially when imaging and E(B)US do not allow a definitive diagnosis [39]. SCM allows sampling upper and lower paratracheal lymph nodes (station 2 and 4, respectively) on both sides, subcarinal lymph nodes (station 7), and retrovascular mediastinal tumors. Complete resection of mediastinal mass has also reported with mediastinoscopy.

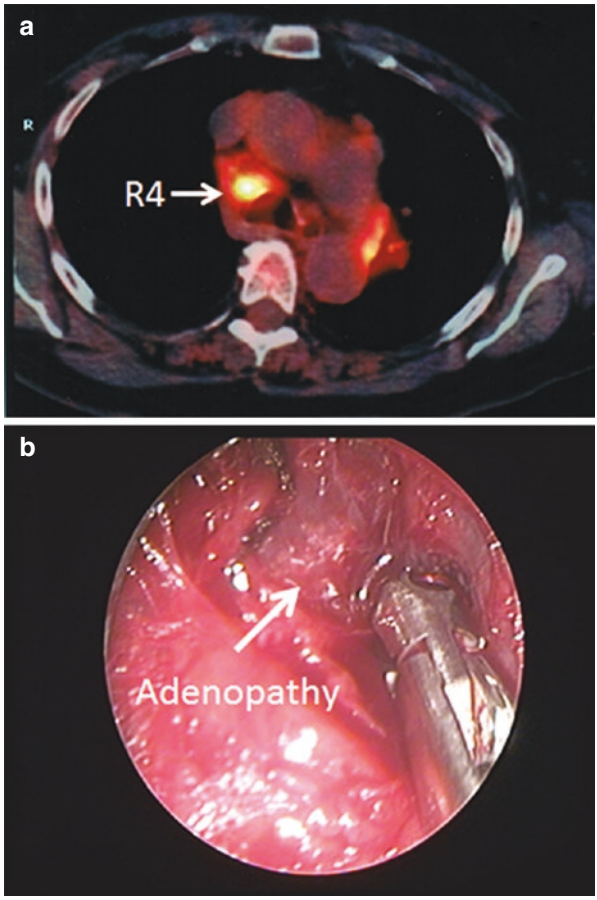

Fig. 5.7 A 63-year-old man presented an enlargement of the paratracheal lymph node with a standard uptake value of 5.9 on PET-CT scan (**a**). A surgical biopsy obtained with mediastinoscopy diagnosed a *sarcoidosis* (**b**)

Relative contraindications include previous mediastinoscopy, radiation therapy, and cervical arthritis [40]. This procedure presented a median sensitivity of 78% and a NPV of 91% according to a recent review [41]. The most false-negative results occurring in posterior subcarinal nodes. Despite the overall morbidity is of 1.07% and mortality of 0.05%, fatal vascular injuries have been reported during mediastinoscopy. Thus, surgeon should be always ready to perform an emergent sternotomy in the presence of uncontrollable bleeding [42–44].

SCM can not biopsy lymph nodes of station 5 and station 6. Bille´ et al. [45] and Cerfolio et al. [46] reported that station 5 was the second common location for N2 disease that was undetected by PET/CT. Gomez-Caro et al. [47] found that in patients with early stage-cN0 lung NPV for APW lymph nodes was 76%. In 1987, Ginsberg et al. [48] proposed the extended cervical mediastinoscopy (ECM) with the aim of exploring the lymph nodes of station 5 and station 6. The technique consists of a dissection through a cervical incision (the same incision as the SCM) of the retrosternal space, between the anterior face of the left innominate vein and the

posterior face of the sternum, separating the fascia lying between both structures. That allows to entry at the level of the aortic arch at the origin of the innominate artery [49]. Freixinet et al. [50] reported that ECM is superior both to VATS and anterior mediastinotomy for sampling station 5 and station 6 lymph nodes. Metin et al. [51] reported that ECM had an 89% of diagnostic yield in a limited series of patients with lymphoma or thymoma previously undergoing inconclusive transcutaneous biopsy. Conversely to ECM, mediastinotomy requires an anterior thoracic incision, and VATS requires selective lung intubation, multiple thoracic incisions, and chest drainage. However, the use of ECM remains controversial, and confirmatory studies examining the safety and accuracy of these techniques are required especially for diagnosing invasive tumor of the anterior mediastinum [52].

Video-Assisted Thoracoscopic Surgery (VATS)

The use of VATS in diagnosing mediastinal masses is well established (Fig. 5.8). VATS allows a complete mediastinal view, and it is indicated in cases of masses with difficult access to mediastinotomy or mediastinoscopy, such as tumors in proximity to neurovascular structures or to the vessels of the heart. In addition to the possibility of allowing selective and large biopsy, VATS also evaluates the relationship of the tumors with the adjacent structures and detects tumor invasion or metastatic spread. VATS is reported to be more accurate than CT-guided biopsy in the pathological diagnosis of the anterior masses having a diagnostic accuracy between 91.9 and 100% [53]. Yet, it may play a role in the staging of lung cancer for the definition of N parameter and T parameter. In fact, it confirms involvement in PET-positive adenopathies that are not accessible by SCM or EBUS and EUS, such as lymph node of station 5 and station 6 or the lymph nodes of the posterior mediastinum (station 8, station 9, and station 10). Despite the station 5 and 6 could be explored also by ECM, the advantage of VATS over ECM is the possibility of simultaneously evaluating pleural involvement, the presence of pleural effusion, and the involvement or invasion of surrounding structures by primary lung cancer. Several authors evaluated the role of VATS in defining the resectability of centrally located T4 tumor [54]. They found that the preoperative imaging results in 27% of primary lung carcinoma being over staged and 18.9% being under staged. In addition, 20% of the centrally located T4 tumors diagnosed as non-resectable by CT scan were found to be resectable by exploratory VATS, while 20% of tumors defined as resectable by preoperative CT were found to be unresectable by VATS.

Over the last two decades, VATS has evolved from a diagnostic to a therapeutic technique. A growing number of papers reported its use for resecting small and capsulate benign mediastinal masses for those a standard open approach seems to be too invasive. With the increasing experience and implementation of instrumentation, VATS resection of mediastinal masses such as teratomas, thymomas, and cysts considered to be challenging for their size or involvement of surrounding structures is also being increasingly reported [55]. VATS is performed in general anesthesia

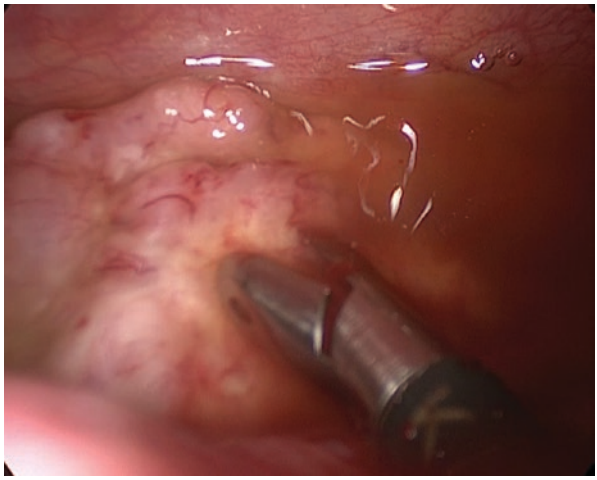

Fig. 5.8 Surgical biopsy with VATS of an anterior mediastinal mass in a 39-year-old woman. Diagnosis was Hodgkin's lymphoma

and selective one-lung ventilation. Two monitors are placed on either side of the patient's head to provide the best view for all members of the team. The positions of the team and scrub nurse change as required. All the surgical instruments for a thoracotomy or sternotomy must be ready in case of any complications. The patient's position varies according to the surgeon's preference and the localization of the target mass. Some authors advocate a semi-supine position or about 15° for approaches to the anterior mediastinum, an about 90° for resecting mass within middle mediastinum, and more toward 120° for resecting posterior mediastinum tumor. In addition, for some approaches to the posterior mediastinum, prone positioning allows the lung to fall away from the area of dissection. This frees up a port site that might otherwise be used to retract the lung. For other approaches, gravity has little impact. Some authors also advocate the use of CO2 insufflation set at 10 mmHg to improve the exposure of the target lesion and the thoracoscopic view. On the left side, the CO2 keeps the heart away from interfering with the ports and instruments. In addition, CO2 can evacuate smoke from the chest cavity during the dissection. The number and the position of the ports vary according to the characteristics of the lesions and the surgeon's experience and ability [55]. Despite a multi-port technique is usually used, resection of different types of mediastinal mass has also been reported using a single incision [56–59]. Generally, the first trocar for the camera is inserted in the seventh or eighth intercostal space on the midaxillary line according to the site of the tumor. Once the tumor has been identified, two other operating trocars (one anteriorly and one posteriorly) are positioned in the fourth, fifth, or sixth intercostal space according to the site of the lesion. Triangulation of the ports and the convergence of the instruments on the tumor is crucial for dissection. Obviously, as the course of the dissection proceeds, the trajectory of the ports could change to facilitate the dissection without traumatizing the intercostal nerve. Removal of large specimens could require a supplementary 3–4 cm incision performed anteriorly in the fourth or fifth intercostal space along the inframammary fold. To prevent the torqueing of the intercostal nerve and to

reduce the postoperative pain, the use of subxiphoid route for extracting large lesions has been also proposed [55]. Finally, the specimen is inserted in a plastic bag to avoid tumor seeding during extraction.

The feasibility of VATS dissection depends on the size of the tumor, its location, and the relationship of the mass with the adjacent structures and the surgeon's ability. Roviaro et al. [60, 61] reported the application of VATS for a wide range of mediastinal lesions, highlighting that VATS provided good exposure of the entire mediastinum, ensured adequate room for surgical manoeuver, and resulted in greatly reduced surgical trauma. Bronchogenic and pleuropericardial cysts are easily removed with VATS [62, 63]. Deflation of the cyst after aspiration of the fluid allows a straight forward dissection and extraction of the cyst through the trocars. Similarly, neurinoma is routinely resected with VATS [64]. The parietal pleura around the mass is incised, the tumor is enucleated with a mounted swab, and vessels are easily electrocoagulated. However, dumbbell tumors cannot be removed with VATS, but a combined open operation in cooperation with the neurosurgeon can be planned [55]. Currently, median sternotomy is widely considered to be the standard approach for thymoma resection especially in patients with myasthenia gravis. From the first case of VATS-extended thymectomy reported by Novellino et al. [65], over the years several centers have attempted to replicate the results of open thymectomy using different VATS approaches. Takeo et al. [66] combined VATS thymectomy with a sternal lifting technique, and Ohta et al. [67] reported an anterior chest wall lifting method to provide a wide field of vision between the sternum and heart. Hsu et al. [68] designed a subxiphoid approach associated with VATS thymectomy to facilitate bilateral mediastinal fatty tissue dissection. The same authors have proposed a bilateral approach of VATS thymectomy using three incisions [69], and recently we have modified our technique using a single bilateral incision [57, 58] (Fig. 5.9). Despite technically feasible, the main concern is whether VATS can achieve the same clearance of thymic and fat tissue as sternotomy. Recent data from the literature [70–74] seem to confirm that extended VATS thymectomy in patients with myasthenia gravis has similar results compared to sternotomy but with the advantages of less morbidity, less length of hospital stay, better cosmetic results, and faster return to daily activity. Lee et al. [70] compared the trans-sternal approach with bilateral VATS and observed no differences in the extent of the resected specimen. In a meta-analysis including 15 studies and involving 1003 MG patients, Ng et al. [71] compared VATS ($n = 533$), transcervical ($n = 449$), and infrasternal mediastinoscopic ($n = 21$) procedures and found that VATS and transcervical surgery had comparable remission rates at the 10-year follow-up (35.4% vs. 38.1%, respectively). Similarly, Zahid et al. [72] found equivalent resolution of MG in patients undergoing VATS vs. sternotomy. Chetty et al. [73] reported that patients who underwent VATS resection of the mediastinal tumor had similar operating time and duration of chest tube drainage compared to open approach but lower levels of pain and shorter hospital stay. Similar data was confirmed also by our recent study [74]. From a technical point of view, it remains unclear whether a unilateral VATS approach is equivalent to a bilateral VATS approach in the management of myasthenia gravis. Liu et al. reported that unilateral VATS offered long-term neurological

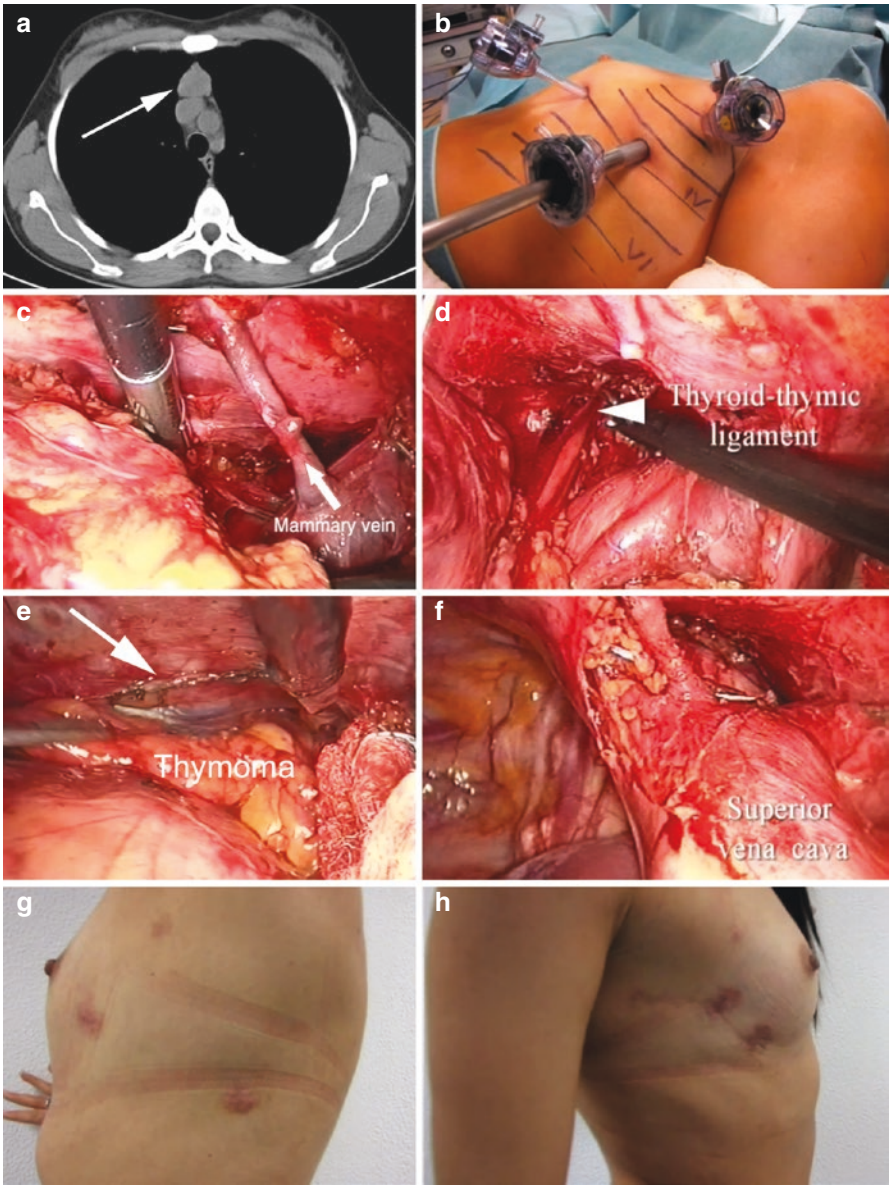

Fig. 5.9 A 35-year-old woman with myasthenia gravis and a 30 × 55 mm thymoma (**a**). Three trocars are inserted within the left hemithorax (**b**). After incision of mediastinal pleura, the thymic dissection is carried out cranially (**c**, **d**), and then thymoma is removed with all mediastinal fatty tissue. After completing the dissection, the contralateral pleura is opened (arrow), and the specimen is pushed into the right pleural cavity (**e**). Right thoracoscopy allowed the complete resection of mediastinal fatty tissue on the right side (**f**). The results of the left (**g**) and right side (**h**) 2 months later

outcomes equivalent to that of bilateral VATS [75], and these results are also confirmed by other authors [76, 77]. Complications from VATS resection of mediastinal masses do not differ greatly from those observed in open surgery. Even though the risk is relatively small in the case of well-encapsulated and benign masses, great caution is necessary to avoid injury of major mediastinal vessels or of the phrenic nerve. Despite several authors reporting the successful resection of large thymomas with VATS [55], we believe that open approach remains the strategy of choice for resecting large mass or tumor with involvement or close proximity to the nerves, airway, esophagus, great vessels, or heart. Additional variables such as histology, benign versus malignant, re-operative surgery, patient's body habitus, and tumor vascularity should be taken into account for the choice of the surgical approach (VATS or open surgery). In presence of any intraoperative complications, the conversion to open approach is mandatory as indicative of good judgment and not of weakness. In the literature the rate of conversion in very high-volume center ranges from 3.5 to 12.3% [78, 79].

Robotic-Assisted Thoracoscopic Surgery

VATS is largely used for the management of pleural and lung disease, but it is not routinely performed as a therapeutic approach for mediastinal mass especially if localized within the anterior mediastinum. The fulcrum effect due to long instruments placed through fixed entry points, the bidimensional screen vision of the surgical field, and the creation of an unnatural visual effect can cause the surgeon to lose orientation and the eye-hand-target axis when the camera is under an assistant's control.

To overcome these limitations, in the last two decades, a robotic system has been developed and applied in the treatment of mediastinal diseases. Yoshino et al. reported the first case of the removal of the thymus and a posterior mediastinal mass with application of robotic system [80, 81]. These results were then reproduced in several series [82–85], showing low conversion rate, low morbidity, and adequate operative time. Cakar et al. [86] found that robotic thymectomy in patients with myasthenia gravis provided the same benefits as open trans-sternal thymectomy with regard to improvement of neuromuscular symptoms and drug dose reduction but with a lower rate of complication and of re-intervention. Additionally, Rückert et al. [87] reported an improved neurological outcome for the robotic thymectomy in respect to thoracoscopic thymectomy, for patients affected by myasthenia gravis. Over the years increasing number of papers reported the feasibility of robotic system to resect masses localized in different areas of the mediastinum. The postoperative morbidity related to robotic resection of mediastinal diseases ranges from 7.2 to 12% [88, 89]. The three-dimensional visualizing system, the lack of tremor due to filtration by computer technology, the seven-degree articulation of the instruments allowing the surgeon to be ambidextrous, and the short learning curve are the main advantages of robotic system over traditional VATS. The lack of tactile feed-

back, the cost of the procedure, and the limited availability are the main limits of robotic technology.

Open Procedures

Median sternotomy is the preferred approach for the resection of the mediastinum tumor. It allows the access to the entire chest cavity including the heart, great vessels, and bilateral lungs (Fig. 5.10). Thoracotomy allows wide access to the right or left chest, and it could be indicated in case of removal of large tumors that are localized to one side or the other. In case of extensive lung tumors involving the mediastinum, or large mediastinal tumors that cannot be managed with a sternotomy or thoracotomy alone, performing a trans-sternal incision combined with bilateral anterior thoracotomies (clamshell incision), or a unilateral thoracotomy combined with a median sternotomy (hemiclamshell incision), could be indicated [90].

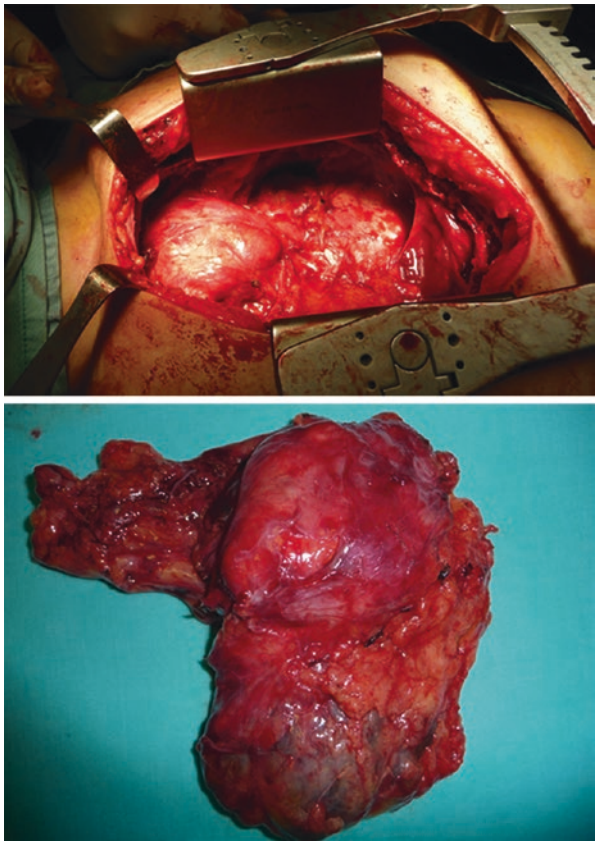

Fig. 5.10 A 57-year-old man with a large thymoma that was resected through sternotomy

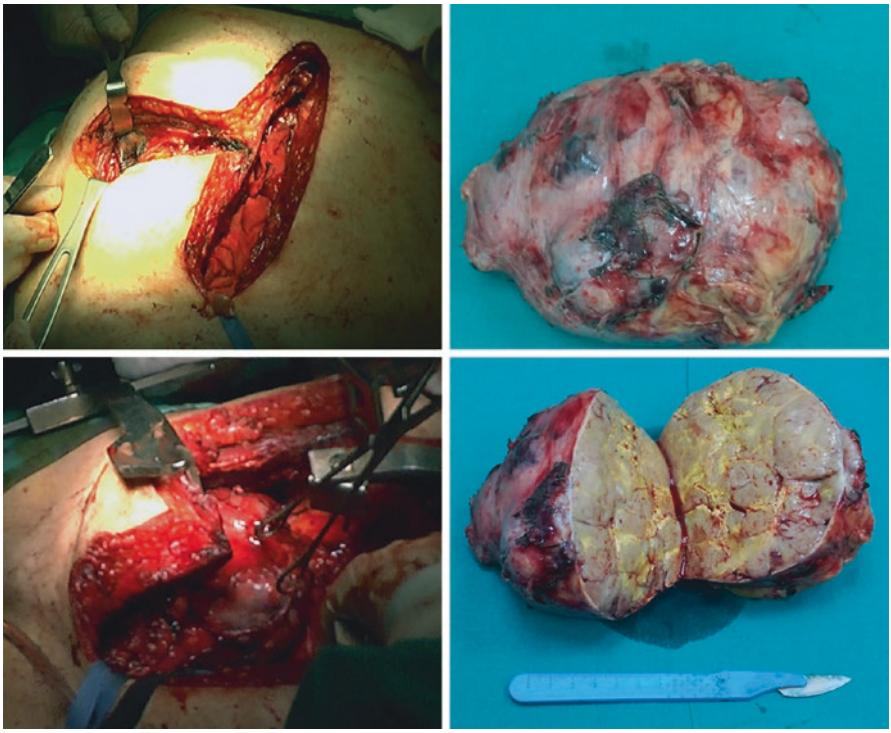

Fig. 5.11 A 63-year-old man with a large thymoma that was resected through left hemiclamshell incision

Clamshell incisions afford much better exposure to the phrenic, vagus, and recurrent laryngeal nerves than that achieved by a median sternotomy. In the hemiclamshell approach, the extension of the median sternotomy incision superiorly to the mandible permits excellent exposure of the carotid and vertebral arteries, the subclavian vessels, as well as the jugular and the innominate veins and also provides exposure of the brachial plexus and lower cervical spine to the T2 vertebral body, allowing remarkable access to anteriorly placed apical tumors [90, 91] (Fig. 5.11).

Open approaches are indicated for the resection of mediastinal tumors after neoadjuvant chemo- or radiotherapy, all mediastinal tumors not resectable with minimally invasive surgery (VATS or robotic system), and in the presence of any complications occurring during VATS or robotic system resection that required a conversion. The main advantages of open compared to minimally invasive approach are the excellent exposition of the mediastinum and its structures with the possibility of performing resection of large mass and the better control of the margins of resection. Compared to minimally invasive procedures, the main limits of open surgery are the invasiveness and the increased length of hospital stay, the worse postoperative pain and cosmetic results, and the higher rate of morbidity.

Conclusions

A variety of strategies including transcutaneous biopsy, endoscopy, anterior mediastinotomy, mediastinoscopy, VATS, robotic system, and open approach are available to obtain a diagnostic tissue and then to plan a prompt treatment of a mediastinal mass. The strategic decision depends on patient's clinical conditions, localization and characteristics of the mass, the expected risk of malignancy, and the familiarity of the surgeon with certain techniques. Detailed preoperative imaging of the mass to assess the anatomy and the exact relationship of the tumor with the surrounding structures are mandatory for the choice of the surgical strategy.

Generally, for mediastinal mass with well-marked margins and without sign of invasiveness or of malignancy (i.e., neurinoma, cystic lesion, noninvasive thymoma, and mature teratoma), complete resection is recommended, being diagnostic and therapeutic. A minimally invasive approach such as VATS or robotic system (if available) should be preferred to standard open strategy since it provides access to most parts of the mediastinum with the advantages of lower length of hospital stay, lower morbidity, and better cosmetic results. On the other hand, open surgery remains the treatment of choice for resecting large mass or mass with involvement or close proximity to the nerves, airway, esophagus, great vessels, or heart.

For lesion adjacent to tracheobronchial tree such as mediastinal adenopathies, the first approach to obtaining a tissue sample is E(B)US. In the case of non-adequate material for a definitive diagnosis, a surgical biopsy by mediastinoscopy (paratracheal and subcarinal lymph node) or by anterior mediastinotomy or VATS (APW and para-aortic lymph node) should be performed.

In the case of anterior mediastinal masses with invasiveness of adjacent structures, a preoperative diagnosis is mandatory before proceeding with surgery. Transcutaneous biopsy with FNAB or CNB is the first approach, but it must be quickly switched to more invasive surgical procedures if the results are non-conclusive. In these cases, mediastinotomy or VATS should be performed, providing a diagnostic accuracy of 100%.

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Chapter 6
Diagnostic Histopathology Approach

Giulio Rossi, Moira Ragazzi, and Alberto Cavazza

Introduction

The thoracic region, and particularly the mediastinum, contains several structures representing all types of cell differentiation, including epithelial organs (e.g., thymus), various mesenchymal tissues (e.g., nerves, vessels), lymphoid component (e.g., thymus and lymph nodes), and many ectopic tissues (e.g., salivary gland). Apart from tumors arising in specific mediastinal organs (e.g., thymus), the wide spectrum of tissues intuitively leads to imagine that virtually all sort of neoplasms may occur in the mediastinum, including metastatic malignancies.

While neurogenic tumors are predominantly located in the posterior mediastinum, the great majority of mediastinal growths develop in the anterior or middle compartments [1–3].

Indeed, the majority of publications have previously subdivided the tumors of the mediastinum based on "geographic"-involved regions, namely, anterior, middle, and posterior mediastinum [1–3]. On the other hand, the classification of the World Health Organization (WHO) of the lung, pleura, thymus, and heart [4] commonly distinguishes the tumors in mediastinum on cell differentiation (epithelial, mesenchymal, lymphoproliferative, germ cell tumors, etc.). However, one of the most difficult tasks for surgical pathologists is represented by frozen section examination of mediastinal masses, basically due to the small size of pieces obtained from the thoracic surgeon, tissue fragmentation and artifacts related to intraoperative procedure, and the great range of benign and malignant lesions that one should consider at the microscope during intraoperative analysis [5–7].

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The alternative design of this chapter is then mainly organized considering the different morphologic patterns with which mediastinal masses may appear on frozen sections and at definitive formalin-fixed and paraffin-embedded sections.

Six main patterns have been arbitrarily identified to discuss this histopathologic approach to mediastinal lesions, as follows: (1) epithelioid cell pattern, (2) spindle cell pattern, (3) small-cell pattern, (4) clear-cell pattern, (5) fibroinflammatory-looking pattern, and (6) cystic pattern.

Provided that this kind of structural classification may be helpful in organizing an initial and logic list of differential diagnoses, pathologists should be aware that overlapping features are frequently seen in lesions involving the mediastinum (e.g., a thymoma with cystic changes, a combined small and large cell neuroendocrine carcinoma, a sarcomatoid carcinoma with bland spindle cell cytology, and a fibroinflammatory background) [8, 9].

Since the pathologic diagnosis of these lesions is made using a variety of techniques including radiologically guided core-needle biopsy or cytology and surgical biopsy through a variety of approaches, the morphology-based scheme here proposed may be likely adopted in different types of samples.

Although small biopsies and cytology from fine-needle aspiration may reach up to 80% of diagnostic adequacy in the hands of expert pathologists, the broad spectrum of tissue types in this region and the variety of cell morphology (even within the same neoplasm) are critical issues recommending an adequate and representative sampling of mediastinal masses [10, 11].

Since the incidence of primary mediastinal tumors is far less common than metastatic neoplasms from other sites, this fact should always be kept in mind when analyzing a tumor growth in this site. Of note, the diagnosis of a mediastinal mass always requires a close integration with clinical data (e.g., age, gender, past medical history, smoking habit) and radiologic features (e.g., solid, cystic, necrotic appearance, location, relationship with neighboring structures), and even laboratory tests (e.g., serum tumor markers) are always mandatory [2, 7].

Finally, the diagnosis of mediastinal mass often requires a surgical approach and then frozen section examination. The most important point to discuss with the thoracic surgeon is whether the mass is completely resectable or not. If resectable, the value of the intraoperative examination is critical, and a rapid, correct diagnosis is mandatory.

If unresectable, the main target to reach by pathologist is to assure an adequate quantity of tissue for definitive diagnosis and appropriately manage the tissue to carry out complementary techniques (e.g., fresh tissue for microbiology and/or frozen tissue for molecular determinations).

Epithelioid Cell Pattern

The differential diagnosis concerning the main lesions with epithelioid cell pattern is concisely summarized in Table 6.1.

Table 6.1 Main differential diagnosis of the *epithelioid cell pattern*

Entities (compartment of mediastinum, mean age)	Cytological features	Pattern of growth	Distinctive immunohistochemistry/ molecular features
Thymomas			
B2 (ant, 49 years)	– Neoplastic polygonal cells with poorly defined eosinophilic cytoplasm – Oval-to-round monomorphic nuclei – Vesicular chromatin – Small but prominent central nucleoli	– Normal thymic cytoarchitecture – Abundance of TdT+ T cells – Clusters of tumor epithelial cells – +/− medullary islands, +/− Hassall corpuscles, +/−perivascular spaces	**Positive** CKs +[a] CK19 +[a] P63/p40 + PAX8 + TdT + (in nonneoplastic immature T cells) **Negative** CD20 − (+ in B cells of medullary islands) CD5 − (+ in T cells) CD117 −
B3 (ant, 55 years)	– Neoplastic cells can be moderately atypical – Absent or rare intercellular bridges	– Normal thymic cytoarchitecture – Sheets of epithelial cells – Paucity or absence of intermingled TdT+ T cells +/− Hassall corpuscles, +/− perivascular spaces	
Thymic carcinoma			
Squamous cell carcinoma (ant, 56 years)	– Atypical neoplastic cells with large vesicular or hyperchromatic nuclei and prominent nucleoli – Intercellular bridges and squamous differentiation – Lack of peripheral nuclear palisading	– Loss of normal thymic cytoarchitecture – Smooth-contoured or irregular, jagged islands – Desmoplastic to sclerohyaline stroma – Variable amount of inflammatory cells – Necrosis	**Positive** CKs + P63/p40 + PAX8 + CD5 + CD117 + Chromogranin/synaptophysin +/− (focal) TTF1 +/− **Negative** TdT − CK20 − EBV −

(continued)

Table 6.1 (continued)

Entities (compartment of mediastinum, mean age)	Cytological features	Pattern of growth	Distinctive immunohistochemistry/ molecular features
Basaloid carcinoma (ant, 60 years)	– Basaloid cells with high nuclear-to-cytoplasmic ratio and evident nucleoli – Peripheral nuclear palisading – Focal squamous differentiation	– Loss of normal thymic cytoarchitecture – Cystic papillary and nesting – Sclerotic or desmoplastic stroma – Comedo-type necrosis	**Positive** CKs + P63/p40 + CD5 +/− CD117 + **Negative** TTF1 − Chromogranin/synaptophysin −
Mucoepidermoid carcinoma (ant, 49 years)	– Squamous (epidermoid) cells – Mucus-secreting (goblet) cells – Intermediate cells – Mild cellular atypia	– Loss of normal thymic cytoarchitecture – Solid nests with microcysts and admixed goblet cells	**Positive** CKs + P63/p40 + MUC2 + (in goblet cells) CK20 +/− t(11;19)(q21;p13) − *MAML2* gene **Negative** CK7 −/+ CD5 − CD117 −
Lymphoepithelioma-like carcinoma (ant, 41 years)	– Poorly differentiated squamous cells – Crowded overlapping nuclei with prominent nucleoli – Vague intercellular bridges and focal squamous differentiation	– Syncytial – Prominent lymphoplasmacytic infiltrate – Coagulative necrosis	**Positive** CKs + P63/p40 + CD5 +/− CD117 +/− EBV + (50%)[b] **Negative** TdT − CK20 − CK7 −

Adenocarcinoma (ant, 56 years)	– Glandular differentiation and/or mucin production – Goblet/signet-ring cells – Nuclear pleomorphism and necrosis (only in ADC NOS)	– Loss of normal thymic cytoarchitecture – Tubulopapillary, cribriform, or glandular structures	**Positive** CKs + P63 + (in adenoid cystic carcinoma-like) CD5 +/– CK20/CDX2/MUC2 (only in intestinal-type mucinous ADC) **Negative** CD117 –
NUT carcinoma (ant, any age)	– Monomorphic small- to intermediate-sized undifferentiated cells – Brisk mitotic activity	– Loss of normal thymic cytoarchitecture – Sheets and nests – Abrupt foci of keratinization – Necrosis	CKs + EMA + P63/p40 + *NUT* rearrangement (NUT carcinoma)
Thymic neuroendocrine tumors			
Carcinoids (ant, 49 years)	– Uniform polygonal cells – Small round nuclei – Finely granular chromatin	– Nests/trabeculae/rosettes, separated by a delicate vasculature – Necrosis (*only in atypical carcinoid*)	**Positive** CKs + (dot-like) More than one of neuroendocrine markers (chromogranin A, synaptophysin, CD56, and NSE) in >50% of tumor cells PAX8 + **Negative** TTF1 –/+ P63/p40 – CD117 – CD5 –
Large cell carcinoma (ant, 51 years)	– Large cells with high-grade morphology – Prominent nucleoli – Apoptotic bodies – > 10 mitoses/2mm^2	– Solid – Extensive necrosis	

(continued)

Table 6.1 (continued)

Entities (compartment of mediastinum, mean age)	Cytological features	Pattern of growth	Distinctive immunohistochemistry/ molecular features
Germ cell tumors of the mediastinum			
Seminoma (ant, all ages)	– Monomorphic cells – Nonoverlapping nuclei, one or more central nucleoli	– Multinodular clusters, sheets, cords, or irregular lobules – Lymphoid infiltrate	CKs −/+ (dot-like) OCT4/SALL4/CD117/SOX17 + D2-40 + CD30/βhCG/AFP/SOX2/glypican 3 −
Embryonal carcinoma (ant, 27 years)	– Large cells – Indistinct borders – Crowded nuclei – Large eosinophilic nucleoli – Atypical mitoses	– Solid growth, complex glandular array or papillae	CKs + OCT4/SALL4/CD30/SOX2 + AFP +/− EMA/βhCG/SOX17 −
Yolk sac tumor (ant, 20–30 years)	– Medium to large cells– Moderate pleomorphism	– Extremely variable: Microcystic or reticular, glandular-alveolar, pseudopapillary with Schiller-Duval bodies, myxomatous, etc.	CKs + Glypican 3/AFP/SALL4+ PLAP/CD117 +/− OCT4/SOX2/D2-40/CD30/βhCG −
Choriocarcinoma (ant, 17–63 years)	– Multinucleated syncytiotrophoblastic cells, mononuclear cytotrophoblastic cells, and intermediate trophoblast– Severe pleomorphism	– Diffuse– Tumor intimately associated with dilated sinusoids– Extensive hemorrhage and necrosis	CKs + βhCG/glypican 3/SALL4+ CD117− OCT4/PLAP/AFP/CEA/CD30 −

Lymphomas of the mediastinum			
PMLBCL (ant, 20–30 years)	– Medium to large neoplastic cells– Abundant, frequently clear cytoplasm– Irregular nuclei with small nucleoli	– Diffuse– Compartmentalizing fibrosis in thymic mass– Intrasinusoidal growth in lymph nodes	**Positive** CD20 + CD79a + PAX5 + CD23 + p63 + CD30 +/– IRF4-MUM1 +/– **Negative** CKs – p40 – CD15 – CD10 – HLADR –
ALCL (any compartment, any age)	– Large cells– Hallmark cells: Abundant cytoplasm, kidney-shaped nucleus, prominent Golgi region	– Cohesive pattern – Intrasinusoidal growth in lymph nodes	**Positive** CD30+ EMA + Cytotoxic molecules + ALK rearrangement (90% of cases in children and 50% in adult) **Negative** Loss of several pan-T-cell antigens
Histiocytic and dendritic cell neoplasms			
Langerhans cell histiocytosis/sarcoma (ant, any age)	– Grooved nuclei and eosinophilic cytoplasm– Overtly malignant cytologic features in sarcoma	– Diffuse, non-cohesive growth– Admixed multinucleated giant cells and eosinophils	**Positive** S100 + CD1a + Langerin + *BRAF* V600E or V600D (50% of Langerhans cell histiocytosis)

(continued)

Table 6.1 (continued)

Entities (compartment of mediastinum, mean age)	Cytological features	Pattern of growth	Distinctive immunohistochemistry/ molecular features
Histiocytic sarcoma (ant, 50 years)	– Pleomorphic large cells with abundant eosinophilic cytoplasm– Irregularly folded and eccentrically placed nuclei– Sarcomatoid areas with spindle cells	– Diffuse, non-cohesive growth– Variable number of reactive cells	**Positive** At least one histiocytic marker (CD163, CD68/PGM1, or KP1, and lysozyme) CD45 + **Negative** S100 −/+ (weak or focal) CD1a − Langerin − CD21 − CD35 − Myeloperoxidase − CD33 −/+ CD13 −/+
Vascular tumors			
Epithelioid hemangioendothelioma (ant, 46 years)	– Epithelioid endothelial cells– Intracytoplasmic lumina– Intranuclear cytoplasmic inclusions	– Diffuse– Variable hyalinized myxo-collagenous or chondroid stroma	**Positive** At least one endothelial marker (CD31, CD34, ERG, FLI) CKs +/− *CAMTA1-WWTR1* fusion gene

ant anterior, *CKs* cytokeratins

[a]Rare cytokeratin-negative thymomas have been reported [Adam P, Hakroush S, Hofmann I, et al. Thymoma with loss of keratin expression (and giant cells): a potential diagnostic pitfall. Virchows Archiv: an international journal of pathology. 2014]

[b]EBV is almost always positive in children and young adults <30 years

Thymomas are rare malignancies overall, but they are the most common mediastinal tumors in adulthood (35%) and exceptional in children. Anterior and superior mediastinum are the most common site of occurrence, even if primary pleural or intrapulmonary thymomas may be uncommonly observed. Type B1 (lymphocyte-rich thymoma) is composed of dispersed epithelial cells, in a dense background of immature T cells, mimicking the non-involuted thymic cortex [4, 8, 12, 13]. Areas of medullary differentiation are always present. It accounts for 17.5% of thymomas, and it occurs most commonly in the fifth and sixth decades of life. Grossly it appears as a nodular encapsulated tumor, ranging in diameter from 5.1 to 7.5 cm. The cut surface is soft, smooth, and tan-pink, with vague lobules delineated by fibrous septa. Necrosis and cystic change may be present. Histologically the tumor could show lobulation or not. Lobules are often larger than those of the normal thymus and traversed by collagenous septa. The neoplastic cells may be difficult to detect on low-power examination, because they are individually interspersed within nonneoplastic immature lymphocytes (Fig. 6.1). They have poorly defined eosinophilic cytoplasm and oval to rounded monomorphic nuclei with vesicular chromatin and small but prominent central nucleoli. Medullary islands appear as pale nodular areas and are characterized by an increased numbers of B cells and mature T lymphocytes; it may contain Hassall corpuscles and myoid cells. Perivascular spaces are often present. Differential diagnosis mainly includes hyperplastic thymus and lymphomas. Type B1 thymoma shows a thicker fibrous capsule and, if present, larger lobules with fibrous septa. In contrast to hyperplastic thymus, type B1 thymoma has a prevalence of cortical areas over medullary islands, which show fewer or absent Hassall corpuscles, and autoimmune regulator (AIRE)-positive epithelial cells [14].

Neoplastic cells of lymphoma are monotonous and atypical, with frequent necrosis and a diffuse pattern of growth, which effaces corticomedullary architecture. Blasts typically infiltrate mediastinal fat, and rearrangement of T-cell receptor is mostly monoclonal. A panel of epithelial markers including keratins and p63 could

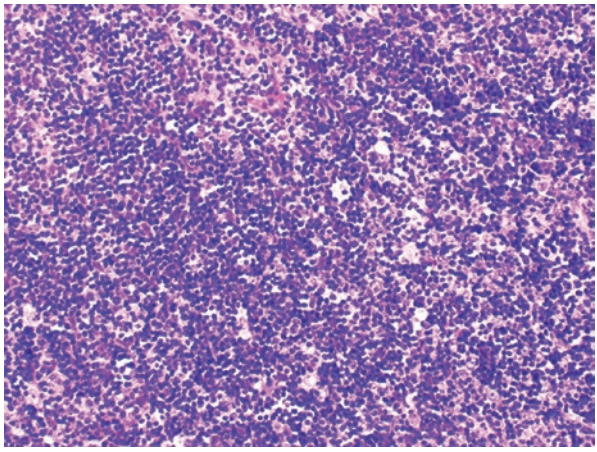

Fig. 6.1 Type B1 (organoid type) thymoma with few, scattered epithelial cells in a background of immature T cells

be useful to exclude the presence of a preserved network of epithelial cells and to definitely exclude type B1 thymoma [15, 16].

Type B2 (lymphocyte-rich thymoma) is a lymphocyte-rich tumor with a content of epithelial cells higher than that seen in type B1 thymoma (clusters of ≥3 cells). It accounts for 26% of all thymoma, with a mean age at presentation of 49 years. Macroscopically a capsule may or may not be present, and invasion of the mediastinal fat or adjacent organs can occur. The cut surface is gray white and soft to firm, with lobules delineated by white fibrous septa. Cystic changes, necrosis, and/or hemorrhage can be observed. Histologically the tumor shows a lobular architecture with a prevalence of immature nonneoplastic T cells and clusters of neoplastic polygonal epithelial cells, which have the same cytological features described in type B1 thymoma (Fig. 6.2). Rare cases can focally show anaplasia. Perivascular spaces composed of a central venule surrounded by a clear space containing proteinaceous fluid or variable numbers of lymphocytes are typically present. Medullary islands are usually inconspicuous [4, 8, 12–15].

Type B3 (lymphocyte-poor thymoma, well-differentiated thymic carcinoma) is characterized by a predominance of polygonal epithelial cells, which form solid sheets, and paucity of admixed nonneoplastic immature T cells, resulting in a pink appearance on H&E stains at low magnification. It accounts for 16% of all thymoma and the mean age at diagnosis is 55 years. Macroscopically it is usually poorly circumscribed with invasion of the mediastinal fat and adjacent organs. The diameter ranges from 5.1 to 6.8 cm. The cut surface is firm and gray or yellow, with multinodular appearance. Necrosis and hemorrhage may be present. Histologically, typical findings include lobular architecture, pushing borders at the invasion front, prominent perivascular spaces with epithelial palisading, absence of intercellular bridge between tumor cells, and epithelial whorls resembling squamous eddies or abortive Hassall corpuscles. Tumor cells are mildly to moderately atypical, with round or oval nuclei of variable sizes and sometimes grooved (Fig. 6.3). Association

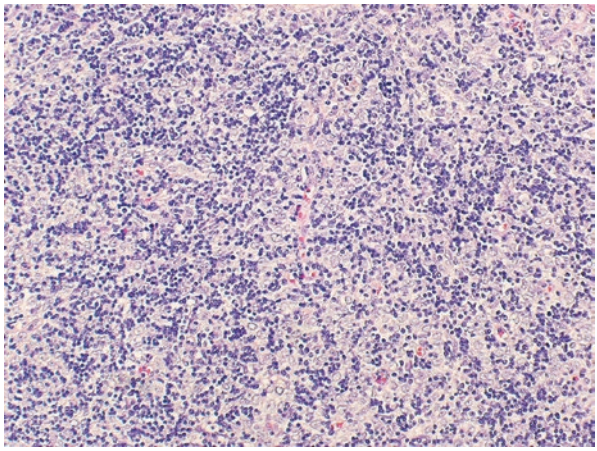

Fig. 6.2 Type B2 (cortical-type) thymoma with clusters of epithelial cells intermingled with immature T cells

with type B2 component is very frequent [4, 8, 12, 13, 16]. Differential diagnosis with thymic squamous cell carcinoma may be challenging, particularly on small biopsy. Thymic squamous carcinoma lacks lobular growth and perivascular spaces and shows infiltrative rather than pushing borders, desmoplasia, more prominent cytological atypia, and presence of intercellular bridges or overt keratinization. Immunohistochemical stains show CD5 and CD117 positivity in 80% of cases of squamous cell carcinoma (Fig. 6.4) together with the absence of TdT + Tcells. Focal expression of CD5 and CD117 in tumors with an otherwise B3 thymoma morphology has been reported [17, 18].

Thymic carcinoma (type C thymic epithelial tumor) accounts for nearly 22% of all thymic epithelial neoplasms and about 10% of mediastinal tumor in adults. Several lung cancer-like variants have been reported, such as squamous cell carcinoma, basaloid carcinoma, clear-cell carcinoma, adenocarcinoma, undifferentiated large cell carcinoma, nuclear protein in testis (NUT)-midline carcinoma, and sali-

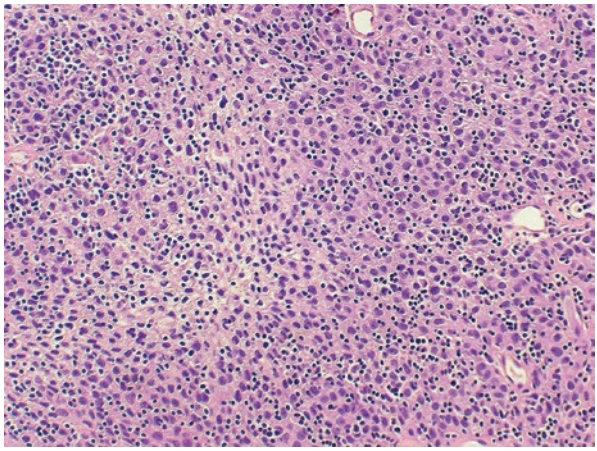

Fig. 6.3 Type B3 thymoma (well-differentiated thymic carcinoma) with a prevalence of squamoid cells and scattered immature T lymphocytes

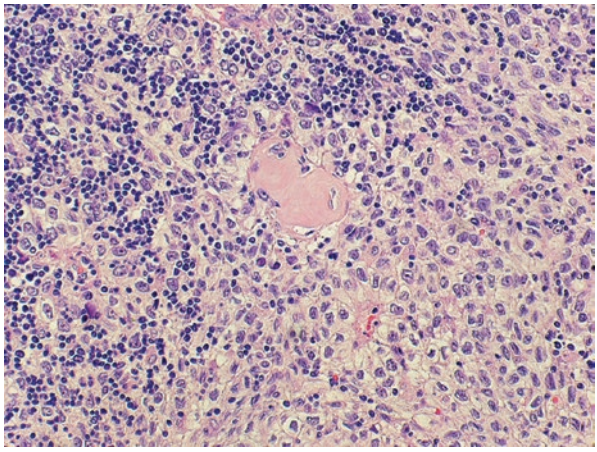

Fig. 6.4 Type B2/B3 thymoma with coexistence of both tumor types

vary gland-derived carcinomas (mucoepidermoid and adenoid cystic carcinoma, adenosquamous carcinoma, sarcomatoid carcinoma, lymphoepithelioma-like carcinoma) [4, 8, 12, 13, 18–24].

Squamous cells carcinoma (SqCC) shows morphological features of SqCC occurring in other organs (Fig. 6.5). Unlike thymoma, it generally lacks resemblance to the normal thymic cytoarchitecture: discrete lobulation, perivascular spaces, and intermingled immature T lymphocytes. It accounts for approximately 70% of all thymic carcinomas. Macroscopically it is a frankly invasive tumor with frequent foci of necrosis and hemorrhage and a mean maximum diameter of 7.2 cm. Histologically, it grows predominantly in the form of anastomosing smooth-contoured islands, but it can show jagged invasion in some cases. SqCC can show a range of differentiation from well to moderate to poor, based on the presence or absence of keratinization, nuclear pleomorphism, and the extent of squamous cell maturation. The relevance of grading is controversial, and there is currently no generally accepted tumor grading system. At immunohistochemical level, neoplastic cells are positive for keratins, p63 (83% of cases), PAX8 (75% of cases), CD5 (74% of cases), CD117 (84% of cases), FOXN1 (68–76% of cases), and CD205 (10–59% of cases) [17–19, 25, 26]. Basaloid carcinoma is characterized by solid and cystic papillary nests of medium- to small-sized cells with a high nuclear-to-cytoplasmic ratio and peripheral palisading. It accounts for <5% of all thymic carcinomas (less than 40 cases reported in English-language literature), with a median age of 60 years and a male predominance (male-to-female ratio, 2.5:1) [20]. Interestingly multilocular thymic cysts were observed in about 50% of the cases and may represent a precursor lesion. Grossly it is generally a well-circumscribed grayish tumor with solid and cystic areas and a mean size of 8 cm. Histologically it shows an admixture of cystic papillary and nesting growth patterns. Foci of comedo-type necrosis are common, and focal squamous differentiation can be observed in up to 40% of cases (Fig. 6.6). Small glands associated with deposits of amorphous basement membrane-like material may be present. Rarely sarcomatoid transformation can occur. Cystic

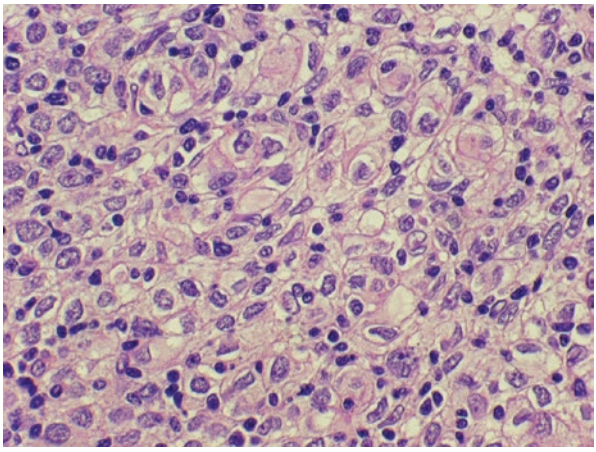

Fig. 6.5 Type C thymic carcinoma, squamous cell carcinoma variant

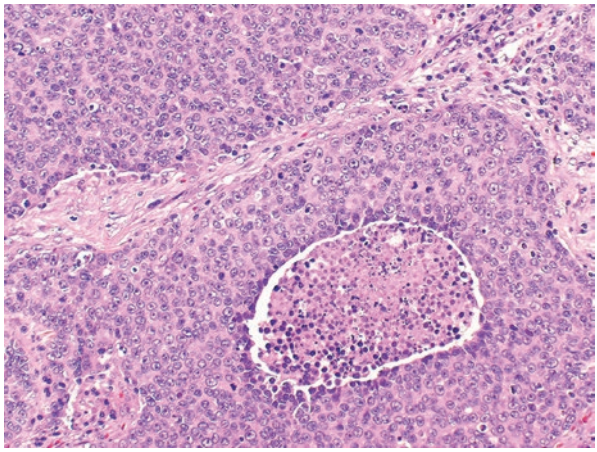

Fig. 6.6 Type C thymic carcinoma, basaloid carcinoma variant

changes can result from pre-existing multilocular thymic cysts, lined by benign-looking squamous cells, or they represent cystic degeneration of the tumor and are lined by neoplastic basaloid cells. At immunohistochemical level, BC cells are positive for p63/p40, CD117, and CD5 (<50% of cases). TTF1, chromogranin, and synaptophysin are negative.

Mucoepidermoid carcinoma represents a particularly unusual type of thymic carcinoma, morphologically similar to the salivary gland counterpart. It is composed of a combination of squamous cells, mucinous cells, and intermediate-type cells [4, 8, 12, 13, 20, 25]. The average age is 49 years. Some cases are associated with multilocular thymic cysts. Grossly tumor size ranges from 4 to 11 cm. The tumor is well demarcated, but infiltration of pericardium can occur. The cut surface shows a variable amount of cystic areas containing mucoid substance. Histologically there are variable combination of epidermoid cells forming sheets or solid islands, goblet cells (positive with mucicarmine or periodic acid-Schiff stain) forming nests or occurring as single cells, and intermediate cells forming nests or lobules or intermingled with squamous or mucus-secreting cells. The majority of cases show low-grade histology, but high-grade cases showing atypia and high mitotic activity (>7 mitosis per 2 mm^2) are on record, and they can mimic adenosquamous carcinoma or mucinous adenocarcinoma. Immunohistochemistry shows positivity for pan-cytokeratin and EMA. CK5/CK6 and p63 are often positive. Unlike MEC of salivary gland, CK7 is rarely positive. CD5 e CD117 are negative in most cases. A useful diagnostic feature is the identification of the translocation t(11;19)(q21;p13), of the MAML2 gene, using FISH [27–29]. This is the same chromosomal rearrangement already described in almost all low-grade MECs and many high-grade MECs of the salivary glands, bronchi, and lung. Lymphoepithelioma-like carcinoma (LELC) is a primary thymic poorly differentiated squamous cell carcinoma associated with a prominent lymphoplasmacytic infiltrate and morphologically similar to nasopharyngeal carcinoma. It accounts for 6–32% of all thymic carcinomas with a median age of 41 years and a bimodal peak at 14 years and 48 years. A male predominance has been reported (male-to-female ratio 2:1). Grossly it is an invasive mass with a

solid cut surface yellow-white, with areas of necrosis. Histologically it consists of anastomosing sheets, nests, and cords of carcinoma cells, with indistinct borders, large vesicular nuclei, and distinct nucleoli, accompanied by abundant lymphocytes and plasma cells. Generally, there is no striking anaplasia. Focal squamous differentiation can be present. Germinal centers, eosinophils, and granuloma may be present. Coagulative necrosis is common. Half of cases are associated with EBV, which is almost always positive in children and young adults, while it is uncommon in adults aged >30 years. The most reliable way to demonstrate EBV is in situ hybridization for EBV-encoded small RNA. Immunohistochemically, tumor cells are positive for pan-cytokeratin and frequently for p63. CK7 and CK20 are negative. There is variable positivity for CD5 and frequent immunoreactivity for CD117. The lymphocytes are mostly CD3+/TdT-mature T cells admixed with B cells and polytypic plasma cells [20, 23, 24, 30].

Adenocarcinomas represent a heterogeneous group of malignant thymic epithelial tumors showing glandular differentiation and/or mucin production. They are very rare with only single reports or small series described [31–36].

Papillary type. It shows an architectural resemblance to papillary thyroid carcinoma or malignant mesothelioma. It consists of tubulopapillary structures lined by cuboidal to polygonal cells with distinct nucleoli and eosinophilic or clear cytoplasm. Complex glomeruloid structures can also be formed. Psammoma bodies may be numerous. Coagulative necrosis can be sometimes massive. This carcinoma is often associated with type A or AB thymoma and is therefore assumed to represent a malignant transformation of thymoma. Another associated lesion is multilocular thymic cyst. Neoplastic cells are positive for epithelial markers (keratins, EMA, BerEp4) and can show focal positivity for CD5.

Adenoid cystic carcinoma-like tumor. It is morphologically similar to its salivary gland counterpart, but does not exhibit the full range of characteristics seen in salivary gland-type ACCs. In particular, there is no tubular growth pattern, no myoepithelial component, and no obvious neurotropism. It is composed of nests of basaloid cells with variable number of pseudocysts filled with homogeneous or granular basophilic membrane material with cribriform structures formation. Nuclear atypia and necrosis are rare. Tumor cells are positive for keratins and p63 but negative for other myoepithelial markers (e.g., smooth muscle actin, S100). The pseudocyst content is positive for collagen IV, laminin, and stromal mucin. Occasional CD5-positive cells could be present, but CD117 is negative. Mitotic activity is low (ki67 < 10%).

Mucinous adenocarcinoma. It resembles the counterpart that occurs in other organs. The carcinoma cells can show goblet cell or signet-ring cell morphology due to cytoplasmic mucin accumulation, or there could be abundant extracellular mucin, in which neoplastic glands or single tumor cells float. This tumor is often associated with thymic cyst supporting a primary thymic origin rather than metastasis. Tumor cells could express an intestinal immunophenotype (CK20 +, CDX2 +, MUC2 +) and show variable positivity for CD5.

Adenocarcinoma, not otherwise specified (NOS). It encompasses adenocarcinoma not conforming to any of the above three subtypes. Nuclear pleomorphism is significant and necrosis is common.

Tumor cells show positivity for keratins and sometimes for CD5.

In general, the finding of an adenocarcinoma in the mediastinum should consistently raise the possibility of a metastasis from other sites. Organ-specific markers (e.g., TTF1, GCDFP-15, thyroglobulin, PSA) may be helpful to confirm extrathymic origin. Search for associated thymic cyst or thymoma areas could be helpful since their presence favors a thymic primary [37].

NUT-midline carcinoma is a poorly differentiated carcinoma genetically defined by the presence of NUT gene translocation [38, 39]. Originally thought to be a disease of children and young adults, NUT carcinoma can occur at any age (from birth to 78 years). Thoracic/mediastinal primary accounts for 57% of all cases of NUT carcinoma, with the contemporary involvement of both the lung and mediastinum at presentation. It characteristically presents as a rapidly growing mass with rapid dissemination. Histologically it is composed of monomorphic poorly differentiated carcinomatous cells that show focal abrupt keratinization. Glandular and mesenchymal differentiation are typically absent. At immunohistochemical level, it is consistently positive for nuclear protein in testis (NUT, aka NUTM1). Pan-cytokeratins and p63/p40 are positive in the majority of cases. Occasionally it expresses chromogranin, synaptophysin, or TTF1. Tumor cells often stain for CD34, which may lead to a misdiagnosis of acute leukemia. Germ cell and lymphoid and myeloid markers are negative. Molecular determination of NUT rearrangement, t(15;19) in 70% of cases, is diagnostic.

Undifferentiated carcinoma is a diagnosis of exclusion: it is a primary carcinoma of the thymus showing no morphological or immunohistochemical feature other than epithelial differentiation (Fig. 6.6). The tumor cells are positive for pan-cytokeratin, CD117 (60%), and PAX8 (40%). Unlike in poorly differentiated thymic squamous cell carcinoma, there is no expression of CK5/CK6, P63, or CD5 [40]. Malignant germ cell tumor markers (such as OCT3/OCT4 and SALL4) and neuroendocrine markers are negative.

Undifferentiated carcinoma should not be confused with a recent entity of large-sized and rapidly progressive undifferentiated sarcomas of the thoracic region characterized by SMARCA4-deficiency [40], mainly occurring in men and appearing as solid growth of mildly discohesive and relatively monotonous epithelioid cells with prominent nucleoli. At histology, these sarcomas show complete/partial absence of SMARCA4 and variable expression of cytokeratins, CD34, SOX2, SALL4, and p53 together with inactivating SMARCA4 mutation.

Thymic neuroendocrine tumors are classified using the same nomenclature and criteria as for lung tumors. The definition of “neuroendocrine differentiation” in both carcinoids or large cell neuroendocrine carcinomas is based on strong and diffuse expression of usually more than one of the four neuroendocrine markers (chromogranin A, synaptophysin, CD56, and NSE) in >50% of tumor cells [41–52]. There are currently no immune-histological markers that can unequivocally distinguish between thymic and pulmonary primaries, although a TTF1-/PAX8 + profile appears to be more common in thymic carcinoids. Clinical and radiological correlation remains the mainstay for the distinction between thymic and lung origin.

Typical carcinoid is a low-grade neuroendocrine epithelial neoplasm of thymic origin with <2 mitoses per 2 mm^2 and lacking necrosis. Grossly it is unencapsulated and it could be invasive. The mean size is 8–10 cm, smaller in Cushing syndrome due to earlier detection. Cut surface is gray white and firm, without the characteristic lobulated growth pattern of thymoma. Oncocytic variant may show a tan or brown cut surface. Calcifications are present in 30% of cases, more often than in extrathymic neuroendocrine tumors. At histology, it shows a solid and trabecular growth pattern with delicate vasculature between tumor masses and rosette-like formation (Fig. 6.7). Tumor variants include spindle cell, pigmented, with amyloid, oncocytic, mucinous, and angiomatoid. Therefore, the major differential diagnoses include spindle cell thymoma and paraganglioma, medullary thyroid carcinoma, metastatic mucinous carcinoma, and hemangioma.

Atypical carcinoid is an intermediate-grade neuroendocrine epithelial neoplasm, presenting 2–10 mitoses per 2 mm^2 and/or foci of necrosis. It is far more common than typical carcinoid, and it affects mainly adult with a mean age of 48–55 years and a male predominance. In a half of cases, lymph node metastases and invasion into adjacent organ are already present at diagnosis. Histologically, all architectural features of typical carcinoid can occur; a more diffuse growth pattern can be observed (Fig. 6.8).

Large cell neuroendocrine carcinoma is a high-grade neuroendocrine epithelial neoplasm composed of large cells with >10 mitoses per 2 mm^2 and frequent necrosis (Fig. 6.9).

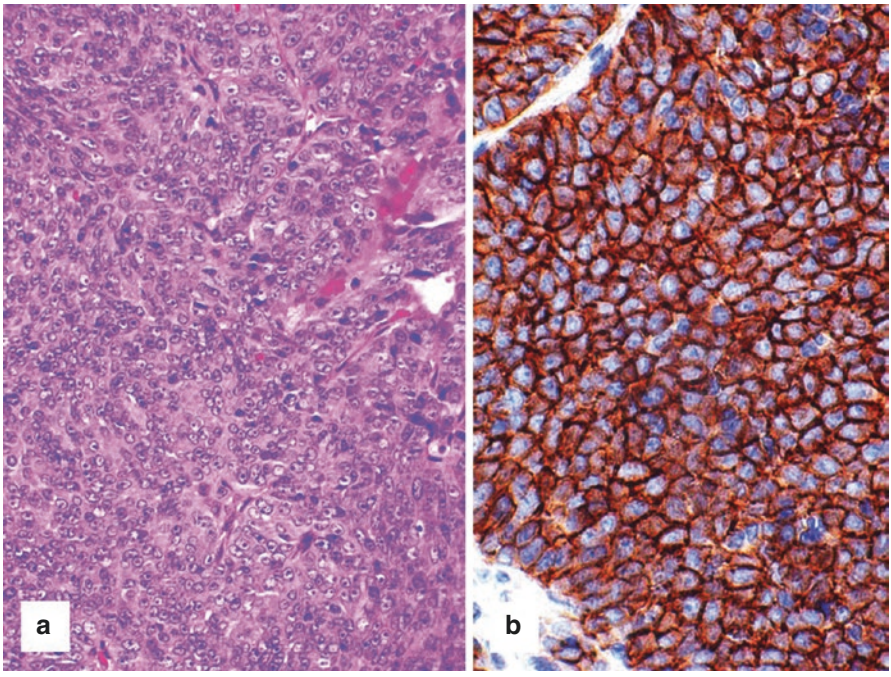

Fig. 6.7 Type C thymic carcinoma, undifferentiated type (**a**) strongly expressing CD117 (**b**)

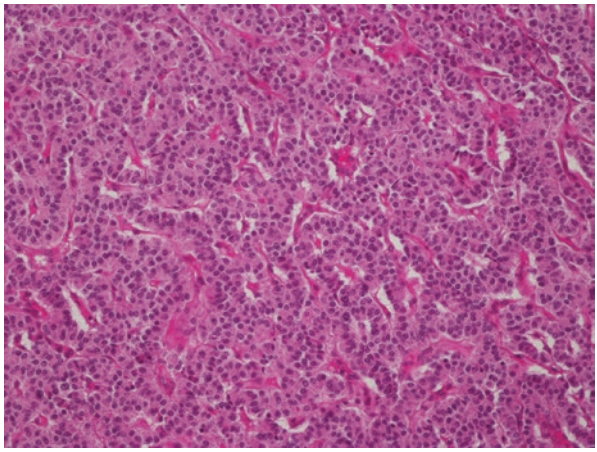

Fig. 6.8 Thymic typical carcinoid

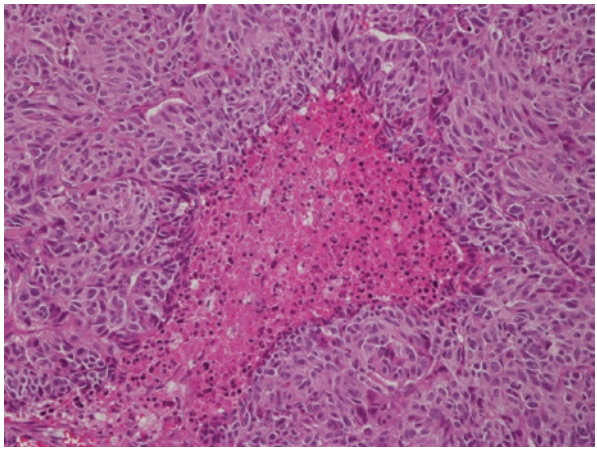

Fig. 6.9 Thymic atypical carcinoid

Differently from the lung counterpart, recent evidences suggested that LCNEC of the thymus may developed from pre-existing CTNNB1-mutated AC upon loss-of-function TP53 and gain-of-function JAK3 mutations or through an epithelial-mesenchymal transition [53].

It is important to keep in mind that neuroendocrine tumors, particularly typical and atypical carcinoids, may rarely originate from teratomas [54] and enter in differentials diagnosis with other mimicking entities, such as paragangliomas (negative with cytokeratins) and glomus tumors (expressing collagen IV, smooth muscle actin but not cytokeratins) [55] (Fig. 6.10).

Germ cell tumors of the mediastinum represent the 15% of mediastinal tumors in adults and nearly 19% in children [4, 21, 56–62]. In prepubertal children they consist only of teratomas and yolk sac tumors, either pure or mixed, while in postpubertal they can be almost any of the histological types of germ cell tumors seen in the gonads, apart from spermatocytic seminoma. The most common histological types are mature teratoma and seminoma.

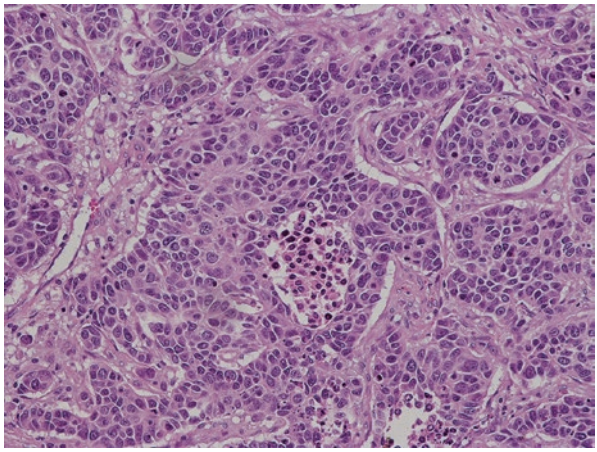

Fig. 6.10 Thymic large cell neuroendocrine carcinoma

Seminoma occurs almost exclusively in men, with exceptional cases of dysgerminoma reported in women. The peak age distribution is between 33 and 39 years. It is composed of large monomorphic cells with nonoverlapping nuclei and one or more central nucleoli, growing in multinodular clusters, sheets, cords, or irregular lobules. A lymphoid infiltrate with or without granulomatous inflammation is frequently present. Scattered syncytiotrophoblastic cells (βhCG-positive) could be seen close to capillaries and/or focal hemorrhage. Immunohistochemistry shows positivity for OCT4, SALL4, SOX17, CD117 in a cell membrane or paranuclear Golgi pattern (70% of cases), and D2-40. Keratins can be positive but in a dot-like pattern. Tumor cells are negative for CD30, βhCG, AFP, SOX2, and glypican 3.

Embryonal carcinoma affects predominantly young male, with a mean age at presentation of 27 years. It is composed of large cells with indistinct borders, crowded nuclei, and large eosinophilic nucleoli, with a solid growth, complex glandular array or papillae. Mitoses are frequent and atypical. Scattered syncytiotrophoblastic cells (βhCG-positive) are present in nearly 30% of cases. Neoplastic cells stain for low-molecular-weight keratins, CD30, SOX2, OCT4, and SALL4. AFP can be focally positive in 30% of cases, while EMA and SOX17 are usually negative.

Yolk sac tumor before the puberty represents the second most common mediastinal germ cell tumor, after teratoma. After puberty, it occurs almost exclusively in males, with a peak incidence in the third decade. Choriocarcinoma is a wide spectrum of histological pattern, often coexisting; microcystic or reticular, glandular-alveolar, and pseudopapillary with Schiller-Duval bodies; and myxomatous, hepatoid, enteric, polyvesicular-vitelline, solid, and spindle (Figs. 6.11 and 6.12). Tumor cells are consistently immunoreactive for cytokeratins, glypican 3, SALL4, and LIN28. They may express also AFP, PLAP (70%), CD117 (40%), CD30 (25%), and EMA (focally in <25% of cases). They are negative for OCT4, NANOG, SOX2, and D2-40.

Choriocarcinoma is a highly aggressive neoplasm, mainly affecting adult male patient. Histologically it appears as a highly polymorphic tumor intimately associ-

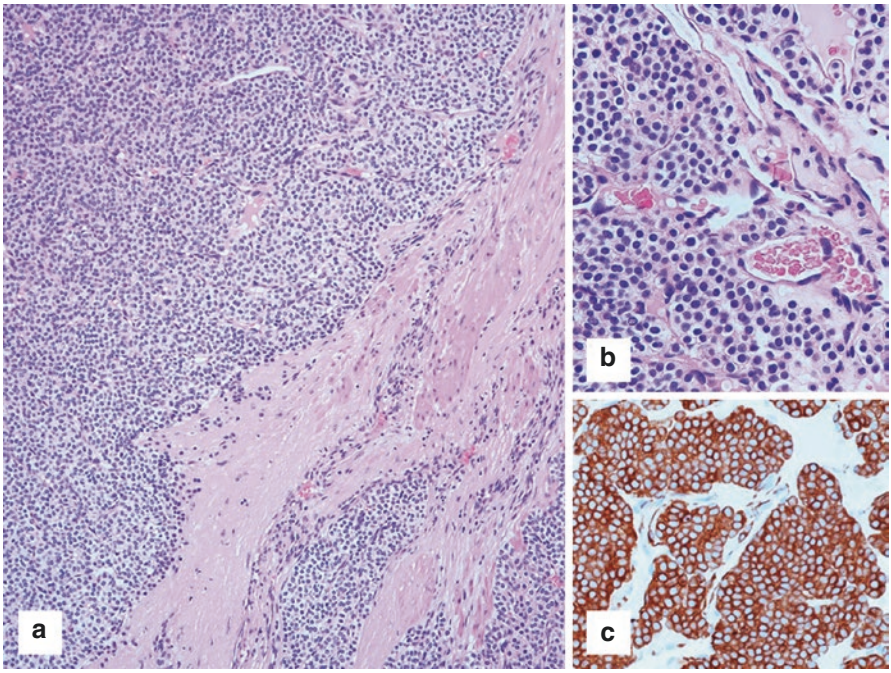

Fig. 6.11 Mediastinal glomus tumor

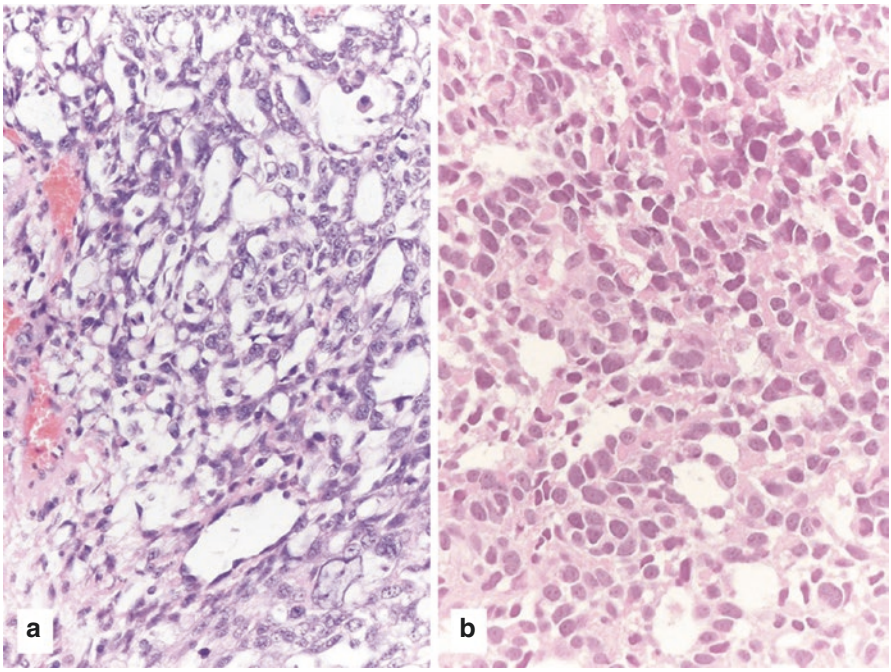

Fig. 6.12 Mediastinal yolk sac tumor with microcystic (**a**) and hepatoid (**b**) patterns

ated with dilated sinusoids filled with blood. It is composed of multinucleated syncytiotrophoblastic cells, mononuclear cytotrophoblastic cells, and variably intermediate trophoblast. Vast areas of hemorrhage and necrosis are often observed. At immunohistochemical level, it is positive for keratin. Syncytiotrophoblastic cells express βhCG and glypican 3, while cytotrophoblastic cells are positive for SALL4. Tumor cells are negative for OCT4, PLAP, AFP, CEA, and CD30.

A brief summary of immunostains in germ cell tumors is reported in Table 6.2.

Lymphomas of the mediastinum account for the 23% of mediastinal tumors in adults and about 12% in children.

Primary mediastinal large B-cell lymphoma is an aggressive large B-cell lymphoma of putative thymic B-cell origin [63–69]. It mainly occurs in the third and fourth decade, with a female predominance. It presents as a tumor mass in the thymic area. Histologically it is composed of clusters or sheets of large neoplastic cells, often compartmentalized in areas of varying sizes by a distinctive fibrosis made up of irregular collagen bands (Fig. 6.13). At the periphery of the mass, reactive cells such as lymphocytes, macrophages, and granulocytes may be present. Lymph nodes are involved with a typical carcinoma-like pattern, starting from marginal sinus, with gradual replacement of lymph nodal parenchyma. Some cases may contain cells with pleomorphic nuclei and may resemble Hodgkin lymphoma or not lymphoid tumors. Immunostaining shows positivity for B-cell markers such as CD19, CD20, CD22, and CD79a, but typically immunoglobulin, PAX5, BOB1, and OCT2 are negative. CD30 is positive (80% of cases) but weak and heterogeneous. Tumor cells also express IRF4/MUM1 (75%) and CD23 (70%) and show a variable positivity for Bcl2 and Bcl6. CD10 is almost always negative. Interestingly positivity for p63 can be present in >90% of cases, while p40 is absent. This is helpful in the differential diagnosis with Hodgkin lymphoma, but it could represent a caveat, since p63 is also expressed in normal and neoplastic thymic epithelial cells, although it is typically accompanied by p40 expression.

Table 6.2 Immunohistochemistry in germ cell tumors

Germ cell tumor entity	CK	OCT4	SALL4	CD117	CD30	AFP	βhCG	Glypican 3	Sox2	SOX17
Seminoma	−[a]	+	+	+	−	−	−[b]	−	−	+
Embryonal carcinoma	+	+	+	−/+	+	+/−	−[b]	−	+	−
Yolk sac tumor	+	−	+	+/−	−	+	−	+	−	NAD
Choriocarcinoma	+	−	+[c]	−	−	−	+	+[d]	NAD	NAD
Immature teratoma	+	−	−/+[e]	−/+	−	−/+[f]	−	+/−	NAD	NAD

CK cytokeratins, *βhCG* β-subunit of human chorionic gonadotropin, *NAD* no available data

[a]Keratins can be positive but in a dot-like pattern

[b]It highlights scattered syncytiotrophoblastic cells

[c]It stains mononuclear trophoblast

[d]It stains syncytiotrophoblast

[e]Focal staining in enteric glands, primitive neuroepithelium, and blastema-like stroma of immature teratoma

[f]It can be positive in the fetal gut, liver, and neuroepithelium

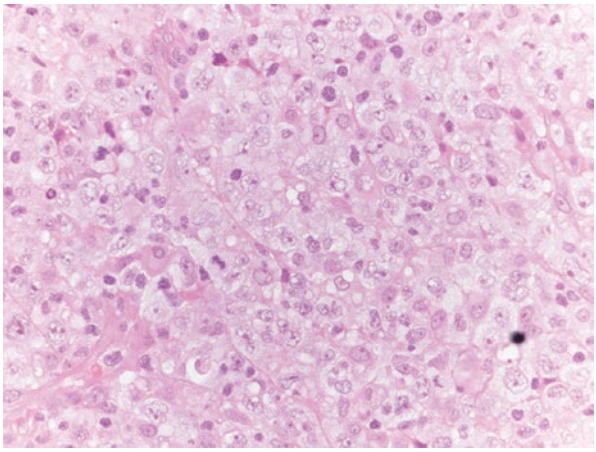

Fig. 6.13 Primary mediastinal large B-cell lymphoma

Anaplastic large cell lymphoma is a mature T-cell lymphoma characterized by strong expression of CD30 and the presence of a variable proportion of hallmark cells with abundant cytoplasm, a kidney-shaped nucleus, and a prominent Golgi region. Translocation of ALK with a variety of other genes, most commonly with NPM1, typically occurs in more than 90% of cases in children and in nearly 50% of adult cases. Thymus and mediastinum involvement is most commonly present in the context of advanced-stage disease. At morphology, anaplastic large cell lymphoma is composed of large cells, including hallmark cells, with a cohesive pattern and sometimes an intrasinusoidal growth in lymph nodes. Tumor cells are positive for CD30 (membranous and Golgi pattern) and EMA. The expression of cytotoxic molecules and the loss of several pan-T-cell antigens are frequently observed. ALK positivity is nuclear and cytoplasmic in case of nucleophosmin-ALK fusion protein, but the subcellular stain distribution depends on the gene involved in the chromosomal translocation.

Langerhans cell histiocytosis and its malignant counterpart, Langerhans cell sarcoma, can rarely involve thymus or mediastinal lymph node, usually in the setting of disseminated disease [70]. On hematoxylin-eosin stain, they are composed of a diffuse infiltrate of Langerhans cells, characterized by grooved or markedly contorted nuclei, fine chromatin, and eosinophilic cytoplasm. Multinucleated giant cells and eosinophils are frequently present. Necrosis can be observed. The Langerhans cells are characterized by immunoreactivity for S100, CD1a, and langerin (CD207), as well as ultrastructural presence of Birbeck granules.

Histiocytic sarcoma is a malignant proliferation of cells with morphological and immunophenotypic features of mature histiocytes. A subset of cases is associated with mediastinal non-seminomatous germ cell neoplasm, most commonly malignant teratoma with yolk sac component. Histologically it is composed of pleomorphic large cells with abundant eosinophilic cytoplasm and a diffuse pattern of growth. The nuclei are typically large, irregularly folded, and eccentrically placed with a dispersed chromatin. Immunohistochemically there is positivity of one or more his-

tiocytic markers (CD163, CD68/PGM1 or KP1, and lysozyme) and negativity of Langerhans cell markers (CD1a and langerin), follicular dendritic cell markers (CD21 and CD35), and myeloid cell markers (myeloperoxidase). Positivity for CD33 and CD13, other myeloid markers, has been described. CD45 is positive too, and weak expression of CD15 can rarely occur. S100 may be expressed but it is typically weak or focal.

Epithelioid hemangioendothelioma (EHE) is a malignant intermediate-grade vascular tumor mainly affecting young adult females [71–73]. Multiple involvement of the lung, skin, bone, and liver occurs in about 20% of cases. The tumor often shows a multinodular appearance with expansive margins, hypocellular chondromyxoid or hyalinized sclerotic stroma, and epithelioid cells with eosinophilic cytoplasm, intracytoplasmic vacuoles, and intranuclear inclusions. At least one vascular marker at immunostains is positive (CD31, CD34, ERG, CAMPTA1, factor VIII), and cytokeratins are expressed in up to 30% of cases. The presence of prominent cellular atypia, spindle cell features, and necrosis and high mitotic rate more often characterize an epithelioid angiosarcoma. Nevertheless, EHE, particularly when myxoid/hyalinized stroma occurs, may enter in differential diagnosis with granulomatous lesions, infarcts, amyloidosis, mesothelioma, and carcinomas (Fig. 6.14).

Even epithelioid angiosarcomas [74] may be present in the mediastinum as aggressive neoplasms mimicking carcinomas (Fig. 6.15). Since cytokeratins are frequently positive in angiosarcoma, careful search for intratumor vessel formation together with consistent expression with at least one vascular marker (it is a good practice to test for all available endothelial stains, namely, CD31, CD34, ERG) is mandatory to achieve the correct diagnosis.

Metastatic tumors to mediastinum are mainly located in lymph nodes, so they are usually in the middle mediastinum, where most mediastinal lymph nodes are situated. Residual nodal component at their periphery could be detected and useful for diagnosis. However, tumors can spread to the thymus or anterior mediastinum too either from adjacent organs or by lymphatic or hematogenous route. Tumors that more often can be confused with primary mediastinal tumors are testicular germ cell tumors, prostatic carcinoma, and melanoma. Many carcinomas can metastasize to the mediastinum, such as the lung, breast, thyroid, kidney, ovary, and nasopharynx. Direct mediastinal extension can also occur from the esophagus, pleura, chest

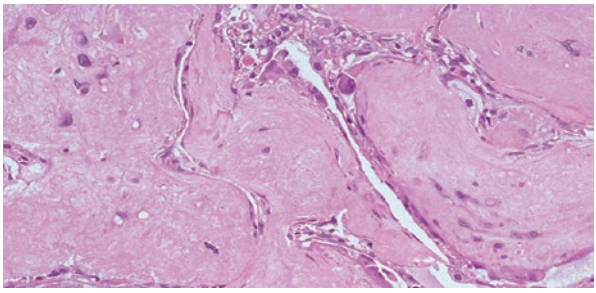

Fig. 6.14 Epithelioid hemangioendothelioma with prominent sclerotic stroma and scattered epithelioid tumor cells

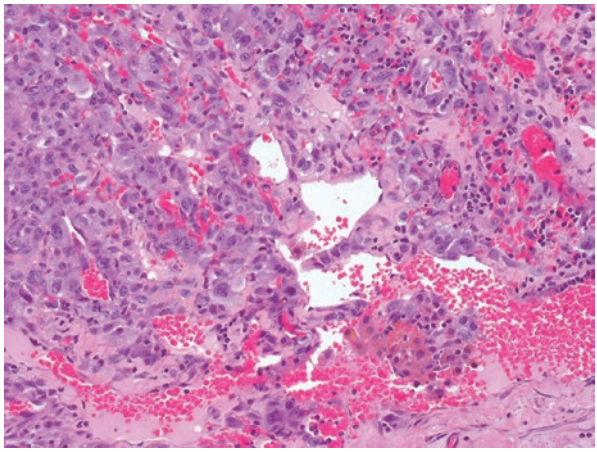

Fig. 6.15 Epithelioid angiosarcoma with atypical epithelioid cells and a vascular hemorrhagic network

wall, and trachea. Immunostains for organ-specific markers can be useful, but differential diagnosis is mainly based on clinical and radiological features [4, 21].

Some benign mediastinal lesions with epithelioid cell pattern include thyroid nodular hyperplasia, parathyroid adenomas, and thymic hyperplasia.

Spindle Cell Pattern

The differential diagnosis concerning the main lesions with spindle cell pattern is concisely summarized in Table 6.3.

Type A thymoma is a relatively uncommon subtype, accounting for 12% of all thymomas. Patient ages range from 8 to 88 years, with a mean age of 64 years, which is higher than the mean age for all thymomas. A slight female predominance has been reported in most studies [4, 21]. It is generally a well-circumscribed or encapsulated tumor ranging in size from 5.9 to 7.4 cm. The cut surface is homogeneous and light tan to white, with vague lobulation. Focal cystic change can be present. Histologically, it is characterized by a high content of bland spindly and oval epithelial cells and paucity or absence of immature TdT+ T cells (Fig. 6.16). Spindle tumor cells show bland nuclear features with no or minimal nuclear pleomorphism, fine nuclear chromatin, inconspicuous nucleoli, and absent or low mitotic activity. Pattern of growth encompasses a wide morphological spectrum that can cause misdiagnosis above all when dealing with small mediastinoscopic biopsies [75–77]. In addition to the diffuse pattern, with spindle cells either arranged in solid sheets without any particular architecture or in a storiform or fascicular pattern, neuroendocrine array can be seen, with cords, ribbons, or rosette-like structures with or without central lumina. Neural pattern, with whorled configuration reminiscent of those typically seen in meningothelial type meningiomas, or schwannoma-like pattern can be present. Adenomatoid pattern with short-spindled epithelial cells alternating with microcystic areas and storiform or hemangioperi-

Table 6.3 Main differential diagnosis of the *spindle cell* pattern

Entities (compartment of mediastinum, mean age)	Cytological features	Pattern of growth	Distinctive immunohistochemistry/molecular features
Thymoma Type A (ant, 64 years)	– Bland nuclear features – Fine nuclear chromatin – Inconspicuous nucleoli – Absent/low mitotic activity	– Variable in the same lesion (diffuse, rosettes, glandular or glomeruloid structures, papillae, etc.) – Paucity or absence of TdT+ T cells	**Positive** CKs + P63/p40 + PAX8 + TdT + (in nonneoplastic immature T cells) CD20 +/– (aberrant expression) **Negative** CK20 – CD5 – CD117 –
Thymoma Type AB (ant, 57 years)		– As in thymoma type A – Abundance of TdT+ T cells focally (impossible to count) or throughout tumor (>10% of the tumor area)	
Thymic sarcomatoid carcinoma (ant, 47 years)	– Pleomorphic nuclei – Prominent nucleoli – High mitotic activity (>10%)	– Fascicles – Necrosis – Focal type A thymoma component or carcinomatous areas or heterologous component(s)	CKs +/– EMA +/– CD5 –/+
Thymic carcinoid tumors (ant, 49 years)	– Small nuclei – Finely granular chromatin	– Nests and trabeculae – Prominent fibrovascular septa	**Positive** CKs + (dot-like) More than one of neuroendocrine markers (chromogranin A, synaptophysin, CD56, and NSE) in >50% of tumor cells PAX8 + **Negative** TTF1 – P63/p40 – CD117 – CD5 –

Solitary fibrous tumor (any compartment, adults)	– Uniform fibroblastic cells – No/mild atypia	– Pattern less – Branching pericytomatous vascular pattern – Stromal hyalinization	**Positive** STAT6 + CD34 + CD99 + BCL2 + **Negative** CKs –
Monophasic synovial sarcoma (ant/post, 35 years)	– Uniform spindle cell – Scant cytoplasm – Indistinct cell borders	– Sheets/fascicle – Pericytomatous vascular pattern – Necrosis	**Positive** CD99 + EMA + t(X;18) with *SS18-SSX* fusion gene **Negative** CKs –/+ STAT6 – CD34 –
Malignant peripheral nerve sheet tumor (post, all ages)	– Mitotically active serpentine-shaped tumor cells – Deeply hyperchromatic nuclei and pale cytoplasm	– Similar to synovial sarcoma – Areas of palisading necrosis – Coexisting neurofibroma	**Positive** S100 +/– (focal) GFAP +/– **Negative** CKs – CD99 – STAT6 – CD34 –

ant anterior, *post* posterior, *CKs* cytokeratins

cytic growth patterns has been described too. Interestingly, in this pattern the spindle cells can have prominent cytoplasmic vacuolation imparting a signet-ring cell-like appearance. These features can be reminiscent of metastatic carcinoma or yolk sac tumor.

Papillary and pseudopapillary growth patterns usually do not comprise more than 50% of the tumor mass and can mimic papillary thyroid carcinoma or papillary thymic carcinoma. They are characterized by a solid pattern with papillary projections, composed of fibrovascular cores, or pseudopapillary proliferation, composed of larger villous-like stromal projections with central edematous or hyalinized changes and areas of calcification with occasional psammoma body formation. Angiomatoid areas with prominent cavernous blood-filled spaces separating spindled epithelial cells have to be differentiated from hemangioma or angiosarcoma.

Eventually, hemangiopericytoma-like pattern can be encountered, with neoplastic spindled epithelial cells with prominent staghorn-like vasculature reminiscent of solitary fibrous tumor. The clues for the diagnosis of type A thymoma are the coexistence of more histological patterns in a monophasic spindle cell tumor with bland cytological features. Immunohistochemical profile may be useful in selected cases for differential diagnosis: thymic epithelial markers (keratins, p63, PAX8, FOXN1, CD205) are positive, while carcinomatous markers (CD5 and CD117) are negative. Moreover, an ectopic expression of CD20 is frequently present, even if focal. TdT+ T cells are completely absent or represent a minority of the CD3+ T lymphocytes, and CD20+ B cells are usually absent.

An atypical variant of spindle cell thymoma is also on record: rarely type A thymomas can show hypercellularity, increased mitotic activity (>4 mitosis/2 mm^2), and focal necrosis, but the clinical significance of these features is still unknown [78].

Type A thymomas with any lymphocyte-dense areas (TdT+ T cells impossible to count), or with moderate infiltrate of TdT+ T cells in >10% of the tumor area, are classified as type AB thymoma (Fig. 6.17). It accounts for 27.5% of thymomas, with an average patient age of 57 years. Macroscopically the tumors are usually encap-

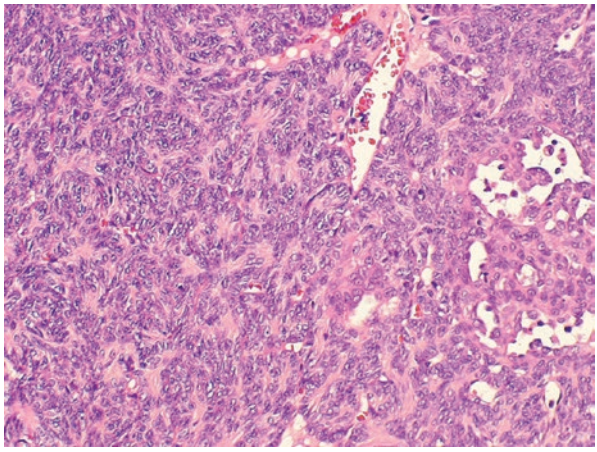

Fig. 6.16 Type A (medullary type) thymoma with rosette-like formation pattern

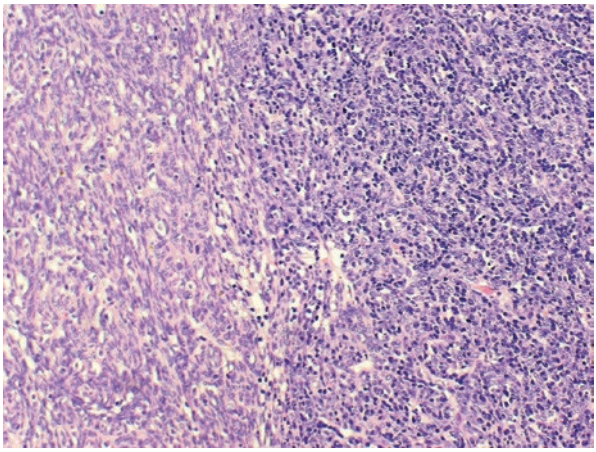

Fig. 6.17 Type AB (mixed type) thymoma with medullary/type A (left) and cortical/type B2 (right) components

sulated, and the cut surface shows multiple nodules of various sizes, separated by white fibrous bands. Histologically, it is a well-circumscribed tumor composed of a lymphocyte-poor spindle cell (type A) component and a lymphocyte-rich (type B-like) component in highly variable proportion, either intermingled or forming separate nodules. All histological patterns of type A thymomas can be present. Type A components may also consist of spindle cell fascicles encircling lymphocyte-rich nodules like cellular fibrous septa. Medullary islands are very rare and Hassall corpuscles are generally absent. Type AB thymoma may enter in differential diagnosis with micronodular thymoma with lymphoid stroma [4, 12, 13, 21]. This rare type of thymoma consists of multiple small tumor nodules of bland spindle or oval epithelial cells surrounded by an epithelial cell-free lymphoid stroma. It accounts for about 1% of all thymomas with an average age at diagnosis of 64.5 years. Macroscopically it is well circumscribed and well encapsulated. The cut surface is often soft and friable and light tan, with occasional cystic spaces. The nodules are composed of neoplastic epithelial spindle cells with elongated nuclei and inconspicuous nucleoli. Mitotic activity or cytological atypia is not observed. The stroma separating the tumor islands is composed of a dense proliferation of small lymphocytes, which may contain lymphoid follicles and germinal centers. Occasional plasma cells may be part of this lymphoid component. Initially thought to be primarily of B-cell lineage, this lymphoid infiltrate is a mixed B- and T-cell population, including occasional immature T cells, as commonly seen in the conventional types of thymoma. Areas corresponding to type A thymoma occur in up to 30% of micronodular thymomas with lymphoid stroma. At immunohistochemical level, the epithelial cells of micronodular thymomas with lymphoid stroma typically lack the expression of CD20. Moreover, the lymphoid stroma is devoid of keratin-positive epithelial cells [4, 21].

Metaplastic thymoma is a biphasic tumor composed of solid areas of epithelial cells and bland-looking spindle cells, with gradual or abrupt transition between the two components (Fig. 6.18) [4, 21]. It is extremely rare with fewer than 40 cases reported in literature. Median age at presentation is 50 years. At histology, a lobular

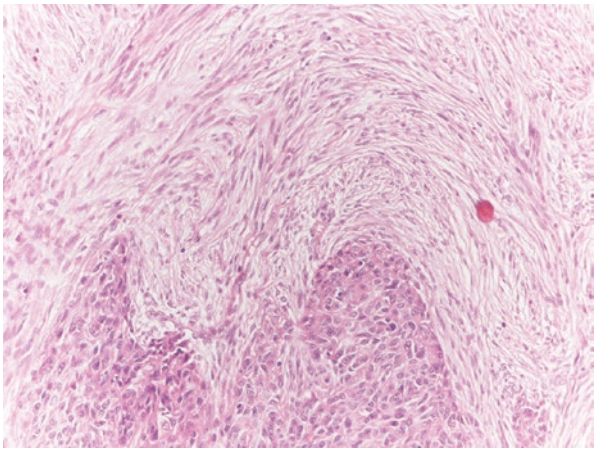

Fig. 6.18 Metaplastic thymoma with clear-cut separated biphasic components

growth pattern is absent. The epithelial cells show squamoid or whorled appearance and form islands or trabeculae. Sometimes they could have enlarged pleomorphic nuclei, but mitotic activity is usually low (ki67 < 5%). Fibroblast-like spindle cells are present in the background, forming short fascicle or storiform arrays. Immature TdT + Tcells are typically absent. At immunohistochemical level, the epithelial component expresses both keratins and p63, whereas fibroblast-like spindle cells are negative for p63 but show at least focal positivity for epithelial markers (e.g., keratins and epithelial membrane antigen) supporting its metaplastic nature. Both components are negative for CD5, CD20, CD34, and CD117. The differential diagnoses include sarcomatoid carcinoma (spindle cell component is of high grade, with necrosis and high proliferative index), solitary fibrous tumor (distinctive immunoprofile CD34 +, CD99 +, BCL2 +, STAT6 +, CK −), and type A thymoma.

Thymic sarcomatoid carcinoma (TSC) consists partly or completely of spindle sarcomatoid cells. In some tumors, heterologous mesenchymal elements could be present (the so-called carcinosarcoma) [4, 21]. It accounts for 5–10% of all thymic carcinomas, and it occurs mostly in the fourth to eight decades. Grossly it is often large with infiltrative borders. The cut surface is fleshy white or gray with areas of hemorrhage, necrosis, and cystic degeneration. Histologically, sarcomatoid cells have pleomorphic nuclei, prominent nucleoli, and high mitotic activity and show fascicles and storiform arrays. A carcinomatous component may coexist, consisting of TSCC, ADC, adenosquamous carcinoma, or TUC. Mesenchymal component is more frequently rhabdomyosarcomatous, but chondrosarcoma or osteosarcoma could be also present. Immunohistochemically sarcomatous cells show variable positivity for keratins and EMA, while CD5 may or may not be positive.

Histiocytic and dendritic cell tumors (follicular dendritic cell sarcoma, interdigitating dendritic cell sarcoma, fibroblastic reticular cell tumor) represent a heterogeneous group of neoplasms with similar morphology consisting of proliferations of spindle cells with indistinct borders, vesicular nuclei with evident nucleoli, and a variable growth pattern: storiform, whorled, fascicular, nodular, diffuse, or even

trabecular. Cytological atypia is variable and foci of necrosis may be present. Immunohistochemical profile is mandatory for a correct diagnosis.

Follicular dendritic cell sarcoma is uncommon, and nearly 12% of reported cases involve the thymus or mediastinal lymph nodes, as a localized disease [79, 80]. It shows an average age of 50 years at presentation. It can occur in the anterior or posterior mediastinum, and it may be associated with a hyaline vascular Castleman disease. The neoplastic cells show positive immunostaining for one or more follicular dendritic cell markers (CD21, CD35, and CD23), while they are negative for CD1a and CD30. CD68 and S100 may be weekly express. Keratin is negative, but EMA is positive in 40–80% of cases, and D2-40 is frequently positive too. This subset of EMA-positive and/or D2-40-positive follicular dendritic cell sarcomas has to be differentiated from cytokeratin-deficient thymomas, meningioma, and mesothelioma (Fig. 6.19).

Interdigitating dendritic cell sarcoma is very rare and mediastinal involvement is even rarer. It almost always affects mediastinal lymph nodes as a component of disseminated disease. The neoplastic cells are strongly positive for S100 and show variable weak staining for CD68, lysozyme, CD4, CD11c, CD14, and CD45. They are always negative for CD1a, langerin, follicular dendritic cell markers, myeloperoxidase, and T-cell and B-cell lineage-specific markers. All other melanocytic markers (such as HMB45, melan-A, SOX10) are negative, and this is useful for the differential diagnosis with metastatic melanoma, which is much more common.

Fibroblastic reticular cell tumor is very rare and involves mediastinum and/or mediastinal lymph node, with median patient age of 61 years old. Tumor cells express vimentin and show variable immunoreactivity for keratin, actin, and desmin. There can be also positivity for CD68, while the tumor should not express markers of follicular or interdigitating dendritic cells. The cytokeratin-positive subsets of fibroblastic reticular cell tumors need to be distinguished from spindle cell epithelial tumors (e.g., atypical type A thymomas, sarcomatoid carcinomas), while the main differential diagnosis for actin-positive or desmin-positive fibroblastic reticular cell tumors is smooth muscle and myofibroblastic tumors.

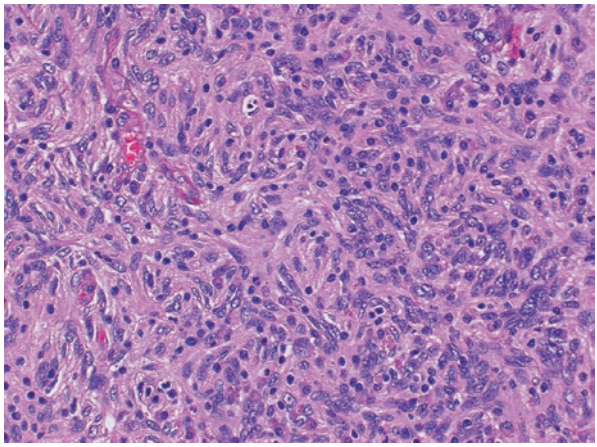

Fig. 6.19 Follicular dendritic cell sarcoma showing a characteristic mixture of spindle cell proliferation and lymphocytes

Several soft tissue neoplasms occur in the mediastinum [81–88], such as liposarcoma with their variants, benign and malignant solitary fibrous tumor, synovial sarcoma, and even angiomatoid fibrous histiocytoma. In the mediastinum synovial sarcoma is rare, accounting for 10% of intrathoracic synovial sarcoma, and it is more commonly monophasic or poorly differentiated [4, 21, 83]. It can occur both in the anterior or posterior mediastina, and the median age of patient at presentation is 35 years. Monophasic synovial sarcoma is composed of uniform spindle cells with hyperchromatic nuclei that tend to overlap, arranged in dense cellular sheets or vague fascicles (Fig. 6.20). Most cases show a focal hemangiopericytoma-like vascular pattern, reminiscent of solitary fibrous tumor. Biphasic subtype is characterized by the presence of epithelial areas, usually in the form of gland-like structures lining by cuboidal or columnar cells in a background of neoplastic spindle cells with a fibroblast-like appearance. The main differential diagnoses are with metaplastic thymoma (squamous features in the epithelial component of synovial sarcoma are exceptional), sarcomatoid carcinoma, and type A thymoma with glandular structures. Immunohistochemically, the neoplastic cells are generally positive for CD99 and show focal positivity for EMA and variable positivity for keratins. S100 expression can be detected, while CD34 positivity is very rare. Nuclear positivity for TLE1 is not specific, as it may also occur in malignant peripheral nerve sheet tumor and solitary fibrous tumor. At molecular level, synovial sarcoma is characterized by the t(x;18) (p11; q11) translocation, which is specific of this tumor. The fusion gene includes SS18 gene (SYT or SSXT) on chromosome 18 and one of the SSX genes on chromosome x, more often SSX1.

Tumors of the peripheral nerves occur in the posterior mediastinum and mainly include schwannoma, neurofibroma, and malignant peripheral nerve sheet tumor. Morphologic features are the same as described for the other sites [4, 21, 84]. Schwannoma and neurofibroma are benign neoplasms composed of bland-looking spindle cells, which express S100 at immunohistochemistry. The distinction

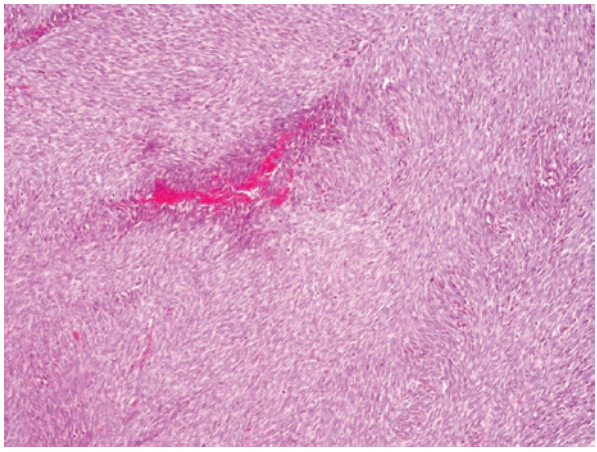

Fig. 6.20 Monophasic synovial sarcoma with intersected fascicles of uniform spindle cells

between the two entities is mainly based on morphology. Schwannomas are encapsulated biphasic tumors with cellular areas (the so-called Antoni A) showing focal palisading (Verocay bodies) alternating with loosely arranged foci (the so-called Antoni B). The presence of thick-walled, hyalinized blood vessels is characterized. Neurofibroma, which is typically unencapsulated, in the mediastinum tends to reach larger size and therefore is frequently surrounded by a fibrous capsule. Spindle cells are smaller than schwannoma, with indistinct cellular borders and comma-shaped nuclei dispersed in a loosely arrangement of collagen fibers and myxoid material. Malignant peripheral nerve sheet tumor is an aggressive neoplasm with poor prognosis, which, in up to 50% of cases, affects individuals with the hereditary syndrome NF1 and is associated with neurofibroma. Histologically, typical cases are composed of mitotically active spindle cells with a fascicular array, branching hemangiopericytoma-like vascular pattern, and alternating hypercellular and hypocellular areas, closely mimicking synovial sarcoma. Immunophenotype shows a focal positivity for S100 in <50% of cases and positivity for GFAP in 20–30%.

Small and Round Cell Pattern

The term small-round-blue-cell tumor broadly indicates a category of tumors descriptively composed of cells with high nuclear-to-cytoplasmic ratio, then including several tumor entities with various cell differentiations. The differential diagnosis concerning the main lesions with small and round cell pattern is concisely summarized in Table 6.4.

Among epithelial tumors, types B1/B2 thymomas, undifferentiated and basaloid thymic carcinomas, and neuroendocrine tumors may enter into this definition.

B1 and B2 thymomas are characterized by a large number of small round monomorphic, resting lymphocytes and scattered larger epithelial cells [4, 12, 13, 21]. The lymphoid population may show different sizes, but it consists of lymphocytes with dark nuclei lacking a significant mitotic rate, and necrosis is absent. The recognition of a dual population of lymphocytes and epithelial cells and the presence of a peripheral fibrotic capsule with septa of dense collagen are helpful features in discriminating type B1/B2 thymomas from a lymphoproliferative process. These thymomas generally have a cleavage plane and then resulting resectable for the thoracic surgeon. This clinical information together with the radiologic findings may be very helpful to rule out lymphoma.

Thymic carcinomas usually appear as overt malignancies with large cells, enlarged nuclei with evident nucleoli, and moderate amount of cytoplasm, but a subset of these tumors are poorly differentiated or, if preferred, undifferentiated neoplasms lacking any keratinization and consisting of a solid proliferation of small-to-intermediate round cells with scant cytoplasm and coarse nuclei with single macronucleoli (Fig. 6.21). These undifferentiated carcinomas have a squamous cell differentiation at immunohistochemistry (expression of p63 and p40) with positive staining for CD5 and CD117. Even undifferentiated carcinomas harboring

Table 6.4 Main differential diagnosis of the *small and round cell pattern*

Entities (compartment of mediastinum, mean age)	Cytological features	Pattern of growth	Distinctive immunohistochemistry/ molecular features
B1 thymoma (ant, adult/elderly)	A large amount of small lymphocytes and scattered polygonal epithelial	Solid growth of lobules of small lymphocytes mimicking lymphoma, but dissected by fibrous septa of dense hyalinized collagen	TdT- and CD99-positive small lymphocytes with scattered p63- and CK-positive epithelial cells
Basaloid and poorly differentiated thymic carcinoma (ant, adult)	Small- and intermediate-sized, monomorphic cells with evidence of single nucleolus and scant cytoplasm, no keratinization, high mitotic rate	Solid growth with lobular pattern	CKs +, CD5 +, p63 +, p40 +, CD117 +
Small-cell neuroendocrine carcinoma (ant, adults)	Small- to intermediate-sized, monomorphic round-to-spindle cells with scant cytoplasm and finely dispersed chromatin and inconspicuous nucleolus, high mitotic rate, necrosis, scattered bizarre large cells may be noted	Solid growth, lobular and organoid pattern; nuclear palisading, rosette-like formation	CKs + (low-molecular-weight CAM5.2 with dot-like pattern), neuroendocrine markers + (chromogranin is more specific than synaptophysin and CD56), high Ki67 labelling index (generally >70%), TTF-1 may be positive
Extranodal MALT-type lymphoma (ant, young adults)	Small- to intermediate-sized lymphocytes with clear cytoplasm (centrocyte-like) and sparse plasma cells; lymphoepithelial lesions, neoplastic B-lymphoid cells with single or multiple nucleoli and centroblastic appearance	Diffuse lymphocytic proliferation with plasma cells and follicles	CD20 +, CD79a +, PAX5 +, CD45/LCA +, IRTA-1 +, monotypic light chain IG (kappa/lambda)
T-lymphoblastic leukemia/ lymphoma (ant, childhood and young adults)	Small- to intermediate-sized blastic lymphocytes with scant cytoplasm, round-to-oval nuclei with dispersed chromatin and small nucleolus, high mitotic rate	Diffuse monomorphic proliferation with starry sky appearance	TdT +, T-cell markers + (CD3, CD2, CD7), CD34 +, CD1a +, CD4 +, CD8 +, CD10 +, a subset expressing CD79a, CD56, CD13, CD33, lacking TdT T-cell clonality and NOTCH mutations may be helpful

Ewing's sarcoma/PNET (ant/middle, childhood, young adults)	Monomorphic small round cells with hyperchromatic nuclei and scant eosinophilic cytoplasm, high mitotic rate	Solid discohesive growth with rosette-like formation	CD99 +, FLI-1 + EWS-FLI-1 rearrangement
DSRCT (all compartments, young adults)	Small round cells similar to PNET and desmoplastic stroma Variants with large cells and lacking desmoplastic stroma are described	Biphasic proliferation with islands of small round cells dissected by desmoplastic stroma	Coordinated expression of CKs, desmin, and WT-1 Stromal cells are smooth muscle actin + EWS-WT-1 rearrangement
Alveolar rhabdomyosarcoma (ant, childhood and young adults)	Monomorphic round small cells with vesicular nuclei, small nucleolus, and bright eosinophilic cytoplasm	Monomorphic solid growth with cell-to-cell discohesion	Myogenic markers + (desmin, myogenin) PAX3-FOXO1 / PAX7-FOXO1 rearrangement
Neuroblastoma (ant/post, childhood and young adults)	Uniform small round cells with scant cytoplasm, hyperchromatic nuclei	Solid growth of monomorphic nests with fibrovascular matrix, Homer-Wright pseudorosettes, neuropil	Neuroendocrine markers + (NSE, chromogranin, synaptophysin, CD56), S100 + Myc-N overexpression and amplification
Synovial sarcoma, poorly differentiated variant (ant, young adults)	Monomorphic round small cells with/without large and spindle elements; rhabdoid cells may be present	Solid growth with vascular-rich hemangiopericytoma-like network	EMA +, CKs (CK7) +/−, calretinin +/−, D2-40 +/−, TLE1 +, CD56 + SYT-SSX rearrangement
Mesothelioma, small-cell variant (all compartments, adult/elderly)	Monotonous small round cells with scant cytoplasm, dispersed nuclear chromatin, and evident nucleolus	Solid growth of monomorphic small round cells, generally associated with conventional epithelioid, sarcomatoid, or desmoplastic component (serial sections and extensive sampling are very helpful)	CKs +, mesothelial markers variably positive (calretinin, WT1, D2-40, CK5/CK6), EMA +

ant anterior, *post* posterior, *CKs* cytokeratins

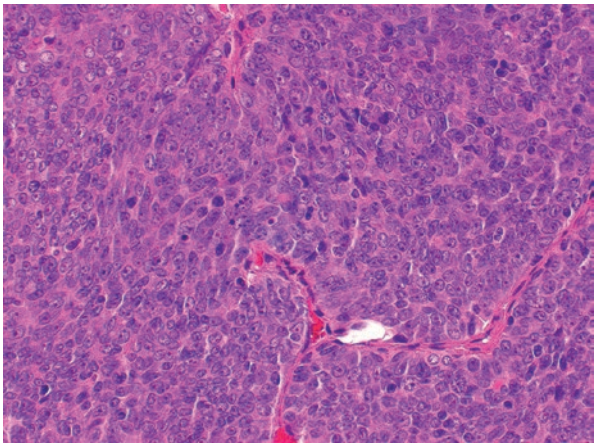

Fig. 6.21 Undifferentiated thymic carcinoma with intermediate-sized, monomorphic tumor cells with evident nucleoli

t(15;19) leading to fusion of the NUT (nuclear protein in testis) gene to BRD4, BRD3, NSD3, or other unknown genes may enter in this category. Indeed, this unusual and highly aggressive malignancy, often occurring in children or young adults without gender predilection, is characterized by a solid growth of small-to-intermediate, round monomorphic cells with scant cytoplasm and coarse chromatin with small nucleoli. The abrupt presence of keratinized squamous/squamoid cell component is very characteristic of this tumor. Differential diagnoses commonly include poorly differentiated squamous cell carcinoma and several other undifferentiated small-round-blue-cell malignancies (small-cell neuroendocrine carcinoma, lymphomas or leukemia, Ewing's sarcoma). The tumor cells generally express pan-cytokeratins, p63 or p40, and variably EMA and carcinoembryonic antigen (CEA). However, demonstration of immunohistochemical nuclear expression of NUT protein or NUT rearrangement by RT-PCR or FISH is diagnostic of NUT carcinoma.

Among neuroendocrine tumors, small-cell carcinoma (SCC) properly enters into the small-round-blue-cell category [4, 21, 41]. Most commonly, SCC arises from the central bronchi of the lung invading the lymph nodes and the tissues of the mediastinum; then in some cases, it is quite difficult, if not impossible, to define the exact origin of SCC. By the way, thymic SCC is a highly aggressive tumor mainly occurring in the anterior mediastinum of adults without gender prevalence. High serum levels of adrenocorticotropic hormone (ACTH) leading to Cushing syndrome are well-described. As in the pulmonary counterpart, tumor consists of cells with high nuclear-to-cytoplasmic ratio, scant cytoplasm, finely dispersed chromatin ("salt-and-pepper" chromatin), and inconspicuous nucleoli (Fig. 6.22). Apoptotic debris, necrosis, and high mitotic rate (>50 × 10 HPF) are consistent features in SCC. Tumor cells may be round, oval, or even spindled. Crush artifacts associated with SCC commonly seen on biopsies are generally not seen on frozen section. Thymic SCCs are basically unresectable, and the differential diagnosis may require some immunostains demonstrating pan-cytokeratin (low-molecular-weight cytokeratins CK8, CK18, and CK19 or cocktails such as CAM5.2 are the most useful, and the

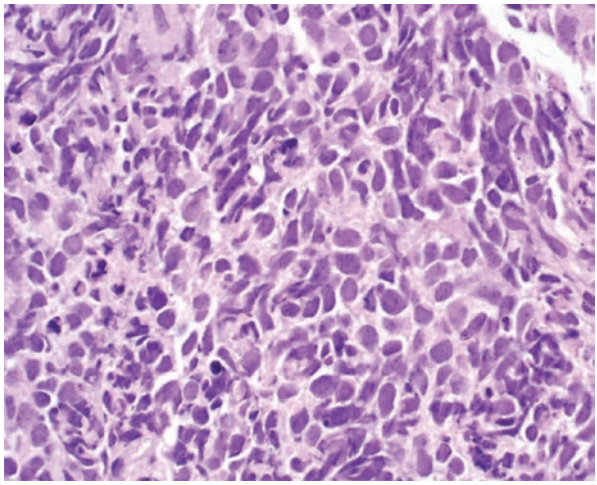

Fig. 6.22 Small-cell carcinoma with high nuclear-to-cytoplasmic ratio and dispersed nuclear chromatin and high mitotic rate

staining pattern is usually dot-like) expression and positivity for neuroendocrine markers (chromogranin, synaptophysin, CD56). TTF-1 may be expressed in pulmonary and extra-pulmonary SCC, while pan-lymphoid markers (e.g., CD45, CD20, CD3), TdT, p63, p40, and CD5 are negative. CD99 expression may be specific and misleading, since SCCs, some small round cell sarcomas (e.g., Ewing's sarcoma, desmoplastic small round cell tumor, poorly differentiated synovial sarcoma) and T-lymphoblastic leukemia/lymphoma, are also positive.

By definition, lymphomas are the prototype of small round cell proliferations, and several different types of lymphoma may occur in the mediastinum. However, lymphoproliferative disorders with this morphologic pattern mainly include extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT-type lymphoma) of the thymus and T-lymphoblastic leukemia/lymphoma. MALT-type lymphoma is a peripheral B-cell lymphoma mainly occurring in adults with autoimmune disorders (e.g., Sjogren syndrome) and often appearing as an encapsulated mass with solid and cystic areas. It consists of a dense proliferation of small, centrocyte-like lymphocytes with plasma cells and scattered centroblast-like cells. Lymphoepithelial lesions around residual Hassall corpuscles and aggregates of plasma cells (with Russell's bodies) are helpful features in the differential diagnosis with type B thymomas. Crystal-storing histiocytes accumulating immunoglobulins into the cytoplasm (Fig. 6.23) may be observed. Immunostaining with CD45, CD20, CD79a, PAX5, IRTA-1 and negativity with cytokeratins (highlighting lymphoepithelial lesions), CD3, CD5, CD23, and cyclin D1 is quite characteristic as well as demonstration of light chain restriction of immunoglobulins with K and lambda stains. Differential diagnosis with benign lymphoproliferative (e.g., follicular lymphoid hyperplasia) and epithelial (e.g., thymic cysts, cystic thymoma) thymic processes may be challenging on frozen section, and closing diagnosis generally requires examination of definitive sections with a panel of immunostains.

T-lymphoblastic leukemia/lymphoma (Fig. 6.24) is another small round cell lymphoproliferative disorder involving the anterior mediastinum rapidly invading

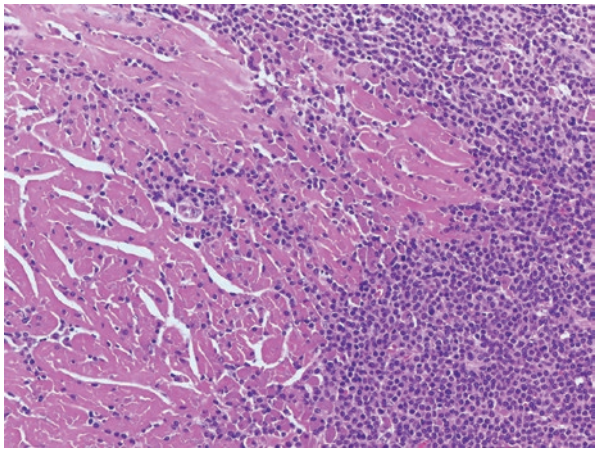

Fig. 6.23 Marginal zone, extranodal MALT-type lymphoma with immunoglobulin-engulfed histiocytes leading to crystal-storing histiocytosis

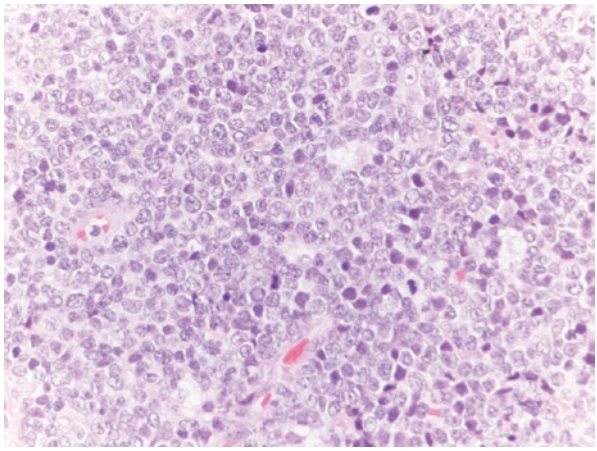

Fig. 6.24 T-lymphoblastic leukemia/lymphoma showing a monomorphic proliferation of round cells

the thoracic organs. It occurs in childhood or young adult, with a male prevalence. The patient generally presents very sick, since a mediastinal mass occurs in up to 80% of cases provoking dyspnea and chest pain or even life-threatening compression of the superior vena cava and tracheobronchial respiratory tract. Tumor cells are small-to-intermediate blasts with scant cytoplasm, round-to-oval or convoluted nuclei with dispersed nuclear chromatin, and indistinct/small nucleoli. Mitotic rate is very high and starry sky is not infrequently observed. The main differential diagnosis is with SCC, type B thymomas, and Ewing's sarcoma. The infiltrative growth of T-lymphoblastic leukemia/lymphoma coupled to the clinical presentation and patient's age are generally sufficient to rule out type B thymomas. Nevertheless, pathologists should be aware that immature TdT-positive T cells are present in B-type lymphomas. Purely on morphology, it could be very hard to discriminate T-lymphoblastic lymphoma from SCC. Although patients with SCC are generally older and tumor growth pattern is more discohesive in lymphoblastic lymphoma,

definitive sections with ancillary tests are required. A panel of markers including TdT, T-cell lineage markers, CD34, CD1a, CD4, CD8, and CD10 is highly suggestive of this lymphoma. Of note, a subset of T-lymphoblastic lymphoma express CD56, CD79a, CD13, and CD33, while TdT may be negative. Rearrangement of T-cell receptor and NOTCH mutations are helpful genetic findings.

Among sarcomas showing a small round cell pattern and developing from mediastinal region, the main concern is with Ewing's sarcoma/PNET, desmoplastic small round cell tumor, and alveolar rhabdomyosarcoma.

All these mesenchymal malignancies rarely occur as primary tumor in the mediastinum. However, Ewing's sarcoma/primitive neuroectodermal tumors (PNET) represent a specific family of tumors with t(11;22) involving EWS-FLI-1 fusion gene [89]. More than 80% of these tumors occur in the skeletal system of children or young adult. Primary EWS/PNET of the mediastinum is quite rare and involves the anterior/middle regions. The tumor consists of a solid growth of small round monomorphic blue cells with hyperchromatic nuclei and scant eosinophilic cytoplasm with rosette-like formation (Fig. 6.25). The diagnosis requires confirmation with expression of CD99 and FLI-1, but molecular identification of t(11;22) using RT-PCR or FISH analysis.

Desmoplastic small round cell tumor (DSRCT) is an exceedingly rare sarcoma affecting young males in their second/third decade of life and characterized by a very dismal outcome [90]. The tumor may arise from the pleura and mediastinum and appears as a proliferation of small round cell islands into desmoplastic stroma. This sort of biphasic appearance in a young patient is very suggestive, but definitive diagnosis requires the presence of coordinated expression of cytokeratins, desmin, and WT1 in the small round cells. The stromal component is usually positive with smooth muscle actin. Confirmation of EWS/WT-1 fusion gene is the most important diagnostic marker.

Alveolar rhabdomyosarcoma is another sarcoma of childhood and adolescents rarely occurring in the anterior mediastinum [91]. Histology is quite similar to other

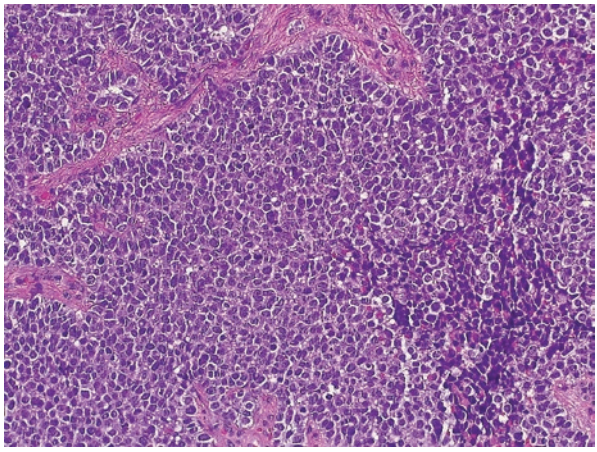

Fig. 6.25 Ewing sarcoma/PNET with a solid growth of monomorphic round blue cells with some rosette-like formations

small round cell tumors with a solid architecture of monomorphic cells with vesicular nuclei, small nucleoli, and brightly fibrillar eosinophilic cytoplasm. Diagnosis requires demonstration of expression of myogenic markers (desmin, myogenin) and t(2;13) or t(1;13) leading to PAX3-FOXO1 and PAX7-FOXO1 gene fusion, respectively.

Neuroblastoma is a tumor of neural crest cells arising in the sympathetic nervous system commonly occurring in children, but even cases of adult neuroblastoma have been reported in the anterior and posterior mediastinum [92]. Neuroblastoma histologically consists of small, round, blue, uniform cells with scant cytoplasm and hyperchromatic nuclei arranged in solid nests in a fibrovascular matrix and Homer-Wright pseudorosettes (up to 50%). The presence of a neuritic process, also called neuropil, is a pathognomonic feature of neuroblastoma cells. Immunostaining reveals positivity with NSE, chromogranin, synaptophysin, CD56, and S100 protein. MYCN overexpression due to gene amplification of the distal arm of chromosome 2 is an important biologic marker.

Mesothelioma may predominantly involve the mediastinal pleura, then appearing as a mass of the anterior-to-posterior mediastinum, and several variants of mesothelioma have been described in literature. Small-cell mesothelioma is a rare form of epithelioid mesothelioma [93, 94]. At histology, the neoplasm is generally associated with a conventional malignant epithelial mesothelioma, and the proportion of the small-cell component is variable, even representing the entire surface in small biopsy. It appears as a solid growth of closely packed monotonous small- to medium-sized cells with open nuclear chromatin, evident nucleoli, and high mitotic activity. Trabecular or papillary arrangement and clear-cell change of the cytoplasm have been described. Immunohistochemically, small-cell mesothelioma is usually positive for cytokeratins (AE1/AE3, CAM 5.2), EMA, calretinin, WT-1, and D2-40, while neuroendocrine markers, CD99, TTF1, CEA, MOC-31, and desmin are negative.

Since thoracic region is the most common visceral site of synovial sarcoma, several examples of this sarcoma have been reported in the mediastinum. The tumor may show a very aggressive small-cell variant poorly differentiated type [95, 96] and generally affects young adults without gender prevalence. Poorly differentiated synovial sarcoma may appear as a monomorphic round cell malignancy, although large cell epithelioid and spindle cell areas may be present. The tumor is highly vascularized with hemangiopericytoma-like dilated thin-walled vessels. Rhabdoid cells may be observed. Differential diagnosis may be very challenging since the tumor co-expresses markers of epithelial (EMA, cytokeratins), mesothelial (calretinin, D2-40), and mesenchymal differentiation. Despite not entirely specific, expression of TLE1 is a helpful marker for synovial sarcoma. Nevertheless, identification of t(X;18) leading to SYT/SSX gene fusion by RT-PCR or FISH is the most important diagnostic test, being reported in nearly all cases.

Clear-Cell Pattern

The finding of a proliferation of cells with clear cytoplasm should raise the suspicion of different neoplasms, mainly thymic tumors (e.g., thymic carcinoma,

clear-cell variant), germ cell tumors (e.g., seminoma), lymphomas (e.g., large B-cell lymphoma), sarcoma (e.g., clear-cell sarcoma), and metastatic tumors (e.g., renal cell carcinoma), among others. The differential diagnosis concerning the main lesions with clear-cell pattern is concisely summarized in Table 6.5.

Germ cell tumors, including seminoma, mainly occur in children, but virtually all ages may be involved, and a primary gonadal location should be ruled out. GCT tends to involve the anterior mediastinum, and knowledge of serologic markers (alpha-fetoprotein, beta-human chorionic gonadotropin) may be of diagnostic help. Among GCT, clear-cell growth mainly characterizes seminoma. The tumor generally shows solid sheets and nests of monotonous round-to-polygonal cells with distinct cell membrane, abundant clear-to-pale cytoplasm containing glycogen, and nuclei with unique prominent eosinophilic nucleoli. Tumor cell proliferation is surrounded by delicate or abundant septa of connective tissue and characterized by

Table 6.5 Main differential diagnosis of the *clear-cell* pattern

Entities (compartment of mediastinum, mean age)	Cytological features	Pattern of growth	Distinctive immunohistochemistry/ molecular features
Seminoma (ant, young adult)	Polygonal cells with distinct cell membrane, abundant clear-to-pale cytoplasm, unique eosinophilic nucleolus	Solid growth with/ without granulomatous inflammation	CKs (−/+), CD117 +, PLAP +/−, OCT4 +, hCG −, alphaFP −, LCA −
Thymic carcinoma (ant, adult)	Polygonal cells with pleomorphic nuclei, prominent nucleoli, and clear cytoplasm with distinct cell membrane, high mitotic rate	Solid growth, squamoid features	CKs +, CD5 +, p63 +, CD117 +
Clear-cell sarcoma (all compartments, young adults)	Epithelioid cells with oval vesicular nuclei and eosinophilic-to-clear cytoplasm	Solid, lobular pattern	S100 +/−, HMB45 +/− EWS rearrangement
DLBC lymphoma (ant, young adults)	Large neoplastic B-lymphoid cells with single or multiple nucleoli and centroblastic appearance	Large diffuse areas comprising large cells with slightly irregular nuclei and very clear cytoplasm	CD20 +, CD79a +, PAX5 +, MUM1 +, CD30 −/+, CD45/LCA +, Ki67 > 70%
Metastatic renal cell carcinoma (all compartments, previous history of renal neoplasm, adult/elderly people)	Large, polygonal cells with clear-to-eosinophilic cytoplasm and nuclei with evident nucleolus	Solid growth with a rich vascular network	Pan-CKs CK7 CD10 PAX8

ant anterior, *post* posterior, *CKs* cytokeratins

infiltrates of reactive lymphocytes. Multinucleated syncytiotrophoblastic cells, lymphoid follicles, granulomas, and dense sclerosis may be observed in seminoma and differential diagnosis with lymphomas (Hodgkin or non-Hodgkin) and granulomatous processes (sarcoidosis and infectious diseases). The tumor may also show cystic changes.

Thymic carcinomas most commonly occur in adult population, and the morphologic details are quite similar to the pulmonary counterpart. Several variants of thymic carcinoma (squamous, basaloid, mucoepidermoid, sarcomatoid, adenocarcinoma, undifferentiated with/without NUT rearrangement, lymphoepithelioma-like) are recognized in the last WHO classification, including the clear-cell type (Fig. 6.26) [97]. This rare malignancy is generally widely invasive at diagnosis (not resectable) and consists of a solid and cohesive growth of overtly malignant cells with large cells exhibiting abundant clear cytoplasm and irregular and enlarged nuclei with evident nucleoli. At least focally, areas of keratinization leading to squamoid/squamous cell differentiation are present, and careful search for this finding is very helpful on small biopsies and at intraoperative examination.

Indeed, thymic clear-cell carcinoma is generally a variant of squamous cell carcinoma. The tumor may be surrounded and intersected by large areas of desmoplastic stroma. The differential diagnoses include a metastasis from renal cell carcinoma and other clear-cell malignancies.

Although rare, even thymoma may partly show a clear-cell component, but nuclear atypia is lacking and mitotic rate very low [98] (Fig. 6.27). Curiously, a couple of cases of sebaceous lymphadenoma characterized by tumor cells with clear cytoplasm with micro-vacuolization have been reported [99].

Among mesenchymal tumors with clear-cell changes involving the mediastinum, clear-cell sarcoma has been rarely described (Fig. 6.28) [100]. The tumor consists of epithelioid cells with vesicular nuclei with a single prominent eosinophilic nucleolus and clear-to-eosinophilic cytoplasm. It derives from neural crest

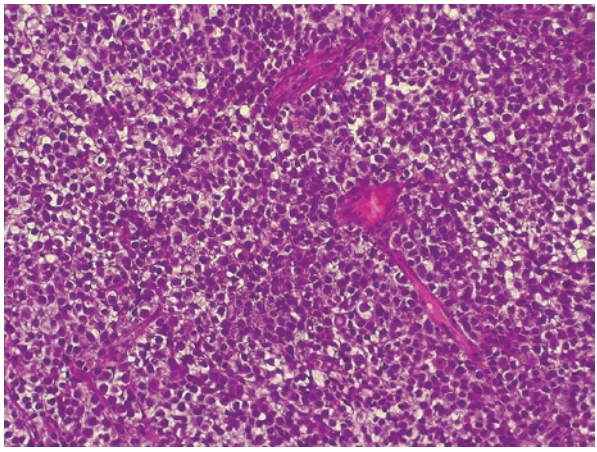

Fig. 6.26 Clear-cell-type thymic carcinoma as an undifferentiated, solid carcinoma with large cells with clear cytoplasm

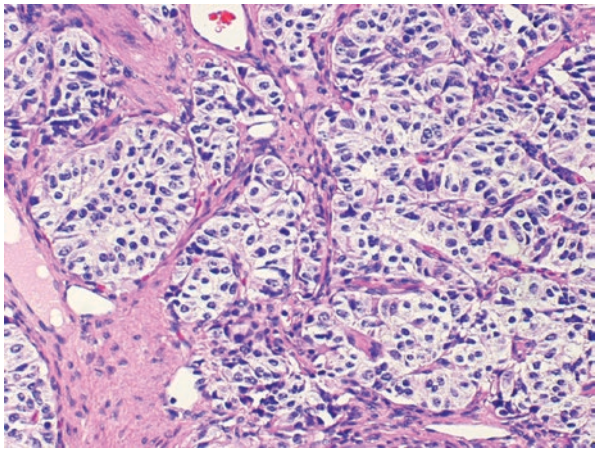

Fig. 6.27 Type A thymoma with clear-cell cytoplasm

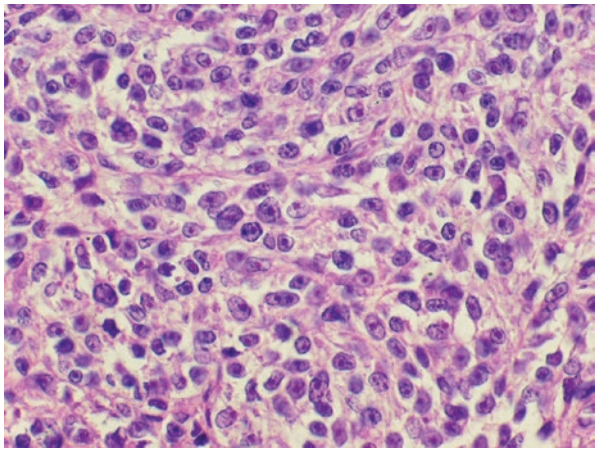

Fig. 6.28 Clear-cell sarcoma consisting of monomorphic cells with clear-to-eosinophilic cytoplasm and nuclei with an evident single nucleolus

cells with melanocytic differentiation and shows an aggressive clinical behavior. The differential diagnoses include primary or metastatic melanoma, thymic carcinoma, lymphoma, and germ cell tumors. Expressions of melanocytic markers (S-100, HMB-45, and/or Melan-A) and identification of t(12;22) involving EWSR1 gene are diagnostic tools.

Clear-cell morphology is not a common feature of lymphoproliferative disorders, but primary mediastinal large B-cell lymphoma represents a variant of diffuse large B-cell lymphoma characterized by the presence of large atypical lymphoid cells with pale-to-clear cytoplasm and round or multilobulated nuclei with evident nucleoli [65, 66]. The presence of intermediate-sized lymphocytes, immunoblasts, and pleomorphic/bizarre cells is often observed. Broad or delicate strands of dense sclerosis may be often observed. Since this lymphoma is thought to originate from thymic B cells, epithelial cysts, Hassall corpuscles, and/or atrophic thymic tissue may be present. Primary mediastinal large B-cell lymphoma primarily affects young

adults with a female prevalence. As expected, the lesion is positive for CD45 and pan B-cell markers (CD19, CD20, CD79a, PAX5) and negative for CD5, CD10, and T-cell markers. CD30 is variably expressed, but CD15 and ALK are lacking.

Other uncommon neoplasms that may occur in the mediastinum and showing a clear-cell pattern include salivary gland-type tumor with prominent myoepithelial component (e.g., myoepithelial carcinoma) (Fig. 6.29), perivascular epithelioid cell-derived tumor (PEComa or angiomyolipoma) (Fig. 6.30), and clear-cell mesothelioma. PEComa generally shows spindle myoid and epithelioid cells surrounded by prominent hemangiopericytoma-like vascular channels and mature adipose tissue with thick-walled vessels, but monomorphic variants do exist. Negative staining with keratins but expression of melanocytic markers (HMB45) and cathepsin K in perivascular cells and smooth muscle actin in spindle and epithelioid cells are the characteristics.

Among metastatic tumor with clear-cell appearance presenting as mediastinal mass, renal cell carcinoma is by far the most common. Metastatic clear-cell renal

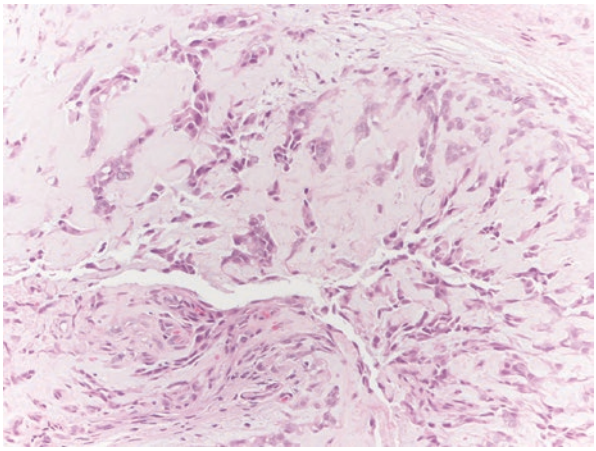

Fig. 6.29 Myoepithelial tumor with deposits of basal membrane collagen and clear tumor cells

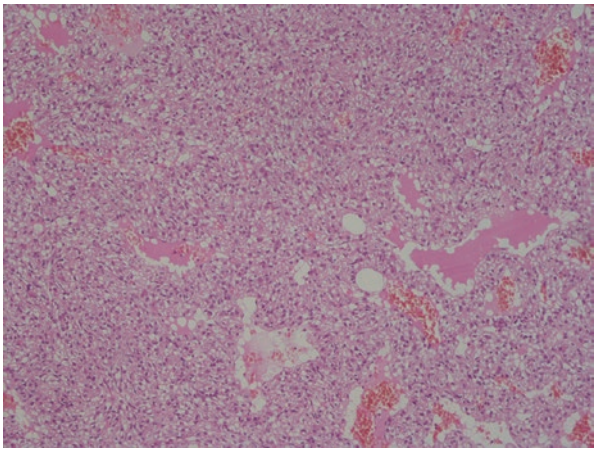

Fig. 6.30 PEComa appears as a bland epithelioid- to spindle-shaped clear-cell proliferation with a rich, hemangiopericytoma-like vascular network

cell carcinoma typically shows a delicate and rich network of vessels, and nuclei of neoplastic cells have small nuclei with a single nucleolus. Tumor cells react with keratins, CD10, and PAX8.

Accumulation of foamy macrophages in the mediastinum may create some diagnostic problems simulating clear-cell neoplasms on frozen section. Some thymomas may show prominent regressive features with solid accumulation of foamy histiocytes. Cholesterol granuloma (cholesteroloma) [101] is a benign, tumor-like mass of the anterior mediastinum consisting of aggregates of cholesterol cleft granuloma with foamy macrophages and foreign body giant cell reaction in response to the presence of cholesterol crystals (often after cardiac surgical procedures), chronic inflammatory infiltrates, and remnants of normal/atrophic thymic tissue.

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis involving the long bones, retroperitoneum, central nervous system, heart, orbit, lungs, and other organs [102]. However, cases of ECD have been described in the posterior mediastinum, and the pathology is characterized by accumulation of foamy-to-pale histiocytes intermingled by bland fibrotic tissue (Fig. 6.31).

Fibroinflammatory-Looking Pattern

Several lesions of the mediastinum are characterized by a combination of fibrous tissue and inflammatory infiltrates leading to a fibroinflammatory-looking pattern. The differential diagnosis concerning the main lesions with fibroinflammatory-looking pattern is concisely summarized in Table 6.6.

Sclerosing mediastinitis (Fig. 6.32) is the paradigmatic entity among these lesions, and differential diagnosis may be posed with inflammatory myofibroblastic

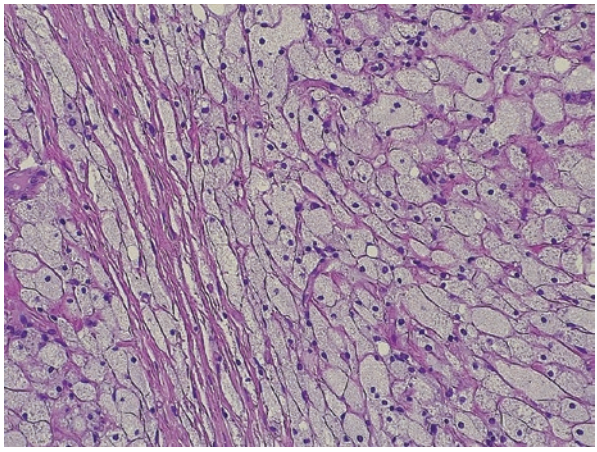

Fig. 6.31 Erdheim-Chester disease with aggregates of foamy histiocytes among inflammatory cells and fibrotic tissue

Table 6.6 Main differential diagnosis of the *fibroinflammatory-looking pattern*

Entities (compartment of mediastinum, mean age)	Cytological features	Pattern of growth	Distinctive immunohistochemistry/ molecular features
Sclerosing mediastinitis (ant, any age)	Hypocellulated mass with fibroblast-/myofibroblast-like spindle-shaped cells and scar-like hyalinized stroma and inflammatory cells	Infiltrative mass with variable amount of hyalinized tissue, inflammatory cells, and scattered fibroblast/ myofibroblast. Granulomas may be present	Special stains for fungi (Grocott, methenamine silver, PAS, mucicarmine) and bacteria (gram, Ziehl-Neelsen) Antibodies against fungi and other infective agents (e.g., *Treponema*) IgG4
Inflammatory myofibroblastic tumor (all compartments, any age)	Spindle and epithelioid cells with myofibroblast features and inflammatory cells	Irregular growth of myofibroblasts (spindle- and epithelioid-shaped), mixed inflammatory cells	Smooth muscle actin +, ALK + (half of cases) ALK rearrangement
Calcifying fibrous tumor (all compartments, any age)	Scattered bland fibroblast-like cells into hyalinized collagenous stroma and psammoma-like calcifications	Well-circumscribed mass with large amount of scar-like collagenous matrix, few fibroblasts, and psammomas	No specific reactivity
Mediastinal thymic LB cell lymphoma (ant, young adults)	Large neoplastic B-lymphoid cells with single or multiple nucleoli and centroblastic appearance	Nodular growth pattern with fibrous bands	B-cell markers + (CD20, CD79a, PAX5, CD19, CD22), MUM1 +, OCT2 +, BOB1 +, CD30 −/+, CD45/ LCA +, variably p63 +, Ki67 > 70%
Nodular sclerosis Hodgkin lymphoma (ant, young adults)	Reed-Sternberg cells, mixed inflammatory infiltrate, fibrous tissue	Nodular growth with lymphoid aggregates including "lacunar" and mummified reed-Sternberg cells and inflammatory cells (small lymphocytes, eosinophils, plasma cells, macrophages) surrounded by sclerotic fibrous bands	CD30 +, CD15 +/−, CD45/LCA −, MUM1 +, CD20 −/+, EMA −/+, and background infiltrate dominated by T cells

Sarcomatoid carcinoma (ant, adult/elderly people)	Spindle cells with nuclear atypia (evident nucleolus and irregular nuclear chromatin) with/without inflammatory cells	Infiltrative growth by atypical spindle cells with a characteristic angiotrophic pattern (attention to vessel invasion is a very helpful clue)	Pan-CKs +, p63/p40 +/−, EMA +, CD5 +/−, CD117 −/+
Histiocytic disorders (ECD, RDD) (mainly posterior compartment, any age)	Histiocytes with large clear xanthomatous/foamy cytoplasm in ECD Large macrophages with abundant pale cytoplasm and emperipolesis in RDD	Histiocytic proliferation and reactive inflammatory cells Some fibrous tissue may be noted in ECD	CD68 +, S100 +/−, factor XIIIa +/−, CD1a − in ECD CD68 +, S100 +, CD1a –, factor XIIIa − in RDD ECD histiocytes harbor V600E BRAF mutation in about 50–60%
Liposarcoma, sclerosing/ inflammatory type (all compartments, any age)	Irregular adipocytes (small to large) with scattered adipoblast and floret cells	Irregular proliferation of atypical adipocytes surrounded by fibrous bands and inflammatory cells (mainly small T lymphocytes)	S100 +, calretinin +, MDM2 +
Sarcomatoid/ desmoplastic mesothelioma (all compartments, adults/elderly)	Spindle cells with overt nuclear atypia (large nucleolus and frequent mitotic rate) in sarcomatoid mesothelioma Dispersed bland-looking spindle cells with myofibroblast-like appearance	Dense and invasive overgrowth of atypical spindle cells in sarcomatoid mesothelioma Patternless pattern with vague nodular growth of bland distanced spindle cells with bland necrotic foci in desmoplastic variant	CKs +/−, mesothelial markers variably expressed (calretinin, D2-40, CK5/ CK6, WT-1), negative staining with CEA, claudin 4, MOC-31 A weak expression for CKs may be the only IHC marker in desmoplastic mesothelioma BAP1 negativity is a highly specific marker of malignancy and greatly helpful tool particularly in desmoplastic mesothelioma

ant anterior, *post* posterior, *CKs* cytokeratins

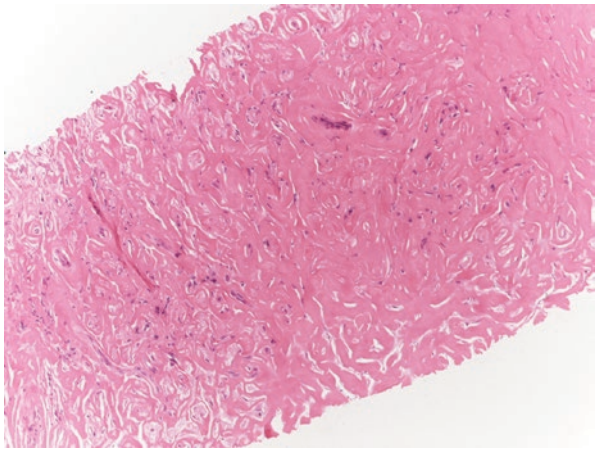

Fig. 6.32 Sclerosing mediastinitis is a hypocellular mass with abundant collagen-rich tissue

tumor, calcifying fibrous tumor, desmoid tumor, sclerosing lymphomas, IgG4-related sclerosing disease, sarcomatoid carcinomas, desmoplastic and histiocytic mesothelioma, inflammatory-sclerosing liposarcoma, and some histiocytic disorders (e.g., Rosai-Dorfman disease, Erdheim-Chester disease) [103–106].

This group of lesions represents the most difficult diagnostic challenge, particularly on small biopsy. Sclerosing mediastinitis involves the anterior mediastinum and may clinically manifest with symptoms secondary to vessel compression (superior vena cava syndrome) or cardiopulmonary involvement. It may occur at any age and radiologically appearing as an invasive mass. Grossly, the lesion is characterized by dense, collagenized, firm, whitish fibrotic tissue, histologically demonstrating deposition of hyalinized hypocellular tissue and sparse inflammatory infiltrates of mature lymphocytes and plasma cells. Scattered granulomas may be noted. Its pathogenesis is unknown, but cases of sclerosing mediastinitis seem to represent a response to *Histoplasma capsulatum* infection or other fungal (aspergillosis, cryptococcosis, and mucormycosis) or bacterial (nocardiosis, actinomycosis, syphilis) infections [107]. Sarcoidosis, drug toxicity (methysergide), and chronic thoracic trauma are other involved etiologies. Half of cases are idiopathic.

Sclerosing mediastinitis may also represent the mediastinal involvement of IgG4-related disease. Serum and/or tissutal demonstration of elevated levels of IgG4-positive plasma cells is a diagnostic hallmark [108].

Inflammatory myofibroblastic tumor (IMT) [109] is regarded as a true neoplastic process characterized by a more cellular lesion than sclerosing mediastinitis that may rarely occur in the mediastinum. IMT is composed of bland spindled elements arranged in a patternless pattern admixed with a variable collection of lymphocytes, plasma cells, eosinophils, and histiocytes (Fig. 6.33). The fusiform cells consistently express smooth muscle actin and ALK1 in about half of cases. ALK expression is related to the presence of ALK rearrangement, and this genetic alteration is a useful molecular target for specific inhibitors in malignant or unresectable IMT.

Calcifying fibrous tumor is a benign/reactive, densely hyalinized collagenous lesion with bland spindle cells and scattered psammoma-like calcification of unknown etiology.

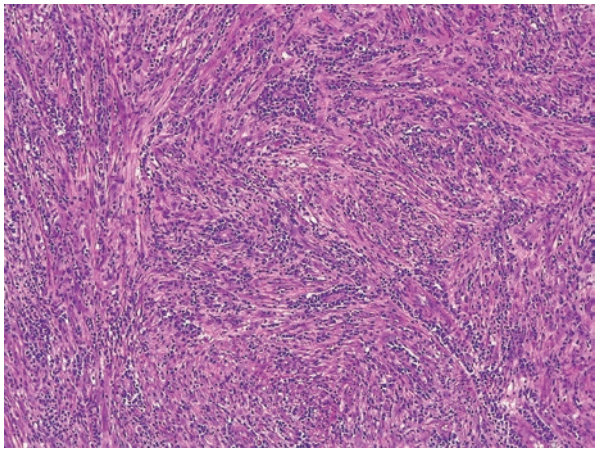

Fig. 6.33 Inflammatory myofibroblastic tumor with spindle cell proliferation of myofibroblast intermingled with a mixed inflammatory infiltrate

A fibrotic tissue similar to that observed in sclerosing mediastinitis may be observed in poorly sampled malignancies, such as Hodgkin and sclerosing mediastinal large B-cell lymphomas, desmoplastic mesotheliomas, inflammatory-like sarcomatoid carcinoma, and sclerosing inflammatory liposarcoma. Serial sections, specific immunohistochemical stains, and/or molecular analyses are often mandatory to identify the scarce amount of diagnostic neoplastic cells avoiding misdiagnosis.

Nodular sclerosis classic Hodgkin lymphoma [68] is the most common lymphoma in the mediastinum with a predilection for the anterior region. The sclerotic tissue can be prominent, producing large areas of acellular collagenous stroma. The neoplastic process may show nodular compartmentalization of cellular nodules with small cellular nodules containing characteristic "lacunar" Hodgkin Reed-Sternberg cells completely or partially surrounded by broad bands of fibrous tissue. The cellular nodules are composed of an admixture of small lymphocytes, plasma cells, eosinophils, and macrophages with the presence of a variable amount of large "lacunar" and "mummified" Hodgkin cells that are characteristically membranous and Golgi pattern expression for CD15 (50–60%), MUM1/IRF4 (multiple myeloma oncogene 1/interferon regulatory factor 4), and CD30 (up to 90%) coupled with negative staining for CD45, CD3, ALK1, OCT2 (octamer transcription factor 2), and BOB1 (B-cell-specific octamer-binding protein-1). CD20 and EMA may be focally positive. The cellular background infiltrate is significantly dominated by small CD3+ T cells with a high CD4:CD8 ratio, and entrapped thymic tissue may be highlighted by pan-cytokeratins and p63.

Primary mediastinal (thymic) large B-cell lymphoma also occurs in the anterior mediastinum, with a predilection for young females. This lymphoma also shows a nodular growth with fibrous bands compartmentalizing the cellular component with neoplastic cells. These cells show intermediate to large centroblast-like nuclei and express B markers (CD19, CD20, CD22, CD79a, PAX5, OCT2, BOB1), CD45, MUM1, and variably CD30 and p63. CD10, CD15, and EBV are negative. Residual thymic tissue may be appreciated even in small biopsy using pan-cytokeratins and p63, while the background infiltrate mainly consists of small T lymphocytes without the polymorphous appearance of Hodgkin disease.

Rosai-Dorfman disease (RDD) and Erdheim-Chester disease (ECD) are non-Langerhans cell histiocytic disorders that may rarely occur in the posterior paravertebral mediastinum. RDD is characterized by histiocytes (macrophages with large and pale cytoplasm with emperipolesis phenomenon, expression of S100 protein and CD68 with negativity for CD1a, factor XIIIa and CD163) intermingled with a mixed inflammatory infiltrate and dense fibrosis [110]. Histology of ECD shows scattered xanthomatous/foamy histiocytes variably expressing CD68, S100, and factor XIIIa, surrounded by dense fibrosis and a lymphoplasmacytic inflammatory infiltrate. BRAF V600E mutation is reported in up to 60% of patients with ECD.

Among liposarcomas occurring in the mediastinum [111], well-differentiated sclerosing-inflammatory type is the most challenging, particularly in small biopsy/cytology. Histology shows irregularly shaped large and small adipocytes, accompanied by fibrous septa with disperse oval- to spindle-shaped or polygonal atypical cells with hyperchromatic nuclei (Fig. 6.34) expressing S100 and MDM2, arranged in a vaguely fascicular or haphazard pattern with fibro-collagenous stroma and lymphocytic inflammation.

Inflammatory spindle cell sarcomatoid carcinoma and lymphohistiocytoid or desmoplastic mesothelioma may rarely occur and more frequently involve the mediastinum. These malignancies [112–114] closely mimic fibroinflammatory processes, and their recognition requires a careful search for cellular atypia and demonstration of epithelial/mesothelial cell differentiation using a specific panel of stains (pan-cytokeratins, mesothelial markers).

Cystic Pattern

The differential diagnosis concerning the main lesions with cystic pattern is concisely summarized in Table 6.7.

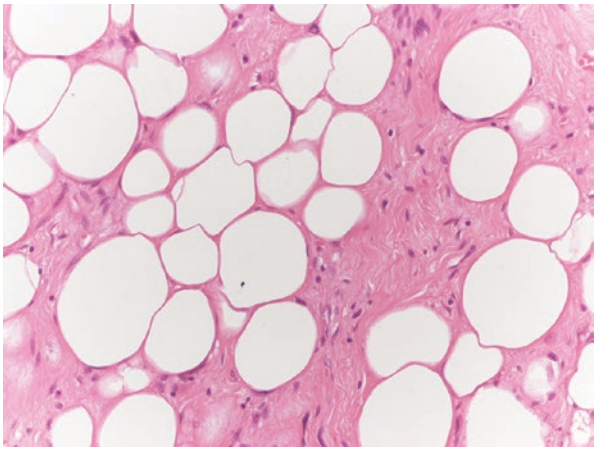

Fig. 6.34 Sclerosing-type liposarcoma with irregular adipocytes intersected by fibrous bands

Table 6.7 Main differential diagnosis of the *cystic pattern*

Entities (compartment of mediastinum, mean age)	Cytological features	Pattern of growth	Distinctive immunohistochemistry/ molecular features
Pericardial cyst	Bland-looking mesothelial cells	Unilocular or multilocular single-layer cyst	Mesothelial markers +
Parathyroid cyst	Regular parathyroid tissue	Unilocular or multilocular cyst lined by normal parathyroid tissue	PTH +
Thymic cysts (ant, any age)	Regular thymic tissue with squamous cells	Unilocular (congenital) or multilocular (acquired) cystic lesions with normal thymic tissue. Internal layer may show squamous cells with columnar cells and even parathyroid and salivary gland tissue A proliferating type with pseudoepitheliomatous hyperplasia being described	CKs +, p63/p40 +
Enteric cyst (post, childhood)	Regular esophageal or gastric tissue	Enteric cysts recapitulate the foregut origin, such as esophageal duplication, enteric cysts	CKs + with expression of the relevant layer (CDX2 in intestinal type, p63/p40 in esophageal mucosa)
Bronchogenic cyst (middle, any age)	Regular respiratory epithelium	Uni- and multilocular cyst lined by normal respiratory epithelium with/without cartilage and smooth muscle	CKs +, CK7 +
Cyst of Hattori (paravertebral mullerian cyst) (post, adults, women)	Fallopian epithelium	Ciliated cyst lined by normal fallopian mucosa	CKs +, hormonal receptors +
Lymphangioma (all compartments, childhood)	Regular endothelium	Multilobulated interanastomosing cysts with lymphatic channels lined by flat/cuboidal endothelium and collagenous stroma and lymphocytic infiltrate	D2-40 +, CD34 +
Teratoma (ant, childhood)	Combination of endodermal, mesodermal, and ectodermal tissue	Combination of several tissues, mainly adipose tissue, bone, hairs, cartilage, and several types of epithelium (squamous, foregut) immature neuroepithelial tissue in immature teratoma Possible association with malignant germ cell tumors	CKs + and variable expression depending on the types of tissues present in teratoma
Cystic changes in tumors (thymoma, seminoma, lymphomas)	See relevant tumors	Cystic changes may rarely be observed in several tumors of the mediastinum Look carefully around the cystic space to disclose tumor tissue Extensive sampling is recommended in cystic lesions so that tumor tissue will not be missed	Variable expression of markers depending on the tumor type (see relevant tumors in previous tables)

ant anterior, *post* posterior, *CKs* cytokeratins

Cystic masses in the mediastinum are relatively uncommon (10–15%) and may characterize benign and malignant lesions. Nevertheless, the vast majority of these lesions are benign, with most being discovered incidentally [115].

When symptoms are present, these are usually the result of compression of adjacent structures. The most common are pericardial and foregut duplication cysts. While in some occasions the origin of a cyst is unclear, location plays a major role in determining the organ from which it may be arising. For example, a cystic lesion in the region of the thymic bed is most likely compatible with a thymic cyst.

Pericardial cyst is a simple cyst with a fibrous wall lined by a single layer of bland-looking mesothelial cells. The cyst is generally located in the cardiophrenic angle, and all mediastinum regions may be involved.

Parathyroid cysts are rare lesions grossly measuring up to 10 cm with thin-walled and containing clear fluid showing a high level of PTH without hypercalcemia. The internal surface is lined by regular parathyroid epithelium.

Thymic cysts are uncommon and represent only 1–3% of mediastinal masses. They are either congenital (usually unilocular) or acquired (often multilocular). They are most commonly encountered in the anterior mediastinum. Congenital thymic cysts are less common than acquired cysts and arise from a remnant of the thymo-pharyngeal duct. They are usually unilocular, thin-walled, and filled with clear fluid (Fig. 6.35). Thymic tissue must be present at least focally within the wall of the cyst. They are rarely inflamed and usually asymptomatic and incidentally detected, but thymic cyst may be considerably large (up to 20 cm). The internal surface consists of bland squamoid cells with a fibrous wall containing inflammatory cells, cholesterol granulomas, and/or hemorrhagic areas. Multilocular thymic cysts have a multilayered lining of squamous cells, columnar cells, and/or cuboidal cells. Hassall corpuscles and parathyroid and/or salivary gland tissue may be observed. Malignant transformation in a thymic cyst is a rare phenomenon, but a proliferating type of multilocular thymic cyst has been described. This latter is characterized by pseudoepitheliomatous hyperplasia of the squamoid epithelium and should not be confused with squamous cell carcinoma [116].

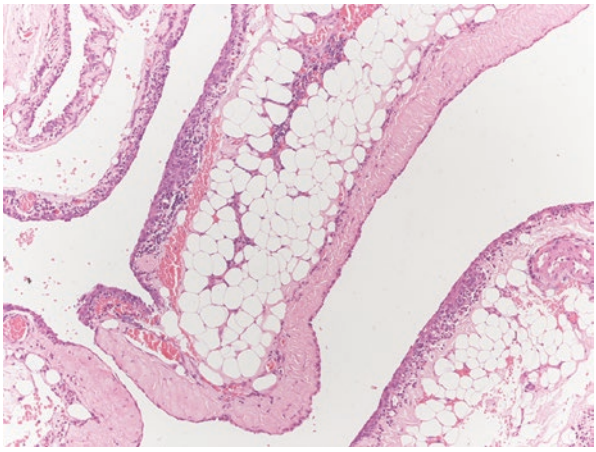

Fig. 6.35 Thymic cyst with single-layer lining epithelium and cystic wall consisting of adipose tissue and lymphocytes

Enteric cysts are confined to the posterior mediastinum and occur in childhood. They may arise from the esophagus or stomach and histologically recapitulate the normal gut. Historically, cysts of foregut origin have been classified into bronchogenic cyst, esophageal duplication cyst, and enteric cyst.

Bronchogenic cysts result from abnormal budding of the ventral foregut, and most are located in the middle mediastinum. They are occasionally associated with other congenital pulmonary malformations, and half of patients present with clinical symptoms (usually related to mass effect). Histology consists of a uni- or multilocular lesion with an internal surface lined by normal respiratory epithelium, and the cystic wall may contain cartilage and smooth muscle (Fig. 6.36).

Mediastinal cystic meningocele is an abnormal herniation of the meninges through a bony defect in a vertebral body rarely presenting as a posterior mediastinal mass. The cyst has a thick fibrous wall lined by mature arachnoidal cells. These frequently occur as a complication of neurofibromatosis type 1 (NF1), Marfan syndrome, and Ehlers-Danlos disease.

Mediastinal paravertebral mullerian cyst (cyst of Hattori) is an asymptomatic ciliated cyst in the posterior mediastinum lined by fallopian epithelium staining positive with estrogen and progesterone receptors, possibly secondary to misplaced mullerian tissues (Fig. 6.37). Patients with mullerian cysts are women generally between the ages of 40 and 60 years [117].

Lymphangiomas (cystic hygroma) are malformations of the lymphatic system, representing embryological remnants of lymphatic tissue. The vast majority of these lesions (90%) present before 2 years of age, with most of these presenting as a cervical mass with extension into the thoracic region. Lymphangiomas are generally asymptomatic and may occur in the anterior, middle, and posterior mediastinum. Grossly, these lesions appear as multilobulated and edematous mass with interanastomosing channels lined by a bland, flat endothelial cells and a collagenous stroma. Eosinophilic, proteinaceous lymphatic fluid is noted into vascular channels.

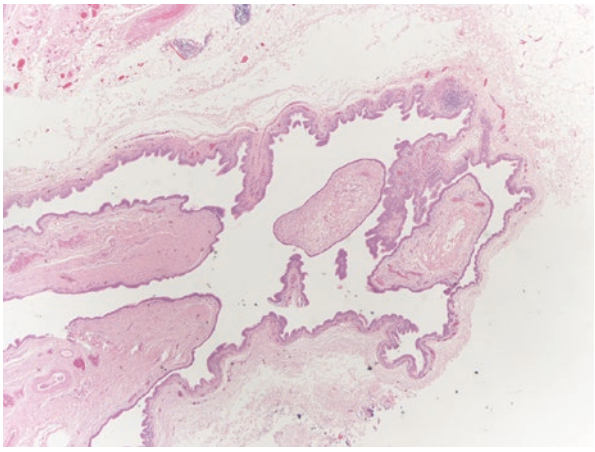

Fig. 6.36 Bronchogenic cyst with regular respiratory epithelium and smooth muscle in the cystic wall

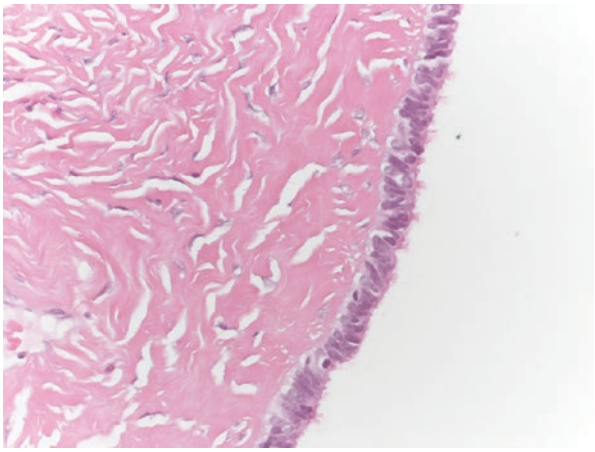

Fig. 6.37 Cyst of Hattori with single layer of fallopian-type ciliated epithelium

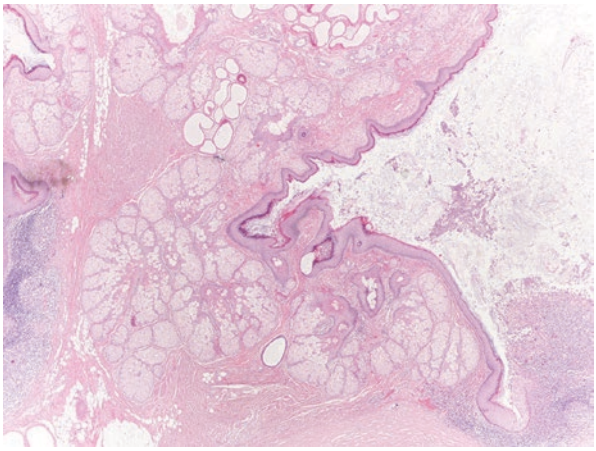

Fig. 6.38 Cystic teratoma predominantly composed of ectodermal tissue

Thoracic duct cysts are rare cystic lesions of the middle or posterior mediastinum communicating with the lymphatic system and the thoracic duct. They contain chylous fluid and histologically show a single layer of flat endothelial cells, smooth muscle, and a fibrous wall with inflammatory infiltrate.

Teratomas are neoplasms derived from endodermal, mesodermal, and ectodermal origin in different combinations (Fig. 6.38). The lesion may be entirely cystic and most commonly seen in the anterior mediastinum of children or young adults. Most patients are asymptomatic, and symptoms may be related to compression of adjacent structures. Given their origin, these lesions are usually filled with sebaceous material, but may also contain adipose tissue, bone, hairs, cartilage, and many other epithelial (squamous, foregut), mesenchymal, and/or neural tissues. Virtually, all tissues may be represented in teratomas. Immature neuroepithelial tissue may be present leading to the diagnosis of "immature teratoma," but neoplasms may arise from all represented tissues. Teratoma may also represent one of the components of mixed malignant germ cell tumor.

Cystic degeneration may characterize thymomas, seminoma, neuroendocrine tumor, sarcomas, and lymphomas [118–126]. Cystic thymoma is a relatively frequent event (up to 40%), but rarely thymomas have extensive cystic changes. Cystic thymoma should show residual solid islands of conventional thymoma, and the prognosis is identical to the solid counterpart.

Cystic change in seminoma is generally due to degenerative processes, such as necrosis and hemorrhage.

Mediastinal Hodgkin lymphoma coexisting with thymic cyst has been reported, but cystic changes may be more often secondary to surgical biopsy or chemoradiotherapy.

Careful examination of mural nodules or solid areas in the cystic wall is mandatory when examining cystic lesions of the mediastinum so that diagnosis of malignancy will not be missed.

Unusual Lesions Appearing as Mediastinal Mass

Ectopic pancreatic tissue of the anterior mediastinum is a rare occurrence possibly derived from enteric cyst or congenital displacement of pancreatic tissue. Differential diagnosis with teratoma is almost impossible in small biopsy, and malignant transformation leading to adenocarcinoma has been well-described. Occurrence of adenocarcinomas into ectopic pancreatic tissue is well-described [127].

Mediastinal masses may often be derived from benign inflammatory processes or infections leading to important lymphadenopathy. Among infections, mycobacteria and fungi (primarily histoplasmosis and coccidioidomycosis) are the most common cause of mediastinal masses. Inflammatory lesions, such as sarcoidosis, silicosis, drug reactions, amyloidosis, heart failure and chronic obstructive pulmonary disease, and Castleman disease may present with mediastinal lesions [128].

Castleman disease [129] is a rare and idiopathic lymphoproliferative disorder of unknown etiology that often involves the thorax, but rarely associated with autoimmune processes, within POEMS syndrome or in association with non-Hodgkin lymphomas, particularly in HIV-positive patients. The disease is often localized and resectable, but a multicentric variant leading to systemic symptoms (fatigue, fever, night sweats, weight loss) and recurrences is described. At histology, the hyaline vascular type is the more frequent (85%) and characterized by lymph nodal tissue with follicular hyperplasia and hyalinized capillaries resulting in the so-called lollipop follicles.

Sarcoidosis [130] commonly involves the mediastinal lymph nodes, possibly leading to mediastinal mass of the middle compartment. The process is characterized by granulomatous inflammation with/without tiny foci of necrosis. Granulomas tend to coalesce, and dense fibrosis replaces granulomatous inflammation with time (Fig. 6.39). Differential diagnosis with infections (particularly mycobacteria and fungi) may be challenging. The use of special stains on serial sections and different paraffin blocks is a useful practice.

On conventional hematoxylin-eosin stain, it is difficult to distinguish dense fibrotic tissue from amyloid deposits, but rare cases of amyloidoma have been reported in the mediastinum [131]. This solitary localized tumor-like deposit of amyloid in the absence of systemic amyloidosis is generally associated with reactive giant cells or granulomatous inflammation, calcification, and, secondary to plasmacytoma, multiple myeloma or other lymphoplasmacytic disorders (e.g., MALT-type lymphoma). A positive Congo red stain with the classic apple green birefringence at polarized light and demonstration of monotypic kappa or lambda expression even in scattered plasma cells are helpful diagnostic features (Fig. 6.40).

The main diagnostic immunohistochemical markers and molecular analyses in the differential diagnosis of neoplastic mediastinal masses are listed in Tables 6.8 and 6.9, respectively.

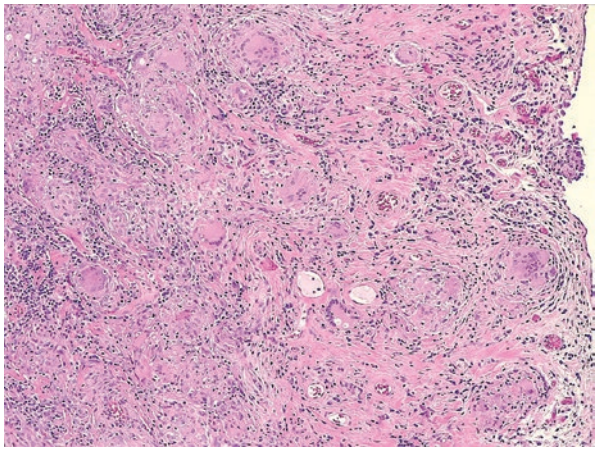

Fig. 6.39 Sarcoidosis of mediastinal lymph nodes leading to mass-forming coalescent granulomas with dense fibrosis

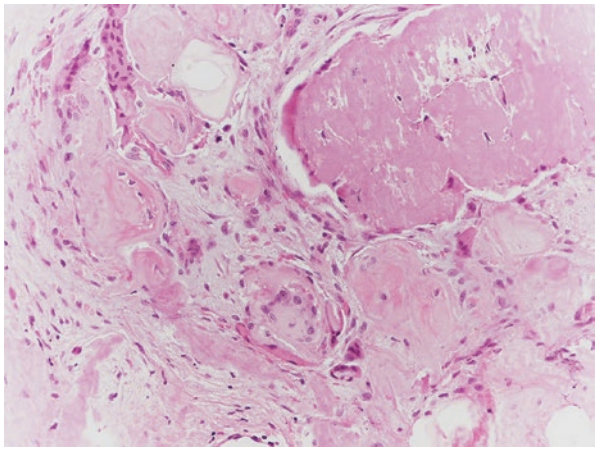

Fig. 6.40 Amyloidoma with abundant amorphic eosinophilic amyloid tissue surrounded by reactive giant cells

Table 6.8 Diagnostic immunohistochemistry in mediastinal masses

Cytokeratins
Thymoma/thymic carcinoma
Neuroendocrine tumors
Mesothelioma
Germ cell tumors (yolk sac, embryonal, teratoma, choriocarcinoma)
Mesothelial markers
Melanocytic markers
Lymphoid markers
Soft tissue markers
Muscle differentiations (desmin, smooth muscle actin, myogenin)
Vascular differentiation (CD34, CD31, ERG, factor VIII)
Neural differentiation (GFAP, neurofilament, S100)
Adipocytic differentiation (S100)
Germ cell markers (alphaFP, βHCG, OCT3–OCT4, SALLA4, PLAP)
Neuroendocrine markers (chromogranin, synaptophysin, CD56)
Others
NUT (midline undifferentiated carcinoma with translocation)
p63 (squamous cell carcinoma, thymoma)[a]
IgG4 (IgG4 production syndrome)
CD117/cKIT and CD5 (poorly-differentiated thymic carcinoma)
ALK (inflammatory myofibroblastic tumor)
VE1/BRAFV600E (Langerhans cell histiocytosis)
TFE3, cathepsin K (PEComa)
STAT6 (solitary fibrous tumor)
CAMPTA-4 (epithelioid hemangioendothelioma)
HHV8 (Kaposi's sarcoma)

[a]p63 may be positive in DLBCL

Table 6.9 Diagnostic molecular biology in mediastinal masses

Rearrangements
NUT (midline undifferentiated carcinoma)
ALK (inflammatory myofibroblastic tumor)
EWS (PNET, Ewing's sarcoma)
SYT (synovial sarcoma)
MAML2 (mucoepidermoid carcinoma)
CIC (undifferentiated sarcoma)
STAT6 (solitary fibrous tumor)
Mutations
BRAF V600E (Langerhans cell histiocytosis, Erdheim-Chester disease)
c-KIT (poorly differentiated thymic carcinoma)

Final Remarks

(a) The mediastinum is a limited anatomic region, but benign and malignant lesions from the epithelial, lymphoid, mesenchymal, and germ cell organs as well as mesothelioma and metastasis may occur in this site.
(b) Knowledge of clinical and radiologic features may be very helpful in guiding pathologists to a correct differential diagnosis [132]. Some specific symptoms may be related to specific pathologies, such as myasthenia gravis (thymic lesions), weight loss, fever and night sweats (lymphoproliferative lesions), autoimmune diseases (thymomas), syndromes due to hormonal production (Cushing, inappropriate secretion of antidiuretic hormone, Eaton-Lambert, type I multiple endocrine neoplasia syndrome in neuroendocrine growths), or hypercalcemia (parathyroid lesions). Even radiologic data are closely related to specific pathologic lesions (thymomas, germ cell tumors, carcinomas, lymphoproliferative lesions and non-neurogenic soft tissue growths in the anterior mediastinum, benign cysts and lymphomas in the middle mediastinum, cysts and neurogenic soft tissue neoplasms in the posterior region).
(c) Although infiltrative gross pattern is associated with malignant processes (lymphomas, carcinomas), even benign lesions (fibrosing mediastinitis, desmoid tumor) may show invasive growth. In general, the presence of an encapsulated lesion is related to a benign entity (cystic lesions) and thymoma. The presence of a lobulated mass with fibrous bands favors thymomas or sclerosing lymphomas. Large necrosis and hemorrhage favor germ cell tumors or metastasis.
(d) Since different vital organs (the heart, large vessels, lungs) reside in the mediastinum, all space-occupying masse may determine compression and displacement leading to general symptoms. Then, all mediastinal lesions may be considered a medical urgency requiring high-priority diagnosis.
(e) Diagnosis of mediastinal masses requires a careful and smart examination of conventional morphology on H&E-stained slides, but special stains, immunohistochemical markers, and molecular biology play an essential role. Continuous update and adequate choice of ancillary techniques should be integrated into clinicopathologic features to obtain the correct diagnosis.

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Chapter 7
Thymic Tumors and Lymphomas: The Clinical Impact of Their Underlying Molecular Features

Francesca Pentimalli, Daniela Barone, and Antonio Giordano

Introduction

Mediastinal masses, which are often identified by imaging analysis of both symptomatic and asymptomatic patients, include a wide range of both benign and malignant diseases that can originate or not within the mediastinum. Given the wide heterogeneity of such pathological lesions, it is often difficult to provide rapidly a correct diagnosis. To aid in narrowing the differential diagnosis (and also to facilitate biopsy, tumor excision, or mediastinal space drainage), it is considered useful to divide, anatomically, the mediastinum in various sectors, and, to this purpose, various classifications have been proposed [1, 2]. However, such divisions, which are often challenged, as also recently [3, 4], are theoretical because no physical boundaries exist in between compartments, and diseases can present or spread across multiple compartments. According to the three-compartment model, the mediastinum can be divided into an anterior compartment, a middle compartment, and a posterior one [2]. The anterior mediastinum accommodates the thymus, mediastinal fat, and lymph nodes; the middle mediastinum hosts the heart, pericardium, aorta, trachea, and main bronchi, as well as lymph nodes, whereas the posterior mediastinum contains the esophagus, the descending thoracic aorta, thoracic duct,

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vagus nerves, and lymph nodes [2]. Regardless of classification systems, it is recognized that although most mediastinal tumors are benign, those residing in the anterior compartment are more commonly found to be malignant. Indeed, mass location, along with patient age and presence/absence of symptoms, are key factors impacting on the likelihood of malignancy [5].

Although the true incidence of anterior mediastinal masses is difficult to assess because of the high variable criteria used across different studies, it seems that 50% and over of mediastinal masses are found within the anterior compartment [6] and include thymic and thyroid lesions, lymphomas, teratomas and germ cell tumors, and also rare mesenchymal tumors such as lipomas [7–9]. Age and gender, coupled with radiographic and clinical features, enable in many cases to establish a presumptive diagnosis [7]. Here, we will focus on the molecular features underlying the most common malignancies occurring in the anterior compartment, such as thymic tumors and lymphomas, which represent approximately 35% and 25%, respectively, of anterior mediastinal masses [7].

Thymic Tumors

Overall, tumors of the thymus account for less than 1% of human cancers. They originate from, or differentiate toward, thymic cellular components and include thymic epithelial tumors (thymomas, thymic carcinomas, and neuroendocrine epithelial tumors), germ cell tumors, lymphoid and hematopoietic neoplasms, and mesenchymal tumors [10]. Although primary tumors are rare, thymoma is the most common histotype: it derives from the thymic epithelial cells which favor T-cell maturation. Indeed, thymomas frequently present with a rich infiltrate of T cells, whose release into circulation is likely responsible for the co-occurrence of autoimmune conditions such as myasthenia gravis, blood disorders, and connective tissue diseases [11].

The etiology of thymic tumors is mostly unknown; no specific inherited, environmental, or lifestyle risk factors have been clearly associated with the development of thymic tumors [11]. Only age and ethnicity are well-established risk factors at present. Consistently, thymoma is uncommon in children and young adults, whereas its incidence rises in middle age peaking in the seventh life decade (despite the progressive involution of the thymus with age). Also, it is more common in African/American and Asians/Pacific Islanders compared with white and Latinos [11]. Interestingly, thymomas arise at a much younger age in blacks than in whites [12]. Patients with thymoma have also a higher risk of developing second tumors, which could be related to the radiotherapy or to the immunosuppression caused by thymectomy during surgery. Indeed the immune dysregulation typically caused by thymomas is likely to predispose individuals to multiple tumor types [12].

The WHO histological classification of tumors of the thymus has been recently published along with an article by Strobel and colleagues on the *Journal of Thoracic Oncology*, which summarized the advances proposed in the new classification [13]

and the major changes compared with the previous, 2004, classification [14]. These articles introduced molecular features and both "obligatory/indispensable" as well as "optional criteria" that can help for the diagnosis of ambiguous cases.

Thymic epithelial tumors include thymomas (type A, AB, B) which arise from or differentiate toward thymic epithelial cells and have no or low/moderate malignant potential, and thymic carcinomas which lack thymus-like organotypic features have a varying differentiation and are termed accordingly (squamous cell, basaloid, mucoepidermoid, etc.) and are almost invariably invasive. Fifteen to twenty percent of thymic epithelial tumors indeed are aggressive tumors with frequent invasion and metastatic spread into adjacent organs such as the lung, bone, and liver [15].

Thymoma classification as A and B types depends on whether the neoplastic epithelial cells/nuclei have a spindle or oval shape (as it is the case of type A thymoma) or whether they have a predominantly round or polygonal appearance (type B thymomas). The latter are further subdivided in subtypes according to the extent of the lymphocytic infiltrate and the degree of neoplastic cell atypia (B1: high content of lymphocytes; B2: intermediate; B3 high content of epithelial cells). Whereas thymomas, which combine type A with B1 or B2 features, are identified as type AB.

The WHO histologic type, the tumor stage (according to the Masaoka classification), and the possibility to achieve complete resection are key prognostic factors. However, the natural history of thymic diseases is often unpredictable including both asymptomatic tumors with an indolent course that can be discovered incidentally and very aggressive tumors [12].

Being thymic tumors very rare and having an often unpredictable natural history, it is recognized that these tumors should be managed by a multidisciplinary approach. Whereas resection through surgery is the mainstay of treatment, complete resection is not always possible, and relapse is common. In these cases adjuvant radiotherapy is widely adopted, whereas systemic chemotherapy is the standard of care for metastatic or inoperable refractory/recurrent disease. No standard treatments or targeted therapies however are defined after first-line failure [12].

The recent appreciation that all thymoma subtypes can present in advanced stages and exhibit malignant behavior makes imperative the identification of criteria which can reliably identify tumors with a more aggressive behavior. Here we briefly review the main thymic tumor types defined by the latest WHO classification (whose morphological and immunohistochemical criteria of identification are discussed elsewhere in this book) and report the main molecular features that characterize these tumors and that have been associated with either recurrences or better prognosis.

Type A Thymoma

Type A thymoma is composed of bland spindle/oval epithelial tumor cells with few or no lymphocytes; it is usually well circumscribed and encapsulated, and it is thought to arise by the normal thymic medullary epithelial cells. Lymphocytes are usually absent [13].The overall survival (OS) of patients with type A thymoma is

highly positive (100% at 5 and 10 years) with a very low risk of recurrence when the tumor can be completely removed surgically. However, exceptional cases of local recurrence or distant metastasis have been reported [13].

Type AB Thymoma

Type AB thymoma is composed of a variable mixture of a type A thymoma and type B-like component. In particular the lymphocyte component appears more numerous than in the type A but may be less numerous than in B1 thymomas. This mixed variant is usually encapsulated and is among the most common type of thymoma accounting for 15–43% of all thymomas. Similarly to type A, it can be associated with paraneoplastic conditions such as myasthenia gravis [13].

As with type A thymoma, also type AB thymoma patients have a positive overall survival (80–100% at 5 and 10 years) consistent with the mostly benign nature of these tumors [13].

Type B1 Thymoma

Type B1 thymoma, which accounts for 6–17% of all thymomas, derives from thymic epithelial cells and presents areas similar to the normal thymus cortex rich of epithelial cells and immature lymphocytes and areas of medullary differentiation, with or without Hassall's corpuscles, similar to normal thymic medulla. It generally presents in the anterosuperior mediastinum (although it can rarely localize to the neck, pleura, or lung) as an encapsulated mass in the majority of cases (stage I). In a minority of more advanced stage cases, it can invade the mediastinal fat or, less frequently, the pleura, pericardium, and adjacent vessels or organs.

Type B1 thymoma patients mostly present at stage I or II and have an overall survival of 90% at 10 years. Consistently, complete surgical resection is achieved in the majority of the cases and less than 10% recurrences are reported [13].

Type B2 Thymoma

Type B2 thymoma, which accounts for 18–42% of all thymomas, is characterized by loose large, polygonal tumor epithelial cells with large vesicular nuclei and nucleoli within a predominant population of immature T cells and presents mostly in the anterior mediastinum or rarely in the head, neck, pleura, or lung. Type B2 thymomas can present either encapsulated or partially circumscribed and can invade mediastinal fat or adjacent organs. Tumors occur as Masaoka stage I (10–48%), stage II (13–53%), stage III (19–49%), metastatic stage IV (8.9%), and rarely with

distant metastases (stage IVB, approximately 3%). Such variety of stages at presentation implies that 5–15% of cases are not surgically resectable and also recurrences after resection are reported in 5–9% of cases. The overall survival for these patients ranges between 50 and 100% at 10 year [13].

Type B3 Thymoma

Type B3 thymoma, which accounts for 7–25% of all thymomas, arises from medium-sized round or polygonal thymic epithelial cells with slight atypia and presents within sparse lymphocytes. Tumors present usually as not encapsulated, possibly with undefined borders that infiltrate the mediastinal fat or adjacent organs. Coexistence of B2 and B3 areas is quite frequent, occurring in 17–29% of cases, whereas in few instances (3%), features of thymic carcinomas can occur. Some tumors show also a high degree of atypia and can be reported as "B3 thymoma with anaplasia." Most type B3 thymomas occur in the anterior mediastinum as Masaoka stage II (15–38%) or stage III tumors (38–66%), more rarely as stage I (4.2%) or stage IV tumors (15%), the latter including cases with either pleural spread (stage IVA) or metastases to the lung, liver, bone, and soft tissues. Tumors are of invasive nature, often unresectable at presentation, and tend to recur locally or metastasize in up to 20% of cases. Overall survival ranges between 50 and 70% at 10 years [13].

Thymic Carcinomas

Thymic carcinomas are rare and comprise a variety of tumors including neuroendocrine epithelial tumors of the thymus. Among these the thymic squamous cell carcinoma is the most frequent subtype, with a frequency higher in Asian than in the Western world. Other thymic carcinomas include basaloid carcinoma; mucoepidermoid carcinoma; lymphoepithelioma-like carcinoma; sarcomatoid carcinoma (carcinosarcoma); clear cell carcinoma; adenocarcinoma; papillary adenocarcinoma; carcinoma with t(15;19) translocation; well-differentiated neuroendocrine carcinomas (carcinoid tumors); typical carcinoid; atypical carcinoid; poorly differentiated neuroendocrine carcinomas; large cell neuroendocrine carcinoma; small cell carcinoma, neuroendocrine type; and undifferentiated carcinoma and combined thymic epithelial tumors, including neuroendocrine carcinomas [13].

Thymic Squamous Cell Carcinoma

Thymic squamous cell carcinoma is thought to derive from thymic epithelial stem cells. Some cases, however, are thought to derive from pre-existing thymomas because both squamous cell carcinoma and thymoma components, mostly of the B3

type, can coexist. Thymic squamous cell carcinoma exclusively presents in the anterior mediastinum, but it lacks the typical encapsulation or fibrous septation that generally characterizes thymomas. Thymic squamous cell carcinoma frequently invades the adjacent lungs, the pericardium, and the large vessels, whereas metastases are found in the proximal mediastinal, cervical, and axillary lymph nodes or distantly to the bone, lung, liver, and brain.

Thymic squamous cell carcinomas, differently from other organ-derived squamous cell carcinomas, stain positively for CD5 and CD70, which turn as useful markers to determine the thymic origin with caution because thymomas are usually negative for CD5 expression, except some B3-type tumors and nasopharyngeal carcinomas and Hodgkin lymphomas could also express CD70. Overexpression of CD117 (KIT) in thymic carcinoma is also useful because most thymoma types and squamous cell carcinomas from other organs do not express this marker [16]. Similarly, FOXN1 and CD205 are new markers that complement CD5 and CD117 as markers that are expressed in the majority of thymic squamous cell carcinomas but not pulmonary squamous cell carcinomas [14]. Most thymic squamous cell carcinomas also show positivity for some neuroendocrine markers.

The prognosis of thymic squamous cell carcinoma depends on tumor stage and grade. Thymic carcinomas are in most cases diagnosed at an advanced stage. Complete resection is the mainstay of treatment although recurrence rates can be high even after complete resection [16].

Molecular Features of Thymic Tumors

Thymic tumors—even if rare—can present a challenge therapeutically. Although their pathogenesis is still to be largely defined, a great effort is ongoing to characterize these tumors from the molecular point of view, which could help not only to identify new diagnostic, prognostic, or predictive factors (of recurrence or of response to treatment) but also new possible targets for therapeutic approaches.

The earlier studies conducted through the analysis of karyotypes identified the t15,19 translocation between chromosomes 15 and 19 [17], which characterizes a small subset of thymic carcinomas [13]. With the advent of newer technologies, such as comparative genomic hybridization (CGH) and microsatellite instability/loss of heterozygosity (LOH) analysis, new chromosomic aberrations have been identified [18, 19]. Overall, type A and AB thymomas have a lower frequency of allelic imbalances compared with type B2 and B3 thymomas. However, when multiple chromosomal aberrations are considered, within a single tumor, the percentage of type AB thymomas (55% of cases) is intermediate between type A (10% of cases) and B2 and B3 thymomas (75–100% of cases) [19]. It has been proposed that the WHO-classified thymoma types generally segregate bearing typical genetic features, with type A thymomas being the most homogeneous tumors and type B2–B3 forming a continuum with evidence of tumor progression [20]. Type AB thymomas show genetic features in common with both type A and type B thymomas, although, when looking at the affected chromosomal regions, they look more similar to the B

type, even when the A component is microdissected [19, 20]. Type B3 and thymic carcinomas have been shown to have a strong relationship concerning their chromosomal imbalances, whereas various chromosomal abnormalities detected in some type A thymomas might underlie the aggressive behavior observed in a few cases of this thymoma subtype [21].

The most frequent genetic alteration occurring in all thymomas affects chromosome 6 in a percentage that varies according to the WHO subtype and the stage [18]. In particular, in a study analyzing 41 microsatellites in 40 thymomas, 5 hotspots were reported on chromosome 6: 6q25.2 (48.6%), 6q25.2–25.3 (32.4%), 6q21.31 (30%), 6q14.1–14.3 (26.3%), and 6q21 (21.6%) [22]. Interestingly, the 6q25.1–25.3 region showed LOH also in other tumors such as breast, ovarian cancer, and non-Hodgkin lymphoma; therefore it is hypothesized that it contains a tumor suppressor gene, whose alteration is crucial for thymoma development. The 6q21.3 locus hosts the major histocompatibility complex (MHC), and its deregulation can help to explain the typical autoimmune phenotype developed in thymoma patients.

Further chromosome abnormalities have been described in thymomas and were clues for the identification of a possible route of thymus tumorigenesis. Indeed, chromosomes 5q21–22, 7p15.3, and 8p11.21 have been found often altered in the aggressive type B2 and B3 thymomas and in some AB thymomas. The 5q21–22 region hosts the locus of the *APC* gene, involved both in intercellular adhesion through E-cadherin and β-catenin and in cell proliferation control through the W*NT* pathway. Inherited or acquired APC defects are associated with familial adenomatous polyposis, an autosomal dominant premalignant disease that predisposes to familial and sporadic colorectal cancer, often triggered by the accumulation of alterations in other tumor suppressor genes such as *RB1* and *TP53* [22]. Interestingly, a similar concomitant inactivation of *APC*, *RB1* (located at 13q14), and *TP53* (17p13) has been found in type B3 thymomas leading Strobel and colleagues to hypothesize a different oncogenic route for B3 tumors compared with the canonical pathway initiated by 6q25 aberrations [19]. Indeed, unlike type B3 thymomas and squamous cell thymic carcinoma, no aberrations in APC, RB1, and p53 tumor suppressors have been identified in type A thymomas suggesting that this could be the basis for type A benign clinical course [13].

B3 thymomas are characterized by a high degree of aneuploidy. Among the recurrent abnormalities, chromosome 1q gains have been reported in 69% of cases, whereas loss of chromosome 6 and 13q has been reported in 38% and 31% of cases, respectively. Loss of chromosomes 6q (6q23.3–q25.3), 3p (3p22–p24.2; 3p14.2, *FHIT* locus), 5q (5q21, *APC* locus), 13q (13q14, *RB1* locus), and 17p (17p13, *TP53* locus) has been described, potentially affecting the indicated tumor suppressor genes [13].

For as concerns genetic alterations, thymic squamous cell carcinomas show both peculiar aberrations, such as loss of chromosomes 16q, 3p, and 17p and gain of chromosomes 17q and 18 as well as alterations in common with B3-type thymomas such as loss of chromosome 6 and gain of 1q. P53 is frequently overexpressed thymic carcinomas and mutated in 30% of tumors, whereas p16 is often inactivated by promoter methylation. The BCL2 antiapoptotic factor is usually overexpressed in most thymic carcinomas, as discussed below [13].

Interestingly, Petrini and colleagues screened a wide set of formalin-fixed paraffin-embedded (FFPE) thymic epithelial tumors analyzing, through CGH, the copy number status of 31 genes involved in thymus development and organogenesis [23]. They identified and confirmed in an independent cohort of thymic epithelial tumors copy number gains of PBX1 and loss of FOXC1, which both have been described to regulate the expression of TBX1, a transcription factor orchestrating thymus development. FOXC1, in particular, is located on the 6p25 chromosome region; the loss of which was observed also in type A thymomas, although at a minor rate compared with the other histotypes (8% vs. 40%). Patients with FOXC1-negative tumors had a shorter time to progression and a trend for a shorter disease related survival, leading the authors to conclude that FOXC1 loss is a useful prognostic marker to identify thymic epithelial tumors with poor prognosis [23].

Petrini and colleagues had also identified, through a previous CGH screening, that copy number losses of *CDKN2A* and 13q (which were mostly mutually exclusive) were poor prognostic markers in thymic epithelial tumors implying the RB pathway deregulation as a crucial event in thymus carcinogenesis [24]. Also, they found gain of 18q21.33, encoding the antiapoptotic BCL2 factor, in 10% of thymic epithelial tumors. This finding, which was consistent with previous data reporting high BCL2 expression, especially in thymic carcinomas but also in type A and some type B thymomas, led the authors to explore the possible use of agents targeting BCL2 family antiapoptotic members, such as ABT263 [25], against thymic tumors [24].

More recently, with the advent of modern technologies such as next-generation sequencing, various studies have contributed to further our understanding of the molecular mechanisms possibly underlying thymus pathogenesis. Among these, a study identified, through sequencing of the whole exome from a cohort of 28 thymic epithelial tumors, a missense mutation (chromosome 7 c.74146970T>A) in the *GTF2I* gene encoding a transcription factor involved in the regulation of genes controlling cell proliferation such as *FOS* and cyclin D1 [26]. Mutations in *GTF2I* were further observed in a series of 274 thymic epithelial tumors and found in 82% of type A and 74% of type AB thymomas but rarely in B1, B2, and B3 thymoma subtypes and only in 8% of the aggressive thymic carcinomas. Consistently with previous data, thymic carcinomas carried a higher number of mutations than thymomas and recurrent mutations of known cancer genes, including *TP53*, *CYLD*, *CDKN2A*, *BAP1*, and *PBRM1*. Interestingly, the prognosis of patients with thymomas carrying *GTF2I* mutations (96% 10-year survival) was significantly better than those with tumors carrying wild-type *GTF2I* (70% 10-year survival). Even in patients with thymic carcinoma, those carrying the *GTF2I* mutation had improved survival rates. Therefore *GTF2I* represents a promising marker to identify a subset of patients with an indolent disease for whom overtreatment with radiation and/or chemotherapy could be probably spared [26, 27].

Many immunohistochemical and molecular studies were aimed at identifying the molecular mechanisms characterizing thymoma development although the lack of cell lines or animal models has long hampered a further understanding of the role of specific alterations.

The expression of the autoimmune regulator gene (*AIRE*), which is located on chromosome 21q22.3, was assessed by immunohistochemistry and reverse transcriptase PCR analysis in thymomas and found deregulated in tumors compared with normal thymus. As, by regulating the expression of peripheral self-antigens, AIRE is crucial for the central thymic T-cell education and deletion of autoreactive clones, its deregulation might correlate with the autoimmune phenotype of patients with thymomas [28, 29].

The epidermal growth factor receptor EGFR, member of the HER protein kinase superfamily, has been extensively studied in thymic epithelial tumors and found overexpressed in 70% of thymomas and 53% of carcinomas, showing positive correlation with advanced tumor stages [12, 18, 19]. Although few mutations in EGFR have been observed in thymic malignancies, FISH analyses have identified gene amplifications, which however poorly correlated with high protein expression (only 7 of 23 specimens) [30]. According to its high expression in thymic tumors, EGFR was seen as an attractive target for therapeutic approaches; however, the clinical trials aimed at assessing the possible use of EGFR-targeting agents (such as the erlotinib and gefitinib, tyrosine kinase inhibitors, or cetuximab) did not show complete remission [18, 19].

Other studies assessed the expression of the HER2 receptor in thymic tumors [31, 32]. HER2 was not overexpressed in the majority of thymomas, whereas high levels were detected by immunohistochemical analysis in 58.3% of thymic carcinomas, although gene amplification is considered a rare event. The same recent study [32] investigated also the expression of other growth factors and receptors of the HER pathway, including EGFR, HER3, transforming growth factor-α (TGF-α), amphiregulin, and epiregulin suggesting that protein expression for HER receptors as well as their ligands occurs commonly in thymic carcinomas.

Among other genes involved in cell proliferation, which were considered as possible targets for molecular therapy, is the oncogene KIT (or CD117). KIT is overexpressed in the majority of thymic carcinomas and only in few cases of thymomas (75–80% vs. 2%), whereas mutations have been detected in only 10% of cases. These observations were at the basis of preclinical and clinical trials testing the use of agents such as imatinib and sunitinib, targeting the KIT kinase, which were recently reviewed in [12, 18, 33]. A recent study also found mutations in KIT in thymic carcinomas and, the same study, also reported positivity for the immune checkpoint regulator PDL1 in 65% of thymic carcinomas compared with 18% of thymomas [34], adding up to the many studies evaluating the expression of immune checkpoint regulators in thymic malignancies [35].

The insulin-like growth factor 1 receptor (IGF1R) is a tyrosine kinase for which an important role in thymus development was recognized. However IGF1R triggers cell proliferation and antiapoptotic pathways through activation of the AKT and MAP kinases. Moreover disease stabilization had been reported for patients with metastatic thymomas who had been treated with drugs targeting IGFR1. This prompted Zucali and colleagues to investigate the protein expression of IGF1R and phosphorylated AKT-serine (Ser) 473 (pAKT) in a series of thymic tumors [36].

They found that IGF1R and pAKT levels were expressed in 20% and 36% of thymic tumors, respectively, more commonly in recurrent disease compared with primary tumors and correlated with aggressive subtypes and more advanced disease stages. IGF1R and pAKT activation were also associated with a trend of worse survival and progression-free survival and suggested to be possibly responsible for the resistance to EGFR inhibitors [36]. Consistently another study reported moderate to high IGF1R staining in 86% of thymic carcinomas and in 43% of thymomas [37]. Another study confirmed high IGF1R expression in 83.8% of thymic carcinomas and also reported gene amplifications [38]. Omatsu and colleagues also reported IGF1R positivity in thymic carcinomas compared with thymomas (73% vs. 27%) and also detected different positivity of PPARγ in these tumor types (32% vs. 4%), suggesting that the inhibition of the PPARγ nuclear receptor could be yet another strategy to target specifically thymic carcinomas [39].

The tyrosine kinases of the tropomyosin receptor kinase (Trk) family, which includes TRKA, TRKB, and TRKC, have also been evaluated in thymic tumors by immunohistochemistry. Most tumors, analyzed with the exception of 1 carcinoma in a 99 series of thymic tumors, showed cytoplasmic TRKA immunostaining, whereas in none it was found immunoreactivity against TRKB or TRKC [40]. TRKA showed also a copy number gain in 45% of thymoma and 72% of thymic carcinomas in a series of 60 paraffin-embedded samples [28], overall suggesting that TRKA could be an important target to counteract thymic tumorigenesis.

A study from Pfister and colleagues extensively analyzed the expression of angiogenic growth factors along with vascularization and pericytes coverage in a series of thymomas and squamous cell carcinomas. They found vascular endothelial growth factor receptors 1 and 2 (VEGFR1 and VEGFR2), examined by quantitative reverse transcription polymerase chain reaction, expressed in vessels of all tumors but at higher levels in the epithelial cells of A and B3 thymomas and squamous cell carcinomas [41]. Another study evaluated through immunohistochemistry the expression of factors involved in vascularization and found a higher proportion of cancer cells expressing the VEGFA, VEGFC, and VEGFD growth factors, and their receptors VEGFR1, VEGFR2, and VEGFR3, in high-risk thymic epithelial tumors (B2, B3, and carcinomas) compared with the low-risk tumors [42]. VEGF levels were also found elevated in the serum of patients with thymic carcinomas compared with healthy volunteers, similarly to the basic fibroblast growth factor (bFGF) serum level. So serum VEGF and bFGF levels were suggested as possible circulating markers for thymic epithelial tumors but not useful to assess their progression (no different levels were assessed among healthy volunteers and patients with thymomas) [43]. These findings again supported the possible use of agents targeting angiogenesis in thymic epithelial tumors.

Interestingly a recent study identified single nucleotide polymorphisms (SNPs) in that PDGFRα, HIF1α, and VEGFR3, genes implicated in angiogenesis, which were associated with patient outcome upon thymectomy by impacting on thymic cancer risk [44].

Various studies have also assessed the impact of epigenetic alterations in thymic epithelial tumors. A study identified various genes, which were recurrently mutated

in thymic carcinomas but not in thymomas, which were involved in histone modification (*BAP1*, *SETD2*, *ASXL1*), chromatin remodeling (*SMARCA4*), and DNA methylation (*DNMT3A*, *TET2*, and *WT1*) [45]. Epigenetic dysregulation as a result of the TET2 mutation were also confirmed in another study [46].

Also deregulation of miRNAs expression has been identified in thymic epithelial tumors. A large microRNA cluster on chr19q13.42 was found to be overexpressed in all A and AB tumors but not expressed in other thymomas and normal tissues and was associated with activation of the PI3K/AKT/mTOR pathway [47].

Another study identified groups of miRNAs differentially expressed between thymic tumors and normal thymic tissues, thymomas and thymic carcinomas, and various histotype groups [47]. Among these microRNAs, which were upregulated in thymic epithelial tumors, miR-21-5p, miR-148a-3p, miR-141-3p, miR-34b-5p, miR-34c-5p, and miR-455-5p were investigated as possible blood plasma circulating noninvasive biomarkers. Indeed, circulating miR-21-5p and miR-148a-3p resulted significantly reduced in follow-up samples after surgery suggesting that they could represent novel non-invasive biomarkers to evaluate prognosis and monitor treatment efficacy [48]. Moreover the epigenetic regulation of miR-145-5p and of its targets could affect both tumor progression and treatment response [49].

A further study analyzed through methylation-specific PCR (MSP) and immunohistochemistry in a set of 66 thymic tumors the methylation status of DNA repair gene O6-methylguanine DNA methyltransferase (MGMT) and found that MGMT methylation was significantly more frequent in thymic carcinomas than in thymomas (74% vs. 29%) and, consistently, MGMT loss of expression was significantly more frequent in thymic carcinomas than in thymomas (87% vs. 23%). Both methylation and protein reduction were significantly more frequent in advanced thymic epithelial tumors (III/IV) than in early tumors (I/II) [50].

Beyond dissecting thymic tumorigenesis with the goal of identifying the mechanisms of tumorigenesis as well as targets for new antitumoral approaches, molecular studies have been devised to identify gene signatures with predictive and/or prognostic value.

A recent study analyzed 120 patients with thymic epithelial tumors from The Cancer Genome Atlas through an approach that incorporated analyses of DNA mutations, mRNA expression, and somatic copy number alterations followed by validation in two independent cohorts. The authors identified four distinct molecular subtypes of thymic epithelial tumors. One group was characterized by a missense mutation in *GTF2I* (*GTF2I* group), which was identified in 38% of patients. Another group included tumors (33%) enriched in the expression of genes involved in T-cell signaling (TS group). The other two groups were distinguished based on their degree of chromosomal stability (CS group) or instability (CIN group) determined through somatic copy number alteration, which corresponded to 8% and 21% of tumors, respectively. Interestingly, these molecularly defined groups were associated not only with tumor histology but also with clinical features such as disease-free survival. Indeed, both disease-free survival and overall survival were favorable in the *GTF2I* group whereas unfavorable in the CIN group [51].

Moreover, the authors found that although the expression of *CD8A* and *PD1*, genes involved in T-cell signaling, was detected in thymic tumors from the *GTF2I*, CS, and CIN groups, they both showed high expression in tumors from the TS group suggesting that this subset could respond favorably to therapies based on immune checkpoint inhibition [51].

Another more recent study, which analyzed multi-omics platform analyses of a 117 thymic epithelial tumors cohort, also defined four tumor subtypes characterized by genomic hallmarks and associated with both survival and the WHO subtypes [52]. Beyond the common *GTF2I* mutations (detected in 39% of cases), mutations in *HRAS*, *TP53*, and *NRAS* were recurrent although at a lower frequency. Interestingly, the authors demonstrated that the A/AB type, B type, and carcinomas are distinct biological entities which do not seem to form a histological continuum of the disease. Moreover, this study demonstrated a significant association of aneuploidy with a cancer-associated autoimmune disease. Indeed, autoimmunity is a hallmark of thymomas with associated myasthenia gravis found in 30% of patients. Here they found that myasthenia gravis was associated with intratumoral overexpression of genes such as *NEFM* and *RYR3*, which showed similarity with major autoimmune targets [52].

As a further proof of the clinical impact of molecular profiling, Badve and colleagues described a validated nine-gene signature that was able to predict the likelihood of thymoma metastasis development more reliably than traditional staging [53, 54]. Whereas another study suggested that the triple combination of p27 low, p21 low, and p53 high expression was the most significant predictor of both imaging and pathologic poor responses to neoadjuvant chemotherapy in invasive thymomas. In this study incomplete resection along with the three-protein combination was also the most significant negative predictor of long-term survival [55].

Lymphoma

Lymphomas are a heterogeneous group of neoplastic disorders arising from cells of the immune system. There are two main categories of lymphoma: Hodgkin disease (HD), first described in 1832 by Thomas Hodgkin, and non-Hodgkin lymphoma (NHL), which includes distinct conditions that have very different signs, symptoms, and causes.

Both HD and NDL are common mediastinal tumors and account for approximately 20% of mediastinal tumors in adults and 50% in children [8]. They can manifest as a primary lesion or as a generalized disease affecting any mediastinal compartment, frequently as lymphadenopathy or as a discrete mass [56]. Since lymphomas infiltrating the mediastinum are a challenge for the physician as well as for the pathologists, who usually are confronted only with small biopsy samples, here we described the most common and difficult to discriminate lymphoma subtypes infiltrating the mediastinum. These lymphoma subtypes are diffuse large B-cell

lymphoma (DLBCL); primary mediastinal large B-cell lymphoma (PMLBCL); classical Hodgkin lymphoma (cHL), in particular the nodular sclerosis subtype; and mediastinal gray zone lymphoma (MGZL).

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common type of malignant lymphoma in the Western world, accounting for approximately 35% of all lymphomas cases worldwide [57]. The median age falls between the sixth and the seventh decade without gender difference. DLBCL represents a biologically heterogeneous group of tumors that if left untreated shows an aggressive and fatal clinical course. Patients present with nodal or extranodal disease, exhibiting rapid growth and different symptoms depending upon tumor localization.

The cause of most DLBCLs remains unknown, but a distinction should be made between cases arising de novo, called primary, and those originating from progression or transformation of a less aggressive lymphoid diseases like chronic lymphocytic leukemia, small lymphocytic lymphoma, follicular lymphoma, etc. [58]. Several chemical substances, such as pesticides, insecticides, and nitrogen fertilizers [59], or medical drugs like alkylating agents, have been suggested as possible etiological agents [58]. Alkylating agents, used to treat solid tumors and hematological malignancies, in combination with radiation therapy, significantly increase the risk of developing secondary lymphomas, mainly after bone marrow and spleen irradiation. DLBCL is also found in patients with inherited immunological disorders such as ataxia-telangiectasia, Wiskott-Aldrich syndrome, X-linked lymphoproliferative disorder, rheumatoid arthritis, systemic lupus erythematosus, and in patients with acquired immunodeficiency syndrome [60]. Even patients with chronic immune system suppression by drug, e.g., after organ transplants, show a higher risk to develop diffuse aggressive lymphomas with central nervous system (CNS) dissemination. The relationship between DLBCL and viruses has also been highly analyzed in the last few years. A frequent association has been found with hepatitis C virus (HCV) [61, 62], human immunodeficiency virus (HIV) [63, 64], hepatitis B virus (HBV) [65, 66], and Epstein-Barr virus (EBV) infection [67, 68].

DLBCLs are a heterogeneous group of malignancies characterized by cellular proliferation that may arise at various steps during physiological B-cell development both in primary lymphoid tissues and in secondary lymphoid organs or in nonlymphoid sites. The World Health Organization (WHO) divided DLBCL in four subtypes based on clinical, morphological, immunological, and genetic features: (1) DLBCL not otherwise specified (DLBC, NOS), (2) DLBCL with predominant extranodal location including PMLBCL discussed later, (3) large cell lymphoma of terminally differentiated B cells, and (4) borderline cases [60].

The diagnosis of DLBCL is obtained only with tissue examination. Excisional biopsy is obligatory for diagnosis to ensure sufficient tissue for morphological and molecular analysis, whereas core needle biopsy should be performed only in case

other approaches are impossible. Once diagnosis has been established, the first step is the staging by analyzing patient's medical history, physical examination, and laboratories studies. This initial evaluation is aimed to determine tumor and host factors that can influence treatment choice and overall prognosis.

The standard staging used for DLBCL is the Ann Arbor classification, proposed at the Ann Arbor Conference in 1971 [69], with the Cotswolds modifications [70]. This system reflects the number of sites involved, the presence of B symptoms (fever >38 °C for at least three consecutive days, night sweats, body weight loss >10% during the previous 6 months), and the presence of extranodal disease. However the Ann Arbor classification system does not accurately distinguish between patients with different long-term prognoses [71]. A careful history and physical examination are important factors in patient's evaluation. Host information includes age, performance status, comorbidities, and organ function. Physical examination consists on evaluation of all abnormal lymph nodes, inspection of Waldeyer's ring, examination of the liver and spleen, inspection of the skin, and detection of other palpable masses. Examination of sinuses, breast in women, and testicles in men is recommended because the involvement of these areas increases the risk of central nervous system (CNS) relapse [72]. An assessment of performance status, according to the Eastern Cooperative Oncology Group (ECOG) scale is important for patients, especially for those entering into clinical trial [58].

The International Prognostic Index (IPI) was developed to predict outcome of patients with NHLs on the basis of clinical characteristics. Factors taken in consideration in IPI include age at diagnosis (<60 vs. >60), LDH levels, tumor stage (I- and II-localized disease vs. III- and IV-advanced disease), number of extranodal sites involved, and ECOG status (0 or 1 vs. ≥2). This model is more accurate than the Ann Arbon classification in predicting survival and divided DLBCL patients in four prognostic groups. Nowadays the most commonly used index in clinical practice is the age-adjusted International Prognostic Index (aa-IPI) which includes only Ann Arbor staging, LDH levels, and ECOG performance status scale as prognostic factors. aa-IPI is helpful in stratifying patients below or over 60 years [58] segregating patients younger than 60 years in four risk groups (Fig. 7.1). The revised International Prognostic Index (R-IPI) was developed after the introduction of rituximab in classical treatment. The R-IPI identifies three distinct prognostic groups with a very good (4-year progression-free survival [PFS] 94%, OS 94%), good (4-year PFS 80%, OS 79%), and poor (4-year PFS 53%, OS 55%) outcome [73]. The R-IPI seems to be a more clinically useful prognostic index that may help guide treatment planning and interpretation of clinical trials [73].

If left untreated DLBCL has a median survival of less than 1 year but with the current treatment strategies the overall outcome is excellent. The choice of first-line treatment is based on the individual IPI score and age, with three major subgroups that should be considered: elderly patients (>60 years, aaIPI 0-3), young patients with low risk (≤60 years, aaIPI 0-1), and young patients with high risk (≤60 years, aaIPI 2-3). Despite the improved efficacy of first-line treatment regimens, 10–20% of patients with low IPI risk and 30–50% of patients with IPI score >2 experience relapse or fail the first-line treatment [58]. This patients' group has a poor outcome

	IPI Factors	
	1. Older than 60 years of age (not used for aa-IPI) 2. Extranodal disease > 1site (not used for aa-IPI) 3. Disease stage III/IV 4. Lactate dehydrogenase level elevated 5. ECOG performance score ≥2	

IPI			aa-IPI	
Risk group	IPI factors		Risk group	IPI factors
Low	0 or 1		Low	0
Low intermediate	2		Low intermediate	1
High intermediate	3		High intermediate	2
High	4 or 5		High	4

Fig. 7.1 International Prognostic Index (IPI) for diffuse large B-cell lymphoma (DLBCL)

with a median age of 6 months or less [57]. CNS dissemination is an infrequent but fatal secondary event in DLBCLs. Since there aren't effective therapies for CNS relapse, generally prophylaxis therapy for high-risk patients is recommended.

Primary Mediastinal Large B-Cell Lymphoma

Primary mediastinal large B-cell lymphoma (PMLBCL o PMBL) is an uncommon type of B-cell lymphoma arising in the anterior mediastinum from B cells of thymic medulla. It was, originally, described in 1980 [74] and officially incorporated in the Revised European-American Lymphoma (REAL) classification in 1994 [75]. Because of its peculiar characteristics, in 2008, the WHO classification of tumors of hematopoietic and lymphoid tissues recognized PMLBCL as a distinct entity under mature B-cell lymphomas [60]. PMLBCL constitutes 2–4% of all NHL and 6–12% of DLBCL [76]. It affects commonly young adults (aged 35–40) with a female predominance but can also occur in children and adolescents with similar clinical, pathological, and genetic features of adults cases [77, 78]. It is uniformly distributed worldwide, and no particular risk factors have been identified [79]. PMLBCL is characterized by a diffuse proliferation of medium and large B cells associated with sclerosis and compartmentalization that causes the formation of a bulky mass. It commonly presents with symptoms related to the mediastinal mass, including cough, dysphagia, hoarseness, and edema from superior vena cava compromise, with or without lymph node involvement. Rarely there is bone marrow implication, whereas pleura/pericardial effusions might be found. The absence of infradiaphragmatic lymph node or bone marrow involvement is as a prerequisite for the diagnosis of PMLBCL in the WHO classification, to exclude systemic DLBCL with

secondary mediastinal involvement [60]. Recurrences of PMBCL may occur soon after initial therapy, and disease may show extranodal spread with a tendency to spare lymph node. Unusual localizations such as in the liver, kidney, pancreas, and ovaries may also be found in relapse.

The first-line treatment and its outcome are critical for managing PMLBCL since it is unusually aggressive with a poorer prognosis compared to other B-cell lymphomas.

Classical Hodgkin's Lymphoma

Hodgkin lymphoma (HL) is a curable but uncommon malignancy representing approximately 11% of all lymphomas in the United States. In developed countries the disease has a bimodal distribution with peaks of incidence in young adults (it is the most commonly diagnosed cancer among adolescents aged 15–19, rare among children <5 years of age, and relatively rare in the adult population) and in people older than 55 years [80]. In economically underdeveloped countries, the overall incidence of HL is lower than in developed countries, with the exception of children under 15 years, where a higher incidence is seen [81]. There are no clearly defined risk factors, and the causes of HL development are still unknown, but the dual peak incidence supports the hypothesis of two different pathogenic processes: an infectious agent of low infectivity may be related to the disease in young people, while a mechanism shared with other lymphomas may account for the pathogenesis of HL in the older age group [81]. A subset of Hodgkin lymphoma is strongly linked to EBV infection [82]; indeed EBV genome has been detected in one third to one half of HLs occurring in patients without immunodeficiencies [83], and the association is much higher in patients under 10 years of age especially in developing countries [84]. The role of HL as an inherited disease remains unclear. In a study performed by Brown in 2008, nearly 40% of patients with HL reported a first-degree relative with cancer in general or with a lymphoproliferative disorders suggesting a genetic component [85].

In the 2008 WHO classification, HL is divided in two different histological types: nodular lymphocyte predominant and the classical HL (cHL). The cHL accounts for about 95% of all HL cases. The pathologic hallmark is the presence of malignant multinucleated giant Reed-Sternberg cells (RSC) even if the salient feature is the rarity (≈1%) of these neoplastic elements in the nonneoplastic cell population, mostly consisting of T lymphocytes. At the time of diagnosis, patients present painless lymphadenopathy; frequently it is present supraclavicular and/or cervical lymph node involvement. More than 50% of patients have a mediastinal mass which can be asymptomatic or provoke dyspnea, cough, or obstruction of the superior vena cava. Systemic symptoms include fever, night sweats, weight loss (more than 10% of bodyweight over 6 months), or chronic pruritus. Alcohol-induced pain, consisting in pain triggered by ingestion of moderate amount of alcoholic drinks and localized in one of the sites involved by disease, could be diagnostic. The most com-

cHL subtypes	Clinical Features	Epidemiology
Nodular Sclerosis	Mediastinal mass present in 80% of patients Prognosis better than in other subtypes of classical disease	70% of calssical Hodgkin's lymphoma in Europe and North America
Mixed Cellularity	Splenic infiltration in 30% of patients Peripheral and abdominal lymphadenopathy	25% of classical disease Prevalent in patients HIV+ and developing countries
Lymphocyte-depleted	Patients frequently present with advanced-stage disease	<1% of cases in Europe and North America Common in patients with HIV infection
Lymphocyte-rich	Mediastinal mass rare Peripheral lymphadenopathy common	≈5% of classical Hodgkin's lymphoma

Fig. 7.2 Classical Hodgkin lymphoma subtypes

mon extranodal sites involved are the spleen, lungs, liver, and bone marrow. Rare clinical presentations are acute spinal cord compression, central nervous system lesion, testicular masses, or intestinal occlusion. In cHL four subgroups can be identified: nodular sclerosis, mixed cellularity, lymphocyte depleted, and lymphocyte-rich (Fig. 7.2). Nodular sclerosis cHL (NSCHL) is the most common subtype accounting for ≈75% of all cHL cases, affecting mainly adolescent and young adults with a lightly higher prevalence in female. Mediastinal mass is present in 80% of patients. From 10 to 40% of patients are EBV positive [86]. The prognosis is better than other subtypes of classical HL [86].

The diagnosis of HL can only be made by biopsy since the fine needle aspiration is inadequate to study the lymph nodes architecture, important feature for an accurate diagnosis [87]. Bone marrow biopsy can be useful.

Staging of HL for prognostication and treatment planning is based on modifications of the Ann Arbor system. The criteria of the Ann Arbor Conference [69] are internationally accepted and defined two major groups: early stage and advanced disease. The early stage is subdivided further in two subgroups: favorable and unfavorable disease according to the presence or absence of different risk factors. Variable used to differentiate "favorable" to "unfavorable" early stages are not universally accepted; the most used classification system are EORTC and GHSG system that are similar [81]. For advanced disease the prognosis is predicted using an international prognostic score also known as the Hasenclever score [88]. This score is calculated basing on seven clinical and laboratory factors (age ≥ 45, male sex, serum albumin concentration <4 mg/dL, hemoglobin concentration <10.5 mg/dL, white blood cell count $\geq 15 \times 10^9$/L, lymphocytes count<600/L, stage IV disease), and the number of factors present has been related to 5-year PFS that is in the range of 45–80% [88]. Each additional factor reduced the predicted rate by about

8% [88]. The prognostic score is also predictive of overall survival. An accurate assessment of the stage of disease is crucial for the selection of therapy.

The mortality of HL has progressively reduced over the last decades. In 1950s this malignancy accounted for 30% of total lymphoma deaths, while nowadays it accounts for only 6% [81]. Untreated HL is rare because both chemotherapy and involved-field radiation therapy (IFRT) are curative.

Mediastinal Gray Zone Lymphoma

In 2008, the 4th edition of the *WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues* introduced a new category of lymphomas called "B lymphoma with features intermediate between DLBCL and cHL," known as "gray zone lymphoma" [89]. Particularly the term "mediastinal gray zone lymphoma" (MGZL) refers to those cases in which morphologic, biologic, and clinical features overlap between PMLBCL and cHL in particular the nodular sclerosis subtype [90, 91].

The clinical characteristics and treatment of MGZL are not well defined because of its rarity and recent identification (before these patients were included in the group of Hodgkin-like anaplastic large cell lymphoma) [92]. Generally MGZLs affected young adults with a male predominance even if in a recent retrospective study performed by Sarkozy et al. [93] it was found a small female predominance. MGZL showed a more aggressive clinical course and a poorer outcome than PMLBCL and cHL [94] as confirmed by the prospective study of the National Cancer Institute Group [92]. Symptoms at diagnosis are very similar to PMLBCL and related to mediastinal mass (cough, dysphagia, hoarseness, and edema from superior vena cava compression). Elevated LDH levels, extranodal disease, and effusions are observed infrequently. Some cases (≈16%) are associated with EBV [93].

The optimal therapeutic management of these lymphomas has not been determined because of their indeterminate pathobiology. A 2001 retrospective study reported that the 5-year event-free survival (EFS) for this entity was worse than that for cHL, suggesting adverse biology and a high rate of treatment resistance, using as initial regimen that for NHLs [95]. A more recent prospective study analyzed the clinical characteristics and outcome of MGZL after treatment with DA-EPOCH-R (rituximab in association with infusional dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone (DA-EPOCH-R) without radiotherapy, therapeutic regimen generally used for PMLBCL patients) [92]. Data suggested a worse outcome compared with that of PMLBCL, despite the patient population had similar clinical characteristics (EFS and OS of 62% and 74%, respectively, vs. 93% and 97% for PMLBCL). In a 2017 retrospective study performed by LYSA (Lymphoma Study Association) the clinicopathological characteristics and outcome of 99 patients with MGZL identified and treated in French, Belgian, and Portuguese LYSA centers were analyzed [93]. Forty-two patients were treated with cHL regimens, 56 cases were treated with DLBCL regimens, 1 patient DA-EPOCH-R, and another with R-CEOP [rituximab plus cyclophosphamide, eto-

poside, vincristine, and prednisone]). There were no difference in EFS and OS rates between patients treated with chemotherapy regimens plus rituximab and those without rituximab suggesting that rituximab did not provide any benefit. These data suggest that MGZL is an aggressive disease that requires an efficient first-line therapeutic strategy. Studies are exploring the biological basis for MGZL poor clinical responsiveness; factors include bulky disease and poor vascularization of this tumor characterized also by large areas of necrosis [90]. Improved biological knowledge may lead to develop more efficient therapies, and patient's management could be individualized.

Molecular Pathogenesis of Mediastinal Lymphomas

Different genomic sequencing techniques have allowed to identify genetic alterations and deregulated signaling pathways that underlie the pathogenesis of lymphomas. Recent data also highlight the importance of tumor microenvironment.

In the last decade, molecular methods such as gene expression profile (GEP) have helped to understand the biological differences between different types of NHL. Regarding DLBCL, GEP has defined three biologically and prognostically different subgroups: germinal center B-cell-like DLBCL (GCB), activated B-cell-like DLBCL (ABC), and primary mediastinal large B-cell lymphoma that in the 2008 WHO classification is considered a separate molecular entity. In GCB all genes that are expressed are hallmarks of normal germinal center; conversely ABC lacks expression of GCB-restricted genes and is related to activated B cells arrested during plasmacytic differentiation. The GCB group has a significantly better survival than the ABC group. For GEP fresh or frozen tissue is required, and this application is not always possible, so immunohistochemical GEP surrogates applicable at low cost to formalin/paraffin-fixed samples are used. Various immunohistochemical algorithms with different biological markers have been proposed, but the most widely used is the Hans algorithm based on the expression of three molecules: BCL6, CD10, and MUM1/IRF4 [96]. This panel showed 71% of GCB and 88% of non-GCB cases concordance. In 2009 Choi proposed a combination of five markers (GCTE1, CD10, BCL6, IRF4, and FOXP1) that closely approximated the GEP classification with 93% concordance [97]. Although ABC and GCB DLBCL have clear genetic and biologic differences, a limited number of antibodies cannot consistently identify individual differentially expressed genes in the two subtypes, and, as a result, these two subtypes are not yet recognized as distinct entities or consistently identified on diagnostic reports [98]. In ≈30% of DLBCL cases, chromosomal translocations of band 3q27 are detected causing the rearrangement of BCL6 [99], a transcriptional repressor expressed at high levels only in mature B cells within the germinal center, the structure where IG genes undergo somatic hypermutation and class switch recombination. Generally BCL6 controls different cellular functions, including DNA damage responses, cell cycle progression, and signal transduction. These chromosomal translocations deregulate its expression by a mechanism called

promoter substitution [100] preventing BCL6 silencing at the conclusion of the germinal center response. In DLBCLs BCL6 can directly regulate the *TP53* gene repressing its transcription [101]. In addition BCL6 also works by repressing miRNAs such as miR-155 that negatively affect the expression levels of important germinal center genes (e.g., AID, SPI1, IRF8, and MYB) [102]. BCL6 (3q27 chromosomal translocations) occurs more frequently in ABC DLBCL than in GCB subgroup but do not seem to have any relevant prognostic significance [103], although in some studies, the presence of a BCL6 translocation was associated with an inferior outcome in no-GC phenotype [104, 105]. The antiapoptotic oncogene BCL2 (18q21) is very often deregulated in DLBCL. The chromosomal translocation t(14;18)(q32;q21) juxtaposes the BCL2 gene with the immunoglobulin heavy chain (IGHV) gene enhancer (14q32), resulting in deregulated expression of BCL2 [98]. The t(14;18) is the most common translocation in GCB DLBCL, detected in 30–40% of cases [106], but it is not specific to DLBCL; it is also present in more than 90% of follicular lymphomas. Mutations in the promoter regions cause loss of MIZ1-mediated BCL6 suppression of BCL2 [107], whereas mutations affecting the coding part of the *BCL2* gene altered the interaction of its protein with other molecules, such as p53 [108]. The clinical relevance of t(14;18) and expression of the BCL2 protein have always been controversial. However, two studies identified BCL2 protein as a marker of poor prognosis in GCB DLBCL but not in ABC DLBCL [109, 110]. Notably, *BCL2* amplifications (chromosome 18q21 amplification) were exclusively detected in the ABC subtype [111] and were associated with worse survival of this ABC subgroup [112], suggesting that this oncogene might not be an exclusive target of GCB DLBCLs. *MYC*, located at chromosome band 8q24, encodes a transcription factor that regulates different mechanisms including proliferation, cell cycle, apoptosis, and cell migration. *MYC* rearrangement, generally chromosomal translocations or an increased copy number, is usually associated with Burkitt lymphoma but occurs also in 7–10% of DLBCL more commonly in GCB. MYC gene activation in DLBCL can occur via translocation (5–14%), copy gain (19–38%), amplification (2%), or mutation (32%) [113] and was significantly associated with shorter overall survival, so could be used as a predictor of survival in the GCB patients [114] even if the presence of *MYC* translocation and expression level per se may not be the best prognosticators [115]. Fifty-eight to eighty-three percent of *MYC*-translocated DLBCL also have concurrent dual or triple translocation with *BCL2* and/or *BCL6* (less likely) identified as "double-hit" or "triple-hit" DLBCL. These lymphomas, particularly "double hit DLBCL," are neoplasms with morphological features overlapping with Burkitt lymphoma. These tumors are characterized by aggressive behavior and poor outcome; these patients often have 12 months or less OS when treated with R-CHOP [113]. One of the most commonly mutated epigenetic modifiers is EZH2 that often exhibits gain-of-function mutations almost exclusively in GCB DLBCL (≈21% of cases). EZH2 is a polycomb-group oncogene which encodes a histone-lysine N-methyltransferase responsible for methylation of histone 3 on lysine 27 (H3K27), leading to transcriptional silencing. The mutations lead to a change in the enzyme affinity for its substrate increasing affinity for H3K27me2 (dimethylated), leading to hypertrimethylation of H3K27

(H3K27me3) [116, 117]. The increase in H3K27me3 is believed to cause tumorigenesis. The dominant mode of action suggests that allele-specific EZH2 inhibitors could be a future therapeutic strategy for this disease; indeed, promising preclinical data have been obtained with the use of EZH2 inhibitors [118–121], and early clinical trials are ongoing. Other mutations affecting genes coding proteins involved in chromatin remodeling are recurrent in DLBCL; these genes are *MLL2 (KMT2D)* (22–32% DLBCL), *CREBBP* (18–20% DLBCL), *EP300* (5–10%), and *MLL3* (KMT2C) (15%) [98]. The acetyltransferase genes *CREBBP* and *EP300* belong to the KAT3 family of histone/protein lysine acetyltransferases, regulating important cellular proteins. In particular, because acetylation of BCL6 by EP300 causes loss of protein transcriptional repressing activity and p53 acetylation is required for p53 activation, CREBBP and EP300 mutations contribute to BCL6 activation and p53 inactivation in DLBCL [122]. NF-κB constitutive activation is the most important alteration found in ABC DLBCL. Constitutive activation of the NF-κB pathway occurs via genetic lesions of a variety of genes including *TNFAIP3* (30% of cases), *CARD11* (10% of cases), *CD79B* and *CD79A* (≈20% of cases), *TRAF2* (3% of cases), *TRAF5* (5% of cases), *RANK* (8% of cases), and *MYD88* (30% of cases) [98]. *TNFAIP3* is one of the most commonly altered and codes for a negative regulator of NF-κB; generally it is inactivated also in other lymphomas. MYD88 is an adapter protein involved in the Toll-like receptor and IL-1 receptor signaling pathways, and it is commonly reported to carry a L256P mutation, which promotes not only NF-κB enhancing but also activation of the JAK-STAT3 pathway. The JAK-STAT pathway is a major regulator of gene transcription and controls different mechanisms like cell proliferation, apoptosis, and angiogenesis. In normal B cell the pathway is activated by interleukins and interferons binding to a variety of receptor which lead to phosphorylation of JAK and STAT molecules and translocation of STAT dimers into the nucleus where they act as transcription factors [77]. Other lesions frequently found in GCB DLBCL are amplifications on chromosome 2p (2p12-p16), but their functional meaning is still unknown; amplifications in the *MIRHG1* locus (13q31.3) (12% of GCB cases) causing an overexpression of the mir-17–92 microRNA polycistronic cluster (this event is correlated with *MYC* rearrangements or amplifications); and deletion of the chromosome 10q23 locus containing *PTEN* (55% of GCB DLBCL and 14% of ABC) with inactivation of PTEN, gains on chromosome 12, possibly causing upregulation of the MDM2 gene encoding a negative regulator of the tumor suppressor p53 and gains affecting chromosome 7 whose effect is unclear but might involve overexpression of a series of miRNAs especially miR-96, miR-182, miR-589, and miR-25 [98]. The presence of 7q gains seems to predict a better outcome and a low probability of bone marrow involvement [123]. In ABC DLBCL more common are genetic lesions involving genes encoding for cell cycle proteins. Frequently it is found the deletion of the INK4/ARF locus at 9p21 (24–30% of cases) encoding the CDKN2B, ARF, and CDKN2A tumor suppressors and is among the most frequently inactivated loci in human cancers. CDKN2A, together with CDKN2B, CDKN2C, and CDKN2D, selectively inhibits the cyclin D-associated kinases, leading to a block in the G1-S phase, while ARF is a protein that stabilizes p53, preventing MDM2-mediated proteasome degradation. Cases of ABC DLBCL

with del(9p21) show a specific gene expression signature characterized by deregulation of the RB/E2F pathway, activation of cellular metabolism, and decreased immune and inflammatory responses [124, 125]. These features may constitute the molecular basis sustaining the unfavorable outcome and chemoresistance of this DLBCL subgroup suggesting targeted treatment approaches. Loss of major histocompatibility complex (MHC) I and MHC II expression is frequent in DLBCLs (about one-third of case) with similar frequency in the GCB and ABC subtypes. The mechanisms for lost expression are multiple, both genetic and epigenetic. B2M (β2-microgolubiln) that forms MHC I with the human leukocyte antigen heavy chain is frequently found inactivated for the presence of mutations or deletions. Conversely, for MCH II downregulation, the most prevalent mechanism is the decrease of CIITA expression. CIITA is a transactivation protein that controls MCH II gene expression forming an enhanceosome complex with several transcription factors including RFX, CREB, and NF-Y. Genetic disruption of the CIITA gene by chromosomal translocations is rare in DLBCL (<5%) but common in PMLBCL (38% of cases exhibit translocations inactivating the gene) [126]. All these mechanisms are at the base for tumor escape from immune surveillance. Other genetic events reported as to possibly contribute to immune escape is CD58 genetic inactivation (21% of cases of DLBCL), more frequently in ABC or CD58 deregulation of protein expression in 67% of all cases of DLBCL (no differences between ABC and GCB subtypes), rearrangements or DNA amplifications of CD274/PDL1 and CD273/PDL2 (≈20% of cases), and inactivation by mutations or deletions of FAS gene [98]. Somatic mutations in the gene coding for the transcriptional factor FOXO1, involved in the PI3K signaling downstream to BCR activation during GC development, have been reported in 8.6% of cases of DLBCL, associated with an inferior outcome (decreased overall survival independent of COO and IPI) [127], with no differences between GCB and ABC subtypes. Their functional significance is still to be defined even if data from the study by Dominguez-Sola et al. in 2015 suggest that constitutively active FOXO1 might contribute to malignant transformation by pathological maintenance of constitutive cell proliferation, block of cell differentiation, and impairment of DNA repair together with deregulated BCL6 expression [128].

Genomic analyses of HL have been hampered by its particular features and scarcity of neoplastic cells (<1%). The malignant multinucleate RSC are very few and surrounded by a large number of nonmalignant infiltrating inflammatory cells including reactive lymphocytes, plasma cells, macrophages, eosinophils, and fibroblasts. This microenvironment supports survival and proliferation of malignant cells using different cytokines and chemokines both in autocrine and in paracrine manner [129]. An example is interleukin 13 (IL-13) that through autocrine and paracrine signaling promotes RSC proliferation and survival by phosphorylated STAT6 maintaining the JAK-STAT pathway constitutively active [130, 131]. In RSC the so-called crippling mutations in the IG genes are present indicating a derivation from GC B cells that should have undergone cell death [129]. Patients with primary cHL display centrosome anomalies leading to a complex hyperdiploid karyotype in RSC [132, 133]. Mutations, affecting one or several base pairs, seem to be rare events in HLs, although

somatic mutations were found in genes encoding IκBα or IκBε (*NFKBIA* and *NFKBIE*, respectively) [134, 135], a negative regulator of NF-κB that is constitutively activated in HL cases and in genes controlling apoptosis such as p53 [136] and Fas/CD95 [137]. Mutations of unknown significance were detected in the 5′ region of the *BCL6* gene, but they probably are irrelevant somatic base substitutions without consequences for BCL-6 protein expression and the pathogenesis of cHL [138]. Moreover, the classical translocations that involved *BCL2* and/or the chromosomal rearrangements of *BCL6* are absent in cHLs and may help pathologists to discriminate these two diseases. Unlike DLBCL that showed high percentages of recurrent gains in different loci, in cHL, only an overrepresentation of two prominent chromosomal regions (2p14-p16 and 9p23-p24) was observed, highlighting the pathogenic role of the underlying genes, *REL* and *JAK2* [139]. Gains or amplifications of the proto-oncogene *REL* at chromosome 2p16, which encodes a subunit of NF-kB, are frequently found in several lymphoma entities, including cHL (55% of all cHLs), with predominance in the nodular sclerosis subtype (88% of cases) [140, 141]. The correlation between overrepresentation of the *REL* gene and nuclear accumulation of the protein in HRS cells is in line with the constitutive NF-kB activity and could be considered a characteristic hallmark of RS cells [140, 141]. Sequence analyses of other genes involving in NF-kB regulation such as *BCL10* did not reveal any alteration [142]. Along with *REL*, the *BCL11A* (B-cell lymphoma/leukemia 11A) gene is often simultaneously overrepresented in HRS cells and is another target gene within the chromosomal region 2p14-p16 [133]. BCL11A is a transcription factor and is essential for normal lymphoid development. Due to translocations with the IG locus or to genomic overrepresentation, *BCL11A* has been suggested to play a role in lymphomagenesis [129]. Although data indicate that *REL* rather than *BCL11A* may be the target of the 2p alterations in cHL [133], the oncogenic potential of augmented numbers of *BCL11A* gene copies remains to be elucidated. The *JAK2* (Janus kinase 2) gene, at the chromosomal locus 9p24, resulted in a copy number increase in the malignant cells of HL [139]. The JAK2 protein is involved in the JAK/STAT pathway, which transmits cytokine-induced stimuli. Many reports have described constitutively active STAT proteins in cHL, preferentially STAT3, STAT5, and STAT6, suggesting continuous activity of this pathway [131, 143]. Moreover negative regulators, such as SOCS (suppressor of cytokine signaling) proteins, prove to be altered. For example, almost 50% of cHL cases analyzed showed a mutated *SOCS-1* gene, and HRS cells with defective SOCS-1 accumulated activated STAT5 in the nuclei [144]. Another chromosomal alteration involved the *HDM2* (human homolog of MDM2) gene in the 12q15 locus. This gene encodes a negative regulator of p53 that is initiated to proteasomal degradation. *HDM2* was found to be amplified in RSC as the result of 12q gains [145]; no mutation of p53 was found in association with increased HDM2 expression level. Other molecular alterations found in cHLs are overexpression of the surface molecules PDL1 and PDL2 [146, 147], DNA hypermethylation leading to transcriptional silencing of several tumor suppressor genes involved in the cell cycle (e.g., p16INK4a, p15INK4b, p18INK4c, and RASSF1A) [148–150], and abnormal expression pattern of so-called polycomb group (PcG)

genes, whose proteins are involved in transcriptional repression and the cell cycle such as BMI-1 [151]. A study of 2005 performed by Kluiver et al. demonstrated high BIC (a member of the noncoding mRNA-like molecules) and miR-155 levels both in HL cell lines and tissues [152] founding also a good relation between these two molecules supporting the hypothesis that BIC is a pri-miRNA that can be processed to miR-155. The relevance of high miR-155 expression in HL is not yet known. One interesting putative target of miR-155 is ICOSL (inducible co-stimulatory molecule ligand) whose signal is important in T-cell activation, proliferation, and cytokine production. Since RSC are surrounded by ICOS expressing T cells, the lack of ICOSL expression may influence immune response [152]. Another miR-155 target is the transcription factor PU.1, a protein required for early B-cell differentiation. Absence of PU.1 protein expression is thought to be associated with defective immunoglobulin transcription in RS cells of cHL [152]. In any case the high expression of BIC is not specific for HLs because PMLBCLs and a large proportion of DLBCL cases are also BIC-positive [152].

Since PMLBCL is recognized as a distinct entity, the number of studies describing its genetic features is increased. PMLBCL has a unique gene expression profile that is different from DLBCL and more closely related to cHL. The first gene studied was *CDKN2A*, encoding for p16/INK, that was found mutated or hypermethylated in a small number of cases [77]. Conventional molecular analysis reveals other genetic alteration including somatic hypermutation of *PIM-1*, *PAX-5*, RhoH/*TTF*, and c-*MYC* [153], mutations in p53 (≈13% of cases) [154], and *MAL* gene overexpression [79]. In contrast to diffuse large B-cell lymphoma, molecular studies of small series of PMBLs have revealed the usual absence of *BCL-6* and *BCL-2* rearrangements/mutations [155, 156]. The NF-kB signaling pathway is one of the most important dysregulated pathways at the base of pathogenesis of different lymphoma types in particular of PMLBCL. In normal B-cell development, the activity of NF-kB complex is regulated by several extrinsic and intrinsic factors, of which the tumor necrosis factor (TNF) receptor plays a major role [77]. In PMLBCLs several genes of this signaling pathway, such as TNF family members, TNF receptor associated factors, and NF-kB complex members, were overexpressed compared to DLBCL, more closely resembled cHL [157]. Consistent with a likely role for NF-κB activation, PMLBCLs exhibited also c-REL nuclear localization [157]. Subsequent studies have described more specific gene alterations leading to constitutive activity of this pathway. In approximately 50% of cases, chromosomal gains or amplifications of *REL* gene on locus 2p14-p16.1 have been found [158, 159]. Although amplification of *REL* does not correlate with elevate mRNA level, this genomic alteration is associated with nuclear localization of this protein. Other chromosomal imbalances involving NF-kB regulators encompass amplification of *BCL10* (1p22) and *MALT1* (18q21) [160]. Moreover, unlike cHL, *NFKBIA* mutations were absent in PMLBCL, suggesting a different landscape of gene mutations in this last disease responsible for the constitutive activation of NF-κB [161]. One hallmark of PMLBCLs is the deregulation of JAK-STAT signaling. In PMLBCL GEP showed high levels of IL-13 receptors expression and of downstream effectors, particularly JAK2 and STAT1, indicating an upregulation of this signaling mechanism. The genetic basis for these observations is the amplification involving JAK2 on chromosome band 9p24, found

in 50–70% of PMLBCL patients [162, 163]. Other molecular mechanisms involved in JAK-STAT activation in PMLBCL are disruption of SOCS-1, a classical negative effector of JAK phosphorylation (targets it for proteasomal degradation), and mutation of STAT6, which proved to be constitutively activated. Somatic mutations of STAT6 are found in approximately 36% of PMLBCL cases in contrast with DLBCLs in which no mutations could be found [77]. The surface molecules PDL1 and PDL2 are highly overexpressed in PDLBCLs, because, besides JAK2, the amplified region at 9p24 includes also the genes encoding for these two proteins involving in the escape to immune surveillance [147]. A substantial number of PMLBCL cases showed a reduced expression of MHCII and correlated with worse outcome, possibly for decreased immunosurveillance [164]. The cause for downregulation of MHC class II is unclear, but data revealed a strong correlation with CIITA expression. In a study of Steidl et al. [126], the evaluation of 263 B-cell lymphomas demonstrated that genomic CIITA breaks are highly recurrent in primary mediastinal B-cell lymphoma (38%) and classical Hodgkin lymphoma (cHL) (15%) and rarely found in DLBCL (3%). Furthermore, authors find that CIITA was also a promiscuous partner of various in-frame gene fusions and, in some cases, breaks occurred in more than one allele leading to complete loss of function. The presence of CIITA rearrangements significantly correlated with a shorter disease-specific survival (10-year disease-specific survival 63.6% compared with 85.0%) [126].

Since MGZL has features of both PMLBCL and cHL, even gene expression profile shows overlap between these two entities. Studies in adults with MGZL demonstrated gains including amplifications of the *REL* locus (2p16) observed in 33% of patients, alterations in 9p24 (JAK2/PDL2 locus) present in 55%, rearrangements of CIITA locus at 16p13, and gains of 8q24 at MYC (both in 27% if patients) [165]. Moreover a large-scale DNA methylation analysis demonstrated that MGZL has a distinct epigenetic profile intermediate between classical Hodgkin's lymphoma and primary mediastinal large B-cell lymphoma but remarkably different from that of diffuse large B-cell lymphoma [166]. MGZLs could be distinguished from PMLBCL and cHL by differential methylation of selected GpC islands such as hypomethylation of HOXA5 observed only in MGZL suggesting a unique role of this gene in MGZL tumorigenesis [166].

Different biologic studies have begun to yield insights into the mechanisms modulating the plasticity of the neoplastic B cells and tumor microenvironment in cHLs and DLBCLs, and they may provide data useful for the development of targeted personalized strategies [89].

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Chapter 8
Therapy: Recommendations for the Oncologists

Francesco Facchinetti, Letizia Gnetti, and Marcello Tiseo

Introduction

The medical management of mediastinal tumors cannot be considered aside from their comprehensive approach, as the multidisciplinary team performs a pivotal role in the continuum of care starting with diagnosis and staging, eventually ending up with systemic treatment. From this point of view, the medical oncologist does not simply prescribe the correct chemotherapy once the diagnosis is obtained but works in a close relationship with other specialists in the different phases of disease course. Depending on the different local realities in which the medical oncologist practices, his figure can coordinate the steps necessary for the correct diagnosis and moreover notice when a urgent treatment is required.

The strict, direct dialogue with radiologists, interventional pulmonologists, surgeons, and pathologists can help in finalizing the most reliable, less invasive way to obtain disease specimens and to have the most accurate histological and molecular diagnosis. Given their peculiar position, moreover, mediastinal tumors can easily give rise to rapidly evolving clinical syndromes (see Chap. 2), thus requiring prompt interventions, with both medical treatments and bronchoscopic and radiotherapy evaluations. In the therapeutic management of malignancies arising in the mediastinum, approached in the detail in the next chapters, the intervention provided by the medical oncologist in terms of cytotoxic or novel systemic treatments is rarely isolated. As depicted in the following sections, the medical therapy almost systematically follows (or is followed) by a locoregional intervention, being surgical or

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radiotherapic. Within these multimodal approaches, chemotherapy can indeed harbor a (neo)adjuvant intent and can be concomitantly or sequentially accompanied by radiotherapy.

Clinical Considerations for the Administration of Systemic Treatments

Selection of the correct treatment for each patient, in the viewpoint of personalized medicine, should always take into account the global status of the subject, considering the acute and late-onset adverse events that can emerge during or after multimodal therapies. It is noteworthy that mediastinal tumors arise in relatively young patients that can eventually and hopefully get rid of their cancers (see Chap. 1). A peculiar attention toward chronic toxicities, too, should therefore be provided, and anamnestic information regarding comorbidities should guide treatment decisions with "long-term" objectives of duration and quality of life. As an example, the classical treatment of several mediastinal tumors (e.g., thymomas and thymic carcinomas, lymphomas) includes regimens containing anthracyclines, whose cardiac effects are potentially relevant [1], even more in the case of radiotherapy fields involving the cardiac area. The eventuality of the onset of pulmonary fibrosis, arising as a consequence of bleomycin administration for germ cell tumors, should be considered in subjects with organic or functional respiratory deficits [2]. In addition, cisplatin administration can be a cause of renal insufficiency and peripheral neuro- and ototoxicity. Given the young age often documented at diagnosis, fertility issues potentially arising after the exposure to cytotoxic drugs require a preventive management before chemotherapy initiation [3, 4]. Importantly, the follow-up should be addressed to the early detection of disease recurrence and, in addition, to novel chemo- or radio-induced tumors in the mediastinal area or in the lung parenchyma [5, 6].

Mediastinal Exacerbations of Lung Tumors

The medical treatment of the specific tumors arising in the differential anatomic portions of the mediastinum is topographically addressed in the next chapters. Nevertheless, the malignant nature of mediastinal masses can be attributed to lung cancer too, the most common among thoracic malignancies [7]. Besides the frequent mediastinal lymph nodal involvement in locally advanced and metastatic lung cancers, these latter can arise even in the absence of detectable pulmonary parenchymal localizations. This represents an additional point in the differential diagnosis of mediastinal masses, and their potential biology of lung tumors should be considered. The correct diagnosis (impacting on treatment strategies and prognosis) often emerges as a result of the integration of clinical radiological, pathological, and

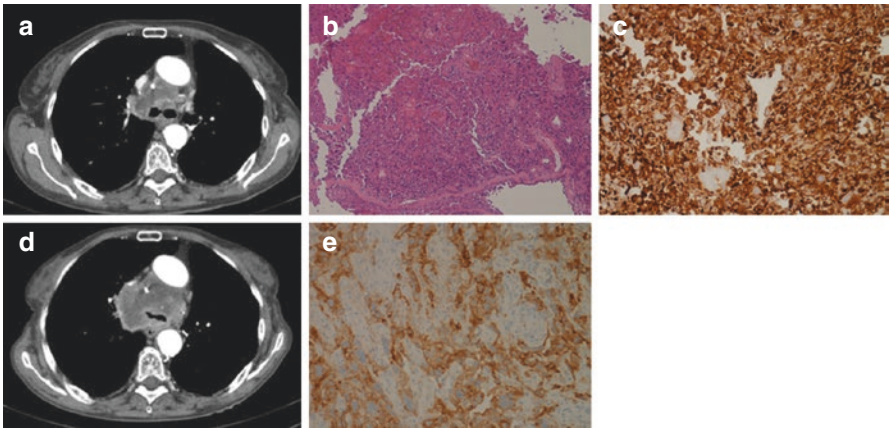

Fig. 8.1 Clinical presentation and pathological diagnosis of a sarcomatoid carcinoma of the lung with exclusive mediastinal involvement. (**a** and **d**) CT scan images documenting the dramatic (40 days) evolution of the radiological scenario, accompanied by a rapidly fatal outcome. The severe stenosis of the trachea at its bifurcation into the two bronchi, developed in such a short time, is depicted here. (**b**) Hematoxylin and eosin staining (20× magnification) revealed pleomorphic, irregular, ovoid, or spindle-like tumor cells. They were characterized by multilobulated nuclei and abundant eosinophilic cytoplasm, being accompanied by a heavy neutrophilic infiltrate. (**c**) The neoplasm reacted strongly and diffusely for vimentin immunohistochemistry (IHC, 40× magnification) in its mesenchymal component. (**e**) IHC for PD-L1 (SP263 clone) documented a membranous and a faint cytoplasmic staining (40× magnification). The percentage of tumor cells considered positive for PD-L1 staining was estimated 70%

immunohistochemical features, not infrequently inconclusive if considered singularly. With particular regard to lung tumors with an exclusive mediastinal presentation, squamous cell carcinomas (that together with adenocarcinomas fulfill the largely widest part of non-small cell lung cancers, NSCLC) and small-cell lung cancers (SCLC) are the most frequently represented. This is likely attributable to the specific epidemiological correlation between tobacco exposure and these histologies, arising from the main bronchus or their direct branches and preferentially developing as central thoracic tumors. As depicted above for "strict" mediastinal tumors, the rapid evolution of these latter observed not infrequently can require a urgent clinical management.

We present a recent dramatic case of a subject treated in our institution that is evocative for the mentioned considerations and for the novel scenarios of therapies of mediastinal tumors. A 73-year-old female patient referred to our hospital referring the rapid onset of significant weight loss, accompanied by exertional dyspnea and asthenia. A CT scan of the thorax and the abdomen revealed a voluminous mass in the medium mediastinum with right-sided development (Fig. 8.1a), without any lesion detectable in the lung parenchyma and no distant metastases. A bronchoscopy was performed, with a transbronchial biopsy allowing the diagnosis of sarcomatoid carcinoma of the lung, a rare and aggressive form of NSCLC (Fig. 8.1b, c). Waiting for staging procedures (brain CT scan 18F-FDG PET) and the complete

definition of the molecular portrait of the tumor (influencing its treatment, see below), the patient developed acute dyspnea and was hospitalized. The new thoracic CT scan performed 40 days after the first exam documented a dramatic local progression of the disease (Fig. 8.1d), conditioning severe tracheal and bilateral bronchial stenosis. Neither bronchoscopic procedures nor a decompression by means of radiotherapy was feasible, given the wide and diffuse erosion of the tracheobronchial walls documented at the fibro-bronchoscopy. No systemic therapies could be administered given the rapid clinical deterioration, frustrating any possible options justified by the clinical urgency. Unfortunately, the patient passed few days after hospitalization, for the rapid worsening of respiratory insufficiency.

Novel Scenarios in the Treatment of Mediastinal Tumors: Immunotherapy

The molecular diagnosis of patient tumor, albeit unfortunately lacking direct clinical utility, allows the approach of the new scenario of systemic treatment of cancers, included the ones arising in the mediastinum. Immunohistochemical analyses revealed indeed that a high quote of tumor cells expressed PD-L1 (programmed-death ligand 1) (Fig. 8.1e), a surface molecule involved, with its receptor PD-1 preferentially expressed by T lymphocytes, in the development of immune tolerance toward malignant cells [8]. The recent discovery of this specific interaction and of its blockade, with therapeutic antibodies neutralizing either one of the two molecules, represents one of the major innovative scenarios in the cure of cancer. Releasing the immune system by interfering with the PD-1/PD-L1 axis has been documented as a valid option of treatment is several malignancies, almost irrespective of the organ of origin [9]. The mentioned patient herself, if the clinical conditions had allowed to perform a systemic treatment, would have received the anti-PD-1 antibody pembrolizumab, whose administration as first-line therapy has recently shown striking outcomes in patients affected by NSCLC with high PD-L1 expression [10]. With specific regard to tumors arising in the mediastinum, nivolumab (another anti-PD-1 agent, utilized in lung malignancies too) has been recently received the FDA and EMA approval for the treatment of relapsed or refractory classical Hodgkin lymphoma (cHL), after autologous stem cell transplant and treatment with brentuximab vedotin [11, 12]. In other settings these agents are in different stages of clinical development, representing a concrete promise in tumors such as thymomas and thymic carcinomas [13]. It is interesting to notice that non-Hodgkin lymphoma was the first malignancy to be treated with a form of immunotherapy, the anti-CD20 monoclonal antibody rituximab [14]. The new generation of targeted antibodies encompasses antibody-drug conjugates, representing a true option in the challenging management of SCLC [15].

Novel Scenarios in the Treatment of Mediastinal Tumors: Targeted Therapies

We take advantage of the reported diagnosis of sarcomatoid carcinoma in this case, as it allows to accost the molecular definitions of lung and mediastinal tumors. Sarcomatoid carcinomas are recently been documented as frequently harboring *MET* gene alterations, whose presence drives tumor biology and clinical courses, concomitantly representing a target for a relatively novel class of drugs [16]. MET aberrations figure among the latest emerging molecular targets in NSCLC, having as ancestor *EGFR* mutations and *ALK* and *ROS1* rearrangements. All the latter alterations are indeed susceptible of specific treatments by means of tyrosine kinase inhibitors (TKIs), whose biological activity is coupled with major clinical improvement in patients' outcomes. Regarding other mediastinal tumors, thymic tumors can benefit from the multi-target antiangiogenic treatment with sunitinib, largely studied in renal cancers and gastrointestinal stromal tumors [17, 18]. Similarly (but more rarely) to the latter, thymic tumors can harbor *KIT* mutations and targets of imatinib, the real progenitor of TKIs in onco-hematology [19, 20]. Depending on their histologic definition, thyroid cancers can moreover be treated with targeted agents [21], with the remarkable mention of the recent results observed with dabrafenib and trametinib in BRAF-mutant anaplastic carcinomas [22], similar to what is seen in melanomas and NSCLC [23, 24].

Final Considerations

As depicted for chemotherapy, it is noteworthy that immunotherapy and targeted agents expose patients to novel differential toxicities. In particular, drugs eliciting the immune system against cancer cells can concomitantly prompt its stimulation against normal tissues, representing clinically meaningful dysimmune adverse events, potentially involving every organ [25]. Radiological evaluation of disease response to these novel therapies has in parallel evolved, from the assessment of necrosis as a sign of response to antiangiogenic drugs [26] to the introduction of specific criteria for patients undergoing immunotherapy [27, 28].

In summary, mediastinal malignancies treatment strictly relies on the optimal differential diagnosis of mediastinal masses, for which the single contribution of specialists is of pivotal importance. As seen for a wide spectrum of tumors, novel treatment strategies besides chemotherapy are already available or are showing promising results.

Conflict of Interest Declaration All authors declare they have no conflict of interest to disclose.

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Part II
Anterior Mediastinum Masses

Chapter 9
Thymic Neoplasm

Mirella Marino, Francesco Facciolo, Yan Shen, Gabriele Alessandrini, and Nicolas Girard

Thymic Epithelial Tumors

The variety of tumors originating in the thymus partially reflects the main cellular types present in the organ, i.e., epithelial cells (EC) and lymphoid cells (LY), giving rise to thymic epithelial tumors and to lymphomas, respectively. However, in the anterior mediastinum, along with the thymus, several structures are located, including the heart and pericardium with great vessels, lymph nodes, phrenic nerves, and adipose tissue. Moreover, due to the midline location of the thymus and to the embryonic routes followed by the thymic anlage as well as other cell types during organogenesis and differentiation, a variety of ectopic tumors occur in the thymus. Mesenchymal tumors of the mediastinum will be the focus of other chapters in this book. Moreover, tumorlike lesions extraordinarily interesting for their complex

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pathogenesis and heterogeneity of clinical features, constituting specific and rare biological entities such as Castleman's disease, occur in the mediastinum [1, 2], more often in the anterior mediastinal lymph nodes [3]. Only a brief mention of the other tumor types and tumorlike neoplasms related to differential diagnosis of thymic epithelial tumors (TETs) will be found here.

Development of the Concept of TET: A Brief Summary

In the twentieth century, the concept of thymoma as tumors of the epithelial components of the thymus emerged after a long debate among pathologists. The term "thymoma" was applied to all tumors arising in the thymus, starting as early as in 1900 with F. Grandhomme [4]. James Ewing, the first descriptor of the type of tumor later named "Ewing's sarcoma," was among the few pathologists who, as early as 1916, did not accept this statement [5]. He proposed to classify thymic tumors in the following manner: (1) lymphosarcomas or thymomas, including lymphocytic and reticulum cell and giant cell tumors (this group included tumors simulating Hodgkin's granuloma); (2) carcinoma; and (3) spindle cell sarcoma or myxosarcoma [6]. Douglas Symmers, in 1932, stressed that in the thymus "from each of the histologic structures enumerated, a particular sort of malignant tumor was capable of arising, epithelioma from the epithelial reticulum and Hassall's corpuscles; lymphosarcoma from the lymphocytic elements" [7]. Although the idea that thymomas were of epithelial nature had been suggested by E. Bell already back in 1917 [8], it was only up until J. Rosai's and GD Levine's electron microscopic work that the epithelial nature of thymoma was firmly established [9]. In the first part of the twentieth century, the relationship between thymomas and myasthenia gravis (MG) was first described and understood. Several years after Carl Weigert's description of myasthenia gravis in a patient with thymoma in 1901 [10], A. Blalock described in 1939 the improvement of MG in a patient after the removal of a thymoma performed in 1936 [11]. In 1956, Lalla Iverson at the Armed Forces Institute of Pathology described the morphological findings of thymoma associated with MG and of tumors *not* connected to MG [12]. In the last 50 years, however, due to seminal work carried out by Juan Rosai and other pathologists [13–15], the main concepts of thymic epithelial neoplasia were established. Nowadays, however, thymic function in both fetal and postnatal age is well accepted, and the main cellular types contributing to the thymus structure and function have been well defined. However, we have come to this understanding after enduring a long process throughout the twentieth century. The seminal work of J.F. Miller should be regarded as a major contribution in the discovery of the thymic function [16]. Further advances in understanding the thymic cellular organization and function/dysfunction were due to immunologists, surgeons, electron microscopists, and pathologists [17–23].

Thymic Epithelial Tumors (TETs) as the Main Mediastinal Neoplasms in Adults

Epidemiology

According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program/SEER database, the incidence rate of TETs, including thymoma (THY) and thymic carcinoma (TC), is 0.13/100,000 per population in the USA [24]. The maximal incidence rate is at middle age with a peak incidence in the seventh decade; however, TETs also occur in children and young adults [25–27]. European cancer registries (CRs) participating in the RARECARE project provided population-based data: TETs showed a slightly higher incidence rate (compared to the USA) of 0.17/100,000 per population and "malignant" thymoma accounting for 0.14/100,000. TC, a much rarer disease than THY, occurs with an incidence rate of 0.2–0.5 per million individuals. In Europe, TETs have the lowest incidence in Northern and Eastern Europe and in the UK and Ireland and have a somewhat higher incidence in Central and Southern Europe [28]. According to the SEER database, the incidence of THY in the USA is higher in African Americans and especially in Asians/Pacific islanders than among Whites or Hispanics [24]. No or only limited differences in the incidence among sexes were reported, females prevailing in THY subtypes A, AB, and B1 and males prevailing in TC.

Although most TETs occur in the anterior superior mediastinum, ectopic TETs [29] have been described to occur everywhere in the thorax: not only in the pleura and in the lungs but also in other mediastinal areas, particularly in the aortopulmonary window, the retrocardiac area, or the right paratracheal area [30], in the posterior mediastinum, and even the presternal area and vertebrae [31]. Hamartomatous components are reported in association with TET [32]. The neck and the thoracic inlet, along the route of the thymic primordium from the third branchial cleft to the definitive mediastinal location, represent the most frequent sites of ectopic tumors outside the thorax [33, 34].

Common tumors as well as rare cancers are often associated with THY, the most frequently associated tumors being non-Hodgkin's lymphoma [24]. As discussed later in the section, most THYs clinically behave like tumors with uncertain malignant potential and a propensity to recur and metastasize, especially in the thorax [35], whereas TCs are highly malignant tumors from the beginning and spread outside of the thorax [36].

The Diagnostic Workup Leading to a TET Diagnosis

The mediastinal compartment involved, the demographical/clinical presentation, and the serological findings play a major role in the diagnostic evaluation of mediastinal masses. Other sections of the book focus on general differential diagnostic problems; here only limited aspects will be discussed.

Table 9.1 Demographical and clinical distribution/onset of mediastinal tumors (Modified from [118, 37, 120])

	Children	Young adult	Adult
Asyntomatic or chronic symptoms onset	Teratoma Thymic cysts Thymic hyperplasia	Thymolipoma Teratoma Cysts	Cysts Teratoma Thymoma Substernal goiter
Subacute	GCT HD PMBCL	PMBCL GCT HL Thymoma	Thymoma Seminoma HL PMBCL
Systemic symptoms	T-LBL Mal. GCT	PMBCL HL GCT Thymoma	Carcinoma NSGCT
Acute	T-LBL	T-LBL	NSGCT T-LBL

GTC germ cell tumor, *HL* Hodgkin's lymphoma, *PMBCL* primary mediastinal B cell lymphoma, *LBL* lymphoblastic (T) lymphoma, *Mal. GCT* malignant germ cell tumor, *NSGCT* non-seminomatous germ cell tumors

Clinical Features and Serological Findings

A detailed history and clinical examination of the patient are needed. Age and gender are among the most important initial features to consider when evaluating patients with an anterior mediastinal mass, as specific lesions tend to be more common in certain demographic groups, together with clinical presentation (Table 9.1). The presence of particular clinical symptoms and the severity and duration of these symptoms can provide important clues to the diagnosis [37]. An age older than the third decade is the most prevalent for TETs, and the anterior mediastinum (anterior superior) is mostly affected, although ectopic TETs have been described in the posterior mediastinum, in the pretracheal, anterior mediastinal, and cardiophrenic fat, posterior to the brachiocephalic (innominate) vein, at the aortopulmonary window and at the base of the skull [29]. Moreover a frequent ectopic site is the lung, determining differential diagnostic problems with a primary lung neoplasm [38]. Serological markers correlated with TETs are mainly related to MG or to other autoimmune diseases; in thymic neuroendocrine tumors (TNET), hormonal production and the related syndromes could be associated with altered hormonal levels in the serum [39].

Imaging Features of TET

A mediastinal mass suspicious for TET in chest radiographs, located in the anterior mediastinum, presents a thickening of the anterior junction line or abnormal lobulated mediastinal border, indicating the necessity to plan an enhanced computed

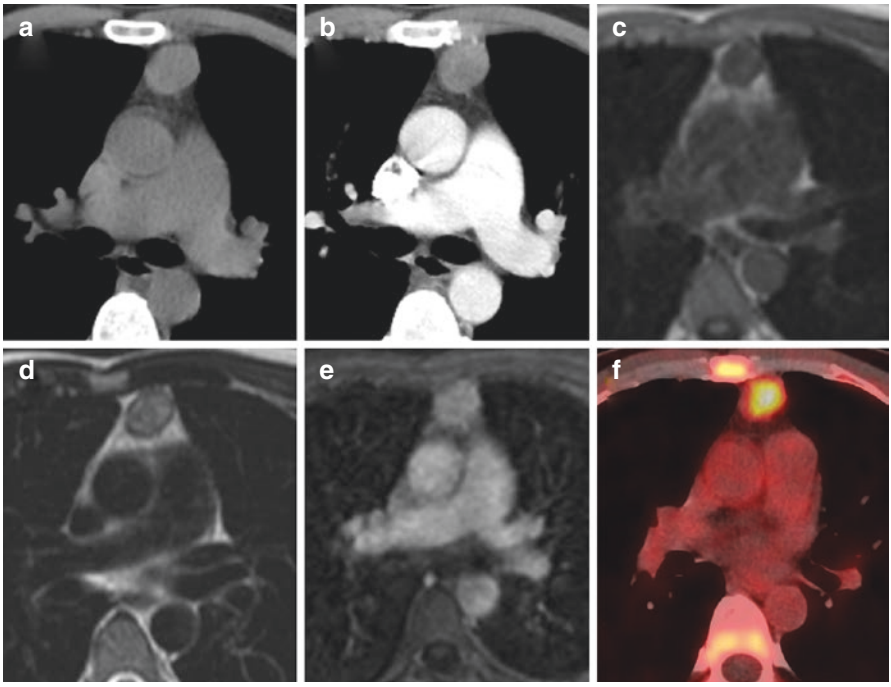

Fig. 9.1 A 41-year-old man with type AB thymoma without invasion. (**a**) Unenhanced CT reveals a round-shaped small mass measuring 2 cm in maximal diameter, at the level of the pulmonary trunk bifurcation in the anterior mediastinum, with smooth contour, which presents soft-tissue attenuation (mean densitometric value, 37 HU), similar to that of muscles and vessels. (**b**) Homogeneous enhancement after contrast medium administration (intensity of enhancement, 59 HU). (**c**) The mass with mild low signal intensity on T1-weighted MR imaging. (**d**) The mass with moderate high signal intensity and smooth capsule which shows low signal intensity on T2-weighted MR imaging. (**e**) The mass presents homogeneous moderate enhancement on axial contrast-enhanced fat-suppressed T1-weighted MR imaging at the same level. (**f**) FDG-PET/CT shows moderate uptake (SUVmax = 5.96) in the anterior mediastinal tumor with non-uptake of the capsule

tomography (CT). The patient's gender and age; tumor size, shape (round/oval/plaque), contour (smooth/lobulated/irregular), and capsule; necrotic or cystic component; calcification; degree of enhancement; enhancement pattern; intensity of enhancement; mediastinal fat obliteration; irregular border with the lung; an elevation of the ipsilateral hemidiaphragm; pleural/ pericardial implantations; effusion; lymphadenopathy; and great vessel invasion should be taken into account while diagnosing a suspicious TET [40]. It is necessary to get 1-mm-thin slice reconstruction of enhanced CT images while predicting invasiveness. A small-sized, round-shaped, smooth contour, homogeneous/heterogeneous anterior mediastinal mass with enhancement in adult often suggests noninvasive THY (Fig. 9.1). Intratumoral fibrous septa with low signal intensity are presented in some THY. Partial obliteration of the fat plane was encountered more often in the invasive mediastinal fat. The

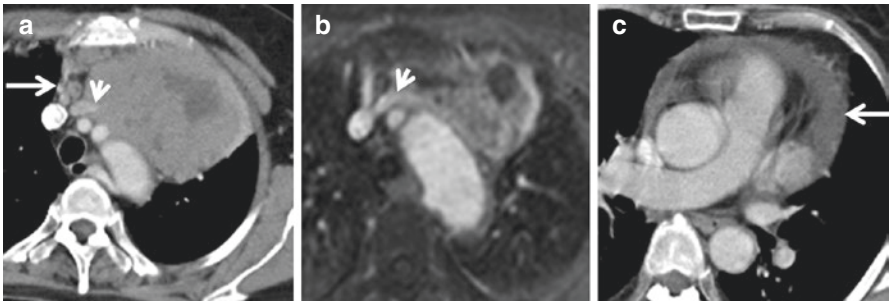

Fig. 9.2 A 60-year-old woman with thymic carcinoid. (**a**) Enhanced CT shows a plaque-shaped mass measuring 10.8 cm in maximal diameter, at the level of the aortic arch in the left anterior mediastinum, with lobulated contour, which presents heterogeneous moderate enhancement (mean densitometric value, 67HU) and nonenhanced cystic changes inside. The left brachiocephalic vein is encased in the tumor and narrowed by the tumor invasion (short arrow). Prevascular lymphadenopathies are showed clearly (long arrow). (**b**) The mass presents heterogeneous moderate enhancement and nonenhanced cystic changes inside on fat-suppressed T1-weighted MR imaging. The left brachiocephalic vein is encased in the tumor and narrowed by the tumor invasion (short arrow). (**c**) Pericardial effusion is found on the following images (arrow)

presence of an intralesional cystic or necrotic component is prevalent in the invasive group, as is the presence of calcifications. Pleural implantations, lymphadenopathies, pericardial effusion, and/or pleural effusion are encountered in low percentages and only in the invasive TET (Fig. 9.2). Magnetic resonance imaging (MRI) is also effective in discriminating anterior mediastinal masses and in allowing staging of TET in patients with contrast allergy and/or renal failure, which preclude evaluation with enhanced CT [41]. In general, the correct diagnosis is reached in 86% of cases by using a combination of CT and MR imaging [42]. Heterogeneous signal intensity secondary to cystic changes, necrosis, and hemorrhage may be present [43]. Thymic carcinoma and carcinoid tumors may demonstrate hyperenhancement [44]. On T2-weighted sequences, cystic changes show very high signal intensity similar to that of the cerebrospinal fluid (CSF), and necrosis typically manifests moderate to low signal intensity due to the contents of the necrosis. Both the cystic changes and necrosis present low signal intensity on T1-weighted sequences. If the area of cystic changes or necrosis is large enough, an irregular thickening tumor capsule is left only with peripheral enhancement, with or without internal septation and septation enhancement, thus indicating a cystic TET (Fig. 9.3). The signal intensity of intratumoral hemorrhage is highly variable and depends on its age. Acute or subacute hemorrhage may demonstrate T1 hyperintensity, while low signal intensity on T1- and T2-weighted sequences as hemosiderin in chronic stage. The major differential diagnoses of anterior mediastinal solid tumors in adults include TETs, lymphoma, germ cell tumor, intrathoracic goiter, and hemangioma. The time-intensity curve (TIC) pattern on dynamic contrast-enhanced MRI

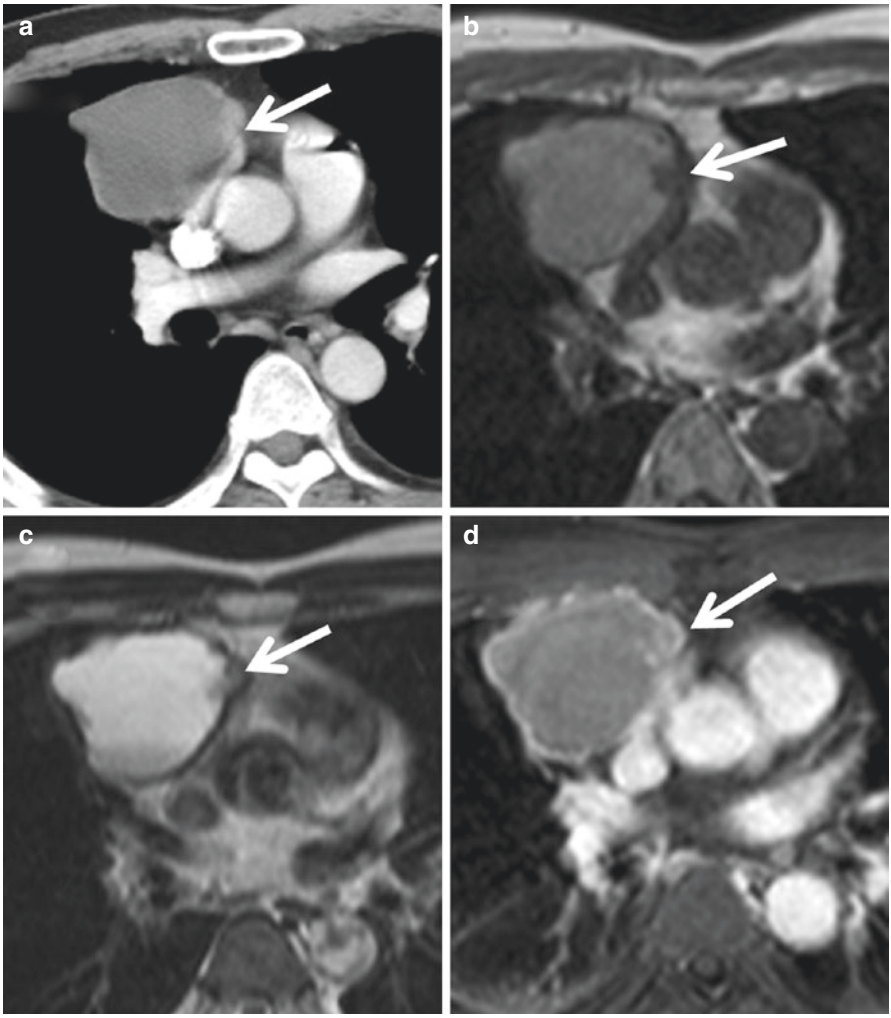

Fig. 9.3 A 43-year-old man with cystic thymic carcinoma. (**a**) Enhanced CT shows a plaque-shaped mass measuring 6.2 cm in maximal diameter, at the level of the right pulmonary trunk in the right anterior mediastinum, with lobulated contour, which presents intratumoral cystic attenuation content (mean densitometric value, 15 HU) and irregular thickening enhanced tumor capsules (mean densitometric value, 61HU). (**b**) The cystic mass shows mild low signal intensity of the tumor capsule and mild high signal intensity of the cystic content compared to that of muscles on unenhanced T1-weighted MR imaging. (**c**) The cystic mass shows mild high signal intensity of the tumor capsule and strongly high signal intensity of the cystic content on T2-weighted MR imaging. (**d**) The cystic mass shows moderate enhancement of the irregular tumor capsule and nonenhancement of the cystic content on axial contrast-enhanced fat-suppressed T1-weighted MR imaging at the same level

(DCE-MRI), the maximum standardized uptake values (SUVmax) on 2-[18F]-fluoro-2-deoxy-D-glucose positron-emission tomography (FDG-PET), and the maximal diameter of the tumor might be useful to differentiate anterior mediastinal solid tumors in adults [45]. The washout pattern on DCE-MRI is seen only in TET. Seminomas occur almost exclusively in young men. SUVmax of lymphoma, malignant germ cell tumors, and TC are significantly higher than that of THY. The mean maximal diameter of TETs is significantly smaller than that of lymphomas and malignant germ cell tumors [45]. Moreover, CT and MR findings of the TETs help differentiate their various subtypes [46]. Diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) values may help assess and characterize the World Health Organization (WHO) classification and clinical staging [47]. Most intrathoracic goiters can be discriminated based on their continuity from the thyroid gland. Hemangioma can be diagnosed based on a typical very high intensity on T2-weighted images, a persistent and centripetal enhancement pattern at DCE-MRI, and phleboliths at CT if present [48, 49]. The major differential diagnoses of anterior mediastinal cystic tumors in adults include cystic thymic tumor, mature cystic teratoma, and cyst with complex contents or inflammation. Cystic thymic tumor often presents irregular thickening of the wall with or without septa which shows moderate enhancement both on CT and MRI or mild uptake on FDG-PET/CT images. The intratumoral contents show low signal intensity for necrosis or very high signal intensity for cystic changes on T2-weighted images and nonenhancement or no uptake on FDG-PET/CT images. Non-neoplastic cysts are distinguishable from solid masses by showing signal suppression on high-b-value DW images or high apparent diffusion coefficient (ADC) values. ADC values of non-neoplastic cysts are significantly higher than that of solid masses [50]. Mature cystic teratoma is characterized with various thickened wall and the combination of fluid, soft tissue, calcification, and/or fat component [42, 51], which is different from lipomas with homogeneous fatty contents. Cysts with inflammation may appear as unilocular/multilocular cysts with a mild thickened wall which strongly enhanced both on CT and MRI and show great uptake on FDG-PET/CT images. CT is the technique of choice in the study of the anterior mediastinum for visualization and precise presurgical characterization of thymic tumors, and it may be integrated with MR and FDG-PET/CT. MRI can partly replace CT for the staging of TET and for follow-up of patients. FDG-PET/CT is useful for the initial evaluation of patients with an anterior mediastinal mass or for staging of TETs [52].

Paraneoplastic Diseases, THY-Associated: Neurological Findings

Paraneoplastic diseases (PND), mostly with neurological signs/symptoms, are associated with thymoma in 50–70% of cases [53]. The most common PND is a thymoma-associated MG (TAMG) [54], followed by hypogammaglobulinemia/Good syndrome [55] and pure red cell aplasia (PRCA) [56]. Autoimmune disorders

such as systemic lupus erythematosus, polymyositis, and myocarditis may also be found [57, 58]. TAMG mainly occurs in subjects aged 40–60 years, with no gender prevalence, causing generalized weakness, often with a rapidly progressive course and early respiratory crises. An "ocular" form of TAMG should be also suspected in patients with asymmetric eyelid ptosis and diplopia, often associated with dysarthria and dysphagia ("bulbar" symptoms) and facial and neck weakness. Proximal limb muscles are usually involved. Severe respiratory weakness may result in crisis or death risk [53]. In patients with thymoma, MG onset or deterioration can herald a tumor relapse [59]. The preoperative patient workup should ascertain the eventual underlying paraneoplastic TAMG, as many patients undergo a so-called myasthenic crisis following tumor removal [60, 61]. Mao et al. performed a systematic literature review and found that the incidence of thymoma in MG was 21% and that, in regard to geographical regions, the incidence was 13% for the American, 23% for European, and 29% for Asian cases. Thymoma incidence was higher among male MG patients and those aged ≥40 years at MG onset in their study [62], whereas only relatively few studies report on the association of MG with TET according to WHO histological subtypes [63, 64].

Surgical Approach to Anterior Mediastinal Masses

It is widely accepted that thymic neoplasms constitute an indication to surgery [65–67]. Surgical options and their specific technical aspects have been described in the dedicated section of this book. Some considerations, though, are worth to be made in this context.

Preoperative Workup and Surgical Indications

Generally, surgery for anterior mediastinal lesions is undertaken on the basis of patient clinical conditions and CT findings, rather than on additional imaging or tumor biopsies [37, 65, 68]. Recently, a survey from the European Society of Thoracic Surgeons [69] brought to evidence that most of the surgeons involved in the management of thymic malignancies in their clinical practice consider CT findings sufficient ground to decide surgical indications, with no need for further investigations. PET-CT with ^{18}FDG, chemical-shift MR imaging [70], and octreotide scan are some of the additional, specific examinations that could enhance diagnostic accuracy, discriminating between thymic hyperplasia, low-replicating tumors, non-surgical diseases (i.e., lymphomas), and rapidly evolving pathologies (i.e., thymic carcinoma) [69]. Nonetheless, a routine employment of these techniques is far from being part of the typical preoperative workup. For the majority of surgeons, the size of the mediastinal tumor and its relation with surrounding structures as shown on the CT scan are key to planning the following steps. A pathologic definition of

mediastinal masses is rarely achieved before surgery. On one hand, larger lesions are frequently approached with bioptic techniques, especially if showing signs of invasion of the near structures or, obviously, if technically inoperable at first glance. Tumors not meeting the criteria for a *d'emblée* resection (and, thus, for which a histological definition is achieved) are usually addressed to induction chemotherapy (less frequently to radiotherapy or a combination of the two) and then reevaluated for surgery [71]. On the other hand, invasive assessment of small anterior mediastinal masses is rarely taken into account in surgical flowcharts [72]. This attitude depends on some factors related to bioptic techniques and how surgeons perceive them. Needle biopsies (whether transthoracic or transtracheal) can be low-yielding, if feasible at all (depending on size and positioning of the lesion), and should be performed by expert specialists, aimed at obtaining deep and multiple samples [65]. Thymic (and, in general, mediastinal) tumors often present with heterogeneous cell populations in their structure, and needle biopsies may be only "a shaft of light in a dark room," allowing identification of just a part of the histological pattern, yielding misleading results [73]. Mediastinoscopy and/or mediastinotomy allows for bold bioptic specimens but is often considered too invasive for small-sized lesions that could be completely excised with minimally invasive techniques, without ignoring the esthetic results of these approaches.

Surgical Approach

Variously depending on some or all of the reasons exposed, surgery for thymic tumors is frequently undertaken having no histological definition of the lesion. This assumption leads to the choice of pursuing radical, and whenever possible, extended resection of mediastinal masses and surrounding tissues, with little space left for conservative, limited resections in the current surgical practice for thymic neoplasms [74–76].

If size matters, larger lesions deserve a thorough dissection of mediastinal tissues and surrounding structures, anyway (in a fashion resembling the Jaretzki's technique for patients with MG), and the surgical attitude should be that of performing en bloc resection of any structure in strict proximity with the neoplasm (i.e., pericardium, pleural linings, brachiocephalic vessels), whenever a clear cleavage plane is not easily evidenced. Justifications for such an approach are much stronger for thymic malignancies undergoing induction treatments. Pericardiectomy, thoracic wall resections, and, sometimes, great vessel resections require prosthetic reconstruction, using a variety of materials ranging from PTFE (mainly for pericardium) to titanium moldable bars (for costal reconstruction) [75, 77, 78]. According to international guidelines, the sternotomic approach is the standard for resection of thymic neoplasms [65]. In our experience, open techniques (sternotomic and, in selected cases, thoracotomic) represent the first choice for treating such cases, allowing full control on a large operating field, bilaterally and cranio-caudally; video-assisted thoracoscopic surgery (VATS) can be useful for a last-minute assessment of pleural cavities immediately before undertaking the resection with radical intent.

Concerning smaller lesions, enucleating nodules suspected of being THY is, in our opinion, a strategy that should be avoided whenever possible: respecting the capsule and the ideal safe margin is mandatory, and these objectives generally supersede the need of performing a frozen section or sparing the mediastinal tissue.

A consideration that in a certain way descends from and at the same time affects all of the above is that the evolution of the minimally invasive techniques and their implementation in current clinical practice contributed to forge the attitude of surgeons toward thymic neoplasms in recent years. International guidelines do not recommend these techniques as a standard, since the associated outcomes cannot be definitely evaluated because of too short follow-up times, as these are relatively young techniques. Nevertheless, the increasing and ubiquitous implementation of minimally invasive surgery in oncology is a fact which surgeons and oncologists have to deal with [79–82]. Robot-assisted thoracic surgery (RATS) has been establishing as a surgical standard since the beginning of 2000. If its applicability to lung surgery remains somewhat questioned in terms of measurable advantages, its role in thymic surgery is well consolidated [83, 84]. Despite concerns about higher costs and slightly longer mean operation times, generally compensated by lower morbidity and shorter LOS, RATS for mediastinal diseases is maintaining constant rates through recent years; this may be justified mainly because of its *open* counterpart, represented by sternotomy, which is way less appealing in terms of perceived invasiveness and esthetic results . Whether if left or right, the sub-mammary three-port accesses (through 0.8–1 cm incisions), the enhanced 3D-stereoscopic full-HD vision, the precision granted by the mechanical control of the instrumentation, and the CO_2-inflation that sensibly increases the room for maneuvers in the small mediastinal space are the strong points of the RATS for thymic neoplasms. In the clinical practice at the Regina Elena National Cancer Institute, a left approach for left-sided and central mediastinal lesions is routinely adopted, reserving the right approach to right-sided tumors.

VATS has been validated as an effective and safe technique through which achieving radical thymic resections: since the early 1990s, various types of successful operations on thymic gland have been described. Since its appearance, and particularly since its employment in major pulmonary resections, VATS has been evolving and expanding its indication may be more than any other surgical technique in recent years [85]. Its cost-effectiveness, the short operatory time and the reduced morbidity and LOS have contributed to its diffusion [86]. At present, the uniportal approach (VATS performed through a single incision of 3–4 cm) is gaining worldwide acceptance and is the technique of choice at the Regina Elena National Cancer Institute. Even if slightly less accurate than RATS, the direct control of surgical instruments returns to the tactile feedback of the surgeon's hand; magnification of the surgical field through full-HD and—when available—3D or 3D-stereoscopic optics allow optimal view; a small single access turns out to be of great advantage in terms of both functional and esthetic results. What makes this technique extremely versatile is that, as demonstrated by the evolving techniques promoted by different centers around the world, the single access can be placed in different positions, allowing an anterior intercostal access (usually entering the IV

or the V intercostal space, between the anterior pectoral muscle and the posterior latissimus dorsi) or a subxiphoid access (on the abdominal midline just below the xiphoid process, tunneling the way to the right or the left pleural space). The latter access results in a relevant postoperative pain reduction, avoiding the insertion of the chest tube through the intercostal spaces.Surgical technique is quite similar for both RATS and VATS approaches, being that the dissection started in the caudal portion of the mediastinal tissue, near the phrenic nerve (which constitutes the anatomical boundary, provided the thymic lesion is at a safe distance) and then proceeds following the pericardial plane cranially until the vascular structures (Keynes veins) are exposed and sectioned. The dissection must be pushed toward the contralateral side (ideally until the contralateral phrenic nerve is exposed) to guarantee the whole lesion and the surrounding tissue are removed.

The introduction of these minimally invasive techniques into current clinical practice by a growing number of surgeons has led to a consolidation of the "surgery rather than biopsy" attitude: knowing that a thymic mass is likely to be radically excised through a 3-cm-wide incision affects the decision-making process when compared to performing the same incision just to get a bioptic sample. Not less relevant, RATS and VATS are followed by mild surgical sequelae, with small and discrete accesses, reduced postoperative pleuritis, and, consequently, minor pleural adherences: considering that the preferred option for recurrent thymic diseases is iterative surgery, when feasible, this aspect is definitely not secondary when choosing the best strategy.

TETs are treated with surgery whenever feasible. Bioptic assessment of the lesion (and surgery itself) has changed over the last few decades, since minimally invasive techniques contributed to shape the indications. Since histology definition following bioptic assessment can be incomplete, misleading, or (in the majority of cases) totally missing, the attitude of every surgeon dealing with TET should be that of reaching the highest level of radicality. RATS and VATS are safe and evolving techniques that allow radical/extended excision of mediastinal masses with mild inflammatory sequelae, leaving room for easier intervention in case of reoperation for tumor relapse.

Pathological Diagnosis of TET

The present 2015 World Health Organization (WHO) classification of TET [87] is largely accepted and diffused (Table 9.2). The WHO classification, first proposed in 1999 by J. Rosai et al. and subsequently developed by H.K. Müller-Hermelink and A. Marx et al. in 2004 [88], had been revised and updated in 2015 by A. Marx and a worldwide representative international panel of pathologists involved in TET diagnosis. The 1999 classification promoted the adoption of a uniform terminology that could facilitate communication among pathologists all around the world and represented a compromise among different views concerning thymic tumors . According to the WHO classification, TET can be named according to the number and shape of

Table 9.2 WHO classification 2015 of thymic epithelial tumors (TET) [87]

Epithelial tumors	Thymic neuroendocrine tumors
Thymoma	Carcinoid tumors
Type A thymoma (including atypical) variant)	Typical carcinoid
Type AB thymoma	Atypical carcinoid
Type B1 thymoma	Large-cell neuroendocrine carcinoma
Type B2 thymoma	Combined large cell neuroendocrine carcinoma
Type B3 thymoma	Small-cell carcinoma
Micronodular thymoma with lymphoid stroma	Combined small-cell carcinoma
Metaplastic thymoma	
Other rare thymomas	
Microscopic thymoma	Combined thymic carcinomas
Sclerosing thymoma	
Lipofibroadenoma	
Thymic carcinoma	
Squamous cell carcinoma	
Basaloid carcinoma	
Mucoepidermoid carcinoma	
Lymphoepithelioma-like carcinoma	
Clear-cell carcinoma	
Sarcomatoid carcinoma	
Adenocarcinomas	
Papillary adenocarcinoma	
Thymic carcinoma with adenoid cystic	
carcinoma-like features	
Mucinous adenocarcinoma	
Adenocarcinoma NOS	
NUT carcinoma	
Undifferentiated carcinoma	
Other rare thymic carcinomas	
Adenosquamous carcinoma	
Hepatoid carcinoma	
Thymic carcinoma, NOS	

Reproduced with permission WHO Classification of Tumours of the Thymus, p. 184–185, from Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. World Health Organization Classification of Tumours of the Lung, Pleura, Thymus and Heart. IARC, Lyon, 2015

epithelial cells (EC) and by the number of lymphocytes in the tumor. The use of two alphabetic letters (A and B) allowed to identify with "A" tumors with a component of spindle-oval EC, variably organized, without LY, and with "B" a component of large EC with dendritic or plump (epithelioid) morphology, i.e., with dendritic cellular processes allowing networks to be established, where LY are attracted. Tumors combining these two morphologies were designated as *type AB*. According to Prof.

Rosai, the first editor of the 1999 WHO classification [89], "A" stands for atrophic (i.e., the effete thymic EC of adult life) and "B" for bioactive (i.e., the biologically active organ of the fetus and infant). However, the new terminology is suggestive, in our opinion, of the concept of "cortical" and "medullary "differentiation in TET, "A type" tumors containing a "medullary" EC component and "B type" containing a "cortical" EC component. This view recalls the "histogenetic" concept of thymoma classification [90]. Nowadays, "cortical" and "medullary" markers had been described and characterized and are also available for immunohistochemical staining [91, 92]. The WHO "type B" thymomas were further subdivided on the basis of the proportional increase (in relation to the lymphocytes) and emergence of atypia of the neoplastic EC into three subtypes, respectively, designated as Bl, B2, and B3. Initially, "C" [89] was used for thymic carcinoma; however later, in the 2004 and in the 2015 WHO editions, the aggressive carcinomas with histotypes similar to neoplasms of other organs/origin were designated as "carcinoma" and further classified as carcinoma arising in other organs. The problems in reproducibility of the 2004 WHO classification had been discussed by an interdisciplinary team of pathologists, two surgeons, and an oncologist, who reviewed prototypic and difficult-to-classify TETs during two consensus slide workshops both supported by the International Thymic Malignancy Interest Group (ITMIG), the first in New York in March 2011 and the second held in Mannheim in December 2011, with additional support by the European Society of Pathology (ESP) [93]. With the publication of the 2015 WHO classification, it appears that the refined diagnostic criteria for type A, AB, and B1–B3 THY and thymic squamous cell carcinoma could improve the diagnostic reproducibility of the classification. Moreover, the clinical relevance of the WHO classification has been reinforced by involving a multidisciplinary expert team [94]. Some recent studies focused on both the major and minor diagnostic criteria according to the ITMIG Consensus, forming the basis of the 2015 WHO classification [95], and also on the new TNM 8th edition staging system, assessing the feasibility and the diagnostic value of the ITMIG consensus statement [96]. Nevertheless, it is worth mentioning that as early as in 1999 some distinctive pathologists (among them S. Suster and C. Moran) considered the heterogeneity of thymomas as a continuous morphologic spectrum exhibited by EC [97]. They disagreed on recognizing distinct TEC subtypes such as those defined by the WHO classification and proposed to classify TET as thymoma (well-differentiated thymic epithelial neoplasm), atypical thymoma (moderately differentiated thymic epithelial neoplasm), and thymic carcinoma (poorly differentiated thymic epithelial neoplasm) [98, 99].

Diagnosis of Thymoma by Histotypes

Major and minor morphological criteria were adopted by the panel of pathologists during the definition of the different TET histotypes to improve diagnostic reproducibility of the WHO classification [93], and they will be briefly mentioned by describing the typical histotypes.

Type A Thymoma

The major criteria indicated by the consensus workshop indicate that oval-spindle sheets of EC constitute type A tumors, with absence or paucity of Tdt-positive lymphocytes (Fig. 9.4a). Solid sheets of spindle EC without atypia are variably arranged, with no pattern or storiform pattern predominating; rosettes, focal glandular formation, and a pericytomatous vascular pattern are frequent (Fig. 9.4b). Reticulum fibers are usually absent. Perivascular spaces and Hassall's corpuscles are absent. These tumors are encapsulated. The aberrant expression of CD20 is typical for most tumors [100]. Type A thymomas do not express "cortical" markers (see section on immunohistochemistry).

The concept of atypical type A thymoma emerged from a literature review [101, 102] and own sporadic observations. Type A thymomas can present "atypia" including increased mitotic activity (4 or more per 10 high power field) and coagulative necrosis. These cases can present advanced stage and metastatic tendency. Hypercellularity, nuclear hyperchromasia, and increased KI67 index were also reported. However these last features were difficult to quantify during the ITMIG consensus workshops. Therefore after the consensus workshop in Mannheim, the WHO classification did not propose further advances for atypical type A THY. A recent paper describes genetic findings in atypical thymomas showing that some

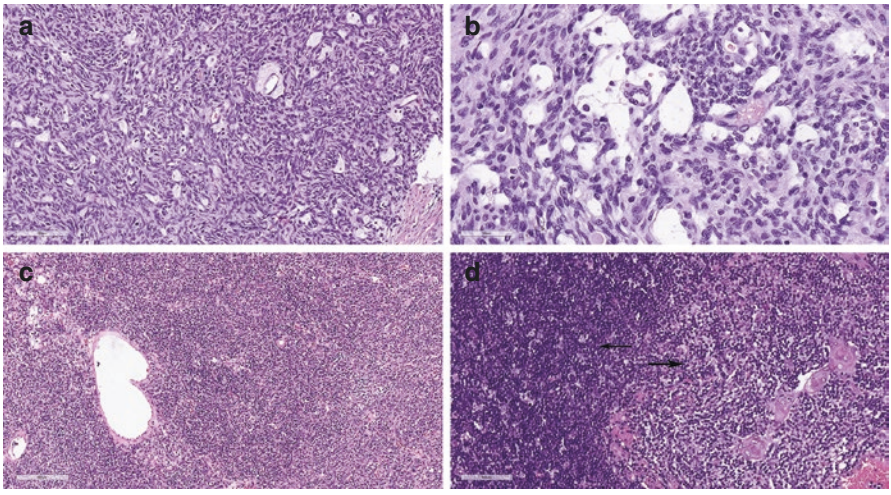

Fig. 9.4 Morphological findings in WHO TET subtypes—I. (**a**) H&E, 200×, type A THY: solid sheets of bland spindle epithelial cells (EC); very few lymphocytes are present. (**b**) H&E, 200×, type A THY: small cysts and pseudoglandular structures are seen. (**c**) H&E, 100×, type AB THY: higher content of lymphocytes, morphological heterogeneity of EC. (**d**) H&E, 200×, type B1 THY; lymphocyte-rich THY, with a darker area on the left, with pale scattered EC in the background of cortical lymphocytes (thymocytes) (thin arrow): this is the typical B1 "organoid thymic-like structure"; on the right a "medullary island" is seen with scattered Hassall's bodies, a less dense lymphocytic background and sparse epithelial network (thick arrow) (digitization of histological slides by Leica Aperio system)

recurrent and atypical type A THY show partially recurrent genomic alterations by comparative genomic hybridization (CGH) [103].

Type AB Thymoma

Usually encapsulated, lobulated tumors contain discrete separate nodules or intermixed A- and B-type areas. The type B EC is small and oval, plump spindly, or polygonal, with dispersed chromatin and inconspicuous nucleoli. Medullary islands are rare, Hassall's corpuscles absent. The immature lymphocytic component is very variable (Fig. 9.4c). The immunohistochemical findings include variable expression of cortical and medullary markers [92]. CD20 may be variably expressed by the EC.

Type B1 Thymoma

B1 thymoma forms a capsulated tumor resembling the normal thymus, with cortex-like areas and medullary areas. EC are dispersed, not forming groupings, and they appear rather small, with dendritic morphology. EC have pale nuclei, small variably conspicuous nucleolus. Medullary differentiation (also called medullary islands) is always present, containing mature T lymphocytes, consistently mature B cells, and eventually myoid cells (Fig. 9.4d). Hassall's corpuscles may be present. This histotype may undergo extensive necrotic changes. Moreover, the abundance of Tdt+ thymocytes could be interpreted as a T-lymphoblastic lymphoma going on [104]. By IHC EC express CK19 and eventually the protein AIRE (in about 50% of cases) [93].

Type B2

Type B2 thymoma is characterized by a fibrous capsule and a lobular structure, with lobules separated by a delicate septa, containing large networks of polygonal EC variably grouped with open chromatin and prominent nucleoli (Fig. 9.5a**).** Medullary islands are absent or inconspicuous. Abortive Hassall's corpuscles can be found in 25% of cases, whereas typical Hassall's bodies are rare. Prominent perivascular spaces are present (Fig. 9.5b). Lymphocytes are abundant, conferring a dark blue color under the microscope, although also EC are frequent. In 17–29% of cases, the B2 and B3 components are present together, in a variable percentage. According to the updated 2015 WHO classification, the major component should be indicated first, with a percentage resulting from accurate sampling, and the second component being also described and measured [87].

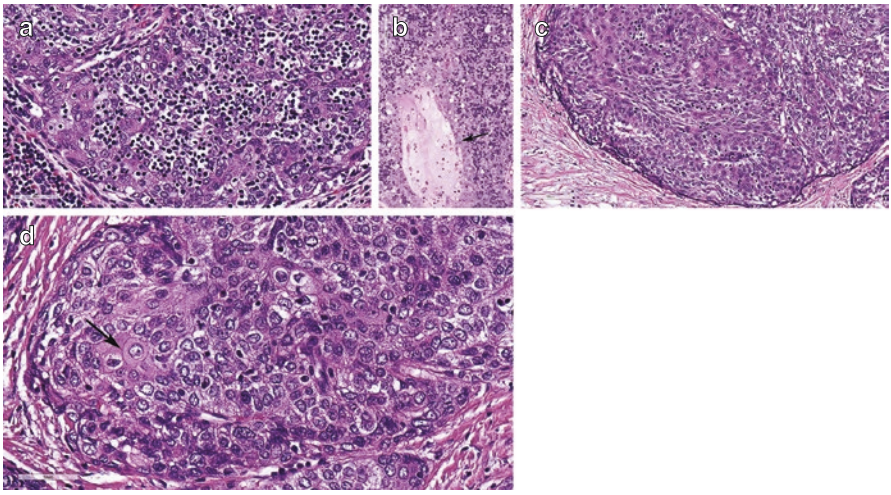

Fig. 9.5 Morphological findings in WHO TET subtypes—II. (**a**) H&E, 400×, type B2 THY: dense network of large epithelial cells (EC), with distinct nucleolus; in the network frequent lymphocytes are located, of the immature (cortical) type. (**b**) H&E, 200×, type B2 THY: a perivascular space (PVS) bordered by an EC palisade (arrow). Lymphocytes are in transit in the PVS. (**c**) H&E, 200×, type B3 THY: smaller EC than in B2 THY, very EC-rich lobule, background almost devoid of lymphocytes, few tight PVS are seen. (**d**) H&E, 400×, type B3 THY: at higher magnification on the left side of the field epidermoid-differentiation is seen: EC with eosinophilic cytoplasm and distinct cell borders (arrow) (digitization of histological slides by Leica Aperio system)

Type B3

Type B3 thymoma is characterized by lobules separated by fibrous septa and composed by EC forming prominent sheets surrounded by perivascular palisades. There is a low lymphocytic content made up of mostly mature T lymphocytes. EC form sheet-like growth with solid or epidermoid pattern. EC do not show intercellular bridges; they are of medium size with small nucleoli and often grooved nuclei (Fig. 9.5c). There are foci of keratinization, mimicking Hassall's corpuscles or squamous eddies (Fig. 9.5d). Medullary differentiation is usually absent.

Incidence of TETs by Subtypes

The geographical distribution of TETs by histotype has been investigated based on the data of the Retrospective ITMIG database, including, as far as the detail in histotype is concerned, **4221** cases. The frequency of type A thymoma is similar in Europe (15%) and the USA (14%), but significantly lower in Asia (6%). Type AB thymoma is more frequent in Asia (27%) than in Europe (23%) and the USA (18%). Type B2 thymoma has a frequency similar in Europe (31%) and the USA (32%) but

significantly lower in Asia (20%). Type B3 thymoma is more frequent in Asia (32%) than Europe (15%) and the USA (16%). The frequencies of type B1 thymoma (16–20%) are not significantly different between geographic regions. Therefore the higher frequency of B2 thymomas is encountered in Europe, and the lower frequency of type A thymoma occurs in Asia. Considering that the phenomenon is observed even in high-volume centers, most of which have pathologists dedicated to thoracic tumors and/or to hematopathology and to mediastinal pathology, the regional differences probably represent real epidemiologic differences as it has been seen in a variety of cancers. Investigating the histotype distribution among migrant populations might help to distinguish genetic from environmental factors in disease etiology [105].

Thymic Carcinoma

Thymic carcinoma (TC), although deriving from thymic EC, resembles carcinomas arising in other organs, the squamous cell carcinoma variant being the more frequent. Table 9.2 reports other variants occurring, including lymphoepithelioma-like carcinoma and sarcomatoid carcinoma, thymic adenocarcinomas being exceedingly rare. The most frequent variant is the thymic squamous cell carcinoma (TSQCC), with variable keratinization and grade (Fig. 9.6a, b). In most cases TCs show a

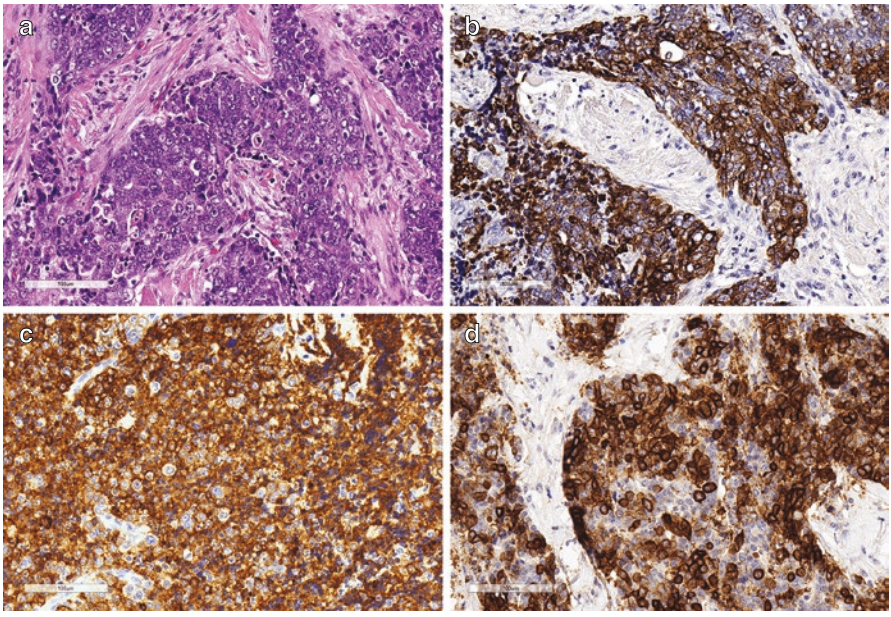

Fig. 9.6 Morphological and immunohistochemical findings in a poorly differentiated thymic squamous cell carcinoma (TSQCC). (**a**) H&E, 400×, TSQCC forming ribbons and trabecules infiltrating the desmoplastic stroma. (**b**) Pan-cytokeratin MNF116 stain marks the epithelial cell (EC) network (400×). (**c**) CD5 stains EC in most thymic SQCC (400×). (**d**) CD117 is a characteristic marker of TSQCC (400×) (digitization of histological slides by Leica Aperio system)

distinctive immunohistochemical phenotype CD5+, CD117+ (Fig. 9.6c, d). TCs are characterized by locoregional invasive growth pleural dissemination and by distant lymphogenous and hematogenous metastases (>10% of cases) [106–108]. Paraneoplastic syndromes are not included in the usual clinical spectrum of TC, in accordance with the absence of thymopoietic capability. Combined forms of TC with THY exist [109, 110]. Diagnostic revised histological criteria of thymoma and TC, refined in the new WHO classification, indicate that, in "combined" tumors presenting aspects of THY and TC, the tumor should be labeled as TC (specifying the percentage and histological type) followed by listing of the accompanying THY components (with quantitation of the percentage) [87].

Thymic Neuroendocrine Tumors (TNET)

Among epithelial tumors, thymic neuroendocrine tumors (TNET) are rare (2–5% of all thymic tumors) primary epithelial neoplasms of the thymus, arising from a minor neuroendocrine cell population scattered in the normal human thymus [111]. The same nomenclature and criteria applied for the lung neuroendocrine tumors have been maintained for TNET in the 2015 WHO classification [87]. The relevance of a smoking habit has not been established yet for TNET, at variance with lung neuroendocrine tumors. Two groups of TNET have been distinguished: a *low-grade TNET* including typical carcinoid and an intermediate-grade atypical carcinoid, with characteristic morphological and immunohistochemical neuroendocrine features (Fig. 9.7a–d), and a *high-grade TNET*, including large-cell neuroendocrine carcinoma (LCNECs) and small-cell carcinoma, both these tumor types showing some neuroendocrine features [87, 112]. Paraneoplastic syndromes such as Cushing's syndrome and multiple endocrine neoplasia syndrome type 1 (MEN1) may be associated with TNET [39, 111, 113]. TNET arising in MEN1 patients (8% of cases) are histologically indistinguishable from their pulmonary or gastrointestinal counterparts [114].

Thymic Carcinoids

Thymic carcinoids, accounting for only 0.4% of all neuroendocrine tumors, show evidence of neuroendocrine differentiation by reactivity with antibodies to neuroendocrine markers: synaptophysin, chromogranin A, and neuron-specific enolase (NSE) [115] . Among the endocrine dysfunctions described, 7–30% of adult carcinoid and >50% of childhood carcinoids of the thymus are associated with Cushing's syndrome [116] due to adrenocorticotropic hormone (ACTH) production . Adult males are most often affected. Among the criteria required for the diagnosis, absence of necrosis and a low mitotic count (<2 mitoses per 2 mm^2) have been included [87]. The survival rate of 50% has been reported at 5 years, being significantly worse than for patients with other non-epithelial mediastinal neuroendocrine tumors (paraganglioma) and for patients with neuroendocrine lung tumors.

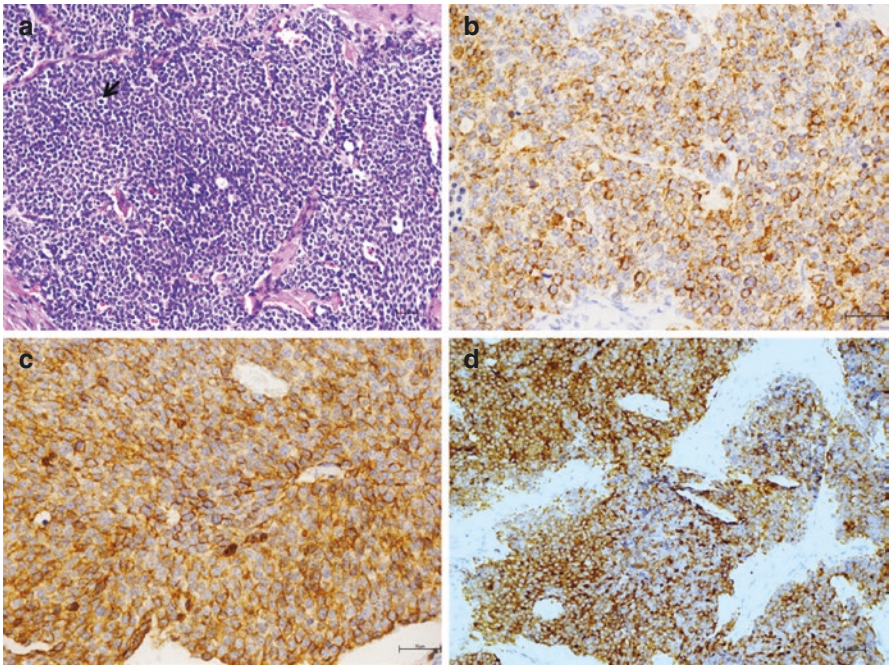

Fig. 9.7 Morphological and immunohistochemical findings in a thymic neuroendocrine tumor (TNET) showing atypical carcinoid features. Morphology and positivity for cytokeratins and two neuroendocrine stains are diagnostic. (**a**) H&E, 200×: rather monotonous sheets of densely packed epithelial cells (EC); a mitosis is seen (arrow). (**b**) CK19 stain of the EC sheets, showing round EC and their cytoplasmic cytokeratin content (400×); granular and punctate cytoplasmic positivity is also seen. (**c**) CD56 stain (400×). (**d**) Synaptophysin (200×) positivity of EC (Microscope Nikon ECLIPSE 55i with digital camera HESP Technology)

Atypical Carcinoid

Atypical carcinoids (AC) are more frequent in the thymus than the typical carcinoids. They affect adult patients with a male predominance. They differ from carcinoids as they exhibit 2–10 mitoses per 2 mm^2 and show foci of necrosis. The clinical presentation includes extrathoracic lymph nodes and parenchymal metastases at presentation. The immunohistochemical features are similar to typical carcinoids (Fig. 9.7). The median survival reported is variable from 20 to 80%, with late recurrence having been reported [87].

High-Grade Neuroendocrine Carcinoma

High-grade neuroendocrine carcinomas of the thymus are composed of either large or small cells. In the large-cell variant (large-cell neuroendocrine carcinoma, LCNC), mitoses overcome the threshold of 10 per 2 mm^2, and necrosis is

prominent. Immunohistochemical expression of keratins (often with dot-like cytoplasmic positivity), of NSE, synaptophysin, and CD56 has been reported. CD117 staining may occur. Necrosis and hemorrhages are constant features. Immunohistochemical positivity of markers such as keratins and neuroendocrine markers has been reported as well as hormonal production. The reported 5-year survival ranges from 30 to 66% [87]. High-grade neuroendocrine carcinomas of the thymus do not occur in the setting of MEN1. In the small-cell carcinoma (SCC) variant, a Cushing's syndrome has been exceptionally described [117].

Immunohistochemistry in TET Diagnosis

An emerging role of immunohistochemistry (IHC) was established by the 2015 WHO classification, due to the relevance of some basic immunohistochemical stainings in the differential diagnosis among histotypes [93] and also of TET with respect to non-thymic epithelial tumors [118–120]. Moreover, IHC helps in the differential diagnosis of TC with respect to carcinoma of other organs and to lymphoma [121–123]. Table 9.3 summarizes old and new findings in the immunohistochemistry of

Table 9.3 Main immunohistochemical markers to distinguishing TET subtypes and their differential diagnosis from other cancers [57, 87, 88, 93, 100, 104, 118–124]

Marker	Reactivity
Cytokeratin19	Thymic/TET epithelial cells
Pan-cytokeratins MNF116	Thymic/TET epithelial cells
CK20	Negative in Thymic/TET epithelial cells May be positive in rare adenocarcinoma
p63	Cortical and medullary thymic EC, TET epithelial cells Cross-reacts with tumor cells of primary mediastinal large B-cell lymphoma (PMBCL)
CD5	T cells EC in ~70% of thymic squamous cell carcinomas Variably positive in thymic (and other) adenocarcinomas
CD20	B cells EC in ~50% of type A and AB thymomas [100]
CD117	EC in ~80% of thymic squamous cell carcinoma (TSQCC)
PAX8	Positive in thymomas and most TC [121]
Terminal deoxynucleotidyl transferase (Tdt)	Immature T cells in thymus and thymoma T-cell lymphoblastic lymphoma (T-LBL)
LMO2	T-cell lymphoblastic lymphoma/leukemia (T-LBL) [122]
Cyclin-dependent kinase 6 (CDK6)	T-cell lymphoblastic lymphoma leukemia (T-LBL) In 90–100% of cases [104] Thymoma lymphocytes in 10–30% of cases
Desmin	Myoid cells of thymic medulla, in B1 thymoma, in rare B2 and B3 THY, and in some TC
Ki-67	Any proliferating cells (immature T cells in normal thymic cortex, most THY, T-LBL

TET. It appears to be of relevant importance the necessity of applying a panel of markers particularly when dealing with needle biopsies [120, 124] and the necessity of experienced pathologists with specific training in TET diagnosis.

Dataset and International Reporting Initiatives

The International Collaboration on Cancer Reporting (ICCR) was established by the Royal Colleges of Pathologists of Australasia and the UK, the College of American Pathologists, and the Canadian Association of Pathologists–Association Canadienne des Pathologists in association with the Canadian Partnership Against Cancer and the European Society of Pathology. ICCR is a nonprofit organization intended to produce standardized, internationally agreed, evidence-based datasets for use throughout the world. In alliance with the International Agency for Research on Cancer (IARC), ICCR aligned the thoracic dataset development schedule with the publication of the 2015 WHO Classification of Tumors of the Lung, Pleura, Thymus, and Heart. The dataset proposed by the multidisciplinary ICCR expert panel for the reporting of TET includes seven "required" (mandatory) and 12 "recommended" (nonmandatory) elements, all validated by a review of current evidence [125]. The reader is also addressed to the second edition of published dataset, available at http://www.iccr-cancer.org/datasets/published-datasets/thorax, following the recent publication of the new TNM staging system of TET.

TET as Source of Immune Dysregulation

Lymphocytes in Thymoma

In the EC networks of TET, LY are situated in variable number, being very high in number in B1 and B2 thymoma and in some cases of AB type, whereas in A type thymoma—by definition—lymphocytes are very scant. In no way should the LY be considered infiltrating, reactive LY. With the exclusion of LY present in the perivascular areas and in the medullary differentiation areas of the tumor, these LY are in large part immature cortical thymocytes undergoing maturation in the tumor. This represents a unique situation occurring in TET as opposed to the overall range of tumors, and their migration to the periphery, where they are eventually exported after maturation (or disordered maturation), is associated with the development and maintenance of immune/autoimmune phenomena. The autoimmune phenomena/syndromes are at the basis of most paraneoplastic syndromes (PND) associated with TET.

MG-Associated TET

Among the PND, present in 50–70% of cases of THY, the most common is myasthenia gravis (MG). In fact 30–50% of THY cases are associated with "paraneoplastic MG" ("thymoma-associated MG," TAMG). On the other hand, thymoma is detected in approximately 15% of all MG cases [54]. MG is an autoimmune disease caused by circulating autoantibodies mostly directed against the acetylcholine receptor of the neuromuscular junction. This disease is expressed in a variety of clinical settings. It is far from this chapter's scope to cover the wide range of tissue-based and experimental studies devoted to explore the role of the thymus in the pathogenesis of TAMG. This disease presents distinct features with respect to other MG subtypes [126, 127], and we will shortly report on the main findings in TAMG in the present context. The autoantibodies associated with TAMG are anti-AChR-ab, anti-Titin-ab, anti-RyR-ab, anti-IL12-ab, anti-IFNα-ab, and anti-IFNω-ab. However, MG is a syndrome more than a single disease, paralleled by a wide range of serological settings, and MG associated with TET has its own peculiarities. The reader is referred to several recent fundamental works relating on the human and experimental models of MG and to recent reviews/paper devoted to the pathology of the thymus in MG [128] and on tumor characteristics [129]. Early-onset MG (EOMG) is instead associated with lymphofollicular hyperplasia of the thymus, and late-onset MG (LOMG) is characterized by age-dependent alteration of the thymus, i.e., by its involution [127].

In summary, MG is almost exclusively associated with TET containing a "B" component, i.e., to TET with a more or less extended EC network with dendritic/epithelioid morphology. These cells resemble morphologically and likely functionally the EC of the thymus cortex, which educate thymic cortical LY during their intrathymic maturation. It has been reported that most cases occur in the "cortical" or "B" component containing thymoma, type A thymoma being associated with MG only in 5% of cases.

In the normal thymus, self-tolerant T cells are produced after selection of autoreactive clones, and mature T cells are exported to the periphery [126]. More than 95% of all thymomas (except for rare types A and B3), at variance with other cancers, generate polyclonal CD4+ and CD8+ single positive thymocytes from bone marrow progenitors [130] due to their thymopoietic capability. In TAMG the intratumoral thymopoiesis generate and export large numbers of mature CD4+ CD45RA+ cells to the blood, setting the stage for MG [127]. Moreover, THYs associated with MG do not express the autoimmune regulator AIRE and have reduced or absent thymic myoid cells [54]. Furthermore, neoplastic EC variably express striational antigen epitopes, including epitopes of titin and various AChR subunits together with reduced levels of MHC class II. These altered properties of neoplastic EC generate altered maturation of thymocytes, interfering with their positive and negative selection and causing defective generation of regulatory T cells by THY. Exported to peripheral lymphatic tissue, the autoreactive T cells gradually replace the patient's

native, more tolerant T cell repertoire and apparently stimulate the pathogenic B cell response. This could happen before, but rarely also after thymoma resection, therefore sustaining TAMG even after tumor removal [127].

Thymic carcinoma in association with MG is rarely reported, as the thymopoietic capability of TC cells is absent. As far as the rarely reported occurrence of MG with thymic carcinoma is concerned, it should be kept in mind that in most cases the diagnosis of thymic carcinoma is performed on bioptic material. Therefore, it cannot be excluded that a limited portion of the tumor, not represented in the bioptic material, is represented by a more differentiated EC component, such as EC with "cortex"-like functional features.

Staging

Several staging systems have been applied to TET and recently reviewed by Filosso et al. [131]. The most widely used staging system in TET had been the Masaoka and the Masaoka-Koga staging systems for several decades [132, 133]. Both were based on a limited series of cases; however, the method appeared to be useful for decades, although there were inconsistencies and difficulties in critical points [134].The 8th TNM staging system for the first time proposed by UICC for TETs is an evidence-based system, deriving from outcome data of more than 10,000 TET cases [135]. Four categories, with progressive levels of invasion by the tumor (T), were identified. T1 including TETs localized to the thymus/anterior mediastinal fat, regardless of capsular invasion, up to and including infiltration through the mediastinal pleura. T2 tumors invade the pericardium; T3 tumors involve relevant mediastinal structures (lung, brachiocephalic vein, superior vena cava, chest wall, and phrenic nerve) either singly or in combination. T4 tumors invade more central structures: aorta and arch vessels, intrapericardial pulmonary artery, myocardium, trachea, and esophagus (Table 9.4). According to the data in the Retrospective ITMIG database representing the source for the 8th TNM for TETs, tumor size was not considered as a prognostic descriptor for stage classification [136]. Nodal involvement zones were divided into anterior (N1) and deep (N2) intrathoracic regions [137], and an ITMIG nodal map defined the location of mediastinal anterior and deep lymph nodes [138]. Metastases were distinguished including pleural or pericardial nodules (M1a) or intraparenchymal pulmonary nodules or metastases to distant sites (M1b) (Table 9.5).

Genetic and Molecular Findings in TET

Molecular pathogenetic events leading to TET development are largely uncovered, due also to the difficulty of investigating a tumor system including a large number of lymphocytes, particularly in some of the TET histotypes. Therefore advances in understanding the genomic changes have been limited [139, 140]. A comprehensive

Table 9.4 TNM staging of TET (8th TNM edition) [175, 135]: T descriptors [136]

T	Descriptors
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor encapsulated or extending into the mediastinal fat, may involve the mediastinal pleura T1a No mediastinal pleural involvement T1b Direct invasion of the mediastinal pleura
T2	Tumor with direct invasion of the pericardium (either partial or full thickness)
T3	A tumor with direct invasion into any of the following: lung, brachiocephalic vein, superior vena cava (SVC), phrenic nerve, chest wall or extrapericardial pulmonary artery or vein
T4	A tumor with invasion into any of the following: aorta (ascending, arch, or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus

Table 9.5 TNM staging of TET (8th TNM edition) [175, 135]: N and M descriptors [137]

Category		Definition (involvement of)
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in anterior (perithymic) nodes
N2		Metastasis in deep intrathoracic or cervical nodes
M0		No metastatic pleural, pericardial, or distant sites
M1	a	Separate pleural or pericardial nodule(s)
	b	Distant metastasis beyond the pleura or pericardium (includes intraparenchymal lung nodules)

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review of the genetic alterations in TET is available in a recent report [141]. Among the relevant advances in the molecular characterization of TET, a gene signature predicting metastatic behavior has been reported, based on a nine-gene signature including upregulation of three genes (*AKR1B10*, *JPH1*, and *NGB*) already known in other cancer types for their association with invasiveness and metastasis. Interestingly, intratumoral heterogeneity was shown to not significantly affect the consistency of the signatures [142]. By next-generation sequencing (NGS), the identification of a GTF2I gene missense mutation (situated in chromosome 7) (c.74146970T>A) in 82% of type A and 74% of type AB thymomas was reported and correlated with better survival. This mutation has been rarely found in the aggressive subtypes [143]. The GTF2I gene encodes a phosphoprotein functioning as a regulator of transcription. Moreover, the study by Petrini et al. identified in TC a higher number of mutations than in THY and recurrent mutations of known cancer genes, such as TP53, CYLD, CDKN2A, BAP1, and PBRM1**.** Other groups reported functional data, by describing, in a thymic squamous cell carcinoma (TSCC) cell line 1889c positive for BIRC3, an anti-apoptotic gene, the spontaneous apoptosis induced by BIRC3 knockdown [144]. A single literature report focused on genomic miRNA in type A/AB THY [145]. Moreover, a mature miRNA expression profile in

TET, detectable in formalin-fixed paraffin-embedded (FFPE) tissues, has been identified by microarray and bioinformatics analysis. Different groups of miRNAs were found differentially expressed between TET and normal thymic tissues and between THY and TC and histotype groups [146]. Correlated putative molecular pathways targeted by these differentially expressed miRNAs included pathways related to cell adhesion/motility and additional pathways related to cancer phenotype such as Wnt, Notch, TGFˇ, ErbB, p53, VEGF, and MAPK signaling pathway. Subsequently, among the most significantly deregulated miRNAs, the significance of the downregulation of miR-145-5p in TET has been investigated in the thymic carcinoma cell line TC 1889. An insight into the functional role of miR-145-5p in TET was provided by the epigenetic treatment of this TC 1889 cell line, resulting in the induction of miR-145-5p expression, in the downregulation of its target genes, and in the improvement of TET tumorigenetic properties [147]. To explore the genomic changes associated with TET, the Cancer Genome Atlas project, promoted by the National Cancer Institute (NCI) in the USA, included TET in the framework of rare tumor genomic studies. The results of this study have been published and provide a comprehensive understanding of the information encoded in TET genome [148].

Principles of Treatment

The management of TET is a paradigm of cooperation between clinicians, surgeons, and pathologists, from establishing the diagnosis to organizing the multimodal therapeutic strategy [65]. Surgery is the mainstay of the curative-intent treatment, as complete resection represents the most significantly favorable prognostic factor on overall survival [149]. Data related to the systemic treatment of thymic malignancies are mostly based on nonrandomized studies and retrospective data, and recommendations rely on expert opinion [65]; this is related to the rarity of the disease, precluding large clinical trials to be developed.

Surgery

As previously discussed in detail, surgery represents the mainstay of the curative-intent treatment, as complete resection represents the most significantly favorable prognostic factor on overall survival [65, 77]. As described above, the standard approach is median sternotomy, which allows the wide opening of the mediastinum and both pleural cavities. Generally, complete thymectomy including the tumor, the residual thymus gland, and perithymic fat is preferred. If the tumor is widely invasive, en bloc removal of all affected structures, including lung parenchyma (usually through limited resection), pericardium, great vessels, nerves, and pleural implants, should be carried out. Minimally invasive surgery is an option for small tumors in the hands of appropriately trained thoracic surgeons.

Postoperative Radiotherapy

Radiotherapy may be delivered in the postoperative setting, aiming to reducing the risk of recurrence; current practices are actually highly variable. The global trend over the past years is toward a less frequent use of postoperative radiotherapy, to reserve it for high-risk cases [65, 74]. This is based on recent reports from large databases [149–154] as well as pooled analyses of retrospective studies indicating:

1. The absence of survival benefit after radiotherapy in stage I thymoma or after R0/1 resection of stage II–III thymoma
2. A similar rate of recurrence but a late survival benefit in patients who received postoperative radiotherapy or not, after complete resection of thymoma [155, 156]
3. A recurrence-free and overall survival benefit with postoperative radiotherapy after resection of thymic carcinoma [153, 154]

Stage and completion of resection are thus the most relevant criteria in the decision-making process, followed by histology; these factors are the most significant predictors of recurrence-free survival [157]. Meanwhile, one must consider that in reported retrospective analyses patients who were administered postoperative radiotherapy were likely to have incomplete resection or higher histological grade tumors. The absence of survival differences in patients who received postoperative radiotherapy or not actually suggests a role of postoperative radiotherapy to reduce or overcome the risk of recurrence in those patients. Another point to consider is that recurrences of TET occur outside the mediastinum in more than 60% of cases [158].

Current modalities of postoperative radiotherapy for TET include:

1. The use of multi-field arrangement conformal radiotherapy and three-dimensional treatment planning.
2. A clinical target volume including the whole thymic space, the tumor and its extensions, and the anterior, superior, and middle mediastinum.
3. A total dose of 45–50 Gy after complete resection and 50–54 Gy after R1 resection, with a boost on areas of concern—as mentioned, surgical clips may be then useful to plan the gross tumor volume.
4. The use of a standard fractionation scheme consisting in daily doses from 1.8 to 2 Gy over a 4- to 6-week period [159].

The field may encompass involved nodes and the site of a resected pleural implant. Prophylactic irradiation of supraclavicular nodes is not recommended.

Postoperative radiotherapy is not indicated after complete resection of Masaoka-Koga stage I thymoma. Postoperative radiotherapy is not recommended after complete resection of stage II thymoma, but may be considered in case of aggressive histology (type B2, B3) or transcapsular invasion (stage IIB). Postoperative radiotherapy is recommended after complete resection of stage III/IVA THY, to prolong recurrence-free and overall survival. After complete resection of TC, postoperative radiotherapy is optional for stage I tumors, should be considered for stage II tumors,

and is recommended for stage III/IVA tumors. Postoperative radiotherapy is recommended in case of microscopically (R1) or macroscopically incomplete (R2) resection, to a total dose of 50–54 Gy and 60 Gy, respectively, with a 10 Gy boost on areas of concern.

Systemic Therapies

Systemic treatment may be delivered in a curative-intent approach, for patients presenting with locally advanced tumor at time of diagnosis, with invasion of intrathoracic neighboring structures, and/or dissemination to the pleura and the pericardium, precluding upfront complete resection to be achieved. In such cases, chemotherapy has been used both to reduce the tumor burden—possibly allowing subsequent surgery and/or radiotherapy—and to achieve prolonged disease control [65, 149, 160]. Postoperative chemotherapy may be an option for thymic carcinomas.

Chemotherapy is also a palliative-intent treatment of unresectable, metastatic, and recurrent tumors, which are rare in THY, but more frequent in TC [65, 69, 160]. Alternative options are emerging, based on the molecular characterization of thymic malignancies, which include targeted agents and even inhibitors of immune-response checkpoint inhibitors [141].

Chemotherapy in Locally Advanced Thymic Malignancies

It is estimated that 30% of patients presents with locally advanced tumor at time of diagnosis. If complete resection is deemed not to be achievable upfront, which is the case in Masaoka-Koga stage III/IVA tumors (classified as stage IIIA/IIIB/IVA in the TNM system), after a biopsy is performed, primary/induction chemotherapy is administered, part of curative-intent sequential strategy integrating subsequent surgery or radiotherapy [65]. In this setting, cisplatin-based combination regimens should be administered; combinations of cisplatin, adriamycin, and cyclophosphamide and cisplatin and etoposide have been recommended, based on historical studies [65]. Whether histologic type—thymoma vs. thymic carcinoma—may impact the choice of chemotherapy regimen remains unclear, given the limited number of patients enrolled in available prospective studies. For thymic carcinoma, carboplatin-paclitaxel, which may represent an option in the metastatic setting, has not been assessed in locally advanced tumors. Usually two to four cycles are administered before imaging is performed to reassess resectability of the tumor.

Surgery should be subsequently offered to patients for whom complete resection is thought to be achievable; extended resections may be required. Postoperative radiotherapy is then delivered. When the patient is not deemed to be a surgical candidate—either because R0 resection is not thought to be achievable or because of

poor performance status or coexistent medical condition—definitive radiotherapy is recommended as part of a sequential chemoradiotherapy strategy [65]. One pragmatic strategy may consist in tumors with aggressive histology (type B3 thymoma and thymic carcinoma) not responding to primary chemotherapy regimen, to administer another line of chemotherapy before delivering radiotherapy.

Primary chemoradiotherapy may also be an option for type B3 thymoma and thymic carcinoma; ultimately, as in locally advanced non-small-cell lung cancer, the optimal sequence of the multimodal approach has to be based on response to chemotherapy, level of invasion, and chance of achieving complete resection.

Postoperative chemotherapy is not recommended after R0-R1 resection of a THY, but may be discussed in TC. Postoperative chemotherapy (including cisplatin, etoposide chemotherapy) with or without radiotherapy (up to a total dose of radiation of 60 Gy) may also be considered after debulking/R2 resection.

Chemotherapy in Advanced Thymic Malignancies

Chemotherapy is offered as the single modality treatment in advanced, non-resectable, non-irradiable, or metastatic (stage IVB) TET to improve tumor-related symptoms. The aim is to improve tumor-related symptoms through obtaining tumor response, while prolonged survival is uncertain [160]. Cisplatin-based combination regimens with anthracyclines and/or etoposide are standard. No randomized studies have been conducted, and it is unclear which regimens are best; multi-agent combination regimens and anthracycline-based regimens appear to have improved response rates compared to others, especially the etoposide, ifosfamide, and cisplatin combination [161]. However, the effect of corticosteroids to deplete the lymphocytic component of THY, without any antitumor effect, may significantly impact radiological response assessment and hamper comparisons between chemotherapy regimens. Combination of carboplatin and paclitaxel is an option for TC, based on results of recent phase II trials; meanwhile, limited data in the literature have been reported with the platin, adriamycin, and cyclophosphamide regimen in advanced TC.

Chemotherapy for Recurrences

Recurrences of TET should be managed using the same strategy as newly diagnosed tumors. Complete resection of recurrent lesions represents the major predictor of favorable outcome [162], and surgery is then recommended in case of resectable lesion. In non-resectable recurrences, several consecutive lines of chemotherapy may be administered when the patient presents with tumor progression. The re-administration of a previously effective regimen has to be considered, especially in case of previous response, late-occurring recurrence, and, for anthracyclines, in a patient in a good medical condition and not having received cumulative doses precluding the safe delivery of at least three additional cycles. Preferred regimens for

second-line treatment include doublets such as carboplatin plus paclitaxel and platin plus etoposide; capecitabine plus gemcitabine is an option, especially for TC. These regimens were evaluated in dedicated phase II trials. Options for subsequent lines are single-agent regimens: pemetrexed (500 mg/m^2/3 weeks) [26], oral etoposide (100 mg daily). In patients with octreoscan-positive thymoma, not eligible to receive additional chemotherapy, octreotide alone (1.5 mg daily) or with prednisone (0.6 mg/kg daily) may represent a valuable option, when stable disease is the objective.

Targeted Agents

KIT Inhibitors

While KIT is overexpressed in 80% of TC, KIT gene mutations are found in 9% of cases, consisting of mutations observed in other malignancies (V560del, L576P) or mutations unique to thymic carcinomas (H697Y, D820E) [141]. Responses and possibly prolonged survival were reported with the use KIT inhibitors, imatinib, sunitinib, or sorafenib, mostly in single-case observations. Non-pretreated reported KIT mutants are not uniformly sensitive to imatinib, based on the clinical and/or the preclinical evidence in TC and/or other KIT-mutant malignancies. KIT sequencing (exons 9–17) is an option for refractory TC in the setting of possible access to off-label use of such inhibitors.

Antiangiogenics

KIT inhibitors also potently inhibit other kinases, including vascular endothelial growth factor receptors, largely expressed in TET [163], and platelet-derived growth factor receptors activated in thymic malignancies. In this setting, a phase II trial recently demonstrated the efficacy of sunitinib (50 mg daily, 4 weeks on treatment, 2 weeks off) in terms of response and disease control rate in TET, including TC (ORR 26%; DCR: 91%) and, to a lesser extent, THY (ORR:6%; DCR:81%); median progression-free survival was 7.2 and 8.5 months, respectively [164].

mTOR Inhibitors

mTOR is emerging as a potential target in TET, following tumor responses observed in phase I trials. Everolimus (10 mg daily) was evaluated in TET in a recently reported phase II trial reporting on a 22% response rate, as well as a 93% disease control rate [165]. Everolimus may then represent an option for refractory tumors, especially TC, based on recent biological data, showing the frequent occurrence of PI3K pathway activation in those tumors.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors represent a new era in the treatment of solid tumors. A phase II study of pembrolizumab, a fully humanized IgG4 Ab that targets the PD-1 receptor, is currently ongoing in patients with TC [166]. As expected, any history of autoimmune disease or other malignancies requiring treatment are exclusion criteria. Pembrolizumab is given at 200 mg every 3 weeks. Out of 30 patients, 4 developed serious autoimmune disorders: 2 cases of polymyositis and myocarditis, with complete recovery with steroids; 1 case of diabetes mellitus; and 1 case of bullous pemphigoid. Response rate was 24%: there were 1 complete response, 5 partial responses, and 10 patients with stable disease. In a routine practice setting, the off-label use of pembrolizumab may be considered with a baseline extensive workup for autoimmunity and a close follow-up of patients by expert teams. Other trials have shown similar outcomes. Meanwhile, patients may be eligible to ongoing clinical trials, such as EORTC 1525 NIVOTHYM, a phase II trial assessing nivolumab in refractory type B3 thymoma and thymic carcinoma.

Rare Tumors and Networks

The management of patients with thymic malignancy requires continuous multidisciplinary expertise at any step of the disease. A dramatic improvement in our knowledge has occurred in the last few years, through the development of databases, translational research programs, and clinical trials [167–170]. While access to innovative strategies represents a major challenge, as the rarity of the tumor precludes specific approval of drugs to be obtained, patient-centered initiatives, such as the establishment of dedicated networks, are warranted. International societies provide infrastructure for global collaboration, and there are many advantages to having strong regional groups working on the same issues. There may be regional differences in risk factors, susceptibility, management, and outcomes. The ability to address questions both regionally as well as globally is ideal to develop a full understanding of thymic malignancies.

National Networks

In France, RYTHMIC (Réseau tumeurs THYMiques et Cancer; www.rythmic.org) is a nationwide network for thymic malignancies, which was appointed in 2012 by the French National Cancer Institute, as part of its rare cancer program [171]. Since then, the management of all patients diagnosed with thymic tumors has been discussed on a real-time basis at a national multidisciplinary tumor board (MTB), which is organized on a twice-a-month basis using a web-based conferencing

system. Decision-making is based on consensual recommendations that were originally established in accordance with available evidence and are updated and approved each year by all members of the network [172, 173]. A prospective database of all patients is hosted by the French Cooperative Thoracic Intergroup. Overall, more than 2000 patients have been enrolled, demonstrating the feasibility of a national MTB for thymic malignancies that, besides ensuring patients' equal access to highly specialized management, provides a comprehensive tool to monitor dedicated actions to improve the management of patients and enroll patients in clinical trials. Similar thymoma-dedicated and mesothelioma-dedicated networks are now being implemented in France and in other European countries, such as Spain and Italy (the TYME collaborative group) [174]. Outside Europe, the Chinese Alliance for Research in Thymomas (ChART) and the Japanese Association for Research on the Thymus (JART) are national groups aiming at building and analyzing retrospective and prospective databases of thymic tumor cases [169, 170].

International Networks and TET

The International Thymic Malignancies Interest Group (www.itmig. org) was created in 2010 and was endorsed and supported by the most representative medical and surgical societies around the globe [168]. The mission of ITMIG is to promote the advancement of clinical and basic science related to thymic malignancies. It provides infrastructure for international cooperation, maintains close collaboration with other related organizations, and facilitates the spread of knowledge about thymic neoplasms. The achievements of ITMIG include:

1. The development of standard definitions based on multidisciplinary consensus, regarding outcome measures, handling of surgical specimens, staging, surgical techniques, radiotherapy, and chemotherapy
2. A significant contribution to the 2015 WHO histopathological classification update
3. The establishment of an international, retrospective database of nearly 10,000 cases that has been a resource for descriptive studies, mostly driven by US-based investigators, as well as for the development of the 2016 TNM-based staging system as a backbone for the survival analyses of clusters of patients [175]

   A prospective database linked to a virtual tumor bank is underway.

European Networks

Research on mesothelioma and thymic malignancies has historically been driven by thoracic surgery societies, including the European Society of Thoracic Surgeons and the European Association for Cardio-Thoracic Surgery (EACTS); especially,

the ESTS published multiple analyses on a retrospective cohort of patients and is currently establishing a prospective database.

The European Society for Medical Oncology recently published the first multidisciplinary, comprehensive clinical practice guidelines for the management of mesothelioma and thymic tumors, integrating all the aspects of the management of the disease; from the diagnosis to the follow-up of patients, the level of evidence of thymic tumor recommendations is far lower than that of guidelines for non-small-cell lung cancer and mesothelioma [65].

Within the European Reference Network EURACAN (http://euracan.ern-net.eu), the rare thoracic tumor domain—referred as to G8 domain—handles a network of 20+ healthcare providers; the objectives of EURACAN include the updating and the assessment of current guidelines, the development of educational programs, dissemination and communication with patients groups, and the establishment of research projects, from the diagnosis workup of the disease to the therapeutic strategies. Achieving the highest quality of patient care is the main objective of EURACAN, and the RYTHMIC model provides some practical tools to be implemented at the European level. The European network also provides an infrastructure for collaboration with diagnosis and pharmaceutical companies; one example may be the opening of dedicated cohorts in basket studies assessing new drugs, for which the network allows a better identification of patients and facilitates the recruitment in the trials.

In Europe, through the integration of national networks with EURACAN, the collaboration with academic societies and international groups, the development of networks in thoracic oncology is expected to provide better integration of clinical care and research, ultimately ensuring equal access to high-quality care to all patients, with the opportunity of conducting high-level clinical and translational research projects.

Conclusions: Perspectives in TET Diagnosis and Treatment

In the past century, several researchers (among them pathologists, immunologists, thoracic surgeons radiologists, and oncologists) established the setting for a modern thymus era. Molecular genetic knowledge of TET is increasing. In this framework, several scientific organizations all around the world from Japan (JART), Europe (ESTS), and China (ChART), the International Thymic Malignancy Interest Group (ITMIG), and now the EURACAN G8 network were recently able to drive the interest and willingness to construct extensive and multidisciplinary collaborative networks. As unique example among rare tumors, the extraordinary worldwide-based collaboration provided the opportunity for fundamental advances in the knowledge and treatment of TET.

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Chapter 10
Primitive Mediastinal Germ Cell Tumors: An Update

Andrea Ronchi, Federica Zito Marino, Gaetano Facchini, Marina Accardo, and Renato Franco

General Features

Mediastinal germ cell tumors (MGCTs) are a group of mediastinal neoplasms that are morphologically characterized by the presence of neoplastic cells similar to germ cells or by the formation of embryonal or adnexal tissues. According to the 2015 WHO classification, MGCTs consist of *seminomatous* and *non-seminomatous* type. The former includes only classical seminoma. Spermatocytic seminoma, a variant of seminoma observed in the testis, has never been described in the mediastinum. The latter includes embryonal carcinoma, yolk sac carcinoma, choriocarcinoma, and teratoma [1]. MGCTs are sometimes composed by two or more histotypes coexisting in the same neoplasm and are referred as *mixed MGCTs* [1]. MGCTs are rare, affect all age groups, and represent up to 16% of all mediastinal neoplasms in adults and 19–25% in pediatric population (<18 years) [2]. The frequency of every single histological type of MGCTs is widely variable according to age and sex of patients. Teratoma is by far the most

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common MGCTs in the prepuberal patients regardless of the sex, as pure form or mixed form, especially in combination with yolk sac carcinoma [3]. In postpubertal patients, the distribution of MGCT histotypes depends on sex: in females, teratoma represents up to 90% of all MGCTs, while in males the distribution is more equilibrated, and the most common forms include teratoma, seminoma, mixed tumors, and yolk sac carcinoma [3]. Epidemiological distribution of MGCTs is represented in Fig. 10.1. Mixed MGCTs account for 16% of all MGCTs and occur almost exclusively in male patients [4]. In pediatric population, the most frequent combination is by far mature or immature teratoma and yolk sac tumor (see Fig. 10.2). In adult population there is a greater morphological variability, and the most frequent components are teratoma (immature more frequent then mature) and embryonal carcinoma. However all the other histotypes may be observed in various combinations [3].

The etiology of MGCTs is substantially unknown. In the same way, it is substantially unknown why the mediastinum is a preferential site for the development of neoplasms classically located in the gonads. According to the classical hypothesis, these neoplasms derive from a wrong midline migration of germ cells during the embryogenesis [5]. The thymus would be particularly prepared to accommodate the germ cells due to the expression of KIT ligands, involved in proliferation and survival of primordial germ cells [6]. Non-seminomatous MGCTs are more common in Klinefelter's syndrome [7]. Although pathogenesis of MGCTs is still substantially unknown, genetic analysis has provided an improved understanding of the biological substrate of these neoplasms. Gains of chromosome arm 12p and aneuploidy are almost constantly observed in gonadal and mediastinal GCTs [8]. Chromosome 12 abnormalities have been demonstrated in 96% of mediastinal seminoma specimens, with 87% resulting in 12p overexpression [8]. There are limited data on the genetic alterations responsible of non-seminomatous GCTs. The most common chromosomal abnormality is an increased copy number of chromosome 12p usually in the form of an isochromosome [9, 10]. A recent study based on whole-exome and transcriptome sequencing analysis showed that primary somatic features of GCTs include highly recurrent chromosome arm-level amplifications, reciprocal deletions, and K-RAS mutations [11].

MGCTs remain clinically asymptomatic for a long time and are often accidentally noticed during radiological examinations performed for other causes. Presenting symptoms are related to the compression of the adjacent anatomical structures and include dyspnea, cough, hoarseness, and chest pain. If the neoplasm reaches large dimension, it may cause mediastinal syndrome. Paraneoplastic symptoms are very rare, but some cases of presumed paraneoplastic encephalitis have been reported [12].

Serum tumor markers are frequently elevated in MGCTs and play an important role for both diagnostic and management purposes. The serum markers most commonly elevated in patients with MGCTs are αFP, β-hCG, and LDH. In particular, αFP is never elevated in patients with pure seminoma, while it is frequently elevated in non-seminomatous GCTs (10–20% in stage I, 20–40% in low-volume stage II,

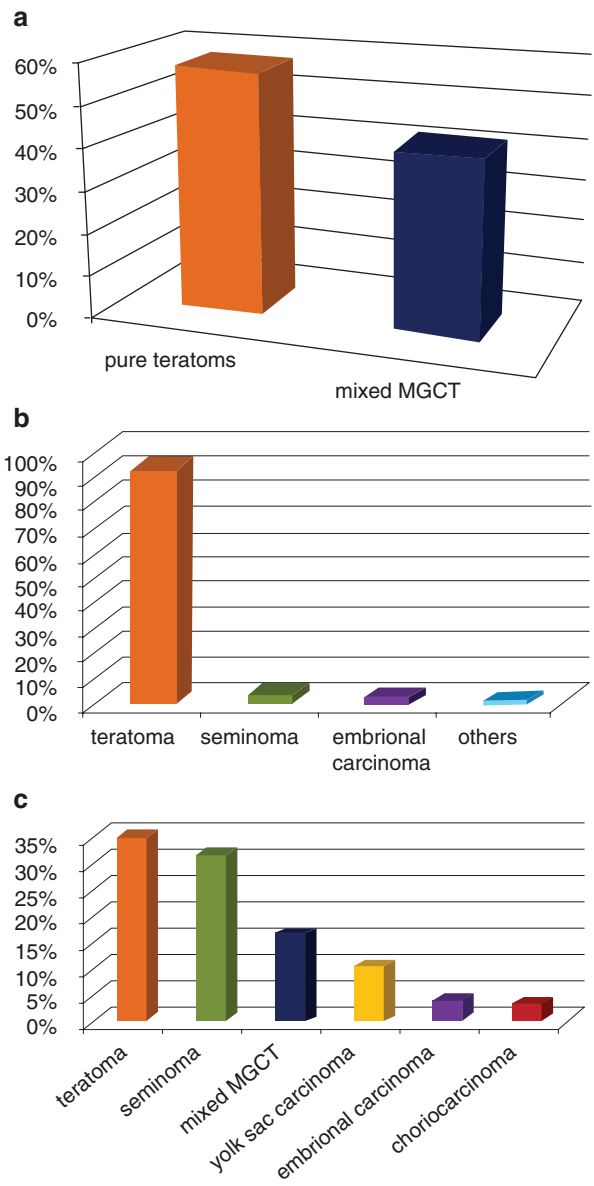

Fig. 10.1 Relative frequencies of MGCTs in clinical subsets. (**a**) Prepuberal patients regardless of the sex. (**b**) Postpubertal female patients. (**c**) Postpubertal male patients [1]

40–60% in advanced disease) [13]. Almost all patients with pure embryonal carcinoma or mixed MGCT with a component of embryonal carcinoma present elevated serum αFP. β-hCG may be elevated in both pure seminoma (15–20% in advanced disease) and non-seminomatous GCTs (10–20% in stage I, 20–30% in low-volume stage II, 40% in advanced disease) [13]. LDH is elevated in 40–60% of

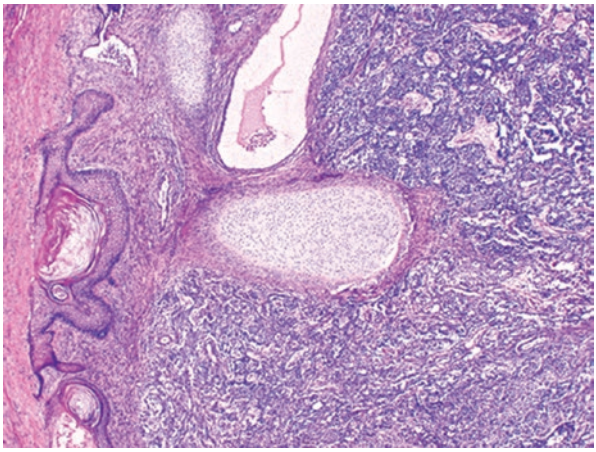

Fig. 10.2 Mixed mediastinal germ cell neoplasm constituted by mature teratoma (on the left) and yolk sac tumor (on the right)

patients with GCTs regardless of the histological type. Caution must be however placed in the interpretation of serum markers, because numerous neoplastic and non-neoplastic conditions can determine their increase. The International Germ Cell Cancer Collaborative Group (IGCCCG) system recommends the use of serum tumor markers to stratify the risk and monitor the treatment of patients with non-seminomatous GSTs but not for patients with seminoma [14].

MGCTs are on average chemo- and radiosensitive neoplasms, so the treatment is primarily based on neoadjuvant chemotherapy and radiotherapy, followed by surgical consolidation in selected cases with residual mediastinal mass. The sample available for primary diagnosis is therefore almost always represented by incisional biopsy or cytology (see Fig. 10.3). As teratoma is not much chemosensitive, it's a frequent event in the case of mixed MGCTs, after chemotherapy, the observation only of the teratomatous component in the primary mass. In the same way, metastasis from mixed MGCTs frequently shows just a teratomatous morphology. This is sometimes observed even in case of pure MGCT; in these instances, a misunderstood primary diagnosis of mixed tumor or a post-therapy differentiation is hypothesized [15].

Patients affected by MGCTs do not present a higher risk of gonadal germ cell tumors, but an association with hematological malignancies has been reported [16, 17]. Prognosis is strictly related to histological type: seminomatous MGCTs have a long-time survival rate of about 90%, whereas non-seminomatous types have a 5-year survival rate of about 45% [18]. MGCTs have a worse prognosis than gonadal counterparts [18]. Non-seminomatous histology, primary mediastinal location, presence of non-pulmonary visceral metastases, and elevated beta-hCG are independent prognostic factors for shorter survival [18].

In rare instances a somatic-type solid malignancy may develop in the context of a MGCT. This event seems to be more frequent in MGCTs than in gonadal counterparts. The majority of cases is observed in adult males, mainly in the setting of pure teratoma or mixed MGCT. Somatic malignancies include sarcomas (mainly embryonal

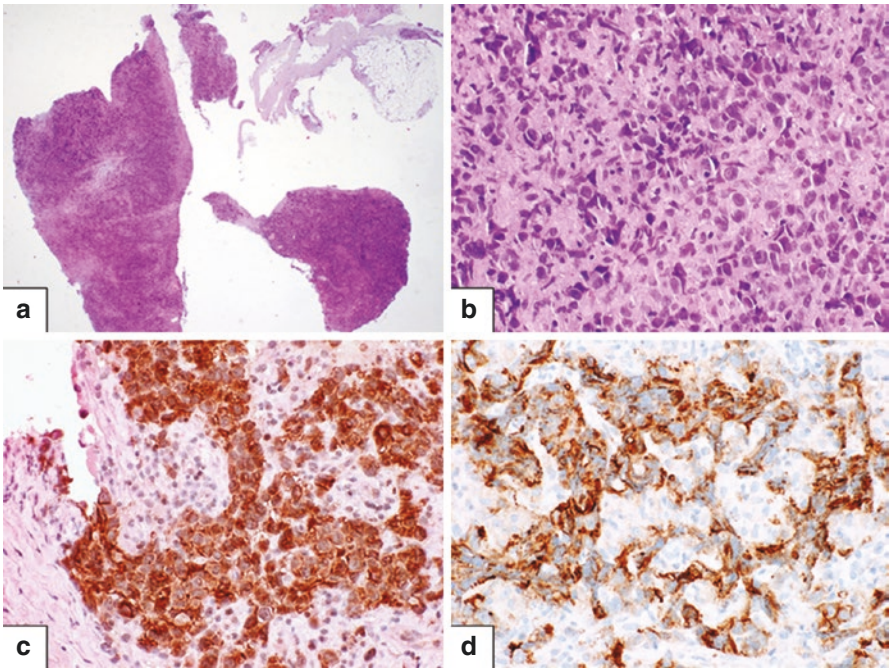

Fig. 10.3 Biopsy sample of a mediastinal seminoma constituted by small fragments (**a**). These samples are often subject of intraoperative examination for rapid on-site evaluation (ROSE) of adequacy. An adequate sample should allow the recognition of morphological features of the neoplastic population and the realization of a sufficient immunohistochemical panel. This example shows large cells with indistinct borders and roundish nuclei (**b**). Immunohistochemically, the cells are positive for CD117 (**c**) and PLAP (**d**)

rhabdomyosarcoma, angiosarcoma, leiomyosarcoma, and neuroblastoma) and carcinomas (mainly intestinal-type adenocarcinoma). The occurrence of a somatic malignancy makes the prognosis worse with a median survival of 9months [18]. A particular type of somatic malignancies associated with MGCTs is represented by hematological malignancies. About 1% of patients (almost exclusively young male patients) affected by MGCTs develop a hematological malignancy clonally related to the germ cell neoplasm [16]. The hematological disorders may develop either in the context of the mediastinal neoplasm or in lymphatic organs or in bone marrow and include acute leukemias, histiocytic sarcoma, myelodysplastic syndromes, myeloproliferative disorders, and mastocytosis [16]. The pathogenetic correlation between MGCTs and hematological disorders is poorly understood. It is hypothesized that hematological neoplasm origins from the differentiation of a primordial germ cell or from an area of intratumoral extramedullary hematopoiesis [19]. Interestingly, this peculiar association has been observed only in mediastinal neoplasms, while it never occurs in the gonadal counterparts. The underlying MGCT is constituted by yolk sac tumor or mixed MGCT in the large majority of cases [20].

Seminoma

Mediastinal seminoma occurs in the anterior mediastinum and represents 3–4% of all mediastinal neoplasms [21]. It is the second most common MGCT in postpubertal male patient after teratoma, corresponding to 32% of cases in this setting, while it is rare in prepuberal patients regardless of the sex and in postpubertal female patients [1]. Most cases present as localized mass at the time of primary diagnosis, but about 40% of patients subsequently develops distant metastasis [18]. The most frequent sites of metastasis include lymph nodes, lung, pleura, brain, liver, adrenal glands, and bones [21]. Macroscopically, mediastinal seminoma is a well-circumscribed mass with a vaguely lobulated, tan-gray or pink cut surface. Tumor size is quite variable, ranging from 1 to 20 cm [22]. Histological features of mediastinal seminoma are the same as gonadal counterparts (see Fig. 10.4). Architectural pattern is mainly lobular, with incomplete thin fibrous septa delimitating irregular neoplastic nodules, but it may include cellular sheets, cords, and strands. The neoplastic population is composed by large, round to polygonal cells with well-represented clear to lightly eosinophilic cytoplasm and roundish, centrally located, nucleus with one or more prominent nucleoli. A lymphoid infiltrate is a common finding, and it is mainly constituted by small mature lymphocytes with a variable number of plasma cells and eosinophils. This infiltrate is more often present in the thickening of the fibrous septa but may be intermingled with the neoplastic cells. In some circumstances the neoplastic population can be obscured or replaced by an extensive fibrotic reaction. In such cases an extensive sampling of the mass is mandatory to find the residual neoplastic component. Some scattered syncytiotrophoblastic cells can be present, especially in cases with the rise of B-hCG. These cells have to be distinguished from multinucleated giant cells of a possible granulomatous reaction, which is often present. Cytological samples of mediastinal seminoma are characterized by a dispersed cell population constituted by large cells with round

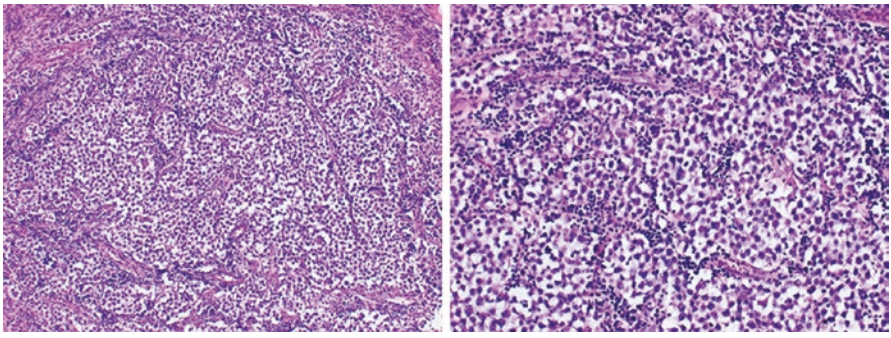

Fig. 10.4 Morphological features of seminoma. The neoplastic population is arranged in irregular nests partially demarcated by thin fibrous septa containing small lymphocytes. Neoplastic cells are large elements with slightly eosinophilic cytoplasm, roundish nuclei with one or more prominent nucleoli

Table 10.1 Immunohistochemical findings of MGCTs

Histotype	CK	αFP	βhCG	CD117	PLAP	CD30	OCT4	SALL4	Glypican 3
SE	Neg[a]	Neg	Neg[b]	Pos	Pos	Neg	Pos	Pos	Neg
EC	Pos	Neg	Neg[b]	Neg	Neg	Pos	Pos	Pos	Neg
YSC	Pos	Pos	Neg[b]	Neg	Pos	Neg	Neg	Pos	Pos
PT	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
CHC	Pos	Neg	Pos	Neg	Neg	Neg	Neg	Pos[c]	Pos/Neg

MGCTs mediastinal germ cell tumors, *SE* seminoma, *EC* embryonal carcinoma, *YSC* yolk sac tumor, *PT* pure teratoma, *CHC* choriocarcinoma
[a]Dot-like positivity can be observed
[b]Syncytiotrophoblastic cells are positive, if present
[c]Positive in mononuclear trophoblastic cells

nuclei, finely granular chromatin and one or more nucleoli. The background is classically described as "tigroid," because of the presence of variable numbers of lymphocytes and plasma cell; epithelioid histiocytes are a possible feature [23]. Immunohistochemically, seminoma shows positivity for PLAP, OCT4, SALL4, and c-kit (CD117). β-hCG is negative but can be positive in syncytiotrophoblastic cells, if present. Although keratins are usually negative, a dot-like staining pattern can be observed; αFP and CD30 are negative [1]. Immunohistochemical features of MGCTs are summarized in Table 10.1.

Embryonal Carcinoma

Mediastinal embryonal carcinoma occurs in the anterior mediastinum and is a rare neoplasm, representing about 2% of all MGCTs [2]. Most of cases affect young adult males, while it is very rare in females and in children [2]. Most cases are at least locally advanced at the time of the diagnosis. Infiltration of the lung and distant metastasis are common events. The most common metastasis locations include the lung, liver, brain, and bones, while lymph node metastases are uncommon [2]. Macroscopically, embryonal carcinoma is a large mass, often with signs of infiltration of adjacent mediastinal soft tissue or lung parenchyma. The cut surface is generally gray or white frequently with large areas of necrosis and hemorrhages. Histologically, embryonal carcinoma presents a variable architectural pattern. A solid, undifferentiated pattern is a common finding, but glandular or papillary patterns are usually at least focally present. These "epithelial" features are important for differential diagnosis from seminoma, and a wide sampling of the neoplasm is consequently mandatory. Coagulative necrosis is variably present, as large irregular areas or microscopic multiple foci. The neoplastic cells are large and polygonal, with indistinct cellular borders. A columnar shape may sometimes be evident. Cytoplasms are more often amphophilic but may be basophilic, eosinophilic, or clear. Nuclei are large and roundish with vesicular chromatin and evident eosinophilic nucleoli (see Fig. 10.5). Some scattered syncytiotrophoblastic cells can be present, while

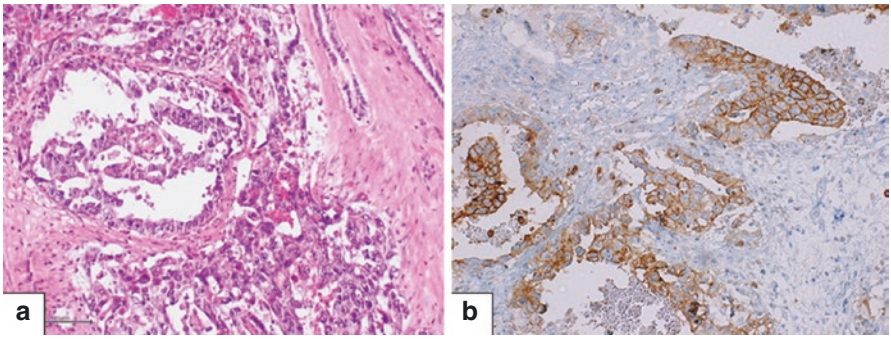

Fig. 10.5 Embryonal carcinoma. (**a**) Neoplastic population is arranged in irregular, poorly formed pseudoglandular elements. Hemorrhagic microspots are evident. Neoplastic cells show large and atypical nuclei with vesicular chromatin and evident nucleoli. Mitotic figures are present. (**b**) CD30 immunostain

granulomatous reaction is rare. Cytological samples of embryonal carcinoma usually show a highly cellular population arranged in sheets or tridimensional clusters. The cells are large and pleomorphic with large nuclei and evident nucleoli. Necrotic debris may be present. The cytological features may be different to differentiate from a poorly differentiated carcinoma of other histogenesis, and immunohistochemical study is mandatory. Immunohistochemically, embryonal carcinoma stains positive for OCT4, low-molecular-weight keratins, and CD30. CD30 is positive in about 85–100% of cases and is an important treatment target for biological therapy, but its expression can be lost during the chemotherapy [24]. αFP is usually negative but can be positive in single cells or small cellular clusters in a minority of cases; B-hCB is negative but can be positive in scattered syncytiotrophoblastic cells; CD117 expression is infrequent, but some cases have been reported [25].

Yolk Sac Tumor

Yolk sac tumor occurs in the anterior mediastinum and is one of the most common MGCTs, with an incidence depending on age and sex of patients [1]. In prepuberal population, YST is the most common malignant MGCTs and the second most common MGCT after teratoma. In adult population, YST represents about 10% of all MGCTs in male patients, while it is very rare in female patients [26]. Almost all cases are at least locally advanced disease at the time of primary diagnosis, with extension to the adjacent fat tissue and lung parenchyma [27]. Distant metastases are relatively frequent, and the most common localizations include the lung, lymph nodes, liver, bone, and brain [2]. Macroscopically, YST is a large mass with a whitish cut surface often presenting gelatinous areas. Hemorrhagic areas and necrosis are relatively frequent, especially in cases removed after neoadjuvant treatment. Histological features of YST are quite variable and include several possible architectural patterns which

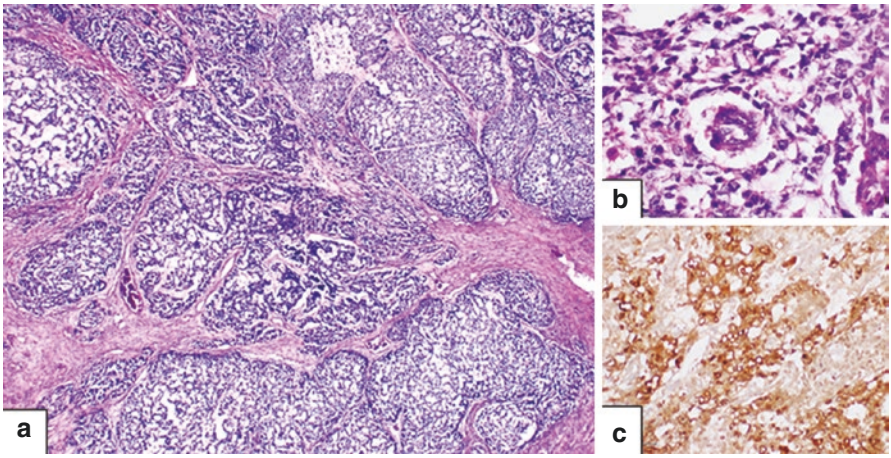

Fig. 10.6 Yolk sac tumor. (**a**) Prominent reticular/microcystic architectural pattern. (**b**) Schiller-Duval body. (**c**) αFP immunostain

often coexist in the same tumor. Most common patterns include reticular/microcystic and pseudopapillary/endodermal sinus. The reticular or microcystic variant is characterized by small cystic spaces and a loose network of irregular channels. Pseudopapillary/endodermal sinus variant shows pseudopapillary structures with the presence of Schiller-Duval bodies. These latter are glomeruloid structures consisting of a roundish cavity circumscribed by germ cells containing a central small vessel covered by another layer of germ cells (see Fig. 10.6). Schiller-Duval bodies are present in about 50% of cases and are almost pathognomonic of YST. Other architectural patterns include glandular, myxomatous, hepatoid, enteric, and solid. The neoplastic cells are medium- or large-sized cells with moderate to abundant cytoplasm and roundish nucleus with irregular chromatin pattern and prominent nucleolus. Nuclear atypias are variably present and more often are focal. Some scattered syncytiotrophoblastic cells can be present, while granulomatous reaction is rare. Cytological samples of YST consist of aggregates of large cells with clumped chromatin and small nucleolus. Debris and metachromatic material are usually present in the background, while lymphocytes are not present. Immunohistochemically, YSTs are positive for cytokeratins (in most cases with a dot-like staining pattern), SALL4, and glypican 3 [28, 29]. The majority of cases are positive for αFP and PLAP. Immunostaining for CD117 and CD30 is variable and most often negative [30].

Teratoma

Teratoma is a germ cell neoplasm characterized by the formation of variable somatic tissues derived from two or three germ layers [1]. Teratoma occurs in anterior and posterior mediastinum and is the most common extragonadal germ cell tumor in

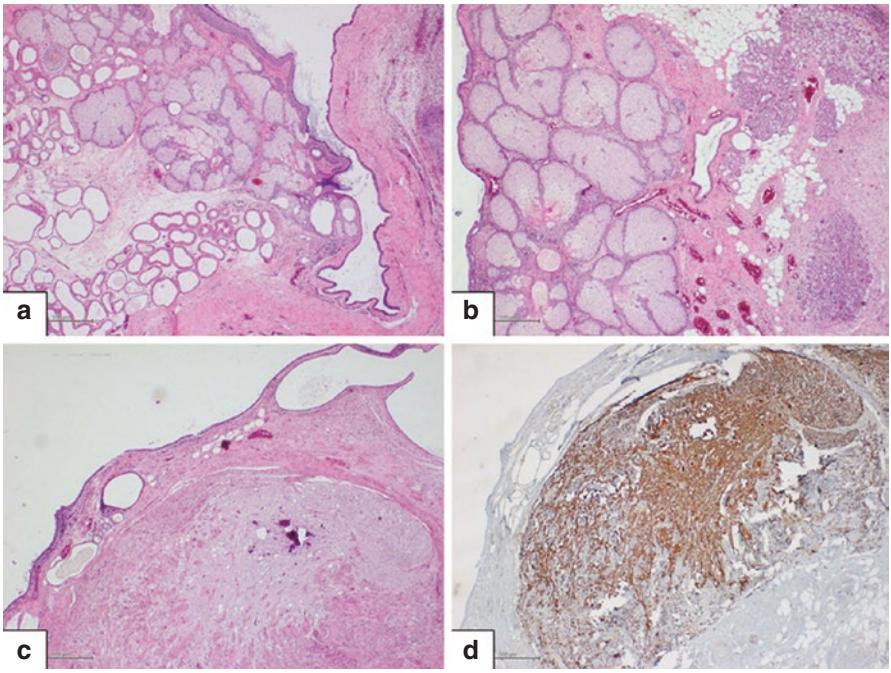

Fig. 10.7 Mature teratoma. (**a**, **b**) The tumor is composed by several mature tissues including squamous and columnar epithelium, hair, sebaceous, and sweat glands. (**c**) Mature nervous tissue. (**d**) S100 immunostain

both prepuberal and postpubertal patients regardless of the sex, accounting for 15% of all mediastinal masses in adults and 25% in children [2]. Mediastinal pure teratoma is a localized neoplasm without neoplastic spread. Macroscopically, the mass appears well-demarcated and encapsulated. The cut surface is variegated depending on the histological components and often comprises soft or fleshy areas, corresponding to fibrous and cartilaginous components, and cystic areas filled with serous, mucoid, or keratinaceous debris. Hair, fat, teeth, or bone is sometimes present. Histological appearance of teratoma is quite variable and characterized by the presence of different somatic tissue in a haphazard distribution. *Mature* teratoma is composed by adult-appearing tissues, which may include skin and adnexa, respiratory mucosa, pancreatic glands, nervous tissue, muscle, fat, cartilage, bone, and teeth. Other tissues are rarely present (see Fig. 10.7). *Immature* teratoma is composed by fetal-appearing tissues, which usually consist of neuroectodermal tissue forming tubules and rosettes. Other fetal tissues are rarely present and include primitive mesenchymal tissue, cartilage, bone, rhabdomyoblasts, and others. Although immunohistochemistry is generally unnecessary for diagnosis of teratoma, it may play a role in the characterization of the immature components. The most useful markers in this setting include S100 and synaptophysin (for neural components), desmin and myogenin (for muscle components), and S100 and glial fibrillary acidic

protein (for cartilaginous components) [1]. Pure mediastinal teratoma has generally a good prognosis in all age groups after the complete resection of the neoplasm. The presence of fetal-type tissues does not seem to affect the prognosis [26].

Choriocarcinoma

Choriocarcinoma is a germ cell neoplasm constituted by trophoblastic tissues. Mediastinal pure choriocarcinoma is an exceedingly rare neoplasm occurring in anterior or posterior mediastinum of adult male patients [2]. Some patients present paraneoplastic symptoms like gynecomastia and thyrotoxicosis [31]. Macroscopically, choriocarcinoma is a poorly demarcated mass with extensive hemorrhagic and necrotic areas. The neoplasm usually infiltrates the mediastinal structures at the time of the diagnosis [26]. Histologically, choriocarcinoma is constituted by syncytiotrophoblastic and cytotrophoblastic cells in variable proportion. Syncytiotrophoblasts are large multinucleated cells with abundant cytoplasm and numerous pleomorphic nuclei. Cytotrophoblasts are mononuclear cells with clear or eosinophilic cytoplasm, roundish nuclei, and prominent nucleoli. Because of the natural tendency of trophoblastic cells to reach to the vessels, choriocarcinoma is a largely vascularized neoplasm with dilated vascular sinusoids and abundant hemorrhagic lacunae. Immunohistochemically, choriocarcinoma cells express cytokeratins, hCG, glypican 3, and inhibin [28]. SALL4 is usually positive only in the mononucleated cells [1]. OCT4, PLAP, αFP, CEA, CD30, and vimentin are negative [1]. Mediastinal choriocarcinoma is a highly aggressive neoplasm with a poor prognosis [2].

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Chapter 11
Thyroid

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Substernal Goiter

Substernal goiter (SG) accounts for 3–12% of mediastinal masses [1, 2]. There is no widely accepted definition of SG. The most commonly accepted definition of SG is a goiter with more than 50% of its mass lying below the thoracic inlet [3–8]. The reported incidence of SG ranges from 2% to more than 20% [4].

SGs can be classified into **primary substernal goiter** and **secondary substernal goiter**. The **primary substernal goiter** also called aberrant or ectopic or isolated mediastinal goiter is a very rare, congenital entity, comprising 1–3% of SGs [9–11]. This entity may be due to an embryological fragmentation of the thyroid as a result of the dislocation of the thyroid that rests into the mediastinum by the descent of the hearth and great vessels [12, 13]. Another explanation is that it may form through a progressive enlargement of exophytic nodular thyroid tissue with an ultimate disappearance of the nodule-thyroid connection over time [12, 14, 15]. Primary SGs lack a direct connection to the cervical thyroid gland and receive its blood supply from the thoracic vessels including the internal mammary artery, the innominate artery, or directly from the intrathoracic aorta [16]. For this reason, such goiters need a thoracic approach to be removed.

The **secondary substernal goiter** is a much more common clinical condition, also called acquired SG. It develops from the cervical goiter as a result of inferior

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growth into the mediastinum, where the negative pressure facilitates its descent. The secondary SG receives its blood supply from the inferior thyroid artery in the neck.

Most of the SGs are located in the anterior mediastinum. Posterior mediastinal goiters with retro-tracheal and retro-oesophageal extension account for 10–15% of all intrathoracic goiters. Nearly all posterior SGs occur on the right side since the great vessels prevent the thyroid mass from descending on the left side.

The anterior SGs are localised anterior to subclavian and innominate vessels and the recurrent laryngeal nerve (RLN), as in the cervical thyroid gland.

Up to 90% of patients with an SG complain respiratory symptoms due to airway compression. Dysphagia due to compression of the oesophagus is common in the posterior mediastinal goiters.

On physical examination an enlarged cervical thyroid gland can be found; the caudal extent of thyroid mass can't be appreciated; facial edema, distension of the neck veins, Pemberton's sign, and Horner's syndrome may be present.

Most SGs have a long natural history, with slow progressive growth, leading to the presentation in the fifth or sixth decade of life. The presence of compressive symptoms such as a cough, stridor, dyspnea, dysphagia, or radiological evidence of tracheal and/or oesophageal compression should be considered as absolute indications for resection [17].

In patients with asymptomatic SGs, the main treatment options are surgery or observation with monitoring. The authors of this topic and others recommend surgery for most patients with asymptomatic substernal goiters that reach the level of the brachiocephalic vein [1, 8, 18–21]. However, other experts prefer observation with monitor for asymptomatic SGs.

Some arguments for removing an asymptomatic substernal goiter are as follows: (a) a percentage as high as 42% of SGs with evidence of upper airway obstruction on flow-volume loops are asymptomatic [22]; (b) generally SGs continue to enlarge and can become more difficult to be removed if obstructive symptoms occur; and (c) the mediastinal component could contain a cancer that cannot be monitored or biopsied. Finally, as patients age, surgical complications are more common and severe [8, 23, 24].

The majority of SGs, as the cervical goiters, are benign. The incidence of malignant transformation of SG is reported to be equivalent to those located entirely in the neck [22]. Most are differentiated thyroid cancers, with good prognosis, but more aggressive carcinomas may occur, such as anaplastic carcinoma or poorly differentiated thyroid cancer.

Workup for SG

The initial evaluation of substernal goiter includes thyroid function tests, imaging studies, and airway assessment. **Thyroid function tests** include serum TSH to evaluate for subclinical or overt hyperthyroidism, as well as to exclude hypothyroidism. Hyperthyroidism in SGs ranges from 1.3 to 7%, but rates of 44% have been reported [15].

Imaging studies include noncontrast computed tomography [CT] or magnetic resonance imaging [MRI], to evaluate the extent of the goiter and its anatomical relationships to the surrounding structures. CT is the gold standard imaging modality in the preoperative workup of patients with SG. It is useful to assess the size and extent of the mass and to reveal tracheal and esophageal compression or vascular involvement. Such information is of critical value to plan the appropriate surgical treatment. A preoperative CT allows the quantification of the thoracic component of the goiter and its shape and position. Preoperative thyroid gland volume estimation by CT may be used to predict the need for a thoracic approach [23] The presence of an extension below the aortic arch or into the posterior mediastinum and a mediastinal component that is wider than the thoracic inlet can be all associated with the need for a thoracic approach [24]. The preoperative CT is useful not only to determine the need for a thoracic approach but also to predict whether a sternotomy or lateral thoracotomy will be necessary for removal of the SG.

Airway assessment includes determination of rate and pattern of respiration (flow-volume loop study), voice quality, and presence of sounds during breathing (i.e., stridor). Inspiratory stridor is typically associated with significant extrathoracic obstruction (commonly laryngeal, subglottic, or upper cervical trachea). Intrathoracic (lower tracheal) obstruction presents with isolated expiratory stridor; in this case, the voice and inspiration are normal.

Flow-volume loop analysis (also called a spirogram) is the most accurate and readily available pulmonary test. The flow-volume loop can aid in the diagnosis and localisation of airway obstruction [15, 25].

Tracheobronchoscopy is useful preoperatively to exclude an invasion of the tracheal wall by a malignant goiter, to document a recurrent laryngeal nerve paralysis, and to evaluate the tracheal compression [26].

Some authors suggest that a fine needle aspiration (FNA) should be included in the preoperative workup of SGs. In this regard, we believe, as well as other Authors, that FNA is not routinely indicated. The surgical indication is established by clinical history, physical examination, and CT scan evaluation. If there is a suspect of cancer in the neck component of the thyroid mass, of course, an FNA of the neck mass can be performed [27]. FNA of a mediastinal goiter should be avoided because of the risk to precipitate respiratory symptoms if bleeding occurs and because FNA results rarely add a substantial contribution to the preoperative assessment of patients with SG [15].

SG Surgery

Given the tendency to progressively enlarge and produce local symptoms, including airway compression, and the lack of other effective treatments, all patients with SGs should be considered for surgery. Total or near-total thyroidectomy should be performed.

The vast majority of acquired SGs can be resected through the standard cervical approach.

A thoracic approach is necessary for the most complex posterior mediastinal goiters, those that descend from the left lobe and cross to the right thorax, either behind both trachea and oesophagus or between the trachea and oesophagus. In the presence of malignant transformation, the mobilisation of the mediastinal component may be difficult through the cervical incision; in this case, a combined cervicothoracic approach is safest and useful even to perform the mediastinal lymph node dissection. Of course, any primary SG needs a thoracic approach to be removed.

Surgical approach: In most of the cases, surgery begins with the cervical thyroidectomy. A large Kocher's incision is recommended, and the platysmal flaps are prepared as usual. The superficial cervical fascia is incised in the midline, and the strap muscles are retracted. In the case of a huge goiter, to facilitate exposure, the strap muscles should be divided without hesitation. First, the upper pole vessels are ligated and divided; the retrosternal component must not be delivered before these vessels have been ligated. This procedure is essential to allow the subsequent upward movement of the thyroid gland from the substernal to a cervical position. The upper pole vessels should be divided individually, to avoid the risk of injury of the external branch of the superior laryngeal nerve.

Particular attention care must be taken to identify and preserve the superior parathyroid glands, as the inferior parathyroids may be challenging to be found and kept in SGs. The surgeon should be aware of this potential, and if necessary parathyroid transplantation should be made to prevent permanent hypoparathyroidism [5, 21].

The recurrent laryngeal nerve is routinely identified. Intraoperative nerve monitoring may be used as an adjunct to direct visualisation of the nerve and for prognostication of postoperative nerve function. The intraoperative management of the recurrent laryngeal nerve may be difficult because the nerve may be fixed and splayed on the surface of the goiter. For these reasons blind mobilisation of the retrosternal mass, without identification of the nerve, should be avoided. The RLN should always be identified before delivering the mediastinal component of the goiter [28].

There is an increased RLN injury risk during surgery for posterior SG because the relationship of the mass and RLN is reversed as compared with the anterior thyroid gland–RLN relationship. In the posterior SGs, in fact, because the thyroid gland extends deeply to the RLN, the nerve may be displaced anteriorly, and if not recognised, it may be stretched, even during a meticulous dissection.

After identification of the recurrent laryngeal nerve, the next step is the delivery of the mediastinal component of the goiter. By initial blunt dissection, the surgeon's finger follows the thyroid gland inferiorly into the chest and lifts the substernal component forward the neck. Then the dissection continues under vision. Morcellation or fragmentation must be avoided. After the substernal part has been elevated, the inferior vessels are divided as near as possible to the gland [5, 21, 29, 30].

In cases of very large substernal goiters, complex posterior mediastinal goiters, invasive tumours, or reoperation, a thoracic approach is needed along with a cervical approach. In most cases, a partial upper sternal split is possible, as an alternative a complete sternotomy is performed. In cases of crossed substernal goiter with an extension from a left-side gland to the right mediastinum, some authors recommend right anterolateral thoracotomy [30].

The surgical option for mediastinal exposure and technical details of thoracic surgical approaches will be treated in another section of this book (see Chap. 5).

Complication of SG Surgery

Although the majority of patients can be treated successfully with minimal morbidity and mortality, in some patients there is an increased operative risk. Substernal goiter has been reported to be an independent risk factor for postoperative complications [31–33]. A careful preoperative evaluation is critical to identify the patients at higher risk and to plan the best surgical approach. An increased risk of airway complications after thyroidectomy for SG has been reported. Old age, the weight of the thyroid gland, and preoperative tracheal compression have been reported as the factors more likely associated with postoperative airway complications [4, 23]. The most frequent postoperative complications, as for the cervical thyroid surgery, are bleeding, RLN nerve injury, and hypoparathyroidism. Severe intraoperative bleeding is reported in 0.5–5.5% of cases. Pneumothorax has been reported 1.4–5.3% of cases. Wound infection has been described in about 2% of patients. Tracheotomy has been reported in 2.1–13% of cases. More rare complication such as oesophageal laceration, atrial fibrillation, and pleural effusion has been described.

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Chapter 12
Parathyroid

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Mediastinal Parathyroid Glands

Mediastinal parathyroid glands are the result of abnormal migration of the parathyroids during embryogenesis. The parathyroid glands develop from the dorsal wing of the third and fourth pharyngeal pouches [1]. The superior parathyroids derive from the fourth pharyngeal pouch, while the inferior develop from the third one. The ventral wing of the third pharyngeal pouch gives rise to the thymus, which descends to its final position in the mediastinum. The inferior parathyroid glands follow the descending route of the thymus; this explains their ectopic location into the mediastinum [1, 2]. Due to their more extensive migration, inferior parathyroids are more often ectopic than the superior ones.

The prevalence of ectopic parathyroid glands is reported to range from 6.3 to 16% in surgical series [3–7], but a rate of 28–42% is reported in autopsy series [8, 9]. Ectopic parathyroids have been reported in up to 45% of patients with persistent/recurrent primary hyperparathyroidism [7].

About 60–80% of the ectopic mediastinal parathyroid can be found in the superior mediastinum within the thymus or at the origin of the great vessels. The remaining mediastinal parathyroids are located in the middle and posterior mediastinum in variable percentages [10].

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A supernumerary or fifth parathyroid gland is reported in 2.5–22% of the ectopic mediastinal parathyroid gland. Supernumerary glands are usually located in the upper anterior mediastinum within the thymus or perithymic fat [6, 7, 10].

Mediastinal parathyroid glands become of concern when hyperparathyroidism (primary or secondary) occurs. Parathyroid adenomas are the most common cause of primary hyperparathyroidism, accounting for about 85% of cases. They are usually solitary, but a double adenoma can be found in 2–4% of cases. Multiglandular hyperplasia is found in 15% to 20% of cases [2, 11]. Parathyroid carcinoma accounts for about 1% of the case. Rare cases of parathyroid carcinoma in mediastinal parathyroid glands have been described; there are a few reports on giant parathyroid carcinomas mimicking substernal goiter [12].

The actual prevalence of mediastinal parathyroid adenoma (MPA) is unknown but has been reported to range from 6 to 30% [13, 14]. The ectopic mediastinal parathyroid gland is the most common cause for unsuccessful operation for either primary or secondary hyperparathyroidism by experienced surgeon [15–17].

The clinical manifestation of primary hyperparathyroidism from MPA has been reported to be more severe than in eutopic parathyroid adenomas. Patients with MPA are more likely to present with higher calcium levels and more severe bone impairment. This may be due either to the prolonged, persistent hypercalcemia or the often delayed localisation of the mediastinal parathyroid adenomas [4].

Preoperative Localisation

Preoperative localization is essential for a successful mediastinal exploration for parathyroid adenomas. Although a variety of preoperative imaging techniques are available, the optimal preoperative localization study for MPA has not yet been determined.

Technetium-99m (Tc-99m) sestamibi scintigraphy has proven to be the single best imaging modality for preoperative localisation of parathyroid adenomas, with a reported sensitivity of 80–90%. For mediastinal parathyroid adenoma, the Tc-99m sestamibi scan sensitivity and specificity are reported to be lower than for the cervical parathyroid adenomas. Tc-99m sestamibi single-photon emission computed tomography (SPECT) is reported to be superior to planar imaging and in combination with computed tomography (SPECT/CT) can improve both sensitivity and specificity compared to planar scan [18, 19].

Computed tomography (CT) and magnetic resonance imaging (MRI) is useful to identify the mediastinal parathyroid tumour and provide relevant information about its anatomical location and relationship with the other structures. Four-dimensional CT is frequently employed in the preoperative workup for localisation of ectopic parathyroid adenomas [20].

The latest preoperative imaging techniques including dual-energy CT and positron emission tomography (PET) MRI have been reported to be useful in

detecting parathyroid adenomas in cases of failure of conventional imaging [21]. Simultaneous PET-MRI is a new hybrid technique of imaging that allows exact fusion of molecular and anatomical imaging providing excellent soft-tissue analysis [22].

Surgical Approaches

Most of the MPAs can be excised through a cervical approach, by removing the anterior mediastinal fat and the thymus either during the first exploration or in the setting of remedial operations [10]. Only 1–2% of ectopic MPAs require a thoracic approach to be resected [15].

For MPAs that cannot be removed through a cervical approach, a variety of thoracic approaches can be employed including open surgery techniques (sternotomy, thoracotomy) and minimally invasive techniques as thoracoscopy (including robotic-assisted), mediastinotomy, and mediastinoscopy [10]. The selection of the appropriate surgical approach depends on the location of the ectopic parathyroid tumour and is critical for successful mediastinal parathyroid tumour identification and excision.

The sternotomy was the preferred approach for surgical excision in the past. This approach allows an excellent operative view and an accurate tumour identification. In the majority of the cases, it is not necessary to perform a total sternotomy as a partial sternotomy is adequate to provide good access to the anterior mediastinum [23]. These surgical approaches have been reported to be associated with significant complications including phrenic and recurrent laryngeal nerve injuries, pleural effusion, innominate vein laceration, wound infections, mediastinitis, and death in up to 12–29% of cases [10, 24, 25].

Recently the minimally invasive approaches have gained popularity, and thoracoscopic surgery has replaced conventional sternotomy or thoracotomy for resection of deep ectopic MPAs. These minimally invasive surgical techniques have been reported to be feasible and safe with a low rate of complications even in the setting of reoperative procedures [26, 27]. Accurate preoperative localisation is necessary to establish the appropriate surgical approach. Some authors have suggested the level of the aortic arch as a landmark for guiding the proper surgical approach. Based on their experience, they assumed that MPAs located in the superior mediastinum above the level of the aortic arch could be removed successfully through a transcervical approach, while for those found below the aortic arch in the middle or posterior mediastinum, a transthoracic procedure should be employed [14]. Lastly, the robotic approach has recently been described for mediastinal ectopic parathyroid glands [28, 29]. Only a few series have been reported in the literature, describing this technique as a promising surgical approach for mediastinal parathyroid adenomas, in selected cases [29]. Intraoperative PTH monitoring is used to confirm parathyroid adenoma resection and cure of hyperparathyroidism. A PTH level decline of >50% and into the normal range 10 min after adenoma excision is used as a predictor of cure [30].

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Chapter 13
Mediastinal Lymphoma

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Thymic Marginal Zone B-Cell Lymphoma, MALT Type

Extranodal marginal zone B-cell lymphoma (MZL) of mucosa-associated lymphoid tissue (MALT) arising in the thymus is a rare disorder, with the largest published series comprising only 15 cases [1]. There is a marked female preponderance (male/female = 1:4), with a mean age of 55 years at diagnosis. All published cases showed a strong association with autoimmune disease, Sjögren's syndrome, and others. Histologically, the tumor shows the characteristic features of extranodal MZL of MALT type, with prominent lymphoepithelial lesions, formed by marginal zone cells infiltrating and expanding Hassall's corpuscles and epithelium lining the relatively common epithelial cysts. A monotypic plasma cell was described in all cases. Notably, most cases expressed an IgA phenotype, in contrast to MZL arising in other localizations. For unknown reasons, crystal-storing histiocytosis has been found in a few cases associated with thymic MZL [2] (Fig. 13.1).

Specific molecular alterations for thymic MZL have not been described. API2-MALT1 gene fusion, a characteristic MALT lymphoma-specific gene abnormality, was not detected in any case [1]. TNFAIP3/A20 deletion has been shown in one case [3]. Thymic MALT lymphoma cases had a high frequency of trisomy 3 (7/14 cases), similarly to what was observed in other MZL MALT type, and no detectable MALT1-associated or IGH-associate gene abnormalities [4]. Thymic MZL have been shown to carry on frequent methylation of DAPK1, CDH1, TIMP3, and p14(ARF) genes [5].

Follow-up data, although incomplete, show a tendency to local growth with little tendency to systemic dissemination, consistently with the observations in other MZL MALT type in different localizations [1].

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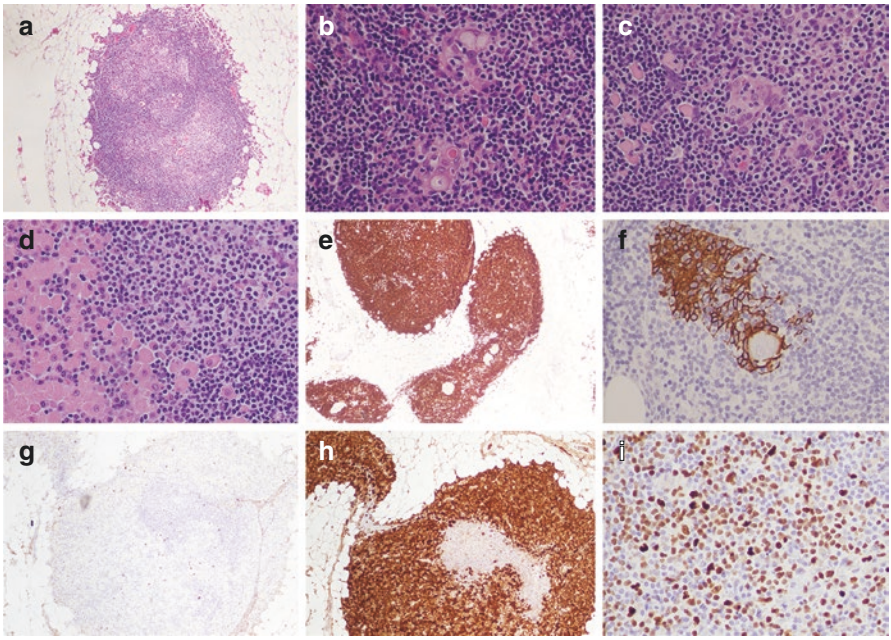

Fig. 13.1 Thymic marginal zone B-cell lymphoma. (**a**–**d**) Morphology of the tumor shows replacement and expansion of the normal thymic medulla by small cells with marginal zone morphology and immunophenotype that infiltrate the Hassall bodies forming lymphoepithelial (**b**, **c**, **f**) lesions. Quite frequently these tumors are associated with crystal-storing histiocytosis (**d**). Tumoral cells express B-cell markers (**e**, CD20), infiltrate the epithelium (**f**, cytokeratin), show light-chain restriction (**g**, kappa; **h**, lambda), and express marginal zone B-cell markers, such as MNDA (**i**)

Nodular Sclerosis Hodgkin Lymphoma

This is a relatively frequent nodal disorder that originates preferentially in the cervical and mediastinal region that typically manifests itself clinically in young adults, although it can be seen at any age.

Neoplastic tissues usually contain scattered large mononucleated and multinucleated tumor cells (designated as Hodgkin and Reed-Sternberg cells or HRS cells) residing in an abundant heterogeneous admixture of nonneoplastic inflammatory and accessory cells. Tumor cells are often ringed by T lymphocytes in a rosette-like pattern [6].

Nodular sclerosis, a pattern commonly seen in mediastinal primary HL cases, is distinguished by the presence of collagen bands encircling tumoral nodules and the presence of lacunar cells together with HRS cells [7] (Fig. 13.2).

The immunophenotype of the neoplastic cells is positive for CD30 in all cases and weakly PAX5-positive in the large majority of cases. CD15 can be found in around 75% of cases, and the B-cell transcriptional program is usually downregulated, with only a weak or partial expression of CD20 and CD79a. EBV expression

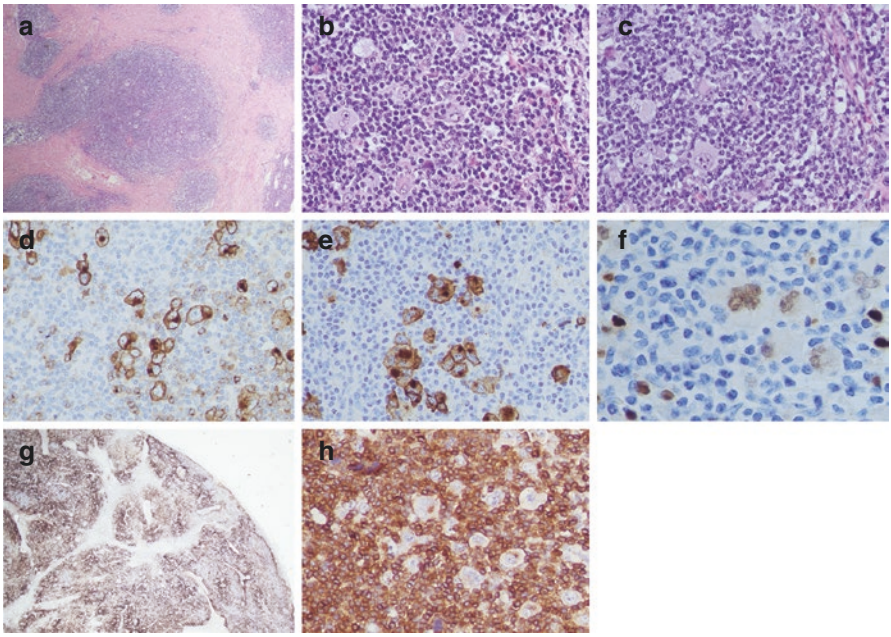

Fig. 13.2 Nodular sclerosis Hodgkin lymphoma-involved tissues show neoplastic nodules encircled by broad collagenous bands (**a**) and SR cells and lacunar cells in a background of small lymphocytes and eosinophils (**b**, **c**). Neoplastic cells are positive for CD30 in all cases (**d**), also frequently for CD15 (**e**) and weakly for PAX5 (**f**). Mediastinal Hodgkin lymphoma displays frequently expression of PDL1 (**g**). Neoplastic cells are surrounded by reactive CD3-positive T-cells (**h**)

is found only in a small proportion of cases, below 20% [8]. The expression of PAX5 is a useful marker in the differential with anaplastic large cell lymphoma, a tumor that only exceptionally expresses this marker [9].

Prognosis and treatment response are basically dependent on the clinical staging and patient age, as advances in therapy have obscured the differences found in cases rich in neoplastic cells (syncytial variant) [9] or showing the so-called fibrohistiocytic variant [10].

Primary Mediastinal Large B-Cell Lymphoma (PMLBCL)

This is an aggressive large B-cell lymphoma, presumably derived from thymic B-cells, arising in the mediastinum, and affecting mainly young adults and most frequently females. The tumor has some peculiar morphological features, including compartmentalization and alveolar fibrosis with the neoplastic cells commonly having a clear cytoplasm (Fig. 13.3).

The tumor has a B-cell phenotype, with lack of Sig but expression of B-cell transcription factors (PAX5, OCT2, BOB1) and CD20/CD79a. CD30 and CD23

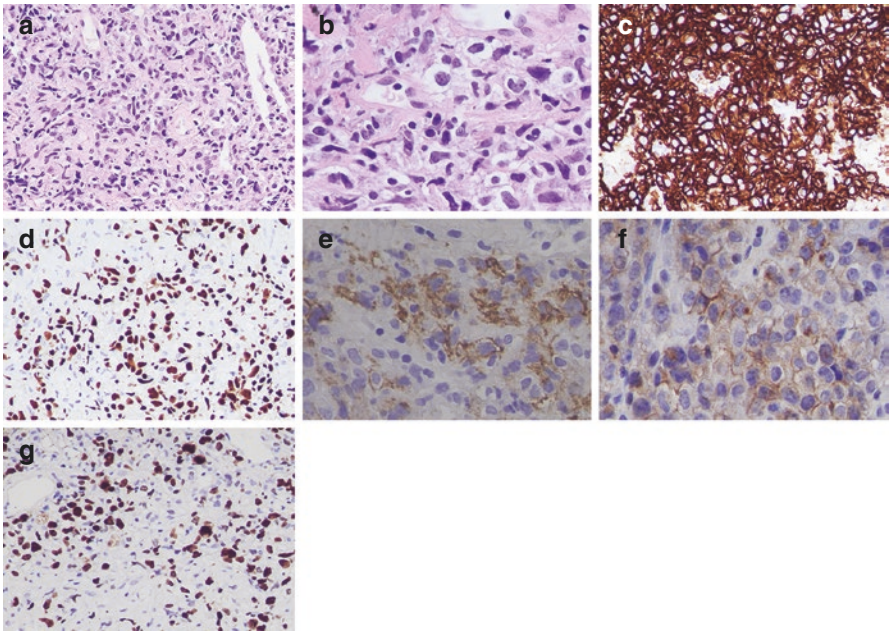

Fig. 13.3 Primary mediastinal B-cell lymphoma typical morphology includes rim and cords of neoplastic cells with clear cytoplasm separated by delicate fibrous bands (**a**, **b**). Neoplastic cells express B-cell markers (**c**, CD20; **d**, PAX5), CD23 (**e**), and CD30 in most cases (**f**) and show high Ki67 index (**g**)

expression is very frequently found (>90%), although these are non-specific findings [11]. PDL1 and PDL2 are usually expressed [12], thus emphasizing the similarity to NSHL phenotype.

Molecular alterations have been described in genes regulating NFKB and JAK/STAT activity, including TNFAIP3 gene deletion, SOCS1 and STAT6 mutations, and markers that can be used in their differential diagnosis [13–15]. Genomic alterations in the major histocompatibility complex (MHC) class II transactivator (CIITA) are frequent in PMLBCL and are associated with diminished MHC class II expression [16].

Although large cell lymphomas with similar features have been described in nonmediastinal sites, diagnosis at nonmediastinal sites requires molecular data confirming TNFAIP3 gene deletion, SOCS1 and STAT6 mutations, or genetic alterations of PDL1/PDL2 locus and CIITA, additionally to a consistent immunophenotype [17].

Primary Mediastinal Gray-Zone BCL

There is strong evidence showing that primary mediastinal large B-cell lymphoma and nodular sclerosis Hodgkin lymphoma have overlapping clinical, morphological, and molecular features. Both tumors are characterized by the expression of a

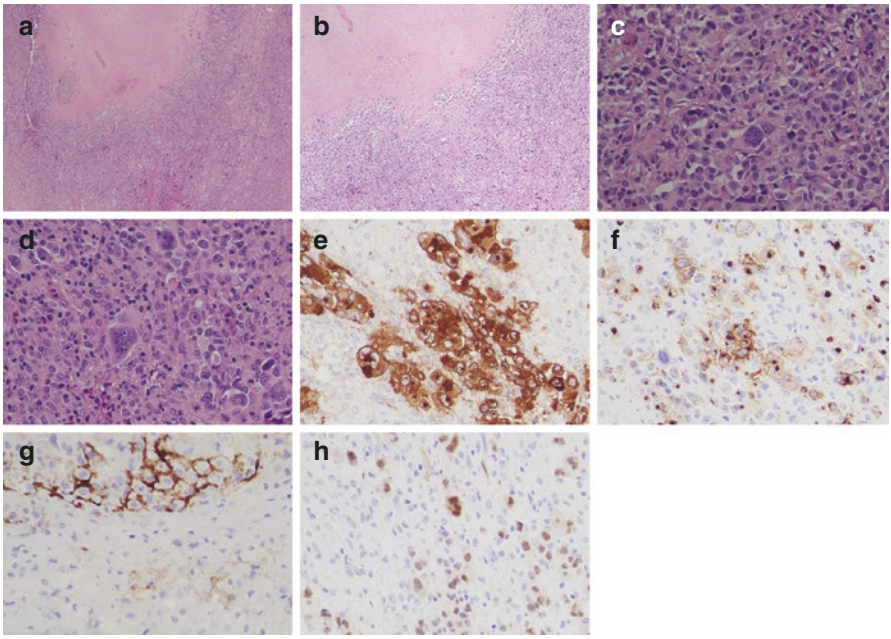

Fig. 13.4 Mediastinal gray-zone lymphoma is a high-grade B-cell lymphoma, with large cell morphology showing intermediate morphological (**a**–**d**) and immunophenotypical features between large B-cell lymphoma and classical Hodgkin lymphoma. Neoplastic cells tend to express Hodgkin (**e**, CD30; **f**, CD15) together with B-cell markers (**g**, CD20; **h**, strong PAX5 staining)

defective B-cell program together with increased expression of CD30 and other activation antigens. Molecular analysis has also yielded overlapping findings for both conditions, with downregulation of the B-cell program, activation of the JAK-STAT pathway, loss of histocompatibility antigens, and amplification or overexpression of PDL1 and other genes located in the 9p24.1 region [18, 19]. Additionally, some patients show composite synchronous or metachronous NSHL and PMLBCL involved samples.

B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classic Hodgkin lymphoma, also called gray-zone lymphoma, is most frequently a mediastinal tumor in young patients but can be found in other localizations and in older ages. By definition it has morphological and/or immunohistochemical features that are intermediate between LBCL and classic HL (Fig. 13.4).

Clinical features of MGZL have been the subject of three recent studies [20–22]. The main difficulty when considering the findings of these studies is the relatively vague definition of the entity, whereby changes in the immunophenotype (increased CD20 expression) are commonly used as the only required diagnostic criteria [22]. This has led to a rather vague definition of the required diagnostic markers [23]. Nevertheless there is a consensus that these tumors have a more aggressive behavior than PMLBCL or NSHL, with poorer response to therapy and more frequent relapses.

Table 13.1 Markers used in the differential between nodular sclerosis Hodgkin lymphoma (NSHL), primary mediastinal large B-cell lymphoma (PMLBCL), and mediastinal gray-zone lymphoma (GZL)

	NSHL (%)	PMLBCL (%)	Mediastinal GZL (%)	Reference
CD30	100	>90	100	[19, 20]
CD20, CD79a	<10	>90	>90	[19, 20]
CD23	10–30	>80	>90	[11]
PDL1	77	66	100	[18]
CD123	23	11	71	[18]
CD200	>90	94	–	[11]
EBV	<20	<5	<5	[19, 20]
CIITA breaks	15	38–53	27	[16, 32, 33]

Some of the markers used to recognize mediastinal GZL are listed in the Table 13.1**.**

The rate of primary refractory disease and the poor results of the standard chemotherapy regimen suggest that an alternative dose-intensive treatment may be required for patients with this disease [22, 24]. A prospective study of DA-EPOCH-R without mediastinal radiation in MGZL demonstrated an inferior outcome compared to patients with PMBL [25].

Recent results from a short series of patients suggest that PD-1 inhibitors may be therapeutically important for mediastinal gray-zone lymphoma, implying that tumoral cells in these tumors have a genetically determined dependence on PD-1 for survival [26].

T-Cell Lymphoblastic Lymphoma

A tumor derived from T-lymphoblasts is present in the normal thymus, and the morphology and immunophenotype resemble the spectrum of the T-lymphoblasts present in the thymus [27]. T-cell lymphoblastic lymphoma (T-LL) patients are predominantly male. The median age of T-LL patients at diagnosis is 29 years, but it can be seen at any age group [28], particularly in young patients, in the second decade, with mediastinal disease.

Morphologically recognizable by the characteristic convoluted nuclear shape and blastic chromatin [29], the neoplastic cells almost constantly express nuclear TdT and various combinations of T-cell markers mimicking the normal T-cell subpopulations present in the cortical and medullary regions of the thymus. CD1a expression (a marker for cortical T-lymphoblasts) and cytoplasmic CD3 (which recognizes the epsilon chain of the CD3 molecule, a T-cell marker) are useful markers for the diagnosis of T-LL, together with the more common use of TdT (Fig. 13.5).

More than 50% of human T-LLs (61% in the largest study) [28] have activating mutations that involve the extracellular heterodimerization domain and/or the C-terminal PEST domain of NOTCH1, a finding providing a strong rationale for therapies targeting NOTCH signaling [30].

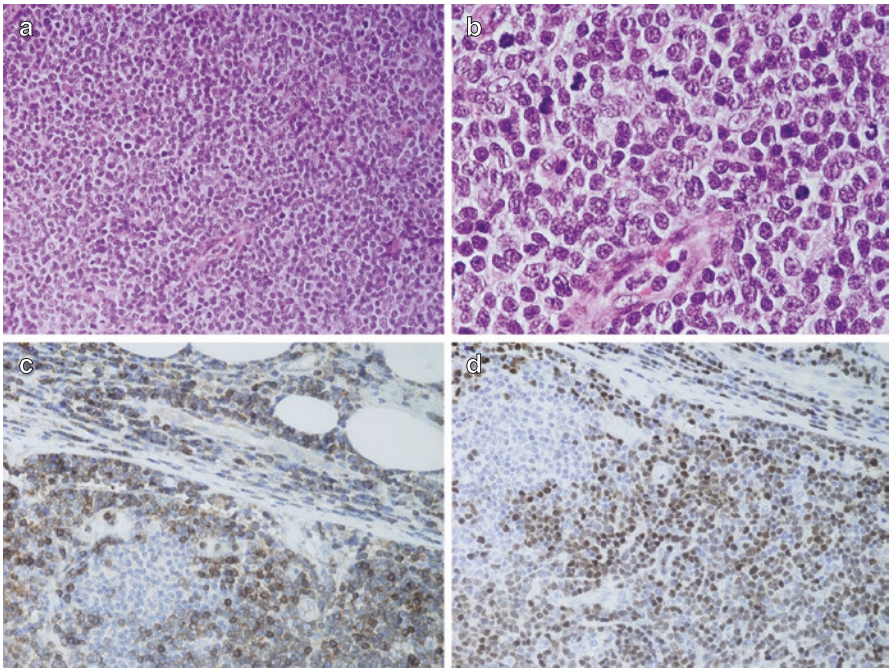

Fig. 13.5 T-cell lymphoblastic lymphoma is an aggressive tumor with a diffuse growth pattern and composed by medium-sized cells with blastic chromatin and convoluted nuclei (**a**, **b**). Tumoral cells in most cases express cytoplasmic CD3 (**c**) and TdT (**d**)

Although survival probability has improved in this condition as a consequence of the new treatments, still 5-year survival is slightly less than 50% [28]. Biological factors associated with a poor outcome have been identified, namely, complex cytogenetics, CD13 positivity, and CD1a negativity [28].

Differential needs to be done with the entity known as indolent T-lymphoblastic proliferation (iT-LBP), an enigmatic condition characterized by its TCR polyclonal nature and normal thymocyte phenotype [31].

Recommendations for Diagnosing Anterior Mediastinum Masses

1. Fine-needle mediastinal aspirates and core biopsies may not yield sufficient material for a mediastinal lymphoma diagnosis. Diagnosis should be done, whenever possible, on excisional biopsies.
2. An integrated analysis of clinical, histological, immunohistochemical, and molecular data is essential in the diagnosis for these lesions.

3. Diagnosis of mediastinal gray-zone B-cell lymphoma requires the presence of intermediate morphology and/or immunophenotype between large B-cell lymphoma and Hodgkin lymphoma.
4. Molecular data may be necessary to differentiate:
   - Mediastinal large B-cell lymphoma vs. disseminated diffuse large B-cell lymphoma
   - T-cell lymphoblastic lymphoma vs. indolent T-lymphoblast proliferation

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Part III
Middle Mediastinum Masses

Chapter 14
Granulomatous Disease

Nicola Martucci, Giuseppe De Luca, and Gaetano Rocco

General Aspects and Physiopathology

Granulomatous disease of the mediastinum comprises a large family sharing the common histological denominator of granuloma formation in the mediastinal lymph nodes [1]. Granulomas are among the most commune abnormalities in pulmonary pathology and often pose a diagnostic challenge [2].

A granuloma is a focal, compact collection of inflammatory cells; it is formed as a result of the persistence of a nondegradable product of active hypersensitivity. The granuloma results from interaction between invading organism or antigen, chemical, drug or other irritant, prolonged antigenemia, macrophage activity, a Th1 cell response, B-cell overactivity, immune complexes, and a vast array of mediators [1].

In general the granulomatous disease of the mediastinum is a chronic, nonmalignant but often progressive inflammatory disease characterized by abnormal enlargement of mediastinal lymph nodes, pathologically characterized by granulomatous inflammation [3]. Mediastinal granuloma is usually asymptomatic or causes few clinical symptoms and may be detected on chest radiographs taken for other reasons. In this evolution the granulomatous disease can led to the mediastinal fibrosis that is a clinical entity characterized by extensive fibrous tissue throughout the middle mediastinum or hilar areas causing compression or invasion of anatomic structures within the mediastinum such as the SVC, pulmonary veins, esophagus, or bronchi, often with serious clinical consequences. In the middle of the spectrum is a clinical entity characterized by enlarged fibrotic or calcified lymph nodes with variable amount of fibrosis that may be asymptomatic, or may cause symptoms by compression or invasion of structures in the mediastinum [3].

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Symptoms depend on the location of enlarged nodes, the degree of fibrosis, and the compression on the mediastinal structures. Clinical manifestations may be due to SVC obstruction, esophageal compression, large airway involvement, pulmonary artery or pulmonary vein narrowing, or laryngeal or phrenic nerve involvement. Diagnosis is traditionally made on the basis of a cytological exam, biopsy, or surgical exploration, either a mediastinoscopy or thoracotomy [3]. However, characteristic findings on computed tomography (CT) of the chest may be sufficient for a diagnosis in some cases. Surgical resection of localized mediastinal granuloma causing symptoms has been performed not infrequently and may prevent mediastinal fibrosis. Lobectomy or pneumonectomy are rare but occasionally can be performed to remove fibrotic or calcified lymph nodes causing persistent symptoms.

Granulomas can be classified into noninfectious and infectious types; in general the noninfectious types include berylliosis, Hodgkin's lymphoma, non-Hodgkin's lymphoma, sarcoid-like lymphadenitis, lymph node draining Crohn's disease, and sarcoidosis. The infectious granulomatous diseases can be classified into suppurative and non-suppurative lymphadenitis [4].

Sarcoidosis

It is the most common noninfectious cause of lung granulomas [2]; the cause is unknown, but it is nonhereditary with a good clinical course. It occurs twice as frequently in women as in men but rarely in children [5]. It involves multiple organs (lungs and hilar lymph nodes 80%, eyes 50%, skin and other lymph nodes 20%), and the respiratory lesions are associated with cough and breathing discomfort [4]. The combination of (1) right paratracheal, (2) right hilar, and (3) left hilar node enlargement is termed the 1-2-3 pattern and is typical of sarcoidosis [6].

The combination of erythema nodosum, bilateral hilar lymphadenopathy, and joint pain is called "Lofgren's syndrome" [7].

The involvement of the respiratory tract can be limited to the mediastinal lymph node (see Fig. 14.1) as far as the pulmonary infiltrate with fibrosis; the intrathoracic nodes are enlarged in 75–90% of the patients [8]; usually this involves the hilar nodes, but the paratracheal nodes are commonly involved. One-third of patients with pulmonary and mediastinal sarcoidosis are asymptomatic, and the disease is discovered by routine chest radiography. The symptoms, if present, include dyspnea, wheezing, and cough. The chest radiography can show hilar adenopathy alone or with diffuse interstitial infiltrates [9].

Traditionally patients are staged radiographically:

- Stage 0: no chest radiographic abnormalities
- Stage 1: hilar or mediastinal adenopathy
- Stage 2: hilar adenopathy and diffuse interstitial infiltrates
- Stage 3: interstitial infiltrates without adenopathy
- Stage 4: pulmonary fibrosis

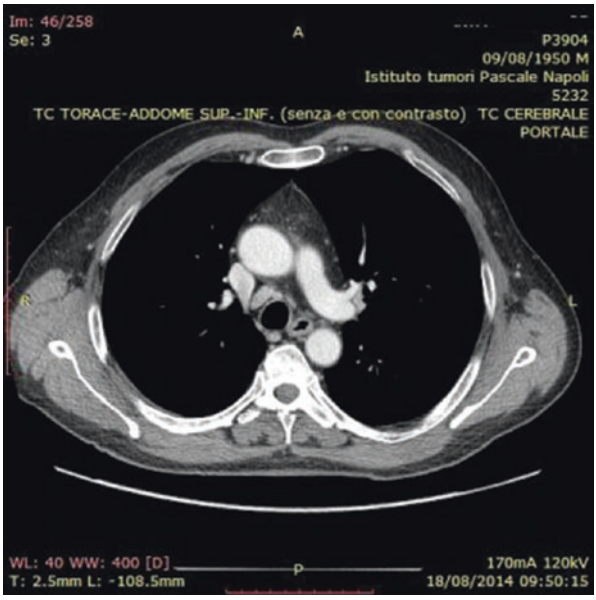

Fig. 14.1 Sarcoidosis of mediastinal lymph node in Barety space

The computed tomography can clearly demonstrate the mediastinal lymph node enlargement with or without nodules along the bronchovascular bundles, major fissures, and subpleural region; in fact a feature of sarcoidosis is the lymphangitic distribution of the granuloma [2].

EBUS-TBNA is the preferred diagnostic test; in fact it allows to get samples for cytological examination; mediastinoscopy and open biopsy are reserved when a histological examination is needed or for the most difficult cases when other measures have not yielded the diagnosis.

Sarcoid-Like Reaction

Epithelioid granuloma resembling sarcoidosis is occasionally observed in lymph nodes with underlying disease [4]. These granulomas may be found in various tumors and in their draining lymph nodes, particularly those draining carcinoma of the lung and stomach. With regard to lung cancer patients, sarcoid reaction can be found in mediastinal lymph nodes but also in the tumor itself and in non-regional tissues [10].

It is a localized reaction within tissues in the absence of any respiratory symptoms; it is often indistinguishable from metastases on radiological studies, so it is difficult to differentiate sarcoid reaction from lymph node metastases.

Symptoms usually depend on the underlying disease so there are no specific clinical symptoms.

EBUS-TBNA is useful for cytologic diagnosis, and with this technology, the patient can avoid mediastinoscopy for diagnosis.

Tuberculosis

Tuberculosis is a chronic granulomatous infection principally caused by *Mycobacterium tuberculosis* and less frequently by ingestion of *Mycobacterium bovis* infected unpasteurized cow's milk or by other atypical mycobacteria [11]. It is a large-scale health hitch with eight million citizens infected yearly and three million people dying from diseases related to tuberculosis complications. The frequency of tuberculosis in underdeveloped nations is snowballing, and this is believed to coexist with poor hygiene environments and increased occurrence of acquired immunodeficiency syndrome [12]. It chiefly affects the pulmonary system with involvement of mediastinal lymph nodes. During primary tuberculosis infection, bacilli reach from the primary focus in the lung to the nearest lymph nodes (hilar-mediastinal) through the lymphatic way and then to the further lymph nodes. They may also spread hematogeneously to reach other lymph nodes, in which they survive for years as dormant bacilli [13]. Tuberculous lymphadenitis commonly develops after primary infection, followed by endogenous reactivation of dormant bacilli after years and finally as a result of an infection in the neighborhood [14]. Lymphadenitis is the main extrapulmonary manifestation of tuberculosis accounting for 35% of cases [PIRINA 1–3]; it is more frequent in children and in females, with peak age of onset in adults between 20 and 40 years. In childhood, tuberculous lymphadenitis is the most common single manifestation of primary tuberculosis (96–100% of cases), generally characterized by conglomerates and localized in multiple sites (mostly in the right paratracheal, hilar, and subcarinal areas), with an inhomogeneous CT enhancement pattern and associated with lung infiltrate in 90% of cases [15]. Lymphadenopathy without a parenchymal infiltrate is very rare and has been observed in patients with acquired immune deficiency syndrome (AIDS) [16]; moreover, TB disease is strongly suggested when a hilar or mediastinal lymph node enlargement is associated with lobar pneumonia. Important pathologies caused by tuberculous lymphadenitis include compression of the adjacent tissues, caseification and disruption of the lymphadenitis, and fibrosis during the healing period of the lymphadenitis [17].

CT of the chest usually reveals right-sided adenopathy and, specifically, right paratracheal lymph node enlargement in tuberculosis [18]. Bilateral hilar lymph node enlargement is less common in tuberculosis than in sarcoidosis. Involvement of pretracheal and prevascular nodes is usual in patients with Hodgkin's lymphoma. The combination of bilateral hilar and paratracheal node enlargement usually allows the differentiation of sarcoidosis from lymphoma. The combination of (1) right paratracheal, (2) right hilar, and (3) left hilar node enlargement is termed the 1-2-3 pattern and is typical of sarcoidosis [6]. The diagnostic value of sputum examination is low in patients without parenchymal lesions of tuberculosis; these patients require procedures such as bronchoscopy, CT-guided fine-needle aspiration biopsy, or mediastinoscopy to establish a diagnosis [19]. In a study on adults with tuberculous mediastinal lymphadenopathy, the incidence of intrathoracic tuberculous lymphadenitis was 2% of 1700 new cases of tuberculosis over a 4-year

period. It also reported that bronchoscopy has a low diagnostic yield in isolated tuberculous mediastinal lymphadenopathy in the absence of lung lesions. Mediastinoscopy is an invasive procedure but provides a tissue diagnosis in most of the cases [20].

Serum ACE (SACE) levels are elevated in 60% of the patients with sarcoidosis and in less than one-third of the patients with chronic disease. Patients with infectious granulomatous diseases such as tuberculosis and histoplasmosis occasionally have an elevated SACE level [21].

Histoplasmosis

Is a fungal infection caused by *Histoplasma capsulatum*? It has been implicated as the most common cause of mediastinal granuloma. The granuloma usually develops in the right paratracheal and hilar area. Increase in size of the mediastinal lymph nodes can give compression of the tracheobronchial tree, SVC, and pulmonary artery, but about 40% of the patients with histoplasmosis are asymptomatic or have poor symptoms as cough, pain in chest, and fever.

Chest X-ray findings are normal in 40–70% of cases; CT scan can identify the structure involved. Depending on the location and suspected diagnosis, various diagnostic methods may be used as, for example, mediastinoscopy, mediastinotomy, thoracoscopy, and thoracotomy.

Clinical Aspects

In general, the clinical manifestations depend on the anatomical location of the enlarged lymph nodes in relation to mediastinal structures. The right paratracheal lymph nodes, subcarinal nodes, and right hilar nodes are most frequently involved, and this condition is associated with SVC obstruction or azygous vein involvement. Lateral extension of subcarinal lymph nodes might obstruct the main bronchi or pulmonary arteries. Posterior extension can give esophageal compression or obstruction [3].

Most patients with mediastinal granuloma are asymptomatic; the initial symptoms are usually cough, dyspnea, hemoptysis, and chest pain [22].

The SVC obstruction is the most serious complication but is more common in advanced mediastinal fibrosis; in fact the enlarging right paratracheal nodes or progressive fibrosis compresses the SVC and causes the typical findings of SVC syndrome: venous distension of the neck and upper extremities, head and upper extremity edema, and enlarged collateral veins across the chest and back [23].

Dysphagia and chest pain are due to the extrinsic compression of the esophagus and also traction diverticula, and gastrointestinal bleeding may occur.

Cough, dyspnea, or hemoptysis may be due to the compression of the major airways; obstruction of the bronchus to the right middle lobe may cause atelectasis of the right middle lobe (right middle lobe syndrome) [24]. Tracheal stenosis is unusual but can occur [25].

Pulmonary arteries, pulmonary veins, or the inferior vena cava may be compressed. Pulmonary hypertension [26], cor pulmonale, and severe right heart failure have all been reported [3].

Compression of the recurrent laryngeal nerves results in vocal cord paralysis and hoarseness. Phrenic nerve involvement results in hemidiaphragmatic paralysis. Horner's syndrome is the sign of compression of autonomic ganglion.

The chest radiograph usually shows mediastinal enlargement, predominantly on the right side especially right hilar enlargement. Chest CT shows the enlargement of the lymph node stations of the mediastinum and, in case of fibrosis, can demonstrate a diffuse homogeneous soft tissue process throughout the mediastinum [27]. CT can also demonstrate the compression of airways and, with contrast, can show the SVC compression or obstruction.

Diagnosis and Treatment

Bronchoscopy is useful because it identifies extrinsic compression of the trachea or large bronchi; bronchoscopic cultures are rarely diagnostic, and the gold standard for diagnosis is the endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA); this technique has been shown to be highly effective in the diagnosis of mediastinal mass [28] and to reduce the number of mediastinoscopies [10].

Cytological exam or biopsy of the abnormal mediastinal mass is important in making the diagnosis in almost all cases of indeterminate mediastinal masses. A calcified mediastinal mass in an asymptomatic patient may be observed and followed carefully without biopsy. However, a noncalcified mass, either asymptomatic or causing compression of an anatomic structure, should be biopsied to differentiate lymphoma, carcinoma, thymoma, goiter, and other causes of mediastinal masses. Nodular Hodgkin's disease can be difficult to distinguish from mediastinal granuloma clinically and pathologically.

In most cases, when a good biopsy is useful, the best diagnostic methods are mediastinoscopy, video-assisted thoracic surgery (VATS), or open thoracotomy.

Surgery is generally performed to obtain a tissue diagnosis, rarely for excision of a mediastinal mass causing anatomic obstruction or compression [9]. Resection of large hilar or subcarinal masses with reconstruction of the main stem bronchi is technically very difficult but may reverse extrinsic compression on adjacent anatomic structures and may relieve symptoms [24].

Bronchoplastic procedures are useful to avoid pneumonectomy or lobectomy in selected cases when the mass invades the bronchial wall causing symptomatic obstruction or bleeding.

Carinal resection has been done for invasive subcarinal fibrosis but may be associated with high mortality [3, 24].

Some authors recommend excision or evacuation of mediastinal granulomas to prevent consequent mediastinal fibrosis [22].

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Chapter 15
Cysts of the Middle Mediastinum

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Cysts of the mediastinum, which are usually benign masses, constitute a small but important diagnostic group, representing from 5 to 18% of all primary mediastinal tumors [1, 2].

Middle mediastinum cysts are lesions caused by abnormal embryological development of the anterior intestine and or coelomic cavity, so they include foregut and pericardial cysts.

Foregut Cysts

Mediastinal cysts of foregut origin constitute up to 15% of all primary mediastinal masses and represent 48.6% of all cysts in the mediastinum [1]. The respiratory system and the esophagus have a common embryologic origin. The laryngotracheal groove appears at the end of the 3rd week of gestation in the embryonic foregut. The dorsal portion of the foregut subsequently elongates to form the esophagus, and the ventral portion ultimately differentiates into the respiratory tract, with ciliated epithelium lining both the fetal esophagus and trachea. Thus there is a tendency to unify the cysts according to their columnar ciliated mucosal lining, whatever their locations. The cleavage between the respiratory tract and the digestive tube occurs on day 28. Errors in the development of the foregut result in clinical malformations [1–4]. The spectrum of foregut cysts of the middle mediastinum includes

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bronchogenic cysts and esophageal duplications. Gastrogenic and bronchogenic congenital mediastinal cysts were first described in 1911 [5].

Bronchogenic Cysts

Bronchogenic cysts are, usually benign, congenital lesions, account for 5–15% of primary mediastinal masses and 34% of the cysts [2, 6]. The prevalence of bronchogenic cysts was reported to be 1:42,000 and 1:68,000 of admissions to two hospitals, but it is difficult to appreciate the exact prevalence because some patients have lesions that remain forever silent [1]. They are a result of abnormal ventral foregut development in the mediastinum during embryogenesis (between 4th and 6th weeks) [1–4]. Bronchogenic cysts arise, usually from middle mediastinum (79–85%), located frequently in the carina area, paratracheal area, bronchus area, and hilar area. In addition, bronchogenic cysts can occur in the lungs, esophagus, stomach wall, paravertebral gutter, skin, and subcutaneous area. Atypical sites are neck, myocardium, pericardium, thymus, lung ligament, diaphragmatic and retroperitoneal region, and abdomen [2, 6–10]. They may appear at any age, but more than 50% cases are diagnosed in patients older than 15 years, and there is no predilection to sex. Histologically these lesions are lined ciliated columnar epithelial cells covering the inner surface of the cyst. The inner cyst wall may contain a cartilaginous component and less frequently bronchial glands [10]. The contents of cysts are liquid, mucoid, and clear or yellow rarely hematic or purulent. The cysts vary in size, these excised at surgery ranges from 20 to 150 mm in diameter [2, 11–13]. Soomro et al. reported a cyst with post-excisional diameter of 210 mm [14]. In most adult bronchogenic cysts are asymptomatic and detected occasionally in a routine radiological study, while in children these are frequently symptomatic [11, 14]. The difference for Ribet et al. depend on the position of the cyst; in their series children cysts are located for 75% on sites where they are more apt at to have compression (above the hilum and at the level of the hilum) and only for 53% in the adults [2]. Furthermore tracheobronchial compression occurs easily in infant and children before 5 years of age because of the relatively soft tracheobronchial tree; in fact lesions small in size may cause mechanical effect. Therefore in infant and young children, there is a complete correlation between compression and symptoms, and they must be suspected in early childhood having noisy breathing, cough, dysphagia, dyspnea, recurrent bronchopulmonary infection, and anorexia [2, 10]. After the age of 5 years, asymptomatic cysts are more frequent, but they may develop by the way symptoms over time [2]. The most frequent symptoms are pain, perhaps caused by irritation of the pleura; cough and dyspnea and dysphagia, determined by compression; fever secondary to the infection; and stridor [6]. Some patients may have acute compression symptoms because of the sudden increase of the cyst after bleeding [10, 11]. A few patients have special manifestations, such as pleural effusion, even under the condition of intact cyst without infection or rupture [3]; in addition other potential complications

including arrhythmia or superior vena cava syndrome may occur [1]. Hemoptysis, hemorrhage, or empyema can occur if the cyst penetrates into other adjacent organs, cavities, lung, trachea, esophagus, and pleural cavity [1, 3, 15, 16]. Malignant transformation is very rare, with only five cases having been reported in the literature [1, 6, 9, 15]. Preoperative diagnosis is established primarily by chest X-ray, CT, and MRI [17]. The chest X-ray is usually the initial radiological investigation of choice [1]. It may show indirect signs of the compression, enlargement of the mediastinum, and rarely reveals a rounded, well-demarcated mass. CT scan is very helpful to reveal information about the size and shape of the cyst and anatomic relationship and compression of the cyst on the adjacent organs. Ct scan is also helpful for the diagnosis of cyst bleeding and infection [16, 17]. MRI is very important for differential diagnosis with accuracy rate of 100% [17–19]. The treatment of bronchogenic cyst is controversial [20], the transparietal [21], transbronchial [22] or mediastinoscopic [23] puncture and aspiration, as temporary measure in case of acute compression or in selected cases, can be used although they are burdened high rate of recurrence. Complete resection is the best treatment, and it is preferred treatment for patients with symptomatic cyst [6]. Some authors believe an aggressive surgical approach is acceptable for asymptomatic patients due to the potential risk of infection and malignant transformation [3, 24, 25]. Various surgical accesses are available for excision. A median or partial split sternotomy had been described in literature. Cervical access for mediastinoscopy with piecemeal removal with biopsy forceps has been described. Both left and right thoracotomies have also been used depending on the location of the cyst. Thoracoscopic resection is the preferred surgery for bronchogenic cyst, because it has the advantage of less trauma and quicker recovery. Thus, video-assisted thoracoscopic surgery might be better accepted by those patients who refuse thoracotomy. The need for conversion to a thoracotomy is possible [2, 10]. A retrospective review of the operative records showed that a central topography, adhesions, and communications of the cysts with the tracheobronchial tree would have made a thoracoscopic approach hazardous in 30% of the children and 11% of the adults [2]. Operative difficulties are so possible, but the most important point is the dissection of the cyst from the tracheobronchial wall, where a thin common membrane or an orifice may exist. In difficult cases, a small patch of cystic wall may be left in place after destruction of the mucosal lining to avoid recurrence [2]. Postoperative mortality is exceptional and complications ranged from 0 to 27%. In patients who did suffer complications of surgery, the majority were generic operative complications with two cases attributed directly to cysts.

Esophageal Duplication Cysts

Gastrointestinal duplication cysts are rare entities, which occur most commonly in ileum, jejunum, esophagus, and colon. Esophageal duplication cyst corresponds to 10–20% of the benign tumors of the esophagus and accounts for 10–15% of all

congenital duplication involving the gastrointestinal tract with estimated prevalence of 0.0122% [26]. In up to 60% of patients, they are usually located adjacent to or within the esophageal wall. Ectopic gastric mucosa in the cyst may cause hemorrhage or perforation of the cyst or infection. Embriologically, the upper gastrointestinal tract develops from the posterior division of the primitive foregut, and errors in the development between 4 and 5 weeks of gestation result in clinical malformations: single cyst (duplication of epithelium) and esophageal duplications (duplications of the mucosa and the muscle wall without duplication of the epithelium). Majority of them are found in the mediastinum, but cases of intraabdominal esophageal duplication cysts have been reported. As many as 80% of these lesions are diagnosed in childhood. Patients with esophageal duplication cysts are usually asymptomatic but can develop symptoms (dysphagia, chest pain, epigastric discomfort, vomiting, stridor), due to compression of surrounding structures. In literature many complications have been reported including infections, hemorrhage, ulcerations, cardiac arrhythmia, and cyst rupture with secondary mediastinitis [26, 27]. Malignant transformation, although extremely rare, has been reported [28, 29]. CT or MRI features of duplication cyst are similar to those of bronchogenic cyst, except for their location which is usually close to the esophagus and within its wall. Definitive treatment of esophageal duplication cyst is complete surgical resection, and nowadays many cases are treated by thoracoscopic technique [27].

Pericardial Cyst

Pericardial cysts are rare, benign anomalies located in the middle mediastinum. Their incidence is about 1:100,000 and comprise 7% of the mediastinal masses and 33% of mediastinal cysts [30–32]. Pericardial cysts are commonly congenital in origin. During embryonic development, the pericardial sac is formed by organization of mesenchymal tissue around the developing heart. Defects in the proper organization of this mesenchyme are believed to result in formation of pericardial cyst [33]. Prenatal diagnosis is possible with ultrasound examination beyond 14th week, and cases of spontaneous regression have also been described in literature [34, 35]. Other causes have been described too: inflammatory cause (rheumatic pericarditis) and infection (tuberculosis). Isolated hydatid cyst of pericardium is extremely rare, and they are usually found in association with myocardial cyst or cyst elsewhere in the body. Pericardial cyst have been determined rarely from chest trauma and post cardiac surgery [33]. Seventy percent of cysts are located at the right cardiophrenic angle and 22% in the left, and the rest are in the posterior or anterior [36]. The cysts vary in size from 2 to 28 cm, usually uniloculate, there is no sex predilection, and the age distribution is not well defined [36, 37]. Most of pericardial cysts (60–75%) are asymptomatic and have a benign natural course [38]. If present, symptoms are usually due to compression of adjacent organs and include atypical chest pain, dyspnea, and persistent cough. Cardiac tamponade, obstruction of right main stem bronchus, and sudden death are the life-threatening emergencies that have been

reported [37]. Cardiac tamponade is usually due to intrapericardial rupture of the cyst, although tamponade due to spontaneous hemorrhage into the cyst has also been reported. Other reported complications include right ventricular outflow obstruction, inflammation and infection, pulmonary stenosis, partial erosion into adjacent structures, atrial fibrillation, and congestive heart failure [37, 39] (see Table 15.1). A few pericardial cysts resolve spontaneously, likely from rupture into the pleural space. The rates of spontaneous resolution or complications have not been reported. The diagnosis is often an incidental finding in chest X-ray or echocardiography. Additional diagnostic methods for pericardial cysts include computed tomography and magnetic resonance imaging of the chest. A CT scan finding of a typical pericardial cyst is the presence of homogeneous mass with the similar attenuation as water, with thin-walled, crisply defined, located near the pericardium and that is not enhanced with contrast (Fig. 15.1a, b). MRI examination also shows the cyst contains serous fluid that produces low signal intensity on T1 weighted and high signal intensity on T2 weighted (Fig. 15.2). On histologic examination, the cyst wall is composed of fibrous tissue lined by mesothelium, like normal pericardium, with mild chronic inflammation [39–42]. Management of pericardial cyst is similar to that of mediastinal mass. Kumar Kar et al. think that their management

Table 15.1 Symptoms and complications

Pericardial cyst	
Symptoms	Complications
• Persistent cough	• Sudden death
• Dyspnea	• Cardiac tamponade
• Chest pain	• Right ventricular outflow obstruction
	• Atrial fibrillation
	• Congestive heart failure
	• Pericarditis
	• Pulmonary stenosis
	• Spontaneous hemorrhage into the cyst
	• Erosion into adjacent structures

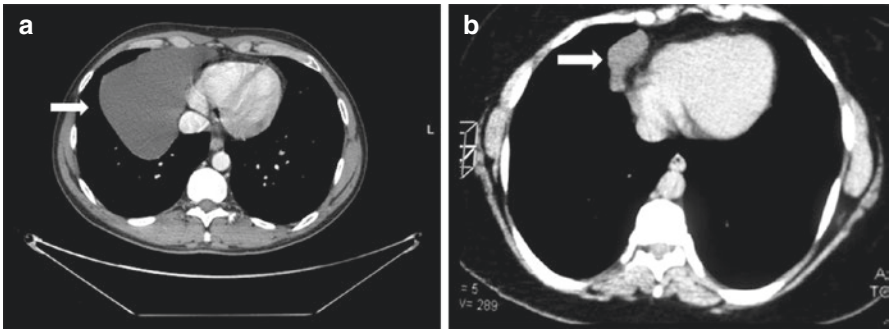

Fig. 15.1 Contrast-enhanced computed tomography images of the thorax showing a 15 × 10 cm (**a**) and a 6 × 7 cm (**b**) well-defined homogenous cystic lesions (*white arrow*)

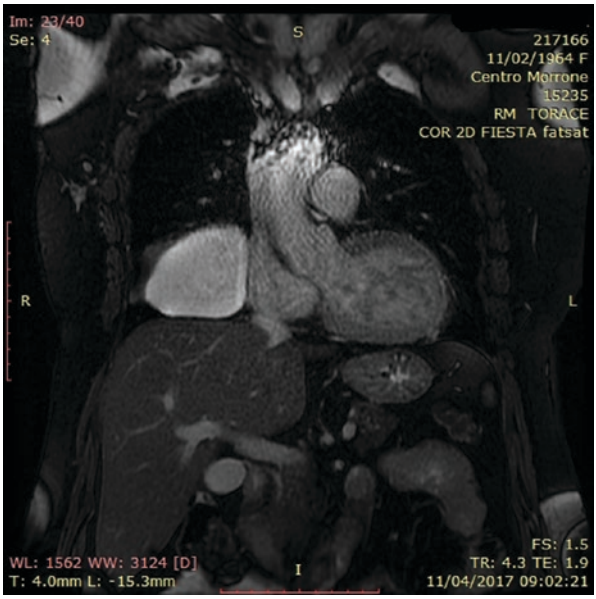

Fig. 15.2 Magnetic resonance imaging view of a pericardial cyst

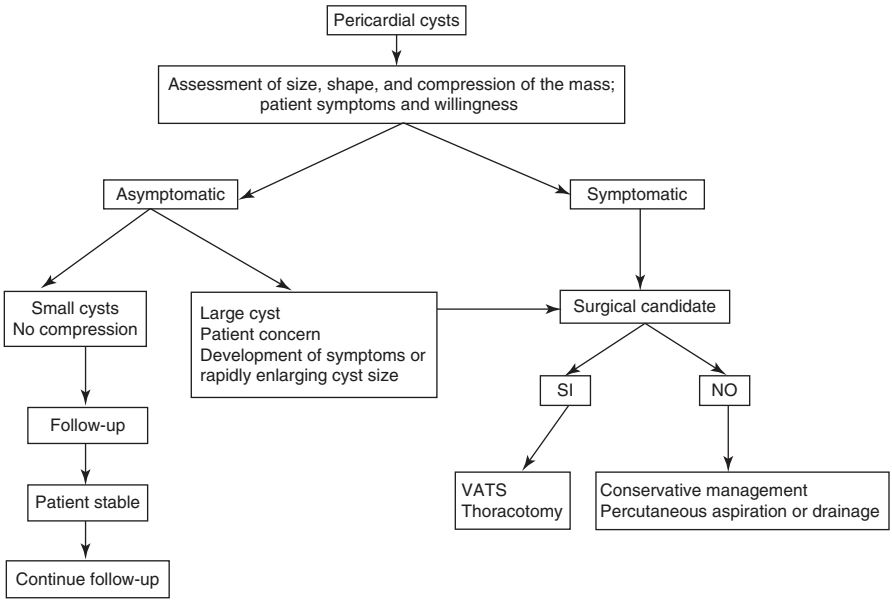

Fig. 15.3 Management of pericardial cyst

should follow an algorithmic approach (see Fig. 15.3) [32]. It includes observation, percutaneous drainage, and resection. Observation is possible with repeated CT scans. Same authors prefer echocardiography over CT scan for follow-up for minor ionizing radiation and recommend CT scan to be reserved for cases with suspect complications [32, 36]. However, for high-risk patients a non-operative strategy may be followed. The indications for resection of pericardial cysts include large size, symptoms, patient concern, uncertainty of malignant potential, and prevention of the life-threatening emergencies. Before, thoracotomy was the approach of choice; currently uniportal VATS is the approach most commonly used. Morbidity and mortality are low. Surgery has been demonstrated as the only definitive curative treatment [40].

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Chapter 16
Tracheal Tumors

Giuseppe De Luca, Nicola Martucci, and Gaetano Rocco

Tracheal tumors are rare malignancies of the upper airway. They are usually malignant in adults (80–90%) and benign in children (60–70%) [1–3].

The annual incidence of tracheal cancer is approximately 0.1 per 100,000 persons [4] accounting for only 0.2 of malignant neoplasms of the respiratory tract and only 0.02–0.04% of all reported malignancies [4–6]. On the other hand, Licht et al. found that 17% of all cases of tracheal carcinoma were found incidentally at autopsy [6].

Tumors in the tracheobronchial tree can be classified as primary malignant tumors, secondary malignant tumors, or benign tumors. Tumors that metastasize to the trachea from other areas, such as the thyroid, esophagus, larynx, or lung, are more common though and may only account for 2% of all upper respiratory tumors [7].

Primary tracheal tumors can arise from the respiratory epithelium, salivary glands, and mesenchymal structures of the trachea [8]. There are three types of malignant tumors. Squamous cell carcinoma is the most common and aggressive tracheal tumor and is usually associated with smoking [9]. It is histologically identical to lung squamous cell carcinoma and is found more often in men between the ages 50 and 70 years. Small-cell carcinoma can be either exophytic or ulcerative and can be distributed over most of the trachea, and about a third of patients have either mediastinal or pulmonary metastases at diagnosis [8–11]. Adenoid cystic carcinoma occurs between the ages of 40 and 60 years, without sex predilection. They are not associated with cigarette smoking and have a propensity to spread along both submucosal and perineural planes, and only 10% of patients have regional lymph node metastases or remote metastases, and they are usually slow growing

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and not related to smoking. Squamous cell carcinoma and cystic adenoid carcinoma account for about two-thirds of tracheal tumors [8, 10].

Carcinoid tumors are a slow-growing abnormal mass that originates in the cells of endocrine or nervous system. Tracheal benign tumors usually are chondromas, hemangiomas, and papillomas [10].

The clinical presentation of patients with tracheal tumors is variable but generally includes signs and symptoms of the upper airway obstruction (dyspnea, wheezing, and stridor), mucosal irritation and ulceration (cough and hemoptysis), or direct invasion and involvement of continuous structures (recurrent nerve palsy and dysphagia).

Diagnosis is often not made until several months after first presentation in adults, possibly because the tracheal lumen has large functional reserve, and tumors do not cause symptoms until they occlude 50–75% of the luminal diameter [8, 12]. Signs and symptoms vary according to the type but not the site of tumor [13].

Haemoptysis is the main symptom in patients with squamous cell carcinoma, with adenoid cystic carcinomas commonly present with wheezing or stridor as the main symptom.

Diagnosis is very difficult, because they are so rare and, in most cases, slow growing. They may be misdiagnosed as another breathing problem, such as asthma, bronchitis, or COPD, because there are no specific symptoms [5, 8, 10]. By the way shortness of breath and wheezing that is unresponsive to bronchodilators should arouse suspicion of a tracheal tumor.

Conventional chest radiographs are rarely diagnostic [5, 8]. In a series of patients with documented tracheal tumors reviewed by Li et al., only one-half of plain chest radiographs demonstrated visible tracheal abnormalities [14]. Computed tomography is the most helpful method of radiologic examination of tracheal tumors. CT demonstrates the intraluminal and extraluminal extent of tumor and delineates the relationship of the tumor to adjacent structures (8). Three dimensional (3D) helical CT scanning is a very useful imaging modality which has replaced the conventional tomogram. When compared to conventional CT, this technique provides complementary details with regard to spatial orientation and precise measurement of tracheal tumor length [15]. MRI provides no clear advantage over CT in the assessment of tracheal tumors [8, 16].

Bronchoscopy is the mainstay of diagnosis and staging of tracheal neoplasms, and it can determine location and extent of disease in the airway (see Figs. 16.1 and 16.2). Biopsies are obtained for tissue diagnosis. Endoscopic ultrasound can also establish the amount of tracheal invasion.

There are several options for treating tracheal tumors (surgery, endoscopic resection, and radiotherapy). Some treatments are for cure and some are aimed at reducing symptoms.

Surgery represents the primary curative treatment for tracheal tumors [1, 5, 8, 11, 13, 16, 17]. In fact 5-year survival is 39% in patients with squamous cell tumors who received resection but only 7% in those who do not. In patients with adenoid cystic tumors, those who have resection have a 5-year survival of 52%, compared with 33% in patients who do not have resection [6, 8].

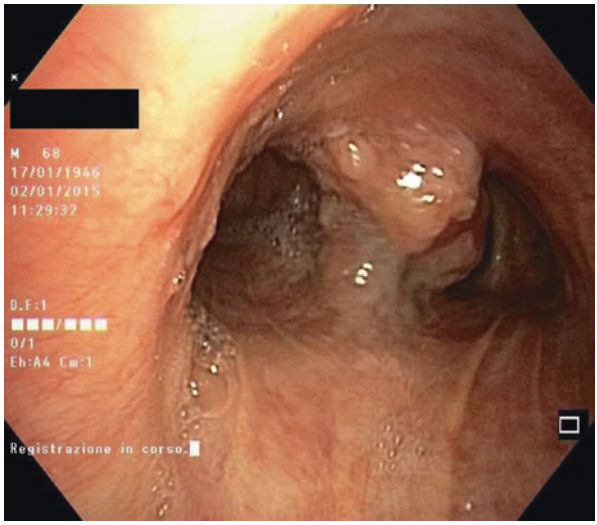

Fig. 16.1 Endoscopic view of a tracheal carina tumor

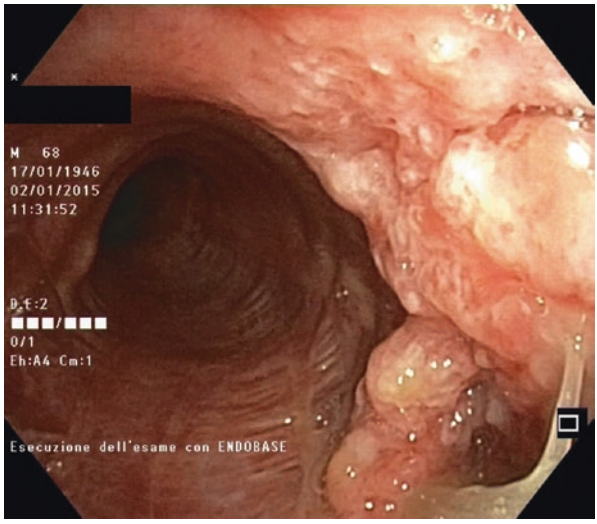

Fig. 16.2 Endoscopic view of tracheal tumor

The goal of surgical resection of a tracheal squamous carcinoma is an R0 resection. This goal can be achieved in about two-thirds of resections in larger center. Various surgical approaches have been described. Neck collar incision usually with a manubriotomy is used for tumors of the cervical and upper most portion of the intrathoracic trachea; median sternotomy or right posterolateral thoracothomy is used for tumor of the lower part of the trachea [8]. In the surgical approach are fundamental the tracheal mobilization techniques; they include suprathyroid laryngeal release [16, 18], suprahyoid laryngeal release, and right pulmonary hilar release; these permit the removal and primary reconstruction of up to one-half the length of

adult trachea [16]. Most primary tracheal tumors are tractable to surgical excision using these techniques. Grillo has reported 71% of tracheal tumors which were operatively explored [19].

Additional operative techniques have been specifically described for carinal tumor resection and reconstruction with preservation of lung parenchyma [11]. Postoperative mortality was initially moderately high (20%), while then reports from experienced centers have demonstrated a reduction in operative mortality to approximately (5–10%) [6, 8]. Postoperative complications are mediastinitis, acute respiratory distress syndrome, bilateral pneumonia, fatal hemorrhage, esophagotracheal fistula, tracheal stenosis, and necrosis [20].

The contraindications to surgery include the presence of many positive lymph nodes, involvement of more than 50% of the trachea, mediastinal invasion of unresectable organs, a mediastinum that has received the maximum radiation dose of more than 60Gy, and distant metastases of squamous cell carcinoma [8].

Several other treatment modalities have been described. Endoscopic resection can be used to relieve airway obstruction but does not provide complete resection, and the chances of a cure are therefore minimal [16].

Radiotherapy can be used as palliation of severe symptoms, or as adjuvant treatment after surgery; very poor survival rates in patients treated with radiotherapy alone are seen in most studies [16, 17, 20]. The role of adjuvant radiation therapy has not been clearly defined in the literature. Radiotherapy has also proven to be an efficient treatment modality for patients with unresectable or residual tumor. Recent reports with modern high-dose radiotherapy suggest good local control and potential cure for patients with tumors confined to the trachea. For patients treated with radiotherapy alone, complete response is significantly related to the total dose [21]. Green in 1985 reported his experience in three patients treated with definitive irradiation of clinically limited squamous cell carcinoma of the trachea. Each of the three patients had tumor 3 cm or less in diameter and received a total dose of 50–70 Gy. Local control was achieved in all three. Biopsy confirmed tumor sterilization in two patients [22]. Mornex et al. in 1998 reported a median survival of 8 months in 84 patients treated with external irradiation (30–70 Gy), but median survival was of 16 months for patients treated with more 50 Gy. Mornex et al. concluded radiation alone to be a good alternative to surgery. Their study identified performance status and radiation dose (>60 Gy) as significant prognostic factors. With a mean follow-up of 141 months, their series showed overall 1-, 2-, and 5-year survival rates of 46%, 21%, and 8%, respectively [21].

Cheung et al. suggested that dose of radiotherapy at 65 Gy or higher may be required to increase the loco regional control of this tumor [23].

Jeremic et al. explored correlation between dose and outcome in a retrospective study of 22 patients. Their median survival was 24 months and 5-year survival was 27%. Mediastinal lymph node involvement was a bad prognostic factor. Survival was not significantly different at a dose of 70 Gy versus 60 Gy, whereas tracheal toxicity was [24].

High-dose rate endotracheal brachytherapy is promising and could improve the local control. Tracheal necrosis should be avoided by systematically using a tracheal applicator.

The intent of chemotherapy is usually palliative, and it can only be advised in patients with a good performance status. In literature has been reported that cisplatinum-based chemotherapy has been used successfully, but no large trials have been reported [25].

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Part IV
Posterior Mediastinum Masses

Chapter 17
Nerve Sheath Tumours, Ganglion Tumours and Neurenteric Cysts

Konstantinos Konstantinidis and Kostas Papagiannopoulos

Anatomy

The mediastinum is the central compartment of the thoracic cavity which is bounded superiorly by the thoracic inlet, inferiorly by the diaphragm, anteriorly by the sternum, posteriorly by the anterior surfaces of the thoracic vertebra and laterally by parietal pleura reflections along the medial aspect of both lungs. There have been several descriptions regarding the compartments of the mediastinum and its boundaries. The three-compartment model divides the mediastinum into three compartments: the anterior, the middle and the posterior [1]. According to the traditional four-compartment model, the mediastinum is divided into superior, anterior, middle and posterior compartments.

Recently, a study from Fujimoto [2] and colleagues proposed a four-compartment model for the division of mediastinal compartments based on axial CT images of 445 pathologically proven mediastinal masses. According to this study, these are the superior portion, the anterior mediastinum or pre-vascular zone, the middle or peri-tracheoesophageal zone and posterior mediastinum or the paravertebral zone. The posterior mediastinum is a defined space between the posterior pericardium and the anterior portion of the thoracic spine up to the inferior border of the T4 vertebra (thoracic plane). It is also called the paravertebral space. It contains the oesophagus along with vagus nerves, the descending aorta, the thoracic duct, the azygos and hemiazygos veins the sympathetic chain, fat and lymph nodes. The anatomical division of the mediastinum seems quite important during the differential diagnosis process of mediastinal tumours as different tumours arise in different compartments.

The posterior mediastinum gives rise to several types of tumours with the commonest of them to be neurogenic in origin. These tumours arise from the intercostal

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nerves and sympathetic or parasympathetic ganglia. There are 12 pairs of intercostal nerves which are spinal nerves and carry motor and sensory and autonomic signals between spinal cord and the human body. They are part of peripheral nervous system. Each intercostal nerve is formed from the combination of nerve fibres from dorsal (afferent) and ventral (efferent) roots. They emerge from the intervertebral foramen, travelling in the intercostal groove and numbered by the vertebra above. Branches from these nerves supply also the paravertebral ganglia of the autonomic nervous system.

The thoracic part of the sympathetic chain is in continuation above with the cervical and below with the abdominal parts. It is running just lateral to the vertebral column along the heads of the ribs on each side of the posterior mediastinum and exits the thorax behind the medial arcuate ligament. It has 12 ganglia. The first thoracic ganglion is fused with the lower cervical ganglion and forms the stellate ganglion. Each ganglion carries white and grey communicants passing to the corresponding spinal (intercostal) nerve. They also carry postganglionic and preganglionic (myelinated) fibres; the latter of them gives rise to the splanchnic nerves.

Embryology

The nervous system as a whole, including the spinal cord, brain, peripheral nerves and ganglia, is derived from ectoderm, and its primordia structure, the neural ectoderm, appears very early in development [3]. Gradually, the ectoderm overlying the notochord transforms to neural tube which is flanked by two longitudinal formations, the neural crests. The sympathetic nervous system is formed around the 5th week of development when cells from the neural crest and ventral portion of the neural tube of the thoracic region migrate on either side of the spinal cord. These cells become the sympathetic neuroblasts. Migrating cells form two chains of sympathetic ganglia on either side of the vertebral column. Derivatives from neural crests are also the ganglia of parasympathetic system and the Schwann cells.

Tumours of the Posterior Mediastinum

Neurogenic tumours of the mediastinum are derived from tissue of the neural crest which includes cells from the peripheral, autonomic and paraganglionic nervous systems. They occur commonly in the posterior mediastinum although they may be found anywhere in the chest. Neurogenic tumours comprise approximately 15–20% of all mediastinal masses, and they affect mainly young adults and children. Ninety-five percent are derived from intercostal nerve rami or the sympathetic chain [4]. These tumours are generally benign in nature in adults, as less than 10% of them are malignant. In contrast, neurogenic tumours in children have 50% chance to be malignant [5].

Box 17.1 Neurogenic Tumours of Posterior Mediastinum

Intercostal nerve tumours (nerve sheath)
- *Neurilemoma (schwannoma)*
- *Neurofibroma*
- *Neurosarcoma*
- *Neurofibrosarcoma*

Sympathetic ganglia tumours
- *Ganglioneuroma*
- *Ganglioneuroblastoma*
- *Neuroblastoma*

Paraganglionic tumours
- *Paraganglioma (pheochromocytomas)*
- *Chemodectoma*

Differential diagnosis (Box 17.1) of neurogenic tumours depends on the type of cell that originates from. Intercostal nerves give rise to neurilemoma (schwannoma), neurofibroma and neurogenic sarcoma. Sympathetic ganglionic tumours include ganglioneuroma, ganglioneuroblastoma and neuroblastoma. Pheochromocytomas (paragangliomas) may also be seen in the posterior mediastinum, and they derived from paraganglionic tissue. Rarely, neurogenic tumours from vagus or phrenic nerves may occur but are commonest in the middle mediastinum.

Takeda and colleagues [6] retrospectively reviewed 146 patients with intrathoracic neurogenic tumours who were treated over a 50-year period. There were 60 paediatric and 86 adult patients. There were 51 ganglioneuromas, 37 schwannomas, 30 neurofibromas, 18 neuroblastomas, 5 ganglioneuroblastomas and 5 lesions classified as "others". One hundred and six of these tumours (93.1%) were located in the posterior mediastinum, and in 13 patients (8.9%), there was an intraspinal extension, the so-called dumbbell tumours. The overall malignancy rate was 20.5% which was predominantly higher in patients younger than 5 years old.

Nerve Sheath Tumours

Neurilemomas (schwannomas) are the most common neurogenic tumour, representing 40–70% of all mediastinal tumours [7]. They arise from nerve sheath of spinal nerves or sympathetic cells and can be found anywhere in the chest. They tend to be benign and they are usually present in costovertebral sulcus. Schwannomas of the vagus or phrenic nerves are very rare, and they are most likely to occur in the middle or superior mediastinum. Neurilemomas are firm, lobulated and encapsulated masses that arise from Schwann cells, and they are found incidentally unless they cause bone erosion or spinal cord or sympathetic ganglion involvement. They are usually solitary masses. Histologically, they may also contain fibroblasts and

mast cells, and they can potentially exhibit cystic degeneration and haemorrhage. The cellular pattern occurs in the endoneurium and consists in spindle cells which are designated Antoni type A and other cells that exhibit myxomatous changes, the Antoni type B cells. Neurilemomas affect equally men and women and are found among 30 and 40 years of age.

Neurofibromas are friable, nonencapsulated but lobulated soft tumours with benign nature. They contain homogenously myelinated and unmyelinated nerve elements, nerve sheath cells, fibroblasts and matrix. One variety, the plexiform neurofibroma, may involve the whole nerve trunks or plexi. About 5% can have malignant transformation in adults, but the rates are significantly higher in children [8]. It is not unusual to be diagnosed as multiple lesions. Twenty-five to forty percent of patients presenting with nerve sheath tumours have neurofibromatosis type I (NF1, von Recklinghausen) [9]. They present during third or fourth decade of life with equal male to female ratio.

Malignant Tumours of Nerve Sheath Origin

Malignant nerve sheath tumours are spindle cell carcinomas and include malignant neurofibromas, malignant schwannomas and neurogenic fibrosarcomas. They are commonly found at upper and lower extremities, and the occurrence in the posterior mediastinum is rare. Mediastinal location of these masses makes them diagnosed when are already large in size compared with the extremities, which makes the complete excision challenging and the prognosis worse [10]. The association with von Recklinghausen disease is well known, and some authors report this occurrence to be 2–29% [11]. Malignant nerve sheath tumours may be sporadic or related to risk factors such as radiation. Additionally, they may arise from neurofibroma. They are often more than 5 cm in diameter but well circumscribed, and symptoms from nerve or vertebral compression are often present. There is no sex prevalence, and they are diagnosed at fourth and fifth decade of life.

Autonomic Ganglion Tumours

Tumours arising from sympathetic ganglia of the posterior mediastinum are ganglioneuroma, ganglioneuroblastoma and neuroblastoma. Their origin is the neuronal primordial neural crest cells and is discovered wherever sympathetic tissue exists such as the neck, the posterior mediastinum, the adrenal medulla, the retroperitoneum and the pelvis.

Neuroblastomas are commonly nonencapsulated elongated masses with varying degree of necrosis and cystic degeneration. It is the most aggressive among the three ganglionic tumours, and it is more common in children under 5 years old. It represents 8–10% of all malignancies in children and is the most common extracranial tumour at this age [12]. Ganglioneuroblastomas exhibit histologic features of neu-

roblastomas and ganglioneuromas, show intermediate differentiation and are moderately invasive. They have varying degrees of ganglion and neuroblasts cells. Additionally, they can be calcified and typically are elongated and vertically extended masses.

Ganglioneuromas are the benign tumours in this category. They are encapsulated masses formatted by clusters of ganglion cells and matrix but no neuroblasts. They are asymptomatic in presentation, but occasionally flashing or palpitations may occur due to secretion of catecholamines.

Paraganglionic Tumours

These are vascular tumours arising from aortic sympathetic paraganglia and vagus nerve. Histologically they contain amino precursor-uptake and decarboxylation cells (APUD), and they are often termed as extra-adrenal pheochromocytomas. Usually they occur at paravertebral sulcus, but they can be found in the middle mediastinum. They are locally invasive and rarely can metastasize [13]. Paragangliomas occur during second and third decade of life.

Clinical Presentation

In the majority, neurogenic mediastinal tumours are completely asymptomatic, and they are diagnosed incidentally during radiological imaging. Nerve sheath tumours in the thorax occur most commonly in either costovertebral sulcus. Occasionally they can present with symptoms such as chest pain, cough, Horner's syndrome and hoarseness. Some of these tumours may cause extradural compression of the spinal cord as a result of growth into the intervertebral foramen (dumbbell tumours). The rare malignant nerve sheath tumours, the neurofibrosarcomas, may produce pain more often than the benign ones due to erosion of the bone structures. Lymph node metastasis is rare but metastasis to distant sites is not unusual.

Tumours arising from sympathetic ganglia are observed in infants and children. Ganglioneuromas, which are benign tumours, may be found in patients more than 20 years old [13]. They present as large round or oval paravertebral masses, and they rarely exhibit intraspinal extension. Neuroblastoma and ganglioneuroblastoma are malignant tumours that are found mostly in children. Incidence of these tumours in adults can be as low as 2.5% [14]. Ganglion tumours are asymptomatic in general, but it is not uncommon to present with symptoms such as chest pain, cough, dysphagia, Horner's syndrome and paraesthesia.

Paragangliomas are tumours arising from chromaffin cells and specialised neural crest cells having the ability to secret neuropeptides and catecholamines. Although not correctly termed, they can be named as mediastinal pheochromocytomas despite the fact that the latter is used for tumours arising specifically from the adrenal medulla. Paragangliomas arising from parasympathetic ganglia are called

chemodectomas, and they do not secrete catecholamines. In contrast, paragangliomas arising from sympathetic ganglia secrete catecholamines and eventually can present with symptoms of hypertension, tachycardia and facial flushing. A 24-h measurement of catecholamines, free plasma metanephrines and VMA is essential in any patient with high index of suspicion of a paragangliomas as if it is missed might be catastrophic during surgery.

Imaging Studies

The initial radiographic examination of neurogenic tumours is a postero-anterior chest radiograph which reveals a paracardiac round shadow for masses of the posterior mediastinum and a paravertebral mass for lesions in the apex as incidental finding. The radiographic appearance of nerve sheath tumours is that of a solitary, smoothly rounded mass in either side of paravertebral sulcus at any level. Computed tomography (Fig. 17.1) may show calcifications in schwannoma; cystic changes can be found in either neurilemoma or neurofibroma. When CT raises the suspicion of intraspinal extension, magnetic resonance is the examination of choice.

Tumours arising from sympathetic chain expand along the spinal axis, and in contrast to nerve sheath tumours, they do not show calcification or cystic changes in computed tomography. Additionally, rarely do they extend through the intervertebral foramen. Ganglioneuromas are homogenous low-attenuation lesions on both enhanced and unenhanced CT [15]. Neuroblastoma is presenting as soft tissue tumours with signs of aggressiveness, and ganglioneuroblastomas have features of both ganglioneuromas and neuroblastomas. Paragangliomas appear with significant enhancement following administration of contrast medium. In MRI studies, ganglioneuromas appear as well-defined mass with heterogeneous high-signal intensity on T2-weighted images [16]. Neuroblastomas and ganglioneuroblastomas show more heterogeneity due to tumour necrosis.

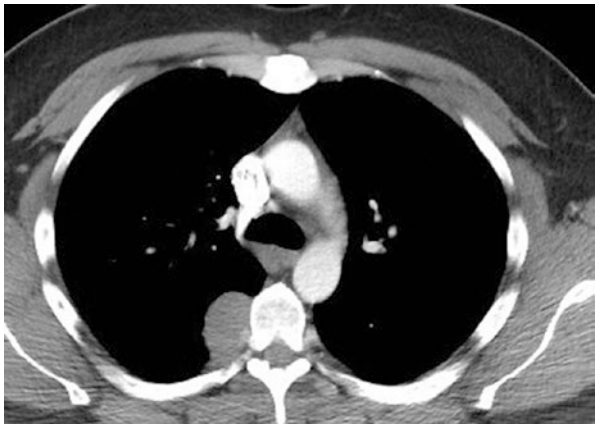

Fig. 17.1 Computed tomography of posterior mediastinal schwannoma

Management

Surgery remains the mainstay of treatment, and complete surgical excision provides definitive diagnosis and cure. The risk of recurrence after complete surgical removal of benign lesions is considerably low, but recurrence or even distant metastasis may occur after operating on malignant ganglion tumours such as neuroblastoma and ganglioneuroblastoma [17]. Despite the not uncommon practice to offer chemotherapy and/or radiotherapy to large malignant tumours, a study from Decarolis et al. [18] showed that patients with R1 resection of ganglioneuroblastoma did not benefit from chemotherapy or radiotherapy when the residual disease was less than 2 cm.

Multiple surgical approaches have been described for access to the posterior mediastinum that they depend mainly on the relationship of the tumour to the spine and the presence or not of intraspinal extension. These are the anterior cervical approach, the posterolateral thoracotomy, the posterior paravertebral approach and the minimally invasive techniques such as video-assisted thoracic surgery (VATS) and robotic-assisted thoracic surgery (RATS).

The anterior transcervical approach is used for posterior mediastinal tumours at the thoracic apex and especially lesions arising from T1 nerve root although thoracoscopic approach in experienced hands may suffice. Brachial plexus injury to these cases after VATS has been reported [19]. The incision is along the anterior border of the sternocleidomastoid muscle and can be extended to the manubrium and then infraclavicularly. This gives access to all the vital vascular structures of the thoracic inlet. Lower tumours can be approached by a posterior paravertebral incision where the tumour is dissected extrapleurally after division of one or more ribs. Standard posterolateral thoracotomy has been traditionally the access of choice for many surgeons, and the intercostal space entered depends on the level of the tumour determined by preoperative workup.

Dumbbell tumours are the most challenging intraoperatively as they mandate initial resection of the tumour from the spinal cord with a laminectomy followed by removal of the rest from the chest. Operation is usually commenced by the neurosurgeon with the patient in the prone position followed by repositioning in lateral decubitus position and entrance into the pleural cavity by a posterolateral thoracotomy. A combined approach using video-assisted thoracoscopic surgery has also been reported [20].

VATS

Minimally invasive techniques have been reported as a safe alternative and even better than open approaches when indicated, demonstrating minimal blood loss, less postoperative stay and shortened length of stay [21]. Access can be made by using one to three ports. The patient is intubated with a double-lumen endotracheal tube

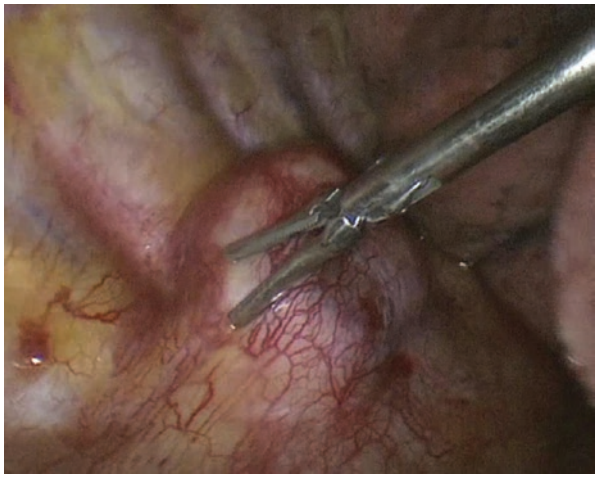

Fig. 17.2 Intraoperative view during VATS resection of posterior mediastinal schwannoma

and placed in a full lateral decubitus position. Entrance to the pleural space is usually by a camera port at the 7th–8th intercostal space at the midaxillary line followed by two ports at the 4th intercostal space, one below the tip of the scapula and the other at the anterior axillary line. The lung is retracted anteriorly, and the parietal pleura covering the tumour is incised. The mass is dissected off the chest wall (Fig. 17.2), and all feeding vessels are ligated using clips or energy device. The intercostal nerve involved is ligated and divided completely with care not to injure the dura when a tumour is close to the intervertebral foramen as this could result to leakage of cerebrospinal fluid to the pleural space. A small-bore chest drain is inserted which can be removed the same day.

Robotic-assisted resection of posterior mediastinal tumours has also been described to be feasible and safe with outcomes similar to traditional thoracoscopic surgery [22]. Major advantages of the robotic system are the three-dimensional visual field, minimal tremor and minimal intercostal trauma by the trocars due to the remote centre technology.

Neurenteric Cysts

Neurenteric cysts are defined as thin-wall cystic structures that are accompanied with a cervical or thoracic vertebra anomaly. The association with vertebral abnormalities has been well documented in the past [23]. The pathogenesis mechanism occurs early in gestation and is speculated that is due to persistence of neurenteric canal, abnormal splitting of the notochord with endoderm-ectoderm adhesion or aberrant escalation of the notochord. They are more common in infants and children, and diagnosis of large cysts can be made by prenatal ultrasonography.

Presenting symptoms depends on the size and the location. Sometimes they are too large that can cause respiratory distress and stridor. Vertebral abnormalities such

as spina bifida, fused vertebra, and hemivertebra have been described [24]. Diagnosis is made with standard chest X-ray. CT and MRI may be adjuncts especially when an intradural extension is suspected. Surgical excision either by thoracotomy or by video-assisted thoracic surgery [25] is the standard of care.

Epilogue

Neurogenic tumours are masses that arise from neural elements of the posterior mediastinum. They comprise 12–21% of all intrathoracic tumours and in 95% are derived from intercostal nerves and sympathetic chain. These are discovered incidentally, and diagnosis is not definite until the surgical excision. Malignant neurogenic tumours are the second commonest cancer in children. Standard surgical approaches are the traditional forms of treatment, but minimally access surgery in terms of video-assisted or robotic-assisted is preferred when indicated.

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Chapter 18
Esophageal Tumors

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Anatomy

Esophagus is a muscular tube with a length of 20–30 cm and extends from the pharynx to the stomach, and its main function is the transfer of food and liquids. It begins from the inferior edge of the cricoid cartilage and descends posterior to the trachea and anterior to the vertebral column into the thorax. It is a structure of the posterior mediastinum and enters the abdominal cavity penetrating the diaphragm along with vagus nerves at the level of T10 vertebra. The intra-abdominal esophageal length just before the cardia is 3–5 cm. In the thorax and below the T5 vertebra, it runs slightly on the right of the midline having the descending aorta on the left. There are important anatomic relations with vital structures through its whole length. The left main bronchus is lying just anterior while crossing the midline causing a natural narrowing. Then the esophagus descends just posterior to the left atrium and enters the abdomen in front of the thoracic duct and medial to azygos vein.

Its arterial supply comes from the inferior thyroid arteries in the neck, the esophageal branches from the descending aorta in the thorax, and the inferior phrenic arteries in the abdominal part. Venous drainage is to the inferior thyroid veins, azygos, and hemiazygos vein systems and to the left gastric and coronary veins which represent portosystemic anastomosis and explains the pathophysiology of esophageal varices in portal hypertension. Innervation of the esophagus comes mainly from the vagus nerves. The recurrent laryngeal nerves supply the cricopharyngeal muscle and the cervical esophagus, so an injury to these nerves may result in aspiration due to dysmotility.

There are two sphincters through the whole length which are the upper and the lower esophageal sphincters. These represent zones of high intraluminal pressure rather than pure anatomical landmarks. The upper esophageal sphincter is formed

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by fibers of cricopharyngeal and inferior constrictor muscles. The lower esophageal sphincter is a high-pressure zone 3–4 cm which is formed by the right and left diaphragmatic crura, the phrenoesophageal membrane, and the acute angle of His [1]. Its main function is to prevent gastric contents to enter the esophagus.

Esophageal wall consists in four layers which are the mucosa, the submucosa, the muscularis propria and the tunica adventitia. Muscular layer has an inner circular and an outer longitudinal layer. Esophagus is the only structure of the alimentary part that has no serosal layer. The thoracic part is covered by parietal pleura. Identification of these layers during endoscopic ultrasound examination (EBUS) is crucial when staging a malignant tumor. The epithelium is squamous and is the transformation of this epithelium to a columnar (enteric metaplasia) which defines Barret's esophagus.

Embryology

Esophagus becomes recognizable approximately at the third week of gestation as a structure separating the pharynx and the stomach [2]. It rapidly elongates during the sixth and seventh weeks mostly by cephalad migration of the laryngopharyngeal area by appearance of paired grooves. These grooves fuse and form the tracheoesophageal septum. This septum divides the foregut to ventral laryngotracheal tube and the dorsal esophagus.

Tumors of the Esophagus

Esophageal tumors may encompass a challenging surgical diagnostic problem, and knowledge of the specific radiographic, histologic, and surgical management is of paramount importance for the general thoracic surgeon. Esophageal cancer is nowadays the sixth most common cause of cancer-related deaths worldwide and is more common in men [3]. The commonest location is at the lower third of the esophagus and often involves the gastroesophageal junction. Benign tumors are rare, and they are categorized according to the layer of origin. They comprise approximately 1% of esophageal tumors.

Carcinoma of the Esophagus

Histologically, esophageal cancers are classified as squamous cell carcinomas and adenocarcinomas. Less common malignancies are leiomyosarcoma, adenoid cystic carcinoma, melanoma, and anaplastic cell carcinoma. Squamous carcinomas occur in a higher rate in Eastern Europe and Asian countries, while adenocarcinomas are the commonest esophageal malignancy in Western countries and the United States.

Tobacco and alcohol use have been demonstrated as the strongest risk factors for squamous cell carcinoma [4]. In contrast, gastroesophageal reflux disease (GERD), Barret's esophagus, and obesity are established risk factors for adenocarcinoma. In nationwide Swedish case-control study, patients with long-standing GERD had a 43 times increased risk of developing adenocarcinoma than control group [5]. Hereditary predisposition syndromes associated with esophageal malignancies such as Fanconi anemia and tylosis are also risk factors. Vitamin deficiencies are not uncommonly related. Squamous cell carcinomas occur in the first two thirds of the esophageal length, and adenocarcinomas involve the middle and distal third commonly at the gastroesophageal junction.

Clinical Presentation

The commonest presenting symptom of patients with esophageal cancer is dysphagia which usually starts with digestion of solids and progresses to liquids. Patients may actually point the site of the obstruction. Other symptoms that may occur are odynophagia, weight loss, anemia, hematemesis, and aspiration pneumonia. Less frequently, hoarseness from recurrent laryngeal nerve invasion or Horner's syndrome may be noticed. In advanced stages, patients may present with pleural effusion, ascites, or supraclavicular lymphadenopathy. Retrosternal and epigastric pain are also symptoms of obstruction. Patients with adenocarcinoma often present with a long-standing history of reflex and regurgitation of foods. Clinical examination may reveal entirely normal findings although cachexia and dehydration can be found. Laboratory studies can show anemia, hypoproteinemia, abnormal liver function tests, or hypercalcemia from distant metastasis.

Diagnostic Workup and Staging of Esophageal Cancer

The first and simplest diagnostic tool that is used for evaluation of any patient with dysphagia is barium swallow contrast study. Esophageal cancers may present as a protruding lesion in the lumen or as ulcerations of the esophageal wall. Additional information which can be obtained during the barium swallow is the presence or not of an esophageal motility disorder, hiatus hernia, or obstruction. As soon as a suspicious lesion is identified, flexible esophagogastroscopy is the gold standard for the diagnosis. Exact location of the tumor and measurement of the distance from the teeth and the gastroesophageal junction are of vital importance when considering surgical intervention. Biopsies should be taken from any suspicious lesions, and the pathology report should include the depth of invasion, grade, histologic type, and the presence of Barret's esophagus [6].

Staging of esophageal cancers (Box 18.1) is based on TNM system and includes squamous cell carcinomas and adenocarcinomas. Computed tomography scans of

Box 18.1 Staging of Esophageal Cancer
American Joint Committee on Cancer (AJCC). TNM Classification of Carcinoma of the Esophagus and Esophagogastric Junction (7th ed., 2010).
Primary Tumor (T)

TX Primary tumor cannot be assessed T0 No evidence of primary tumor Tis High-grade dysplasia.
T1 Tumor invades lamina propria, muscularis mucosae, or submucosa.

T1a Tumor invades lamina propria or muscularis mucosae.
T1b Tumor invades submucosa

T2 Tumor invades muscularis propria
T3 Tumor invades adventitia
T4 Tumor invades adjacent structures

T4a Resectable tumor invading pleura, pericardium, or diaphragm.
T4b Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed.
N0 No regional lymph node metastasis.
N1 Metastasis in 1–2 regional lymph nodes.
N2 Metastasis in 3–6 regional lymph nodes.
N3 Metastasis in seven or more regional lymph nodes.

Distant Metastasis (M)

M0 No distant metastasis.
M1 Distant metastasis.

(Reprinted from Edge, Stephen B. and American Joint Committee on Cancer. AJCC Cancer Staging Manual, 7th ed. New York: Springer Science and Business Media; 2009.)

the chest and abdomen (Fig. 18.1) as well as positron emission tomography can define the M status of the disease and to a lesser degree the N status. The advent of endoscopic ultrasonography (EUS) has dramatically increase the accuracy of preoperative T and staging caring the ability to obtain tissue samples with the use of fine needle aspiration (FNA). The pooled sensitivity and specificity of EUS to diagnose T1–T4 tumors are 81.6–92.4% and approximately 95%, respectively [7]. The use of FNA can improve the sensitivity and specificity of N status to 95%. Accurate staging is of paramount importance as endoscopic mucosal resection (EMR) is indicated in high-grade dysplasia and even in early stages of the disease [6, 8]. Surgical staging with means of VATS or laparoscopy can also provide 95% accuracy and has been proposed by several reports [9, 10].

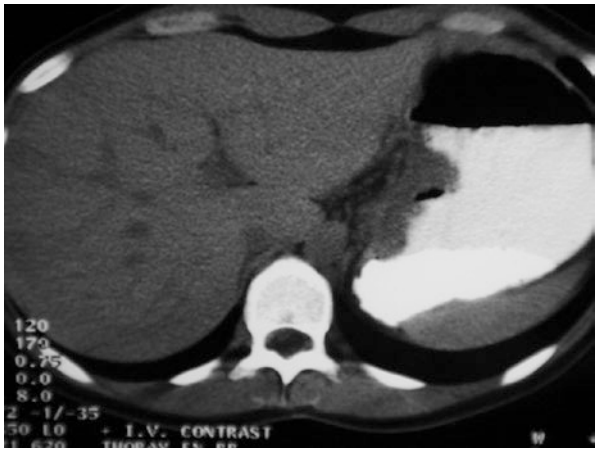

Fig. 18.1 CT showing carcinoma of the cardia

Surgery for Esophageal Cancer

Surgical treatment of esophageal cancer in terms of esophagectomy offers the best chance of cure and relief of symptoms. Several approaches have been described with no evidence supporting one technique over the other. The surgical approach depends on the location of the tumor, the extent of the lymph node dissection, and the preference of the surgeon. Many conduits for replacement of the esophagus have been utilized such as the stomach (best option), colon, and jejunum. Surgical approaches include the transhiatal esophagectomy, Ivor-Lewis esophagogastrectomy, McKeown esophagogastrectomy, and left thoracoabdominal approach. The location of the tumor is the best determinant of the surgical approach. Mid- and upper-esophageal cancers are approached better with the McKeown (three-hole) operation while tumors of the lower third by Ivor-Lewis or left thoracoabdominal procedures.

It is the surgeon's responsibility to assess the fitness of every patient before the operation evaluating carefully the performance status, the presence of cardiovascular and respiratory problems, and the type of the procedure that he should undertake. Every patient should have a baseline electrocardiogram, pulmonary function tests, and blood tests including albumin, ferritin, and electrolytes. Nutritional support prior to the operation has a substantial role as many patients with esophageal cancer are malnourished and dehydrated.

Regardless of what technique will be used, some important steps are mandatory for a safe and effective procedure. After intubation with a double-lumen endotracheal tube, the operation commences from the abdomen with mobilization of the stomach. The left gastroepiploic artery is identified and entrance to the lesser sac is achieved. Dissection continues along the greater curvature with division of the short gastric vessels. The left gastric artery is identified from its takeoff from the celiac artery, and any lymph nodes are excised. After ligation of the left gastric artery, further mobilization of the duodenum with a Kocher maneuver is achieved to gain enough length for

an intrathoracic positioning of the stomach. A draining procedure such as pyloroplasty or pyloromyotomy is performed at this stage. Dissection proximally to the crura diaphragm is then accomplished, and the proximal stomach with preservation of the fundus is divided with a linear stapler, so a tube is created. A jejunostomy tube is being placed normally at this stage. Then the patient is placed at the decubitus position, and a posterolateral thoracotomy typically at the level of the fifth or sixth intercostal space is performed. This stage is performed initially at McKeown procedure. After entrance into the pleural space, the lung is retracted anteriorly, and the inferior pulmonary ligament is divided. Dissection of the esophagus is up to the level azygos vein, but if additional surgical margins are needed, azygos can be divided. Further dissection down to the diaphragm facilitates the removal of the specimen (Fig. 18.2). The esophagus is divided proximally and the gastric tube is pulled up to the chest. An intrathoracic anastomosis is created either with anastomotic devices or hand-sewn. Transhiatal esophagectomy doesn't include a thoracic part, but instead the dissection is carried on blindly into the posterior mediastinum. A neck incision is then performed with further mobilization of the cervical esophagus, and the anastomosis is performed at this point. This reduces the risk of an increase in morbidity and mortality after an anastomotic leak which is easier to be managed in the neck compared to the thorax. The left thoracoabdominal approach involves division of the diaphragm and the costal cartilages. Again, an intrathoracic anastomosis is achieved. Minimally invasive approaches in terms of video-assisted or robotic-assisted thoracic surgical procedures offer minimal blood loss, reduced postoperative pain, and early return to daily activities [11] but longer operative times where observed.

Postoperative care of the patient undergoing esophageal surgery is essential. The most common complications involve the respiratory system with the form of atelectasis, infection, and aspiration in cases of recurrent laryngeal nerve injury. Early pulmonary toilet and mobilization attempt to minimize these risks. Maintenance of optimal cardiovascular status is crucial for the perfusion and oxygenation of the conduits and the anastomosis. Anastomotic leak is a serious complication after esopha-

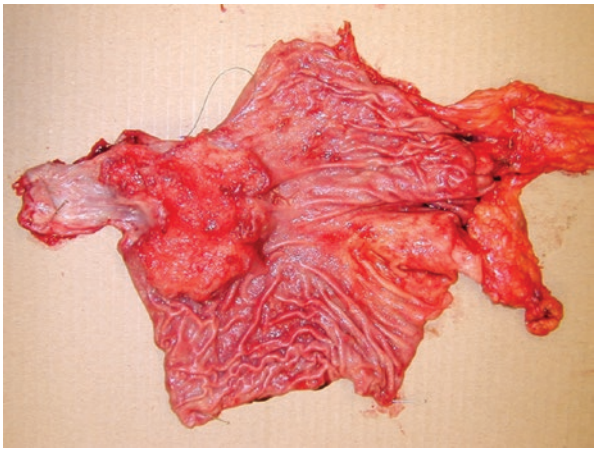

Fig. 18.2 Specimen after Ivor-Lewis esophagogastrectomy showing carcinoma of the cardia

gectomy and occurs more commonly after cervical anastomosis, but it can be managed conservatively in most cases. In contrast, leakage of an intrathoracic anastomosis may cause significant respiratory complications such as empyema, and management depends on the size and the general status of the patient. Low-output leaks may heal spontaneously, and all needed is adequate drainage of the pleural cavity, nutritional support, antibiotic cover, and nil by mouth. Larger leaks should be addressed more aggressively and the mortality is high. Management of small leaks with the use of stents has also been described with a favorable outcome [12]. Chylothorax after esophagectomy may occur with an incident of 2–10% [13]. There are no sufficient data to support prophylactic mass ligation of the thoracic duct and surrounding tissue. Late complications of esophagectomy include anastomotic stricture which can be managed with endoscopic dilatation, delayed gastric emptying, and recurrence.

Despite innovation in modern chemo-radio therapeutic agents and surgical techniques, survival for esophageal cancer remains poor. Most of the patients are diagnosed in advanced stage, and the role of the general thoracic surgeon is often palliative. A multidisciplinary approach should be applied for every patient diagnosed with esophageal malignancy.

Benign Tumors of the Esophagus

Benign esophageal tumors are rare clinical entities with a percentage less than 1% [14]. Classification of these lesions based on the layer of origin is the most useful method for diagnostic and management workup. Tumors of the mucosa are squamous papillomas and fibrovascular polyps. Lipoma, neurofibroma, granular cell tumor, and salivary gland tumor arise from the submucosa. Leiomyoma is the most common benign tumor of the esophagus and originates from muscularis propria. Duplication cysts and foregut cysts are also benign tumors of the esophagus.

Benign esophageal tumors are usually asymptomatic, and they are discovered incidentally during investigation for other reasons. Dysphagia may be the only presenting symptom. Endoscopy and EUS remain the most valuable diagnostic tests for accurate description of this pathology. The distinct of EUS is the ability to visualize every layer of esophageal wall.

Squamous Papilloma and Fibrovascular Polyps

Esophageal papillomas are very rare and small in size sessile projection in the distal esophagus which are found incidentally. Biopsy of these lesions differentiates them from superficial squamous carcinoma. Although the etiology is unknown, association with chronic inflammation due to GERD and human papillomavirus has been described [15]. Fibrovascular polyps are cylindrical lesions with a large pedicle which are commonly found on the cervical esophagus. Histopathologic features

include fibrous, vascular, adipose, and neural tissue. Occasionally they can reach considerably large size and cause symptoms of obstruction. Endoscopic resection is usually the first line of treatment.

Lipoma, Granular Cell Tumor, and Neurofibroma

Lipomas are soft yellowish tumors that protrude to esophageal lumen. EUS can safely provide the diagnosis. They are clearly benign and can be followed up. Granular cell tumors are the second most common cause of benign stromal tumors after leiomyomas. Patients can present with dysphagia or retrosternal discomfort, but this is a minor percentage as most of them are asymptomatic. Although most granular cell tumors have indolent course, it is estimated that 1–3% of them are malignant with a 5-year survival less than 35% [16]. Endoscopic mucosal resection or submucosal dissection has been demonstrated as the therapy of choice for these lesions. Neurofibromas are rare, benign tumors of the esophageal submucosa and may be confused with other smooth muscle tumors such as leiomyomas, leiomyosarcomas, or gastrointestinal stromal tumors (GIST). Histologic examination is best obtained with EUS rather than superficial biopsies and demonstrates spindle-cell structures, no epithelioid features, and a prominent lymphoid pattern. Endoscopic enucleation is easily achieved, but larger lesion may warrant open or thoracoscopic esophageal resection especially with masses larger than 5 cm in diameter and when malignancy needs to be excluded [17].

Leiomyoma

Leiomyomas are benign smooth muscle tumors that arise from the muscularis propria. They represent the commonest nonmalignant esophageal tumor and account for more than 70% of these neoplasms (Fig. 18.3). They arise from inner circular muscle and located in the middle or distal third of the esophagus. Of all gastrointestinal leiomyomas, only in 10% of cases are found in the esophagus [18]. They can sometimes cause dysphagia, chest discomfort, or bleeding. Barium esophagogram may show a filling defect, and further evaluation with endoscopic examination reveals a typical bulging inside the esophageal lumen covered by normal epithelium.

Surgical enucleation for tumors larger than 5 cm or for those causing symptoms usually through a posterolateral thoracotomy or minimally invasive approach is the management of choice [19]. Giant leiomyomas are defined as larger than 10 cm in diameter, and in these cases esophagectomy may be the optimal treatment [20]. Prognosis is excellent. Although malignant transformation is rare, simultaneous presentation of leiomyoma with leiomyosarcoma has been described [21, 22].

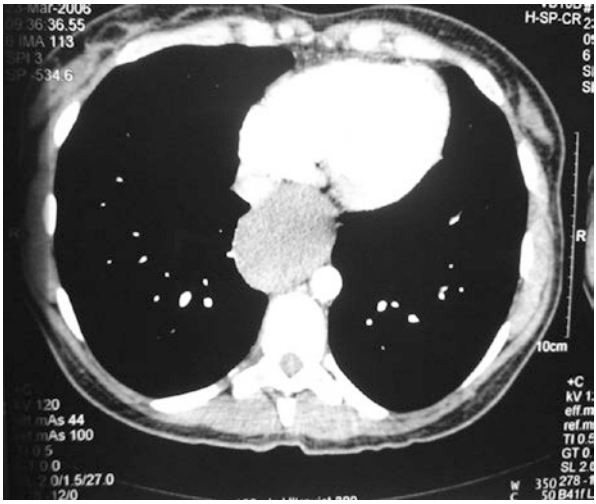

Fig. 18.3 CT appearance of esophageal leiomyoma

Esophageal Cysts

Esophageal cysts are the second most common benign esophageal tumors accounting in 20% of cases. The defect responsible for esophageal cysts is the failure of proper development of the posterior division of primitive foregut. They can be pure epithelial cysts and congenital foregut cysts lined by squamous, respiratory, or columnar epithelium and may contain smooth muscle, fat, or cartilage. Esophageal duplication cyst is another type of congenital foregut cyst which is lined by squamous epithelium and can contain gastric mucosa. They are attached to esophagus or tracheobronchial tree, and typically they are not in continuation with native esophagus as they develop separately. Additionally, they can present along with other congenital abnormalities such as tracheoesophageal fistula, vertebral abnormalities, and spinal cord anomalies [23].

Many patients with foregut cysts present in the first year of life with life-threatening respiratory compromise due to a mass effect. Barium swallow studies can demonstrate an extrinsic compression of the lumen, but they may be missed if there is no connection with esophageal wall and arise from periesophageal tissue. Computed tomography is the examination of choice. Endoscopic ultrasound can define the intramural or extraesophageal nature of the tumor. These lesions are found typically in the posterior lower mediastinum and when they are seen in adults are more common to be symptomatic [24]. Symptoms that may occur are cough, stridor, and cardiac arrhythmias due to compression of the cyst to surrounding structures. They can also rarely be complicated by infarction, rupture, or malignancy [25]. Removal of these lesions when diagnosed is advised. Endoscopic drainage of esophageal cysts has been reported, but it is more likely for recurrence to develop as the lining of the cyst is not destroyed. In general, simple cysts may be enucleated, but foregut cysts should be properly excised either with open or minimally invasive techniques.

Epilogue

Esophageal tumors are challenging cases regarding diagnosis and management. Cancer of the esophagus mandates a multidisciplinary approach, and the role of the thoracic surgeon is to assess the fitness of the patient to undergo a major operation and what surgical approach is preferred for each case. Despite development of new chemotherapeutic agents and progress in surgical techniques and postoperative care, prognosis remains low. Benign tumors are less than 1% of all masses, and every patient with an esophageal tumor should be evaluated to exclude or confirm malignancy.

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Correction to: The Mediastinal Mass

Renato Franco, Federica Zito Marino, and Antonio Giordano

Correction to:
R. Franco et al. (eds.), *The Mediastinal Mass,*
Current Clinical Pathology,
https://doi.org/10.1007/978-3-319-90368-2

The figures were missed to include in the chapters (11 and 12) and placed below.

Chapter 11: Thyroid

Maria Grazia Chiofalo, Sergio Venanzio Setola, Fabio Sandomenico, Orlando Catalano, Raffaella D' Anna, Paolo Vallone, and Luciano Pezzullo
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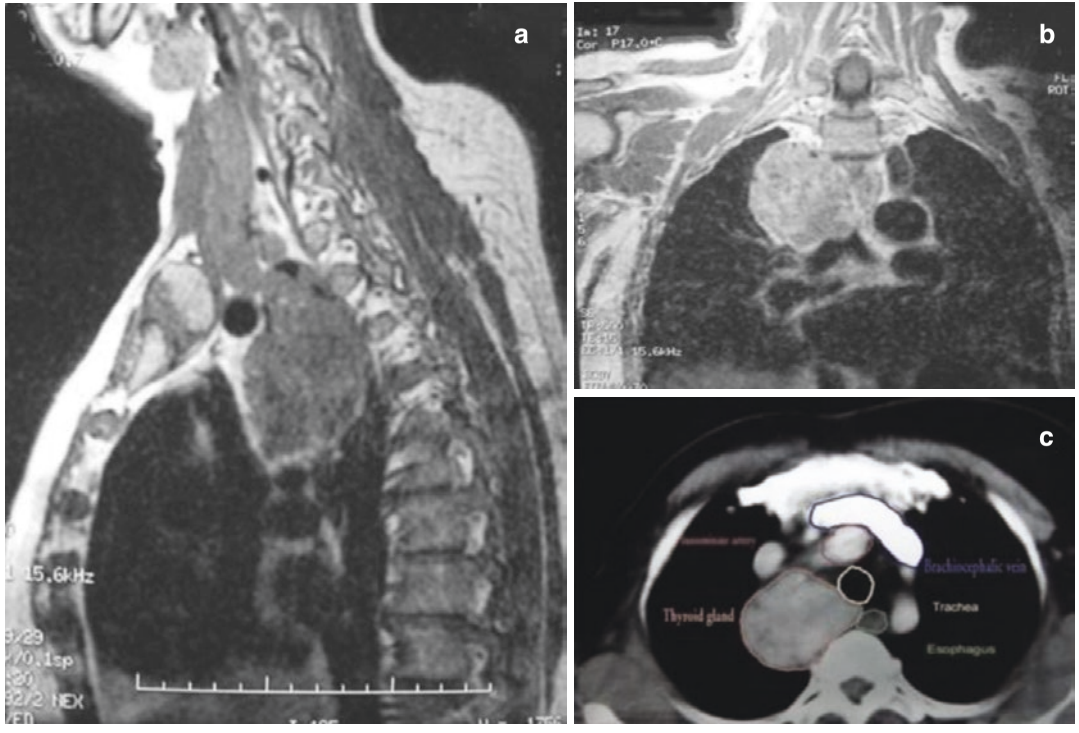

Fig. 11.1 Voluminous posterior mediastinal goiter. MRI T1-w sagittal and coronal plane and CT scan axial plane after intravenous contrast administration

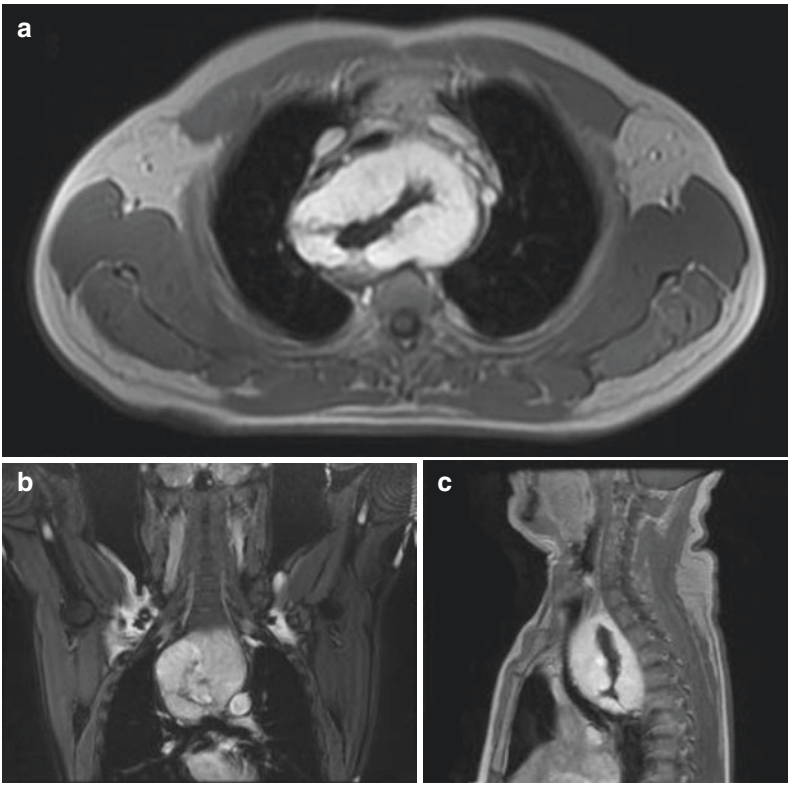

Fig. 11.2 Voluminous posterior mediastinal thyroid mass with tracheal and great vessels displacement. MRI T1-w FS after intravenous contrast administration. A) Axial plane B) Coronal plane C) Sagittal plane

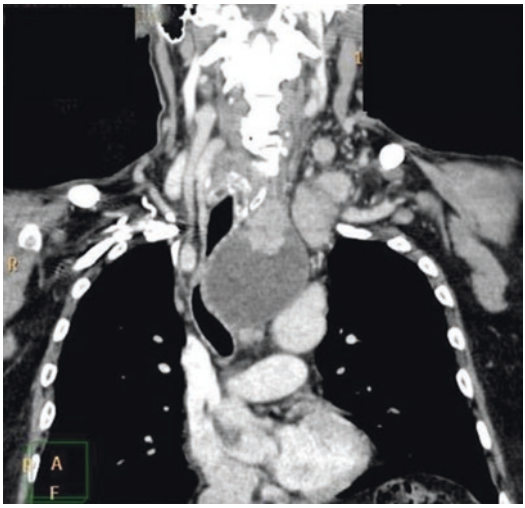

Fig. 11.3 Mediastinal extension of large thyroid carcinoma with severe tracheal compression and dislocation and left neck lymph node metastases. Coronal plane CT scan after intravenous contrast administration

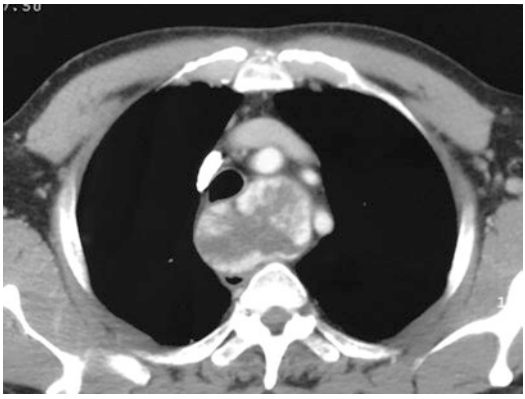

Fig. 11.4 Voluminous posterior mediastinal goiter with tracheal, esophageal and great vessels dislocation. Axial plane CT scan after intravenous contrast administration

Chapter 12: Parathyroid

Maria Grazia Chiofalo, Sergio Venanzio Setola , Fabio Sandomenico, Orlando Catalano, Raffaella D'Anna, Paolo Vallone, and Luciano Pezzullo
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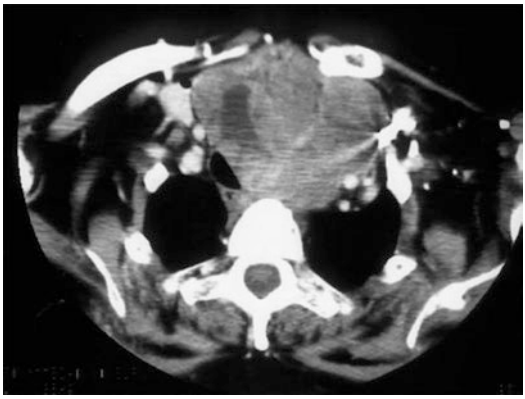

Fig. 12.1 Huge parathyroid carcinoma: large solid left neck mass, with extension to the anterior mediastinum and displacement of the trachea, oesophagus and great vessels. Axial CT scan after intravenous contrast administration

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