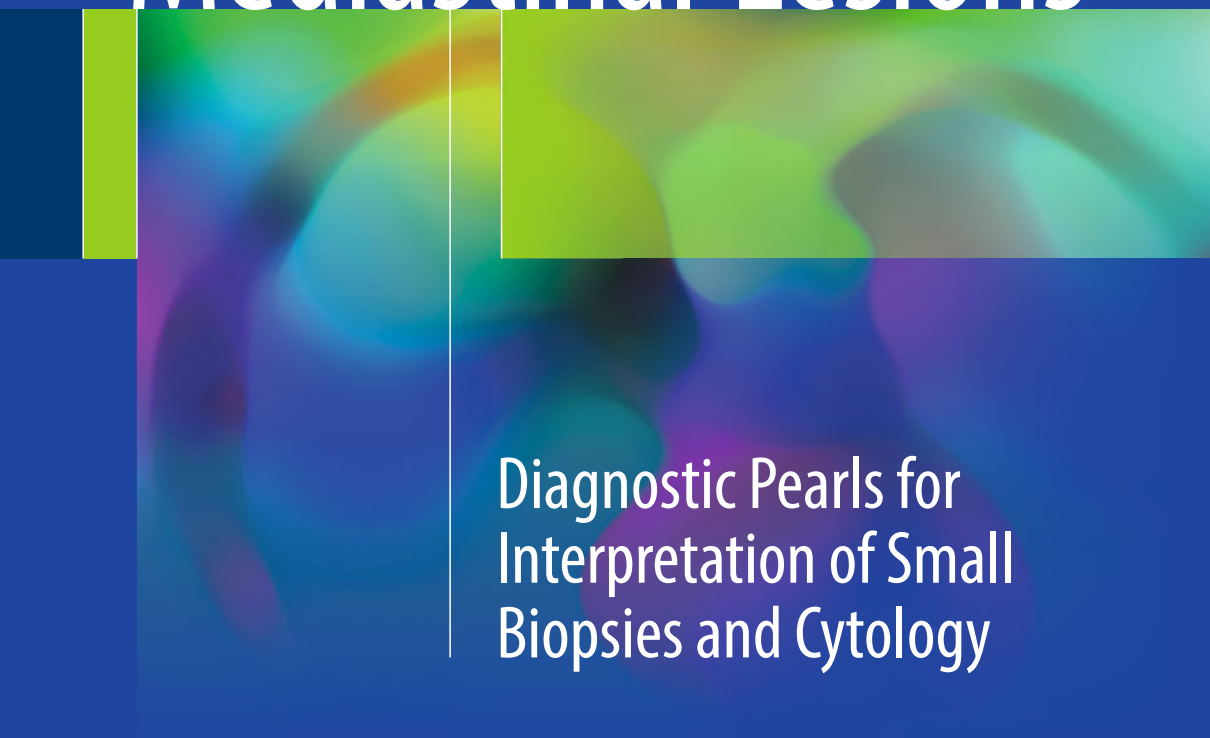
Anja C. Roden
Andre L. Moreira
Editors

Mediastinal Lesions



Diagnostic Pearls for Interpretation of Small Biopsies and Cytology

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Preface

Mediastinal tumors are rare. Because of the paucity of these lesions, the experience of the practicing pathologist with biopsies from mediastinal lesions might be limited. Furthermore, mediastinal lesions are commonly biopsied because treatment differs based on diagnosis, and a surgical resection may not be performed or only after neoadjuvant therapy. Although the biopsies are primarily from malignancies, other lesions such as sclerosing mediastinitis or IgG4-related disease might also be encountered and are equally challenging.

This book will focus on common mediastinal lesions and will also highlight some uncommon entities that are important because they might require different treatment modalities. We will highlight morphologic, immunophenotypic, and molecular features that can help to distinguish the disease entities in the mediastinum. Furthermore, the book will provide an overview of surgical procedures and challenges pertinent to mediastinal lesions. We also added a chapter on radiologic features of mediastinal lesions. These contributions will emphasize the need of a multidisciplinary approach to the diagnosis of mediastinal lesions. Moreover, a systematic approach to a mediastinal biopsy is beneficial and clinical history (other neoplasms, temporal evolution of disease, age and gender of patient, serologic results, etc.), findings on imaging studies, type and location of the biopsy, and mediastinal compartment of the lesion are important aspects and assets for the histopathologic evaluation of a mediastinal biopsy.

Mediastinal lesions can be primary or metastatic. Furthermore, many of the lesions that are primary to the mediastinum can also occur elsewhere in the body (i.e., germ cell tumors, neuroendocrine tumors, soft tissue neoplasms, or IgG4-related disease); however, some histopathologic and immunophenotypic features are unique to the mediastinal location. For example, while the neoplastic cells in mediastinal seminoma are cytological similar to their gonadal counterpart, granulomatous reaction and cyst formation are common in mediastinal seminomas sometimes masking the neoplastic cells. Also, a dot-like staining pattern with certain keratins appears to be more common in mediastinal seminoma. Morphology and immunophenotype can be overlapping between primary mediastinal lesions. In addition, the differential diagnosis of primary mediastinal lesions is different from tumors with similar histologic features elsewhere. Also, some tumors occurring in the mediastinum are very rare such as NUT carcinoma, but available promising

clinical trials together with a poor prognosis require a rapid diagnosis. Other neoplasms are unique to the mediastinum such as thymic epithelial tumors. Thymic epithelial tumors have to be considered in the differential diagnosis, especially of lymphomas, as treatment and prognosis are quite different. However, these tumors are particularly prone to misdiagnosis because of their morphologic and immunophenotypic overlap specifically with lymphomas.

The mediastinum represents a unique location because of the vital structures that are present in that location leading potentially to life-threating situations. For instance, tumors might compress or invade large vessels such as superior vena cava, aorta or pulmonary artery, cardiac structures or large airways. These situations can lead to an anxious clinician which might add to complicated situations.

This book will highlight cytologic, morphologic, immunophenotypic, and molecular pearls and emphasize pitfalls in the diagnosis of mediastinal neoplasms on biopsies. A large number of photographs will help pathologists in their day-to-day practice with difficult and unusual lesions and also with common problems encountered in the pathology of mediastinal lesions. These include:

- The distinction of thymoma from lymphoma, thymic carcinoma, and neuroendocrine tumors.
- The distinction of primary mediastinal neoplasm from metastatic disease.
- The identification of common germ cell tumors, specifically seminomas, and how to distinguish them from its mimics such as lymphoma, thymoma, and thymic carcinoma.
- The workup of small round blue cell tumors in the mediastinum.
- The understanding of morphologic, immunophenotypical, and molecular features of NUT carcinoma and when to consider the diagnosis.
- The diagnostic approach to mediastinal mesenchymal tumors.
- The distinction of non-neoplastic from neoplastic fibrosing lesions.
- The recognition of limitations of small mediastinal biopsies and what can or cannot be diagnosed on these specimens.
- The optimal utilization of ancillary techniques in the diagnosis of mediastinal lesions on small biopsies.

It is our sincere hope that you will find this book useful when confronted with a biopsy from the mediastinum.

Rochester, MN, USA — Anja C. Roden
New York, NY, USA — Andre L. Moreira

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Rochester, MN, USA Anja C. Roden

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Introduction

1

Frank Detterbeck

Establishing the diagnosis of mediastinal tumors is viewed as challenging. Why? One reason is that these are relatively rare conditions, meaning that very few physicians have a large experience. This is compounded by the fact that the number of different tumors and conditions is large, thus further segmenting mediastinal tumors into multiple even smaller subgroups. Furthermore, the fundamental nature of mediastinal lesions is quite varied, ranging from fulminant to indolent malignant tumors and from benign conditions with little impact on a patient's life to life-threatening benign lesions. In addition, the features of a mediastinal lesion that are most useful to suggesting or establishing a diagnosis vary, including clinical presentation, imaging characteristics, and microscopic appearance. There is a strong need from a management perspective to establish the diagnosis with a reasonable degree of confidence before a treatment intervention, yet the optimal approach to obtaining tissue is varied and depends on the suspected diagnosis. Finally, most clinicians lack a structure of how to approach mediastinal tumors, and often explore various avenues (i.e., imaging, biopsy) without a clear understanding of what is at the top of their differential diagnosis list and their rationale for a particular approach (e.g., liquid vs. tissue biopsy).

A structure for approaching mediastinal lesions has been proposed by the International Thymic Malignancy Interest Group (ITMIG), a global multispecialty organization devoted to promoting medical science regarding mediastinal tumors in general, not only thymic tumors [1, 2]. This begins with basic patient characteristics that are known (age, sex), which already focus the differential diagnosis. Sometimes there are particular features that establish a diagnosis with a high degree of certainty (e.g., imaging features that are diagnostic for a substernal goiter or a benign

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teratoma, the presence of myasthenia gravis or other thymic paraneoplastic syndromes in a patient over 40 with an anterior mediastinal mass). In such cases a biopsy is usually not needed.

More often, a combination of clinical, imaging, and histologic information is needed to establish a diagnosis. The prioritization of the differential diagnosis list, and the relative impact of clinical, imaging and histologic information varies depending on aspects of the case. This highlights the importance of approaching these patients in a multidisciplinary fashion. Unless there are pathognomonic features as mentioned above, a discussion between the clinician, radiologist, and pathologist is tremendously beneficial in aggregating the information, narrowing the diagnostic question, and pointing out the best way to confirm suspected conditions.

Progress in the area of mediastinal tumors has been slow. As with all rare tumors, it is imperative to establish widespread collaboration in order to have an evidence base that can scientifically advance knowledge. The advent of ITMIG has been instrumental in creating a foundation for collaboration. A preliminary step is to establish a common language to allow clear communication. Through a series of international workshops, ITMIG established a series of standards, including a modern CT-based definition of mediastinal compartments [3], standards for interpretation and reporting of small mediastinal biopsy specimens [4], clarification of major and minor features of the WHO types of thymoma [5, 6], standards for surgical and pathologic handling and reporting of thymic resection specimens [7], and the first official stage classification of thymic malignancies [8–10]. However, much remains to be done.

There is a great need to collate and disseminate the knowledge that we have regarding mediastinal lesions. This book has been written in this spirit. It is written by a multidisciplinary team of experts with the goal of providing practical information to practicing physicians. It is focused specifically on liquid and tissue biopsy specimens for mediastinal lesions—a critical area because the microscopic information plays a defining role in establishing the diagnosis and the development of a treatment strategy in most patients with a mediastinal tumor. It is important that clinicians have an appreciation for the issues faced by pathologists in evaluating these samples, and it is equally important for pathologists to understand the information available from clinical and imaging features and how they influence the differential diagnosis under consideration.

References

1. Carter B, Okumura M, Detterbeck F, et al. Approaching the patient with an anterior mediastinal mass: a guide for radiologists. J Thor Oncol. 2014;9:S110–8.
2. Carter B, Marom EM, Detterbeck F. Approaching the patient with an anterior mediastinal mass: a guide for clinicians. J Thorac Oncol. 2014;9:S102–9.
3. Carter B, Tomiyama N, Bhora F, et al. A modern definition of mediastinal compartments. J Thorac Oncol. 2014;9:S97–101.

4. Marchevsky A, Marx A, Strobel P, et al. Policies and reporting guidelines for small biopsy specimens of mediastinal masses. J Thorac Oncol. 2011;6:S1724–9.
5. den Bakker M, Roden A, Marx A, et al. Histologic classification of thymoma: a practical guide for routine cases. J Thorac Oncol. 2014;9:S125–30.
6. Marx A, Strobel P, Badve S, et al. ITMIG consensus statement on the use of the WHO histological classification of thymoma and thymic carcinoma: refined definitions, histological criteria and reporting. J Thorac Oncol. 2014;9:596–611.
7. Detterbeck F, Moran C, Huang J, et al. Which way is up? Policies and procedures for surgeons and pathologicsts regarding resection specimens of thymic malignancy. J Thorac Oncol. 2011;6:S1730–8.
8. Detterbeck F, Stratton K, Giroux D, et al. The ITMIG/IASLC thymic epithelial tumors staging project: proposal for an evidence-based stage classification system for the forthcoming (8th) edition of the TNM classification of malignant tumors. J Thor Oncol. 2014;9:S65–72.
9. Kondo K, van Schil P, Detterbeck F, et al. The ITMIG/IASLC thymic epithelial tumors staging project: proposals for the N and M components for the forthcoming (8th) edition of the TNM classification of malignant tumors. J Thorac Oncol. 2014;9:S81–7.
10. Nicholson A, Detterbeck C, Marino M, et al. The ITMIG/IASLC thymic epithelial tumors staging project: proposals for the T component for the forthcoming (8th) edition of the TNM classification of malignant tumors. J Thor Oncol. 2014;9:S73–80.

Mediastinal Biopsy Techniques

2

Robert J. Korst

Introduction

The mediastinum represents the central portion of the thoracic cavity located between the right and left hemithoraces and contains vital structures and organs including the heart, great vessels, esophagus, trachea, main bronchi, thymus, nerves, lymphatics, connective and fatty tissues. Any tissue in the mediastinum may give rise to a primary tumor, either malignant or benign, and the mediastinum is also a common site for metastatic malignancies that have originated elsewhere in the body. Given the diversity of mediastinal abnormalities and lesions, the acquisition of a tissue sample is of paramount importance in establishing the correct diagnosis and tumor characteristics.

Mediastinal Anatomic Considerations

Tumors and lesions of the mediastinum have historically been classified according to their anatomic location, with classification schemes dividing the mediastinum into "compartments". Traditionally, this concept has included anterior, middle, and posterior compartments, based on the lateral chest radiograph [1, 2]. A more

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modern definition of mediastinal divisions has been proposed by the International Thymic Malignancy Interest Group (ITMIG) [3], and is based on computed tomographic imaging of the chest (Figs. 2.1 and 2.2). According to ITMIG, the "prevascular" compartment extends from the thoracic inlet down to the diaphragm in the craniocaudal dimension, and includes all tissue anterior to the great vessels and pericardium. The thymus, left brachiocephalic vein, lymph nodes, and fatty tissue are contained in the prevascular compartment. The "visceral" compartment lies posterior to the prevascular compartment and contains the pericardium and its contents, great vessels, central tracheobronchial tree, lymphatic structures/organs, and esophagus. This compartment extends posteriorly to a plane that lies one centimeter posterior to the anterior border of the vertebral bodies. The "paravertebral" compartment is the most posterior mediastinal compartment, and contains mediastinal structures posterior to the visceral compartment, including the thoracic spine and paravertebral soft tissues and nerves.

The significance of these anatomic subdivisions is twofold. First, since certain tumors/lesions have a predilection for specific compartments, it allows clinicians to organize the mediastinum conceptually, with each compartment having a different differential diagnosis (Table 2.1). As an example, when a patient presents with an anterior mediastinal mass, the most likely diagnosis is a thymic neoplasm or lymphoma. Conversely, a patient with a paravertebral mediastinal mass is most likely to have a neurogenic tumor. This classification then helps dictate further workup because the clinician will tailor the diagnostic maneuvers to the most likely diagnoses. Second, each of the mediastinal compartments has anatomic boundaries that make it accessible to different approaches for biopsies and surgical resection. A lesion in the prevascular compartment is approached in a markedly different manner than in the visceral and paravertebral compartments when it comes to obtaining a tissue diagnosis or performing surgical resection (Table 2.1).

Lesions in the prevascular compartment are best approached percutaneously for biopsies. The most commonly diagnosed lesions in this region are thymic neoplasms, lymphoma, and germ cell tumors, although a variety of other very rare tumors may arise here as well, including sarcomas. This compartment is isolated from the tracheobronchial tree and esophagus by the great vessels and pericardial contents, limiting access using transtracheal or transesophageal technologies. In addition, the prevascular compartment lies directly posterior to the sternum and anterior chest wall, with no other intervening structures or lung. Percutaneous approaches include image-guided needle core biopsies and aspirations, or surgical procedures through the anterior chest wall, the most common being the anterior mediastinotomy (AM) (Chamberlain procedure). The prevascular compartment is not accessible to standard cervical mediastinoscopy, since this approach follows the airway down into the visceral compartment. A variation of cervical mediastinoscopy, termed extended cervical mediastinoscopy, allows access to certain limited prevascular areas, but is uncommonly performed given the ease of percutaneous biopsy. Finally, the prevascular compartment can be accessed through either pleural space, typically with video-assisted thoracic surgical (VATS) technology. However, the transpleural approach is less popular because of potential

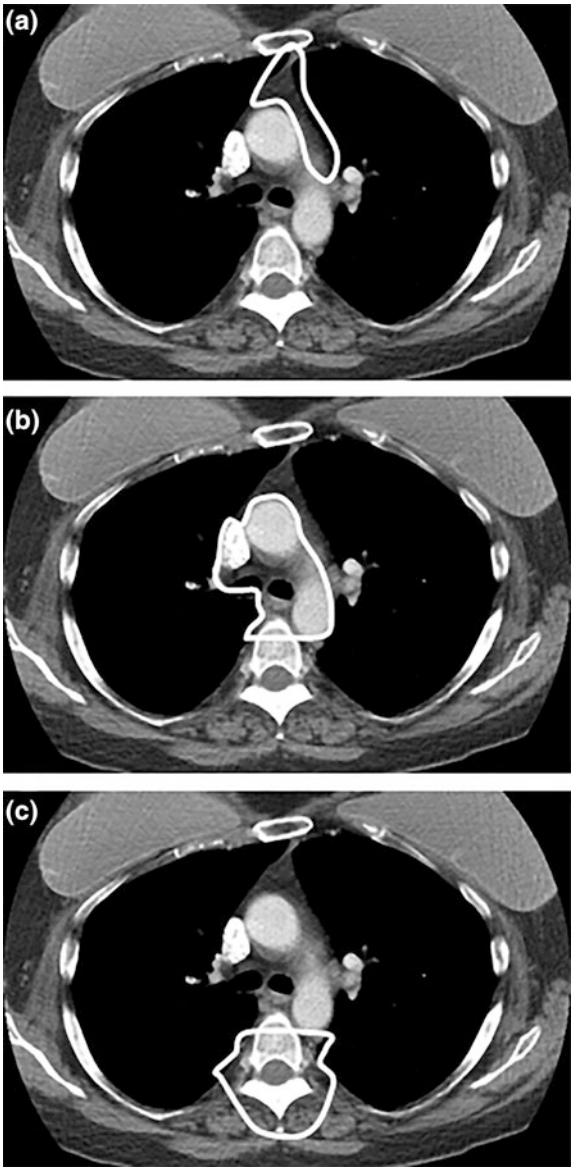

Fig. 2.1 Division of the mediastinum into prevascular, visceral, and paravertebral compartments, based on cross-sectional imaging as defined by the International Thymic Malignancy Interest Group. *Panel A* prevascular compartment. *Panel B* visceral compartment. *Panel C* paravertebral compartment. The *white outline* depicts the referenced compartment in all panels

postoperative pain issues, the potential need for a chest tube, and the fear of pleural space seeding when performing biopsy of a malignant tumor.

The visceral mediastinal compartment is less accessible to percutaneous biopsy approaches because it lies in the center of the mediastinum, although percutaneous needle biopsies can still be performed. The most common malignant lesions that are situated in this region are lymphoma and metastatic lymph node disease from other

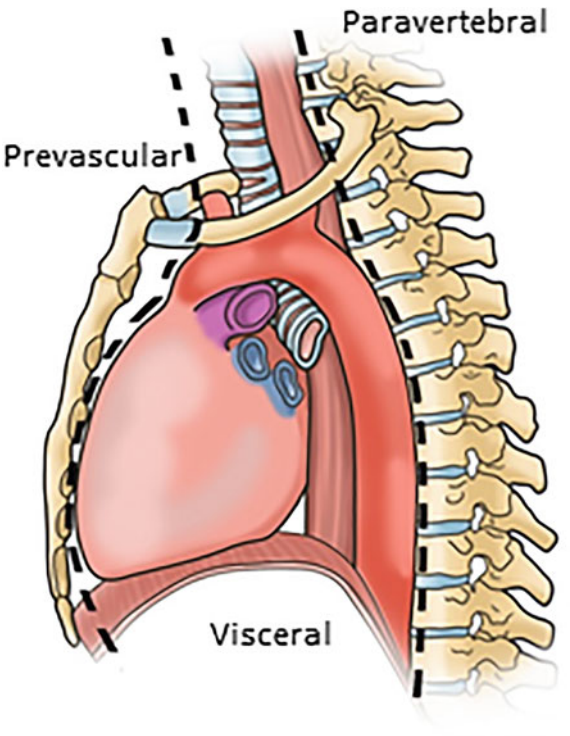

Fig. 2.2 Lateral view of the thorax indicating the boundaries of the mediastinal compartments as defined by the International Thymic Malignancy Interest Group

Table 2.1 Impact of compartment location on differential diagnosis and biopsy approaches for mediastinal lesions

Compartment	Commonly encountered lesions[a]	Common biopsy approaches[b]
Prevascular	Thymic neoplasms and cysts Lymphoma Germ cell tumors	Image-guided percutaneous biopsy Anterior mediastinotomy VATS[c] Extended cervical mediastinoscopy
Visceral	Cystic lesions Metastatic lymphadenopathy Benign lymphoproliferative disease Lymphoma Esophageal tumors	Endobronchial/endoscopic ultrasound Cervical mediastinoscopy VATS Image-guided percutaneous biopsy
Paravertebral	Neurogenic tumors Cystic lesions	Image-guided percutaneous biopsy VATS

[a]Excluding mediastinal thyroid tissue
[b]Listed in decreasing order of use
[c]Video-assisted thoracic surgery

sites, most notable lung cancer. In addition, several benign processes also occur here, including benign lymphoproliferative disorders and mediastinal cysts. Historically, the most commonly utilized approach to obtain tissue samples from the

visceral compartment has been cervical mediastinoscopy. However, since the central tracheobronchial tree and esophagus traverse this compartment, approaches that utilize endoscopic and endobronchial technologies are extremely useful when working in the visceral compartment, and have replaced cervical mediastinoscopy in most circumstances. Similar to the prevascular compartment, the visceral area can be approached transpleurally, but this is less desirable for the aforementioned reasons.

Given that the paravertebral compartment once again lies in close proximity to the chest wall, percutaneous, image-guided needle biopsy techniques are once again utilized commonly to obtain a tissue sample. The most common lesions in this compartment are neurogenic tumors and cysts, however, other more rare tumors such as sarcomas can also arise here. Although VATS can also be utilized to obtain a tissue diagnosis from this compartment, it is not commonly used unless an excisional biopsy is intended.

Indications for Mediastinal Biopsies

Undiagnosed mediastinal masses and lymphadenopathy. Given that the radiographic appearances of many mediastinal tumors and lesions are similar, in the vast majority of cases tissue sampling is necessary prior to formulating a treatment plan. A notable exception may be hormonally active germ cell tumors, which may arise as primary tumors in the prevascular compartment. Patients with non-seminomatous malignant germ cell tumors in the prevascular compartment may be treated with chemotherapy if their serum tumor markers (α-fetoprotein [AFP], β-human chorionic gonadotropin [β-HCG]) are significantly elevated, in the absence of a biopsy [4, 5]. Primary tumors of the mediastinum are treated differently depending on their histology, with some optimally managed with upfront surgical resection (thymic and neurogenic tumors) and others managed primarily with systemic therapies (germ cell tumors and lymphomas).

In addition to primary mediastinal tumors, the etiology of mediastinal lymphadenopathy is very diverse, with a range of malignant and benign conditions potentially capable of causing enlarged lymph nodes. Benign lymphoproliferative disorders mainly consist of reactive hyperplasia, granulomatous inflammation (infectious and noninfectious), as well as Castleman's disease. Malignant disorders associated with mediastinal lymphadenopathy are similarly diverse, ranging from primary malignancies (lymphomas) to metastatic lesions. Metastatic lymphadenopathy is frequently associated with primary tumors of the thorax, most commonly lung and esophageal cancer. Additionally, many extrathoracic malignancies may also metastasize to the mediastinal lymph nodes, especially head and neck and colon cancers.

Staging of thoracic cancers. In patients with a known or suspected diagnosis of lung or esophageal cancer, appropriate clinical staging of the tumor often requires biopsy of the mediastinal lymph nodes. In this regard, standardized lymph node

staging maps have been proposed and adopted for these and other thoracic cancers, including thymic malignancies [6–8]. For non-small cell lung cancer, it is often necessary to perform biopsies of several lymph node stations, which may require more than a single biopsy approach (Fig. 2.3). In these cases, it is frequently

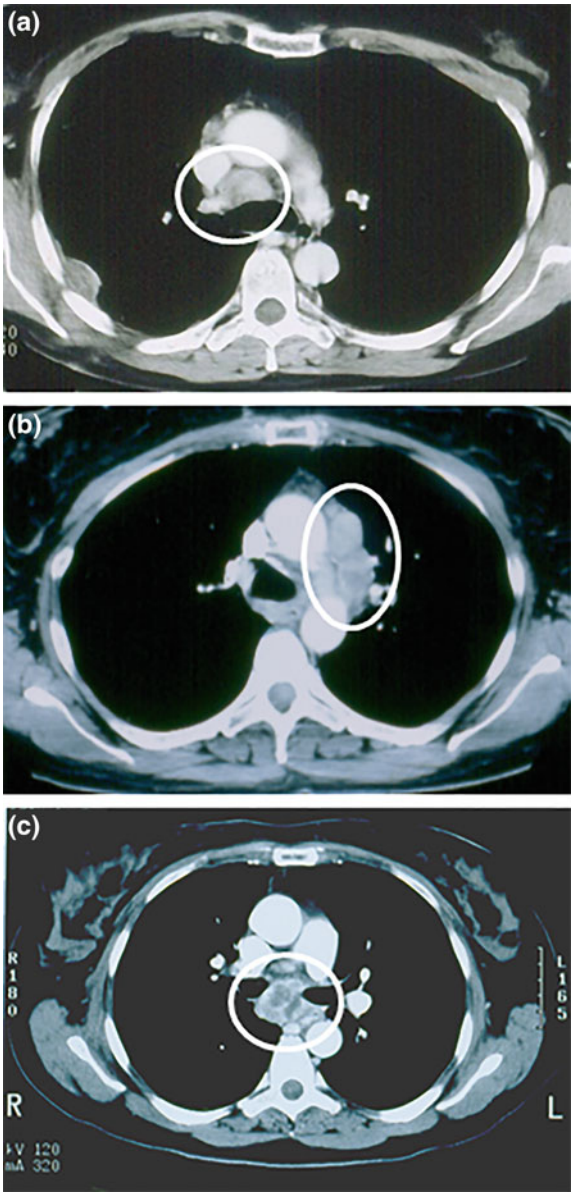

Fig. 2.3 Lymph node stations commonly biopsied for lung cancer staging. In each panel, the designated lymph nodes are within the white circle. *Panel A* Right level 4 (paratracheal), most commonly accessed using either cervical mediastinoscopy or endobronchial ultrasound. *Panel B* Level 6 (preaortic) most commonly accessed using anterior mediastinotomy or video-assisted thoracic surgery. *Panel C* Level 7 (subcarinal), most commonly accessed using endobronchial ultrasound, endoscopic ultrasound, or cervical mediastinoscopy

possible to obtain a tissue sample from the primary tumor as well, if deemed necessary.

Tissue for molecular testing. As molecular and genetic alterations in human malignancies become more clearly defined, the use of therapies targeted toward these alterations becomes more commonplace. This is especially pronounced in non-small cell lung cancer [9]. The most well characterized of these changes is related to the epidermal growth factor receptor (EGFR), where response rates to targeted therapies are profound [10]. Given this revolution in "personalized" cancer therapies, oftentimes it becomes important to obtain additional tissue in patients in whom the diagnosis and stage have already been established.

Although "liquid" biopsies looking for genetic alterations in peripheral blood are under active investigation [11], it is frequently necessary to perform mediastinal biopsies of the malignant lesions themselves to evaluate the tumor for these molecular changes. The biopsy technique utilized for this purpose has to provide enough tissue to perform the analyses desired, but as expertise and technology improves, most of this testing can be performed on needle cores and even aspirates in many circumstances. In the realm of lung cancer, endobronchial ultrasound-guided needle aspirations of mediastinal and hilar lymph nodes have been demonstrated to be sufficient for these purposes [12].

Incisional versus excisional biopsy. When obtaining tissue for analysis from a patient with a mediastinal lesion, a decision must be made regarding not only the biopsy approach and technique, but also the "extent" of biopsy. An "incisional" biopsy implies that only a small portion of the lesion is removed for analysis and is performed using techniques that utilize needles and small biopsy forceps. Although the phenomenon of "needle tract seeding" has been reported, this appears to be a rare event, especially given the large proportion of needle biopsies performed for both lesions in the mediastinum and other body regions [13]. Another approach is to perform an "excisional" biopsy, which implies that the entire lesion is removed. An excisional biopsy is both diagnostic and therapeutic when performed for a mediastinal lesion that would require removal anyway once diagnosed. The decision of whether to perform an incisional or an excisional biopsy needs to take into account several factors, as outlined in Table 2.2. In general, an excisional biopsy is performed for smaller, easily resectable lesions that are likely to represent histologies where surgical resection is the preferred treatment. Examples include small

Table 2.2 Factors affecting the choice of incisional versus excisional biopsy in the mediastinum

Type of biopsy	Presumptive diagnosis	Size	Likelihood of tumor aggressiveness
Incisional	Lymphoma Germ cell tumor Metastatic disease	Large	High
Excisional	Thymic lesions Cystic lesions Neurogenic tumors	Small	Low

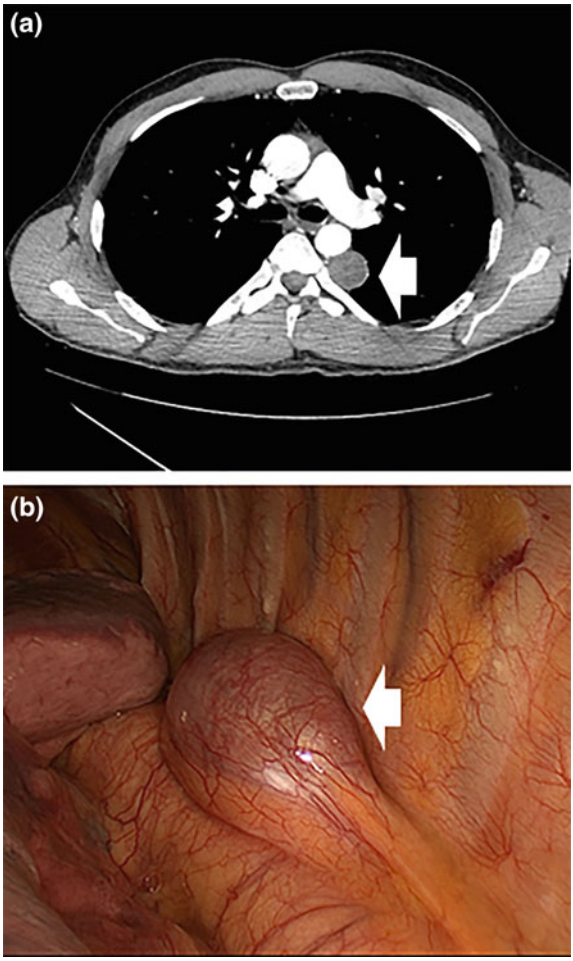

Fig. 2.4 Benign neurogenic tumor for excisional biopsy. *Panel A* Computed tomographic image of tumor in the paravertebral compartment. *Panel B* Image obtained using video-assisted thoracic surgery at the time of excisional biopsy. In both panels, the *white arrow* indicates the tumor

prevascular masses that are likely to be thymomas, cysts in the visceral compartment, and benign neurogenic tumors in the paravertebral compartment (Fig. 2.4).

Mediastinal Biopsy Techniques and Approaches

There are multiple techniques and approaches that can be used to perform biopsies of various mediastinal lesions. Each choice has its advantages and drawbacks, making no single technique ideal for all indications (Table 2.3). Over the past two decades, technology and expertise has become more evolved and sophisticated, with several new, safe options commonly performed at many centers.

Table 2.3 Advantages and disadvantages of mediastinal biopsy techniques

Biopsy technique	Advantages	Disadvantages
Image-guided percutaneous biopsy (IGPB)	Less invasive Local anesthesia Minimal postprocedure pain	Risk of nondiagnostic biopsies Incisional biopsies only
Cervical mediastinoscopy (CM)	Larger biopsies than IGPB Some excisional biopsies	General anesthesia Visceral compartment only
Anterior Mediastinotomy (AM)	Larger biopsies than IGPB Some excisional biopsies	General anesthesia Postoperative pain Risk of cosmetic deformity
Endoscopic ultrasound (EUS)	Less invasive Minimal postprocedure pain	Visceral compartment only Incisional biopsies only
Endobronchial ultrasound (EBUS)	Less invasive Minimal postprocedure pain	Visceral compartment only Incisional biopsies only
Video-assisted thoracic surgery (VATS)	Access to all 3 compartments Excisional biopsies Evaluation of lung and pleura	General anesthesia Postoperative pain Potential for chest tube

Image-guided percutaneous biopsy (IGPB). Percutaneous needle biopsy of mediastinal lesions using imaging modalities as guidance is a commonly utilized mediastinal biopsy approach, especially given advances in technology, imaging,

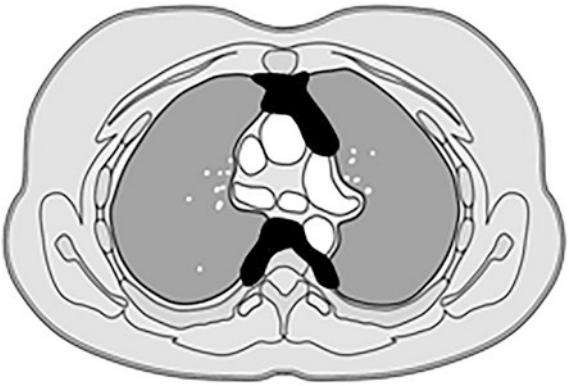

Fig. 2.5 Mediastinal regions where image-guided percutaneous biopsies are typically performed. The *black areas* represent the most common regions where image-guided percutaneous biopsy is employed

and expertise. Although IGPB can be used to access any lesion in all three mediastinal compartments [14], it is usually utilized to obtain tissue from lesions in the prevascular and paravertebral regions (Fig. 2.5). This is because these two compartments lie just deep to the chest wall, eliminating the need to traverse the pleural space in most circumstances. Although the visceral compartment is accessible percutaneously, this region is farther away from the chest wall, the pleural space may need to be traversed, and newer, endoluminal image-guided technologies are available and are rapidly becoming widely adopted for access to this region.

The most commonly used imaging modality for IGPB is computed tomography (CT) due to its precision in imaging both the target lesion and surrounding vital structures, however, ultrasound (US) is also utilized, especially for larger lesions in the prevascular compartment. US may be used in these latter cases when a patient with a large prevascular mass cannot lie supine for CT imaging. US also allows passage of the biopsy needle under real-time guidance, whereas the needle is advanced in increments sequentially with CT guidance to verify proper targeting. In most circumstances where IGPB is employed, the operator uses the coaxial technique, where a larger guide needle is placed in or adjacent to the target lesion. Once located with the larger guide needle, the lesion is sampled with either fine needles or larger core needles through the channel of the guide needle. The coaxial technique eliminates the need to repeatedly pass needles through the skin and surrounding mediastinal tissues with each sampling [14, 15].

Adverse events resulting from IGPB of the mediastinum are uncommon, and consist mainly of bleeding, pneumothorax, and failure to obtain a definitive diagnosis [15]. Significant bleeding is an extremely unusual event, but may result in mediastinal, chest wall and pulmonary hematomas, hemothorax, and even pericardial tamponade. It is important to avoid inadvertent damage to the internal mammary vessels when performing a biopsy of a prevascular mass. The risk of pneumothorax becomes significant when the pleural space is traversed during the procedure, however, the need to place a chest tube is infrequent [15, 16].

The rate of failure of IGPB to provide a definitive diagnosis is dependent on multiple factors, including operator experience, type of needle utilized, size and location of the target, and the histology of the target. Since core needles are easily passed using the coaxial technique, most mediastinal biopsies are performed using core needles, as opposed to only fine needle aspirations (FNA) for cytologic examination [14]. Core needle biopsies have been reported to have a higher diagnostic yield than FNA for mediastinal tumors [17], and in many circumstances enough tissue is obtained for both diagnosis as well as molecular testing. IGPB of carcinomatous mediastinal lesions tends to have a high diagnostic yield, whereas the yield for other lesions may be lower due to the presence of necrosis and/or fibrosis (e.g., nodular sclerosing Hodgkin lymphoma) [17–19]. IGPB provides a definitive diagnosis in the majority of lesions that ultimately prove to be thymic neoplasms [17, 19], with some reports even reporting high yields with FNA for these lesions [20].

Cervical mediastinoscopy (CM). First introduced by Carlens in 1959, CM has become a mainstay for mediastinal biopsy over the ensuing decades [21]. Although performed through an anterior cervical incision, it is important to understand that the rigid mediastinoscope is introduced in the anterior tracheal space down into the visceral compartment, and that the prevascular compartment is not accessible using this approach (Fig. 2.6). Extended cervical mediastinoscopy is a variation of CM where the mediastinoscope is introduced into the anterior compartment to sample preaortic (level 6) lymph nodes [22], however, it is not performed frequently. CM is performed under general anesthesia, with the patient's neck in full extension. Lesions accessible to this approach are located adjacent to the anterior and lateral trachea and main bronchi, as well as the subcarinal space (Fig. 2.7). Given that these regions contain the lymph node basins that are commonly associated with lung cancer metastases (levels 2, 4, 10 and 7), the most frequent indication for CM

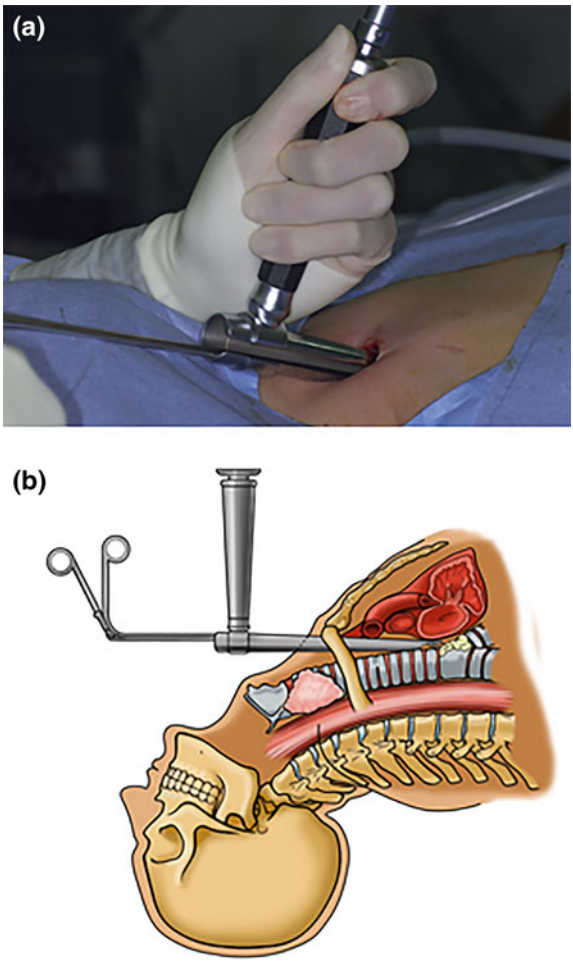

Fig. 2.6 Cervical mediastinoscopy. *Panel A* the mediastinoscope is inserted through an incision in the suprasternal notch. *Panel B* the mediastinoscope is advanced into the visceral compartment

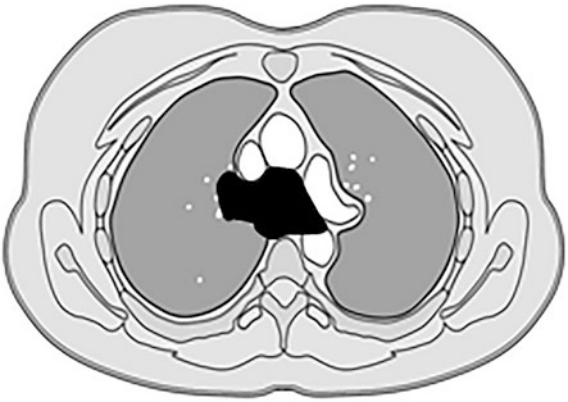

Fig. 2.7 Mediastinal regions where cervical mediastinoscopy and endobronchial ultrasound are utilized to perform biopsies. The *black region* represents the accessible mediastinal areas

is the routine staging of patients with lung cancer prior to treatment. However, its use has recently fallen into decline as endobronchial ultrasound (EBUS) has become more commonplace. Many patients will now have an initial attempt at EBUS-guided biopsies, and proceed to CM only if a definitive diagnosis is not obtained.

Complications of CM are rare, but can be significant when they occur [23]. These include bleeding associated with the need to perform emergent sternotomy or thoracotomy to obtain control, as well as esophageal perforation and left recurrent laryngeal nerve injury. The most vulnerable vascular structures include the superior vena cava, right pulmonary artery, and the aortic arch [23]. Although CM is typically used for incisional biopsies using standard biopsy forceps, excisional biopsies of lymph nodes, small masses and cysts can also be performed through the mediastinoscope [24]. In addition, some surgeons will routinely perform complete mediastinal lymph node dissection for resectable lung cancer through the mediastinoscope [25].

Mediastinotomy. Surgical exposure of the mediastinum for biopsy is referred to as mediastinotomy. Also known as the Chamberlain procedure, AM is a surgical biopsy procedure that provides access to the prevascular compartment [26]. Similar to CM, general anesthesia is utilized, and a 3 cm transverse incision is made typically over the second costal cartilage (Fig. 2.8). The incision can be placed on either side of the sternum, and moved superiorly or inferiorly, depending on the location of the lesion in the anterior compartment. The left second costal cartilage is most commonly the level used because this provides the best exposure to the preaortic (level 6) and aortopulmonary window (level 5) lymph node basins which oftentimes need to be sampled during the staging process for left upper lobe lung cancers (Fig. 2.3, Panel B). The perichondrium is then opened and the costal cartilage is excised. The prevascular compartment is then entered lateral to the internal mammary vessels which are clearly visible. An analogous approach has been described to enter the paravertebral compartment, referred to as posterior

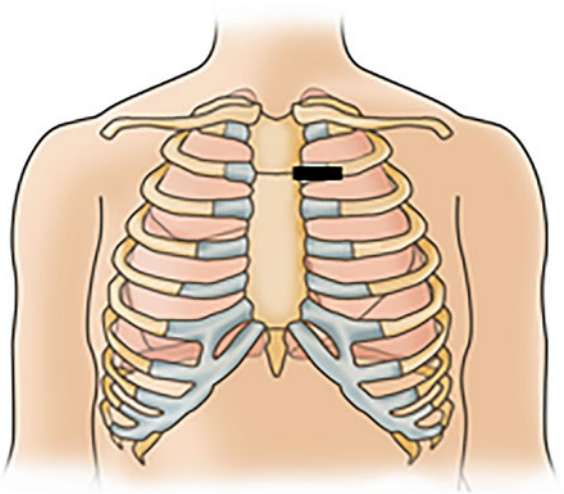

Fig. 2.8 Anterior mediastinotomy. The *black line* indicates the position of the incision

mediastinotomy [27]. However, this approach is of historical interest only given the adoption of IGPB as well as VATS for accessing the paravertebral compartment.

Disadvantages of AM include postoperative pain, cosmetic issues in thin patients with potential indentation over the bed of the resected cartilage, and the potential need for a chest tube if the pleural space is entered and the lung is manipulated. Given these issues, combined with the widespread adoption of VATS, the use of AM has waned through the years. For many clinicians, VATS has replaced AM as the method of choice for staging left upper lobe lung cancers because VATS has the added benefit of allowing complete evaluation of the lung and pleural space. AM, however, is still commonly utilized in many centers to obtain tissue from an unresectable, prevascular mediastinal mass, especially if prior IGPB is nondiagnostic.

Endoluminal image-guided biopsy. Given that the esophagus and central tracheobronchial tree traverse the center of the visceral compartment, attempts to perform biopsies of lesions in this area through the lumen of these structures have existed for decades. Transbronchial needle aspiration using standard, white light bronchoscopy was first popularized by Wang, and commonly utilized for obtaining tissue from a subcarinal mass [28]. However, with the addition of ultrasound technology to flexible endoscopes, the approach to the visceral compartment has evolved into an accurate, minimally invasive means to perform biopsies of this area.

1. **Endoscopic ultrasound (EUS).** Lesions in juxtaposition to the esophagus may be sampled using EUS throughout the entire intrathoracic course of this organ. EUS has evolved into a standard procedure in many centers for the clinical staging of esophageal cancer. Intramural esophageal masses are easily visualized and biopsied using a combination of this technology and standard, white light flexible esophagoscopy. In addition, paraesophageal masses and lymph nodes are readily sampled when visualized ultrasonographically using needles

of a variety of sizes that are passed through the scope. A distinct advantage of ultrasound technology is that the needles are passed into the target under real-time image guidance, which may reduce injury to surrounding structures. EUS may be performed either under general anesthesia or conscious sedation, depending on the clinical circumstances.

Complications of EUS mediated biopsies are rare, with an occasional case of mediastinitis having been reported [29]. The technology is heavily dependent on operator experience, however, and standard frequency ultrasound probes are of limited usefulness when evaluating superficial esophageal cancers. High frequency probes are used by some centers to address this latter limitation [30].

2. **Endobronchial ultrasound (EBUS).** Analogous technology to EUS has also evolved in the arena of flexible bronchoscopy as well. With the addition of an ultrasound transducer to the end of the flexible bronchoscope, EBUS is playing a continually larger role in the realm of mediastinal biopsies. Similar to EUS, the visceral compartment is accessible by EBUS, with tissues adjacent to the central tracheobronchial tree easily sampled using this approach (Fig. 2.7). An added benefit of EBUS is the ability to perform biopsies from both pulmonary hila, an area that was previously difficult to access without entering the pleural space (Fig. 2.9). EBUS is rapidly replacing CM in many centers throughout the world, given that no incisions are necessary and complication rates are extremely low. As with EUS, EBUS may be performed either under general anesthesia or conscious sedation, however, many operators favor general anesthesia because the patient's respirations are controlled compared to a spontaneously breathing patient, reducing target movement. Biopsies are once again performed under real-time image guidance, potentially reducing injury to surrounding structures. In addition to visceral compartment masses, EBUS is also as effective as CM [31] and is rapidly becoming the standard for lymph node sampling when performing clinical staging of lung cancer (Fig. 2.10), with CM only being utilized when the needle biopsies obtained with EBUS are nondiagnostic [32]. However, only needle biopsies are achievable with EBUS (19–22 gauge), and CM still needs to be performed if an excisional biopsy or complete lymph node dissection is the goal. In addition, similar to standard CM, lymph node basins in the prevascular compartment (levels 5 and 6) are not accessible to EBUS, instead requiring IGPB, AM or VATS to acquire tissue.

Adverse events associated with EBUS are rare, and consist mainly of hypoxia, bronchospasm, bleeding, and maintaining the ability of the patient to ventilate should the airway fill with blood or clots. With regard to bleeding, it is not unusual that the EBUS biopsy needle penetrates into a large vascular structure (superior vena cava, aorta) during the procedure without any adverse consequences. In addition, reports exist of intentional transvascular EBUS-guided biopsies in the mediastinum, with minimal bleeding consequences [33]. Diagnostic yields are high using EBUS, whether or not the procedure is used for diagnosing mediastinal masses or lymphadenopathy [32, 34, 35]. EBUS is also effective in distinguishing

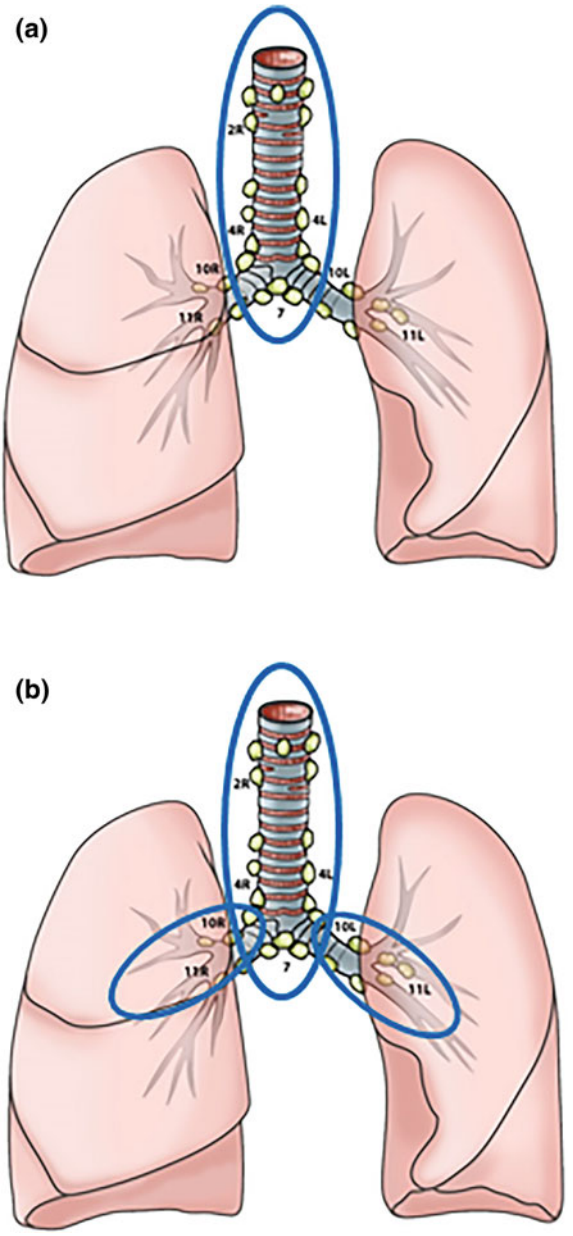

Fig. 2.9 Access to thoracic lymph nodes. *Panel A* nodes accessible to cervical mediastinoscopy. *Panel B* nodes accessible to endobronchial ultrasound

between specific types of lymphoproliferative disorders of the mediastinum [36]. In addition, in the majority of circumstances enough tissue can be obtained to perform further molecular and genetic testing, if indicated (e.g., lymph node metastases from pulmonary adenocarcinoma) [12, 34]. Furthermore, EBUS is a less expensive

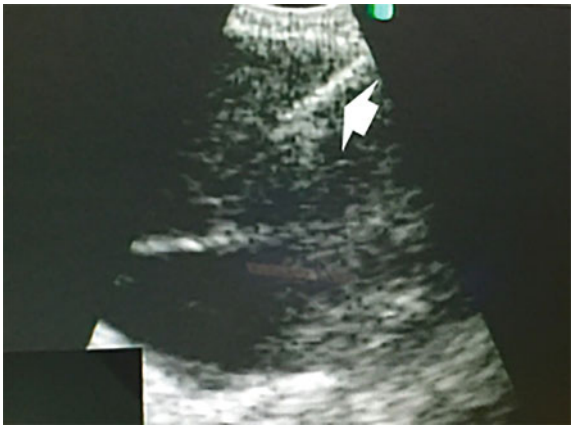

Fig. 2.10 Real-time image from an endobronchial ultrasound-guided biopsy of a level 7 mediastinal lymph node in a patient with lung cancer. The *arrow* indicates the 21 gauge needle entering the 2 cm lymph node

alternative to CM [37]. Although some authors champion the role of rapid on site cytologic examination of the specimen during EBUS [36], this has not been demonstrated to be essential, and its use is dependent on the availability of an experienced cytopathologist. The macroscopic appearance of the specimen obtained with EBUS is also considered to be important in determining its adequacy for obtaining a diagnosis [38].

Video-assisted thoracic surgery (VATS). Also referred to as thoracoscopy, VATS involves entering the pleural space using video technology through small "ports", generally less than one centimeter in size. Three decades ago in its infancy, VATS was used mainly for simple procedures, such as biopsies of the pleura, lung, and mediastinum. Presently, however, VATS technology and expertise is utilized to perform complex thoracic surgical procedures and resections, but remains a useful tool for both incisional and excisional biopsies of mediastinal abnormalities. Although not an absolute requirement, most patients undergoing VATS for mediastinal procedures undergo general anesthesia and intubation with a double lumen endobronchial tube for mechanical ventilation during the procedure. The latter allows for temporary collapse of the lung in the instrumented hemithorax in order to facilitate visualization of the mediastinal structures. Most patients will have a chest tube placed at the completion of the procedure to monitor blood loss and air leak, if applicable.

All three mediastinal compartments are accessible with VATS, where lesions and masses may either be sampled or excised, depending on the clinical circumstances. The choice of performing VATS on the right versus the left side for mediastinal lesions depends on the location of the abnormality, as well as the suspected disease process (Fig. 2.11). A right sided approach is generally utilized for lesions in the right side of the anterior compartment, the right paratracheal space, the subcarinal space, and the right paravertebral area. The left side tends to be used for lesions located in the left side of the anterior compartment (including the level 5 and 6 lymph node basins when staging a left upper lobe lung cancer), as well as the left paravertebral region. Access to the visceral compartment using left

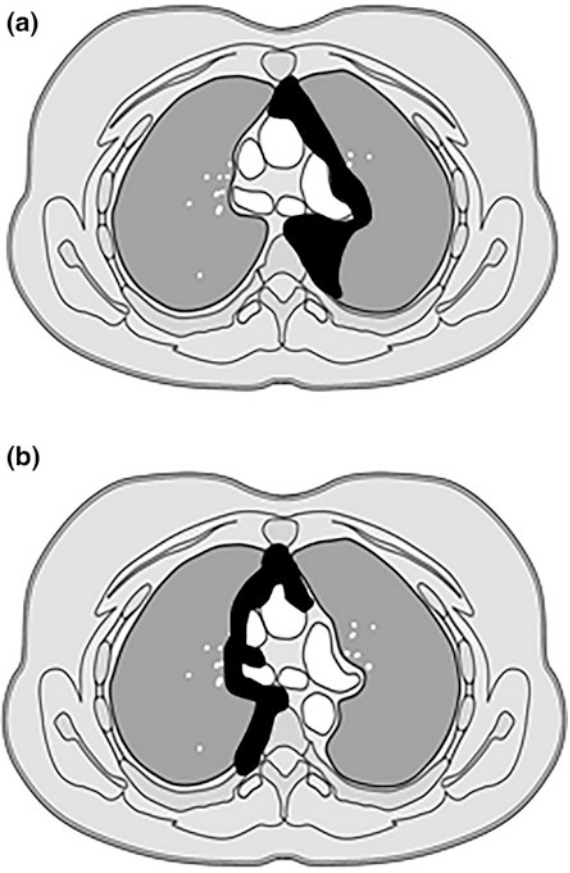

Fig. 2.11 Mediastinal regions accessible to video-assisted thoracic surgical biopsies. *Panel A* areas accessible through the left pleural space. *Panel B* areas accessible through the right pleural space. In both panels, the *black region* represents the accessible mediastinal regions

VATS is somewhat limited due to the position of the heart. Further, it is important to note that a complete thymectomy can be performed using VATS from either a right or left approach.

In general, VATS is utilized to perform mediastinal biopsies in one of two circumstances. First, if attempts have failed to obtain the appropriate amount of tissue using less invasive approaches (IGPB, EBUS, EUS), or second, if the operator makes the decision to perform an excisional biopsy. This latter circumstance is especially relevant when faced with smaller lesions where the most likely diagnosis would require resection anyway (e.g., small thymomas, benign neurogenic tumors, mediastinal cysts), and imaging suggests that complete resection is achievable.

Take home messages

- The mediastinum contains many vital structures, any of which may give rise to an abnormality that may require tissue sampling

- The mediastinum is anatomically divided into compartments, which influences the technique that may be used to perform a biopsy
- Historically, mediastinal biopsies were performed using surgical procedures, but new, minimally invasive technologies have been developed that allow easy access to all mediastinal regions
- Mediastinal biopsies may be incisional or excisional, depending on the clinical circumstances
- Prevascular and paravertebral compartment lesions are best approached with IGPB, unless excisional biopsy is to be performed, in which case VATS may be the best option
- Sampling of visceral compartment lesions is best performed using endoluminal, image-guided technologies including EUS and EBUS
- Mediastinal biopsies are safe, regardless of the approach utilized

Conflict of Interest/Financial Relationships None.

References

1. Shields TW. Primary tumors and cysts of the mediastinum. In: Shields TW, editor. General thoracic surgery. Philadelphia: Lea & Febiger; 1983. p. 927–54.
2. Fraser RG, Paré JA. The normal chest. In: Fraser RG, Paré JA, editors. Diagnosis of diseases of the chest. 2nd ed. Philadelphia: WB Saunders; 1977. p. 1–183.
3. Carter BW, Tomiyama N, Bhora FY, Rosado de Christenson ML, Nakajima J, Boiselle PM, et al. A modern definition of mediastinal compartments. J Thorac Oncol. 2014;9:S97–101. doi:10.1097/JTO.0000000000000292.
4. Hainsworth JD. Diagnosis, staging and clinical characteristics of the patient with mediastinal germ cell carcinoma. Chest Surg Clin. 2002;12:665–72.
5. Kesler KA. Germ cell tumors of the mediastinum. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AEMR, Luketich JD, Rice TW, editors. Pearson's thoracic and esophageal surgery. 3rd ed. Philadelphia: Churchill Livingstone; 2008. p. 1615–21.
6. Mountain F, Dresler CM. Regional lymph node classification for lung cancer staging. Chest. 1997;111:1718–23.
7. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti III, A, editors. AJCC cancer staging handbook, 7th ed. New York: Springer; 2010. p. 297–323.
8. Bhora FY, Chen DJ, Detterbeck FC, Asamura H, Falkson C, Filosso PL, et al. The ITMIG/IASLC thymic epithelial tumors staging project: a proposed lymph node map for thymic epithelial tumors in the forthcoming 8th edition of the TNM classification of malignant tumors. J Thorac Oncol. 2014;9:S88–96. doi:10.1097/JTO.0000000000000293.
9. Rothschild SI. Targeted therapies in non-small cell lung cancer-beyond EGFR and ALK. Cancers (Basel). 2015;7:930–49. doi:10.3390/cancers7020816.
10. Ellis PM, Coakley N, Feld R, Kuruvilla S, Ung YC. Use of the epidermal growth factor receptor inhibitors gefitinib, erlotinib, afatinib, dacomitinib, and icotinib in the treatment of non-small-cell lung cancer: a systematic review. Curr Oncol. 2015;22:e183–215. doi:10.3747/co.22.2566.
11. Esposito A, Criscitiello C, Locatelli M, Milano M, Curigliano G. Liquid biopsies for solid tumors: understanding tumor heterogeneity and real time monitoring of early resistance to targeted therapies. Pharmacol Ther. 23 Nov 2015. doi:10.1016/j.pharmthera.2015.11.007 (pii: S0163-7258(15)00220-X).

12. Jurado J, Saqi A, Maxfield R, Newmark A, Lavelle M, Bacchetta M, et al. The efficacy of EBUS-guided transbronchial needle aspiration for molecular testing in lung adenocarcinoma. Ann Thorac Surg. 2013;96:1196–202. doi:10.1016/j.athoracsur.2013.05.066.
13. Robertson EG, Baxter G. Tumour seeding following percutaneous needle biopsy: the real story! Clin Radiol. 2011;66:1007–14. doi:10.1016/j.crad.2011.05.012.
14. Gupta S, Seaberg K, Wallace MJ, Madoff DC, Morello FA Jr, Ahrar K, et al. Imaging-guided percutaneous biopsy of mediastinal lesions: different approaches and anatomic considerations. Radiographics. 2005;25:763–86.
15. Lal H, Neyaz Z, Nath A, Borah S. CT-guided percutaneous biopsy of intrathoracic lesions. Korean J Radiol. 2012;13:210–26. doi:10.3348/kjr.2012.13.2.210.
16. Loubeyre P, Copercini M, Dietrich PY. Percutaneous CT-guided multisampling core needle biopsy of thoracic lesions. AJR Am J Roentgenol. 2005;185:1294–8.
17. Petranovic M, Gilman MD, Muniappan A, Hasserjian RP, Digumarthy SR, Muse VV, et al. Diagnostic yield of CT-guided percutaneous transthoracic needle biopsy for diagnosis of anterior mediastinal masses. AJR Am J Roentgenol. 2015;205:774–9. doi:10.2214/AJR.15.14442.
18. Priola AM, Priola SM, Cataldi A, Ferrero B, Garofalo G, Errico L, et al. CT-guided percutaneous transthoracic biopsy in the diagnosis of mediastinal masses: evaluation of 73 procedures. Radiol Med. 2008;113:3–15. doi:10.1007/s11547-008-0233-1.
19. Ahrar K, Wallace M, Javadi S, Gupta S. Mediastinal, hilar, and pleural image-guided biopsy: current practice and techniques. Semin Respir Crit Care Med. 2008;29:350–60. doi:10.1055/s-2008-1081279.
20. Zakowski MF, Huang J, Bramlage MP. The role of fine needle aspiration cytology in the diagnosis and management of thymic neoplasia. J Thorac Oncol. 2010;5:S281–5. doi:10.1097/JTO.0b013e3181f23e19.
21. Carlens E. Mediastinoscopy: a method for inspection and tissue biopsy in the superior mediastinum. Dis Chest. 1959;36:343–52.
22. Ginsberg RJ, Rice TW, Goldberg M, Waters PF, Schmocker BJ. Extended cervical mediastinoscopy. A single staging procedure for bronchogenic carcinoma of the left lung. J Thorac Cardiovasc Surg. 1987;94:673–8.
23. Park BJ, Flores R, Downey RJ, Bains MS, Rusch VW. Management of major hemorrhage during mediastinoscopy. J Thorac Cardiovasc Surg. 2003;126:726–31.
24. Lesaffer J, Heremans B, De Leyn P, Van Raemdonck D. Video-assisted mediastinoscopic resection of a large symptomatic bronchogenic cyst. Interact CardioVasc Thorac Surg. 2011;12:1071–3. doi:10.1510/icvts.2010.262899.
25. Zieliński M. Technical pitfalls of transcervical extended mediastinal lymphadenectomy–how to avoid them and to manage intraoperative complications. Semin Thorac Cardiovasc Surg. 2010;22:236–43. doi:10.1053/j.semtcvs.2010.10.010.
26. McNeill TM, Chamberlain JM. Diagnostic anterior mediastinotomy. Ann Thorac Surg. 1966;2:532–9.
27. Shields TW. Posterior mediastinotomy. In: Shields TW, LoCicero III J, Ponn RB, Rusch VW, editors. General Thoracic Surgery. 6th edition. Philadelphia: Lippincott Williams and Wilkins; 2005. p. 2453–4.
28. Wang KP, Nelson S, Scatarige J, Siegelman S. Transbronchial needle aspiration of a mediastinal mass: therapeutic implications. Thorax. 1983;38:556–7.
29. Bohle W, Zoller WG. Mediastinitis after EUS-FNA in a patient with sarcoidosis—case report with endosonographic features and review of the literature. Z Gastroenterol. 2014;52:1171–4. doi:10.1055/s-0034-1385071.
30. Yoshinaga S, Oda I, Nonaka S, Kushima R, Saito Y. Endoscopic ultrasound using ultrasound probes for the diagnosis of early esophageal and gastric cancers. World J Gastrointest Endosc. 2012;4:218–26. doi:10.4253/wjge.v4.i6.218.
31. Yasufuku K, Pierre A, Darling G, de Perrot M, Waddell T, Johnston M, et al. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared

with mediastinoscopy for mediastinal lymph node staging of lung cancer. J Thorac Cardiovasc Surg. 2011;142(1393–400):e1. doi:10.1016/j.jtcvs.2011.08.037.
32. Lee BE, Kletsman E, Rutledge JR, Korst RJ. Utility of endobronchial ultrasound-guided mediastinal lymph node biopsy in patients with non-small cell lung cancer. J Thorac Cardiovasc Surg. 2012;143:585–90. doi:10.1016/j.jtcvs.2011.11.022.
33. Panchabhai TS, Machuzak MS, Sethi S, Vijhani P, Gildea TR, Mehta AC, Almeida FA, Cicenia JC. Endobronchial ultrasound-guided transvascular needle aspiration: a single-center experience. J Bronchology Interv Pulmonol. 2015;22:306–11. doi:10.1097/LBR.0000000000000227.
34. Choi YR, An JY, Kim MK, Han HS, Lee KH, Kim SW, et al. The diagnostic efficacy and safety of endobronchial ultrasound-guided transbronchial needle aspiration as an initial diagnostic tool. Korean J Intern Med. 2013;28:660–7. doi:10.3904/kjim.2013.28.6.660.
35. Yang H, Zhao H, Garfield DH, Teng J, Han B, Sun J. Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of non-lymph node thoracic lesions. Ann Thorac Med. 2013;8:14–21. doi:10.4103/1817-1737.105714.
36. Marshall CB, Jacob B, Patel S, Sneige N, Jimenez CA, Morice RC, Caraway N. The utility of endobronchial ultrasound-guided transbronchial needle aspiration biopsy in the diagnosis of mediastinal lymphoproliferative disorders. Cancer Cytopathol. 2011;119:118–26. doi:10.1002/cncy.20134.
37. Medford AR, Bennett JA, Free CM, Agrawal S. Mediastinal staging procedures in lung cancer: EBUS, TBNA and mediastinoscopy. Curr Opin Pulm Med. 2009;15:334–42.
38. da Cunha Santos G, Boerner SL, Geddie WR. Maximizing the yield of lymph node cytology: Lessons learned from rapid onsite evaluation of image- and endoscopic-guided biopsies of hilar and mediastinal lymph nodes. Cancer Cytopathol. 2011;119:361–6. doi:10.1002/cncy.20166.

Radiologic Features of Mediastinal Lesions

3

Brett W. Carter and Edith M. Marom

Introduction

Mediastinal masses are relatively uncommon and include a wide variety of histopathologic entities of neoplastic, congenital, vascular, and lymphatic origin. Therefore, most radiologists, pathologists, and other health care providers will only encounter many of these abnormalities infrequently. Imaging plays an important role in the identification and evaluation of mediastinal lesions, enables formulation of an appropriate differential diagnosis for a particular abnormality, and can be very useful in avoiding unnecessary and potentially misleading biopsies or additional tests. In some instances, characteristic radiologic features can be identified that suggest a specific diagnosis. In other cases, a combination of imaging and clinical information is necessary to narrow the differential diagnosis and guide management. In this chapter, we present key imaging features of mediastinal lesions that most health care providers are likely to encounter in clinical practice.

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Classification of Mediastinal Compartments

Assignment of a particular mediastinal abnormality to a specific compartment can be quite useful in narrowing the differential diagnosis. A wide variety of classification systems have been devised and employed by anatomists, clinicians, and radiologists. However, the existing radiology schemes represent arbitrary divisions of the chest based primarily on the lateral chest radiograph that are non-anatomical. A computed tomography (CT)-centric classification scheme is necessary as the diagnosis, work-up, and formulation of treatment strategies are typically determined by CT findings and not by chest radiography. A modern CT-based definition of mediastinal compartments has been developed by the International Thymic Malignancy Interest Group (ITMIG) [1] building upon work done by radiologists associated with the Japanese Association for Research on the Thymus (JART) [2]. The ITMIG classification scheme is a three-compartment model defining

Table 3.1 ITMIG definition of mediastinal compartments

Compartment	Boundaries	Major contents
Prevascular	**Superior:** Thoracic inlet **Inferior:** Diaphragm **Anterior:** Sternum **Lateral:** Parietal (mediastinal) pleural reflections; lateral margin of the bilateral internal thoracic arteries and veins, and superior and inferior pulmonary veins **Posterior:** Anterior to the pericardium, along the anterior margin of the superior vena cava, ascending aorta, and the lateral rim of the aortic arch, superior and inferior pulmonary veins	Thymus Fat Lymph nodes Left brachiocephalic vein
Visceral	**Superior:** Thoracic inlet **Inferior:** Diaphragm **Anterior:** Posterior boundaries of the prevascular compartment **Posterior:** A vertical line connecting a point on each thoracic vertebral body at 1 cm posterior to its anterior margin	Nonvascular: Trachea, main bronchi, esophagus, lymph nodes Vascular: Heart, ascending thoracic aorta, aortic arch, and descending thoracic aorta, superior vena cava, intrapericardial pulmonary arteries, thoracic duct
Paravertebral	**Superior:** Thoracic inlet **Inferior:** Diaphragm **Anterior:** Posterior boundaries of the visceral compartment **Posterolateral:** Vertical line against the posterior margin of the chest wall at the lateral margin of the transverse process of the thoracic spine	Paravertebral soft tissues

prevascular, visceral, and paravertebral mediastinal compartments with specific boundaries and structures included (Table 3.1).

The boundaries of the prevascular compartment include: (1) superiorly—the thoracic inlet, (2) inferiorly—the diaphragm, (3) anteriorly—the sternum, (4) laterally—the parietal mediastinal pleura, and (5) posteriorly—the anterior aspect of the pericardium as it wraps around in a curvilinear fashion (Fig. 3.1). Based on these anatomic landmarks, the major contents of the prevascular mediastinum include the thymus, fat, lymph nodes, and the left brachiocephalic vein. The most common lesions originating in the prevascular compartment include thymic masses (cysts, hyperplasia, and thymic epithelial neoplasms), germ cell neoplasms, lymphoma, metastatic lymphadenopathy, and intrathoracic goiter.

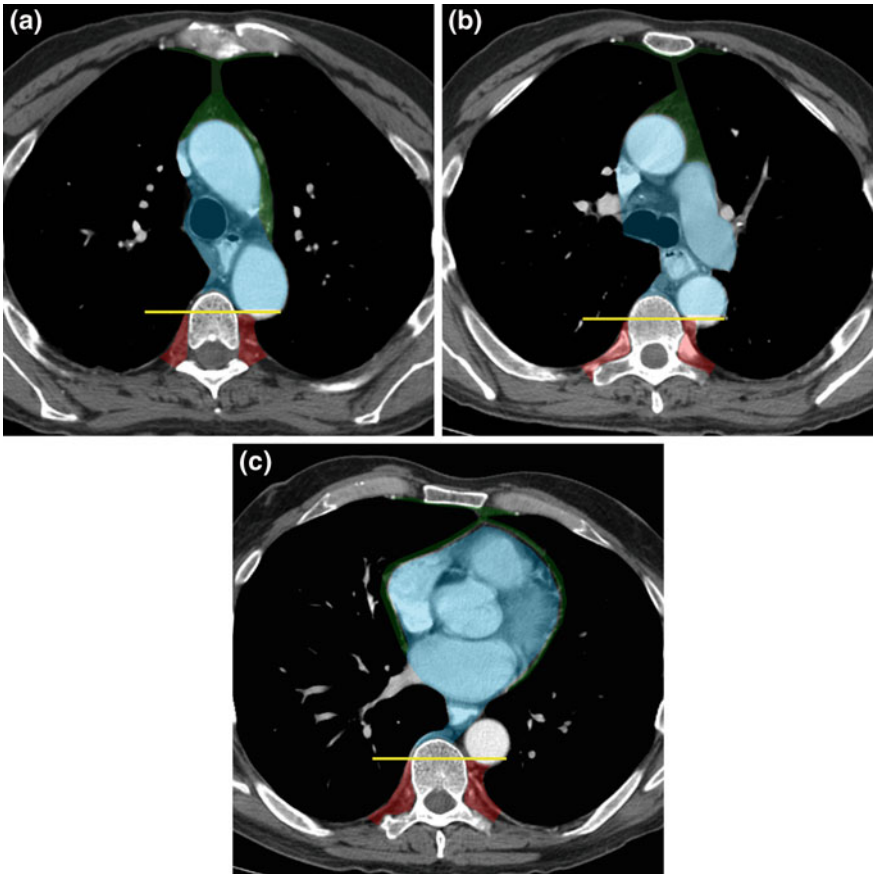

Fig. 3.1 Contrast-enhanced axial CT images slightly below the *aortic arch* (**a**), at the level of the left pulmonary artery (**b**), and at the level of the left atrium (**c**) demonstrate the ITMIG classification system of mediastinal compartments. *Green*, prevascular compartment; *blue*, visceral compartment; *red*, paravertebral compartment; *yellow line*, visceral–paravertebral compartment boundary line

The boundaries of the visceral compartment include: (1) superiorly—the thoracic inlet, (2) inferiorly—the diaphragm, (3) anteriorly—the anterior aspect of the pericardium (which envelops the distal aspect of the superior vena cava, the proximal aspect of the ascending aorta and lateral rim of the aortic arch, and the intrapericardial pulmonary arteries), and (4) 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) (Fig. 3.1). The major contents of the visceral compartment fall into two main categories: (1) vascular (including the heart, superior vena cava, ascending thoracic aorta, aortic arch, and descending thoracic aorta, intrapericardial pulmonary arteries, and the thoracic duct) and (2) nonvascular (including the trachea, carina, esophagus, and lymph nodes). In the ITMIG description, all of the structures contained within the pericardium are included in the visceral compartment. The most common lesions originating in the visceral compartment include lymphadenopathy (related to lymphoma or metastatic disease), foregut duplication cysts, tracheal lesions, and esophageal neoplasms. Abnormalities of the heart, pericardium, and great vessels may also be encountered in this compartment.

The boundaries of the paravertebral compartment include: (1) superiorly—the thoracic inlet, (2) inferiorly—the diaphragm, (3) anteriorly—the visceral compartment, and (4) posterolaterally—a vertical line along the posterior margin of the chest wall at the lateral aspect of the transverse processes (Fig. 3.1). The major contents of the paravertebral compartment include the thoracic spine and paravertebral soft tissues; therefore, most abnormalities in this region are neurogenic neoplasms arising from the dorsal root ganglia/neurons adjacent to the intervertebral foramina, as well as lesions related to infection and trauma.

General Considerations

More than half of all mediastinal masses are located in the prevascular compartment. One-fourth of mediastinal lesions are present in the visceral mediastinum, and another one-fourth of masses occur in the paravertebral mediastinum [3–12]. The prevalence of specific mediastinal lesions is difficult to establish from the medical literature for multiple reasons. For instance, different radiologic and/or clinical classification systems may be used to define the mediastinal compartments. Additionally, the inclusion of non-neoplastic lesions such as thymic, pericardial, and foregut duplication cysts and various types of lymphoma is variable between different studies.

Despite the aforementioned limitations in determining the true prevalence of mediastinal abnormalities, several studies have shown that the most common prevascular mediastinal masses include the following entities: thymic malignancy (35%), lymphoma (25% overall; 13% Hodgkin lymphoma or HL and 12% non-Hodgkin lymphoma or NHL), thyroid and other endocrine neoplasms (15%),

benign teratoma (10%), malignant germ cell tumors (10% overall; 4 seminoma and 7% non-seminomatous germ cell tumor or NSGCT), and benign thymic cysts (5%). [3, 6, 8].

Role of Imaging

Mediastinal lesions may be first detected on chest radiography given the widespread use and availability of the modality. Small lesions may not be readily identified, whereas large masses may manifest as an extra soft tissue mass or opacity. One particular tool referred to as the "silhouette sign," which describes the loss of normal borders of intrathoracic structures on radiography, increases the sensitivity of detecting mediastinal abnormalities (Fig. 3.2). Primary mediastinal neoplasms are usually focal, unilateral lesions that abut the mediastinum and preclude radiographic visualization of a medial lesion border (Fig. 3.3). These neoplasms typically displace the normal mediastinal interfaces and manifest as mediastinal contour abnormalities. Once a lesion is identified on chest radiography, cross-sectional imaging techniques are used to characterize the abnormality, generate a differential diagnosis, assess for other abnormalities, and guide further management. CT with intravenous (IV) contrast has traditionally been the imaging modality of choice for the evaluation and characterization of mediastinal masses. In an analysis of 127 anterior mediastinal masses of various etiologies, investigators demonstrated that CT was equal or superior to magnetic resonance imaging (MRI) in diagnosing specific lesions except for thymic cysts [13]. MRI is the most useful imaging modality to evaluate a suspected cystic mediastinal lesion, because MRI is superior to CT in distinguishing cystic from solid masses (e.g., thymic cysts from thymic neoplasms) and discerning cystic and/or necrotic components within solid masses [14]. Specific chemical shift techniques can be used to differentiate thymic hyperplasia from thymic epithelial neoplasms and other malignancies [15, 16]. Unenhanced MRI may also be performed to characterize masses in patients who are unable to undergo contrast-enhanced CT due to renal failure or severe allergy to IV contrast. 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT is not routinely performed to evaluate or characterize mediastinal masses, but may be used for staging, assessing response, and evaluating for disease recurrence. However, it is important to note that imaging with FDG-PET/CT can be misleading, given that normal and hyperplastic thymus and infectious and inflammatory lesions in the mediastinum may be FDG-avid [12].

Imaging Approach to Mediastinal Lesions

In many cases, the identification of certain characteristics on CT may suggest a fairly specific diagnosis on imaging alone. Findings such as hyperdense and enhancing lesions that communicate with the thyroid gland, intralesional fat, cystic

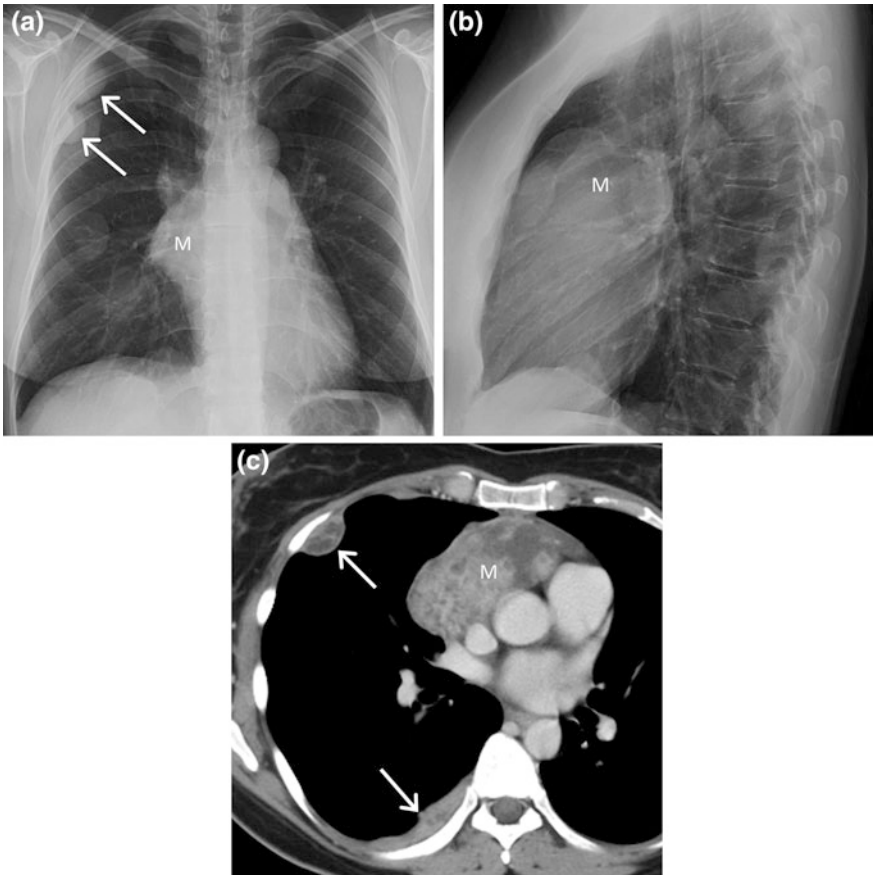

Fig. 3.2 Thymoma in a 43-year-old woman. **a** and **b** Frontal chest radiograph (**a**) demonstrates a mass-like opacity (*M*) in the right mediastinum silhouetting the right heart border suggesting an anterior location, which is confirmed on the lateral radiograph (**b**). Multiple pleural metastases (*arrows*) are present in the right hemithorax. **c** Contrast-enhanced axial CT of the same patient shows the right prevascular mass (*M*) consistent with biopsy-proven thymoma and right pleural metastases (*arrows*). The "silhouette sign" describes the loss of normal borders of intrathoracic structures on radiography and increases the sensitivity of detecting mediastinal abnormalities

components, and regions of soft tissue attenuation may be used to narrow the differential diagnosis. Calcification, whether punctate, coarse, or curvilinear, cannot discriminate benign from malignant mediastinal lesions [12, 17]. In other cases, while the imaging findings may not enable a definitive diagnosis, a combination of clinical information/context and cross-sectional imaging features can help narrow the differential diagnosis and guide further management.

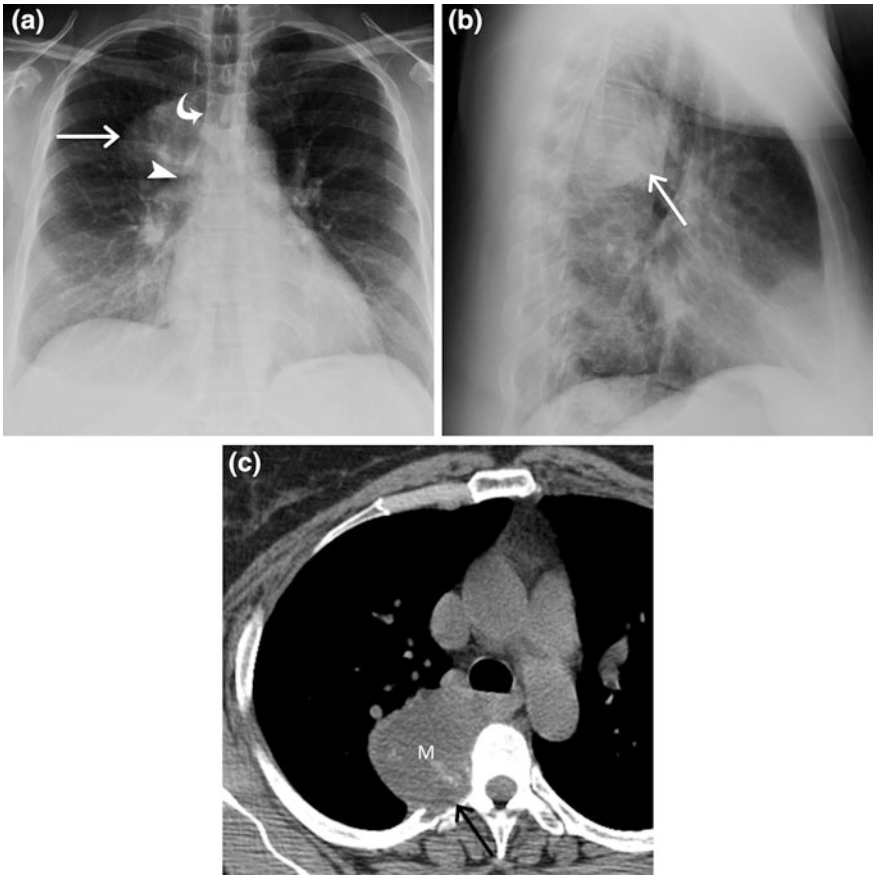

Fig. 3.3 Chondrosarcoma in a 52-year-old woman. **a** and **b** Frontal chest radiograph (**a**) shows an ill-defined mediastinal mass (*arrow*). Since it does not silhouette the anterior aorta interface (*arrowhead*) or the right paratracheal line (*curved arrow*), it has to be located posteriorly in the paravertebral compartment, confirmed on the lateral radiograph (**b**). **c** Unenhanced axial CT of the same patient demonstrates a soft tissue mass (*M*) in the right paravertebral mediastinum invading the adjacent rib (*arrow*). CT-guided biopsy revealed primary chondrosarcoma

Fat-Containing Lesions

Teratoma

The presence of visible areas of intralesional fat on CT, measuring between −40 and −120 Hounsfield units, within a heterogeneous prevascular mediastinal mass is highly suggestive of a benign teratoma. These germ cell neoplasms typically demonstrate various amounts of fat, fluid, calcification (including bone and tooth-like elements), and soft tissue (Fig. 3.4) [17, 18]. Fat is identified in approximately 50%

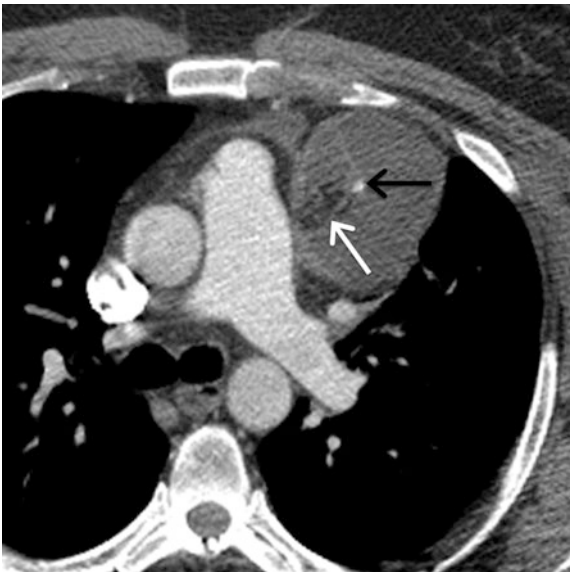

Fig. 3.4 Benign teratoma in a 34-year-old man. Contrast-enhanced axial CT demonstrates a left prevascular mediastinal mass composed of macroscopic fat (*white arrow*), calcification, (*black arrow*), and fluid. Surgical resection was performed due to severe chest pain and pathology revealed benign teratoma. When a complex mass containing various amounts of fat, fluid, calcification, and soft tissue is present in the prevascular mediastinum, the most likely diagnosis is a benign teratoma

of cases [17]. Although a fat–fluid level is highly specific for teratoma, this finding is much less common [19]. Benign mediastinal teratomas are usually seen in young patients and account for approximately 25% of prevascular lesions in ages 10–19, 10–15% in ages 20–49, and less than 5% over age 50 in both men and women.

Thymolipoma

When a large predominantly fat-containing mass is identified in the prevascular mediastinum or in one of the cardiophrenic angles, thymolipoma should be considered. Thymolipoma is a benign encapsulated lesion that usually contains 50–85% fat and a small amount of solid tissue and fibrous septa, and may be very large at presentation with an average size of 20 cm (Fig. 3.5). The presence of a direct connection with the thymus is confirmatory [18, 20, 21]. Although patients are usually asymptomatic at presentation, anecdotal associations between thymolipoma and myasthenia gravis, Grave's disease, and hematological disorders have been reported [21]. Thymolipoma is a relatively uncommon lesion, representing <5% of prevascular mediastinal lesions, but the diagnosis can be suggested when the lesion consists almost entirely of fat [12].

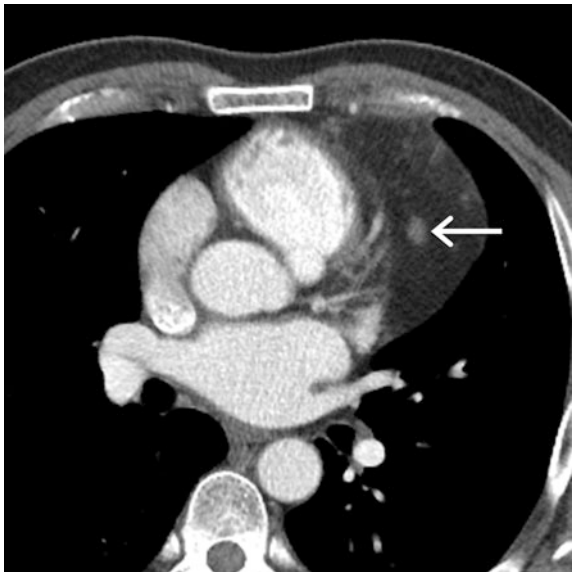

Fig. 3.5 Thymolipoma in a 41-year-old man. Contrast-enhanced axial CT shows a predominantly fat-containing mass in the left prevascular mediastinum with only a small amount of internal soft tissue (*arrow*). Given the presence of internal soft tissue, mediastinal liposarcoma could not be excluded and surgical resection was performed. Pathology revealed thymolipoma, a benign neoplasm typically containing 50–85% fat

Lipoma and Liposarcoma

Additional but less common mediastinal neoplasms with intralesional fat include lipoma and liposarcoma. Lipomas account for 2% of all primary mediastinal tumors and manifest as encapsulated lesions predominantly composed of fat with a small amount of soft tissue and vessels in the prevascular mediastinum [22]. Liposarcomas represent more aggressive malignancies that can be distinguished from lipomas through features such as increased soft tissue components, local invasion, lymphadenopathy, and metastatic disease (Fig. 3.6) [22, 23].

Cystic Lesions

Thymic Cyst

When a well-circumscribed lesion that is homogeneous and round, oval, or saccular in shape is present in the prevascular compartment near the thymic bed, thymic cyst should be included in the differential diagnosis. Thymic cysts usually measure

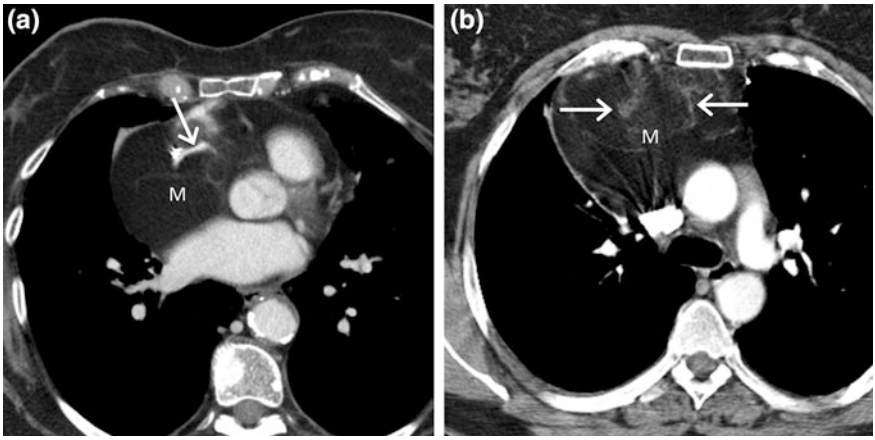

Fig. 3.6 Mediastinal lipoma and liposarcoma. **a**.Contrast-enhanced axial CT of a 73-year-old woman demonstrates a prevascular mediastinal mass (*M*) composed predominantly of fat with only minimal internal soft tissue, consistent with a lipoma. Note the narrowing of the superior vena cava (*arrow*), which remained patent. **b** Contrast-enhanced axial CT of a 57-year-old woman shows a prevascular mediastinal mass (*M*) that contains a large amount of fat but demonstrates more internal soft tissue components (*arrows*) than a thymolipoma or lipoma. CT-guided biopsy demonstrated primary mediastinal liposarcoma

water or fluid attenuation on CT, between 0 and 20 Hounsfield units; however, they can demonstrate regions of high attenuation that can make differentiation between solid and cystic lesions/components difficult. In this scenario, MRI should be performed, as the modality is superior to CT in this regard. Cystic lesions with no soft tissue nodules or internal septations on MRI can reliably be diagnosed as unilocular thymic cysts (Fig. 3.7). Those that do demonstrate soft tissue components represent either multilocular thymic cysts or cystic thymoma, the latter of which should be strongly considered when symptoms related to myasthenia gravis or other paraneoplastic syndrome are present (Fig. 3.8) [12, 24].

Teratoma

Although many benign mediastinal teratomas are composed of various amounts of fat, calcification, fluid, and soft tissues as previously stated, mature cystic teratomas, or dermoid cysts, manifest as predominantly cystic masses (Fig. 3.9). Although these lesions can arise from any mediastinal compartment, most originate in the prevascular mediastinum, with only 3–8% occurring in the paravertebral mediastinum [17].

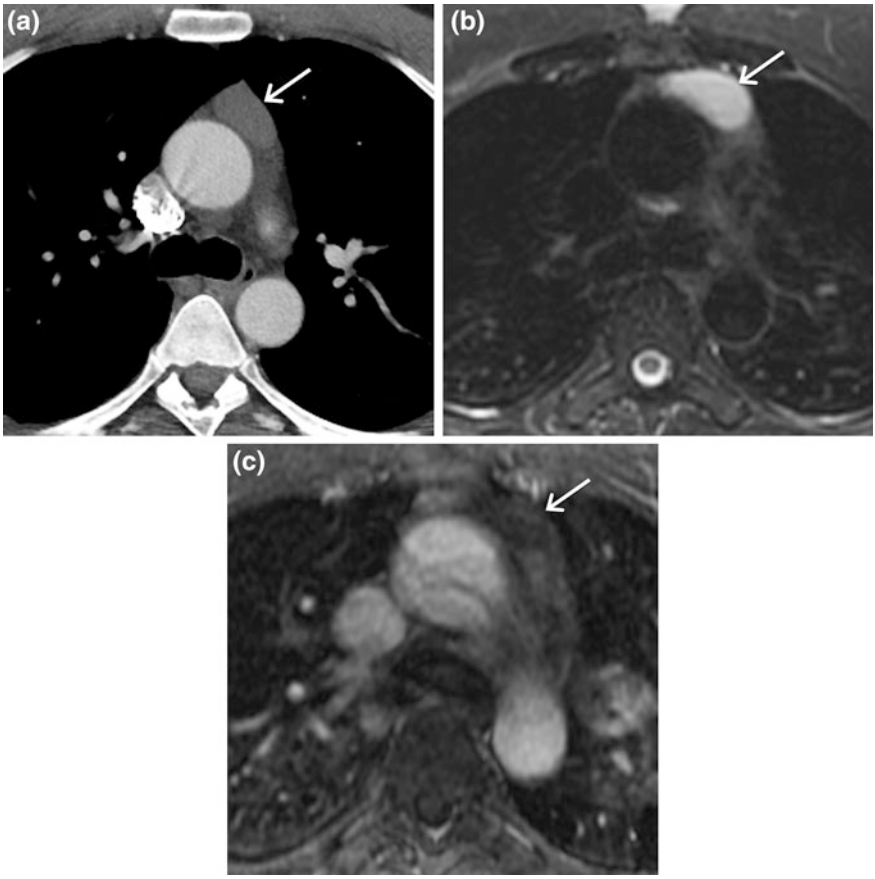

Fig. 3.7 Unilocular thymic cyst in a 43-year-old man. **a** Contrast-enhanced axial CT shows a well-circumscribed, fluid/water attenuation mass (*arrow*) in the prevascular mediastinum. MRI was subsequently performed to evaluate for internal soft tissue components. **b** and **c** T2-weighted (**b**) and T1-weighted post-contrast (**c**) MRI of the same patient demonstrates a purely cystic lesion with no evidence of enhancing soft tissue components. Cystic lesions with no soft tissue nodules or internal septations on MRI can reliably be diagnosed as unilocular thymic cysts or cystic teratomas

Pericardial Cyst

Pericardial cysts are benign lesions composed of connective tissue and a single layer of mesothelial cells. Although these lesions are always connected to the pericardium, only a few cases show visible communication with the pericardial sac on imaging [25]. A homogeneous, low-density lesion measuring water or fluid attenuation with thin or imperceptible walls in one of the cardiophrenic angles can be confidently diagnosed as a pericardial cyst without the need for further evaluation (Fig. 3.10) [25, 26].

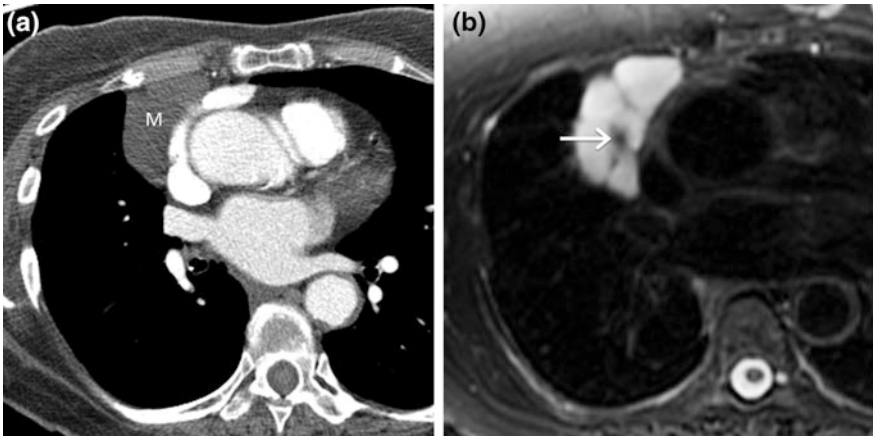

Fig. 3.8 Multilocular thymic cyst in a 74-year-old woman. **a** Contrast-enhanced axial CT demonstrates a low-attenuation lesion (*M*) in the right prevascular mediastinum. MRI was subsequently performed to evaluate for internal soft tissue components. **b** T2-weighted MRI of the same patient shows a cystic lesion with multiple internal septations which, one of them with focal thickening (*arrow*). Based on the imaging appearance alone, the mass could represent a multilocular thymic cyst or a cystic thymoma; the former was demonstrated at the time of surgical resection

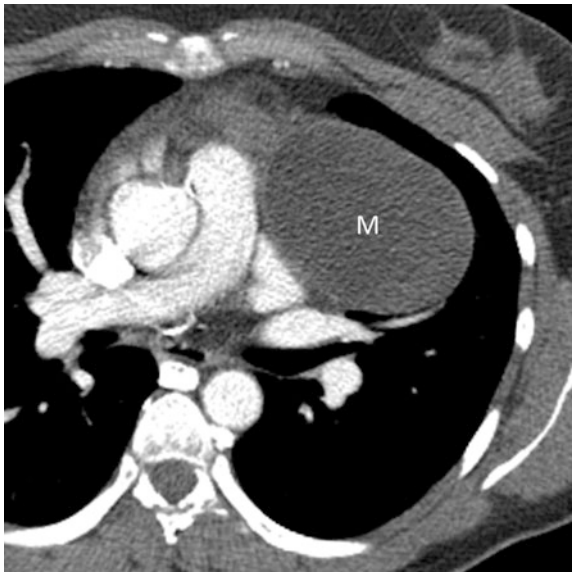

Fig. 3.9 Cystic teratoma in a 30-year-old woman. Contrast-enhanced axial CT demonstrates a well-circumscribed, homogeneous, fluid/water attenuation lesion (*M*) in the left prevascular mediastinum. MRI (not shown) was subsequently performed to evaluate for internal soft tissue components and revealed a purely cystic lesion. Based on this imaging appearance alone, the differential diagnosis would include a unilocular thymic cyst or cystic teratoma; the latter was demonstrated at the time of surgical resection

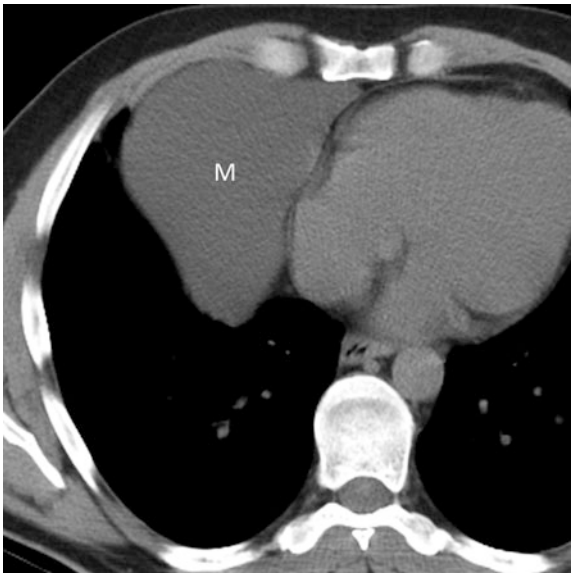

Fig. 3.10 Pericardial cyst in a 47-year-old man. Unenhanced axial CT shows a well-defined, homogeneous, fluid/water attenuation mass (*M*) in the right cardiophrenic sulcus. These findings are pathognomonic for a pericardial cyst and no further evaluation is necessary

Bronchogenic Cyst

Bronchogenic cysts are benign lesions resulting from abnormal ventral budding or branching of the tracheobronchial tree during development. Although these cysts may arise from any mediastinal compartment, they are most commonly identified near the carina in the visceral compartment. On CT, bronchogenic cysts manifest as solitary masses in smooth, round, or elliptical shapes with thin imperceptible walls. Although most lesions demonstrate homogeneous low attenuation, regions of internal high attenuation may be present when complicated by hemorrhage or infection or when proteinaceous components are present (Fig. 3.11) [26]. Hounsfield units greater than 100 due to high protein content or calcium oxalate have been reported [26–28]. Additional findings such as internal foci of air, suggestive of secondary infection and communication with the airways, calcification, and fluid–fluid levels may be present [26]. Following the administration of IV contrast, thin peripheral enhancement of the cyst wall may be present, but no internal enhancement of the cyst components should be seen.

Esophageal Duplication Cyst

Esophageal duplication cysts are congenital abnormalities that are classified as foregut cysts of either bronchogenic or neurenteric origin [29]. Most lesions are identified in the visceral compartment adjacent to the esophagus. The typical imaging appearance of an esophageal duplication cyst is a spherical, unilocular mass of fluid or water attenuation on CT (Fig. 3.12) [30, 31]. Cysts complicated by

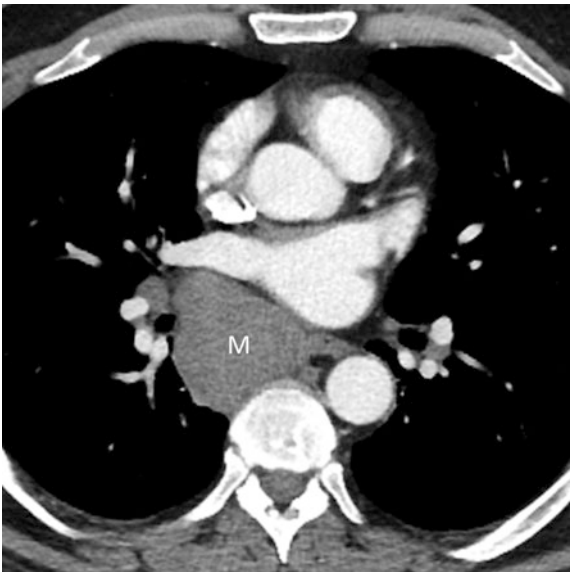

Fig. 3.11 Bronchogenic cyst in a 47-year-old woman. Contrast-enhanced axial CT shows a large mass (*M*) arising from the subcarinal region of the visceral compartment. Internal regions of high attenuation were concerning for soft tissue components. Subsequent MRI (not shown) demonstrated a completely cystic mass containing extensive proteinaceous components, consistent with a bronchogenic cyst. Although most bronchogenic cysts demonstrate homogeneous fluid/water attenuation, regions of internal high attenuation may be present when complicated by hemorrhage or infection or when proteinaceous components are present

hemorrhage or infection, or those containing internal proteinaceous components, may demonstrate higher attenuation. Following the administration of IV contrast, peripheral enhancement of the cyst wall may be present, but no internal enhancement of the cyst components should be seen. In instances in which regions of internal high attenuation or soft tissue are present, these cysts may be mistaken for solid lesions and MRI can be performed for further evaluation.

Meningocele

An intrathoracic meningocele represents an anomalous herniation of the leptomeninges through a defect in an intervertebral foramen or vertebral body and is often associated with neurofibromatosis [26]. These lesions arise from the paravertebral mediastinal compartment and manifest as well-defined, homogeneous, low-attenuation masses (Fig. 3.13) [26]. Associated abnormalities such as enlargement of the intervertebral foramina, vertebral and/or rib anomalies, and scoliosis may be present.

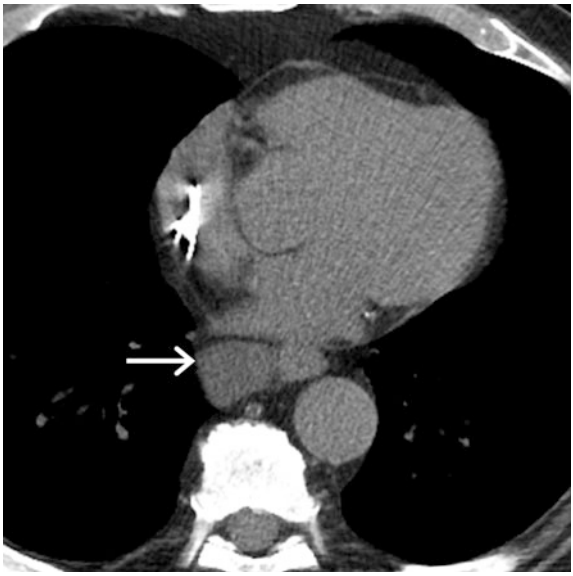

Fig. 3.12 Esophageal duplication cyst in a 74-year-old man. Unenhanced axial CT demonstrates a well-circumscribed, fluid/water attenuation mass (*arrow*) adjacent to the distal thoracic esophagus. When such an abnormality is identified in the visceral compartment adjacent to the esophagus, an esophageal duplication cyst can be strongly suggested

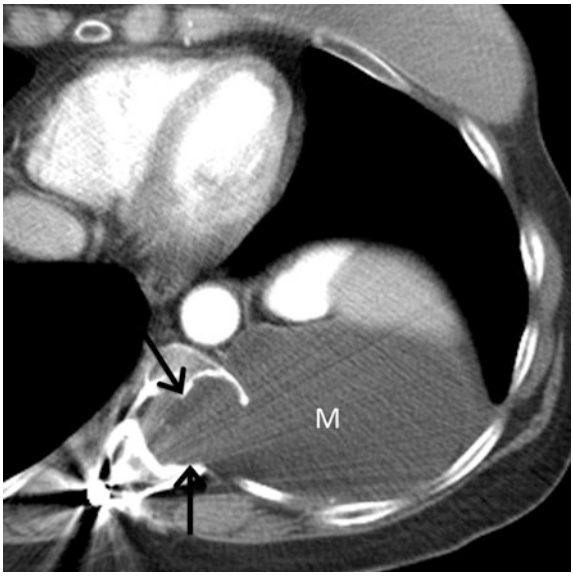

Fig. 3.13 Meningocele in a 32-year-old woman with neurofibromatosis. Contrast-enhanced axial CT demonstrates a large, fluid/water attenuation mass (*M*) in the left paravertebral region communicating with and expanding the left neural foramen and spinal canal (*arrows*). Most thoracic meningoceles are present in the setting of neurofibromatosis

Soft Tissue Lesions

Thyroid Goiter

A heterogeneous mass in the prevascular mediastinum that is intrinsically hyperdense, enhances following the administration of IV contrast, and demonstrates continuity with the cervical thyroid gland can dependably be diagnosed as a mediastinal goiter. The majority of these lesions demonstrate high attenuation on unenhanced CT with Hounsfield units measuring 70–85 due to the presence of iodine. Internal regions of low attenuation within goiters representing cystic changes and calcification may also be present (Fig. 3.14). Prolonged and sustained enhancement is usually present following the administration of IV contrast. It is important to note that not all mediastinal goiters demonstrate connection to the thyroid gland; nevertheless, when they are separate, they often demonstrate similar imaging features. In the setting of a goiter and loss of distinct mediastinal fascial planes or presence of associated cervical or mediastinal lymphadenopathy, thyroid malignancy should be suspected [12, 32].

Thymic Epithelial Neoplasms

Thymic epithelial neoplasms are a group of primary malignancies arising from the thymus that includes thymoma, thymic carcinoma, and thymic carcinoid. A homogeneous or slightly heterogeneous prevascular mediastinal mass in men and women older than age 40 likely represents a thymoma. When these findings are

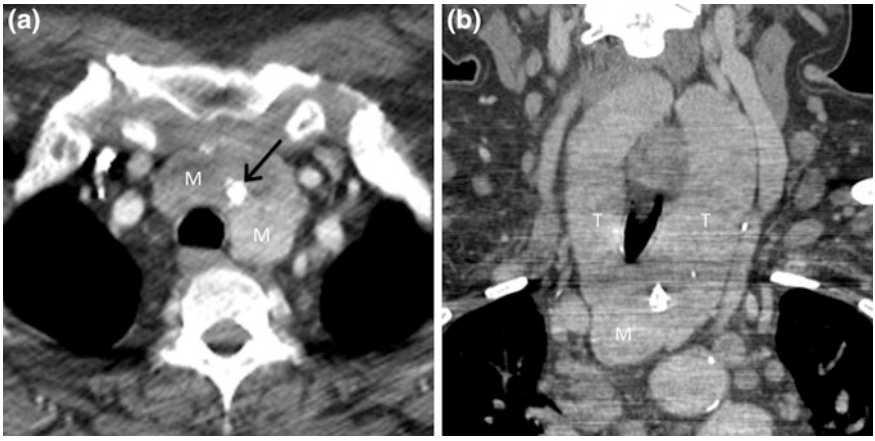

Fig. 3.14 Thyroid goiter in a 65-year-old woman. **a** Contrast-enhanced axial CT shows an enhancing mass (*M*) in the prevascular mediastinum with internal calcification (*arrow*). **b** Coronal reformatted CT of the same patient demonstrates continuity of the mediastinal mass (*M*) with the thyroid gland (T). These imaging findings are pathognomonic for a thyroid goiter

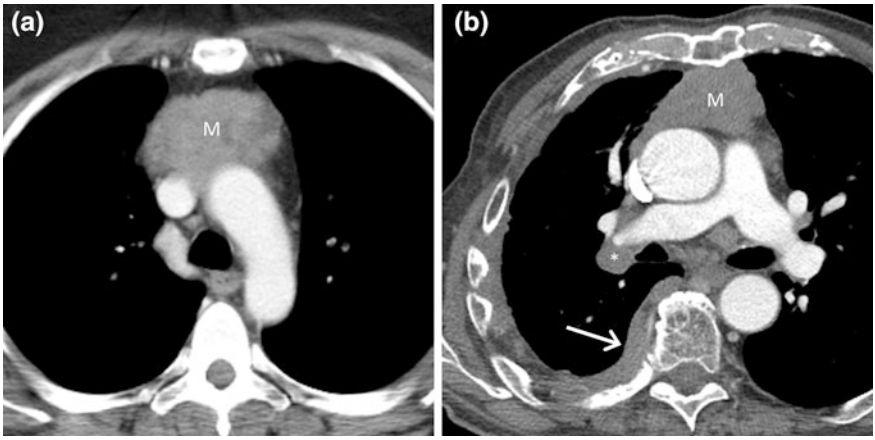

Fig. 3.15 Thymic epithelial neoplasms. **a** Contrast-enhanced axial CT of a 50-year-old woman presenting with symptoms of myasthenia gravis demonstrates a slightly heterogeneous mass (*M*) in the prevascular mediastinum. This combination of clinical and imaging findings was highly suggestive of a thymoma, which was confirmed by CT-guided core needle biopsy. **b** Contrast-enhanced axial CT of a 73-year-old man shows a prevascular mediastinal mass (*M*) with extensive pleural metastatic disease in the right hemithorax (*arrow*) and right hilar lymphadenopathy (*asterisk*). In contrast to thymoma, features such as heterogeneity, local invasion, lymphadenopathy, and pleural effusion are more commonly seen with thymic epithelial neoplasms other than thymoma such as thymic carcinoma and thymic carcinoid

present in the setting of clinical symptoms of myasthenia gravis or other paraneoplastic syndromes such as pure red cell aplasia/Diamond-Blackfan syndrome or hypogammaglobulinemia, the diagnosis should be strongly suspected (Fig. 3.15) [33]. Lymphadenopathy is typically absent, but pleural and/or pericardial spread may be identified in advanced disease. In contrast, when a large prevascular mediastinal mass with features such as heterogeneity, local invasion, lymphadenopathy, and pleural effusion is identified, other thymic epithelial neoplasms such as thymic carcinoma and thymic carcinoid should be considered (Fig. 3.15) [34].

Lymphoma

Lymphoma should be considered in patients with mediastinal lymphadenopathy or a lobulated soft tissue mass in the prevascular mediastinum on cross-sectional imaging; associated lymphadenopathy in the lower neck or axillae may or may not be present. Although lymphoma may be difficult to distinguish from other etiologies of mediastinal soft tissue masses, many types of lymphoma behave in an infiltrative manner. When these imaging findings are present in the setting of "B" symptoms such as fever, weight loss, and night sweats, lymphoma should be strongly suspected (Fig. 3.16). Further work-up typically entails core needle biopsy

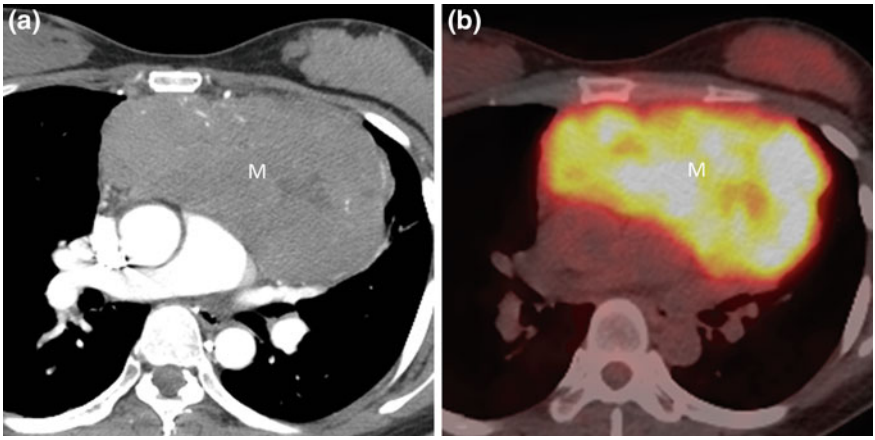

Fig. 3.16 31-year-old woman with lymphoma. **a** Contrast-enhanced axial CT shows a heterogeneous prevascular mass (*M*). CT-guided core and fine needle aspiration biopsies revealed Hodgkin lymphoma. **b** Fused axial FDG-PET/CT of the same patient demonstrates intense FDG uptake within the mass

combined with aspiration for flow cytometry or surgical biopsy. Once a diagnosis of lymphoma has been established, FDG-PET/CT is the imaging modality of choice for staging, and assessing for treatment response and recurrence (Fig. 3.16). FDG-PET/CT is better than CT at detecting involved lymph nodes, with a sensitivity of 94% and a specificity of 100%, respectively, compared with 88% and 86% for CT [35]. The sensitivity and specificity of FDG-PET/CT in detecting organ involvement are 88% and 100%, respectively, compared with 50% and 90% for CT [35].

Non-Teratomatous Germ Cell Tumors

The mediastinum is the most common extragonadal site of origin of germ cell tumors (GCTs), which represent 10–15% of prevascular mediastinal masses in adults and 25% in children [16]. Approximately, 3% of mediastinal GCTs arise from the paravertebral compartment [36]. Young men are typically affected [37]. These GCTs are often separated into seminomas and NSGCTs, the latter of which include yolk sac, and mixed germ cell tumors, embryonal carcinomas, and choriocarcinomas.

When a large, lobular homogeneous prevascular mediastinal mass is identified on cross-sectional imaging in a young man 10–39 years of age, seminoma should be considered (Fig. 3.17) [38]. Pulmonary metastases are common whereas pleural effusions are rare [12]. Approximately, 10% of seminomas are associated with slightly elevated serum β-human chorionic gonadotropin (β-HCG) but α-fetoprotein (AFP) is typically normal [39, 40]; serum lactate dehydrogenase

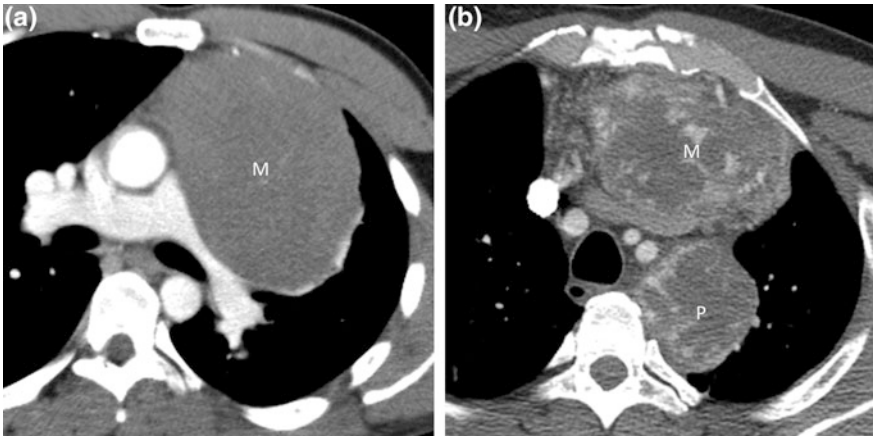

Fig. 3.17 Non-teratomatous germ cell neoplasms. **a** Contrast-enhanced axial CT of a 24-year-old man presenting with chest pain demonstrates a large soft tissue mass (*M*) in the prevascular mediastinum. Serum levels of β-HCG and LDG were elevated, suggesting a primary mediastinal seminoma, which was confirmed at surgical resection. **b** Contrast-enhanced axial CT of a 30-year-old man shows a large, heterogeneous prevascular mediastinal mass (*M*) with regions of internal vascularity. **a** large left pleural metastasis (P) is present. Markedly elevated serum α-FP levels were present, suggesting NSGCT, which was confirmed with CT-guided core needle biopsy

levels are usually elevated [40, 41]. When a heterogeneous prevascular mediastinal mass is present with lung metastases in patients younger than 40 years of age, NSGCT should be considered (Fig. 3.17) [17, 42]. Markedly elevated serum AFP or β-HCG levels are present in 90% of NSGCTs and strongly support the diagnosis [39, 40, 43, 44].

Thymic Hyperplasia

Normal thymic tissue is typically seen in young patients and should decrease in amount and size with increasing age. For instance, by 40 years of age, the thymus is replaced by fat in the majority of individuals. Thymic hyperplasia should be considered when uniform enlargement of the thymus is seen in young patients or when soft tissue is present in the thymic bed that is similar in configuration to the normal thymus. In patients who have been treated with chemotherapy, radiation therapy, or corticosteroids, have experienced stresses such as burns or injuries, or who have disorders such as myasthenia gravis, hyperthyroidism, collagen vascular diseases, or human immunodeficiency virus (HIV) infection, thymic hyperplasia should be considered when a low-attenuation mass is present in the prevascular compartment or there is diffuse, symmetric enlargement of the thymus. Intralesional fat resulting in ill-defined regions of low attenuation on CT may be present but is much less common. In other cases, the CT appearance is not straightforward and thymic hyperplasia may appear more nodular or bulky in configuration, resembling a

thymoma or lymphoma. In such scenarios in which the cross-sectional imaging findings are not characteristic, short interval follow-up imaging (~3 months) or chemical shift MRI with in-phase and out-of-phase gradient echo imaging can be performed. Thymic hyperplasia and the normal thymus demonstrate loss of signal on out-of-phase imaging due to the suppression of microscopic fat interspersed between non-neoplastic thymus, whereas thymic epithelial neoplasms, lymphoma, and other malignancies do not suppress on out-of-phase imaging [Fig. 3.18].

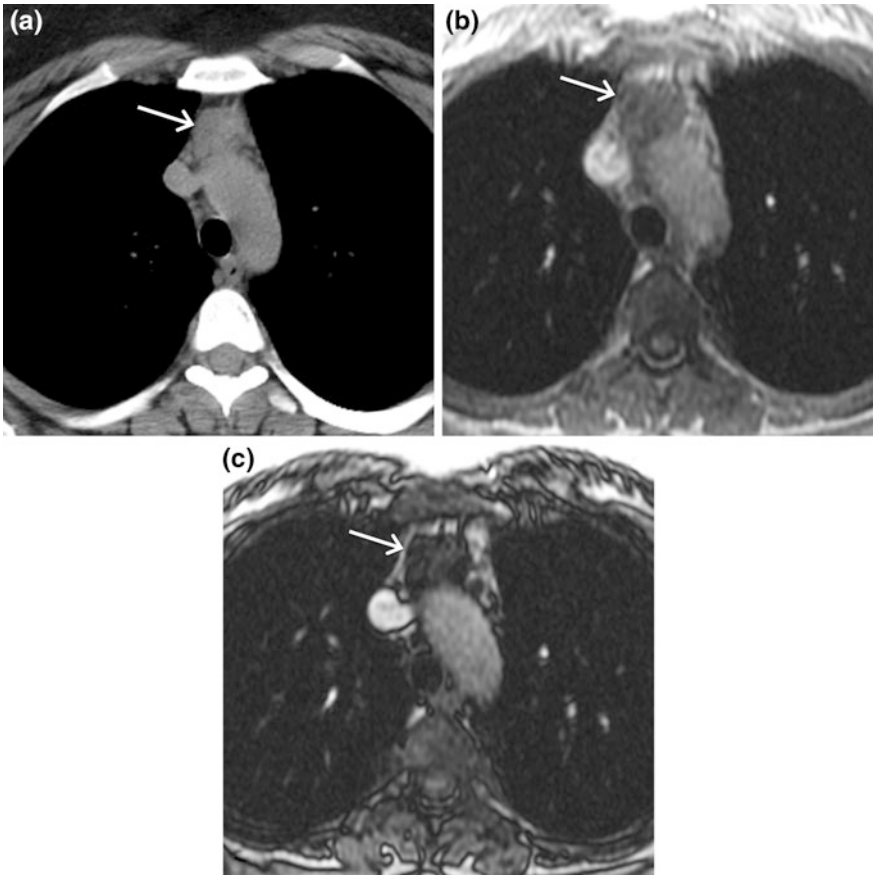

Fig. 3.18 Thymic hyperplasia in a 23-year-old woman. **a** Unenhanced axial CT demonstrates a soft tissue mass (*arrow*) in the prevascular mediastinum that is nonspecific and could be malignant or benign in etiology. **b** and **c** Axial T1-weighted in-phase (**b**) and out-of-phase (**c**) MRI of the same patient shows uniform high signal (*arrow*) on the in-phase sequence but complete loss of signal (*arrow*) on the out-of-phase sequence, confirming the presence of microscopic fat interspersed between hyperplastic thymic tissue

Esophageal Neoplasms

When asymmetric or circumferential thickening of the esophageal wall or a focal soft tissue mass associated with the esophagus is identified in the visceral compartment on CT, primary esophageal malignancy should be strongly suspected [Fig. 3.19]. The most common types of esophageal cancer include squamous cell carcinoma and adenocarcinoma; other histologic types are much less common. Diagnosis requires histologic sampling, typically obtained through endoscopic ultrasound-guided biopsy. Although CT is useful for identifying lymph node involvement and metastatic disease, differentiation between various degrees of primary tumor invasion is unreliable [45].

Neurogenic Neoplasms

Neurogenic neoplasms are the most common etiology of a paravertebral mediastinal mass, and account for 20 and 35% of all mediastinal tumors in adults and children, respectively [46]. The majority of these lesions are benign and patients are typically asymptomatic. Neurogenic neoplasms can be grouped into peripheral nerve sheath neoplasms, sympathetic ganglion tumors, and paragangliomas.

Peripheral nerve sheath tumors represent the majority of neurogenic neoplasms of mediastinal origin, the most common of which include schwannomas and neurofibromas. These lesions arise from the paravertebral mediastinum in a "dumbbell" or "hourglass" configuration as a result of extension through the adjacent intervertebral foramen and spinal canal. Internal hemorrhage and cystic changes can

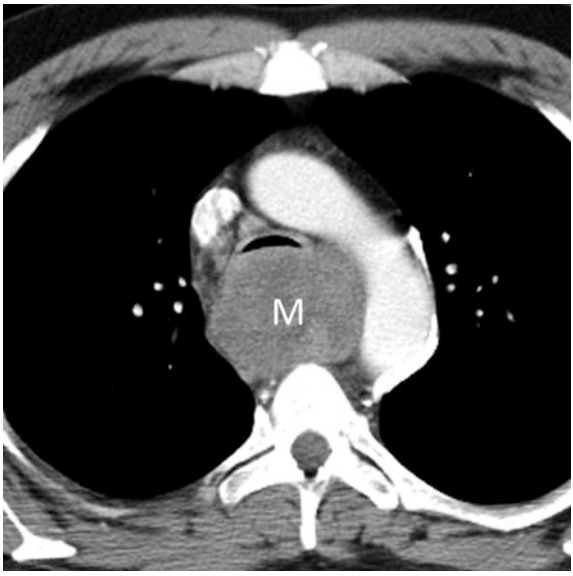

Fig. 3.19 Esophageal cancer in a 51-year-old woman. Contrast-enhanced axial CT image shows a soft tissue mass (*M*) arising from the esophagus and obliterating the fat plane between it and a portion of the transverse thoracic aorta, confirming its location in the visceral compartment. Endoscopic biopsy revealed esophageal cancer

result in regions of heterogeneity and more commonly affect schwannomas than neurofibromas (Fig. 3.20) [46]. Malignant transformation of a neurofibroma to a malignant peripheral nerve sheath tumor should be suspected when a neurofibroma increases in size and the affected patient develops neurological symptoms, particularly in patients with neurofibromatosis type 1 [47]. Sympathetic ganglion neoplasms include ganglioneuromas, ganglioneuroblastomas, and neuroblastomas. Compared to peripheral nerve sheath neoplasms and other sympathetic ganglion tumors, neuroblastomas are highly aggressive lesions that tend to metastasize early.

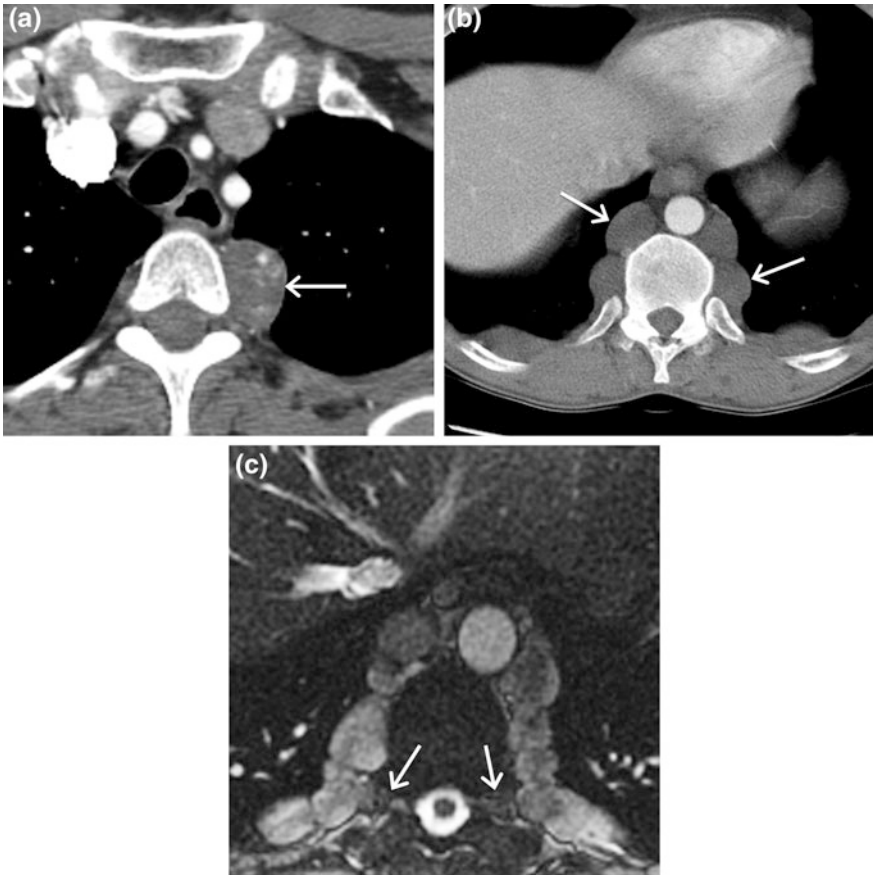

Fig. 3.20 Peripheral nerve sheath neoplasms. **a** Contrast-enhanced axial CT of a 52-year-old woman presenting with back pain demonstrates a well-circumscribed, heterogeneous mass (*arrow*) arising from the left paravertebral mediastinum. Surgical resection was performed because of the patient's symptomatology, and pathology revealed a benign schwannoma. **b** and **c** Contrast-enhanced axial CT (**b**) of a 29-year-old man with neurofibromatosis shows multiple well-circumscribed, homogeneous paravertebral masses (*arrows*) consistent with neurofibromas. Axial T2-weighted MRI (**c**) of the same patient demonstrates the high signal intensity neurofibromas communicating with and expanding the neural foramina (*arrows*)

These malignancies are heterogeneous on cross-sectional imaging and often demonstrate regions of internal hemorrhage, cystic degeneration, necrosis, or calcification [47].

Miscellaneous Lesions

Paraspinal Abscess

Paraspinal abscess represents phlegmon surrounding a peripherally enhancing fluid collection, typically the result of direct extension from adjacent infection, transcutaneous infection of deep tissue, and hematogenous spread from distant sites. Predisposing conditions include intravenous drug use and immunocompromised states. On CT, paraspinal abscess manifests as amorphous, ill-defined soft tissue lesions in the paravertebral region, and low-density intramuscular fluid collections with or without internal foci of gas. Following the administration of IV contrast, diffuse or peripheral enhancement may be present. Paraspinal abscess due to tuberculosis infection may demonstrate partial or complete calcification. Associated osseous changes include destruction of the vertebral body endplates and spinal deformities.

Parathyroid Adenoma

Ectopic parathyroid adenomas rarely occur in the mediastinum, and most are found in the prevascular compartment. These lesions manifest as small soft tissue nodules with or without calcification [47]. While this imaging appearance is relatively nonspecific, these abnormalities should be suspected in the clinical setting of hyperparathyroidism. Technetium-99 sestamibi single-photon emission computed tomography scans are typically better than CT for diagnosing ectopic parathyroid adenoma.

Extramedullary Hematopoiesis

Extramedullary hematopoiesis represents a proliferation of hematopoietic cells outside of the bone marrow in the setting of failing marrow hematopoiesis, and has been associated with myelofibrosis, β-thalassemia, hereditary spherocytosis, hemolytic anemia, and sickle cell anemia. Most patients are asymptomatic and the lesions are discovered incidentally on imaging; however, cord compression may rarely complicate intraspinal involvement. The typical appearance of extramedullary hematopoiesis on CT is well-defined soft tissue masses in the paravertebral regions along the costovertebral junctions. Although lesions are usually purely soft tissue, regions of internal fat density may be seen in burned-out lesions.

Following the administration of IV contrast, mild or heterogeneous contrast enhancement may be seen. MRI is superior to CT in demonstrating the presence and extent of intraspinal extension.

Take Home Message

In the evaluation of mediastinal masses, the diagnosis can be suggested in many cases by imaging findings alone. However, other lesions exhibit inconclusive imaging features; when the imaging correlates with specific clinical information a presumptive diagnosis can be quite reliable. The approach outlined in this chapter, based on localization to a specific compartment and key imaging features on cross-sectional imaging, can facilitate a more streamlined and efficient discussion and further evaluation of patients presenting with these abnormalities.

- Location of the lesion to specific compartments in the mediastinum is key for differential diagnosis in radiology.
- In many cases of mediastinal masses, the diagnosis can be made by imaging findings alone, based on characteristic appearance of the lesions.
- In other cases, where the imaging studies are not characteristic, clinico-radiographic correlation can be reliable for a presumptive diagnosis.

References

1. Carter BW, Tomiyama N, Bhora FY, et al. A modern definition of mediastinal compartments. J Thorac Oncol. 2014;9(9 Suppl 2):S97–101.
2. Fujimoto K, Hara M, Tomiyama N, et al. Proposal for a new mediastinal compartment classification of transverse plane images according to the Japanese Association for Research on the Thymus (JART) general rules for the study of mediastinal tumors. Oncol Rep. 2014;31:565–72.
3. Davis RD Jr, Oldham HN Jr, Sabiston DC Jr. Primary cysts and neoplasms of the mediastinum: recent changes in clinical presentation, methods of diagnosis, management, and results. Ann Thorac Surg. 1987;44:229–37.
4. Levasseur P, Kaswin R, Rojas-Miranda A, et al. Apropos of a series of 742 operated patients. Nouv Presse Med. 1976;5:2857–9.
5. Cohen AJ, Thompson L, Edwards FH, Bellamy RF. Primary cysts and tumors of the mediastinum. Ann Thorac Surg. 1991;51:378–84. (discussion 385).
6. Rubush JL, Gardner IR, Boyd WC, Ehrenhaft JL. Mediastinal tumors. Review of 186 cases. J Thorac Cardiovasc Surg. 1973;65:216–22.
7. Wychulis AR, Payne WS, Clagett OT, Woolner LB. Surgical treatment of mediastinal tumors: a 40 year experience. J Thorac Cardiovasc Surg. 1971;62:379–92.
8. Mullen B, Richardson JD. Primary anterior mediastinal tumors in children and adults. Ann Thorac Surg. 1986;42:338–45.
9. Takeda S, Miyoshi S, Minami M, et al. Clinical spectrum of primary mediastinal tumors: a comparison of adult and pediatric populations (Abstract). Chest. 2000;118:206S.

10. Whooley BP, Urschel JD, Antkowiak JG, Takita H. Primary tumors of the mediastinum. J Surg Oncol. 1999;70:95–9.
11. Azarow KS, Pearl RH, Zurcher R, Edwards FH, Cohen AJ. Primary mediastinal masses. a comparison of adult and pediatric populations. J Thorac Cardiovasc Surg. 1993;106:67–72.
12. Carter BW, Okumura M, Detterbeck FC, Marom EM. Approaching the patient with an anterior mediastinal mass: a guide for radiologists. J Thorac Oncol. 2014 9 Suppl 2:S110–8.
13. Tomiyama N, Honda O, Tsubamoto M, et al. Anterior mediastinal tumors: diagnostic accuracy of CT and MRI. Eur J Radiol. 2009;69:280–8.
14. Ackman JB, Wu CC. MRI of the thymus. AJR Am J Roentgenol. 2011;197:W15–20.
15. Inaoka T, Takahashi K, Mineta M, et al. Thymic hyperplasia and thymus gland tumors: differentiation with chemical shift MR imaging. Radiology. 2007;243:869–76.
16. Takahashi K, Al-Janabi NJ. Computed tomography and magnetic resonance imaging of mediastinal tumors. J Magn Reson Imaging. 2010;32:1325–39.
17. Rosado-de-Christenson ML, Templeton PA, Moran CA. From the archives of the AFIP. Mediastinal germ cell tumors: radiologic and pathologic correlation. Radiographics. 1992;12:1013–30.
18. Molinari F, Bankier AA, Eisenberg RL. Fat-containing lesions in adult thoracic imaging. AJR Am J Roentgenol. 2011;197:W795–813.
19. Wright C. Germ cell tumors of the mediastinum. In: Pearson F, Cooper J, Deslauriers J, Ginsberg RJ, Hiebert C, Patterson G, Urschel H, editors. Thoracic Surgery. New York: Churchill Livingstone; 2002. p. 1711–9.
20. Gaerte SC, Meyer CA, Winer-Muram HT, Tarver RD, Conces DJ Jr. Fat-containing lesions of the chest. Radiographics 2002;22 Spec No:S61–S78.
21. Nishino M, Ashiku SK, Kocher ON, et al. The thymus: a comprehensive review. Radiographics. 2006;26:335–48.
22. Munden RF, Nesbitt JC, Kemp BL, Chasen MH, Whitman GJ. Primary liposarcoma of the mediastinum. AJR Am J Roentgenol. 2000;175:1340.
23. Hahn HP, Fletcher CD. Primary mediastinal liposarcoma: clinicopathologic analysis of 24 cases. Am J Surg Pathol. 2007;31:1868–74.
24. Choi YW, McAdams HP, Jeon SC, et al. Idiopathic multilocular thymic cyst: CT features with clinical and histopathologic correlation. AJR Am J Roentgenol. 2001;177:881–5.
25. Feigin DS, Fenoglio JJ, McAllister HA, Madewell JE. Pericardial cysts. A radiologic-pathologic correlation and review. Radiology. 1977;125:15–20.
26. Jeung MY, Gasser B, Gangi A, et al. Imaging of cystic masses of the mediastinum. Radiographics 2002;22 Spec No:S79–S93.
27. Mendelson DS, Rose JS, Efremidis SC, Kirschner PA, Cohen BA. Bronchogenic cysts with high CT numbers. AJR Am J Roentgenol 1983; 140:463–5. (CrossRef, Medline).
28. Yernault JC, Kuhn G, Dumortier P, Rocmans P, Ketelbant P, De Vuyst P. "Solid" mediastinal bronchogenic cyst: mineralogic analysis. AJR Am J Roentgenol. 1986;146:73–4.
29. Fitch SJ, Tonkin IL, Tonkin AK. Imaging of foregut duplication cysts. RadioGraphics. 1986;6:189–201.
30. Kuhlman JE, Fishman EK, Wang KP, Siegelman SS. Esophageal duplication cyst: CT and transesophageal needle aspiration. AJR Am J Roentgenol 1985; 145:531–2. (CrossRef, Medline).
31. LeBlanc J, Guttentag AR, Shepard JA, McLoud TC. Imaging of mediastinal foregut cysts. Can Assoc Radiol J. 1994;45:381–6.
32. Naidich DP, Webb WR, Muller NL, Krinsky GA, Zerhouni EA, Siegelman SS, editors. Mediastinum. In computed tomography and magnetic resonance of the thorax, 3rd Ed. Philadelphia, PA: Lippincott Williams and Wilkins, 1999. p. 82–3.
33. Benveniste MF, Rosado-de-Christenson ML, Sabloff BS, Moran CA, Swisher SG, Marom EM. Role of imaging in the diagnosis, staging, and treatment of thymoma. Radiographics 2011;31:1847–61. (discussion 1861).

34. Rosado-de-Christenson ML, Strollo DC, Marom EM. Imaging of thymic epithelial neoplasms. Hematol Oncol Clin North Am. 2008;22(3):409–31.
35. Schaefer NG, Hany TF, Taverna C, et al. Non-Hodgkin lymphoma and Hodgkin disease: coregistered FDG PET and CT at staging and restaging–do we need contrast-enhanced CT? Radiology. 2004;232:823–9.
36. Duwe BV, Sterman DH, Musani AI. Tumors of the mediastinum. Chest. 2005;128(4):2893–909.
37. Tian L, Liu LZ, Cui CY, Zhang WD, Kuang YL. CT findings of primary non-teratomatous germ cell tumors of the mediastinum–a report of 15 cases. Eur J Radiol. 2012;81(5):1057–61.
38. Strollo DC, Rosado-de-Christenson ML. Primary mediastinal malignant germ cell neoplasms: imaging features. Chest Surg Clin N Am. 2002;12:645–58.
39. Economou JS, Trump DL, Holmes EC, Eggleston JE. Management of primary germ cell tumors of the mediastinum. J Thorac Cardiovasc Surg. 1982;83:643–9.
40. Bokemeyer C, Nichols CR, Droz JP, et al. Extragonadal germ cell tumors of the mediastinum and retroperitoneum: results from an international analysis. J Clin Oncol. 2002;20:1864–73.
41. Bukowski RM, Wolf M, Kulander BG, Montie J, Crawford ED, Blumenstein B. Alternating combination chemotherapy in patients with extragonadal germ cell tumors. A southwest oncology group study. Cancer. 1993;71:2631–8.
42. Lee KS, lm J-G, Han CH, Han MC, Kim C-W, Kim WS. Malignant primary germ cell tumors of the mediastinum: CT features. AJR Am J Roentgenol. 1989;153:947–51.
43. Wright CD, Kesler KA, Nichols CR, et al. Primary mediastinal nonseminomatous germ cell tumors. Results of a multimodality approach. J Thorac Cardiovasc Surg. 1990;99:210–7.
44. Kesler KA, Rieger KM, Ganjoo KN, et al. Primary mediastinal nonseminomatous germ cell tumors: the influence of postchemotherapy pathology on long-term survival after surgery. J Thorac Cardiovasc Surg. 1999;118:692–700.
45. Hong SJ, Kim TJ, Nam KB, et al. New TNM staging system for esophageal cancer: what chest radiologists need to know. Radiographics. 2014;34(6):1722–40.
46. Nakazono T, et al. MRI findings of mediastinal neurogenic tumors. AJR Am J Roentgenol. 2011;197:W643–52.
47. Juanpere S, Cañete N, Ortuño P, et al. A diagnostic approach to the mediastinal masses. Insights Imaging. 2013;4:29–52.

Cytologic Features of Mediastinal Lesions

4

Andre L. Moreira

Introduction

The mediastinum is the central thoracic compartment surrounded by several organs. The region can be affected by a variety of pathological processes including inflammatory, developmental, and neoplastic diseases that can cause significant diagnostic difficulties due to the rarity of these processes and significant overlap of morphologic features (Table 4.1). Therefore, knowledge of the radiographic appearance, location of the lesion, and clinical information (age, sex, history of prior malignancy) are important factors to be considered in the differential diagnosis. The mediastinum can be compartmentalized into prevascular, visceral, and paravertebral chambers. However, the older terminology of anterior, posterior, and middle mediastinum (site of hilar pulmonary lymph nodes) can still be found [1]. Each compartment is more commonly affected by a different set of diseases, for example, sarcomas and soft tissue tumors are more common in the posterior mediastinum, thymomas and germ cell tumors are more common in the prevascular area, whereas metastatic disease is more common in the visceral mediastinum. Although aspiration biopsies of the mediastinum are rare, mediastinal lesions can be explored by fine-needle aspiration biopsy (FNAB) obtained under radiographic guidance, either through a transthoracic, esophageal, or bronchoscopic approach. The reported diagnostic accuracy of FNAB is approximately 85% (range 71–100%) [1–6]. Knowledge of the cytological features of primary tumors of the site is an important step for establishing diagnosis and patient management.

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Table 4.1 Differential diagnosis of mediastinal lesions according to location

Prevascular Mediastinum
- Metastatic carcinoma
- Thymoma and thymic carcinoma
- Germ Cell Tumor
- Lymphoma
- Thymic cyst
- Pericardial cyst
- Thymic hyperplasia
Visceral Mediastinum
- Metastatic carcinoma
- Lymphoma
- Sarcoidosis
- Bronchogenic cyst
Paravertebral Mediastinum
- Schwannoma
- Ganglioneuroma
- Malignant peripheral nerve sheet tumor
- Neuroblastoma
- Other sarcomas

In this chapter, we will concentrate on thymic epithelial tumors, germ cells tumors, and inflammatory lesions; following a pattern recognition approach that are helpful in establishing a differential diagnosis among the heterogeneous group of diseases that can affect the site. The cytological features of lymphoproliferative lesions and soft tissue tumors follow the same criteria of these tumors elsewhere.

Thymoma: Challenges and Pitfalls

Thymoma, a neoplasm of the thymic epithelium, is the most common primary neoplasm of the anterior mediastinum in adults, representing approximately 50% of tumors occurring at the site. However, thymomas are rare neoplasms [7]. The tumor can present with several morphologic variations and histological types which are a challenge for classification and diagnosis. The accuracy of aspiration biopsy and small biopsy for diagnosis of thymoma ranges from 80 to 100%, in several series [1–6]. The hallmark for the diagnosis of thymoma in a small biopsy sample is the presence of two cell populations, one composed of bland epithelial cells and the other of lymphocytes [8]. However, this classical feature may not be present in a large number of cases due to the variation of histological presentation seen in these tumors. Each histological type of thymoma elicits a different cytological pattern (Table 4.2) and therefore a different set of differential diagnosis.

In this chapter, we will use the 2015 WHO classification of thymic epithelial tumors in an attempt to correlate the cytological features with the histological classification. Briefly, in the WHO classification [9, 10], thymomas are classified as type A, which is composed predominantly of spindle-shaped cells (spindle-shaped pattern) and type B, composed of a mixture of bland epithelial cells and

Table 4.2 Differential diagnosis according to cytological pattern

Spindled-shaped cell pattern
- Thymoma, type A
- Carcinoid tumor (Typical or atypical)
- Schwannoma
- Sarcoma
- Mature teratoma
Epithelioid-rich pattern
- Metastatic carcinoma
- Thymoma, type B
- Thymic carcinoma
- Carcinoid tumor
- Germ cell tumor
✓ Seminoma
✓ Yolk sac tumor
✓ Embryonal carcinoma
✓ Choriocarcinoma
✓ Mature teratoma
Lymphocyte-rich pattern
- Lymphoma
✓ Large B-cell lymphoma
✓ Acute lymphoblastic lymphoma
✓ Other
- Thymoma, type B1
- Thymic hyperplasia
- Thymic follicular hyperplasia
Small Blue Cell pattern
- Small cell carcinoma
- Neuroblastoma
- Ewing sarcoma
- Immature teratoma
Inflammatory pattern
- Hodgkin lymphoma
- Sarcoidosis
- Infectious granuloma
- IgG4 sclerosing disease
Cystic pattern
- Thymic cyst
- Cystic teratoma
- Pericardial cyst
- Bronchogenic cyst
- Cystic thymoma
- Other

lymphocytes. Type B thymomas are subdivided into B1, B2, and B3, depending on the ratio of epithelial cells to lymphocytes. B1 thymomas are rich in thymic lymphocytes (lymphocyte-rich pattern) and B3 thymomas are predominantly composed of epithelial cell (epithelioid pattern, with or without lymphocytes) (Table 4.3). In addition, type B thymomas, often present with a combinations of different sub types in a spectrum of B thymoma within the same tumor mass (e.g., predominant type B2 with areas of B1). Another common combination is Type AB thymoma which is

Table 4.3 Cytological patterns of thymoma

WHO type	Cytological pattern
A	Spindle-shaped cells
B1	Lymphocyte-rich
B2	Epithelioid-rich with lymphocytes
B3	Epithelioid-rich without lymphocytes

composed of a mixture of types A and B. Therefore, it may be very difficult to accurately classify a type B thymoma in small biopsy and cytological specimen due to sampling bias. In addition, there have been no studies that correlate histological classification with predictive response to therapy. Histologic subtype is not currently relevant for treatment and patient management. Therefore an accurate subclassification of thymomas in cytology is not desirable, whereas an accurate diagnosis of thymoma in conjunction with clinical and radiographic staging of the disease is important for patient management [10–12].

One of the most important pitfalls for the diagnosis of thymoma occurs when the tumor is not considered in the differential diagnosis of a biopsy of the anterior mediastinum. Similarly, thymoma should enter the differential diagnosis of FNAB of any site, especially pleural-based lesion, if the presence or history of an anterior mediastinal mass is noted. In fact, FNAB and small biopsies are often used in the diagnosis of metastatic site, whereas the primary diagnosis of thymoma is often made by surgical resection.

Pattern recognition approach: **Spindle-shaped cells**

The differential diagnosis for this group includes: spindle cell (type A) thymoma, spindle cell carcinoid tumor, sarcoma (primary or metastatic), and a spindle cell component of germ cell tumor.

Thymoma Type A

This type of thymoma can occur at any age group, with a peak around the sixth to seventh decade of life. This tumor is often seen in a low clinical stage, most are confined to the thymus, although pleural implants and distance metastasis can occur [13, 14]. An aspiration biopsy of a Type A thymoma shows cohesive clusters of spindle-shaped cells arranged in bundles and large sheets. The cells have elongated nuclei and some of the nuclei may be wavy. Cytoplasm is evident but the cell border is poorly defined (Fig. 4.1). Lymphocytes can also be seen in the background or permeating the clusters of spindle-shaped cells. In a majority of cases, the lymphocytes are not prominent but can be seen within the epithelial cell clusters [3, 15]. Cell block preparations are helpful in identifying these features. The nuclei of the spindle-shaped cells are bland with clear, vesicular or evenly dispersed chromatin, which can suggest a neuroendocrine tumor (Fig. 4.2) [16].

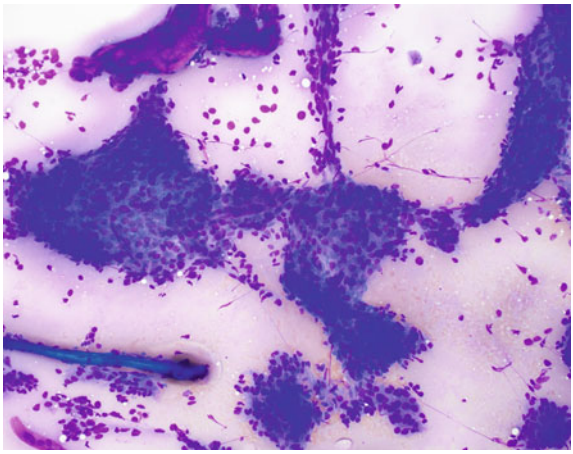

Fig. 4.1 Thymoma type A-Smear showing tight clusters of spindle-shaped cells with poorly defined cell borders. (Modified Giemsa stain)

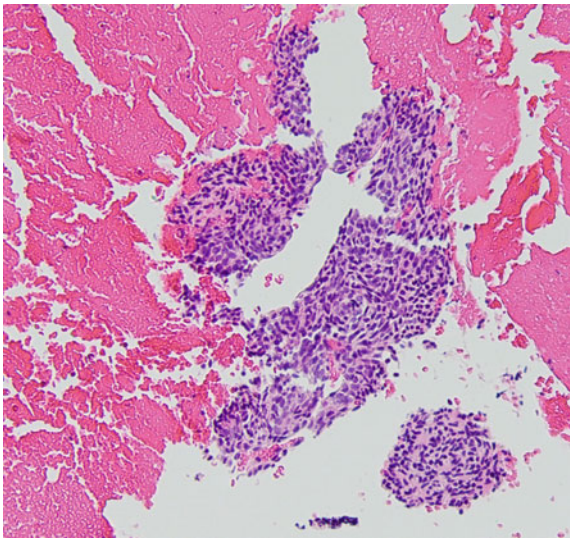

Fig. 4.2 Thymoma type A-Cell block preparation showing clusters of spindle-shaped cells. *Note* stippled chromatin pattern resembling a neuroendocrine tumor. The tumor cells are negative for neuroendocrine markers. (Hematoxylin and Eosin stain)

Type A thymomas have a variety of histological patterns, which can lead to misdiagnosis, including a cylindromatous pattern mimicking adenoid cystic carcinoma [17]. The elongated nuclei and tight cell clusters may resemble a low-grade soft tissue tumor, such as solitary fibrous tumor. The diagnosis can be made with the use of ancillary test such as immunocytochemical stains. In thymomas, the epithelial nature of the spindle-shaped cells is revealed by a positive staining pattern for pan-keratin, and p63/p40, however, when present, the characteristic immunophenotype of the thymic T-cells can help in asserting the correct diagnosis. The thymic T-cells are positive for CD3, CD5, CD99, CD1a, and TdT. Therefore, the presence of these markers on the lymphocytes is suggestive of a thymic origin.

Cytological features

- Tight cohesive clusters of spindle-shaped cells
- Lymphocytes may be seen in the background or associated with cell clusters
- Open chromatin pattern, wavy nuclei.

Spindle Cell Carcinoid Tumor

Spindle cell carcinoid is a rare neoplasm at this site, but nevertheless can be present in the mediastinum. The cells have the characteristic neuroendocrine morphology of "salt and pepper" chromatin distribution of tumor nuclei. The cell clusters may have similar arrangement to the one described for a spindle cell thymoma, but in carcinoid tumors, the cell clusters tend to be loosely cohesive whereas in thymomas the tumor cells form tight clusters. The presence of apoptotic bodies in carcinoid tumors may be confused with infiltrating lymphocytes thus mimicking a thymoma. However, immunocytochemical stains can help differentiate the two entities. In carcinoid tumor, the cells are positive for chromogranin, synaptophysin or other neuroendocrine markers with no predominant immature T-cell population. A positive labeling for neuroendocrine markers in the absence of immature T-cells points towards a diagnosis of a spindle cell carcinoid tumor.

Cytological features:

- Loosely cohesive cell clusters
- Salt-and-pepper chromatin pattern.

Soft Tissue Tumors

Schwannoma and malignant peripheral nerve sheath tumor are more commonly seen in the posterior mediastinum. In these cases, the presence of palisading spindle cells with wavy nuclei is suggestive of neural differentiation. The appropriate immunohistochemical stains guide the pathologist into the correct diagnosis. Tumor cells in these cases are positive for S-100 protein and negative for keratin. Solitary Fibrous Tumor (SFT) can be confused with Thymoma WHO type A. The tumors cells are bland and present as tight clusters. However, SFT are positive for CD34, BCL-2, and STAT-6, whereas thymomas are positive for keratins.

If the spindle-shaped cells mark for smooth muscle or skeletal muscle, a sarcoma with muscle differentiation or a component of a germ cell tumor enters the differential diagnosis. In these cases, careful observation of the cell type and

characteristics of the cell are helpful features in pointing towards the correct diagnosis. Cells with malignant characteristics guide the pathologist toward the diagnosis of a sarcoma. Metastatic sarcomas are more commonly seen in the prevascular and visceral mediastinum, primary sarcomas of these sites are extremely rare.

Cells with a benign smooth muscle differentiation occurring in a cystic lesion in a young patient point towards a benign component of a mature teratoma. In addition, correlation with radiographic images is helpful in reaching the accurate diagnosis [18].

Epithelioid-Rich Pattern

The differential diagnosis for this group includes: thymoma WHO type B, thymic carcinoma, carcinoid tumors, germ cell tumor, including seminoma, and metastatic carcinoma. Epithelioid lesions of the mediastinum can be further subdivided in two categories: those that contain lymphocytes and those without lymphocytes. The presence of lymphocytes in an epithelioid lesion of the mediastinum raises the possibility of a thymoma WHO type B, metastatic carcinoma to a lymph node or thymus and seminoma. Epithelioid pattern without lymphocytes, include thymic carcinoma, other germ cell tumor including yolk sac tumor and embryonal carcinoma, and metastatic carcinoma.

Thymoma WHO Type B

As discussed earlier, it is very difficult to accurately subclassify type B thymomas on a small biopsy or in an FNAB. Thymomas types B2 and B3 fall in the group of "predominantly epithelioid cells with lymphocytes". The aspiration biopsy of a B2 or B3 thymoma is usually moderately to highly cellular, with a characteristic dual population of neoplastic epithelial cells and small lymphocytes (Fig. 4.3). The epithelial cells are polygonal shaped, mostly arranged in cohesive tridimensional clusters or in flat sheets (Fig. 4.4). The cells have regular nuclear contours with open or vesicular chromatin and delicate nucleolus. In other cases, the nucleoli can be prominent [8, 19]. The cytoplasm is delicate and the epithelial clusters may have interspersed lymphocytes (Fig. 4.5). The number of lymphocytes may vary, depending on the preparation and sampling of the tumor. Immunohistochemical stains are helpful to identify the origin of infiltrating lymphocytes. The epithelial cells are positive for pan-keratin and p63/p40. The lymphocytes have the characteristic immunophenotype of immature thymic lymphocytes.

There have been reports that thymic epithelial tumor can be positive for PAX-8 [20], however, the positivity for this marker in thymomas is highly dependent on the clone of antibody, whether it is a polyclonal or monoclonal antibody [21, 22].

It can be very difficult to differentiate a thymoma type B3 from a thymic carcinoma on FNAB or even core biopsy if necrosis and cytological atypia is encountered. Pleomorphic nuclei can be seen in thymoma, thus resembling a poorly differentiated carcinoma (Fig. 4.6) [23]. However, most thymomas will retain an open or vesicular chromatin pattern, which can be differentiated from the

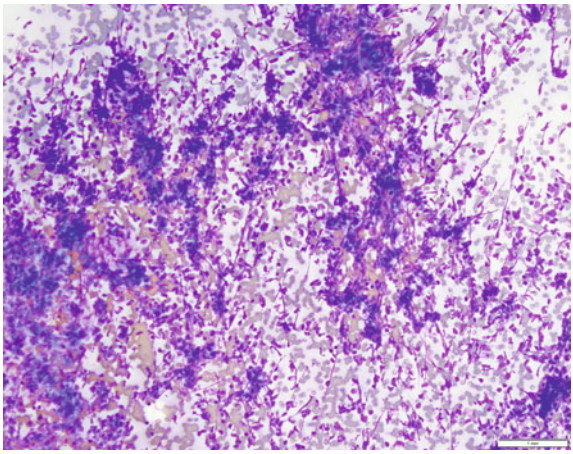

Fig. 4.3 Thymoma type B-Smear showing dual population of cells, one composed of tight clusters and another of dispersed lymphocytes and lymphoid tangles. (Modified Giemsa stain-low power magnification)

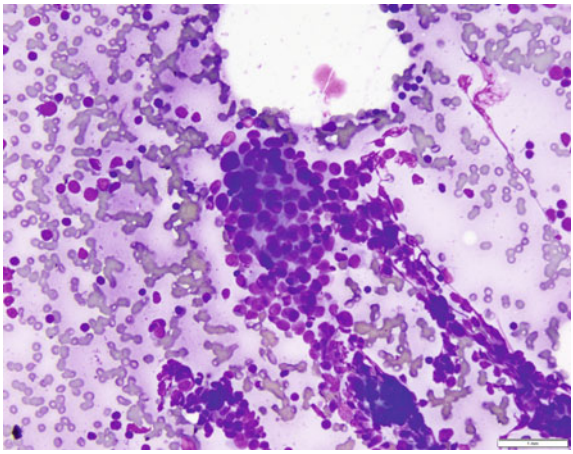

Fig. 4.4 Thymoma type B-Smear showing tight clusters of polygonal cells with interspersed lymphocytes in the background (Modified Giemsa stain-higher magnification from case illustrated in Fig. 4.3)

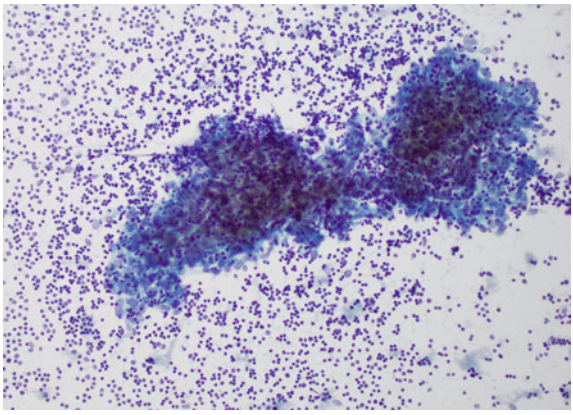

Fig. 4.5 Thymoma type B-Smear showing tight clusters of polygonal cells with open chromatin patterns and dispersed lymphocytes in the background (Papanicolaou Stain)

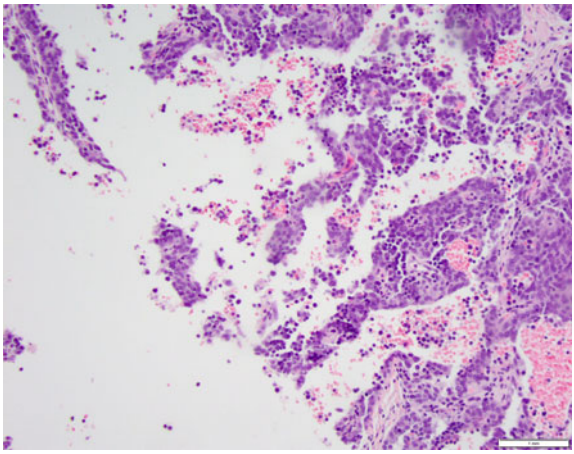

Fig. 4.6 Thymoma type B-Cell block preparation showing clusters of epithelial cells associated with lymphocytes. *Note* pseudo papillary configuration of the clusters which may be confused with an adenocarcinoma. *Note* the open chromatin pattern in epithelial cells. Immunohistochemical stains demonstrating the presence of thymic lymphocytes (CD3, CD5, TdT positive) are helpful in reaching the correct diagnosis. (Hematoxylin and Eosin stain)

hyperchromatic nuclei with dense chromatin pattern commonly seen in thymic carcinomas. When a predominantly epithelial neoplasm with cellular atypia is encountered, it is advisable to suggest these two entities in the differential diagnosis. Immunohistochemical studies can also be helpful in this differential diagnosis. The epithelial cells of a thymic carcinoma are positive for CD5 and CD117 (KIT) in approximately 40–60% of the cases [24–26]. Therefore, if the stains are positive, a diagnosis of thymic carcinoma can be suggested, but the stains are not useful if negative, since thymic carcinoma cannot be fully excluded. When lymphocytes are present, thymic lymphocytes (CD1a, TdT, and CD99-positive) are suggestive of a thymoma and not thymic carcinoma.

The differentiation between thymic carcinoma and thymoma is very important and clinically relevant. Most thymomas type B3 and thymic carcinomas present in advanced stage, where induction chemotherapy is used before resection, if the tumor is surgically resectable [27]. Different regimens of chemotherapy may be used depending on the diagnosis [28].

Another differential diagnosis of a B2 or B3 thymoma is a metastatic carcinoma to a lymph node and germ cell tumor such as a seminoma. Age and clinical presentation are very helpful in the interpretation of these biopsies as well as ancillary studies.

Type AB thymoma and other rarer types of thymomas such as micronodular thymoma with lymphoid stroma or metaplastic thymoma may be very difficult to classify correctly in a small biopsy or aspiration biopsy material. Similar to the more common types, the diagnosis of a thymoma can be made by the presence of a dual population of cells, namely bland epithelial clusters and thymic T-cells.

Cytological features

- Cohesive clusters of epithelial cells admixed with the lymphocytes
- Epithelial cells with smooth nuclear contours, open or vesicular chromatin and delicate nucleolus.

Thymic Carcinoma

Thymic carcinoma is characterized by clearly malignant features of the epithelial cell component. Contrary to thymomas, the characteristic T-lymphocytic infiltrate is often absent. Thymic carcinomas can be present with several different histological types. The WHO has classified primary thymic carcinoma, into several histologic subtypes including neuroendocrine carcinomas. Squamous cell carcinoma is the most common type of thymic carcinoma, but it is morphologically indistinguishable from squamous cell carcinomas from other sites, therefore, clinical, radiographic, and immune profile of the tumor must be evaluated before ascribing the carcinoma as being of thymic origin.

Thymic carcinomas are seen in the group of "predominant epithelioid pattern without lymphocytes". Cytology preparations of these carcinomas are similar to their more common counterparts, which arise in the lung and elsewhere. In general, the malignant cells have enlarged nuclei, coarse chromatin, discrete macronucleoli, and a moderate amount of cytoplasm (Fig. 4.7). Necrosis is frequently seen.

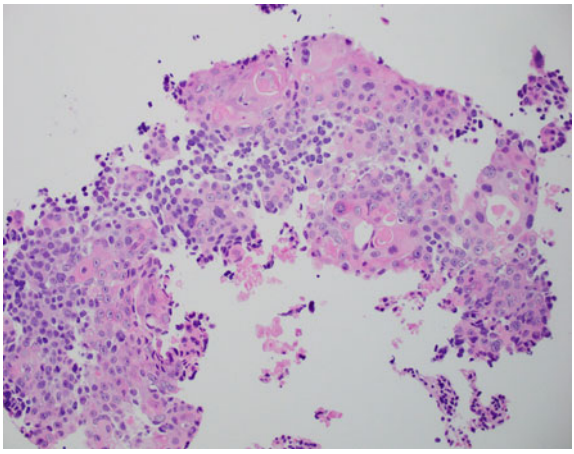

Fig. 4.7 Thymic carcinoma (squamous cell carcinoma)—Cell block preparation of an aspiration biopsy of a mediastinal mass. *Note* features of a keratinizing squamous cell carcinoma. The tumor is indistinguishable from squamous cell carcinomas from other organs. Approximately 60% of thymic carcinoma are positive for CD5 and KIT (Staining is present in the epithelial cells). Often thymic lymphocytes are not present. (Hematoxylin and Eosin stain)

Lymphoepithelioma-like carcinoma of the thymus has been described in the cytology literature, in which the smears show tight clusters of large cells, surrounded and focally infiltrated by small mature lymphocytes. These cells show large rounded often overlapping nuclei. Nucleoli are easily seen, and in some cells are markedly enlarged. Lymphoepithelioma-like carcinoma can be particular difficult to be diagnosed in cytology preparation due the amount of lymphocytes present, thus mimicking the cytomorphological features of a thymoma type B.

Other histological types of thymic carcinoma such as adenocarcinomas, mucoepidermoid carcinomas, basaloid carcinomas, clear cell carcinomas, sarcomatoid carcinomas, and even neuroendocrine carcinomas follow the same cytological features of these tumors elsewhere [29–34].

Thymic squamous cell carcinomas are positive for keratin, p63/p40, similar to thymomas, and can be positive for CD5 and KIT (CD117). However, immature thymic T-cells should be absent in thymic carcinomas. Lymphoepithelioma-like carcinoma can be positive for EBV antigen, similar to other organs.

Cytological features

- Cells have enlarged nuclei, coarse chromatin, discrete macronucleoli, and a moderate amount of cytoplasm.
- Necrosis
- Lymphocytes may be present or not
- Morphological similarities to carcinoma of other organs.

Carcinoid Tumors

Neuroendocrine tumors of the thymus are very rare and can be classified, as typical or atypical carcinoid tumors, similar to the classification used for pulmonary carcinoid tumors. Atypical carcinoid is the most frequently encountered neuroendocrine tumor of the thymus. Atypical carcinoids of the thymus are more often seen in males in the age group of the fourth and fifth decade of life. The cytological criteria for carcinoid tumors of the thymus are similar to the criteria established elsewhere for these tumors [16, 35, 36]. Typically, aspiration biopsy smears show isolated round to plasmacytoid cells with typical salt-and-pepper chromatin pattern (Fig. 4.8). Additionally, small cohesive clusters of neoplastic cells with fine granular chromatin can be identified. Numerous apoptotic cells can be present on the smears, mimicking lymphocytes; therefore the differential diagnosis includes thymoma. Carcinoid tumors of the thymus are often misclassified as thymoma, due to failure to consider this diagnosis or lack of familiarity with this entity occurring in the thymus [16]. The differentiation between typical carcinoid and atypical carcinoid is difficult to make in a small biopsy sample similar to other sites of origin. However, the presence of necrosis or mitotic figures on the smears may suggest the

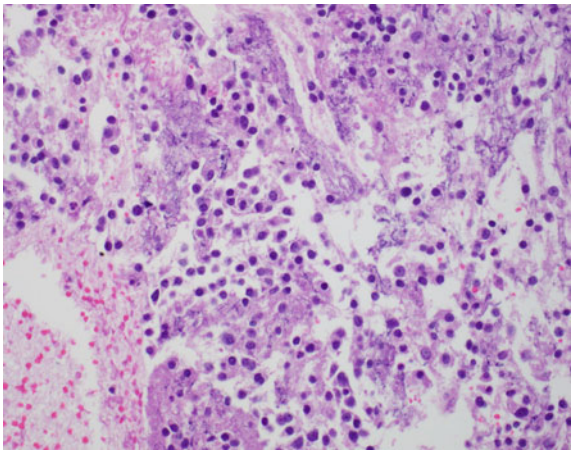

Fig. 4.8 Carcinoid tumor-Cell block preparation of a thymic carcinoid tumor. *Note* the cells are plasmacytoid with stippled chromatin pattern and form loosely cohesive clusters. Nucleolus may be present. (Hematoxylin and Eosin stain)

diagnosis of atypical carcinoid. Other authors have suggested the use of proliferation markers such as Ki-67 (MIB-1) as a diagnostic tool to differentiate between low-grade carcinoid tumors, including an atypical carcinoid from a high-grade neuroendocrine neoplasm [35–38]. However, Ki-67 is not a reliable marker to separate typical from atypical carcinoid tumors. The diagnosis of high-grade neuroendocrine carcinomas (large cell neuroendocrine carcinomas and small cell carcinomas) follows the criteria for the diagnosis of these entities in the lung. It might be difficult to distinguish a high-grade neuroendocrine tumor of the thymus from metastases from a primary lung neoplasm.

Cytomorphologic features

– Isolated round to plasmacytoid cells with typical salt-and-pepper chromatin pattern

Germ Cell Tumors

Germ cell tumor of the mediastinum with seminoma, embryonal carcinoma, yolk sac tumor, and choriocarcinoma are also part of the group “epithelioid-rich pattern”. These tumors are present as high-grade malignant epithelioid neoplasm. As often in the case of germ cell tumors, serum markers and the young age of the patient are helpful clinical clues in establishing the diagnosis.

Seminoma

Aspiration biopsy of a seminoma can be moderately to highly cellular. The neoplastic cells are large and can be dispersed singly or in small flat aggregates. The seminoma cells have delicate cytoplasm and the nuclei have reticular to open chromatin with large prominent nucleolus (Fig. 4.9). When intact cells are present, they are described as having a "fried egg" appearance (Fig. 4.10). Due to the fragility of the cytoplasm, a so-called "tigroid" background is seen on the cellular smears. Although not pathognomonic, the presence of tigroid background, naked nuclei with prominent nucleoli, and lymphocytes are good criteria for the diagnosis of seminoma. In paucicellular smears, a tigroid background is often absent [39–42]. Poorly formed granuloma can be seen on smears in association with neoplastic cells. The presence of granuloma with a lymphocytic background and paucity of neoplastic cells may lead to misdiagnosis of the entity.

Similar features are described in core biopsies when large atypical epithelioid cells interspersed with lymphocytes are present. Knowledge of age of the patient, radiographic appearance of the lesion, and serum markers is helpful in establishing the diagnosis of germ cell tumors. Pure mediastinal seminomas are often associated with elevated serum levels of lactate dehydrogenase (LDH) and low levels of β-human chorionic gonadotropin (β-HCG); these findings however are not specific and can be seen in association with other germ cell tumor components. The presence of high serum levels of α-fetoprotein (AFP) and β-HCG raises a possibility of a mixed germ cell tumor, where the seminoma being the only sampled component.

Immunohistochemical studies show that seminoma cells are positive for OCT-4 and SALL4, both nuclear stains. The tumor cells are also positive for KIT (CD117), D2-40 and may show reactivity for keratin, often in a dot-like pattern [43].

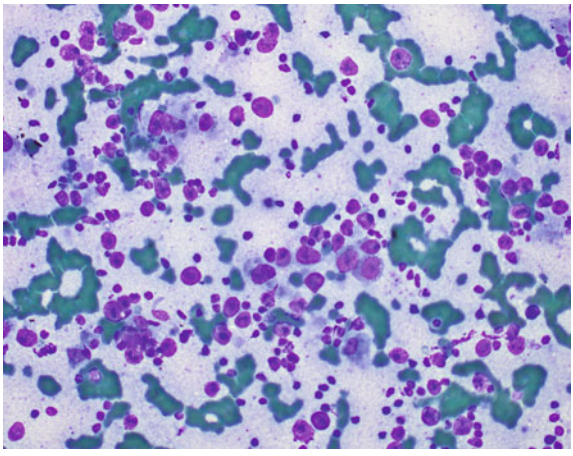

Fig. 4.9 Seminoma-Smear shows large epithelioid cells with prominent nucleolus interspersed with lymphocytes. *Note* many naked nuclei and proteinaceous back ground (tigroid pattern) (Modified Giemsa stain)

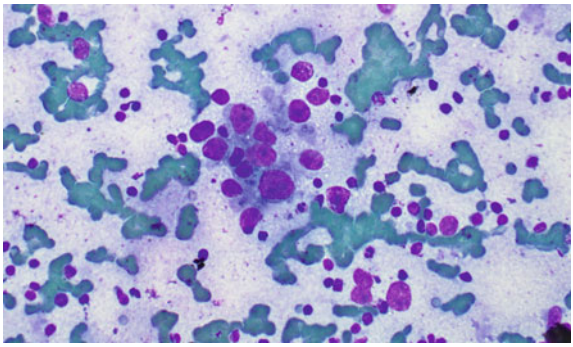

Fig. 4.10 Seminoma-Smear shows large cells with a "fried egg" appearance and tigroid background (Modified Giemsa stain)

Cytological features

- Large nuclei with prominent nucleoli
- Many naked nucleoli
- Tigroid background
- Presence of lymphocytes and poorly formed granuloma in the background.

Embryonal Carcinoma

Pure embryonal carcinoma is extremely rare. It is more commonly seen as a component of mixed germ cell tumor. Similar to seminoma, this is a tumor that occurs mostly exclusively in young men centered in the third and fourth decade of life. There is no specific serum marker associated with this tumor, like seminoma; there might be elevated serum levels of LDH and β-HCG.

The cytological features of embryonal carcinoma are that of a high-grade, poorly differentiated malignant carcinoma. The malignant cells are large, pleomorphic, and show dense hyperchromatic chromatin pattern. Nucleoli are prominent. The tumor cells are arranged in small tridimensional clusters often with the formation of papillary or acini structures (Fig. 4.11) [41, 44]. The correct diagnosis can be reached with immunohistochemical studies. Embryonal carcinoma cells are reactive to pan-germ cell tumor markers such as SALL4, as well as OCT-4. In addition, the tumor cells are positive for CD30 and keratin. Focal positivity for AFP can be present.

Cytological features

- High-grade malignant cells, indistinguishable for other poorly differentiated carcinomas.
- Large, pleomorphic cells with prominent nucleoli and coarse chromatin pattern.
- Papillary and acini formation can be seen.

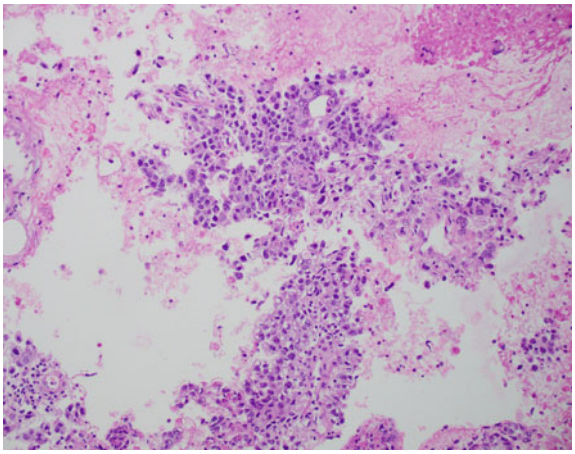

Fig. 4.11 Embryonal Carcinoma-Cell block preparation showing clusters of malignant cells that form acinar and papillary structures. The cells resemble a high-grade carcinoma. *Note* necrotic background. The diagnosis can be reached by immunohistochemical stains (Tumor cells are positive for Sall4, OCT-4 and CD30) and correlation with clinical and radiographic studies. Pure embryonal carcinoma is extremely rare; this is often a component of a mixed germ cell tumors of the mediastinum. (Hematoxylin and Eosin stain)

Yolk Sac Tumor

Yolk sac tumor of the mediastinum occurs almost exclusively in young men. This tumor has a high association with elevated serum levels of AFP, an important diagnostic clue. Pure Yolk sac tumors are rare, and similar to other germ cell tumors, they are more commonly seen as a histological component of mixed germ cell tumor.

Similar to embryonal carcinoma, the cytological features of yolk sac tumor are that of a high grade, poorly differentiated carcinoma. The cells are large, pleomorphic, and have prominent nucleoli with coarse chromatin pattern. Necrosis is often seen in the background. A helpful feature for the diagnosis of this tumor is the presence of intracytoplasmic or extracellular dense matrix (Fig. 4.12) best seen in modified Giemsa stains, where the dense matrix becomes metachromatic and identified as bright pink globules [41–46].

The characteristic Schiller-Duval bodies seen in histological sections are not seen in cytological preparations, but can be appreciated in cell block material.

Yolk sac tumors have a characteristic immunophenotype. The tumor cells are positive for pan-germ cell tumor marker SALL4, whereas negative for OCT-4. The tumor cells are also positive for AFP, glypican-3, and keratin stains.

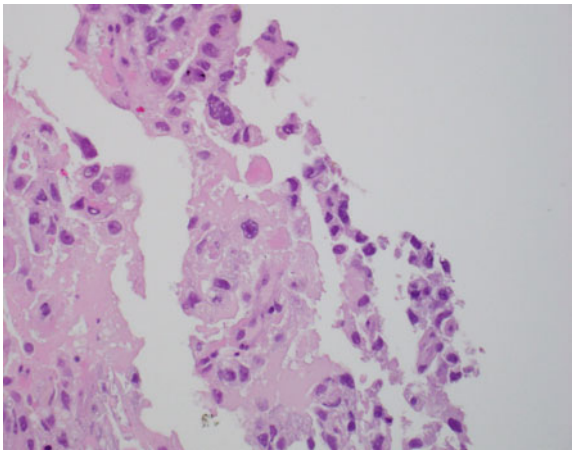

Fig. 4.12 Yolk Sac Tumor-Cell block preparation showing malignant cells with large pleomorphic nuclei. *Note pink* globules within cell clusters. The tumor cells are positive for Sall 4, Glypican-3 and alpha fetal protein, whereas negative for OCT-4 by immunohistochemical stains. Clinical and radiographic correlation is mandatory, since Yolk sac tumor is often a component of a mixed germ cell tumors of the mediastinum. (Hematoxylin and Eosin stain)

Cytological features

- Clusters indistinguishable from that of a poorly differentiated carcinoma
- Presence of intracellular and extracellular dense material (metachromatic in modified Giemsa stain)
- Necrotic background.

Choriocarcinoma

Pure choriocarcinoma of the mediastinum is rare, but a highly aggressive tumor. Similar to other germ cell tumors, the choriocarcinoma is more commonly encountered as a component of mixed germ cell tumor in young men. The presence of choriocarcinoma is associated with high serum levels of β-HCG.

The cytological features are characterized by the presence of small clusters of malignant cells in a necrotic background. Choriocarcinomas are composed of two cell population, syncytiotrophoblasts and cytotrophoblasts. Both cell types are seen on cytological preparations.

Syncytiotrophoblasts are large multinucleated cells with often bizarre nuclei with dense chromatin and eosinophilic cytoplasm. Syncytiotrophoblasts are easily seen. In contrast, the presence of cytotrophoblasts may not be evident. The latter cell type is composed of medium sized mononucleated cells with basophilic and vacuolated cytoplasm [42, 44, 47, 48]. Immunocytochemical studies show that the tumor cells are positive for β-HCG and keratin. Cytotrophoblasts are often positive for SALL4, whereas negative for OCT-4.

Cytological features

- Dual population of cells
- Syncytiotrophoblasts are large, multinucleated cells with eosinophilic cytoplasm
- Cytotrophoblasts are medium sized, mononuclear with basophilic cytoplasm
- Necrotic background.

Clinical management of patients with germ cell tumors is dependent on the histological type of the tumor. Therefore, the cytological diagnosis of these tumors should always be correlated with clinical parameters to avoid sampling biases. For example, the cytological diagnosis of a seminoma in a patient with high serum levels of AFP may indicate the presence of a yolk sac component that was not sampled. Clinical management of a patient with pure seminoma is different from a patient with mixed germ cell tumor [43, 46].

Metastatic Carcinoma

In the category of epithelioid-rich pattern, the differential diagnosis also includes metastatic carcinoma. In fact, metastatic carcinomas are the most common tumors of the mediastinum. Metastatic carcinomas are more commonly encountered in the visceral mediastinum, the site of the pulmonary hilar lymph nodes, but can also present as a predominant prevascular mediastinal mass. Clinical-radiographic correlation such as patient's age, history of prior carcinoma, and the presence of a mass somewhere else are important information to reach the correct diagnosis and guide the workup of the case. Whenever possible, review of prior material is recommended for comparison of morphological features. Small cell carcinoma and pulmonary adenocarcinomas are the most common tumors to involve the mediastinum; however, carcinomas from any other sites can be seen as well.

Immunocytochemical studies are helpful in excluding a primary mediastinal tumor (thymoma and germ cell tumor). The immunocytochemical workup should be used in association with clinical information and targeted to a possible site of origin.

Lymphocyte-rich pattern

The differential diagnosis for this group includes: thymoma WHO type B1, lymphoma, thymic hyperplasia and lymphoid hyperplasia.

Thymoma WHO Type B1

The cytomorphological characteristics of B1 thymomas are an abundance of lymphocytes over epithelial clusters. The lymphocytes are seen dispersed throughout the smears. The lymphocytes are polymorphous with a predominance of small lymphocytes which resemble smears of benign reactive lymphoid hyperplasia. Small cohesive clusters of epithelial cells are admixed with the lymphocytes (Fig. 4.13). The epithelial clusters can be difficult to visualize because they can be obscured by lymphocytes and show crushing artifact, thus resembling large lymphoid tangles or smears of germinal centers (Fig. 4.14). The epithelial cells when visualized are similar to other thymomas; the cells have regular nuclear membrane with open or vesicular chromatin pattern (Fig. 4.13). The diagnosis of a type B1 thymoma is very difficult in a small biopsy; clinical–radiographic information about the mass and the inclusion of thymoma in the differential diagnosis are the best way to reach the correct diagnosis, leading for a search of epithelial cells. The latter can be best visualized in cell block preparations. In type B1 thymomas, the epithelial clusters, similar to other thymomas are positive for pan-cytokeratin. In cell block preparations, the keratin-positive cells form a mesh-like structure embedded within the lymphocytes. Tumor nuclei are also positive for p63 or p40.

Most importantly, the lymphocytes show a characteristic pattern of thymic T-cells, since lymphomas enter the differential diagnosis of thymoma type B1. It is not unusual for flow cytometric analysis to be initiated at the time of triage of the specimen using rapid onsite evaluation (ROSE). Flow cytometry reveals a

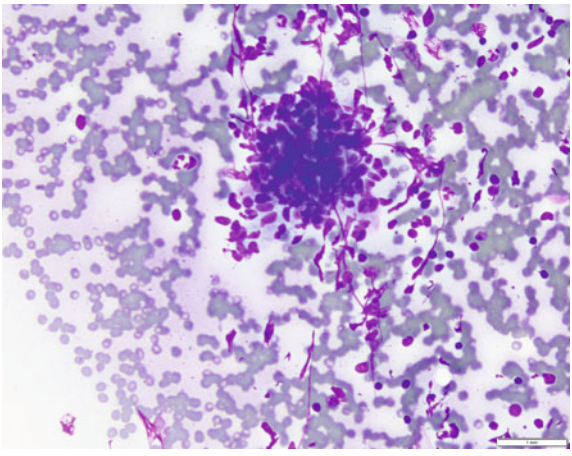

Fig. 4.13 Thymoma type B1-Smear show small clusters of cells admixed with lymphocytes. The tumor cells are positive for keratin and lymphocytes are thymic lymphocytes (Modified Giemsa Stain)

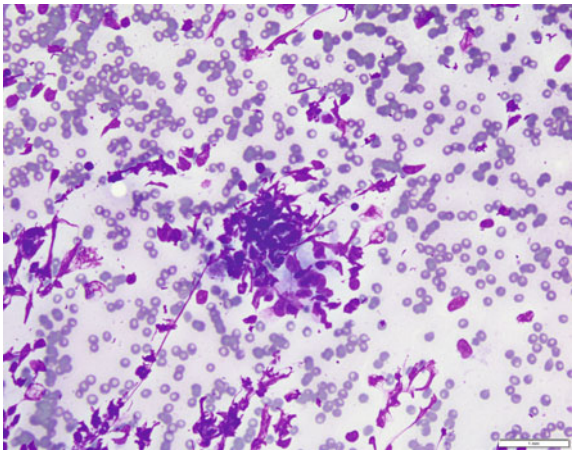

Fig. 4.14 Thymoma type B1-Smear show clusters of crushed cells admixed with lymphocytes. This is a major pitfall for the diagnosis of lymphocyte-rich thymomas by aspiration biopsy. A cell block preparation and subsequent immunohistochemical stains are helpful in reaching the correct diagnosis (Modified Giemsa Stain)

predominant T cell population typical of thymic lymphocytes without a clonal population.

Cytological features

- Abundance of a polymorphous population of lymphocytes
- Large "lymphoid-tangles" or structures resembling germinal center
- Cytokeratin stains show a mesh-like structure, best seen in cell block material.

Lymphoma

Large B-Cell Lymphoma

Most of the lymphomas occurring in the thymus are B-cell lymphomas in contrast to the T-cell nature of the lymphocytic infiltrate in B1 thymomas. Therefore, flow cytometric study is an important ancillary study to define the diagnosis in this group category.

Large B-cell lymphoma, primary mediastinal large B-cell lymphoma and lymphoblastic lymphoma are the most common in the mediastinum. Hodgkin lymphoma is also a common lymphoproliferative disorder to affect the site, but it will be discussed in another pattern, since it is not part of the "predominant lymphocyte group".

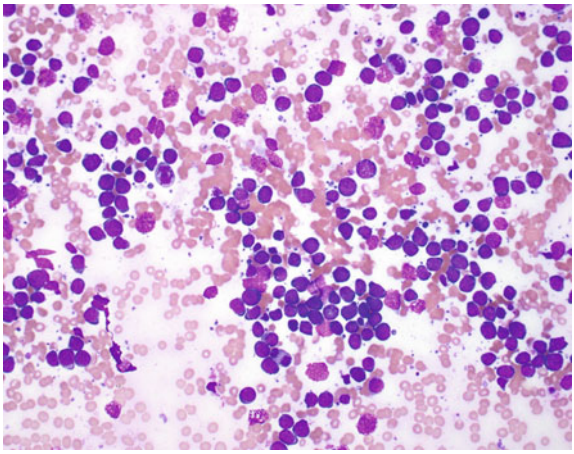

Fig. 4.15 Diffuse Large B-Cell Lymphoma-Smears shows a monotonous population of large lymphocytes. Mitotic figures can be seen. *Note* large amounts of lymphoglandular bodies in the background (Modified Giemsa Stain) (Photograph provided by Dr. Oscar Lin, Memorial Sloan Kettering Cancer Center—MSKCC)

The differential diagnosis of primary mediastinal large cell lymphoma and systemic large cell lymphoma with mediastinal involvement cannot be made on cytological features alone.

Both tumors are characterized by the presence of large and irregular lymphocytes arranged predominantly as single cells, although small clusters with crush artifact can be seen. The neoplastic cells have oval to irregular nuclei, nucleoli are often present. The cytoplasm is basophilic and vacuolization can be present. Numerous lymphoglandular bodies are present (Fig. 4.15). Flow cytometry and immunohistochemical studies of cell block material are essential for the diagnosis. A panel of immunohistochemical stain follows the same diagnosis workup of lymphomas from other sites.

Cytological features

- Large and irregular lymphocytes
- Most arranged as single cells, but small clusters can be present
- Background shows numerous lymphoglandular bodies.

Acute Lymphoblastic Lymphoma

T-lymphoblastic lymphoma (T-LBL) is the most common lymphoma of the site in young male.

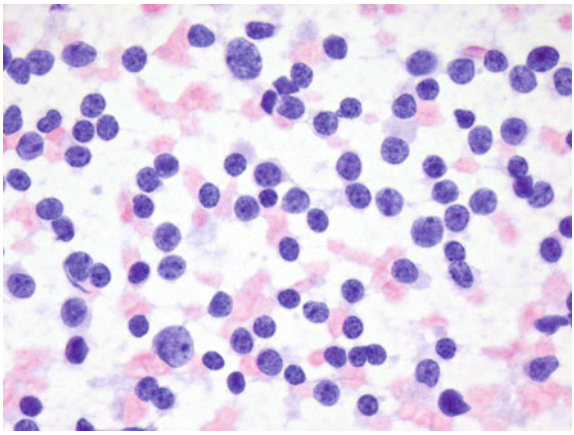

Fig. 4.16 Acute Lymphoblastic lymphoma (ALL)—Smears show monotonous population of intermediate sized lymphocytes. The tumor cells have irregular nuclear contour, fine chromatin pattern, and inconspicuous nucleoli. (Papanicolaou Stain) (Photograph provided by Dr Oscar Lin, MSKCC)

The aspirates are characterized by a monotonous population of intermediate sized lymphocytes. The tumor cells have irregular nuclear contour, fine chromatin pattern, and inconspicuous nucleoli (Fig. 4.16). Frequent mitotic figures are seen.

Flow cytometry shows the presence of CD3 positive lymphocytes. Evaluation of cell block material may need to be complemented with molecular studies for evaluation of T-cell receptor rearrangement.

An important pitfall for the diagnosis of T-LBL in small biopsy is that thymic lymphocytes and T-LBL are positive for CD3 and TdT, a marker of immature T-cells. The presence of contaminating mesothelial cells or other epithelial cells may be highlighted by a keratin stain, thus mimicking a thymoma. Careful evaluation of the cytomorphological features of the neoplastic cells and correlation of cell type and immune stains are helpful in preventing misdiagnosis of this tumor.

Cytological features

- Monotonous population of lymphocytes
- Neoplastic cells have irregular nuclear contour, fine chromatin pattern and inconspicuous nucleoli.

Thymic Hyperplasia

It might be extremely difficult to distinguish thymic hyperplasia from a B1 thymoma on a small specimen. Thymic hyperplasia in general does not form a well-defined mass in the mediastinum but rather an ill-defined tumor [49].

A pure thymic hyperplasia is considered a reactive process, leading to enlargement of the thymic tissue. The process is self-limited and often seen in patients following chemotherapy. In fact, most patients with thymic hyperplasia are asymptomatic and discovered during routine follow-up chest CT scan of patients with malignancies [50].

Cytological features are similar to that of a B1 thymoma and often the false positive diagnosis of thymomas is made. Thymic hyperplasia is associated with diffuse symmetric enlargement of the gland, in contrast to a mass-forming lesion seen in thymomas, and therefore not often biopsied. Therefore, radiographic correlation is essential to achieve the correct diagnosis in these cases.

Follicular thymic hyperplasia is also a reactive process that leads to proliferation of B-lymphocytes and not T-lymphocytes. There is enlargement of the thymic tissue and in histological sections, lymphoid follicles are abundant. Follicular thymic hyperplasia can be seen in association with myasthenia gravis [49]. Aspiration biopsies or even core biopsies of follicular thymic hyperplasia show characteristics of a normal thymus but the lymphoid infiltrate is a mixture of T- and B-lymphocytes, therefore careful evaluation of the subsets of lymphocytes by flow cytometry or immunohistochemical studies to characterize the lymphocytic infiltrate are very helpful. Both tests can show the presence of large numbers of B-lymphocytes that are not commonly seen in the normal thymus or thymoma.

A micronodular thymoma with lymphoid stroma is the only thymoma type that presents with large number of B-lymphocytes. Although, this type of thymomas has been diagnosed in core biopsy [51], the best way to make the diagnosis of micronodular thymoma with lymphoid stroma is histological evaluation of the mass.

Small Blue Cell Pattern

The presence of small blue cells in the mediastinal aspiration or core biopsy brings Ewing sarcoma, immature teratoma, and small cell carcinoma into the differential diagnosis.

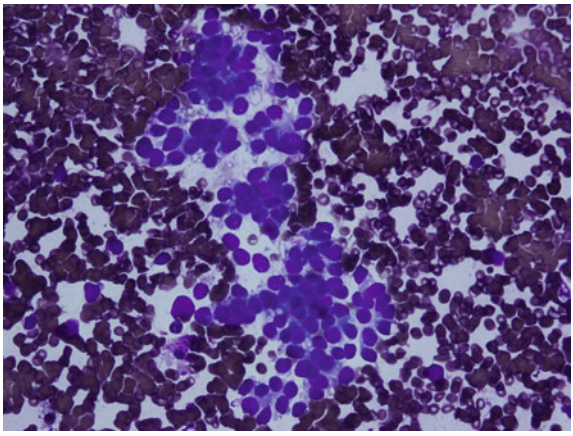

Fig. 4.17 Ewing Sarcoma-Smear show loose clusters of *small blue* cells. Prominent nucleolus can be seen, best appreciated in fixed slides. (Modified Giemsa Stain) (Photograph provided by Dr N. Agaram-MSKCC)

Ewing Sarcoma

Ewing sarcoma, although very rare in the mediastinum, can also be seen as a mediastinal mass in children. In most of the cases, the tumor arises in the ribs and grows into the mediastinal space, thus mimicking a mediastinal mass. In Ewing sarcoma, the cells are small blue cells with sometimes prominent nucleolus. The cells are often organized in small loose clusters; pseudo-rosettes formation can be seen (Fig. 4.17). The absence of lymphoglandular bodies on the smears is a clue to suggest a small blue cell tumor (sarcoma) rather than a lymphoma. Immunohistochemical stains are helpful to distinguish between Ewing sarcoma and lymphoma, including an acute lymphoblastic lymphoma. Contrary to T-LBL, Ewing sarcoma is negative for CD3 and TdT. However, the diagnosis of Ewing sarcoma cannot be made with certainty by immunohistochemistry, identification of a characteristic *EWS* gene translocation t [11, 22] by molecular techniques is diagnostic [52].

Cytological features

- Small blue cells arranged in small clusters
- Nucleoli can be present and prominent
- Identification of EWSR1-LI1 translocation is diagnostic.

Small Cell Carcinoma

This is one of the most common metastatic carcinomas present in the mediastinum. The aspiration biopsy and core biopsy will show small blue cells with prominent nuclear molding and scant cytoplasm. The cells have the characteristic appearance

of a neuroendocrine neoplasm. Immunohistochemical stains for keratin, TTF-1, and neuroendocrine markers (chromogranin, synaptophysin, and CD56) help in establishing the diagnosis.

Cytological features

- Small cells with scant cytoplasm, salt-and-pepper chromatin patterns
- Nuclear molding and irregularities
- Positive for neuroendocrine markers
- Necrotic background
- High MIB-1 proliferation index.

Neuroblastoma

Neuroblastoma is a tumor more commonly seen in the posterior mediastinum. The neoplastic cells have delicate chromatin resembling a neuroendocrine neoplasm. The smears are often cellular. The neoplastic cells are small with scant cytoplasm and seen dispersed on the smears. Small cellular clusters can be seen often with smearing crush artifact. Rosette formation with fibrillary material is a good diagnostic clue. The nuclei have coarse chromatin patterns and indistinct nucleoli [52]. Large ganglion cells can be present and may indicate a differentiation to glanglioneuroblastoma (Fig. 4.18). Immunohistochemical stains are only helpful in

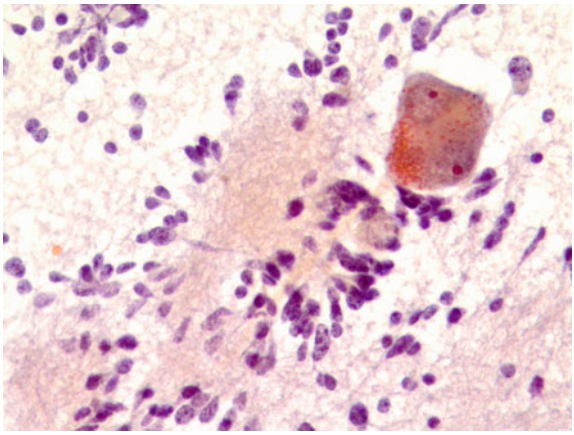

Fig. 4.18 Glanglioneuroblastoma-Smear show *small blue* cells arranged in rosettes, *Note* the fibrillary material around the tumor cells and a large binucleated cell with prominent nucleoli (Ganglion cell) admixed with the *small blue* cells. (Papanicolaou Stain) (Photograph provided by Dr. Xiao-Jun Wei-NY University Langone Medical Center)

differentiating from a neuroendocrine carcinoma. Neuroblastomas are positive for synaptophysin but negative for chromogranin.

Cytological features

- Cellular smears composed of small cells with scant cytoplasm admixed with fibrillary material
- Rosette formations are often seen.

Immature Teratoma

The smears of immature teratoma are cellular and characterized by small blue cell tumors arranged in small clusters and isolated tumor cells. Immature neuroepithelium is the most common element in an immature teratoma and it resembles the cytological description of neuroblastoma. The cells have hyperchromatic nuclei, scant cytoplasm, rosettes, and fibrillary material may be present as well. Contrary to neuroblastoma, immature teratomas occur predominantly in the anterior mediastinum. Therefore, clinical and radiographic correlation is essential for the correct diagnosis. Other components of an immature teratoma such as rabdomyoblasts, immature cartilage and blastemal cells are rarely seen. The identification of immature epithelial cells is also helpful in reaching the correct diagnosis.

Cytological features

- Cellular smears with dispersed small blue round tumor cells or in small cluster
- Rosette formation is often found in neuroepithelium component
- Presence of immature epithelium along with small blue cells
- Presence of necrosis is common.

Inflammatory Patterns

In this category, infectious disease characterized by necrotizing or non-necrotizing granulomatous inflammation, sarcoidosis, and also Hodgkin's disease enter the differential diagnosis.

Granulomatous Infectious Diseases

Granulomatous inflammation is more commonly seen in visceral mediastinal biopsy and may represent several entities such as sarcoidosis and an infectious process. Clinical-radiographic correlation is essential for the accurate diagnosis as well as microbial cultures and special stains for microorganisms. A negative culture and/or negative special stains do not exclude an infectious process. Tuberculosis and fungal infections are the most common infectious processes to affect the mediastinum.

Sarcoidosis

Sarcoidosis is a systemic disease. Most of the patients are asymptomatic and present with enlarged bilateral lymphadenopathy (visceral mediastinum), but the disease can also involve the prevascular mediastinum. The diagnosis of sarcoidosis is clinical; the role of the pathologist is to rule out other conditions and to indicate the presence of non-necrotizing granuloma. The smears can be cellular or not; and are characterized by the presence of tight clusters of epithelioid macrophages. Often the nuclei of epithelioid macrophages are "carrot-shaped" (Figs. 4.19 and 4.20).

Necrotic background should favor the presence of an infectious process, rather than sarcoidosis. In any case, the finding of granulomatous inflammation should prompt the search for an infectious cause with special stains and microbial cultures.

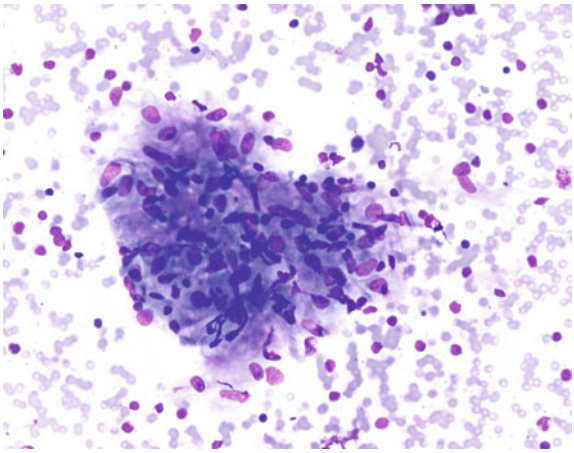

Fig. 4.19 Granuloma-Smears show tight clusters of cells in an organoid patterns forming a syncytium. The nuclei are oval and some have tapered ending impacting a "carrot- shaped" nuclei. The presence of necrosis is suggestive of an infectious etiology. (Modified Giemsa stain)

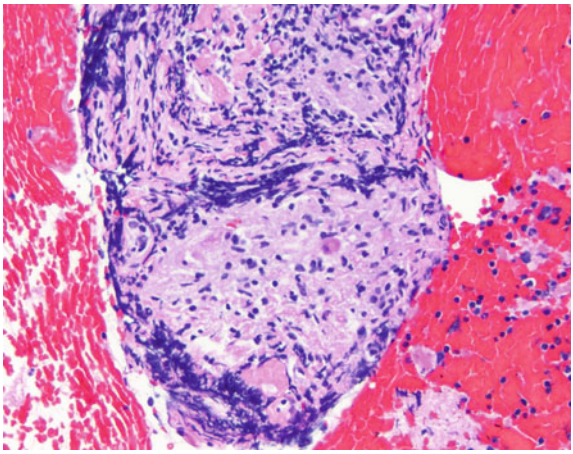

Fig. 4.20 Granuloma-cell block preparation. Organoid clusters of epithelioid macrophages. (Hematoxylin and eosin stain)

Cytological features

- Tight tridimensional clusters of epithelioid macrophages
- Nuclei with "carrot-shape" spindle-shaped that thins out in one end of the nuclei
- Presence of necrotic background favors an infectious process.

Hodgkin Lymphoma

Hodgkin disease is rare in the mediastinum, but when present, classical Hodgkin lymphoma (nodular sclerosing type) is the most common form of Hodgkin's affecting the site. The identification of diagnostic Reed–Sternberg cells may be difficult due to sampling error. The presence of a fibrosing lesion with an inflammatory background including eosinophils should raise a suspicion for Hodgkin lymphoma, and should be communicated to the treating physician (Fig. 4.21).

One important point to remember is that granulomas can be seen in association with Hodgkin disease and germ cell tumor. The finding of granulomas, when the clinical suspicion for these diseases is high, should not preclude the diagnosis.

The smears may have variable cellularity due to sampling. When cellular, the smears contain lymphoplasmacytic background (inflammatory background). Eosinophils may be present. The diagnostic Reed–Sternberg cell is characterized by a large nucleus, classic bi-nucleation, and prominent nucleoli. The cytoplasm can be abundant, but often there are stripped nuclei in the background as well. However, variants of Reed–Sternberg cells can also be present [53].

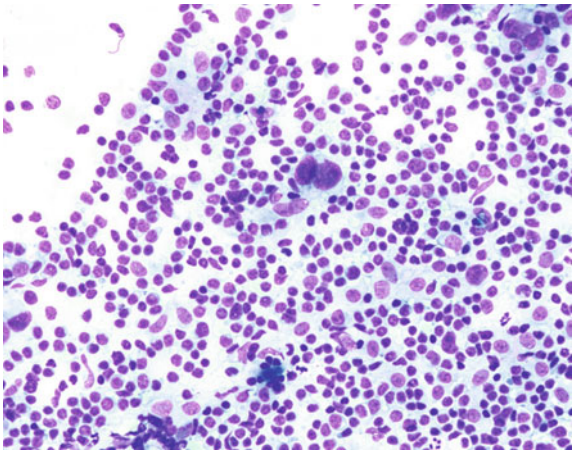

Fig. 4.21 Hodgkin Lymphoma-Smear shows large atypical cells with prominent macronucleoli in a background of mixed inflammatory cells, often containing plasma cells and eosinophils. (Modified Giemsa Stain) (Photograph provide by Dr. Aylin Simsir, New York University Langone Medical Center)

The neoplastic cells are positive for CD30 almost universally in a classical membranous pattern with an accentuation of the Golgi area in the cytoplasm impacting a dot-like reactivity and CD 15. CD20 and EBV-encoded small RNA can be positive in a percentage of Reed-Sternberg cells.

Cytological features

- Presence of binucleated large cells with prominent nucleoli (Reed–Sternberg cell)
- Presence of inflammatory background containing eosinophils, plasma cells, and small poorly formed granuloma.

Cystic Pattern

Cystic lesions of the mediastinum are frequent. They are, however, very difficult to diagnose by aspiration biopsy because, in most cases, the smears are acellular or may contain small amounts of benign cells that can be interpreted as contaminants from nearby organs and are not representative of the target lesion. Therefore, sampling error followed by interpretative errors is the most common factor for a non-diagnostic specimen.

In this pattern, the differential diagnosis includes non-neoplastic lesions such as thymic cysts, bronchogenic cysts, pericardial cysts as well as cystic neoplasms like cystic thymoma and cystic teratoma.

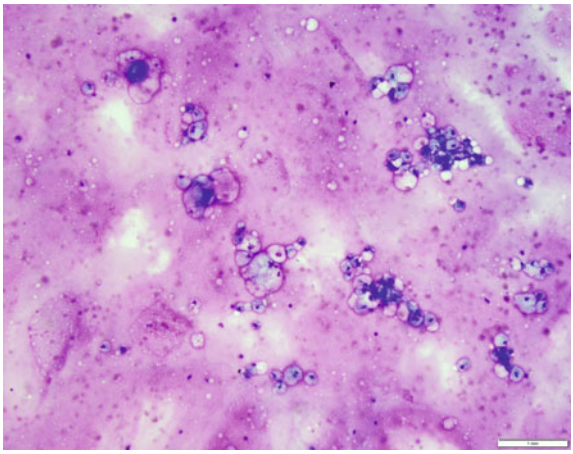

Fig. 4.22 Benign Mediastinal cysts-Smears may show only cyst contents composed of proteinaceous debris and foamy macrophages (Modified Giemsa stain)

Thymic Cysts

Thymic cysts are considered to be a reactive process and are often found in patients with another neoplasm. There is a good association between thymic cysts and other malignancies such as Hodgkin lymphoma and thymoma [54–58]. Thymic cysts are usually small and patients are asymptomatic, however due to the association with other neoplasms, the lesion may be investigated by aspiration biopsy. A thymic cyst is defined as a cystic lesion with thymic tissue within its wall; therefore, the anterior mediastinum is the most common location. The epithelial lining can be composed of flat squamous epithelium as well as respiratory epithelium; it may be impossible to differentiate a thymic cyst from a bronchogenic cyst by aspiration biopsy. The smears are often paucicellular and may contain benign squamous epithelium or ciliated columnar cells in a proteinaceous background with foamy macrophages (Fig. 4.22).

In large thymic cysts, the differential diagnosis includes a cystic thymoma, which may be almost impossible to separate by cytological features alone.

Mesothelial/Pericardial Cysts

Pericardial cysts are often asymptomatic and detected on imaging studies for other reasons; these lesions are described as circumscribed and unilocular. Pericardial cysts are more commonly seen in the anterior or medial mediastinum, close to the heart and diaphragm. The aspiration biopsy of a mesothelial/pericardial cyst is often acellular. The aspirate is a clear, transparent fluid with a few scattered macrophages and mesothelial cells. Therefore a specific diagnosis is very difficult to render because this finding may be interpreted as mesothelial contamination and not part of

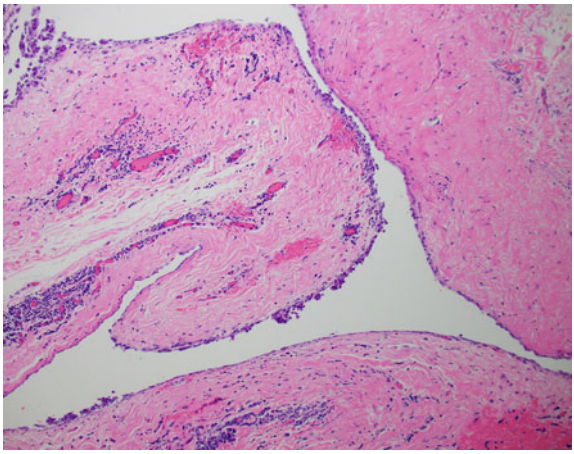

Fig. 4.23 Mesothelial cyst-Resection. The cytological diagnosis of mesothelial cysts is very difficult. Often the aspirates show foamy macrophages and/or mesothelial cells that can be interpreted as contaminant. The diagnosis can be made by excision of the cyst and shows a simple cyst *lined* by benign mesothelial cells. (Hematoxylin and eosin stain)

the lesion. Clinico-radiographic correlation is required to reach the correct diagnosis, however, only excision of the nodule provides a definite histopathologic classification (Fig. 4.23). A descriptive diagnosis listing the benign cellular elements on the smear in a cystic background is helpful to the referring physician to plan a course of treatment.

Bronchogenic Cyst

Bronchogenic cysts are considered a developmental abnormality originating from the remnants of the foregut and are more commonly seen in the visceral mediastinum. Bronchogenic cysts are more common in children; however, they can occur or be detected in adulthood. Most patients are asymptomatic. Patients with large cysts may come to medical attention due to mass effect with compression of esophagus and tracheobronchial tree, leading to cough, dyspnea, dysphasia, and chest pain.

Radiographic images show a round, circumscribed cyst, often unilocular, but multilocular cysts have been described. Mucoid impaction can give an appearance of a solid mass by CT-Scans. Similarly, air-fluid levels can be seen, when a connection to the tracheobronchial tree is present.

Aspiration biopsy of bronchogenic cysts may contain clear or mucoid material in the background. The aspirates are often paucicellular. Ciliated respiratory epithelium and squamous metaplastic cells can be seen, as well as fragments of cartilage and smooth muscle. Similar to all benign cystic lesions, these findings may lead to

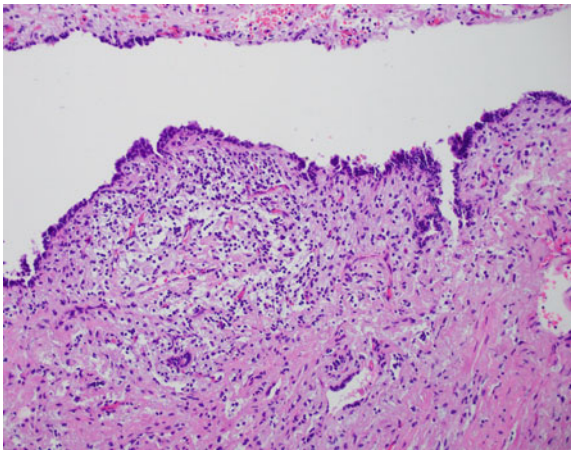

Fig. 4.24 Bronchogenic cyst- Resection. Section from the excised lesion shows a cyst *lined* by respiratory epithelium. Metaplastic squamous epithelium and cartilage may be present as well. (Hematoxylin and eosin stain)

interpretation error, by assuming the aspirate represents contaminant of the normal structures (trachea-bronchial tree). Often the diagnosis is made in the resected specimen (Fig. 4.24).

Mature Teratoma

Mature teratoma of the mediastinum is a rare tumor; however, it is the most common germ cell tumor affecting the site. Mature teratoma can occur both in pre-pubertal and post-pubertal patients, affecting men and women equally.

Most patients are asymptomatic, but symptoms may develop in patients with large tumors and are characterized by mass effect symptoms like cough, dysphagia, dyspnea, hemoptysis, and chest pain.

Radiographically, mature teratomas are multilocular cysts, well-demarcated from surrounding structures, although invasion into adjacent organs can occur. The presence of different tissue densities and calcifications are common. The identification of bone or tooth formation is diagnostic.

The cytological diagnosis of teratoma is extremely difficult. There must be a strong clinical suspicion with good clinical-radiographic evidence in order to make this diagnosis on cytology basis alone.

Although mature teratomas are often part of the "cystic pattern", this tumor can also present in an epithelioid-rich or spindle cell pattern, depending on the area that is aspirated.

Smears from cystic teratomas are often paucicellular and are characterized by the presence of small amounts of benign epithelium in a cystic background. Benign squamous epithelium and anucleated squames are common (Figs. 4.25 and 4.26), but are often interpreted as contaminants and not representative of the target lesion. Similarly, the presence of ciliated respiratory epithelium and fragments of cartilage,

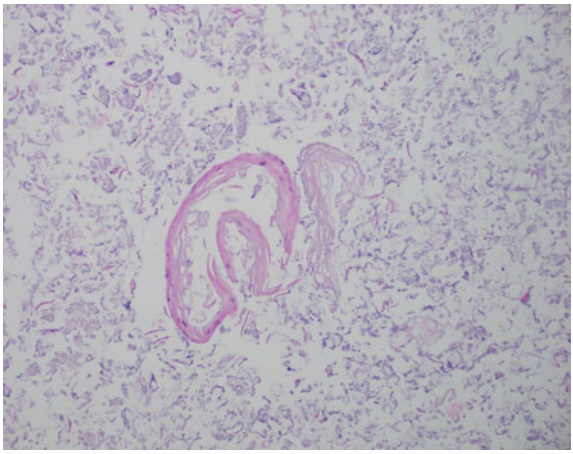

Fig. 4.25 Mature teratoma-Cell block preparation showing numerous clusters and isolated anucleated squamous cells in a cystic background (Hematoxylin and eosin stain)

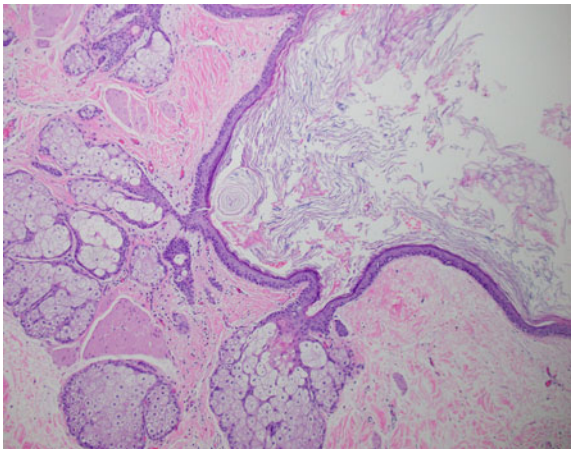

Fig. 4.26 Mature teratoma-Excision of the same tumor from Fig. 4.25, showing a cyst *lined* by squamous epithelium, adnexal glands, smooth muscle and adipose tissue. (Hematoxylin and eosin stain)

both commonly seen in mature teratoma, can be interpreted as contaminant from the bronchial tree. Rarely, an aspirate shows the presence of more than one type of epithelial cell (squamous cells and glandular epithelium etc.), cartilage and adipocytes. In these circumstances, the diagnosis of mature teratoma can be entertained. It is important to be mindful that the clinical management of a patient with mature teratoma is surgical excision. Therefore, clinical-radiographic correlation must be procured before finalizing the diagnosis.

Cytological features

- Scant cellularity
- Presence of benign epithelial cells and small amounts of fat and cartilage
- Cystic background with macrophages and proteinaceous material.

Cystic Thymoma

Cystic thymomas are rare, but can cause significant diagnostic difficulties. Most thymomas present as solid masses, the presence of a cystic component may sway the treating physician or radiologist from the diagnosis.

In addition, thymomas can occur in association with thymic cysts [54, 55] and cystic degeneration can occur as a consequence of necrosis. Cystic degeneration not associated with necrosis or infarct has also been described [59, 60]. In contrast, the presence of myasthenia gravis symptoms is a good clue to the diagnosis of cystic thymoma.

Aspiration biopsy of a cystic thymoma may be nonspecific if only the cystic component is sampled. Smears are paucicellular, with scant macrophages, inflammatory cells or necrotic debris. The diagnosis may be made if the cellular component of the thymoma is sampled. In these cases, the diagnosis follows the same cytomorphologic criteria as for other thymomas.

Major Pitfalls for the Cytological Diagnosis of Thymoma

- Include thymoma in the differential diagnosis of anterior mediastinal mass
- Include thymoma in the differential diagnosis of a patient with history (even remote) of mediastinal mass
- Common metastatic sites: pleura, liver, regional lymph nodes.

References

1. Adler OB, Rosenberger A, Peleg H. Fine-needle aspiration biopsy of mediastinal masses: evaluation of 136 experiences. Am J Roetgenol. 1983;140(5):893–6.
2. Morrisey B, Adams H, Gibbs AR, Crane MD. Percutaneous needle biopsy of the mediastinum: review of 94 procedures. Thorax. 1993;48(6):632–7.
3. Wakely PE. Fine needle aspiration in the diagnosis of thymic epithelial neoplasms. Hematol Oncol Clin N Am. 2008;22:433–42.
4. Zakowski MF, Huang J, Bramlage MP. The role of fine needle aspiration cytology in the diagnosis and management of thymic neoplasia. J Thorac Oncol. 2010;5(10 Suppl 4):S281–5.
5. Shabb NS, Fahl M, Shabb B, Haswani P, Zaatari G. Fine-needle aspiration of the mediastinum: a clinical, radiographic, cytologic, and histologic study of 42 cases. Diag Cytopathol. 1988;19(6):428–36.
6. Assaad MW, Pantanowitz L, Otis CN. Diagnostic accuracy of image-guided percutaneous fine needle aspiration biopsy of the mediastinum. Diag Cytopathol. 2007;35(11):70509.
7. Engels EA. Epidemiology of thymoma and associated malignancies. J Thorac Oncol. 2010;5 (10 Suppl 4):S260–5.
8. Chhieng DC, Rose D, Ludwig ME, Zakowski MF. Cytology of thymomas: emphasis on morphology and correlation with histologic subtypes. Cancer. 2000;90(1):24–32.
9. Travis WD, Marx A, Brambilla E, Nicholson A, Burke A, editors. WHO classification of tumors of the lung, pleura, thymus and heart. 4th ed. Lyon: IARC; 2015.

10. Marx A, Chan JK, Coindre JM, Detterbeck F, Girad N, Harris NL, Jaffe ES, Kurrer MO, Marom EM, Moreira AL, Mukai K, Orazi A, Strobel P. The 2015 world health organization classification of tumors of the thymus: continuity and changes. J Thorac Oncol. 2015;10 (10):1383–95.
11. Kim DJ, Yang WI, Choi SS, Kim DK, Chung KY. Prognostic and clinical relevance of the World Health Organization schema for the classification of thymic epithelial tumors: a clinicopathologic study of 108 patients and literature review. Chest. 2005;127(3):755–61.
12. Leuzzi G, Rocco G, Ruffini E, Sperduti I, Detterbeck F, Weder W, Venuta F, Van Raemdonck D, Thomas P, Facciolo F. ESTS Thymic working group. J Thorac Oncol. 2016;151(1):47–57.
13. Jain RK, Mehta RJ, Henley JD, Kesler KA, Badve S. WHO types A and AB thymomas: not always benign. Mod Pathol. 2010;23(12):1641–9.
14. Huang PM, Chang KM. Solitary metastasis to the breast after complete resection of encapsulated type AB thymoma: a case report. J Med Case rep. 2015;9:63.
15. Slagel DD, Powers CN, Melaragno MJ, et al. Spindle-cell lesions of the mediastinum: diagnosis by fine-needle aspiration biopsy. Diagn Cytopathol. 1997;17:167–76.
16. Renshaw AA, Haja JC, Neal MH, Wilbur DC. Distinguishing carcinoid tumor of the mediastinum from thymoma. Correlating cytologic features and performances in the College of American Pathologists interlaboratory comparison program in nongynecologic cytopathology. Arch Pathol Lab Med. 2006;130:1612–5.
17. Hang JF, Hsu CY, Lai CR. Fine-needle aspiration cytology of a type A thymoma with adenoid cystic pattern: a case report with emphasis on peculiar hyaline globules in cytology smears. Diagn Cytopathol. 2015;43(3):247–50.
18. Geisinger KR. Differential diagnosis considerations and potential pitfalls in fine-needle aspiration biopsies of the mediastinum. Diagn Cytopathol. 1995;13(5):436–42.
19. Wakely PE Jr. Cytopathology-histolopathology of the mediastinum: epithelial, lymphoproliferative, and germ cell neoplasm. Ann Diagn Pathol. 2002;6(1):30–43.
20. Weissferdt A, Moran CA. Pax8 expression in thymic epithelial neoplasm: an immunohistochemical analysis. Am J Surg Pathol. 2011;35(9):1305–10.
21. Ordonez NG. Value of PAX8 immunostaining in tumor diagnosis: a review and update. Adv Anat Pathol. 2012;19(3):140–51.
22. Toryama A, Mori T, Sekine S, Yoshida A, Hino O, Tsuta K. Utility of PAX8 mouse monoclonal antibody in the diagnosis of thyroid, thymic, pleural and lung tumors: a comparison with polyclonal PAX8 antibody. Histopathol. 2014;65(4):465–72.
23. Riazmontazer N, Bedayat C, Izadi B. Epithelial cytologic atypia in a fine needle aspirate of an invasive thymoma a case report. Acta Cytologica. 1991;36(3):387–90.
24. Pan CC, Chen PC, Chiang H. KIT (CD117) is frequently overexpressed in thymic carcinomas but is absent in thymomas. J Pathol. 2004;202:375–81.
25. Asirvatham JR, Esposito MJ, Bhuyia TA. Role of PAX-8, CD5, and CD 117 in distinguishing thymic carcinoma from poorly differentiated lung carcinoma. Appl Immunohistochem Mol Morphol. 2014;22(5):372–6.
26. Marx A, Rieker R, Toker A, Langer F, Strobel P. Thymic carcinoma: is it a separate entity? From molecular to clinical evidence. Thorac Surg Clin. 2011;21(1):25–31.
27. Riely GJ, Huang J. Induction therapy for locally advanced thymoma. J Thorac Oncol. 2010;5: S323–6.
28. Girard N. Chemotherapy and target agents for thymic malignancies. Expert Rev Anticancer Ther. 2012;12(5):685–95.
29. Kapila K, Pathan SK, Amir T, Joneja M, Hebbar S, Al-Ayadhy B. Mucoepidermoid thymic carcinoma: a challenging mediastinal aspirate. Diagn Cytopathol. 2009;37(6):433–6.
30. Shin HJ, Katz RL. Thymic neoplasia as represented by fine needle aspiration biopsy of anterior mediastinal masses. A practical approach to the differential diagnosis. Acta Cytol. 1988;42(4):855–64.

31. Posligua L, Ylagan L. Fine-needle aspiration cytology of thymic basaloid carcinoma: a case study and review of the literature. Diagn Cytopathol. 2006;34(5):358–66.
32. Matsuno Y, Morozumi N, Hirohashi S, Shimosato Y, Rosai J. Papillary carcinoma of the thymus: a report of four cases of a new microscopic type of thymic carcinoma. Am J Surg Pathol. 1998;22(7):873–80.
33. Ra SH, Fishbein MC, Baruch-Oren T, Shintaku P, Apple SK, Cameron RB, Lai CK. Mucinous adenocarcinomas of the thymus: a report of 2 cases and review of the literature. Am J Surg Pathol. 2007;31(9):1330–6.
34. Moser B, Schiefer AI, Janik S, Marx A, Prosch H, Pohl W, Neudert B, Scharrer A, Klepetko W, Mullauer L. Adenocarcinoma of the thymus, enteric type: a report of 2 cases, and proposal for a novel subtype of thymic carcinoma. Am J Surg Pathol. 2015;39(4):541–8.
35. Stoll LM, Johnson MW, Burroughs F, Li QK. Cytologic diagnosis and differential diagnosis of lung carcinoid tumors a retrospective study of 63 cases with histologic correlation. Cancer Cytopathol. 2010;118(6):457–67.
36. Huang CC, Collins BT, Flint A, Michaels CW. Pulmonary neuroendocrine tumors: an entity in search of cytologic criteria. Diagn Cytopathol. 2013;41(8):689–96.
37. Pelosi G, Rindi G, Travis WD, Papotti M. Ki-67 antigen in lung neuroendocrine tumors: unraveling a role in clinical practices. J Thorac Oncol. 2014;9(3):273–84.
38. Pelosi G, Rodriguez J, Viale G, Rosai J. Typical and atypical pulmonary carcinoid tumor overdiagnosed as small cell carcinoma on biopsy specimens: a major pitfall in the management of lung cancer patients. Am J Surg Pathol. 2005;29(2):179–87.
39. Fleury-Feith J, Bellot-Besnard J. Criteria for aspiration cytology for the diagnosis of seminoma. Diagn Cytopathol. 1989;5(4):392–5.
40. Caraway NP, Fanning CV, Amato RJ, Sneige N. Fine-needle aspiration cytology of seminoma: a review of 16 cases. Diagn Cytopathol. 1995;12(4):327–33.
41. Gupta R, Mathur SR, Arora VK, Sharma SG. Cytologic features of extragonadal germ cell tumors: a study of 88 cases with aspiration cytology. Cancer. 2008;114(6):504–11.
42. Chao TY, Nieh S, Huang SH, Lee WH. Cytology of fine needle aspirates of primary extragonadal germ cell tumors. Acta Cytol. 1997;41(2):497–503.
43. Moreira AL, Chan JKC, Looijenga LHJ, Marx A, Strobel P, Ulbright TM, Wick M. Seminoma. In: Travis WD, Marx A, Brambilla E, Nicholson A, Burke A, editors. WHO classification of tumours of the lung, pleura, thymus and heart. 4th ed. IARC: Lyon; 2015.
44. Collins KA, Geisinger KR, Wakely PE Jr, Olympio G, Silverman JF. Extragonadal germ cell tumors: a fine needle aspiration biopsy study. Diagn Cytopathol. 1995;12(3):223–9.
45. Motoyama T, Yamamoto O, Iwamoto H, Watanabe H. Fine needle aspiration cytology of primary mediastinal germ cell tumors. Acta Cytol. 1995;39(4):725–32.
46. Akhtar M, Al DF. Is it feasible to diagnose germ-cell tumors by fine-needle aspiration biopsy? Diagn Cytopathol. 1997;16(1):72–7.
47. Sangalli G, Livraghi T, Giordano F, Tavani E, Schiaffino E. Primary mediastinal embryonal carcinoma and choriocarcinoma. A case report. Acta Cytol. 1986;30(5):543–6.
48. Hoover LA, Hafiz MA. Fine-needle aspiration diagnosis of extragonadal choriocarcinoma with immunoperoxidase studies. Diagn Cytopathol. 1989;5(1):84–7.
49. Priola AM, Priola SM. Imaging of thymus in myasthenia gravis: from thymic hyperplasia to thymic tumor. Clin Radiol. 2014;69(5):e230–45.
50. Scheinpflug K, Schmitt J, Jentsch-Ullrich K, Roessner A, Franke A. Thymic hyperplasia following successful treatment for nodular-sclerosing Hodgkin's disease. Leuk Lymphoma. 2003;44(9):1615–7.
51. Chen CW, Chuang SS, Pan ST. Micronodular Thymoma with Lymphoid Stroma Diagnosed with Core Needle Biopsy. A Case Report. Analytical and quantitative cytopathology and histopathology. 2015;37(3):206–10.
52. Das DK. Fine-Needle aspiration (FNA) cytology diagnosis of small round cell tumors: value and limitations. Indian J Pathol Microbiol. 2004;47(3):309–18.

53. Das DK, Francis IM, Sharma PN, Sathar SA, John B, George SS, Malik MK, Sheikh ZA, Haji BE, Pathan SK, Madda JP, Mirza K, Ahmed MS, Junaid TA. Hodgkin's lymphoma: diagnostic difficulties in fine-needle aspiration cytology. Diagn Cytopathol. 2009;37(8): 564–73.
54. Nakamura S, Tateyama H, Taniguchi T, Ishikawa Y, Kawaguchi K, Fukui T, Mizuno T, Ishiguro F, Yokoi K. Multilocular thymic cyst associated with thymomas: a clinicopathologic study of 20 cases with emphasis on the pathogenesis of cyst formation. Am J Surg Pathol. 2012;36(12):1857–64.
55. Butcovan D, Tinica G, Stefanescu C, Ionescu L. Pathological comparative assessment of two cases of thymic cyst and cystic thymomas and review of the literature. Rev Med Chir Soc Med Nat Iasi. 2012;116(3):812–6.
56. Steinmuller F, Traeger T, Kuhn JP, Busemann A, Evert M. Rare case of large mediastinal cyst involved in Hodgkin's lymphoma. Pathol Res Pract. 2012;208(5):306–9.
57. Maturu VN, Dhooria S, Agarwal R, Behera D. Endobronchial ultrasound-guided aspiration of an endotracheal bronchogenic cyst: case report and systematic review of the literature. J Bronchology Interv Pulmonol. 2016;23(2):163–7.
58. Twehues A, Islam S. Cystic lesions of the thorax: role of the endobronchial ultrasound-guided transbronchial needle aspiration. J Bronchology Interv Pulmonol. 2011;18(3):265–8.
59. Rieker RJ, Aulmann S, Schnabel PA, Sack FU, Otto HF, Mechtersheimer G, Schirmacher P, Blaker H. Cystic thymoma. Pathol Oncol Res. 2005;11(1):57–60.
60. Dyer NH. Cystic thymomas and thymic cysts. Thorax. 1967;22(5):408–21.

Thymic Epithelial Tumors and Benign Thymic Lesions

5

Alexander Marx, Cleo-Aron Weis, Alexandar Tzankov and Philipp Ströbel

Thymic Epithelial Tumors: Thymomas, Thymic Carcinomas, Neuroendocrine Tumors

Thymic Epithelial Tumors: Definition and Terminology

Thymic epithelial tumors (TETs) comprise thymomas and thymic carcinomas (TCs) that are now listed separately from carcinoids, large-cell neuroendocrine carcinomas, and small-cell carcinomas [1].

Thymomas are epithelial tumors that the World Health Organization [1, 2] classification subdivides into the malignant type A, AB, B1, B2, B3, and metaplastic thymomas, and rare other types (Table 5.1). They usually maintain thymic functions such as the capacity of thymopoiesis, as reflected by the occurrence of intratumorous immature T cells. Since this thymopoesis fails to induce immunological tolerance,

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Table 5.1 Proportion (%) of thymoma types in relation to all thymomas; epidemiological and clinicopathological features [1]

	Relative frequency[a]	Age (y) range (average)	Gender (male:female)	Myasthenia Gravis (+)[b] range (mean)	Masaoka stage				
					I (%)	II (%)	III (%)	IVa (%)	IVb (%)
Type A	11.5% (3.1–26.2)	8–88 (64)	1:1.4	0–33 (17)	60	31	8	0.5	0.5
Type AB	27.5% (15–43.0)	11–89 (57)	1:1.4	6–42 (18)	67	26	6	1	–
Type B1	17.5% (5.9–52.8)	6–83 (50)	1:1.6	7–70 (44)	50	37	9	3	1
Type B2	26.0% (8.0–41.1)	4–83 (49)	1:1	24–71 (54)	32	29	28	8	3[c]
Type B3	16.0% (3.4–35.1)	8–87 (55)	1:0.8	25–65 (50)	19	36	27	15	3[d]
MNT[2]	1.0%	41–80 (65)	1.5:1	Rare	62	36	–	2	–
Metaplastic thymoma	<1.0%	28–71 (50)	1:1	Very rare	75	17	8	–	–

[a]Average (range); [b]MNT, micronodular thymoma; [c,d]Ranges 0–5% (B2) and 0–15% (B3)

thymomas are often associated with autoimmune diseases and immunodeficiencies, the commonest being Myasthenia Gravis and hypogammaglobulinemia, respectively [3].

TCs are also derivatives of thymic epithelial cells but histologically resemble carcinomas of other organs. This explains their "conventional" nomenclature (squamous cell carcinomas, adenocarcinomas, etc.). Neoplastic epithelial cells of TCs are usually devoid of thymic functions like the capacity for thymopoiesis. Accordingly, paraneoplastic autoimmune diseases are rare in TCs.

Tumor Heterogeneity, Proper Sampling, Reporting of Histology and Tumor Stage

Tumor heterogeneity due to different histological patterns in a single tumor, is common (up to 50%) in thymomas [4, 5]. Thymomas with WHO type B2 and B3 patterns are the commonest [5]. Heterogeneity is rare among TCs and TETs showing a thymoma and TC component(s) are even rarer [1, 2]. To detect heterogeneity, at least 1 block per cm maximal tumor diameter, preferably a minimum of 5 blocks, should be submitted for histological evaluation in resection specimens [6].

In resection specimens, the components in heterogeneous tumors should be reported in 10% increments. This rule does not apply to type AB thymomas that are, by definition, almost always composed of type A and type B-like components (and the latter should not be subclassified, e.g., as B1 or B2, either) [1, 2]. In heterogeneous thymomas as well as TCs, reporting should start with the most prevalent component, followed by the second most prevalent component, etc. However, if a given TET shows areas of thymoma and TC, reporting should always start with the carcinoma component, even if it is the minor component. Heterogeneous tumors with a small-cell carcinoma or large-cell neuroendocrine carcinoma component of whatever proportion should be labeled as "combined small-cell carcinoma" or "combined large-cell neuroendocrine carcinoma" followed by the other component(s). The common heterogeneity in TETs implies caution when reporting on small biopsies (see below).

Tumor stage of thymomas is reported following the Masaoka-Koga system [7] that reflects the fact that thymomas commonly exhibit pleural spread (stage IVa) while lymph node and extrathoracic metastasis (stage IVb) are rare ($\sim$2%). By contrast, lymph node and distant metastases are common in TCs (up to 40%). The Masaoka-Koga system is commonly used also for TCs but a UICC/AJCC approved TNM system will soon replace or complement the Masaoka-Koga system [7].

Epidemiology

Thymomas are rare tumors (incidence 1–4 per 10^6 per year) without clear gender bias. Although they rarely occur in children, their incidence peaks between 40 and 60 years of age [1, 2]. Thymic carcinomas are even rarer (incidence 0.1–0.4 per 10^6 per year), more common in men and occur with increasing frequency from adolescence onward [1, 2].

Etiology and Molecular Pathogenesis

The etiology of thymomas and thymic carcinomas is unknown. Rare familial [8] and syndromal thymoma cases (e.g., HNPCC) have been reported [9]. Thymoma patients show a higher frequency of nonthymic solid and hematopoietic cancers than the general population [10]. Since almost all thymomas show medullary and cortical differentiation [11] they are thought to arise from a bipotent thymic epithelial stem cell. In TCs, the (stem) cell of origin is enigmatic.

TETs show recurrent genetic gains and losses that increase from type A to B3 thymomas and further to TCs [12]. Genetic alterations in thymomas and TCs overlap partially [13]. Overlap with other cancers is limited [12]. The commonest chromosomal deletion of thymomas and TCs concerns the 6p25 region that contains the FOXC1 tumor suppressor gene [14]. The most common gains are at 1q23 (PBX1) and 8q24.3 (GLI4) [14, 15]. The commonest alteration overall is a point mutation in the GTF2I oncogene that is most prevalent in type A and AB thymomas ($\sim$80%), less common in type B thymomas (20–40%), rare in TCs (5–10%) and apparently absent in other cancers [16]. The only predictive biomarkers identified so far are activating KIT exon 11 gene mutations in 5% of TCs that correlated with transient responses to imatinib [17]. Markers predicting the response of many TCs to multikinase inhibitors are elusive [18].

Clinical Considerations

Thymoma and TC can cause pain, respiratory distress, vena cava superior syndrome or be fortuitous findings. Myasthenia gravis, pure red cell aplasia, acquired hypogammaglobulinemia (Good syndrome), and mucocutaneous candidiasis are "indicator autoimmune diseases" of thymomas but not of other cancers [3]. Therefore, their diagnosis should prompt a search for thymoma and their detection prior to surgery of a mediastinal mass makes the diagnosis of TC, lymphoma, germ cell, or mesenchymal tumor unlikely. Other thymoma-associated autoimmune diseases are not thymoma-specific, e.g., thyroiditis, type I diabetes, hepatitis, encephalitis, and SLE [19]. Autoimmune diseases in TCs (e.g., polymyositis) are very rare and not specific. Enlargement of mediastinal lymph nodes in association with a mediastinal mass argues against thymoma (see staging) and is in favor of a diagnosis of TC, lymphoma, or germ cell tumor (GCT).

Problems with Small Biopsies and Biopsy Indications—General Considerations

Biopsies of mediastinal masses are indicated if there are nonsurgical treatment options, e.g., in neoadjuvant settings or if lymphomas and germ cell tumors are differential diagnostic possibilities. Biopsies are usually dispensable in myasthenic patients, since thymoma is the only likely diagnosis and surgery is the curative therapy. Although small biopsies help to guide treatment [20], reporting of diagnoses based on small biopsies should be cautious for the following reasons:

- The notorious tumor heterogeneity of thymomas may be missed in small biopsies and may cause discrepancies between a (homogeneous) biopsy and a (heterogeneous) resection specimen.
- The highly proliferative cortical regions of normal or reactive thymus and lymphocyte-rich thymomas may be difficult to distinguish from each other and from T-lymphoblastic lymphoma.
- Thymic epithelial hyperplasia, thymic cysts, or thymic Hodgkin lymphoma may mimic thymoma or TC.
- The rare focal spillover of immature T cells from thymomas into mediastinal fat and the rare loss of keratin expression in thymomas may entail an erroneous diagnosis of T-lymphoblastic lymphoma.
- Nuclear expression of p63 by tumor cells of primary mediastinal B-cell lymphoma (PMBL) is prone to be mistaken for thymoma or TC in small biopsies.
- Many mimics of thymomas, e.g., synovial sarcoma resembling type A thymoma may be even more difficult to recognize in small biopsies than in resection specimens as detailed below.

Thymomas

Type A Thymoma, Including the "Atypical Type a Thymoma" Variant

Definition Type A thymoma is composed of bland spindle/oval neoplastic epithelial cells, with few or no admixed immature T cells. The atypical variant can display hypercellularity, increased mitotic activity and focal necrosis, of which the latter appears to be correlated with increased invasiveness.

Epidemiology and stage distribution of type A thymoma are summarized in Table 5.1. This usually indolent tumor has been delineated from "atypical type A thymoma", i.e., a rare variant that infiltrates extensively, metastasizes, and shows histologic features of aggressiveness [1, 2].

Clinical peculiarities Due to the new definition as a tumor that is lymphocyte-poor throughout, type A thymoma is rarely associated with Myasthenia gravis (see above). Whether the new definition has an impact on the prevalence of other autoimmune diseases is not known.

Macroscopy Type A thymomas are usually encapsulated or well circumscribed (stage I or II). The cut surface is gray to white and usually shows a fascicular texture, few fibrous septae, and small cysts. Atypical type A thymoma may be poorly circumscribed, extend into adjacent organs, and exhibit necrotic areas and distant metastasis [21–23].

Histology and immunohistochemistry Type A thymoma can show fascicular, storiform, glandular/adenoid, glomeruloid, solid, rosette-forming, hemangiopericytoma-like, and "pseudoendocrine (paraganglioma-like)" patterns, often within a single tumor. Bland spindle or oval cells with small, spindly, or oval

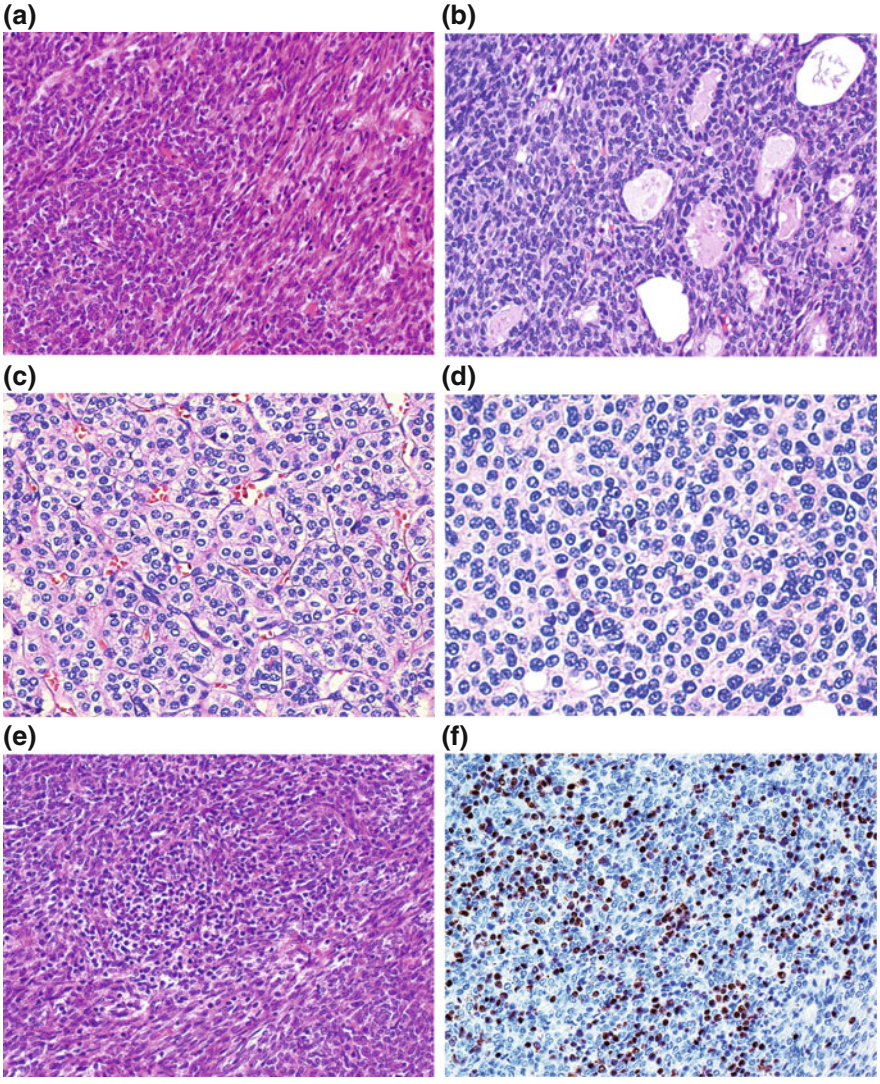

Fig. 5.1 WHO type A thymoma. **a** Conventional type A thymom composed of bland-looking spindle cells (*right*) adjacent to small polygonal cells (*left*). **b** Typical microcysts and single glands. **c** Paraganglioma-like pattern with polygonal tumor cells. **d** Solid pattern with polygonal tumors cells. **e** Focal increase of lymphocytes may require TdT staining to distinguish type A from AB thymoma. **f** Moderate number of immature, TdT(+) T cells; if more than 10% of the investigated tumor area reveals this density of TdT(+) T cells, a diagnosis of type AB thymoma should be rendered (HE: **a**, **b**, **e** ×100; **c**, **d** ×200; immunperoxidase: **f** ×100)

nuclei with fine chromatin und without prominent nucleoli accompanied by thin-walled hemangiopericytomatous vessels are encountered at least focally in almost all properly sampled cases (Fig. 5.1a, b). Polygonal tumor cells are an

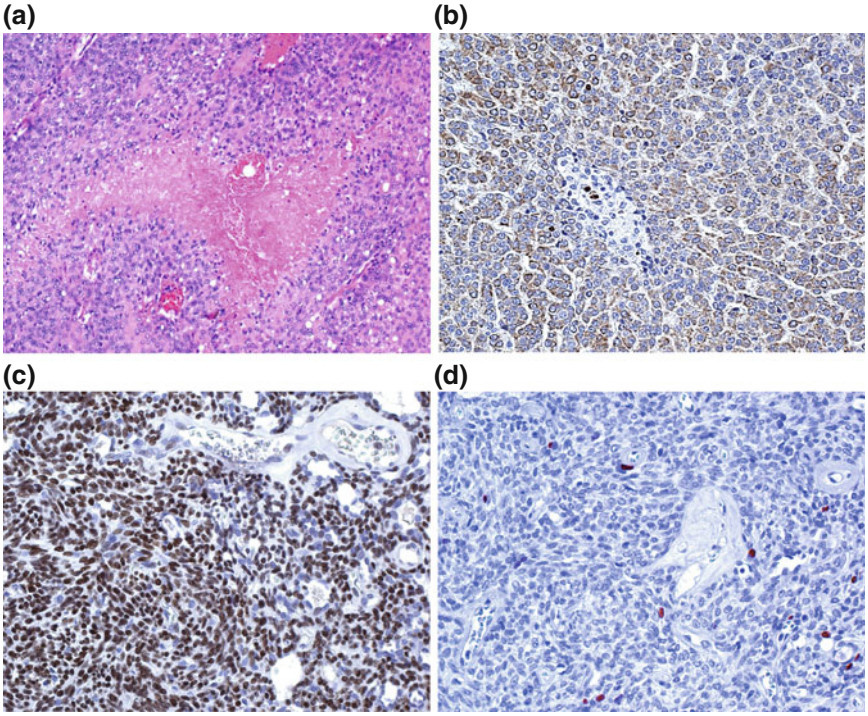

Fig. 5.2 Atypical WHO type A thymoma. **a** Comedo-type necrosis in atypical type A thymoma is the most consistent sign of clinical aggressiveness. **b** Comedo-type necrosis in a more polygonal cell area of atypical type A thymoma (pan-keratin, AE1/3). **c** P63 expression is typical of all thymoma subtypes, including atypical type A thymoma. **d** A low proliferation rate (Ki67 index <2% in epithelial cells) is typical of conventional type A thymoma but does not exclude atypical type A thymoma (HE: **a** ×50; immunperoxidase: **b–d** ×100)

optional and sometimes predominant feature (Fig. 5.1c–d). By definition, lymphoid cells are scarce (Fig. 5.1e, f). Mitoses, apoptotic cells, and perivascular spaces are uncommon. Coagulation necrosis (e.g., of comedo type) is usually restricted to "atypical type A thymomas" (Fig. 5.2). Hassall corpuscles are absent.

Immunohistochemistry Type A thymomas [1, 2] harbor no or rare immature T cells as identified by staining for TdT (recommended), CD1a, or CD99. Any dense ("crowded") accumulation of immature T cells or moderate numbers of immature T cells (Fig. 5.1e, f) in >10% of the evaluable tumor area implies a diagnosis of type AB thymoma. Epithelial cells of type A thymoma consistently stain for CK19 und p63/p40, commonly for CD20 (focally) but not for CK20, CD5, and CD117.

Molecular pathology Recurrent structural genetic alterations are rare [13], while hot spot point mutations in the *GTF2I* gene show the highest prevalence (80%) among all thymomas [16].

Problems with small biopsies in type A thymoma

If only lymphocyte-poor (TdT−) areas of type AB thymomas and micronodular thymoma with lymphoid stroma (MNT) are sampled in a small biopsy, an erroneous diagnosis of type A thymoma may be inevitable. Fortunately, this is rarely of clinical relevance. Focal spindle cell areas in rare type B3 thymoma can be challenging: prominent perivascular spaces and Hassall corpuscles argue for B3 thymoma, while epithelial expression of CD20 and a ki67 index <2% [24] in epithelial cells are in favor of type A thymoma, leaving quite some tumors that may defy classification in small biopsies. While spindle cell (sarcomatoid) carcinoma is usually easily recognized by striking atypia, brisk proliferative activity and common CD5 and CD117 expression, spindle cell carcinoids, mesenchymal neoplasms (e.g., synovial sarcoma, solitary fibrous tumor, inflammatory myofibroblastic tumor, nerve sheath tumor), desmoplastic melanoma, various dendritic cell neoplasms [1] and even reactive changes (e.g., sclerosing mediastinitis, thymic fibrosis [25], inflammatory spindle cell tumors [26]) may need immunohistochemical analysis for recognition.

Therapy and prognosis Complete surgical removal is the only definite treatment and usually achievable due to the circumscription and low tumor stage of most classical "type A" thymomas. Removal may be challenging in "atypical" and metastatic cases [22, 27]. The 10-year survival rates reach 80–100% [5, 28, 29]. Survival rates for atypical type A thymomas have not been reported.

Type AB Thymoma

Definition Type AB thymomas are epithelial thymic tumors with a lymphocyte-poor (type A) and lymphocyte-rich ("type B-like") component in highly variable proportions. The B-like component should not be subtyped (e.g., as B1-like or B2-like).

Epidemiology and stage distribution of this commonest thymoma subtype (up to 40%) [28–30] are summarized in Table 5.1.

Clinical peculiarities Myasthenia gravis (occurring in 20–40%) and other paraneoplastic autoimmune diseases [1, 19] are frequent in this usually indolent tumor [27].

Macroscopy Most cases are well circumscribed [28]. On the cut surface, a nodular architecture and biphasic pattern with firm, whitish (lymphocyte-poor) areas separated by coarse septae from lymph node-like gray (lymphocyte-rich) regions is typical. "Atypical cases" with features that are analogous to those of "atypical type A thymoma" (i.e., advanced stage and necrosis) are rare (<5%) [23].

Histology and immunohistochemistry Fibrous septae that separate large tumor lobules are more common than diffuse and fibrosclerotic variants. The type A areas can exhibit the broad spectrum of type A thymoma morphologies, while tumor cells in the B-like areas are typically spindly, oval, or rarely polygonal with small nuclei and inconspicuous nucleoli and, thus, look different from tumor cells in type B1, B2, and B3 thymomas (Fig. 5.3a). Rarely, light staining medullary islands can occur in

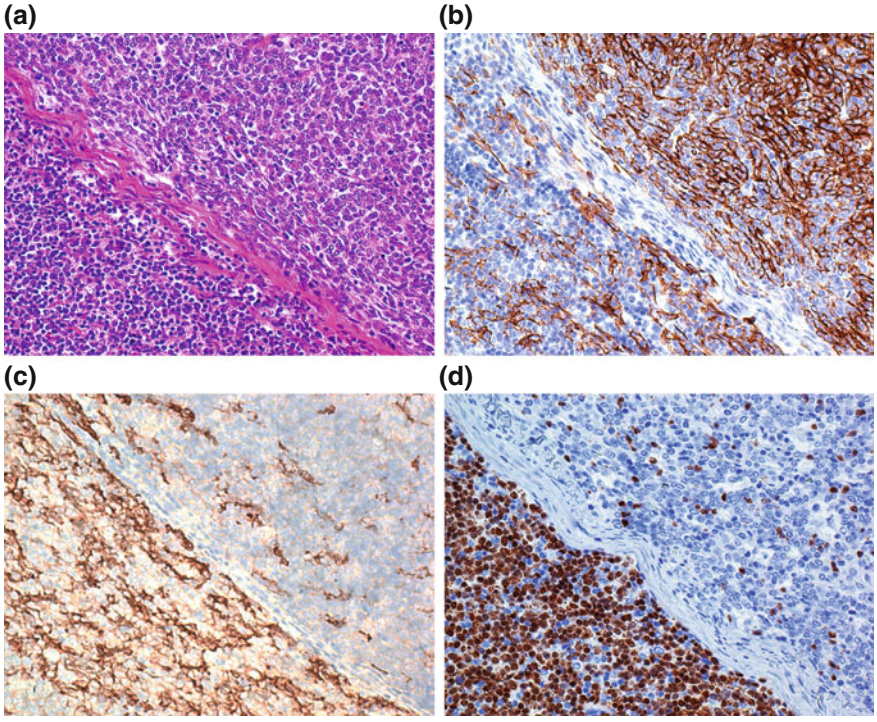

Fig. 5.3 WHO type AB thymoma. **a** Classical biphasic pattern with sharply delineated lymphocyte-poor spindle cell areas (type A, *upper right*) and lymphocyte-rich (type B-like) areas with barely recognizable tumor cells (*lower left*). **b** Keratin expression (AE1/3 antibody) of variable density in both areas (serial section). **c** CD20 expression in epithelial cells with spindly and dendritic morphology but not in small, round B cells (serial section). This pattern of CD20 positivity allows for the diagnosis of type AB thymoma even in apparently monophasic lymphocyte-rich cases. **d** Lymphoid cells in the lymphocyte-rich areas are mainly immature, TdT (+) T cells. Even small foci with this degree of "crowding" of TdT(+) T cells imply a diagnosis of type AB thymoma (compare with Fig. 5.1f) (HE: **a** ×100; immunoperoxidase: **b–d** ×100)

type AB thymomas. Type A and B-like areas may be sharply separated or show gradual transition. The proportions of type A and B-like areas are variable. Rarely, type AB thymomas are immature T-cell-rich throughout, i.e., type A areas and a biphasic pattern with lymphocyte-poor regions are not absolutely required for the diagnosis. Spindle-shaped tumor cells and a typical immunohistochemical profile (e.g., CD20 expression; see next) are helpful to recognize these challenging cases.

Immunhistochemistry reveals that type AB thymomas are epithelial-rich tumors that show a dense but delicate network of tumor cells expressing various keratins (Fig. 5.3b) and p63/p40. Focal epithelial expression of CD20 occurs in 30–50% of cases (Fig. 5.3c), and spindle cells in septal structures often stain for EMA [31]. Complex expression of cortical and medullary markers is typical [11]. Lymphocytes mainly consist of immature, highly proliferative CD3+ TdT+ T cells (ki-67

index >90%) (Fig. 5.3d), but in medullary islands mature CD3+ TdT− Ki67^{low} T cells prevail.

Molecular pathology Structural genetic alterations are more common in type AB than type A thymomas [15, 16, 32], while *GTF2I* mutations occur at the same high frequency (74–80% of cases) [16].

Problems with small biopsies in type AB thymoma. The commonest challenge is the distinction between lymphocyte-rich type AB, B1, and B2 thymomas. In type AB thymomas epithelial cells and their often oval or elongated nuclei are smaller and less conspicuous than in type B1 and B2 thymomas. Even minor spindle cell areas favor a diagnosis of type AB thymoma. While medullary islands occur in all lymphocyte-rich thymomas, Hassall corpuscles almost never occur in type AB thymomas but are frequent in B1 and not uncommon in B2 thymomas. Keratin stains highlight the consistently dense epithelial network in AB (and B2) thymomas, as compared to the delicate network in B1 thymomas. Epithelial CD20 expression is restricted to AB (and type A) thymomas. For the distinction between lymphocyte-poor type AB from type A thymoma and its mimics, see Fig. 5.1e, f. To separate biphasic AB thymomas from micronodular thymomas with lymphoid stroma (MNT), one has to recognize that the complex lymphoid component of MNTs (see below) is localized outside the epithelial component. Of note, heterogeneous tumors featuring type A or AB thymoma and an MNT component are quite common.

Therapy and prognosis. Complete resection is usually achieved and curative due to the common low tumor stage. The 10-year overall survival rates are over 80% [29, 33]. The impact of exceedingly rare metastases on survival has not been studied [22].

Type B1 Thymoma

Definition Type B1 thymomas resemble the normal childhood thymus in terms of abundance of immature T cells, paucity of epithelial cells, and absence of epithelial cell clustering. The "organoid pattern" with concurrence of prevailing cortical areas and medullary regions is another diagnostic prerequisite, while occurrence of Hassall corpuscles is optional.

Epidemiology and stage distribution of this infrequent thymoma subtype are given in Table 5.1.

Clinical peculiarities Myasthenia gravis is frequent (−45%), while other paraneoplastic autoimmune diseases, e.g., hypogammaglobulinema (Good syndrome) are rare (5%). "Pure" B1 thymomas usually follow an indolent clinical course and show stages I and II in over 80% of cases [5, 28, 33].

Macroscopy Most cases are well circumscribed and may reach large diameters due to late infiltration [28]. While the capsule may be firm, the cut surface is usually soft, and large tumor nodules may be separated by delicate or coarse fibrous septae.

Histology and immunohistochemistry In H&E stained sections, type B1 thymomas usually show little or no lobulation on low power. Dark cortical regions almost always dominate massively over lighter "medullary islands (MIs)"

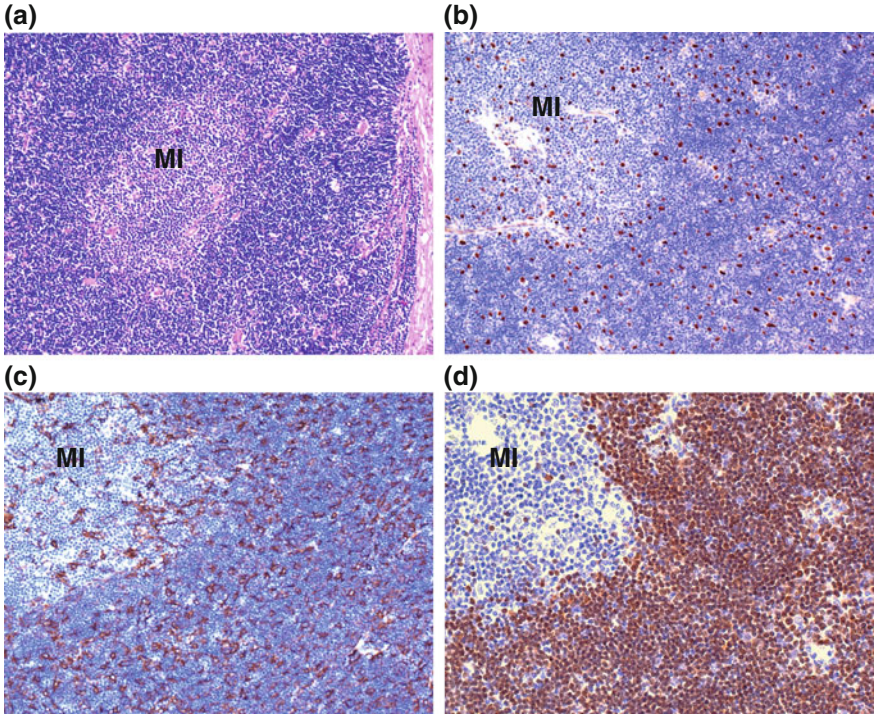

Fig. 5.4 WHO type B1 thymoma. **a** Obligatory organoid architecture with predominance of dark staining cortical areas and obligatory light staining "medullary islands (MI)" (here without a Hassall's corpuscle). **b** P63 expression in scattered, mostly single epithelial cell nuclei both in the cortex and MI. **c** Delicate network of keratin(+) (AE1/3 antibody) epithelial cells in cortical and medullary regions. **d** Confluent cells with TdT(+) nuclei in the cortex (HE: **a** ×50; Immunperoxidase: **b–d** ×100)

(Fig. 5.4a). In contrast to normal childhood medulla, MIs are not consistently "burried" in cortical areas but are commonly misplaced to the periphery of tumor lobules or along fibrous septae. Hassall corpuscles are common but not obligatory constituents of MIs. By definition, the frequency of epithelial cells must be similar to that of the normal thymus and must not show epithelial cell clustering (i.e., 3 or more contiguous tumor cells) as can be highlighted by p63 stain (Fig. 5.4b). Tumor cell nuclei resemble those of normal thymus, exhibiting round contours, vesicular chromatin, and variably prominent nucleoli. Keratin stains highlight a delicate epithelial network that is attenuated in MIs (Fig. 5.4c). In cortical regions, immature TdT+ T cells may obscure tumor cells. MIs are dominated by CD3+/TdT(−) mature T cells (Fig. 5.4d) and CD20+ B cells, and may harbor desmin-positive myoid cells and AIRE-positive epithelial cells.

Molecular pathology Genetic gains and losses are less frequent than in the more aggressive B2 and B3 thymomas [12, 34, 35]. The *GTF2I* mutation occurs in 32% of cases [16].

Problems with small biopsies in type B1 thymoma

In small biopsies, distinction of B1 thymomas from normal thymus, post-chemotherapeutic rebound hyperplasia, true thymic hyperplasia, B-like areas of AB thymoma, and T-lymphoblastic lymphoma (T-LBL) may be challenging or even impossible—requiring cautious reporting. In contrast to non-neoplastic thymus, excess of cortical over medullary areas, irregular and misplaced medullary islands (MIs), and lack of Hassall corpuscles may be clues to the diagnosis of B1 thymoma, while immunohistochemistry (ki67 index close to 100%; delicate epithelial cell network) is usually not helpful. Lymphocyte-rich areas of AB thymomas may be another challenge, particularly when MIs are present: spindle cells, a denser than normal keratin(+) epithelial cell network and epithelial CD20 expression hint to the diagnosis of AB thymoma (Fig. 5.3). As to T-LBL, the clinical setting, i.e., dramatic local and systemic symptoms and absence of Myasthenia gravis, is usually different. Atypical blastic infiltrates that destroy/attenuate keratin-positive epithelial networks and infiltrate (epithelial-free) mediastinal fat are characteristics of T-LBL. Immunohistochemistry in T-LBL may reveal antigen loss (e.g., of CD1a) or abnormal expression of Notch1 and/or LMO2 [36] in TdT+ lymphoblasts. However, in many T-LBLs, the immunohistochemical profile is normal. Clonality analyses may help to clarify such cases. Rarely, T-LBL develops in thymoma [37].

Therapy and prognosis Over 90% of type B1 thymomas are resectable. Recurrences and metastasis are rare [1]. The 10-year and 20-year survival rates is 85–100% [29, 33].

Type B2 Thymoma

Definition Type B2 thymomas are immature T-cell-rich tumors with a content of polygonal and dendritic neoplastic epithelial cells that is higher than in B1 thymomas and normal thymus. Spindle tumor cells are absent. Cortical differentiation is slightly reduced and medullary features are often strongly attenuated in B2 compared to B1 thymomas [11].

Epidemiology and stage distribution are given in Table 5.1. Occurrence in children is rare [11].

Clinical peculiarities Myasthenia gravis (MG) occurs in up to 50% of cases [5, 28], pure red cell aplasia and hypogammaglobulinemia (with or without accompanying MG) in 5%. Pleural effusions and the SVC syndrome are more common than in A, AB, and B1 thymomas.

Macroscopy Type B2 thymomas are often only partially encapsulated and infiltrate adherent soft tissue and pleura, lung, heart, or large vessels. The cut surface is gray or white and may show poor septation, necrosis, hemorrhage, and cysts.

Histology and immunohistochemistry Fibrous septae typically delineate small tumor lobules, and dominant lymphocytes impart a dark or blue impression (Fig. 5.5a, b). Tumor cell nuclei have distinct membranes, vesicular chromatin, and prominent nucleoli (Fig. 5.5b). Perivascular spaces with palisading of tumor cells (Fig. 5.5c) and pale medullary islands (MIs) with or without Hassall corpuscles are optional findings. Intratumorous lymphoid follicles are common in MG-associated cases (Fig. 5.5d). Neoplastic epithelial cells are either dispersed but more numerous than in normal thymus or B1 thymoma, or occur in clusters of at least three contiguous epithelial cells that can be highlighted by p63 immunohistoochemistry (Fig. 5.5e). Fourty percent of B2 thymomas show a minor B3 or B1 thymoma component (Fig. 5.5e). Tumor cells express many keratins (e.g., CK5/6 and CK19) and p40/p63 but are negative for CK20. Most lymphocytes are immature, highly proliferative CD3+ CD5+ CD4+ CD8+ TdT+ T cells (Fig. 5.5f).

Molecular pathology The number of genetic alterations in B2 thymomas is intermediate between AB thymomas on the one hand, and B3 thymomas on the other hand. B2 and B3 thymomas share losses of 6q25.2–q25.3 and 3p and gains of 1q [12, 34, 35, 38]. 22% show *GTF2I* mutations [16].

Problems with small biopsies in B2 thymomas Type B2 thymomas must be distinguished from the less aggressive B1 thymomas and from T-LBL. Small tumor lobules, more abundant than normal and clustered polygonal epithelial cells, and a dense keratin(+), p63(+) epithelial network are hints that the diagnosis is type B2 but not B1 thymoma. Cytologically atypical, TdT+ lymphoblasts that destruct and efface the normal thymic epithelial cell network is the hallmark of T-LBL. A pitfall in this respect is the rare (usually partial) loss of keratin expression in B2 thymomas [39]. Since epithelial expression of p40/p63 is almost always maintained in keratin (−) thymomas, it is recommended to stain for p40/p63 whenever the differential diagnosis between thymoma and T-LBL is problematic.

Therapy and Prognosis Complete surgical removal is achieved in 70–90% of cases [29, 34, 40]. The 10-year recurrence rates reach 32 and 41% in completely resected Masaoka stage II and III B2 thymomas, respectively, arguing for adjuvant radiotherapy in stage III thymomas [41, 42]. Postoperative radiotherapy is also used for incompletely resected thymomas, although it is usually not curative [43]. Nonresectable thymomas may be successfully treated by multimodal concepts [44]. The 10-year survival rates of B2 thymoma patients reach 70–90% [5, 28, 29].

Type B3 Thymoma

Definition Type B3 thymomas are epithelial-predominant tumors that harbor a minor number or (rarely) no immature T cells. Neoplastic epithelial cells have largely lost cortical differentiation and medullary features are generally missing [11].

Epidemiology and stage distribution are given in Table 5.1. Occurrence in children is rare [45].

Clinical peculiarities Myasthenia gravis occurs in 40–50% of cases, other paraneoplasias are rare [28]. Since advanced tumor stages occur in 50% of cases, thoracic pain and superior vena cava syndrome are common at presentation.

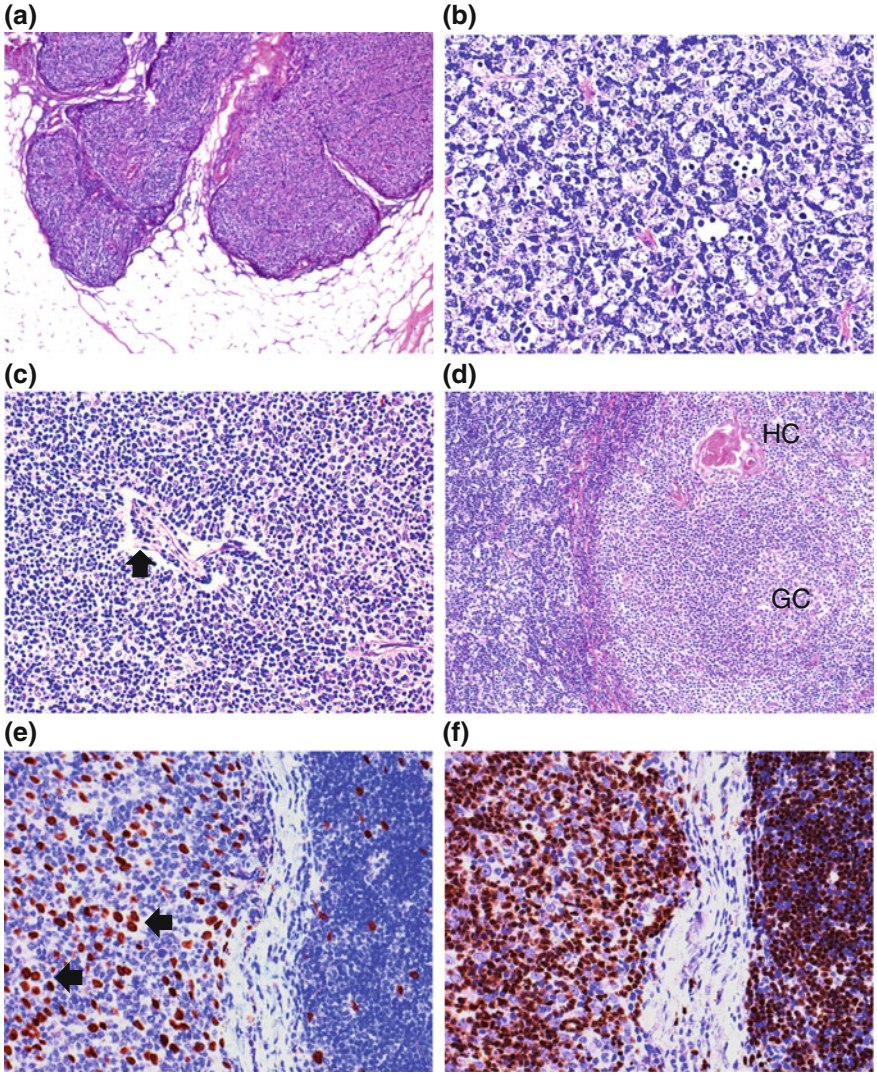

Fig. 5.5 WHO type B2 thymoma. **a** Typical lobular architecture and plump invasion into mediastinal fat. **b** Obligatory blue appearing, lymphocyte-rich tumor with highly increased number of neoplastic epithelial cells (when comparedwith cortical regions of normal thymus); epithelial cells with vesicular nuclei and distinct nucleoli. **c** Lymphocyte-rich, blue appearing tumor with perivascular space (*arrow*). **d** Type B2 thymoma with (optional) medullary island that harbors a lymphoid follicle with germinal center (GC) close to a Hassall's corpuscle (HC); lymphoid follicles often hint to thymoma-associated Myasthenia gravis. **e**, **f** Tumor heterogeneity in thymoma: WHO typ B2 thymoma components on the left, type B1 thymoma component on the right; increased number of focally clustered, p63(+) epithelial cells (*arrows*) in the B2 component (**e**); very high density of immature, TdT(+) T cells in the B1 component (**f**) (HE: **a** ×25, **b** ×400; **c**, **d** ×100; immunoperoxidase: **e**, **f** ×200)

Macroscopy Type B3 thymomas are often poorly circumscribed due to infiltration into adjacent soft tissue and organs. On the firm, gray/white cut surface, hemorrhage, necrosis, and cysts are common.

Histology and immunohistochemistry Fibrous septae separate tumor lobules that are composed of sheets of polygonal neoplastic epithelial cells. The sheets of tumor cells impart a *pink* impression on low power (in contrast to the *blue* hue that is one of the hallmarks of B2 thymomas) (Fig. 5.6a). Plump, sharply delineated lobules of tumor cells form the invasion front of B3 thymomas (Fig. 5.6a), while single-cell infiltration and prominent desmoplasia are more common in thymic carcinoma. Tumor cell nuclei can be varied: bland looking with inconspicuous nucleoli or moderately atypical with anisonucleosis and prominent nucleoli. Sheets of tumor cells are usually sprinkled with few lymphocytes (Fig. 5.6b). Rarely lymphocytes are absent. Perivascular spaces surrounded by palisades of tumor cells are usually conspicuous (Fig. 5.6b). Hassall corpuscles occur rarely. Focal occurrence of spindle cells and clear cell features may occur (Fig. 5.6c, d). Diffuse epithelial expression of keratins (e.g., CK19, CK5/6, CK8/18) (Fig. 5.6e) and p40/p63, and focal expression of GLUT1 and EMA are typical [1], while CD20 is absent (in contrast to many type A and AB thymomas). Focal CD5 and CD117 expression has been described as rare exception. The lymphocytes are mainly TdT+ immature T cells (Fig. 5.6f). Perivascular spaces may harbor mature and immature T cells and plasma cells.

Molecular Pathology Type B3 thymomas show the highest prevalence of genetic alterations among thymomas [12, 15, 34, 35]. Changes that are largely restricted to B3 thymomas comprise losses of 13q, 16q, and 17p and gains of 4p and 17q [15, 16, 34, 35, 46]. *GTF2I* mutations occur in 21% of cases [16].

Problems with small biopsies Distinction of a relatively lymphocyte-rich (but still pink appearing) B3 thymoma from a relatively lymphocyte-poor (but still blue appearing) B2 thymoma is inevitably subjective (but clinically of minor relevance). Tumors showing both B3 and B2 patterns are more common than pure B3 thymomas, and small biopsies often fail to sample this tumor heterogeneity. Therefore, we comment on this possibility if we encounter pure B3 and B2 thymomas in small biopsies. Rare B3 thymomas can show focal spindle epithelial cells, raising the differential diagnosis of type A thymoma. This distinction may be impossible if the focal and inconsistent CD20 expression of type A thymomas, or prominent perivascular spaces of B3 thymomas are missing in small biopsies. The distinction of B3 thymomas from thymic squamous cell carcinomas (TSQCC) is clinically relevant and difficult since well-differentiated TSQCC may have perivascular spaces, and small biopsies may fail to sample the single cell or finger-like infiltration pattern at the invasion front. Prominent intercellular bridges, strong and usually extensive expression of CD5 and CD117 (in 80% of TSQCCs), and absence of TdT+ immature T cells favor a diagnosis of TSQCC [1]. Whenever a suspected "B3 thymoma" shows unusual features, alternative diagnoses should be seriously considered (e.g., melanoma; seminoma; carcinoid; synovial sarcoma; parathyroid adenoma).

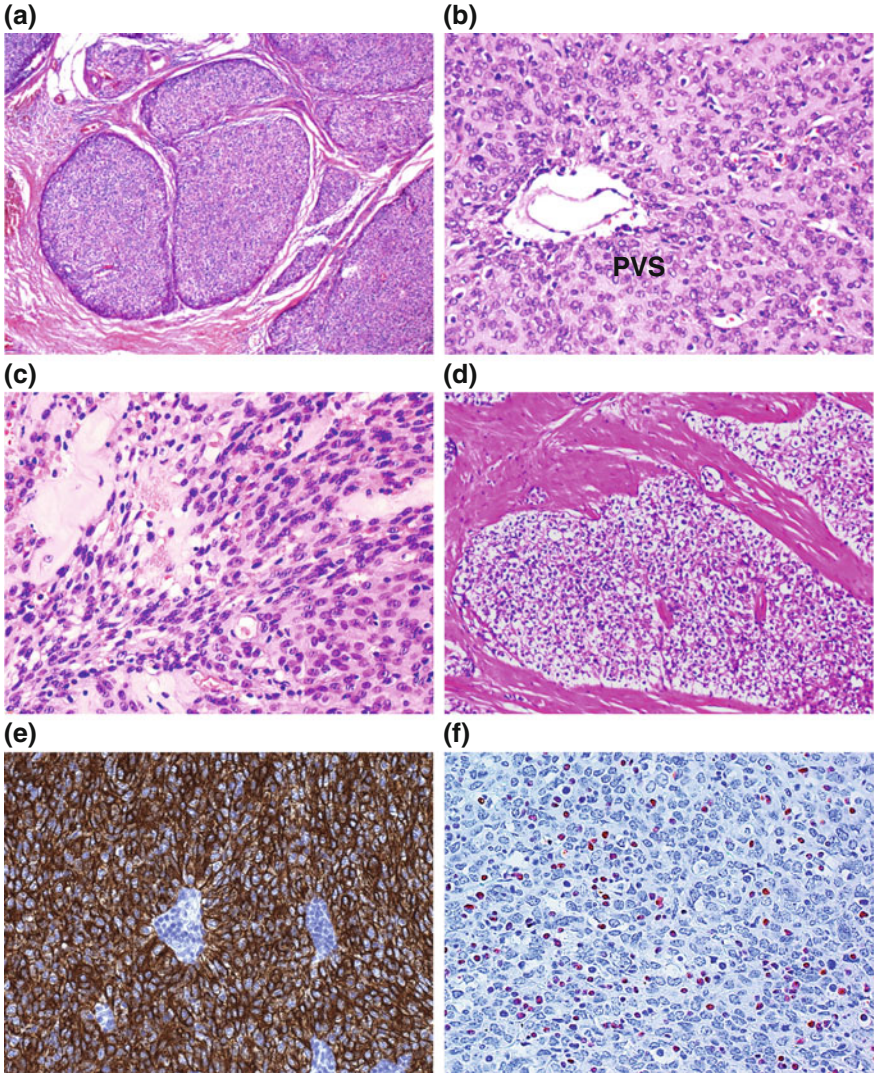

Fig. 5.6 WHO type B3 thymoma. **a** Typical lobular architecture and plump invasion front facing desmoplastic stroma. **b** Pink appearing, epithelial-rich, lymphocyte-poor tumor with minor atypia and prominent perivascular space (PVS). **c** Small focus of spindle cells; minor spindle cell foci against a background of typical B3 thymoma are compatible with the diagnosis of B3 thymoma. **d** Focal clear cells features are common in otherwise typical (*pink*) B3 thymomas. **e** Keratin(+) sheets of tumor cells with palisading around epithelial-free perivascular spaces (antibody AE1/3). **F** Paucity of TdT(+) non-neoplastic immature T cells among neoplastic epithelial tumor cells (HE: **a**, **d** ×25; **b**, **c** ×200; immunoperoxidase: **e**, **f** ×200)

Therapy and Prognosis Therapeutic principles are the same as in B2 thymomas (see above). 30% of B3 thymomas recur within 10 years [28]. The 10-year overall survival rates are 50–70% [5, 29]. MG-associated cases may have a better prognosis due to earlier detection [40, 47].

Micronodular Thymoma with Lymphoid Stroma (MNT)

Definition MNTs are biphasic tumors composed of nodules of neoplastic, bland-looking spindle epithelial cells that are surrounded by a non-neoplastic, epithelial-free lymphoid stroma.

Epidemiology and stage distribution of these rare thymomas are given in Table 5.1.

Clinical peculiarities Paraneoplastic phenomena, including Myasthenia gravis (MG), are virtually nonexistent in MNTs. 95% are in stage I or II and fortuitous findings.

Macroscopy Most MNTs are encapsulated or well circumscribed and commonly contain cysts on the soft, gray cut surface.

Histology and immunohistochemistry Multiple, small, and sharply delineated tumor nodules are composed of type A thymoma-like, bland spindle and (rarely) polygonal epithelial cells that may form cysts and rosettes (Fig. 5.7a, b). Inside the nodules there are few or no lymphocytes. Outside the epithelial compartment, the lymphoid stroma is dense and usually shows lymphoid follicles. Some TdT+ immature T cells typically surround the nodules and are accompanied by mature, CD3+ T cells, CD20+ B cells, and lymphoid follicles containing CD23+ follicular dendritic cells. Rarely, monoclonal B cells and low-grade intratumorous B-cell lymphomas occur inside MNTs [48]. In contrast to many type A and AB thymomas, epithelial cells of MNTs are CD20(−).

Molecular pathology Recurrent genetic alterations have not been reported.

Problems with small biopsies MNT can be mixed up with type AB thymoma, if the lack of epithelial cells in the T-cell- and B-cell-rich compartments of MNT is not appreciated. AB thymomas are epithelial-rich throughout and largely devoid of B cells. Lymphoid follicles in epithelial cell-free areas of MNT may prompt the diagnosis of thymic follicular hyperplasia (TFH) in small biopsies. However, TFH is almost always associated with MG, while MNT almost never is. Low-grade B-cell lymphomas inside MNTs may be impossible to distinguish from primary thymic (e.g., MALT) lymphomas if the characteristic nodules of MNT are missing in small biopsies. Imaging studies may give a hint: MNTs are usually well circumscribed, while conventional thymic lymphomas show fuzzy borders. Micronodular thymic carcinoma with lymphoid hyperplasia [49] shows the same growth pattern as MNT but tumor cells are clearly atypical and TdT+ immature T cells are absent.

Therapy and Prognosis Surgical removal is almost always possible. Recurrences and tumor-related deaths have not been reported.

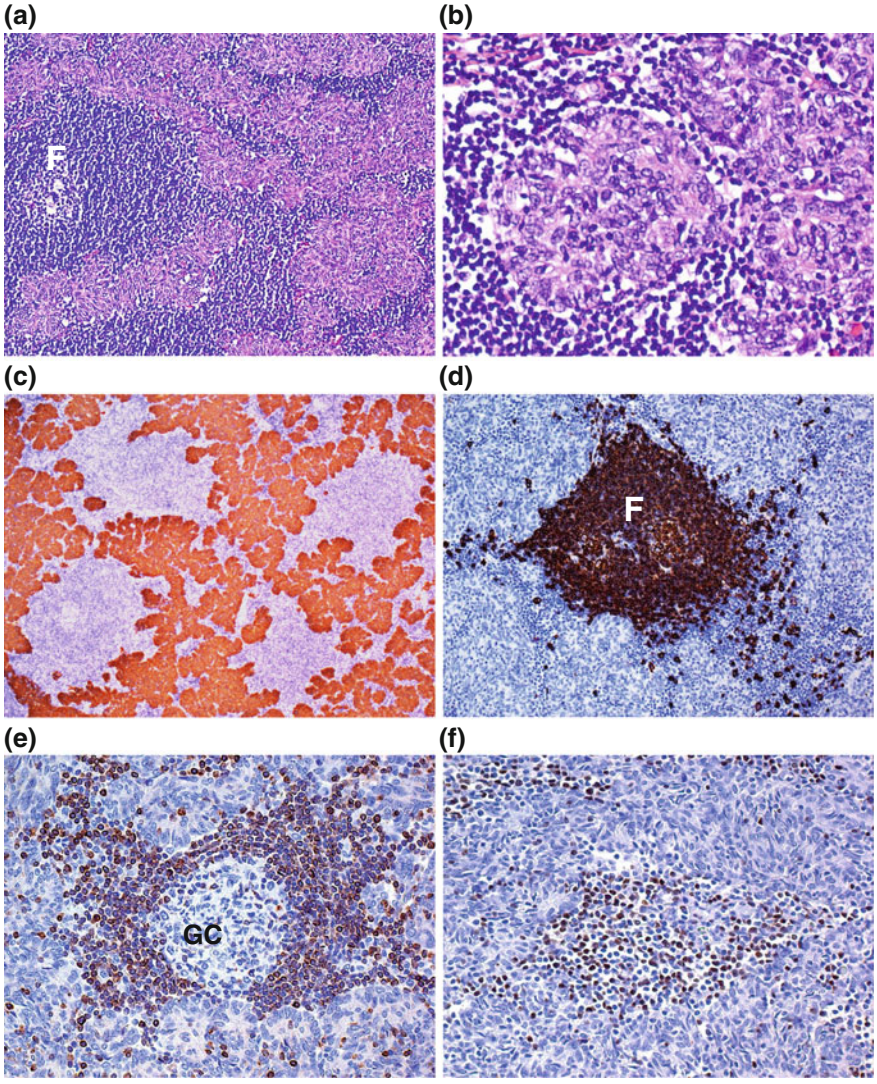

Fig. 5.7 Miconodular thymoma with lymphoid stroma (MNT). **a** Single or confluent nodules of pink appearing spindel cells are surrounded by a lymphocyte-rich, desmoplasia-free stroma including a lymphoid follicle (F). **b** Nodules are composed of bland-looking spindle and oval cells with inconspicuous nucleoli. **c** Keratin expression (antibody AE1/3) in the nodules; no expression in the lymphoid stroma. **d** CD20 expression in a lymphoid follicle within the lymphoid stroma; note typical absence of CD20 expression in epithelial cells of MNT e. BCL2(−) reactive germinal center (GC). **f** TdT(+) immature T cells occur in the lymphoid stroma close to but barely inside epithelial nodules (HE: **a** ×25; **b** ×200; immunoperoxidase: **c** ×25; **d**–**f** ×100)

Metaplastic Thymoma (MPT)

Definition MPTs are biphasic tumors showing solid areas of epithelial cells in addition to a bland, spindle cell (metaplastic) component.

Epidemiology and stage distribution are given in Table 5.1.

Clinical peculiarities MPTs have not been reported to be associated with Myasthenia Gravis (MG) or other autoimmune diseases. Almost all MPTs show low tumor stages and are fortuitous findings.

Macroscopy MPTs are usually well circumscribed with a homogenous gray to white cut surface.

Histology and immunohistochemistry MPTs show no lobular growth pattern. The polygonal or plump spindly cells of the epithelial component form islands or anastomosing trabecular structures, while the spindle cell component resembles bland fibroblasts growing in storiform or fascicular patterns (Fig. 5.8a). The transition between both components can be sharp or gradual. The epithelial cells show mildly atypical nuclei and small nucleoli. Lymphocytes are usually absent. The epithelial component is strongly positive for keratins, p63, and usually EMA, while the fibroblast-like component may express keratins and EMA faintly and focally and is p63(−) (Fig. 5.8b) [1, 2]. CD5, CD20, CD34, and CD117 are not expressed and TdT+ T cells are absent. Proliferative activity is mostly low (ki67 index < 5%).

Problems with small biopsies Distinction of MPTs from sarcomatoid thymic carcinomas, biphasic synovial sarcomas, and solitary fibrous tumors (SFTs) may be difficult. Striking atypia and high proliferative rate are typical of sarcomatoid carcinomas, while the immunoprofiles of synovial sarcoma (p63(−), TLE1+) and SFT (p63(−), CD34+, CD99+, BCL2+, nuclear STAT6+) are distinctive.

Therapy and prognosis Complete surgical removal is the treatment of choice. Recurrences are exceedingly rare and a single tumor-related death has been reported [1, 2].

Rare Other Thymomas

So-called "microscopic thymomas" are tiny (<1 mm) epithelial nodules that are found fortuitously on histological examination of non-neoplastic thymuses. The nodules are composed of bland-looking plump spindle and polygonal cells and are typically devoid of immature T cells (Fig. 5.8c). They are of no clinical relevance and need to be separated from "microthymomas" that represent small conventional thymomas measuring <1 cm in diameter [50].

So-called "sclerosing thymoma" is not an entity but a mediastinal mass that mostly seems to represent the fibrous end stage of a regressing thymoma. In most cases, the histotype of the underlying thymoma is not recognizable (Fig. 5.8d). Rarely, sclerosing thymomas seem to result from enigmatic collagen production in perivascular spaces and in the outskirts of conventional thymomas (usually type B2

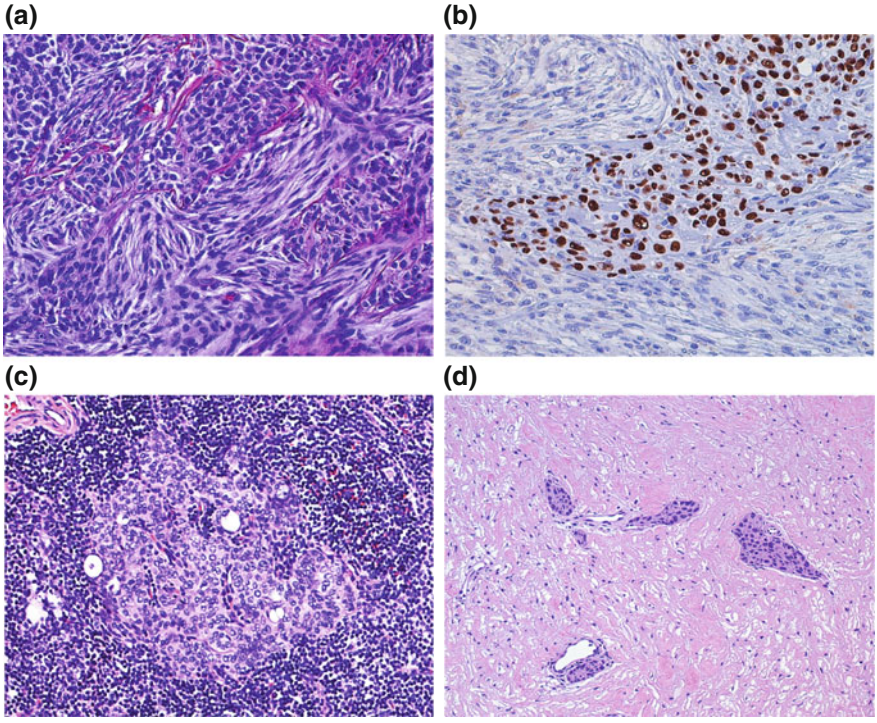

Fig. 5.8 Metaplastic thymoma and other rare thymomas. **a** Metaplastic thymoma exhibiting epitheloid tumor cell islands surrounded by bland-looking spindle-shaped tumor cells. **b** Nuclear p63 expression exclusively in the epithelioid tumor component. Note moderate degree of nuclear atypia in the epithelioid component. In case of substantial mitotic activity and spindle cell atypia, the differential diagnosis of sarcomatoid carcinoma needs consideration. **c** So-called "microscopic thymoma" fortuitously detected in a thymectomy specimen resected for Myasthenia gravis. The cells of this supposedly hyperplastic epithelial proliferation resemble those of type A thymoma and are devoid of interepithelial immature T cells. **d** Sclerosing thymoma (large mediastinal mass): Collagen-rich fibrous stroma surrounds, islands' of epithelial cells. As is the case here, the underlying cause, supposedly a regressively changed thymoma, cannot be classified with certainty (HE: **a**, **c**, **d** ×50; **b** ×200; immunoperoxidase)

or B3) [1]. Sclerosing thymoma must be distinguished from sclerosing mediastinitis, diffuse thymic fibrosis [25], sclerosing lymphomas, germ cells tumors, and mesenchymal tumors [1].

Thymic Carcinomas (TCs)

TCs are derivatives of thymic epithelial cells like thymomas but morphologically resemble analogously labeled carcinomas in other organs. There are no subtype-specific clinical peculiarities and tumor stage and resection status (R0 vs. R1/R2)

but not histological subtype appear to have an impact on prognosis [51–53]. Therefore, TCs will not be described in detail here but typical diagnostic pitfalls and problems with small biopsies in TCs will be highlighted. Since neoplastic epithelial cells of TCs are devoid of thymus-specific functions (e.g., the capacity to support thymopoiesis), TCs are almost never accompanied by Myasthenia gravis and other autoimmune and immunodeficiency diseases that are typical of thymomas. Instead, pain and other local symptoms are common at presentation. The distinction of thymomas from TCs is clinical relevant:

- The prognosis of TCs is worse than the prognosis of thymomas [29, 51].
- Lymph node metastases are common (30%) in TCs but rare in thymomas (2%) [54].
- Distant (hematogenous) metastases are frequent in TCs (50%) while pleural dissemination is the most common type of metastasis in thymomas, and extrathoracic spread is rare [55].
- Therapeutic management is different in TCs and thymomas. Even completely resected stage II TCs should receive postoperative radiotherapy and rare TCs with activating KIT mutations may be candidates for second-line imatinib treatment. In contrast to thymomas, a subset of otherwise refractory TCs profits from multikinase inhibitor therapy [28, 56–58].

Genetic complexity is higher in TCs than thymomas [12, 16, 38, 59]. Despite considerable mutational overlap, some alterations are largely restricted to TCs: gains on 17q and 18p; losses on 3p, 16q, and 17p; and mutations with impact on epigenetics and apoptosis [14, 60, 61]. The most common mutations in TCs concern *TP53* (40%), and members of the PI3 K and RAS pathway [60, 62, 63], while mutations of *GTF2I* are rarer (8%) than in thymomas (20–80%) [16]. Interestingly, thymic mucoepidermoind carcinomas (MECs) show the same *MAML2* rearrangement as MECs in other organs [64], while mutational profiles of squamous cell carcinomas (SQCCs) of thymus and lung are very different [12]. This reflects the etiological role of smoking in lung but not thymic SQCCs.

Thymic Squamous Cell Carcinoma (TSQCC)

TSQCC make up 80% of TCs, are more common in males, and typically present in patients over 50 years of age [53, 63]. If Myasthenia gravis is present, this usually hints to a rare thymoma component [65]. 90% of cases are in advanced tumor stages at presentation [66]. Histology can be quite varied (Fig. 5.9). Morphological peculiarities of TSQCCs are: (i) structures resembling perivascular spaces; however, optically empty spaces around central vessels that are typical of thymomas are often effaced by fibrosis; (ii) plump instead of infiltrative invasion in many well-differentiated cases; (iii) epithelial cells expressing CD5 in 60% and CD117 (Fig. 5.10) and FOXN1 in 70–80%; (iv) frequent expression of neuroendocrine markers in a minority (<50%) of tumor cells; (v) rare fully encapsulated (stage I)

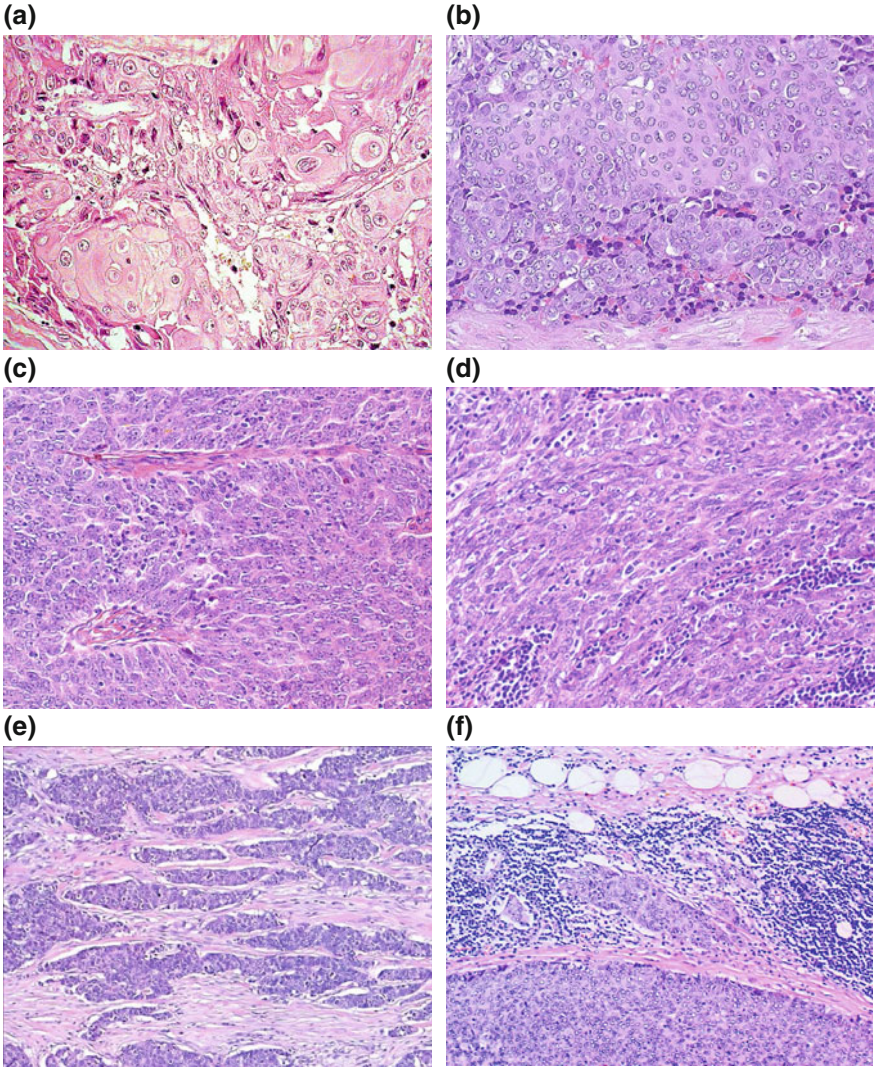

Fig. 5.9 Spectrum of thymic squamous cell carcinoma (TSQCC). **a** Solid growth pattern of keratinizing TSQCC. **b** Nonkeratinizing TSQCC. **c** TSQCC mimicking B3 thymoma due to prominent palisading of tumor cells around vessels; in contrast to optically empty or lymphocyte-filled "true" perivascular spaces, the perivascular zones in TSQCC are typically obliterated by variably collagen-rich fibrosis and commonly harbor plasma cells. **d** Focal spindling of tumor cells in TSQCC; in case of extensive spindling, the differential diagnoses of spindle cell carcinoma (i.e., a variant of sarcomatoid carcinoma) or of "combined thymic carcinoma" need consideration. **e** Trabecular growth pattern of TSQCC contrasting with the lobular growth pattern of type A or B3 thymoma. **f** Infiltrative growth at the invasion front is typical of TSQCC but not thymoma; however, the "pushing border" type of invasion that is characteristic of thymoma occurs in some TSQCC as well (HE: ×200)

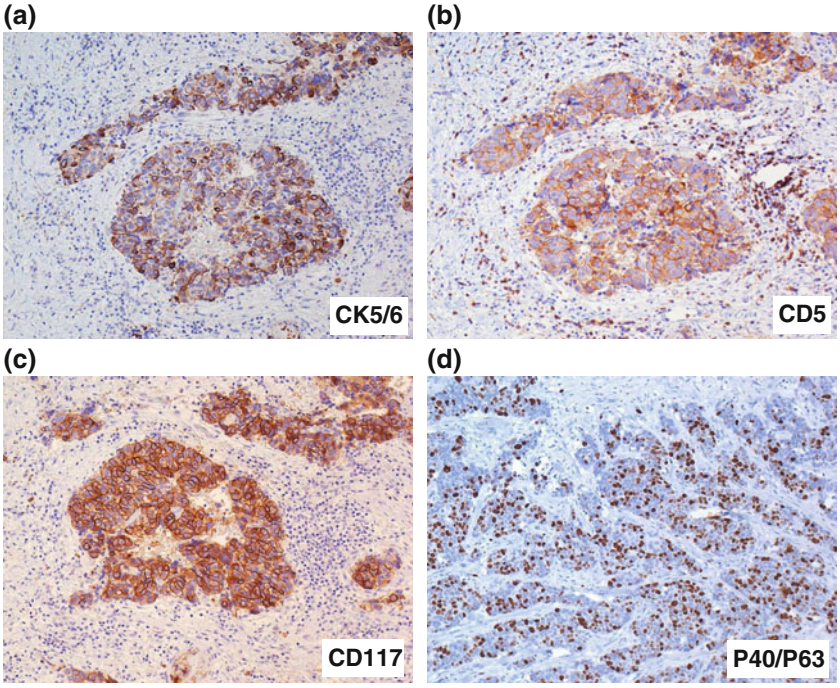

Fig. 5.10 Immunohistochemical profile of thymic squamous cell carcinoma (TSQCC). **a** Cytokeratin 5/6 (CK5/6) expression is a must and usually extensive. **b** Epithelial CD5 expression. **c** Epithelial CD117 expression. **d** Nuclear p40/p63 positivity in virtually all tumor cells. This "full house pattern" occurs in 60–80% of TSQCC and is almost pathognomonic for a thymic primary. In case of mediastinal CD5-/CD117-squamous cell carcinomas, clinicopathological correlation is needed to distinguish TSQCC from mediastinal involvement by extramediastinal squamous cell carcinomas (e.g., from the lung). If squamous differentiation is lacking, expression of CD5 and/or CD117 is not per se indicative of a thymic origin of a given carcinoma, since nonsquamous cancers from many organs can be CD5+ and CD117+ (Immunoperoxidase, ×100)

"cystic well-differentiated TSQCCs" with excellent prognosis [67]. A molecular peculiarity is "targetable" KIT mutations in 5–10% of cases [13]. The 10-year survival rate is 60–65% [53, 68].

Problems with small biopsies and differential diagnosis The strategy to distinguish TSQCC from B3 thymomas has been detailed in the "B3 thymoma chapter".

TSQCC can be accompanied by dense lymphoid and plasma cell-rich infiltrates, raising the possibility of lymphoepithelioma-like carcinoma (LELC). Since both cancer types can be CK5/6+, CD5+, and CD117+, negativity on EBER in situ hybridization (ISH) and solid instead of syncytial tumor complexes would support diagnosis of TSQCC.

Poorly differentiated carcinomas resembling TSQCC should routinely be checked for EBV association using EBER-ISH. By definition, EBER+ carcinomas

are counted among LELCs, even if they resemble SQCCs and completely lack lymphoid stroma (see below) [1].

TSQCCs that show transition to undifferentiated or small-cell carcinoma components should be stained for neuroendocrine markers to exclude "combined large-cell neuroendocrine carcinoma" or "combined small-cell carcinomas" of the thymus; and for NUT protein to exclude the aggressive "NUT carcinoma" [69]. In biopsies the poorly differentiated component of NUT carcinoma can be missed. Therefore, in young patients, centrally located tumors and/or TSQCCs in small biopsies should be tested for NUT expression. To distinguish poorly differentiated TSQCC from undifferentiated carcinoma, staining for CK5/6, p63, and CD5 is required. By definition, all these staining are negative in undifferentiated carcinomas of the thymus [1].

Distinguishing TSQCC from metastases of pulmonary or head-and-neck SQCCs is straightforward in small biopsies, if the TSQCC is CD5+ CD117+ FOXN1+. In SQCCs that are negative for these markers (20% of TSQCCs) imaging studies are needed to resolve this differential diagnostic problem.

Basaloid Carcinomas

Basaloid thymic carcinomas (BTCs) make up 5% of TCs, are more common in males, and typically occur in elderly patients. 60% show stage III and IV disease at presentation [1]. Striking palisading of tumor cells at the periphery of tumor infiltrates is the hallmark of BTCs and necrosis is common (Fig. 5.11a–c). Large, cystic tumors with papillary, nested, or "cylindromatous" growth patterns are frequent. Tumor cells usually are quite monotonous giving a blue or clear cell impression. Keratinization and transition to sarcomatoid components may occur [70]. Like TSQCC most BTCs express CK5/6, p63, CD5, and CD117 (Fig. 5.11d) and are TTF1(−) [70]. The prognosis is similar as in TSQCC.

Problems with small biopsies and differential diagnoses Distinction of BTC from poorly differentiated TSQCC may be difficult in small biopsies. Atypia in TSQCCs is usually more striking. NUT carcinoma needs consideration and staining for NUT protein in cases with sharp transition between keratinizing and small-cell areas, particularly in young patients [69] might be helpful. Adenoid cystic carcinoma-like tumor usually shows some cribriform areas, less palisading than BTC and is usually CD117(−) [71].

Lymphoepithelioma-Like Carcinoma (LELC)

Thymic LELCs make up 5% of TCs, are more common in males and often occur in children and young adults. 70% are in stage III or IV at presentation. Syncytial growth of poorly delineated cells with large nuclei, vesicular chromatin, and

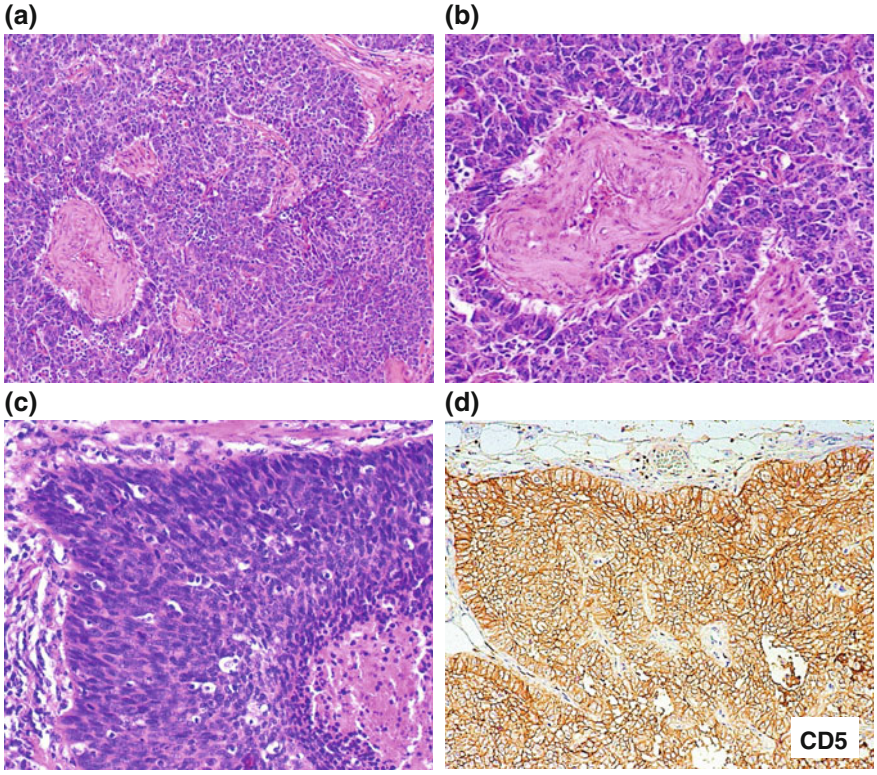

Fig. 5.11 Basaloid carcinoma of the thymus. **a** Typical solid growth pattern of basophilic tumor cells with high nuclear/cytoplasmic ratio showing palisading at the periphery of tumor lobules and around vessels. **b** High power view of palisading of tumor cells. **c** Frequent mitoses, apoptotic bodies, and necrotic areas are characteristic. **d** CD5 expression is at least as common as in thymic squamous cell carcinomas and—in the absence of extensive neuroendocrine features—argues against a diagnosis of large-cell neuroendocrine carcinoma (HE: **a**, **c** ×50; **b** ×200; Immunoperoxidase: **d** ×200)

prominent nucleoli in a lymphoid and plasma cell-rich stroma with no or little desmoplasia is typical (Fig. 5.12). Keratinization is rare [53, 72]. 50% of classical, lymphocyte-rich cases are EBV-associated, particularly those in patients under 30. By definition, EBV(+) carcinomas without lymphoid stroma are also called LELCs, even if they look like TSQCC or undifferentiated carcinoma (Fig. 5.13a) [1, 2]. EBV detection needs EBER in situ hybridization (EBER-ISH) due to insensitivity of LMP1 immunohistochemistry. Tumor cells typically express keratins, p63, CD5, and CD117 (Fig. 5.13b–d). Lymphocytes are mature, TdT(−) T and B cells. Plasma cells are polyclonal. The prognosis is similar as in TSQCC.

Problems with small biopsies and differential diagnosis Tumor cells can be easily overlooked due to overwhelming numbers of lymphoid cells, arguing for keratin staining of all unclear mediastinal processes. Poorly differentiated TSQCC

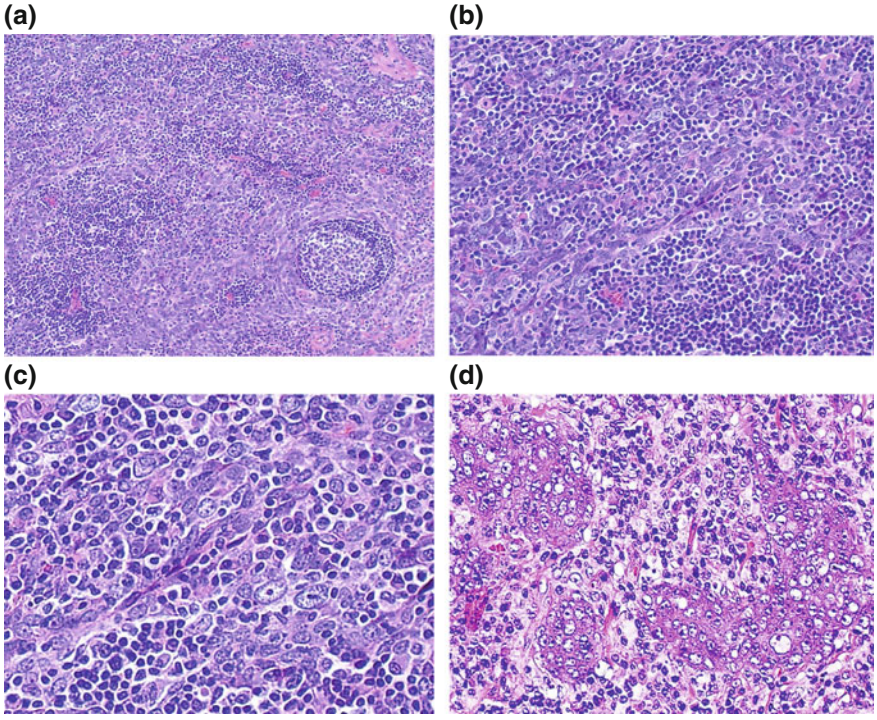

Fig. 5.12 Classical lymphoepithelioma-like carcinoma (LELC) of the thymus. **a** Barely visible tumor cells among an overwhelming number of lymphoid cells and plasma cells (including a lymphoid follicle). **b**, **c** Spindle tumor cells at intermediate and high power with large nuclei and prominent nucleoli forming a delicate network with invisible cell borders in HE-stained sections. **d** Dense lymphoid infiltrate around nodules of atypical tumor cells that show large nuclei, prominent nucleoli but lack visible cell borders between tumor cells ("syncytial growth pattern"). Since only 50% of thymic LELC are EBER+ on in situ hybridization, diagnosis does not depend on EBV detection. Immunohistochemistry is recommended here to exclude mesenchymal and dendritic cell tumors (see text). (HE: **a** ×50; **b**, **d** ×200; **c** ×400)

and undifferentiated thymic carcinoma with or without lymphoid stroma by definition must be EBV(−) and, therefore, need EBER-ISH for classification and distinction from LELC. In contrast to EBER(−) lymphocyte-rich LELCs, lymphocyte-rich TSQCC shows solid or trabecular islands of tumor cells, distinct cell borders, intercellular bridges, and marked desmoplasia, while undifferentiated TCs, by definition, are large-cell carcinomas with a nonendocrine, p63(−), CD5(−) immunophenotype [1, 2]. Micronodular thymic carcinoma with lymphoid hyperplasia [49] shows sharply delineated islands of atypical epithelial cells surrounded by a desmoplasia-free, lymphoid stroma (see below). Mediastinal seminomas with lymphoid hyperplasia can be a pitfall: They can be keratin+/CD117+ [73] and may need OCT4 or SALL4 staining for recognition. Lymphomas with inflammatory stroma as well as metastases need consideration as well.

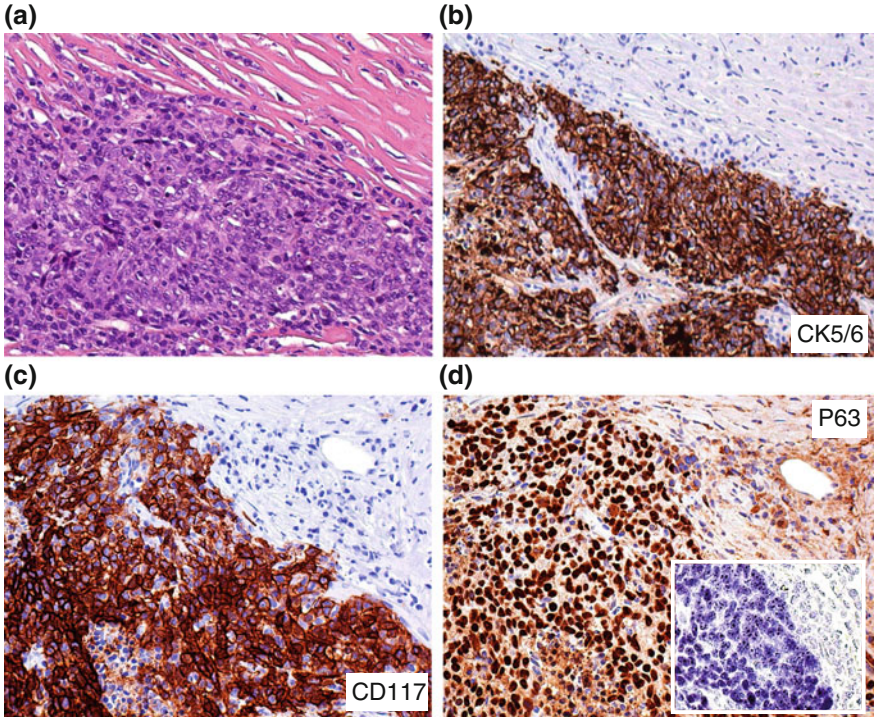

Fig. 5.13 Non-classical lymphoepithelioma-like carcinoma (LELC) of the thymus. **a** Solid tumor mimicking nonkeratinizing thymic squamous cell carcinoma (TSQCC) in a lymphocyte-poor, collagen-rich desmoplastic stroma. **b–d** Immunohistochemical profile of TSQCC: **b** cytokeratin 5/6 (CK5/6)(+); **c** CD117(+); **d** p63(+). By definition, EBER positivity (*inset* in **d**) switched the diagnosis from TSQCC to the correct LELC. We perform EBER in situ hybridization (ISH) in all mediastinal cancers in which poorly differentiated TSQCC, basaloid carcinoma and undifferentiated thymic carcinoma are diagnostic considerations. (HE: **a** ×200; immunoperoxidase: **b–d** ×200; EBER-ISH: *inset* in **d**)

Mucoepidermoid Carcinoma

Mucoepidermoid carcinomas (MECs) of the thymus make up 5% of TCs [53, 68] and show no gender bias. Their incidence peak is at 50 years of age. About 50% are in stage III and IV at presentation. Macroscopically, partially cystic and mucinous tumors are characteristics; association with multilocular thymic cysts is common. They resemble MECs in salivary glands and lung genetically (*MAML2* rearrangement) [64, 74] and histologically, showing highly variable proportions of tumor cells with mucinous or squamous differentiation, including intermediate and PAS+ goblet cells (Fig. 5.14a–c). High-grade histology is rare. Tumor cells express CK7 and p63, but are typically negative for CK20, CD5, CD117, TTF1, and napsin. Mucinous cells can be highlighted by CEA staining (Fig. 5.14d). The prognosis is similar as in TSQCC.

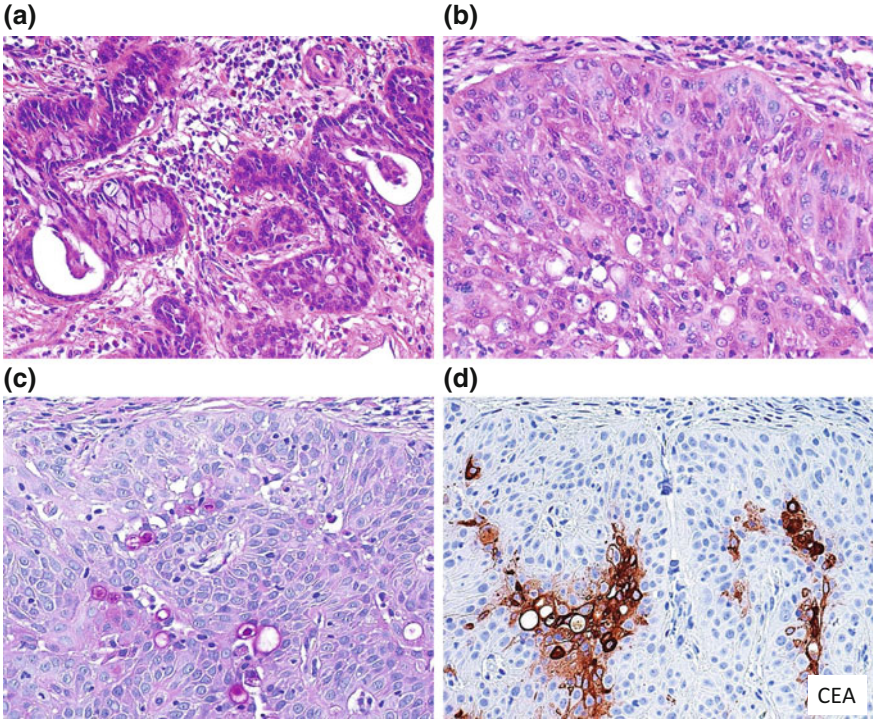

Fig. 5.14 Mucoepidermoid carcinoma (MEC) of the thymus. **a** Well-differentiated MEC with largely balanced proportions of nonkeratinizing epidermoid cells and mucinous cells. **b–d** MEC resembling squamous cell carcinoma with predominance of nonkeratinizing epidermoid cells and a minority of mucin-producing, periodic acid Schiff (PAS)(+) cells that stain for carcinoembryonic antigen (CEA). (HE: **a** and **b** ×200; PAS: **c** ×200; immunoperoxidase: **d** ×200)

Problems with small biopsies and differential diagnosis Depending on the proportions of the squamous and mucinous components, MECs can be confused with TSQCCs, thymic adenocarcinomas (see below), or metastases. In small biopsies, thymic MECs and metastasis of pulmonary MECs are indistinguishable and imaging studies are indispensable.

Clear Cell Carcinoma

Clear cell carcinomas of the thymus are very rare cancers, slightly more common in males, and appear to be restricted to adults. They show a lobular growth pattern, may be accompanied by massive desmoplasia, and often have tumor cells with a broad, clear, PAS+ cytoplasm. They are variably CD5+, CK5/6+, and p63+ (Fig. 5.15). The prognosis is similar as in TSQCC.

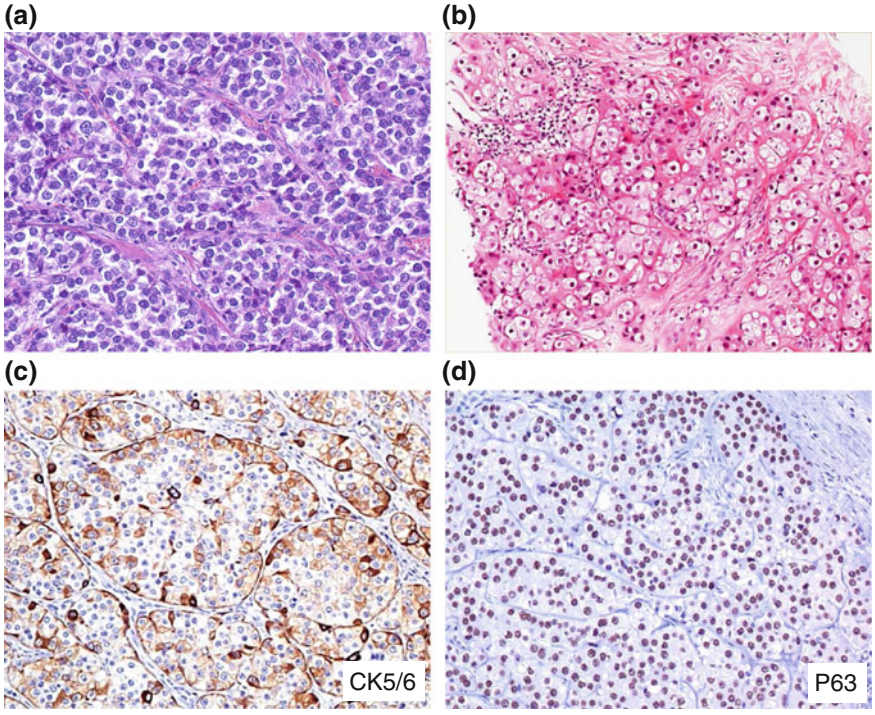

Fig. 5.15 Clear cell carcinoma of the thymus. **a** Tumor cells with clear cytoplasms forming tumor lobules that are separated by delicate fibrous septae; absence of perivascular spaces, no interstitial lymphocytes. **b–d** Another case with lobular growth pattern, however with desmoplastic stroma; on immunohistochemistry, tumor cells stained partially for CK5/6 and extensively for p63. (HE: **a**, **b** ×200; immunoperoxidase: **c**, **d** ×200)

Problems with small biopsies and differential diagnosis Other epithelial tumors with eventual clear cell features (TSQCCs, B3 thymomas, metastasis of clear cell carcinomas) and nonepithelial tumors (seminoma, primary mediastinal B-cell lymphoma, PEComa, and melanoma) need consideration.

Sarcomatoid Carcinoma

Sarcomatoid carcinomas of the thymus are rare and mostly occur in the elderly. Macroscopically, the tumors are usually large, infiltrate adjacent organs and often exhibit extensive necrosis and hemorrhage. Histologically, tumors show highly atypical spindle cells either as the sole component (Fig. 5.16) or adjacent to thymoma (e.g., type A or metaplastic thymoma) or other carcinomas (squamous, lymphoepithelioma-like, or undifferentiated carcinomas). Cases showing frank sarcomatous (heterologous) elements (such as rhabdomyosarcoma, leiomyosarcoma,

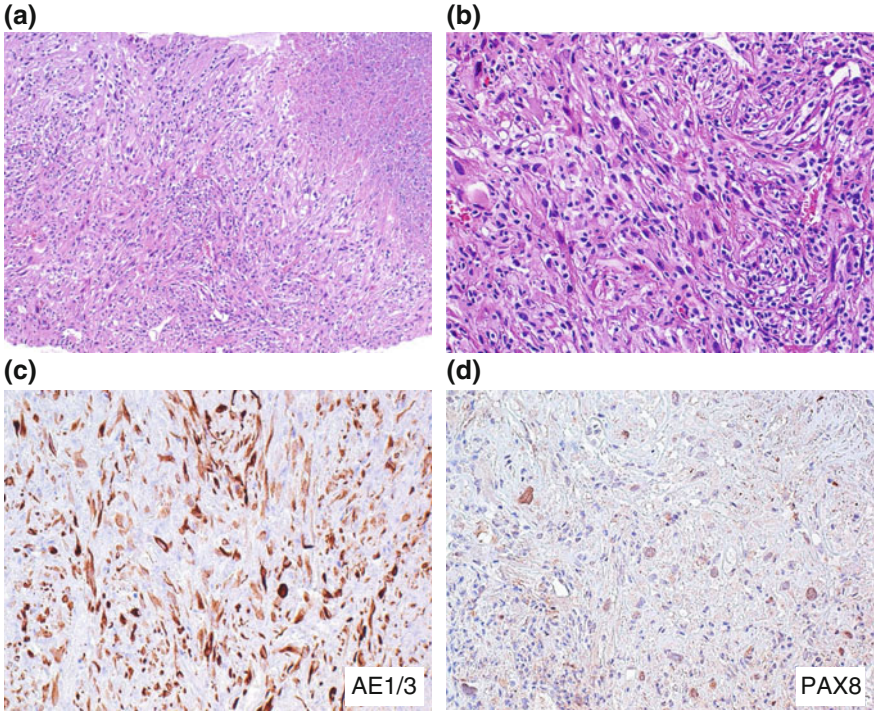

Fig. 5.16 Sarcomatoid carcinoma. **a** Partially necrotic tumor mainly composed of spindle cells with hyperchromatic nuclei. **b** High power view illustrating the sarcoma-like morphology and atypia of tumor cells. **c** Reactivity of tumor cells with the pan-keratin antibody, AE1/3. **d** Expression of PAX8 in some tumor cell nuclei hints to thymic origin of the tumor; extensive sampling and immunohistochemistry did not reveal heterologous elements (e.g., rhabdomyosarcoma or osteosarcoma) (HE: **a** ×50; **b** ×200; immunoperoxidase: **c**, **d** ×200)

or osteosarcoma) are called carcinosarcomas [1]. The prognosis is similar as in TSQCC.

Problems with small biopsies and differential diagnosis The distinction of sarcomatoid carcinoma from atypical type A thymoma has not yet been clearly established. Expression of typical carcinoma markers (CD5, CD117) would speak in favor of sarcomatoid carcinoma. Metaplastic thymoma may show atypical epithelioid cells but the spindle cell component is bland looking and mitoses are rare. Undifferentiated carcinoma is a pleomorphic large-cell carcinoma (see below) but should not exhibit a significant spindle cell component. Bland-looking, desmin(+) myoid cells in a thymoma or thymic carcinoma should not be confused with a rhabdomyosarcoma component of sarcomatoid carcinoma. Immunohistochemisty and molecular studies are needed to identify spindle cell neurooendocrine tumors, thymic sarcomas, mesothelioma, and melanoma. Metastatic sarcomatoid carcinomas to the mediastinum must always be excluded by clinicopathological correlation [1].

Adenocarcinoma

Primary adenocarcinomas of the thymus are very rare. Mucinous, papillary [75, 76], adenoid cystic carcinoma-like carcinomas [71] and "adenocarcinomas, not otherwise specified (NOS)" are distinguished. Papillary carcinomas by definition are low-grade tumors that often occur in association with type A and AB thymomas from which they probably arise. They often show papillary, tubular, and glomeruloid features and psammoma bodies, may express CD5 but are CD117(−) and TTF1(−) but may show an enteric CK20+, CEA+, CDX2+, TTF1(−) immunophenotype (Fig. 5.17). Mucinous carcinomas resemble adenocarcinomas of the gastrointestinal tract, and part of them exhibits an enteric immunophentype as well. Thymic carcinomas with adenoid cystic carcinoma-like features show cribriform and solid tumor areas that are composed of basaloid cells. Other than their salivary gland counterparts they lack an actin+ and CK5/11+ myoepithelial basal cell layer and are CD117(−) but usually p63+ and may also express CD5. Ki67 index is <10%. Adenocarcinomas that do not fulfill criteria of the above specific subtype are classified as "thymic adenocarcinomas, NOS" (Fig. 5.18). The prognosis is similar as in TSQCC.

Problems with small biopsies and differential diagnosis Metastasis to the mediastinum is the main differential diagnosis. Since thymic adenocarcinomas express no site-specific markers, imaging studies are necessary to separate primary from metastatic cancers. In contrast to adenocarcinoma, poorly differentiated mucoepidermoid carcinomas show epidermoid features, and a subset may harbor *MAML2* mutations [77].

NUT Carcinoma

These rare, highly aggressive carcinomas are characterized by translocations of the *NUT* (nuclear protein in testis) gene and are not specific to the thymus [69]. Most commonly, the *NUT* gene is fused to the *BRD4* (bromodomain containing protein 4) gene [t(15;19)]. NUT carcinomas occur in all age groups but typically in adolescents and young adults with advanced tumor stage at presentation. Histologically, small to medium sized sheets of monotonous tumor cells or noncohesive infiltrates without recognizable differentiation often accompanied by inflammatory cells are common. Abrupt transition between undifferentiated cells and foci of keratinization is characteristic. Immunohistochemical detection of NUT protein (or of the fusion gene by FISH) is key, but variable detection of keratins, p63, p40, and CD34 can give a hint to the diagnosis. Napsin and neuroendocrine makers are typically absent, while TTF1 positivity is a rare pitfall (Fig. 5.19). NUT carcinomas are resistant to conventional therapies. Whether "bromodomain and extra terminal" (BET) inhibitors can improve the dismal prognosis (reported mean survival at less than 1 year) needs further studies [78].

Problems with small biopsies and differential diagnosis If small biopsies of NUT carcinomas do not contain foci with keratinization, NUT carcinomas can resemble

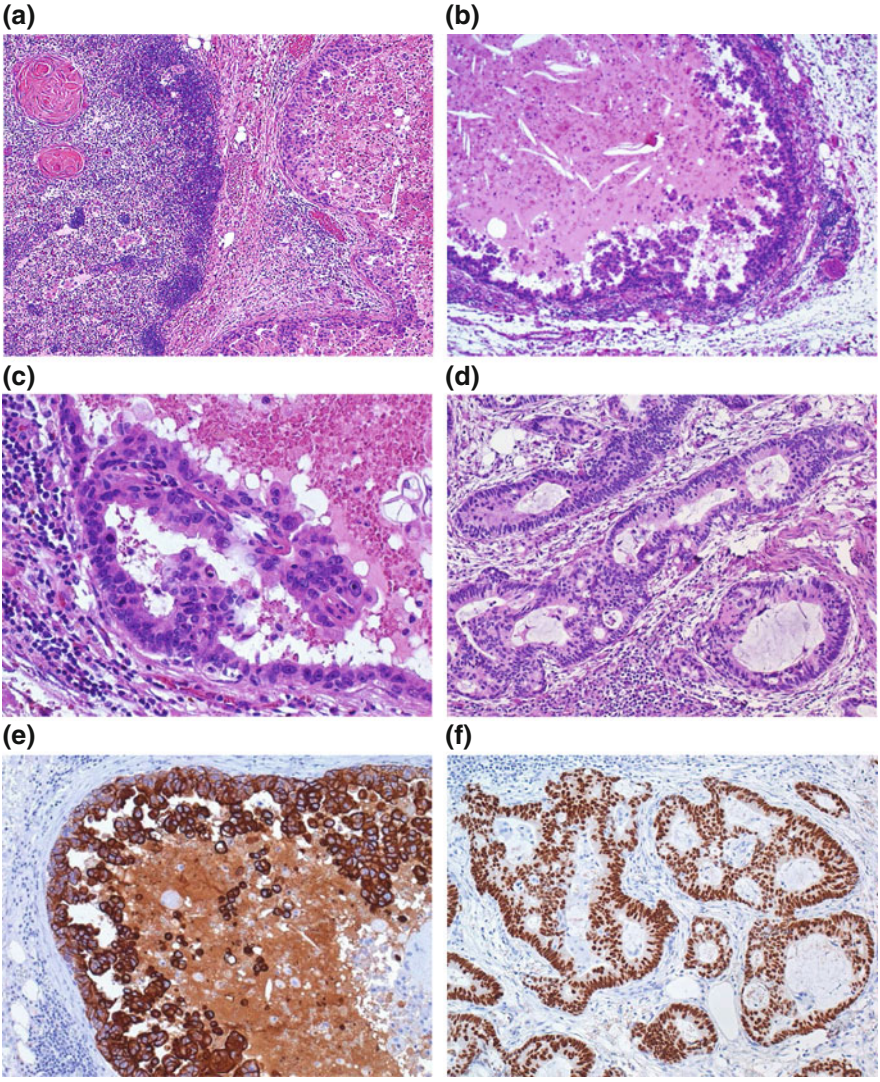

Fig. 5.17 Papillary and glandular adenocarcinoma of the thymus, enteric type. **a** Papillary and cystic tumor component (*right side*) adjacent to thymus with Hassall's corpuscles (*left side*). **b**, **c** Intermediate and high power of the prevailing papillary and cystic component. **d** Minor tumor component with glandular growth pattern resembling colcorectal carcinoma. **e** Strong expression of cytokeratin 20 (CK20). **f** Strong nuclear expression of CDX2; the papillary and glandular component showed the same CK20(+)/CDX2(+) immunophenotype. Staging revealed no other primary tumor (HE: **a** ×25; **b** ×100; **c**, **d** ×200; immunoperoxidase: **e**, **f** ×100)

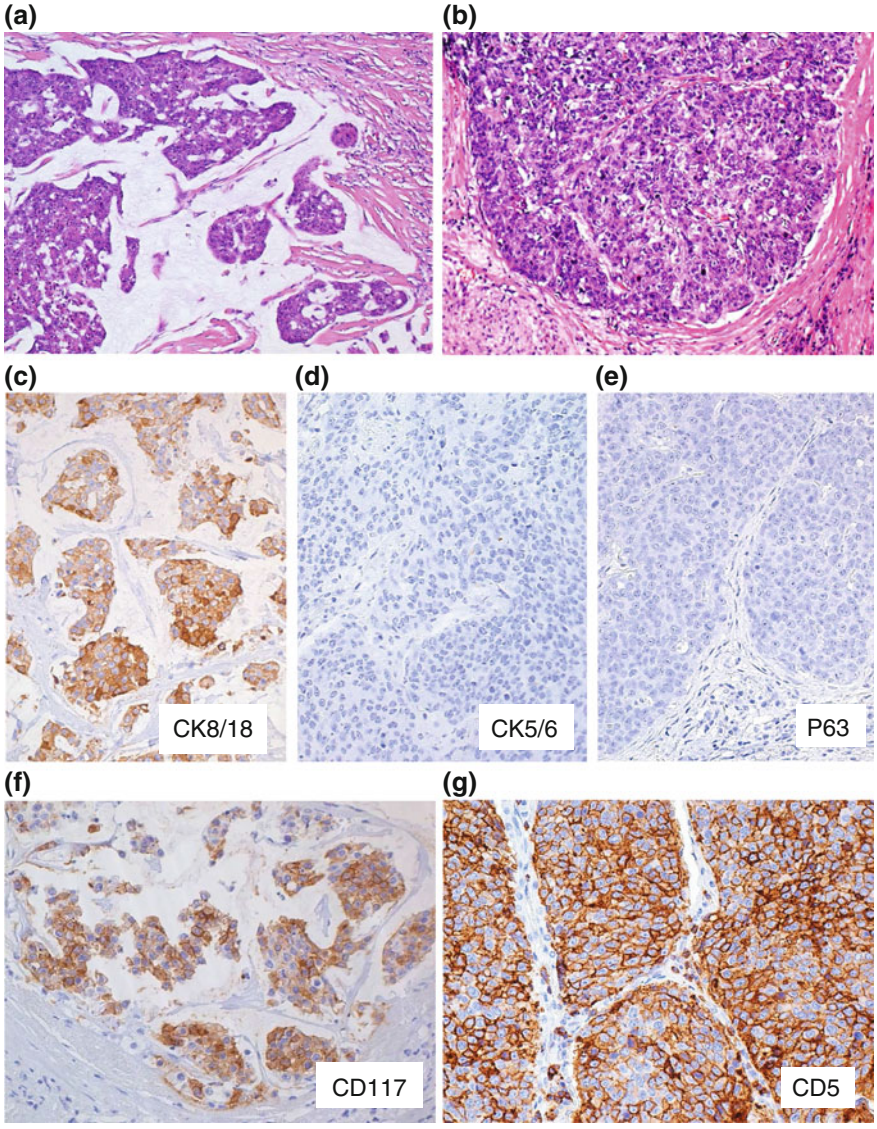

Fig. 5.18 Thymic adenocarcinoma, not otherwise specified (NOS). **a**, **b** Adenocarcinoma of the thymus partially with mucinous morphology, partial with solid growth pattern (considered to be a poorly differentiated, high-grade component). **c–g** Both components showed an unusual cytokeratin 8/18 (CK8/18)(+)/CK5/6(−)/p63(−)/CD117(+)/CD5(+) immunophenotype. Adenocarcinomas, NOS comprise adenocarcinomas that do not fit into any of the specific subtypes. Staging revealed no other primary tumor. (HE: **a**, **b** ×100: immunoperoxidase: **c**, **f** ×100)

lymphomas, various round cell sarcomas, neuroblastoma, and small-cell carcinoma. On the other hand, NUT carcinoma in small biopsies can look like conventional squamous cell carcinoma even on the immunohistochemical level, or mimic EBV (−) lymphoepithelioma-like carcinoma when there is substantial inflammatory stroma. Staining for NUT protein expression may resolve these differential diagnostic challenges.

Undifferentiated Carcinoma

Undifferentiated thymic carcinoma (UTC) is a diagnosis of exclusion. UTC is rare (<1% of TCs) and usually presents with high tumor stage in the elderly. Histologically, UTC shows large, pleomorphic and often anaplastic tumor cells (Fig. 5.19a). Mitoses can be abundant. Necrosis is frequent. On immunohistochemistry, UTC reacts with pancytokeratin antibodies (Fig. 5.19b) and may be

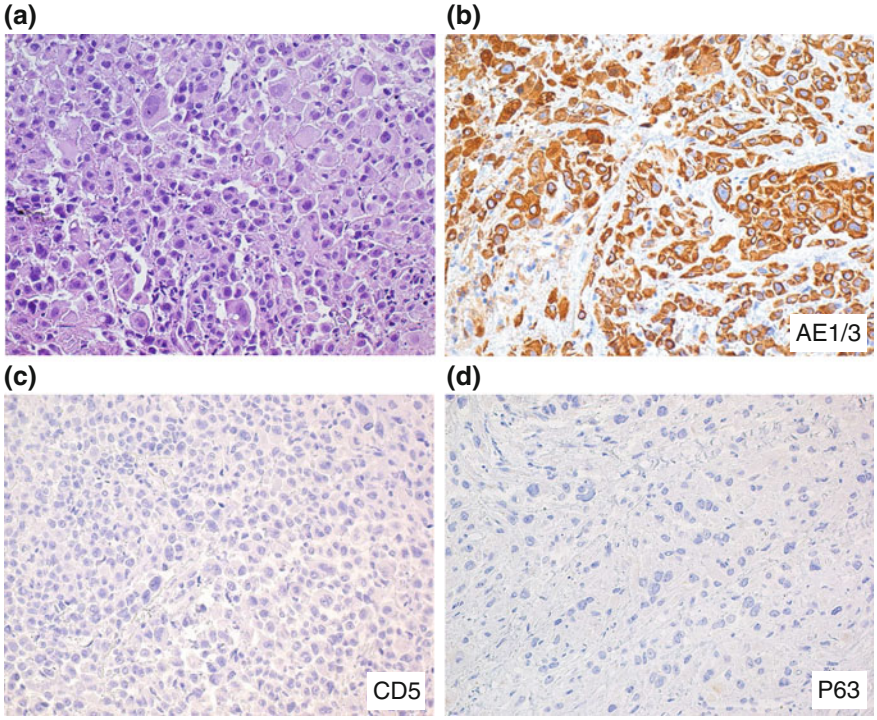

Fig. 5.19 Undifferentiated carcinoma of the thymus. **a** Large and pleomorphic, poorly cohesive tumor cells. **b** Immunoreactivity of tumor cells with the pan-keratin antibody, AE1/3 but no other antikeratin antibodies. **c**, **d** Negative imunoreactivity for CD5 and p63, respectively. By definition, undifferentiated carcinomas must not express CK5/6, CD5, p63, and NUT and are EBV(−) by EBER in situ hybridization (not shown). (HE: **a** ×200; immunoperoxidase: **b–d** ×200)

CD117+. By definition, UTC must not show features of squamous, neuroendocrine, sarcomatoid, and adenocarcinomas. Therefore, the diagnosis of UTC requires immunohistochemistry (Fig. 5.19c, d): expression of CK5/6, p63, p40, CD5, and of neuroendocrine markers must be excluded. OCT3/4, SALL4, and CD30 are negative. Prognosis is poor.

Problems with small biopsies and differential diagnosis The main differential diagnosis of UTS is poorly differentiated, nonkeratinizing thymic squamous cell carcinoma that can be recognized only by immunohistochemical detection of p63/p40, almost consistent expression of CK5/6, and CD5 positivity in 60% of cases [1]. Since neuroendocrine features in large-cell neuroendocrine carcinomas can be unevenly distributed and missed in small biopsies, distinction from UTS may not always be possible. Other differential diagnostic challenges comprise embryonal carcinoma (CD30+, OCT3/4+, SALL4+), seminoma (that can be keratin + and CD117+ but is OCT3/4+ and SALL4+), NUT carcinoma (NUT+, focally CK5/6+ and p63+), melanoma, large-cell lymphoma, and metastasis.

Other Rare Thymic Carcinomas

Adenosquamous carcinoma, hepatoid carcinomas, and thymic carcinoma, not otherwise specified (TC, NOS) are other rare thymic carcinomas [1]. Among the TC, NOS, the "micronodular thymic carcinoma with lymphoid hyperplasia" [49] is not that uncommon. Its architecture mimics "micronodular thymoma with lymphoid stroma (MNT)": well-delineated nodules and strands of epithelial cells are surrounded by a desmoplasia-free, dense lymphoid stroma that commonly contains lymphoid follicles with germinal centers (Fig. 5.20a–c). In contrast to MNT, tumor cells of micronodular thymic carcinoma with lymphoid hyperplasia exhibit clear-cut atypia (Fig. 5.20b), immature, TdT+ T cells are missing (Fig. 5.20d) and epithelial cell proliferation is high (Fig. 5.20e). Another differential diagnosis is lymphoepithelioma-like carcinoma (LELC) that usually shows a desmoplasia-free, dense lymphoid stroma as well. However, epithelial cells of LELC either form delicate epithelial cell networks (Fig. 5.12a–c) or nodules made up of epithelial cell syncytia without distinct cell borders (Fig. 5.12d). EBV association is revealed by EBER in situ hybridization in 50% of thymic LELC but not in micronodular thymic carcinoma with lymphoid hyperplasia.

Neuroendocrine Tumors of the Thymus

General considerations Neuroendocrine tumors (NETs) of the thymus are rare (5% of thymic malignancies) [79–81]. They are now classified and named like respective NETs in the lung, distinguishing low-grade "typical carcinoids" (TC), intermediate-grade "atypical carcinoids" (AC), and high-grade "large -cell neuroendocrine carcinomas" (LCNEC) and "small-cell carcinoma" (SCC) (Table 5.2) [1].

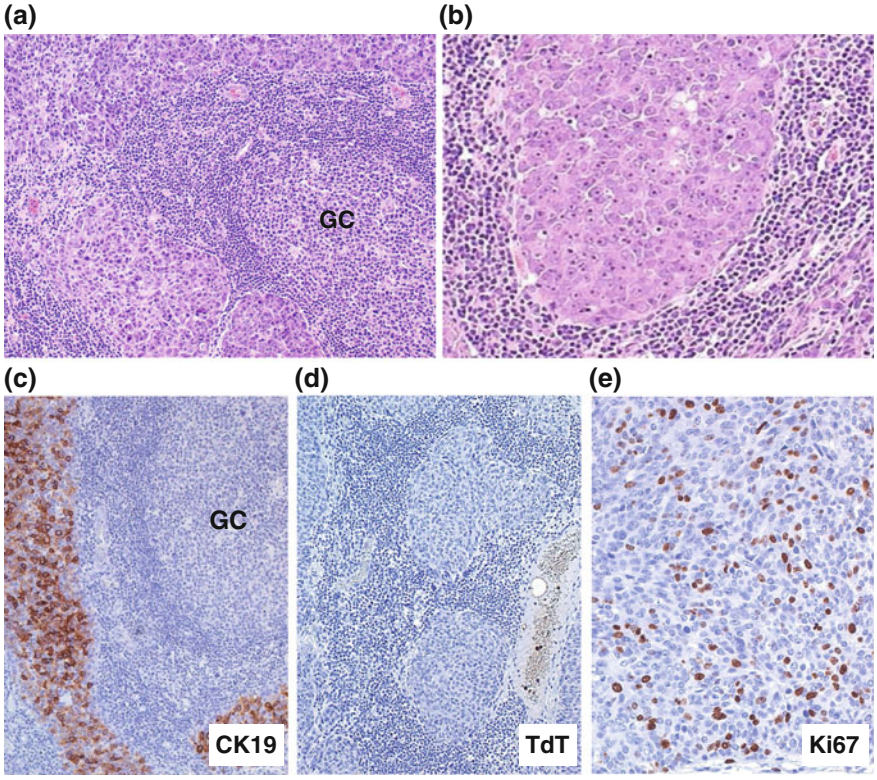

Fig. 5.20 Micronodular thymic carcinoma with lymphoid hyperplasia. **a** Well-delineated nodules of tumor cells set in a desmoplasia-free, lymphoid stroma with florid follicular hyperplasia mimicking micronodular thymoma with lymphoid stroma (MNT) (germinal center, GC; compare with Fig. 5.7). **b** High power reveals atypical polygonal tumor cells with prominent nucleoli. **c** Lymphoid stroma devoid of epithelial cells (cytokeratin 19, CK19; germinal center, GC). **d** Absence of immature, TdT(+) T cells around epithelial cell nodules (opposite to what is typical of MNT). **e** High proliferative rate (HE: **a** ×50; **b** ×400: immunoperoxidase: **c**, **d** ×50; **e** ×200)

Table 5.2 Classification and criteria of thymic neuroendocrine tumors

"Low grade"	"Intermediate grade"	"High grade"	
Typical carcinoid No necrosis <2 mitoses per 2 mm^2	Atypical carcinoid Necrosis and/or 2–10 mitoses per 2 mm^2	LCNEC No small-cell morphology >10 mitoses per 2 mm^2	SCC Small-cell morphology >10 mitoses per 2 mm^2

LCNEC large-cell neuroendocrine carcinoma; *SCC* small-cell carcinoma

In contrast to the lung, SCC is not the most common but the least frequent thymic NET. Paragangliomas are not counted among NETs. TC and AC are much more common and LCNECS are slightly more common in males than females. SCC shows

no sex predilection. Heterogeneous tumors with a LCNEC or SCC component of whatever proportion are called "combined LCNEC" and "combined SCC", respectively, listing the other component(s) thereafter [1]. While the diagnosis of TC, AC, and LCNEC needs demonstration of neuroendocrine markers, SCC may or may not show such features. In addition to histotype, resection status, tumor stage, and recurrence have prognostic impact [82].

Clinical findings Local symptoms are encountered in half of the patients with NETs. Paraneoplastic cushing syndrome, hypercalcemia, hypophosphatemia, and acromegaly are less common and largely restricted to TCs and ACs. Symptoms of a "carcinoid syndrome" are exceptional. Lymph node metastases [54] are very common in all NETs, including TCs and ACs. Distant metastasis to lung, bone, liver, and adrenal glands are common in LCNECs and SCCs.

Molecular features Only TC and AC (25% of cases) are associated with a MEN-1 syndrome [83] and most of these patients are middle-aged males, many with a smoking history. The etiology of other thymic NETs is unknown. The number of genetic alterations increases from TCs through ACs to LCNECs and SCCs [84]. In spite of identical histological features, the genetic aberrations in thymic TC and AC (but not of LCNECs and SCCs) are different from those of their pulmonary counterparts [84].

Typical and Atypical Carcinoids

TCs and ACs show neuroendocrine features in HE-stained sections and immunohistochemical positivity for keratins and neuroendocrine markers. ACs are distinguished by increased proliferation (2–10 mitoses per 2 mm^2) or necrosis. TCs and ACs account for 20 and 50% of thymic NETs, respectively [84]. Two-thirds occur in males (mean age 50 years; pediatric cases are rare) [81]. At first presentation, most cases are in advanced tumor stage (25% show distant metastasis) [84]. The 5-year survival rates are 50–100% for TCs, and 20–80% for ACs [80, 81, 84, 85].

Macroscopically, TCs and ACs are poorly circumscribed, firm tumors, often with calcifications [80]. Except for consistent absence of any necrosis and a mitotic rate of <2 per 2 mm^2 in TCs (Table 5.2), TCs and ACs show identical histology (Figs. 5.21, 5.22): Polygonal or spindle cells with bland nuclei, finely granular chromatin, small nucleoli, and rare pigmentation; variable growth patterns (trabecular, rosetting, solid, glandular) and stroma (vascular, sclerotic, mucinous, chondroid or amyloid containing); and common lymphatic invasion. TCs and ACs consistently express keratins (using AE1/3 or CAM5.2) and neuroendocrine markers (synapthophysin, chromogranin, and CD56) in almost all tumor cells, but not p40. ACTH or somatostatin may be focally positive. TTF1 expression is absent in most cases and TTF1 positivity raises the strong possibility of metastatic disease from the lung [86, 87]. Genetic abnormalities are more common in ACs than TCs, with considerable overlap [84].

Problems with small biopsies and differential diagnosis The distinction between TCs and ACs may not be possible in small biopsies if areas of necrosis or mitotic

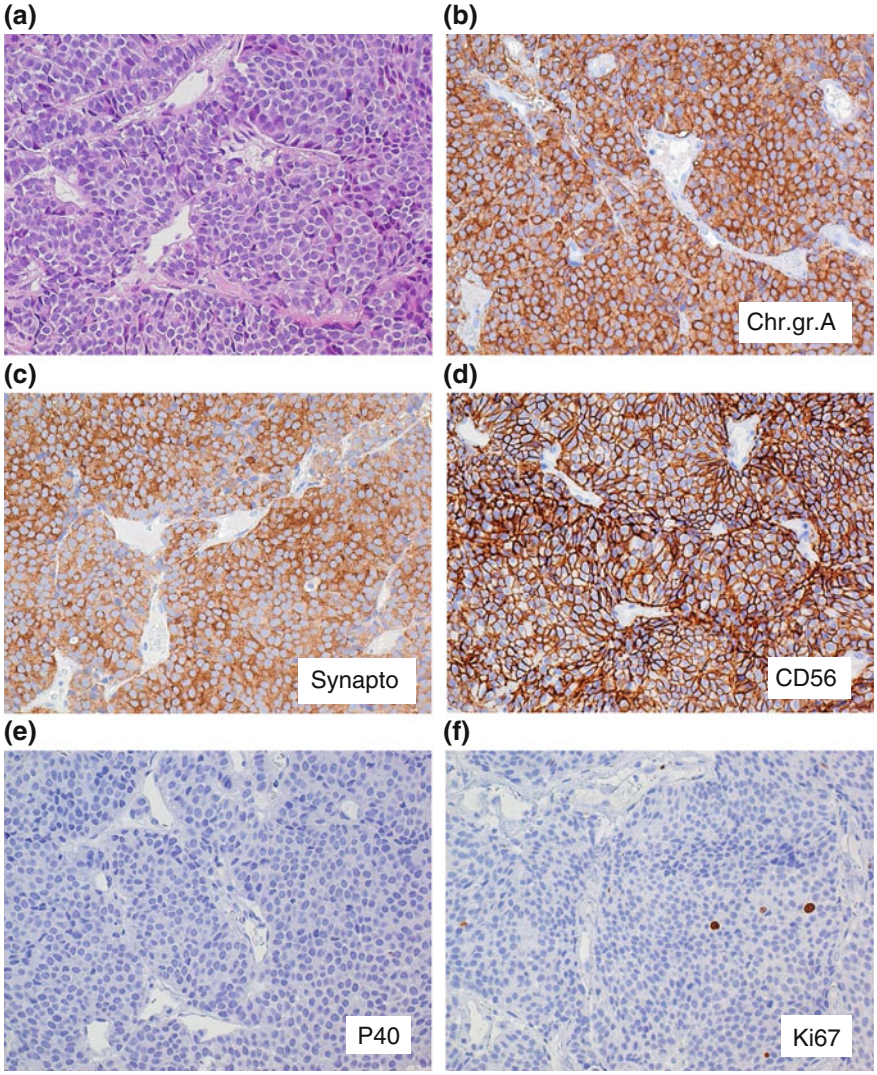

Fig. 5.21 Typical carcinoid of the thymus. **a** Solid growth pattern of polygonal tumor cells with fine nuclear chromatin and inconspicious nucleoli (more growth patterns in Fig. 5.23); delicate vasculature, no necrosis and no interstitial lymphocytes. **b–d** "Full house" pattern of neuroendocrine features in virtually all tumor cells: strong cytoplasmic expression of chromogranin A (chr.gr.A), and synaptophysin (synapto) and CD56 positivity of tumor cell membranes. **e** P40 negativity of tumor cell nuclei. **f** Minimal proliferative activity (Ki67) is typical of typical carcinoid but does not exclude atypical carcinoid. (HE: **a** ×200; immunoperoxidase: **b–f** ×200)

"hot spots" are not sampled to determine the distinguishing diagnostic criteria (Table 5.2). Sampling error may also preclude distinction between ACs and those LCNECs that look like ACs except for their higher mitotic activity of >10 mitoses

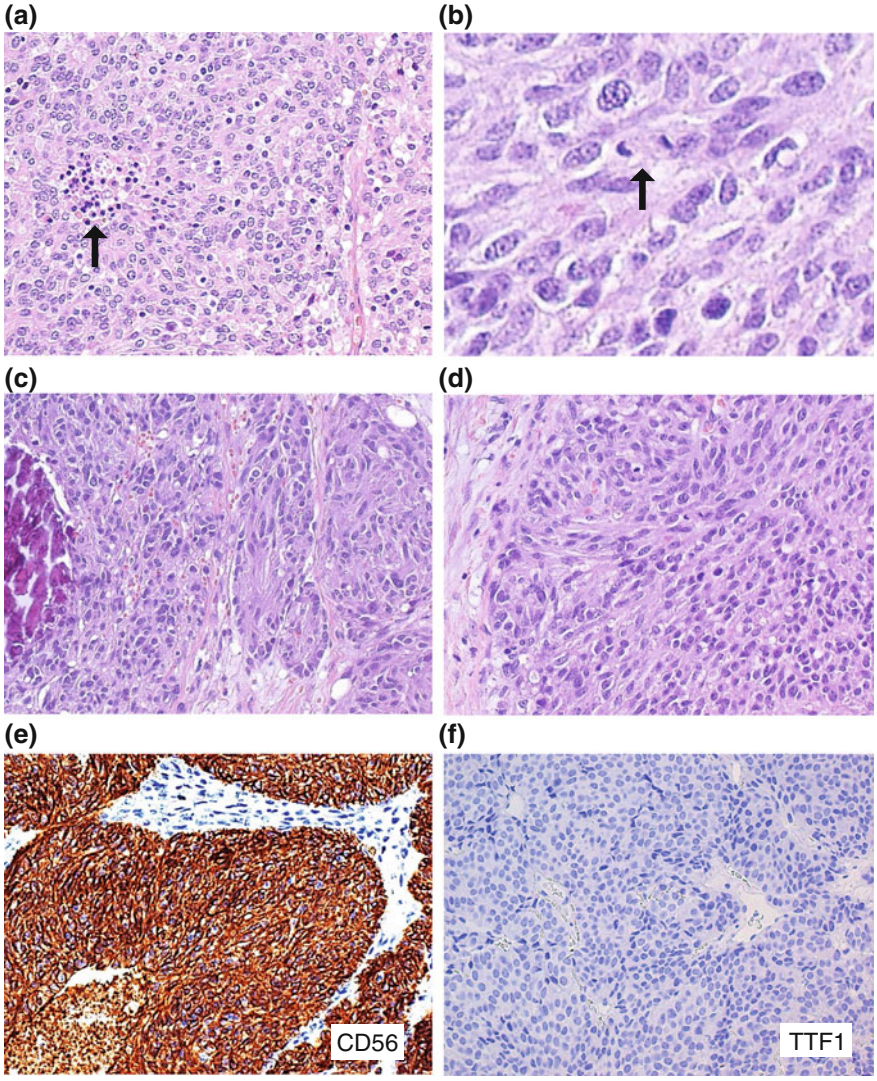

Fig. 5.22 Atypical carcinoid of the thymus. **a** Solid tumor with small comedo-type necrosis (*arrow*) and numerous apoptotic cells (*dark dots*); delicate vasculature. **b** Bland-looking, mitotically active tumor cells with fine chromatin and inconspicuous nuleoli. **c** Calcification of tumor necrosis and rosette formation. **d** Spindling of bland-looking tumor cells, mimicking type A thymoma. **e** CD56 expression along tumor cell membranes in a partially necrotic tumor lobule. **f** TTF1 negativity is characteristic of typical and atypical thymic carcinoids but does not exclude metastasis from a pulmory primary (HE: **a**, **c**, **d** ×200, **b** ×400; immunoperoxidase: **e**, **f** ×200)

per 2 mm^2 (Fig. 5.22). Distinction of carcinoids with amyloid and calcitonin expression from heterotopic or metastatic medullary thyroid carcinomas relies on clinicopathological correlation, as does the distinction of mediastinal metastases of

nonthymic primaries. The suggestion that a PAX8+/TTF1(−) profile may favor a diagnosis of thymic over pulmonary TC and ACs [87] needs confirmation.

Small biopsies may fail to retrieve areas of combined thymic carcinomas, in which TCs and ACs concur with a thymoma or thymic carcinoma. Carcinoids may also represent "somatic type malignancy" in germ cell tumors that may escape recognition in small biopsies [88].

Paraganglioma and type A thymoma may strikingly resemble carcinoids [89], but the former does not express keratins, while the latter is devoid of neuroendocrine markers.

Large-Cell Neuroendocrine Carcinoma

Large-cell neuroendocrine carcinoma (LCNEC) is a high-grade cancer with neuroendocrine, non-small-cell morphology, expression of neuroendocrine markers, high mitotic rate (>10 per 2 mm^2), and frequent necrosis. LCNECs account for 15–25% of thymic NETs. Two-thirds occur in males. Median age at presentation is 51 years [81]. At first presentation, 75% of LCNECs are in advanced tumor stages, 25% show distant metastasis [84]. The 5-year survival rate is 30–66% [84, 90].

Macroscopically, the majority of tumors are poorly circumscribed. Histologically, two patterns occur: One that mimics ACs but shows higher proliferation than AC (>10 mitoses per 2 mm^2) (Fig. 5.23a). The other pattern mimics any other large-cell carcinoma (e.g., nonkeratinizing squamous cell carcinoma or undifferentiated carcinoma) but with strong expression in more than 50% of tumor cells of at least one neuroendocrine marker (synaptophysin, chromogranin, CD56) (Fig, 5.23b, c). Mitoses in such LCNECs are commonly very frequent (>20 per 2 mm^2) and sometimes atypical (Fig. 5.24d). In addition to consistent keratin expression (AE1/3; CAM5.2), CD117 and TTF1 (but not CD5) may rarely be expressed [91]. Genetic aberrations of LCNECs are more common than in ACs but overlap with those of ACs (e.g., *MYC* amplification) [84].

Problems with small biopsies and differential diagnosis Thymic LCNEC must be distinguished from other large-cell TCs with neuroendocrine features (e.g., TSQCC or UTC). By definition, these TCs are positive for neuroendocrine markers in <50% of tumors cells, usually with weak intensity [92]. This differential diagnosis may not be possible in small biopsies. Vice versa, all TCs with large-cell morphology must be tested for neuroendocrine differentiation to exclude LCNEC. As described above, sampling error may preclude definitive distinction of LCNEC with AC-like morphology from AC in small biopsies if the proliferative activity cannot be assessed. The Ki67 index was not approved by the new WHO classification for the distinction of the various thymic neuroendocrine tumors [1]. Of note, the Ki67 index supports a diagnosis of LCNEC over AC only, if it is very high (>50%) (Fig. 5.23e, f).

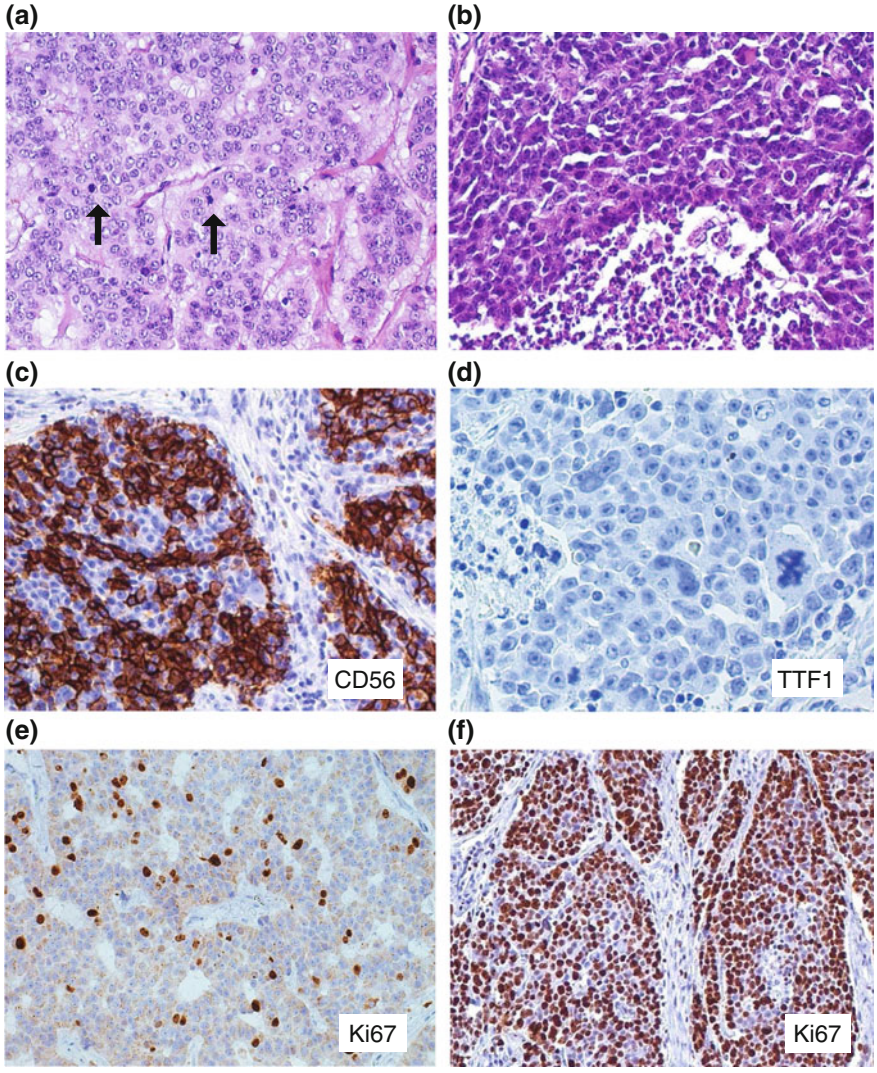

Fig. 5.23 Thymic large-cell neuroendocrine carcinoma (LCNEC). **a** LCNEC resembling atypical carcinoid except for mitoses (*arrows*) in excess of 10/2 mm^2. **b** LCNEC resembling basaloid or undifferentiated carcinoma except for expression of at least one neuroendocrine marker in >50% of tumor cells. **c** CD56 expression: in contrast to most carcinoids, this LCNEC harbors a significant population of CD56(−) tumor cells. **d** TTF1 negativity in thymic LCNEC. **e** Ki67 expression: This intermediate proliferation would be unusually high for typical carcinoids (see Fig. 5.22) but can occur in atypical carcinoids as well as LCNEC; indeed, mitotic count is the only WHO approved proliferation marker to classify thymic neuroendocrine tumors. **f** LCNEC with extremely high Ki67 index that largely excludes an atypical carcinoid but resembles proliferation of small-cell carcinoma. (HE: **a**, **b** ×200; immunoperoxidase: **c**, **e**, **f** ×100; **d** ×200)

Small-Cell Carcinoma

Small-cell carcinoma (SCC) of the thymus is a rare high-grade cancer that resembles its pulmonary counterpart in morphological and genetic terms [84]. It accounts for only 10% of thymic NETs. There is no sex predilection and no association with smoking. Median age at diagnosis is 58 years [1, 2]. At first presentation, most SCC are in advanced tumor stage, commonly with distant metastasis [84, 85]. The median survival is 14 months, the 5-year survival rate close to 0% [84, 90].

Macroscopically, SCC can be soft and extensively necrotic. Tumor cells with scant cytoplasm, nuclei with salt-and-pepper-type chromatin, lack of prominent nucleoli, numerous mitoses and apoptotic bodies, and crush artifacts are typical. SCC usually express keratins but may not be positive for neuroendocrine markers (Fig. 5.24). Frequency of TTF1, CD117 and p16 positivity, and Ki67 indices have not been documented.

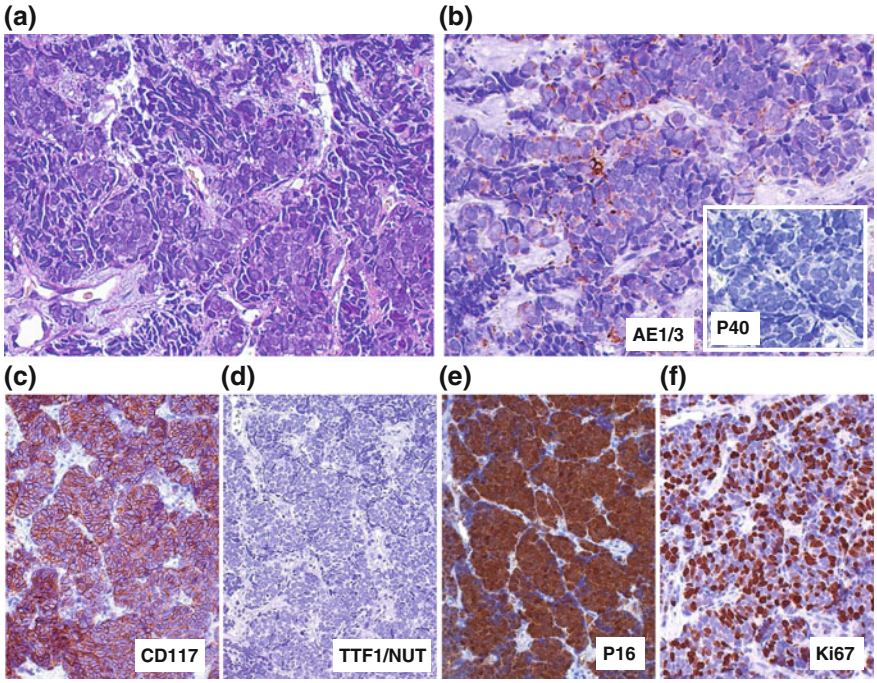

Fig. 5.24 Small-cell carcinoma of the thymus. **a** Intermediate size, crowded tumor cells showing crush artifacts, hyperchromasia and no or inconspicuous nucleoli. **b** Faint diffuse cytoplasmic cytokeratin expression in a minority of tumor cells (AE1/3, anti-pan-keratin antibody); no p40 expression (*inset*). **c** Diffuse membranous expression of CD117. **d** Lack of TTF1 expression (and of NUT, not shown). **e** Strong p16 positivity. **f** High proliferative rate (Ki67); neuroendocrine markers were not detectable. (HE: **a** ×200; immunoperoxidase: **b** ×200; **c**–**f** ×100)

Problems with small biospies and differential diagnosis Distinction of thymic SCC from the metastasis of a pulmonary or other primary is not possible by morphology but requires clinical pathological correlation. Combined SSC may be missed due to sampling error. Immunohistochemistry is usually required to exclude other small-cell tumors such as T-lymphoblastic lymphoma, NUT carcinoma, and sarcomas (e.g., of the Ewing group, rhabdomyosarcoma, synovial sarcoma, or small-cell osteosarcoma).

Thymic Hyperplasias

General considerations Thymic hyperplasias are non-neoplastic enlargements of the thymus due to autoimmune diseases (lymphofollicular hyperplasia), cessation of chemotherapy or immunosuppressive treatment (rebound hyperplasia) or due to largely unknown reasons (true thymic hyperplasia; LESA-like hyperplasia) (see below). The diagnosis of lymphofollicular hyperplasia typically requires histological examination of an apparently normal-for-age looking thymectomy specimen in the setting of Myasthenia gravis, while rebound hyperplasia is usually detected as mild and nonprogressive thymic enlargement by imaging studies during follow-up of cancer patients and mostly does not need resection. By contrast, true thymic hyperplasia and LESA-like hyperplasia can form enormous mediastinal masses with life-threatening respiratory and circulatory complications that often require emergency surgery. Except for rebound hyperplasia, the thymic hyperplasias show different alterations of the normal thymic compartments. The latter are depicted in Fig. 5.25.

True Thymic Hyperplasia

Definition and Terminology: True thymic hyperplasia (TTH) is a tumor-like hyperplasia of the thymus with normal histology for age, a weight above the age-adjusted maximal upper normal limit and unknown etiology and pathogenesis (Table 5.3). Mediastinal fat around the thymus must be removed before measuring the true thymic weight. "Secondary TTHs" have similar histology but known causes.

Epidemiology: TTH is rarer than thymomas and thymic follicular hyperplasia. It typically occurs in newborns, children, and adolescents [93, 94] and rarely in adults [95].

Etiology and Pathogenesis: "Secondary TTH" can occur in Graves and Addison disease, hypopituitarism, acromegaly, Widemann–Beckwich syndrome, and anencephaly [93, 94].

Clinical considerations: Respiratory distress, dysphagia, and hemorrhage are potentially life-threatening symptoms and complications [96, 97].

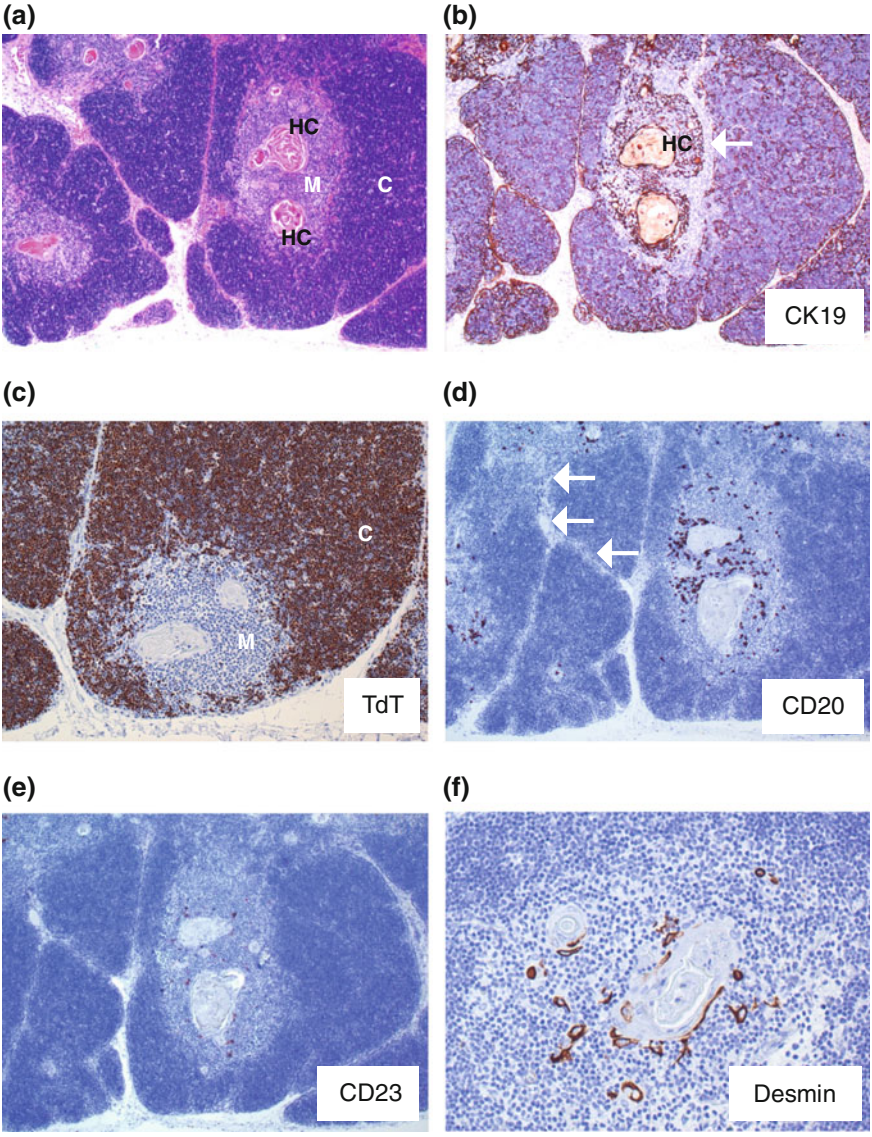

Fig. 5.25 Normal thymus. **a** Compartments and landmarks of the normal thymus: Cortex (C), medulla (M), Hassall's corpuscles (HC). **b** Cytokeratin 19 (CK19) staining highlights an epithelial-free perivascular space (*arrow*) between cortex and medulla (corticomedullary junction). **c** TdT(+) immature T cells in the cortex. **d** CD20(+) B cells in the medulla; *arrows* indicate a perivascular space that reaches from outside the thymic parenchyma through the cortex to the corticomedullary junction. **e** Some medullary B cells are CD23(+); CD23(+) follicular dendritic cell networks are absent. **f** Desmin(+) myoid cells in the medulla close to Hassall's corpuscles (HE: **a** ×25; immunoperoxidase: **b**–**e** ×25; **f** ×200)

Table 5.3 Normal mean and normal maximal values of thymus weights in healthy individuals in relation to age [106–108]

Age	Approximate mean weight (g)	Normal maximal weight (g)
Birth	12	25
12 months	20	45
7–30 years	25–35	50
40–60 years	10–15	30

Macroscopy: The thymus is diffusely enlarged. Weights up to 800 g and maximal diameters of 19 cm are on record [98].

Microscopy: Thymic architecture, including its capsule, cytology, and immunohistological findings (that are usually dispensable) is usually normal for age. Lymphoid follicles are absent and molecular clonality studies reveal polyclonal rearrangements of the T-cell receptor genes. Recently, we observed a primary case in a 3-month-old infant with focal subtle architectural abnormalities of the thymus (slightly misplaced and apparently "immature" medullary islands) (Fig. 5.26). This observation needs confirmation and may hint to pathogenetic heterogeneity underlying TTH.

Problems with small biopsies and differential diagnosis The distinction of TTH (and normal thymus) from B1 thymoma may be impossible in a small biopsy. In addition to age, the following peculiarities may give a clue to the correct diagnosis of B1 thymomas: a thickened fibrous capsule, miniature medullary islands compared to overwhelming cortical areas, lack of Hassall corpuscles, juxtaposition of medullary islands to septal structures, and, in 50% of cases, lack of desmin-positive myoid cells and AIRE-expressing epithelial cells [99]. By contrast, immunophenotyping of the immature, TdT+ lymphoid cells with Ki67 indexes of up to 95% is not distinctive. Normal-for-age looking thymic tissue can represent a sampling error with the relevant process (thymoma, germ cell tumor, lymphoma) having been missed.

If a small biopsy contains only cortical tissue of TTH, normal thymus, or B1 thymoma, T-lymphoblastic lymphoma (T-LBL) enters the differential diagnosis. In about 50% of T-LBLs, the immunophenotype of immature T cells is identical to that of normal cortical thymocytes. Disruption of attenuated epithelial cell networks and molecular clonality studies may be helpful in some but not all such cases. In the other half of T-LBL cases, abnormal immunophenotypes of lymphoblasts with loss of common antigens (e.g., CD1a, CD2, CD5, CD8) or abnormal expression of Notch1 and LMO2 [36, 100] can hint to underlying T-LBL.

In contrast to TTH, the weight gain of thymolipoma is due to an increase of interlobular thymic fat.

Rebound hyperplasia of the thymus: This usually slight, tumor-like enlargement of the histologically normal appearing thymus is mostly fortuitously detected 6–24 months [101], and rarely up to 60 months [102] after severe illnesses,

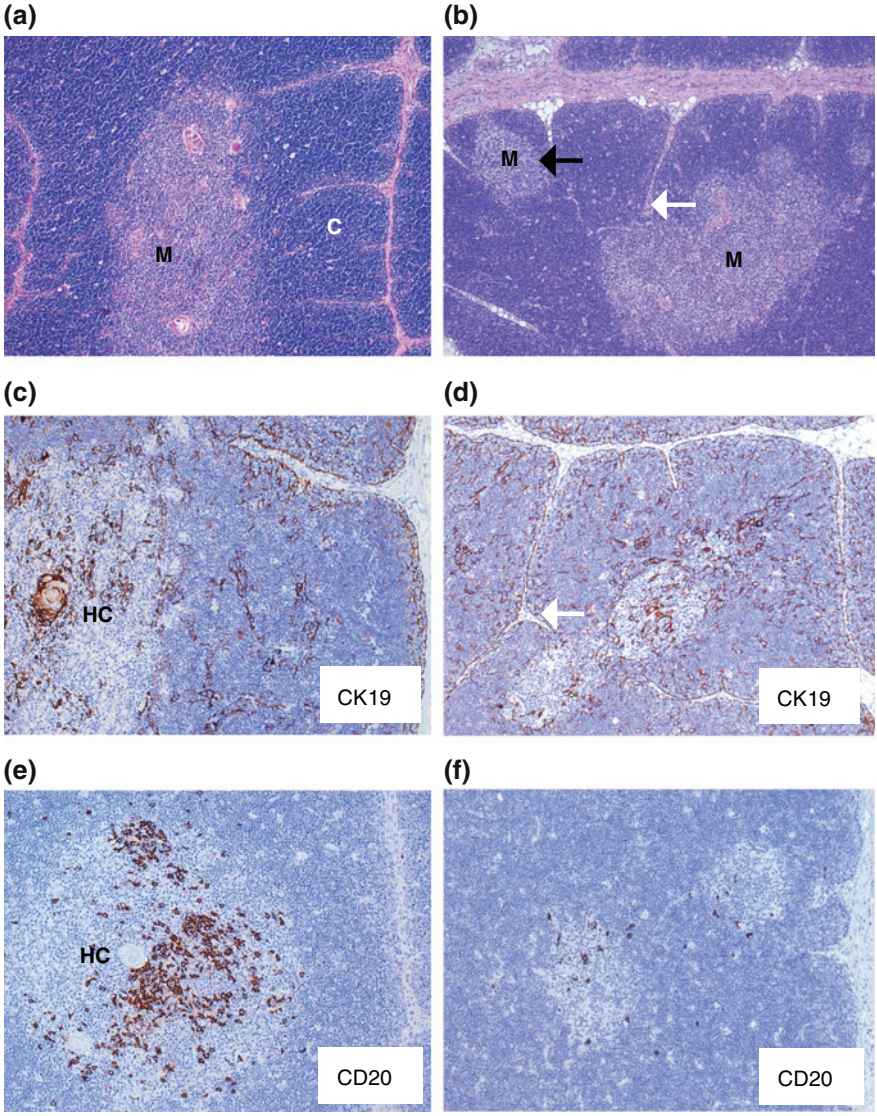

Fig. 5.26 True thymic hyperplasia (TTH) with focal disturbance of thymic architecture: mediastinal mass of 280 g in a 3-month-old infant with respiratory distress. **a**, **c**, **e** Normal-for-age architecture of the thymus in TTH: centrally localized medulla (M) surrounded by cortical areas (C); immunohistochemistry highlights cytokeratin 19 (CK19)(+), well-developed Hassall's corpuscles (HC) (**c**) and normal abundance of CD20(+) medullary B cells (**e**). **b**, **d**, **f** Focally disturbed architecture in this case of TTH: Abnormally localized medullary area (*black arrow*) in the subcortical region (**b**); lack of HC on CK19 staining (**d**); near absence of CD20(+) B cells in light blue-staining medullary areas (**f**). *White arrows* hint to perivascular spaces that were well developed throughout the organ. The frequency of focal architectural changes in TTH as described here is unknown. (HE: **a**, **b** ×50; immunoperoxidase: **c**–**f** ×50)

termination of hypercortisolism [103] or cessation of chemotherapy, radiotherapy or radioactive iodine ablation therapy. It can be misdiagnosed as tumor recurrence [101, 102, 104]. It is detected in 1–12% of patients after cancer therapies [105] and is usually reversible after 12 months [103]. The underlying molecular mechanisms are unknown. It mostly occurs in children and young adults but rarely in patients in their 60s [105]. The histology is normal for age or may look too-young-for-age (own observation) without inflammatory changes. The clinical history is the essential clue to the diagnosis and biopsy may be dispensable.

Overall, because the diagnosis of TTH requires the weight of the thymus, this diagnosis cannot be established on a biopsy alone but requires clinical pathological correlation.

Thymic Follicular Hyperplasia (TFH)

Defintion: Thymuses with TFH show increased numbers of lymphoid follicles in the medulla and perivascular spaces, usually with adequate-for-age corticomedullary architecture (if not treated with corticosteroids). While single lymphoid follicles in rare thymic lobules can occur in healthy persons [109–111], follicles in more than a third of thymic lobules are typical of "pathological TFH" [112].

Epidemiology: The incidence of TFH is unknown. It is mostly found in thymectomy specimens of patients less than 50 years of age with anti-acetylcholine receptor autoantibody-positive "early onset myasthenia gravis" (EOMG) that has an incidence of 1–10 per 1.000.000 per year [113]. TFH occurs in rare MG patients till age 55 in males and 65 in females [114].

Etiology and pathogenesis: In addition to EOMG, thymoma-associated MG (with TFH occurring in the remnant thymus) [115], MG due to autoantibodies to LRP4 [116], and many other autoimmune diseases alone or associated with EOMG can be associated with TFH [98, 117, 118]. The initiation of TFH is unknown [119]. In EOMG, genetic polymorphisms of immune genes [120, 121] apparently favor an abnormal inflammatory response following an elusive trigger that leads to germinal center formation and autoantibody production inside the thymus [122–125]. Functionally abnormal effector and regulatory T cells are involved as well [126]. Since production of autoantibodies in EOMG is higher inside than outside the thymus, the thymus is considered as the primary site of autoimmunization in EOMG [127], providing the rational for early thymectomy in EOMG [119].

Clinical considerations: In contrast to TTH, TFH does not elicit local symptoms. Systemic symptoms in TFH are due to the underlying autoimmune disease(s).

Macroscopy: Size and weight of thymuses with TFH are normal or slightly increased for age [109]. Following corticosteroid treatment, the thymus may shrink substantially.

Histology and immunohistochemistry: Thymuses from corticosteroid-naïve patients show a normal-for-age cortex (Fig. 5.27a) with TdT+ immature T cells. By contrast, medullary areas are expanded at sites where lymphoid follicles occur (Fig. 5.28b–f). Follicles harbor CD21+, CD23+ follicular dendritic cell (FDC) networks (Fig. 5.27f) and may or may not show CD10+, BCL6+, BCL2(−) reactive germinal centers. The number of Hassall corpuscles is normal. Lymphoid follicles disrupt the normally continuous, AE1/3+ epithelial network that separates the medulla from epithelial-free perivascular spaces, leading to fusion and expansion of both compartments in which mature CD20+ B cells and CD3+ T cells are increased [128, 129]. Prolonged TFH can induce thymic epithelial hyperplasia (Fig. 5.27d). Corticosteroid treatment leads to a starry sky pattern and shrinkage of the thymic cortex, and collapse of germinal centers and FDC networks. Prolonged, high-dose corticosteroid and azathioprine treatment can completely abolish cortical structures and TFH [130], induce shrinkage of the medulla and may efface Hassall's corpuscles. A grading system of TFH has been proposed [112]. The detection of developing TFH, and remnant follicles after corticosteroid treatment is facilitated by staining FDC networks for CD23 (Fig. 5.27e, f) [112].

Problems with small biopsies and differential diagnosis Lymphoid follicles adjacent to TdT+ lymphocyte-rich cortical structures or medullary areas with or without Hassall corpuscles can occur in MG-associated type B1 and B2 thymomas. In small biopsies, distinction from TFH may be impossible. However, a thick fibrous capsule or abnormally localized medullary structures abutting fibrous septae may hint to a B1 thymoma, while increased numbers and clustered epithelial cells among immature T cells suggest B2 thymoma [2]. Lymphoid follicles inside micronodular thymoma with lymphoid stroma are also often accompanied by TdT+ T cells, but recognition is easy, if nodules of spindle epithelial cells are sampled. Sampling of remnant thymus with TFH adjacent to an MG-associated thymoma is a pitfall, too. Therefore, correlation with imaging findings is recommended.

"Thymic hyperplasia with lymphoepithelial sialadenitis (LESA)-like features" (Fig. 5.29) is a focal (tumor-like) or diffuse inflammatory (polyclonal) process of the thymus of unknown etiology [131]. Although it is characterized by an almost back-to-back accumulation of B-cell-rich, florid lymphoid follicles in medullary and perivascular structures, it is mostly a fortuitous finding, and myasthenia gravis is typically absent. A hint to the diagnosis (in addition to the clinical setting) is the subtotal lack of TdT+ cortical structures without a history of corticosteroid treatment. Since lymphoepithelial lesions and infiltration of B cells into (epithelial-free) mediastinal fat typically occur (Fig. 5.28), immunohistochemistry and molecular clonality studies must exclude MALT lymphoma.

Other settings, in which lymphoid follicles occur without adjacent TdT+ T cells (and usually in patients without MG) are mediastinal cysts (see below) [132], thymic carcinomas, germ cell tumors (particularly seminoma) [133], and thymic

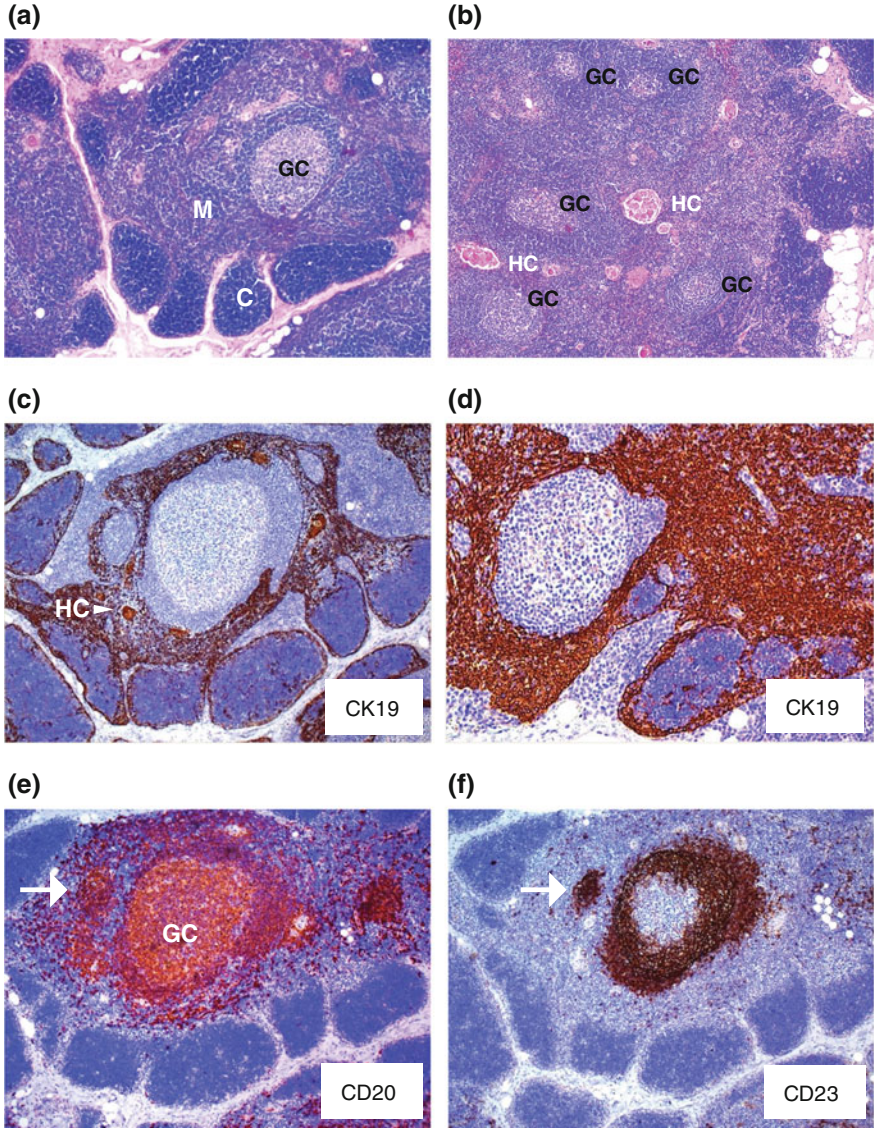

Fig. 5.27 Thymic follicular hyperplasia (TFH) in corticosteroid treatment-naïve Myasthenia gravis. **a** Expansion of the medulla (M) due to a lymphoid follicle with germinal center (GC); well-maintained cortex (C). **b** High-grade (grade IV) TFH with more than three follicles per low power field (×50) [112]. **c**, **d** Cytokeratin 19 (CK19) staining highlights occurrence of follicles in epithelial-free areas; the latter areas represent massively expanded perivascular spaces; well-maintained cortex. **d** Epithelial hyperplasia in long standing TFH can be mistaken for sheets of epithelial tumor cells in small biopsies. **e** Increased number of CD20(+) B cells in the medulla (*white arrow* indicates primary B cell follicle). **f** CD23 staining can identify follicular dendritic cell networks at early stages of follicle development (*white arrow*) prior to the emergence of GC. (HE: **a**, **b** ×50; immunoperoxidase: **c**–**f** ×50)

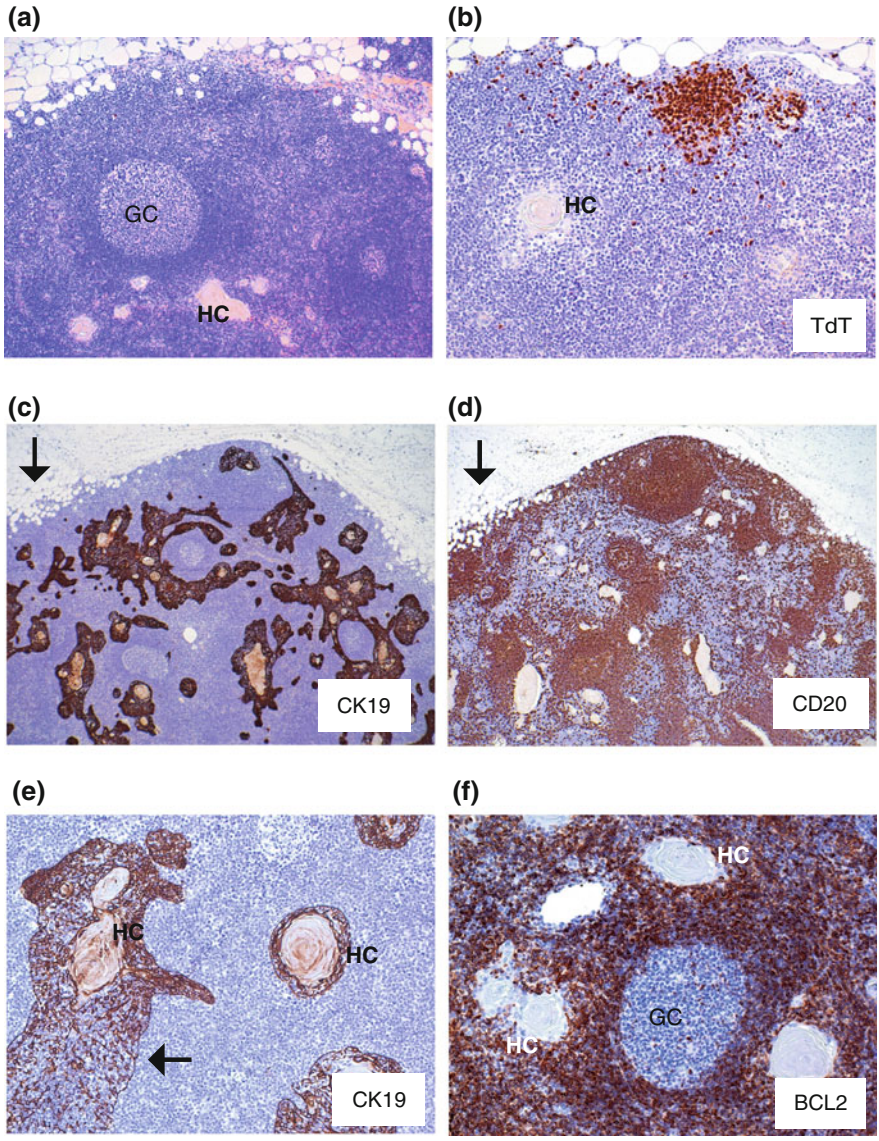

Fig. 5.28 Thymic hyperplasia with lymphoepithelial sialadenitis (LESA)-like features. **a** Well-circumscribed, unencapsulated, lymphocyte-rich tumoral lesion with lymphoid follicular hyperplasia and germinal centers (GC); lack of (dark staining) cortical areas despite absence of antecedent corticosteroid treatment; Hassall's corpuscle (HC). **b** Near absence of cortical structures highlighted by paucity of immature, TdT(+) T cells. **c** Cytokeratin 19 (CK19) staining reveals collapsed epithelial structures and extension of lymphoid infiltrates beyond epithelial networks into mediastinal fat (*arrow*). **d** Abundance of CD20(+) B cells forming follicles and infiltrating mediastinal fat (*arrow*). **e** Identification of lymphoepithelial lesion (*arrow*) on CK19 staining. **f** Reactive, BCL2(−) GC (HE: **a** ×25; immunoperoxidase: **b**, **e**, **f** ×100; **c**, **d** ×25)

MALT lymphoma [133]. Follicular lymphoma and Castleman disease are also worth consideration.

Thymic Cysts

Thymic cysts account for 15% of mediastinal lesions in adults [134]. Primary (congenital) cysts are distinguished from secondary (acquired) cysts. The latter are often "indicator lesion" of underlying inflammatory and neoplastic diseases. Since most cysts elicit symptoms [135], they are usually removed when detected. Biopsy is rarely indicated in operable cases.

Primary (Congenital) Thymic Cysts

These unilocular cysts account for 10–20% of mediastinal cysts, occur in the prevascular and visceral mediastinum of mostly asymptomatic young adults and, on average, measure 4–6 cm [136, 137]. The typically delicate cyst wall often contains thymic tissue and is usually lined by cuboidal epithelium that stains for CK5/6 but not for mesothelial markers (Fig. 5.29). Unilocular thymic cysts can show extensive squamous metaplasia, inflammatory changes, and calcifications. In the latter case, they may not be distinguishable from secondary thymic cysts in small biopsies.

Secondary (Acquired) Thymic Cysts

Secondary thymic cysts develop in connection with neoplastic and inflammatory processes from preexisting thymus and are typically multilocular ("multilocular thymic cysts", MTCs). Thymomas, thymic carcinomas, germ cell tumors, and lymphomas may be accompanied by MTCs [138, 139]. Inflammatory etiologies are HIV infection [140]) and thymic follicular hyperplasia in autoimmune diseases, particularly myasthenia gravis and rheumatoid arthritis [141]. Secondary cysts can measure more than 15 cm in diameter [140], are lined by cuboidal, columnar, or squamous epithelium and typically show thickened cyst walls because of inflammatory infiltrates (including lymphoid follicles) and fibrosis [132, 142]. Necrosis, hemorrhage and cholesterol granulomas are common [132] (Fig. 5.30).

Problems with small biopsies and differential diagnosis: Since MTCs can be much larger than their causative neoplastic etiologies, underlying thymomas, thymic carcinomas [143], germ cell tumors, and lymphomas can be missed in small biopsies [67, 144, 145]. Distinction from bronchogenic cysts with squamous metaplasia can be challenging if smooth muscle is inconspicuous and cartilage is not sampled (Fig. 5.31a, b). Foregut cysts are another differential diagnostic challenge (Fig. 5.31c, d) Squamous pseudoepitheliomatous hyperplasia that can occur

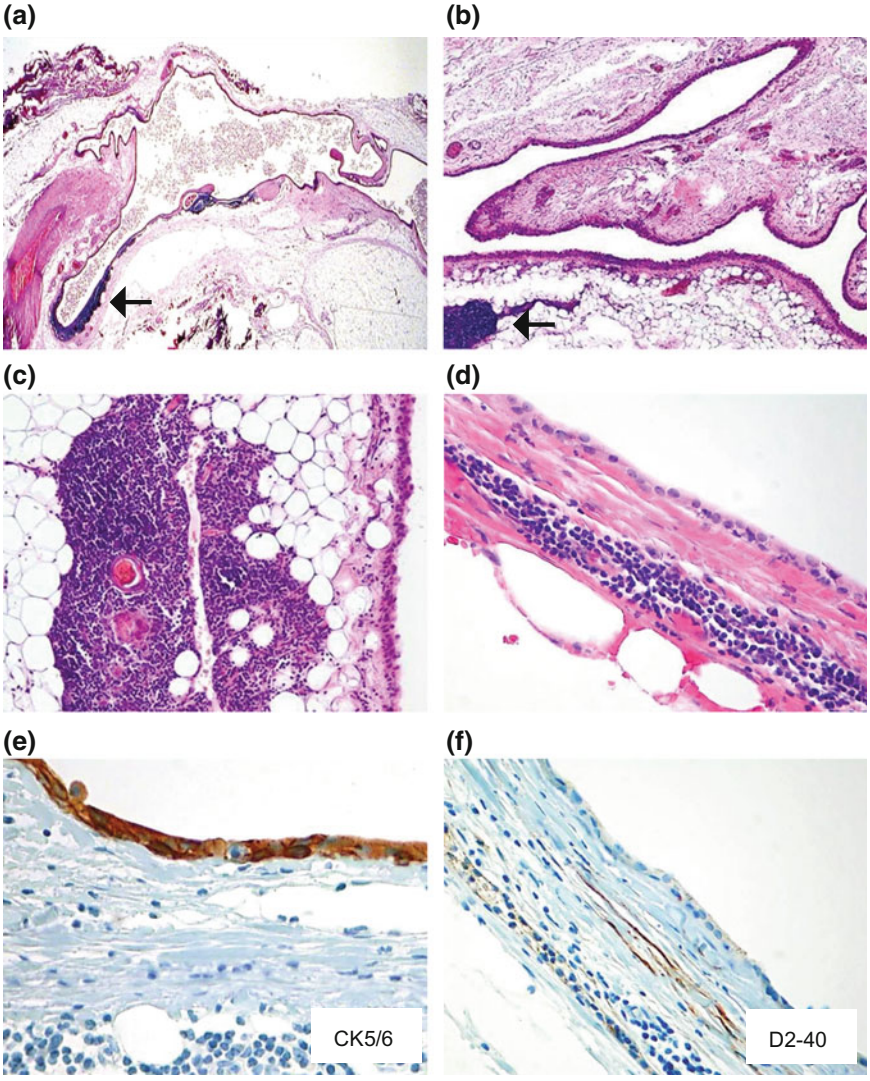

Fig. 5.29 Unilocular thymic cyst. **a–c** Thin-walled cyst intimately associated with normal thymic tissue (*arrows*); lack of thymic folliculat hyperplasia and of inflammatory infiltrates. **d** Lining of cyst wall by cuboidal cells with small round nuclei without atypia. **e** Cells lining the cyst wall express cytokeratin 5/6 (CK5/6). **f** Lining cells do not express mesothelial markers (D2-40) (HE: **a** ×25; **b** ×50; **c** ×100; **d** ×200; immunoperoxidase: **e**, **f** ×200)

in any heavily inflamed MTCs [138], particularly in association with Hodgkin lymphoma, may be impossible to distinguish from well-differentiated cystic TSQCC [67] in small biopsies if epithelial expression of CD5 and CD117 is missing. As to the distinction of MTC-associated thymic follicular hyperplasia and MALT lymphoma, lymphoepithelial lesions and monotypic, mostly IgA+ plasma

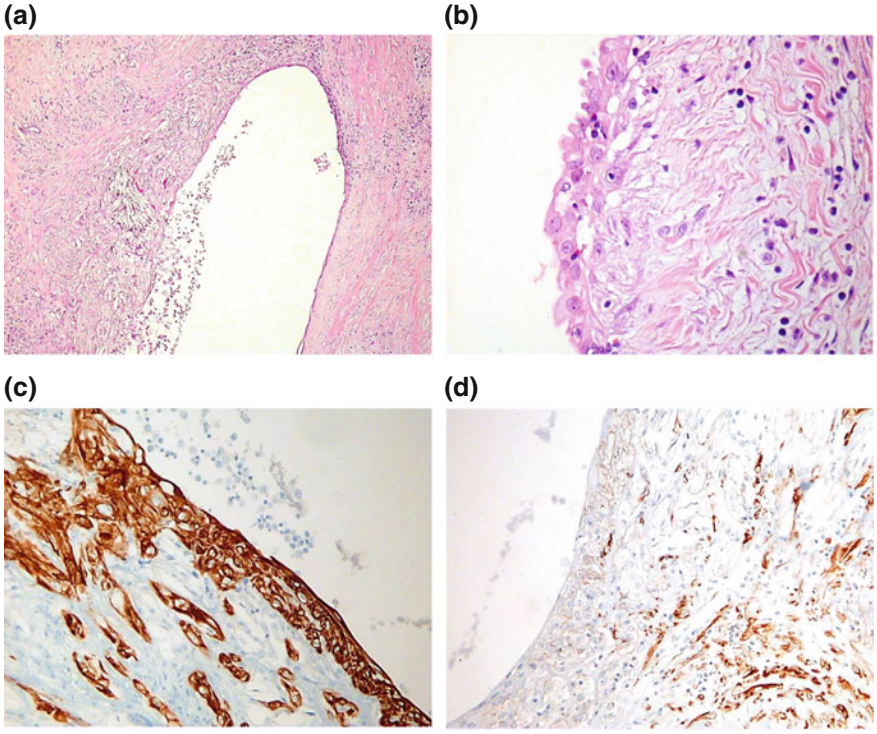

Fig. 5.30 Multilocular thymic cyst. **a** Thick-walled cyst with extensive collagen deposition, cholesterol granuloma, and extensive denudation of cellular lining. **b** Remnant lining cells with squamous features. **c** Cytokeratin 5/6 (CK5/6) expression by stratified epithelial cells lining the cyst wall. **d** Absence of mesothelial markers in lining cells (D2-40). No underlying etiology was detected in this case (HE: **a** ×50; **b** ×200; immunoperoxidase: **c**, **d** ×200)

cells argue in favor of lymphoma. Of note, cystic variants of virtually any primary mediastinal tumor must be distinguished from MTC (Fig. 5.31e, f) [67, 145–151].

Take Home Messages

1. Thymoma classification is feasible on the basis of HE-stained sections in almost all resection specimens; rarely, standard antibodies (to TdT, keratins, p40, CD20) are needed to distinguish thymoma subtypes and resolve rare findings (e.g., keratin loss in thymomas).
2. The distinction between thymoma and thymic carcinoma (TC) is based on HE morphology but CD5, CD117, and TdT immunohistochemistry is a usefull

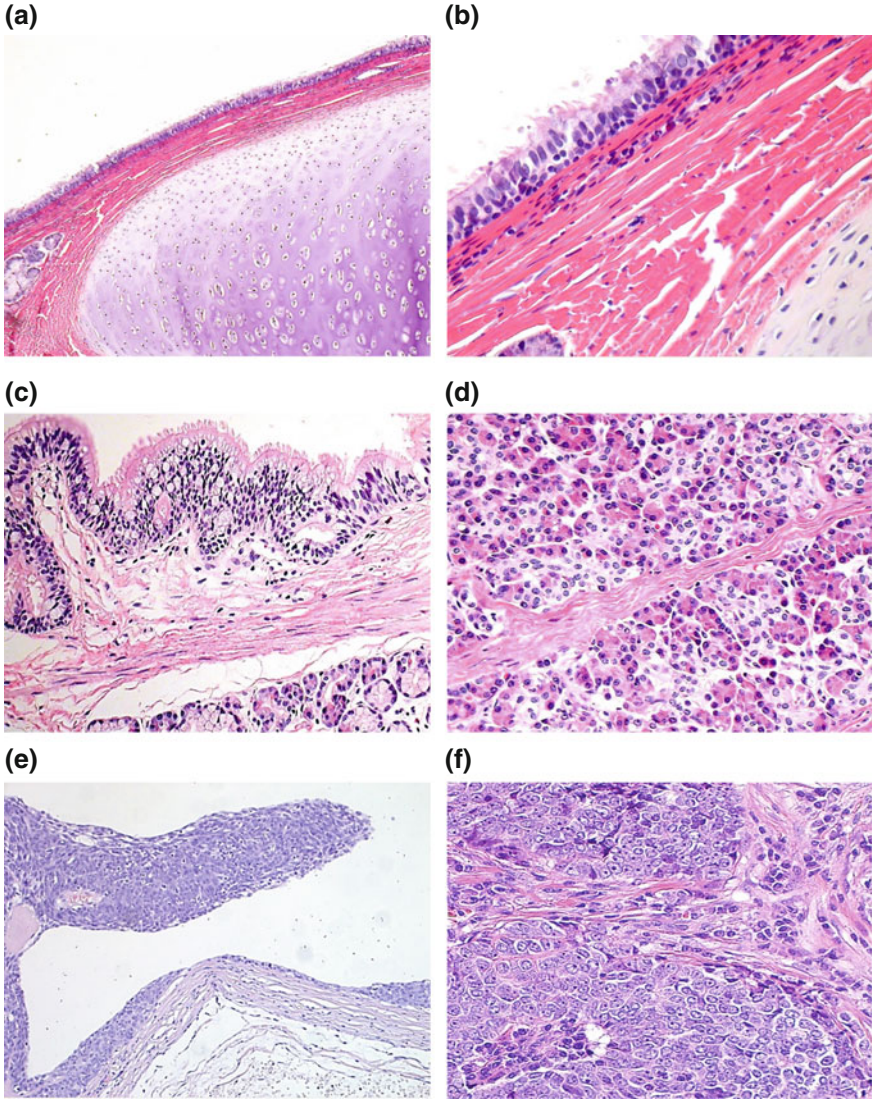

Fig. 5.31 Developmental and neoplastic cysts to be considered in the differential diagnosis of thymic cysts. **a**, **b** Bronchogenic cyst lined by bland ciliated epithelial cells; the cyst wall contains cartilage and small salivary type glands (*left* in **a**). **c**–**d** Foregut cyst with bland-looking ciliated epithelial cells lining the cyst wall; smooth muscle cells and heterotopic exocrine pancreatic glands in the cyst wall; this setting requires exclusion of teratoma. **e**, **f** Cystic nonkeratinizing squamous cell carcinoma; the cyst wall is lined by dysplastic epithelial cells without infiltative growth in this area (**e**); another area with numerous plasma cells inside the carcinoma and at the plump invasion front. (HE: **a**, **c**, **e** ×50; **b**, **d**, **f** ×200)

adjunct. Neuroendocrine markers may be needed to recognize carcinoids mimicking type A and B3 thymomas and TC.
3. The diagnosis of some TC subtypes (TSQCC, undifferentiated carcinoma, NUT carcinoma) and the distinction between TC and large-cell neuroendocrine carcinoma *by definition* require immunohistochemistry (CK5/6, p40, CD5, NUT, neuroendocrine markers) and EBER-ISH.
4. Apart from CD5+/CD117+ TSQCC, other mediastinal carcinomas and neuroendocrine tumors need staging investigations to distinguish thymic from extrathymic primaries.
5. Diagnoses based on small biopsies face the problem of sampling error and should be rendered only after clinicopathological correlation and with a comment of caution, taking into account (i) the occurrence of two or more histological patterns in many thymoma and some TC; (ii) the focal morphological overlap between thymomas, normal and hyperplastic thymus and thymic lymphomas; (iii) the occurrence of pseudoepitheliomatous hyperplasia due to inflammatory and neoplastic etiologies (e.g., Hodgkin lymphoma).
6. Acquired (multilocular) thymic cysts should be understood as "indicator lesions" of underlying inflammatory and neoplastic causes arguing for extensive sampling and thorough search for the causative etiology.

References

1. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG, editors. *WHO classification of tumours of the lung, pleura, thymus and heart*. 4th edn. Vol. 7. 2015: IARC.
2. Marx A, et al. The 2015 World Health Organization classification of tumors of the thymus: continuity and changes. J Thorac Oncol. 2015;10(10):1383–95.
3. Marx A, et al. Thymoma related myasthenia gravis in humans and potential animal models. Exp Neurol. 2015;270:55–65.
4. Moran CA, et al. Thymomas I: a clinicopathologic correlation of 250 cases with emphasis on the World Health Organization schema. Am J Clin Pathol. 2012;137(3):444–50.
5. Strobel P, et al. Tumor recurrence and survival in patients treated for thymomas and thymic squamous cell carcinomas: a retrospective analysis. J Clin Oncol. 2004;22(8):1501–9.
6. Moran CA, Suster S. On the histologic heterogeneity of thymic epithelial neoplasms. Impact of sampling in subtyping and classification of thymomas. Am J Clin Pathol. 2000;114(5):760–6.
7. Detterbeck FC, et al. The Masaoka-Koga stage classification for thymic malignancies: clarification and definition of terms. J Thorac Oncol. 2011;6(7 Suppl 3):S1710–6.
8. Rotstein DL, Bril V. A family with myasthenia gravis with and without thymoma. Can J Neurol Sci. 2012;39(4):539–40.
9. Pande M, et al. Cancer spectrum in DNA mismatch repair gene mutation carriers: results from a hospital based Lynch syndrome registry. Fam Cancer. 2012;11(3):441–7.
10. Gadalla SM, et al. A population-based assessment of mortality and morbidity patterns among patients with thymoma. Int J Cancer. 2011;128(11):2688–94.
11. Strobel P, et al. Corticomedullary differentiation and maturational arrest in thymomas. Histopathology. 2014;64(4):557–66.

12. Girard N, et al. Comprehensive genomic analysis reveals clinically relevant molecular distinctions between thymic carcinomas and thymomas. Clin Cancer Res. 2009;15(22): 6790–9.
13. Rajan A, Girard N, Marx A. State of the art of genetic alterations in thymic epithelial tumors. J Thorac Oncol. 2014;9(9 Suppl 2):S131–6.
14. Petrini I, et al. Copy number aberrations of genes regulating normal thymus development in thymic epithelial tumors. Clin Cancer Res. 2013;19(8):1960–71.
15. Zettl A, et al. Recurrent genetic aberrations in thymoma and thymic carcinoma. Am J Pathol. 2000;157(1):257–66.
16. Petrini I, et al. A specific missense mutation in GTF2I occurs at high frequency in thymic epithelial tumors. Nat Genet. 2014;46(8):844–9.
17. Strobel P, et al. Thymic carcinoma with overexpression of mutated KIT and the response to imatinib. N Engl J Med. 2004;350(25):2625–6.
18. Marx A, Weis CA. Sunitinib in thymic carcinoma: enigmas still unresolved. Lancet Oncol. 2015;16(2):124–5.
19. Marx A, et al. Thymoma and paraneoplastic myasthenia gravis. Autoimmunity. 2010; 43(5–6):413–27.
20. Marchevsky A, et al. Policies and reporting guidelines for small biopsy specimens of mediastinal masses. J Thorac Oncol. 2011;6(7 Suppl 3):S1724–9.
21. Nonaka D, Rosai J. Is there a spectrum of cytologic atypia in type a thymomas analogous to that seen in type B thymomas? A pilot study of 13 cases. Am J Surg Pathol. 2012;36(6): 889–94.
22. Jain RK, et al. WHO types A and AB thymomas: not always benign. Mod Pathol. 2010; 23(12):1641–9.
23. Green AC, et al. Type A and AB thymomas: histological features associated with increased stage. Histopathology. 2015;66(6):884–91.
24. Roden AC, et al. Diagnostic significance of cell kinetic parameters in World Health Organization type A and B3 thymomas and thymic carcinomas. Hum Pathol. 2015; 46(1):17–25.
25. Shilo K, et al. Diffuse thymic fibrosis: histologic pattern of injury or distinct entity? Am J Surg Pathol. 2010;34(2):211–5.
26. Zhang Z, et al. Inflammatory pseudotumor of the thymus: A case report and review of the literature. Oncol Lett. 2014;7(5):1414–8.
27. Pan CC, Chen WY, Chiang H. Spindle cell and mixed spindle/lymphocytic thymomas: an integrated clinicopathologic and immunohistochemical study of 81 cases. Am J Surg Pathol. 2001;25(1):111–20.
28. Weis CA, et al. The impact of thymoma histotype on prognosis in a worldwide database. J Thorac Oncol. 2015;10(2):367–72.
29. Okumura M, et al. The World Health Organization histologic classification system reflects the oncologic behavior of thymoma: a clinical study of 273 patients. Cancer. 2002; 94(3):624–32.
30. Guerrera F, et al. Does the World Health Organization histological classification predict outcomes after thymomectomy? Results of a multicentre study on 750 patients. Eur J Cardiothorac Surg. 2015;48(1):48–54.
31. Weissferdt A, et al. Spindle cell thymomas: an immunohistochemical study of 30 cases. Appl Immunohistochem Mol Morphol. 2011;19(4):329–35.
32. Petrini I, et al. Copy number aberrations of BCL2 and CDKN2A/B identified by array-CGH in thymic epithelial tumors. Cell Death Dis. 2012;3:e351.
33. Chen G, et al. New WHO histologic classification predicts prognosis of thymic epithelial tumors: a clinicopathologic study of 200 thymoma cases from China. Cancer. 2002;95(2): 420–9.

34. Penzel R, et al. Clusters of chromosomal imbalances in thymic epithelial tumours are associated with the WHO classification and the staging system according to Masaoka. Int J Cancer. 2003;105(4):494–8.
35. Lee GY, et al. Genome-wide genetic aberrations of thymoma using cDNA microarray based comparative genomic hybridization. BMC Genom. 2007;8:305.
36. Menter T, et al. Diagnostic Utility of the Germinal Center-associated Markers GCET1, HGAL, and LMO2 in Hematolymphoid Neoplasms. Appl Immunohistochem Mol Morphol. 2015;23(7):491–8.
37. Ertel V, et al. Thymoma with molecularly verified "conversion" to T lymphoblastic leukemia/lymphoma over 9 years. Leuk Lymphoma. 2013;54(12):2765–8.
38. Inoue M, et al. Correlating genetic aberrations with World Health Organization-defined histology and stage across the spectrum of thymomas. Cancer Res. 2003;63(13):3708–15.
39. Adam P, et al. Thymoma with loss of keratin expression (and giant cells): a potential diagnostic pitfall. Virchows Arch. 2014;465(3):313–20.
40. Chalabreysse L, et al. Correlation of the WHO schema for the classification of thymic epithelial neoplasms with prognosis: a retrospective study of 90 tumors. Am J Surg Pathol. 2002;26(12):1605–11.
41. Korst RJ, et al. Adjuvant radiotherapy for thymic epithelial tumors: a systematic review and meta-analysis. Ann Thorac Surg. 2009;87(5):1641–7.
42. Gomez D, et al. Radiation therapy definitions and reporting guidelines for thymic malignancies. J Thorac Oncol. 2011;6(7 Suppl 3):S1743–8.
43. Myojin M, et al. Stage III thymoma: pattern of failure after surgery and postoperative radiotherapy and its implication for future study. Int J Radiat Oncol Biol Phys. 2000; 46(4):927–33.
44. Venuta F, et al. Long-term outcome after multimodality treatment for stage III thymic tumors. Ann Thorac Surg. 2003;76(6):1866–72. (discussion 1872).
45. Rod J, et al. Surgical management of thymic epithelial tumors in children: lessons from the French Society of Pediatric Oncology and review of the literature. Pediatr Blood Cancer. 2014;61(11):1910–5.
46. Petrini I, et al. Whole genome and transcriptome sequencing of a B3 thymoma. PLoS ONE. 2013;8(4):e60572.
47. de Jong WK, et al. Thymic epithelial tumours: a population-based study of the incidence, diagnostic procedures and therapy. Eur J Cancer. 2008;44(1):123–30.
48. Strobel P, et al. Micronodular thymoma: an epithelial tumour with abnormal chemokine expression setting the stage for lymphoma development. J Pathol. 2005;207(1):72–82.
49. Weissferdt A, Moran CA. Micronodular thymic carcinoma with lymphoid hyperplasia: a clinicopathological and immunohistochemical study of five cases. Mod Pathol. 2012;25(7): 993–9.
50. Cheuk W, Tsang WY, Chan JK. Microthymoma: definition of the entity and distinction from nodular hyperplasia of the thymic epithelium (so-called microscopic thymoma). Am J Surg Pathol. 2005;29(3):415–9.
51. Ruffini E, et al. Tumours of the thymus: a cohort study of prognostic factors from the European Society of Thoracic Surgeons database. Eur J Cardiothorac Surg. 2014;46(3): 361–8.
52. Omasa M, et al. Postoperative radiotherapy is effective for thymic carcinoma but not for thymoma in stage II and III thymic epithelial tumors: the Japanese Association for Research on the Thymus Database Study. Cancer. 2015;121(7):1008–16.
53. Ahmad U, et al. Thymic carcinoma outcomes and prognosis: results of an international analysis. J Thorac Cardiovasc Surg. 2015;149(1):95–100, 101 e1–2.
54. Kondo K, Monden Y. Lymphogenous and hematogenous metastasis of thymic epithelial tumors. Ann Thorac Surg. 2003;76(6):1859–64. (discussion 1864–5).
55. Huang J, et al. Comparison of patterns of relapse in thymic carcinoma and thymoma. J Thorac Cardiovasc Surg. 2009;138(1):26–31.

56. Thomas A, et al. Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial. Lancet Oncol. 2015;16(2):177–86.
57. Strobel P, et al. Sunitinib in metastatic thymic carcinomas: laboratory findings and initial clinical experience. Br J Cancer. 2010;103(2):196–200.
58. Girard N, et al. Thymic epithelial tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v40–55.
59. Inoue M, et al. Chromosome 6 suffers frequent and multiple aberrations in thymoma. Am J Pathol. 2002;161(4):1507–13.
60. Wang Y, et al. Mutations of epigenetic regulatory genes are common in thymic carcinomas. Sci Rep. 2014;4:7336.
61. Hirabayashi H, et al. p16INK4, pRB, p53 and cyclin D1 expression and hypermethylation of CDKN2 gene in thymoma and thymic carcinoma. Int J Cancer. 1997;73(5):639–44.
62. Tateyama H, et al. p 53 protein expression and p53 gene mutation in thymic epithelial tumors. An immunohistochemical and DNA sequencing study. Am J Clin Pathol. 1995'104(4): 375–81.
63. Moreira AL, et al. Massively parallel sequencing identifies recurrent mutations in TP53 in thymic carcinoma associated with poor prognosis. J Thorac Oncol. 2015;10(2):373–80.
64. Roden AC, et al. Analysis of MAML2 rearrangement in mucoepidermoid carcinoma of the thymus. Hum Pathol. 2013;44(12):2799–805.
65. Zhao Y, et al. Surgical treatment and prognosis of thymic squamous cell carcinoma: a retrospective analysis of 105 cases. Ann Thorac Surg. 2013;96(3):1019–24.
66. Vladislav T, et al. Extrathoracic metastases of thymic origin: a review of 35 cases. Mod Pathol. 2012;25(3):370–7.
67. Weissferdt A, Kalhor N, Moran CA. Cystic well-differentiated squamous cell carcinoma of the thymus: a clinicopathological and immunohistochemical study of six cases. Histopathology. 2016;68(3):333–8.
68. Ruffini E, et al. Thymic carcinoma: a cohort study of patients from the European society of thoracic surgeons database. J Thorac Oncol. 2014;9(4):541–8.
69. French C. NUT midline carcinoma. Nat Rev Cancer. 2014;14(3):149–50.
70. Brown JG, et al. Thymic basaloid carcinoma: a clinicopathologic study of 12 cases, with a general discussion of basaloid carcinoma and its relationship with adenoid cystic carcinoma. Am J Surg Pathol. 2009;33(8):1113–24.
71. Di Tommaso L, et al. Thymic tumor with adenoid cystic carcinomalike features: a clinicopathologic study of 4 cases. Am J Surg Pathol. 2007;31(8):1161–7.
72. Ruffini E, et al. Tumours of the thymus: a cohort study of prognostic factors from the European Society of Thoracic Surgeons database. Eur J Cardiothorac Surg. 2014;46(3):361–8.
73. Suster S, et al. Germ cell tumors of the mediastinum and testis: a comparative immunohistochemical study of 120 cases. Hum Pathol. 1998;29(7):737–42.
74. Tonon G, et al. t(11;19)(q21;p13) translocation in mucoepidermoid carcinoma creates a novel fusion product that disrupts a Notch signaling pathway. Nat Genet. 2003;33(2):208–13.
75. Maeda D, et al. Mucinous adenocarcinoma of the thymus: a distinct variant of thymic carcinoma. Lung Cancer. 2009;64(1):22–7.
76. Moser B, et al. Adenocarcinoma of the thymus, enteric type: report of 2 cases, and proposal for a novel subtype of thymic carcinoma. Am J Surg Pathol. 2015;39(4):541–8.
77. Prieto-Granada CN, Inagaki H, Mueller J. Thymic mucoepidermoid carcinoma: report of a case with CTRC1/3-MALM2 molecular studies. Int J Surg Pathol. 2015;23(4):277–83.
78. Stathis A, et al. Clinical response of carcinomas harboring the BRD4-NUT oncoprotein to the targeted bromodomain inhibitor OTX015/MK-8628. Cancer Discov. 2016.
79. Gaur P, Leary C, Yao JC. Thymic neuroendocrine tumors: a SEER database analysis of 160 patients. Ann Surg. 2010;251(6):1117–21.
80. Moran CA, Suster S. Neuroendocrine carcinomas (carcinoid tumor) of the thymus. A clinicopathologic analysis of 80 cases. Am J Clin Pathol. 2000;114(1):100–10.

81. Soga J, Yakuwa Y, Osaka M. Evaluation of 342 cases of mediastinal/thymic carcinoids collected from literature: a comparative study between typical carcinoids and atypical varieties. Ann Thorac Cardiovasc Surg. 1999;5(5):285–92.
82. Zhao Y, et al. Evaluation of the proposed International Association for the Study of Lung Cancer (IASLC)/International Thymic Malignancies Interest Group (ITMIG) staging revisions in thymic well-differentiated neuroendocrine carcinoma patients. Eur J Cardiothorac Surg, 2015.
83. Teh BT, et al. Thymic carcinoids in multiple endocrine neoplasia type 1. Ann Surg. 1998;228(1):99–105.
84. Strobel P, et al. Tumor genetics and survival of thymic neuroendocrine neoplasms: a multi-institutional clinicopathologic study. Genes Chromosomes Cancer. 2014;53(9):738–49.
85. Tiffet O, et al. A clinicopathologic study of 12 neuroendocrine tumors arising in the thymus. Chest. 2003;124(1):141–6.
86. Oliveira AM, et al. Thyroid transcription factor-1 distinguishes metastatic pulmonary from well-differentiated neuroendocrine tumors of other sites. Am J Surg Pathol. 2001;25(6):815–9.
87. Weissferdt A, et al. Comparative immunohistochemical analysis of pulmonary and thymic neuroendocrine carcinomas using PAX8 and TTF-1. Mod Pathol. 2013;26(12):1554–60.
88. Schaefer IM, et al. Neuroendocrine carcinoma in a mediastinal teratoma as a rare variant of somatic-type malignancy. Virchows Arch. 2013;463(5):731–5.
89. Weissferdt A, Moran CA. Spindle cell thymomas with neuroendocrine morphology: a clinicopathological and immunohistochemical study of 18 cases. Histopathology. 2014;65(1):111–8.
90. Shoji T, et al. Thymic large-cell neuroendocrine carcinoma: a disease neglected in the ESMO guideline? Ann Oncol. 2011;22(11):2535.
91. Chetty R, Batitang S, Govender D. Large cell neuroendocrine carcinoma of the thymus. Histopathology. 1997;31(3):274–6.
92. Lauriola L, Erlandson RA, Rosai J. Neuroendocrine differentiation is a common feature of thymic carcinoma. Am J Surg Pathol. 1998;22(9):1059–66.
93. Lack EE. Thymic hyperplasia with massive enlargement: report of two cases with review of diagnostic criteria. J Thorac Cardiovasc Surg. 1981;81(5):741–6.
94. Hofmann WJ, Moller P, Otto HF. Thymic hyperplasia. I. True thymic hyperplasia. Review of the literature. Klin Wochenschr. 1987;65(2):49–52.
95. Tani T, et al. A case of true thymic hyperplasia showing slow growth as revealed by chest X-ray. Nihon Kyobu Shikkan Gakkai Zasshi. 1994;32(2):194–8.
96. Judd RL. Massive thymic hyperplasia with myoid cell differentiation. Hum Pathol. 1987;18(11):1180–3.
97. Eifinger F, et al. True thymic hyperplasia associated with severe thymic cyst bleeding in a newborn: case report and review of the literature. Ann Diagn Pathol. 2007;11(5):358–62.
98. Hofmann WJ, Moller P, Otto HF. Thymic hyperplasia. II. Lymphofollicular hyperplasia of the thymus. An immunohistologic study. Klin Wochenschr. 1987;65(2):53–60.
99. Strobel P, et al. Deficiency of the autoimmune regulator AIRE in thymomas is insufficient to elicit autoimmune polyendocrinopathy syndrome type 1 (APS-1). J Pathol. 2007;211(5):563–71.
100. Jegalian AG, Bodo J, Hsi ED. NOTCH1 intracellular domain immunohistochemistry as a diagnostic tool to distinguish T-lymphoblastic lymphoma from thymoma. Am J Surg Pathol. 2015;39(4):565–72.
101. Kissin CM, et al. Benign thymic enlargement in adults after chemotherapy: CT demonstration. Radiology. 1987;163(1):67–70.
102. Chertoff J, Barth RA, Dickerman JD. Rebound thymic hyperplasia five years after chemotherapy for Wilms' tumor. Pediatr Radiol. 1991;21(8):596–7.

103. Tabarin A, et al. [Paraneoplastic Cushing's syndrome. Pseudotumors of the thymus occurring after correction of hypercorticism. 3 cases]. Presse Med. 1993;22(38):1908–10, 1915.
104. Shin MS, Ho KJ. Diffuse thymic hyperplasia following chemotherapy for nodular sclerosing Hodgkin's disease. An immunologic rebound phenomenon? Cancer. 1983;51(1):30–3.
105. Jeon TJ, et al. Rebound thymic hyperplasia detected by 18F-FDG PET/CT after radioactive iodine ablation therapy for thyroid cancer. Thyroid. 2014;24(11):1636–41.
106. den Bakker MA, Oosterhuis JW. Tumours and tumour-like conditions of the thymus other than thymoma; a practical approach. Histopathology. 2009;54(1):69–89.
107. Shimosato Y, Mukai K, Matsuno Y. Tumors of the mediastinum. American Registry of Pathology (2010).
108. Bratton AB. The normal weight of the human thymus. J Pathol Bacteriol. 1925;28(4): 609–20.
109. Strobel P, et al. The ageing and myasthenic thymus: a morphometric study validating a standard procedure in the histological workup of thymic specimens. J Neuroimmunol. 2008;201–202:64–73.
110. Okabe H. Thymic lymph follicles; a histopathological study of 1356 autopsy cases. Acta Pathol Jpn. 1966;16(1):109–30.
111. Middleton G, Schoch EM. The prevalence of human thymic lymphoid follicles is lower in suicides. Virchows Arch. 2000;436(2):127–30.
112. Marx A, et al. Thymus pathology observed in the MGTX trial. Ann N Y Acad Sci. 2012;1275:92–100.
113. Meyer A, Levy Y. Geoepidemiology of myasthenia gravis [corrected]. Autoimmun Rev. 2010;9(5):A383–6.
114. Chuang WY, et al. Late-onset myasthenia gravis - CTLA4(low) genotype association and low-for-age thymic output of naive T cells. J Autoimmun. 2014;52:122–9.
115. Skeie GO, Romi F. Paraneoplastic myasthenia gravis: immunological and clinical aspects. Eur J Neurol. 2008;15(10):1029–33.
116. Zouvelou V, et al. Double seronegative myasthenia gravis with anti-LRP 4 antibodies. Neuromuscul Disord. 2013;23(7):568–70.
117. Ferri C, et al. Thymus alterations and systemic sclerosis. Rheumatology (Oxford). 2006; 45(1):72–5.
118. Dalla Costa M, Mangano FA, Betterle C. Thymic hyperplasia in patients with Graves' disease. J Endocrinol Invest. 2014;37(12):1175–9.
119. Marx A, et al. The different roles of the thymus in the pathogenesis of the various myasthenia gravis subtypes. Autoimmun Rev. 2013;12(9):875–84.
120. Renton AE, et al. A genome-wide association study of myasthenia gravis. JAMA Neurol. 2015;72(4):396–404.
121. Gregersen PK, et al. Risk for myasthenia gravis maps to a (151) Pro → Ala change in TNIP1 and to human leukocyte antigen-B*08. Ann Neurol. 2012;72(6):927–35.
122. Weiss JM, et al. SDF-1/CXCL12 recruits B cells and antigen-presenting cells to the thymus of autoimmune myasthenia gravis patients. Immunobiology. 2013;218(3):373–81.
123. Vincent A, et al. In-vitro synthesis of anti-acetylcholine-receptor antibody by thymic lymphocytes in myasthenia gravis. Lancet. 1978;1(8059):305–7.
124. Scadding GK, et al. Acetylcholine receptor antibody synthesis by thymic lymphocytes: correlation with thymic histology. Neurology. 1981;31(8):935–43.
125. Berrih-Aknin S, et al. CCL21 overexpressed on lymphatic vessels drives thymic hyperplasia in myasthenia. Ann Neurol. 2009;66(4):521–31.
126. Gradolatto A, et al. Both Treg cells and Tconv cells are defective in the Myasthenia gravis thymus: roles of IL-17 and TNF-alpha. J Autoimmun. 2014;52:53–63.

127. Hohlfeld R, Wekerle H. Reflections on the "intrathymic pathogenesis" of myasthenia gravis. J Neuroimmunol. 2008;201–202:21–7.
128. Kirchner T, et al. Immunohistological patterns of non-neoplastic changes in the thymus in Myasthenia gravis. Virchows Arch B Cell Pathol Incl Mol Pathol. 1986;52(3):237–57.
129. Leite MI, et al. Myasthenia gravis thymus: complement vulnerability of epithelial and myoid cells, complement attack on them, and correlations with autoantibody status. Am J Pathol. 2007;171(3):893–905.
130. Schalke BC, et al. Long-term treatment with azathioprine abolishes thymic lymphoid follicular hyperplasia in myasthenia gravis. Lancet. 1987;2(8560):682.
131. Weissferdt A, Moran CA. Thymic hyperplasia with lymphoepithelial sialadenitis (LESA)-like features: a clinicopathologic and immunohistochemical study of 4 cases. Am J Clin Pathol. 2012;138(6):816–22.
132. Suster S, Rosai J. Multilocular thymic cyst: an acquired reactive process. Study of 18 cases. Am J Surg Pathol. 1991;15(4):388–98.
133. Weissferdt A, Moran CA. Mediastinal seminoma with florid follicular lymphoid hyperplasia: a clinicopathological and immunohistochemical study of six cases. Virchows Arch. 2015;466(2):209–15.
134. Kelleher CM, et al. Case records of the Massachusetts General Hospital. Case 10-2012. A 16-year-old boy with epigastric pain and a mediastinal mass. N Engl J Med. 2012;366 (13):1241–9.
135. Le Pimpec-Barthes F, et al. Mediastinal cysts: clinical approach and treatment. Rev Pneumol Clin. 2010;66(1):52–62.
136. Esme H, et al. Primary mediastinal cysts: clinical evaluation and surgical results of 32 cases. Tex Heart Inst J. 2011;38(4):371–4.
137. Zambudio AR, et al. Non-neoplastic mediastinal cysts. Eur J Cardiothorac Surg. 2002; 22(5):712–6.
138. Suster S, et al. Multilocular thymic cysts with pseudoepitheliomatous hyperplasia. Hum Pathol. 1991;22(5):455–60.
139. Weissferdt A, Moran CA. Primary MALT-type lymphoma of the thymus: a clinicopathological and immunohistochemical study of six cases. Lung. 2011;189(6):461–6.
140. Tamagno M, et al. Giant multilocular thymic cyst in an HIV-infected adolescent. J Pediatr Surg. 2011;46(9):1842–5.
141. Matsumoto S, et al. Multilocular thymic cyst associated with rheumatoid arthritis. Kyobu Geka. 2012;65(3):205–8.
142. el-Kashef HA, Hofman WF, Ehrhart LC. Effect of a lipoxygenase inhibitor on vasoconstriction in dog lung. Am J Physiol. 1989;257(6 Pt 2):H1977–82.
143. Weissferdt A, Moran CA. Thymic carcinoma associated with multilocular thymic cyst: a clinicopathologic study of 7 cases. Am J Surg Pathol. 2011;35(7):1074–9.
144. Nakamura S, et al. Multilocular thymic cyst associated with thymoma: a clinicopathologic study of 20 cases with an emphasis on the pathogenesis of cyst formation. Am J Surg Pathol. 2012;36(12):1857–64.
145. Suster S, Rosai J. Cystic thymomas. A clinicopathologic study of ten cases. Cancer. 1992; 69(1):92–7.
146. Tajima S, et al. Cystic synovial sarcoma of the pleura mimicking a cystic thymoma: a case report illustrating the role of decreased INI-1 expression in differential diagnosis. Int J Clin Exp Pathol. 2015;8(3):3262–9.
147. Iwamoto N, et al. Mediastinal seminoma: a case report with special emphasis on SALL4 as a new immunocytochemical marker. Diagn Cytopathol. 2013;41(9):821–4.
148. Moran CA, Suster S. Cystic well-differentiated neuroendocrine carcinoma (carcinoid tumor): a clinicopathologic and immunohistochemical study of two cases. Am J Clin Pathol. 2006;126(3):377–80.

149. Sadohara J, et al. Thymic epithelial tumors: comparison of CT and MR imaging findings of low-risk thymomas, high-risk thymomas, and thymic carcinomas. Eur J Radiol. 2006; 60(1):70–9.
150. Kim JH, et al. Cystic tumors in the anterior mediastinum. Radiologic-pathological correlation. J Comput Assist Tomogr. 2003;27(5):714–23.
151. Borgna-Pignatti C, et al. Thymic cyst appearing after treatment of mediastinal non-Hodgkin lymphoma. Med Pediatr Oncol. 1994;22(1):70–2.

Mediastinal Germ Cell Tumors

6

Anja C. Roden

Introduction

Primary mediastinal germ cell tumors (PMGCT) are rare. They comprise approximately 1–15% of all mediastinal neoplasms in adults and 11% in children [1–3]. The incidence of PMGCT increases at puberty and the mean age of patients at diagnosis is 29 years (range, 2–67 years). The age of the patient largely depends on the PMGCT-type. While teratomas and yolk sac tumors occur predominately in very young patients, seminomas are usually diagnosed in patients 10 years and older [4]. Mixed malignant PMGCTs are more common with increasing age. Sarcomatous elements are rarely found in PMGCT of children [5]. In adults, PMGCT predominantly occur in men.

The histological, immunophenotypical, and ultrastructural features of PMGCT are identical to their gonadal counterpart [6]. However, the behavior of at least a subgroup of PMGCT is different from gonadal germ cell tumors (GCT). For instance, in contrast to gonadal GCT, in adults, non-teratomatous components of PMGCT are regarded as malignant. Furthermore, PMGCT have distinct differential diagnoses due to their location. It is important to differentiate PMGCT from other lesions in the mediastinum because of differences in treatment and outcome.

Most PMGCT (82% in a radiology study) occur in the prevascular mediastinum [7] and are commonly associated with the thymus [8]. In 14%, multiple mediastinal compartments are affected [7]. Because of the relative large space in the prevascular mediastinum, PMGCT, especially slow growing mature teratomas or seminomas, are often found incidentally [9–11]. Symptoms usually occur if the PMGCT

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compresses adjacent organs including large airways, great vessels, heart and phrenic nerve and include cough, chest pain, hemoptysis, dyspnea, postobstructive pneumonia and/or superior vena cava syndrome [12–15]. The tumor might erode into a bronchus which could lead to expectoration of hair (trichoptysis) or sebaceous debris in teratomas [16]. Other rare complications include erosion of the PMGCT into the pericardium, adjacent vascular structures, or through the skin to form a draining fistula [17, 18]. Gynecomastia has been reported in a patient with seminoma [19]. Klinefelter syndrome is the only risk factor that has been identified for PMGCTs. Klinefelter syndrome was found in 8–22% of male patients with PMGCT [14, 15, 20]. PMGCT associated with Klinefelter syndrome occur in general in patients that are younger (4.5–31 years old) than patients without the syndrome [14, 15, 21, 22]. Also PMGCT are strongly associated with precocious puberty in young boys with Klinefelter syndrome. Therefore, a karyotype analysis should be part of the clinical workup of boys with precocious puberty and PMGCT [23].

PMGCTs most commonly metastasize to lung and bone but metastases have also been found in liver, spleen, brain, tonsils, and subcutaneous tissue [24]. Metachronous testicular tumors were reported in 1–20% men with mediastinal GCT [25, 26]. A diagnosis of PMGCT requires the absence of a testicular or ovarian tumor on physical examination and imaging studies. However, overall, mediastinal metastases from at least gonadal seminomas are rare in the mediastinum, particularly in the absence of retroperitoneal lymph node metastasis.

Histologic Classification of Primary Mediastinal Germ Cell Tumors

PMGCTs are classified according to the WHO [27]. Tumors can be divided into seminomatous and non-seminomatous tumors. Non-seminomatous tumors are slightly more common encompassing 52–60% of PMGCTs and include yolk sac tumor (YST), embryonal carcinoma, choriocarcinoma, mixed germ cell tumors, and teratomas [28, 29]. In many studies teratomas are the most common PMGCT (43–75%) followed by seminoma (10–37%), YST (2–12%), embryonal carcinoma (2–8%), and choriocarcinoma (2%) [29, 30].

While the majority of PMGCT only has one tumor component, 34% of tumors have multiple components [11]. These tumors are classified as mixed PMGCT. The most common component is seminoma, but embryonal carcinoma, malignant teratoma, choriocarcinoma, and YST are also identified [11, 28, 31, 32].

Histologic Features of Primary Mediastinal Germ Cell Tumors

Teratoma

Teratomas are the most common PMGCT. They occur in pre- and postpubertal patients without sex predilection. Mature mediastinal teratomas have been reported in patients between 1 month and 73 years old with a peak incidence in early adulthood and a mean age of 28 years [17]. They are usually located in the prevascular mediastinum but occasionally can be seen in the paravertebral mediastinum [17, 29, 33]. Teratomas can become quite large and have been described up to 27 cm in greatest dimensions. Cysts might occur within the tumor [33].

Dependent on the elements identified, teratomas are divided into mature (63%) and immature teratomas (4%) and teratomas with other malignant components (i.e., sarcoma, other malignant germ cell elements, or carcinoma) (33%) [29]. Mature teratomas are exclusively comprised of mature, adult-type tissues (Fig. 6.1). Monodermal teratomas such as struma ovarii have not been reported in the mediastinum. However, biopsies might only contain tissue from one germ layer due to sampling bias. Immature teratomas contain immature, embryonic, or fetal tissues either exclusively or in addition to mature tissue. In adult mediastinal teratomas, the distinction between mature and immature teratoma is important as immature teratoma have in general a worse prognosis. Therefore, the search for an immature teratoma component is critical, even though it might not be present in small biopsies. Moreover, in cystic teratomas only the cyst wall might be sampled and teratomatous elements are not identified in the biopsy. Therefore, correlation with imaging studies and clinical presentation are important. For instance, in 25% of teratomas, imaging studies show calcifications [7, 17]; teeth or bone are also suggestive of teratoma. Occasionally, areas of radiolucency suggest fat. A multilocular cystic anterior mediastinal mass with fat content on CT scan is virtually diagnostic of mature teratoma.

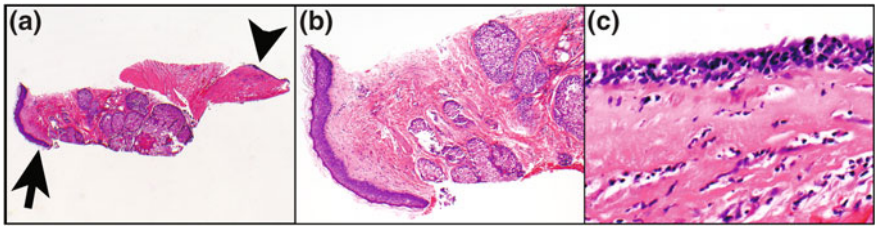
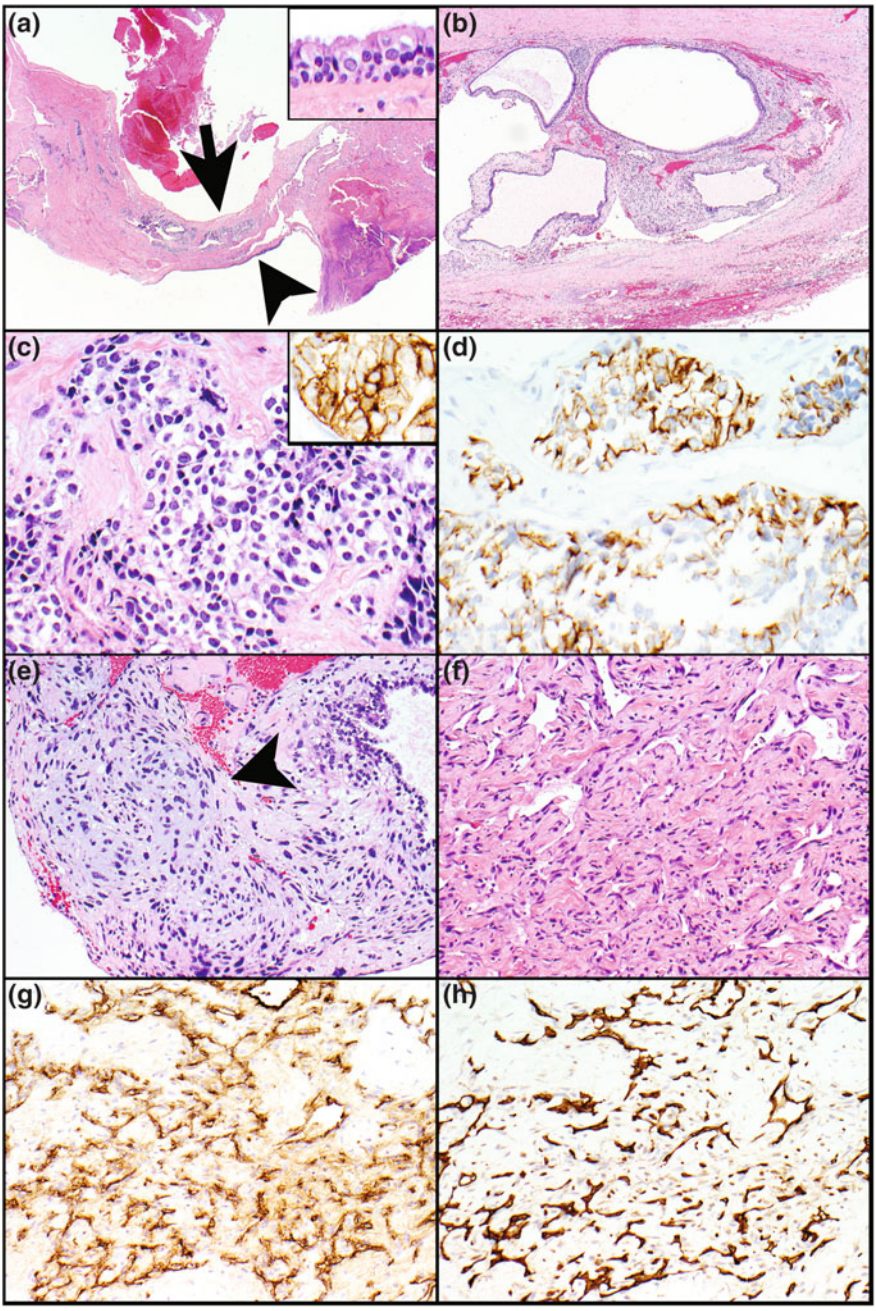


Fig. 6.1 Mature teratoma. A needle core biopsy shows skin with epidermis (**a**, *arrow*, **b**), and sebaceous glands. In another area (**a**, *arrowhead*, **c**), respiratory epithelium is present. These findings are consistent with a mature teratoma comprised of ectoderm (skin) and endoderm (respiratory system). Resection confirmed a mature cystic teratoma. Magnification, × 20 (**a**), × 100 (**b**), × 600 (**c**)

Cysts and sampled cyst linings can be a pitfall in the biopsy of a mediastinal mass as they not only occur in mature teratomas. They also can be seen in many other entities in the mediastinum including thymic cyst, seminoma, and bronchogenic cyst amongst others. Therefore, if a cyst lining is identified in a biopsy of a mediastinal lesion, a thorough morphologic examination of the cyst wall is important to exclude a GCT. The threshold for ancillary studies including immunostains and possibly isochromosome 12p [i(12p)] by fluorescence in situ hybridization (FISH) should be low. Bronchogenic cysts may closely mimic mature teratomas because they are comprised of respiratory (ciliated) epithelium, smooth muscle, and mature cartilage and/or seromucinous glands. In general, the presence of tracheobronchial structures and respiratory epithelium in the absence of enteric-type epithelium, immature elements, atypia, and tumor necrosis favors bronchogenic cyst [34]. Expression of CK7 by the epithelial cells in the absence of CDX2 expression further supports a bronchogenic cyst. In contrast, teratomas in general have a mixture of enteric and respiratory epithelium and the majority of the glands express CK7, CK20, CDX2, and TTF-1. In fact, coexpression of CDX2 and TTF-1 is only reported in teratomas [34]. However, as only limited material is present in small biopsies, a definite distinction between mature teratoma and bronchogenic cyst might not always be feasible and the possibility of an undersampled teratoma should be raised. In contrast to mature teratomas, thymic cysts harbor thymic tissue within the cyst wall and lack any heterologous elements. Recognizing Hassall corpuscles, the hallmark of thymic glandular tissue, helps to distinguish a thymic cyst from a cystic mature teratoma. In infants and children, meningoceles might present as paravertebral mediastinal cysts [35]. As meningoceles can show various amounts of neural tissue and calcification, they might be confused with teratomas. However, the clinical and radiographic features are usually characteristic of meningocele.

Mature teratomas can harbor malignant germ cell elements such as seminoma, embryonal carcinoma, or YST. They also can show morphologic features to suggest sarcomatous or carcinomatous transformation. In addition, teratomas might be associated with hematologic malignancies. As these tumors have a worse outcome it is crucial to recognize a malignant component in a lesion that otherwise shows elements of a mature teratoma (Fig. 6.2).

Fig. 6.2 Mature teratoma with component of immature teratoma, embryonal carcinoma and ▶ angiosarcoma. **a** A biopsy reveals a fibrotic, cellular (*arrow*) and necrotic neoplasm. Respiratory epithelium is identified (*arrowhead*, *insert*). **b** Cystic spaces are also lined by respiratory epithelium suggestive of mature teratoma. **c** High power view of the cellular area highlighted in figure **a** (*arrow*) shows nests of embryonal carcinoma as characterized by epithelioid cells with clear cytoplasm and large round to oval nuclei with prominent nucleoli. The neoplastic cells are positive for CD30 (**c**, insert), CAM 5.2 (**d**) and OCT4 and negative for PLAP and CD117 (not shown). **e** Immature cartilage is consistent with an immature teratoma component. **f** Large areas of the neoplasm are comprised of abnormal vascular channels lined by atypical spindle cells that mark with Factor VIII **g,** CD31 **h,** and CD34 (not shown), consistent with angiosarcoma. Magnification, × 20 (**a**), × 400 (**a**, insert, **c**, **d**), × 40 (**b**), × 200 (**e**–**h**)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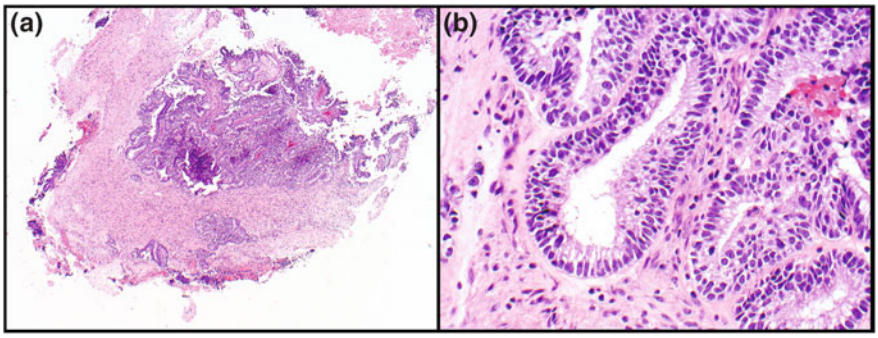


Fig. 6.3 Pulmonary blastoma. **a** A low power view of this biopsy reveals a glandular (*upper right*) and a stromal (*lower left*) component. **b** At high magnification the glands are lined by columnar epithelium with cells containing supranuclear vacuoles, features mimicking fetal adenocarcinoma. The glands are surrounded by spindle cells resembling the embryonic mesenchyme. Magnification, × 40 (**a**), × 400 (**b**)

Morphologic mimics of immature teratoma in the mediastinum include pleomorphic carcinoma, carcinosarcoma, and pulmonary blastoma amongst others [36–38]. Small biopsies might only contain a sarcomatous or blastomatous component and lack the more typical non-small cell carcinoma component that would help to distinguish these tumors from immature teratomas. Pulmonary blastoma might be the most difficult tumor to distinguish from an immature teratoma. This tumor occurs predominantly in adults and is composed of fetal-type adenocarcinoma and embryonic mesenchyme, both of which resemble fetal lung (Fig. 6.3) [39]. Fetal-type adenocarcinoma is characterized by glands or tubules that are lined by pseudostratified columnar, nonciliated epithelial cells with supranuclear or subnuclear vacuoles. Squamous morular metaplasia can occur and might result in an endometrioid appearance. The embryonic mesenchyme is characterized by condensation of spindle cells around the glands and might show heterologous differentiation which makes it even more difficult to distinguish from an immature teratoma. The fetal-type glands seen in pulmonary blastoma are most helpful to distinguish this tumor from an immature teratoma.

Yolk Sac Tumors

YST are overall the second most common PMGCT. While they are the most common malignant PMGCT in patients less than 15 years of age [27], after puberty, YST are relatively less common, occur almost always in men and its incidence peaks in the third decade. Before puberty, metastases occur in 30% of mediastinal YST, most commonly to the lung, lymph nodes, liver, bone, and brain. After puberty, metastases occur in about half of patients, usually to the lung or intrathoracic lymph nodes; extrathoracic metastases are uncommon at that age.

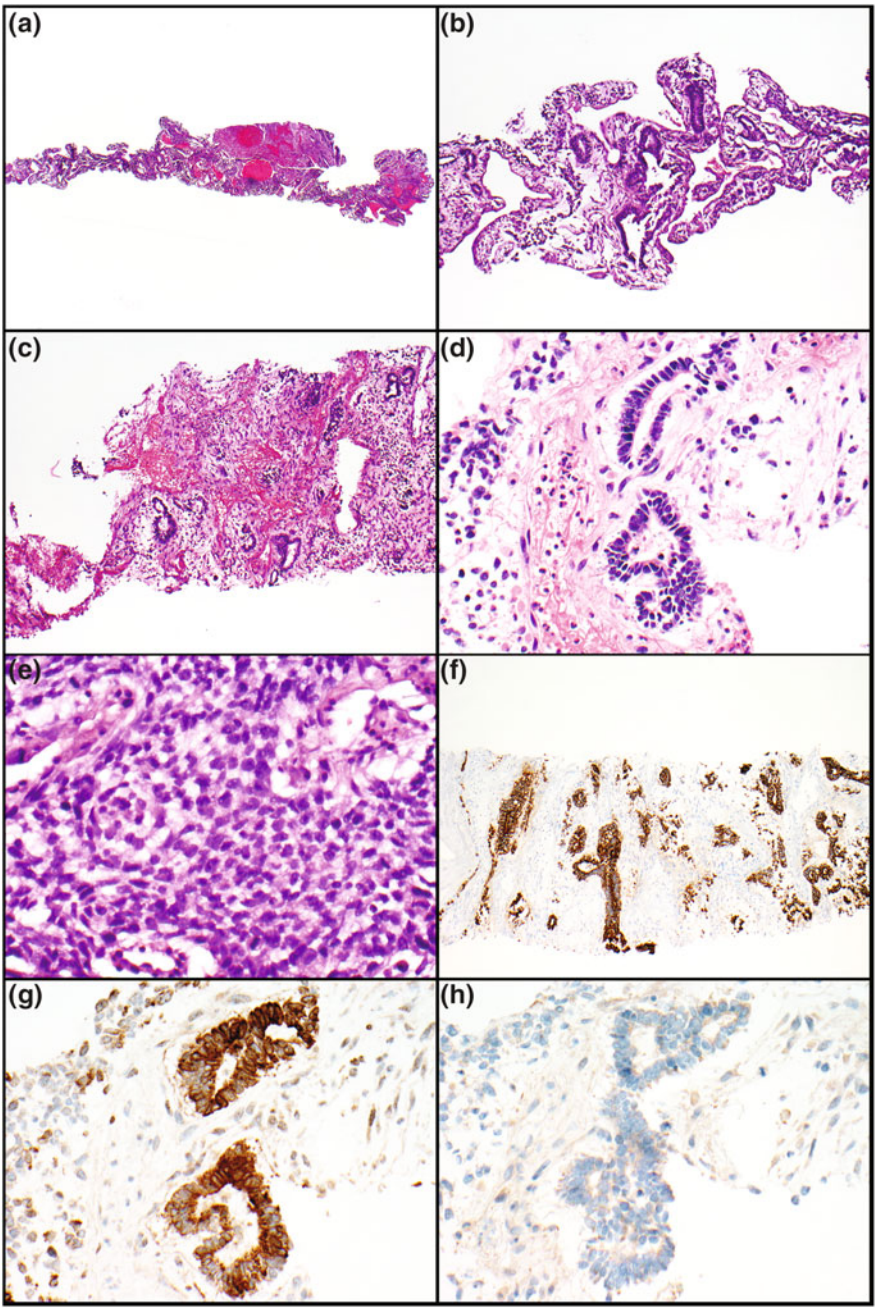
As in the gonads, YST in the mediastinum can be comprised of a variety of morphologic patterns including microcystic (reticular), macrocystic, glandular–alveolar, endodermal sinus (pseudopapillary), myxomatous, hepatoid, enteric, polyvesicular, vitelline, solid and spindle cell pattern (Fig. 6.4). Usually, more than one pattern is identified. Schiller-Duval bodies are the hallmark of YST. Schiller-Duval bodies are comprised of a central blood vessel surrounded by tumor cells and a capsule that again is lined by an outer (parietal) rim of tumor cells. These structures are reminiscent of a glomerulus. However, they might not always be present in YST, and specifically small biopsies might lack Schiller-Duval bodies. Syncytiotrophoblasts can be admixed in an otherwise typical YST. Hematological malignancies (specifically acute leukemias and myelodysplastic syndrome) are commonly seen associated with mixed GCT with a yolk sac component (58%) but also in pure YST (25%).

Seminoma

Seminomas usually occur in the prevascular mediastinum of men [9, 13, 24, 30, 40–43]. They are not found in prepubertal patients. The reported age ranges between 11 and 79 years with a mean age of 46.5 years in one study [43]; other studies report a peak in the third decade [24]. Seminomas can also become quite large with tumors described of over 16 cm in greatest diameter [9].

A few morphologic features appear to be unique in mediastinal seminomas including involvement of the thymus (Fig. 6.5), thymic epithelial cell hyperplasia, and cyst formation [44, 45]. In fact, prominent cystic changes have been described in 8% of mediastinal seminomas [45]. These tumors characteristically show areas of lymphoid hyperplasia, cysts lined by squamous epithelium, and cholesterol cleft granulomas. The lymphoid hyperplasia and the fact that the tumor cells might grow along the cyst wall makes the distinction of seminoma from thymic follicular hyperplasia or thymoma challenging. A high level of suspicion and low threshold for an OCT-4 stain is necessary to identify these tumors in a cystic lesion of the thymus. Non-necrotizing epithelioid granulomas might further obscure the tumor cells. Moreover, a granulomatous reaction, especially in a small biopsy, will present a pitfall as it might be misinterpreted as a possible infectious process. Mediastinal seminomas can also mimic thymomas, at least at low magnification on a small biopsy as the neoplastic cells can sometimes be arranged in cell nests that are separated by thin fibrovascular septa. In fact, fibrous septa/stroma have been described in 91% of seminoma [45]. The fibrovascular septa sometimes are infiltrated by a large number of lymphocytes. Cystic seminomas may histologically mimic multilocular thymic cysts [44].

As elsewhere in the body, the tumor cells of mediastinal seminomas are in general characterized by clear cytoplasm, distinct cell border, and prominent nucleoli. Cellular pleomorphism and necrosis can occur. A few cases of anaplastic seminoma have been reported in the anterior mediastinum [46]. Rarely, intercellular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◀ **Fig. 6.4** Yolk sac tumor. **a** A needle core biopsy reveals some glandular structures which are scattered throughout the biopsy (**b**–**d**). **c** Higher magnification shows a somewhat myxoid background. **e** Sheets of tumor cells comprise a solid component of the tumor. The neoplastic cells are positive for keratin AE1/AE3 (**f**), glypican 3 (**g**) and weakly AFP (**h**) and are negative for CD30 and PLAP (not shown). Magnification, × 20 (**a**), 100 (**b**, **c**, **f**), × 400 (**d**, **e**, **g**, **h**)

edema and syncytiotrophoblasts have been described [9]. Mediastinal seminomas can be associated with another non-GCT component such as leiomyosarcoma but that is rare in that location [47].

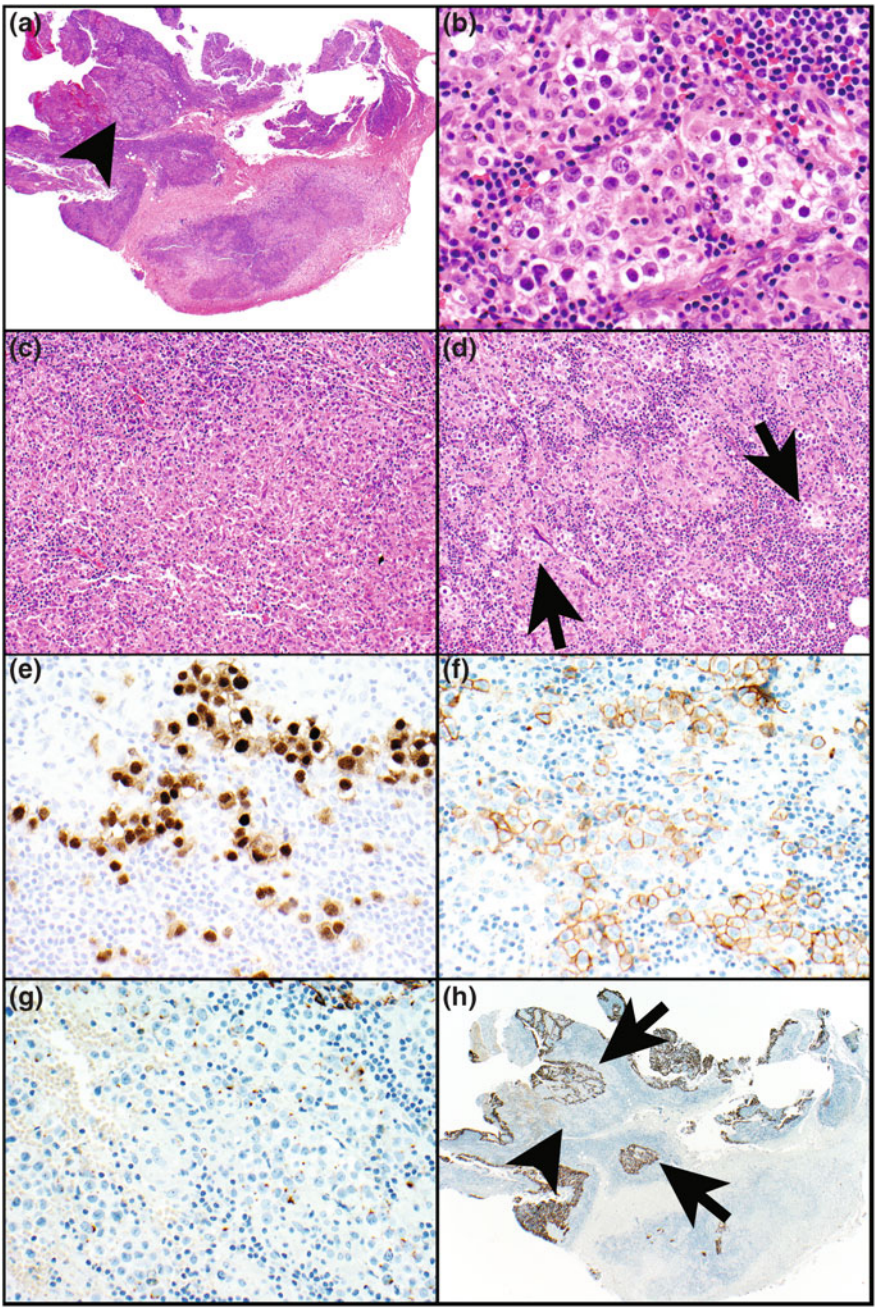
Choriocarcinoma

Choriocarcinomas are also rare in the mediastinum, comprising only 3% of PMGCT. Almost all mediastinal choriocarcinomas have been reported in adult males (age range, 17–63). Choriocarcinomas are highly aggressive tumors with early hematogeneous dissemination. These tumors are characterized by a mixture of syncytiotrophoblasts and cytotrophoblasts with or without intermediate trophoblasts (Fig. 6.6). Syncytiotrophoblasts are large multinucleated cells with numerous, pleomorphic, dark-staining nuclei, variable number of nucleoli, and abundant dense eosinophilic or amphophilic cytoplasm [27]. These cells might contain cytoplasmic lacunae. Cytotrophoblasts are more uniform, polygonal cells with round nuclei, prominent nucleoli, and clear or eosinophilic cytoplasm. Atypical mitoses and cellular atypia are common. Intermediate trophoblasts might grow in sheets of mononuclear cells. Choriocarcinomas are typically intimately associated with dilated vascular sinusoids.

Embryonal Carcinoma

Embryonal carcinomas are rare in the mediastinum and account only for up to 2% of PMGCT. It is predominantly a tumor of young men. Local tumor spread and hematogeneous metastases (lung, liver, brain, bones) are common; a quarter of patients have lung metastases at time of presentation. Lymphogeneous metastases are much rarer.

The morphologic features of mediastinal embryonal carcinoma are identical to their gonadal counterpart [27]. Tumor cells are characteristically large and polygonal or columnar and have indistinct cell borders. They grow in solid sheets, tubules, and/or papillary structures. Tumor cell nuclei usually have large single or multiple eosinophilic nucleoli. Mitotic activity is in general readily recognizable and tumor necrosis is common. Scattered single or small groups of syncytiotrophoblasts can occur in about one-third of cases.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◀ **Fig. 6.5** Seminoma. **a** A small biopsy is comprised of cellular areas (*arrowhead*) and fibrosis. **b** A high power view from the area highlighted by the arrowhead in figure **a** shows nests of large epithelioid cells characterized by clear and focally eosinophilic cytoplasm and round to oval nuclei with conspicuous nucleoli, morphologically suggestive of seminoma. **c** Non-necrotizing granulomas are also present. **d** Clusters of neoplastic cells similar to those in figure **b** are obscured by non-necrotizing granulomas. The neoplastic cells are positive for OCT4 (**e**) and CD117 (**f**) and show a peculiar dot-like staining pattern with keratin AE1/AE3 (**g**). **h** The keratin AE1/AE3 stain also highlights the background of benign thymic parenchyma. Magnification, × 20 (**a**, **h**), × 600 (**b**), × 200 (**c**, **d**), × 400 (**e**–**g**)

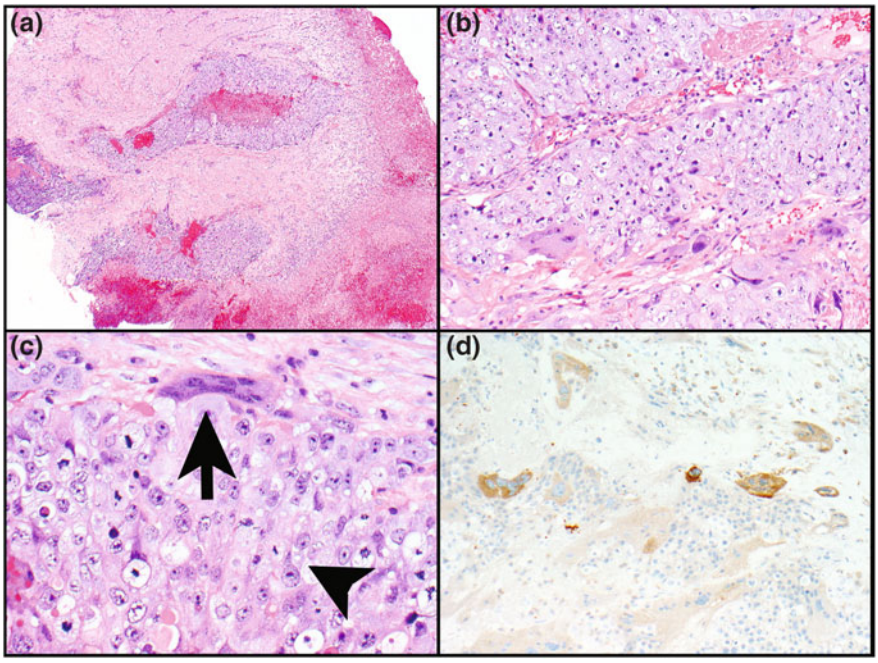

Fig. 6.6 Choriocarcinoma. **a** This biopsy is comprised of nests of neoplastic cells with central necrosis in a background of fibrosis. **b** The majority of the neoplastic cells are cytotrophoblastic and intermediate trophoblastic cells that are characteristically large and polygonal and have a single large round to oval nuclei with open nuclear chromatin and prominent nucleoli (**c**, *arrowhead*). **c** These cells are "capped" by syncytiotrophoblastic cells (*arrow*) that are comprised of dark-staining (in this case basophilic) cytoplasm and multiple nuclei. **d** Human placental lactogen mainly highlights the syncytiotrophoblastic cells. Magnification, × 40 (**a**), × 200 (**b**, **d**), × 400 (**c**)

Mixed Primary Mediastinal Germ Cell Tumors

As in the gonads, mixed PMGCT are comprised of at least two distinct types of GCT. In adults they account for 16% of all PMGCT, second only to teratomas and seminomas. Virtually, all patients are male. In children, most tumors are a combination of YST and teratoma (mature or immature). In adults, teratoma and

embryonal carcinoma are the most common components; YST, seminoma, and choriocarcinoma are less common part of mixed PMGCT. While in adults the teratoma component is more often immature, in children, the teratoma component is more commonly mature. All components should be listed, however, not all components might be present in a biopsy. Adult mixed GCT are frequently associated with somatic malignancies.

Germ Cell Tumors with Somatic-Type Solid Malignancy

Sarcomatous differentiation of GCT is most frequently seen in the mediastinum. It may occur in association with mature teratomas or, less commonly, with other malignant PMGCTs including immature teratoma, choriocarcinoma, YST, and seminoma [48]. Rhabdomyosarcoma is the most common type of heterologous differentiation; angiosarcoma, leiomyosarcoma, glioblastoma multiforme, malignant peripheral nerve sheath tumor, epithelioid hemangioendothelioma and undifferentiated sarcoma might also occur [48]. Cases with components of chondrosarcoma, osteosarcoma, liposarcoma, malignant fibrous histiocytoma, primitive neuroectodermal tumor, and neuroblastoma have also been reported. Any somatic-type malignancy should be reported because PMGCT with sarcomatous differentiation do not respond to conventional GCT therapy and their prognosis is dismal [48]. Furthermore, patients with PMGCT with sarcomatous component appear to have a worse prognosis than their gonadal counterparts.

In a biopsy, maybe only a sarcomatous component is identified while the GCT per se is not present. If there is any clinical suspicion of an associated germ cell tumor, i(12p) might be helpful as sarcomatous components of GCT might harbor i(12p) [49].

Because of the poor prognosis of patients with PMGCT with sarcomatous component, its distinction from immature mesenchyme in an immature teratoma is critical. In general, the spindle cell component of immature teratomas is cytologically bland, relatively monomorphic and is typically condensed around teratomatous glands with a concentric, swirling growth pattern. In contrast, sarcomatous differentiation usually shows a higher architectural complexity with storiform growth pattern and intersecting fascicles infiltrating into surrounding tissues. Components of sarcomatous differentiation also commonly have more nuclear pleomorphism and hyperchromasia, obvious mitotic activity, obvious malignant heterologous differentiation, and lack intimately admixed glands. In addition, sarcomatous differentiation shows independent growth replacing teratomatous glands or other germ cell elements [50].

Ancillary Studies

Ancillary studies might be utilized to diagnose and type PMGCT and to distinguish them from other mediastinal tumors. Immunohistochemical and cytogenetic studies or karyotyping are most helpful. Serum markers might also be suggestive of certain GCT. However, while the immunophenotype and cytogenetic abnormalities of PMGCT are similar or even identical to their gonadal counterparts, some unique antigen expression patterns can be seen in PMGCT. Moreover, the expression of some antigens on PMGCT can harbor a pitfall as similar expression patterns might occur in mediastinal tumors that are in the differential diagnosis. Therefore, the threshold for ordering additional immunostains and/or cytogenetic studies should be low in the workup of a mediastinal tumor.

Immunohistochemical Studies (Table 6.1)

OCT-4 is an excellent immunostain to distinguish PMGCT such as seminoma and embryonal carcinoma from carcinomas in the mediastinum. 91–100% of seminomas and nearly 100% of embryonal carcinomas show nuclear reactivity with OCT3/4, and the specificity seems superior to other available markers [45, 51–55].

Keratin has been shown to be expressed in up to 43–88% of mediastinal seminomas, potentially leading to a misdiagnosis of carcinoma [43, 45, 50, 51, 56]. However, in most cases, keratin highlights only a small proportion of tumor cells with variable intensities [45]. CAM5.2 expression shows a rather strong dot-like paranuclear staining pattern in primary mediastinal seminomas [51, 56].

Strong membranous CD117 (kit) immunoreactivity has been reported in 75–100% of seminomas [57, 58]. However, in the mediastinum, CD117 is not specific to seminomas because it is also expressed in non-germ cell tumors including thymic carcinomas [59, 60], small cell carcinoma and adenocarcinomas of the lung [61]. In addition, embryonal carcinoma, YST, and choriocarcinoma may show some degree of weak CD117 reactivity.

CD30 is expressed in over 80–100% of embryonal carcinomas. CD30 is also expressed in various hematopoietic malignancies that can occur in the mediastinum such as mediastinal large B-cell lymphoma or Hodgkin lymphoma [62], occasionally in YST and rarely in seminoma [56]. Otherwise, embryonal carcinoma uniformly stains for low-molecular-weight keratins while EMA, CEA, and vimentin are usually negative. SOX2 expression helps to distinguish embryonal carcinoma from seminoma as it is expressed in embryonal carcinomas but not in seminomas [51, 58]. SOX2 is also not expressed in YST or choriocarcinoma. However, SOX2 is not specific to GCT and can be expressed in some carcinomas, melanomas, and other tumors. Scattered syncytiotrophoblastic cells that might be seen in embryonal carcinomas are positive for beta HCG.

Table 6.1 Immunophenotype of primary mediastinal germ cell tumors and their mimickers [Frequency (% positive cases)]

Immunostain	Seminoma	Embryonal carcinoma	Yolk sac tumor	Teratoma	Choriocarcinoma	Lung adenocarcinoma	Small cell carcinoma	Thymic carcinoma
OCT 4 [45, 52, 58, 70, 71]	100	100	0	0	0	N/A[a]	N/A	0
OCT 3/4 [51, 72–76]	91-100	82–100	38	0	0	0	N/A	N/A
CD117 [45, 57–61, 76–80]	75–100	77–100	30–59	43	0	17	82	80–86
SALL4 [58, 76, 81]	100	97	100	29	0	6	19	0
AFP [56, 58, 64, 65, 76, 77, 82]	0	0	56–100	N/A	0	60[b]	N/A	N/A
Beta-HCG [56, 65, 66, 76, 82, 83]	3	33	0	10–60	100	7–60	0	0
PLAP [45, 56, 58, 76, 82, 84–86]	43–100	59	40	0	0	25–67	N/A	0
Glypican 3 [51, 58]	0	7	100	34 (immature)	100	3	N/A	N/A
CAM 5.2 [45, 56, 76, 80, 86–89]	48–88	100	100	100	100	100	100	100[c]
Keratin AE1/AE3 [45, 56, 76, 77, 87, 88, 90]	0–43	100	100	100	100	100	50–100	100
High molecular weight keratin [45, 88, 91–93]	0–39	0	N/A	N/A	N/A	25–82	0	100[d]
EMA [45, 72, 76, 86, 87, 91, 94–96]	2–9	33	29	100[e]	54	95–100	N/A	100

(continued)

Table 6.1 (continued)

Immunostain	Seminoma	Embryonal carcinoma	Yolk sac tumor	Teratoma	Choriocarcinoma	Lung adenocarcinoma	Small cell carcinoma	Thymic carcinoma
CD30 [45, 56–58, 72, 76, 86, 97]	0–2	73–100	0–11	40[f]	0	0	0	N/A
TTF-1 [34, 76, 80, 83, 84, 86, 92, 95, 98–101]	0	0	0	50	N/A	57–89	85–95	0

Modified from [102]
[a]N/A, not available
[b]60% of hepatoid lung adenocarcinoma
[c]Thymic carcinoma with clear cell features
[d]Spindle cell thymic carcinoma
[e]EMA is expressed in all non-neural components of mature teratoma
[f]Presence of CD30 confined to respiratory component, squamous component, GI epithelium, nerve or cartilage [72], negative in immature teratoma

SALL4 is nearly uniformly expressed in seminomas, embryonal carcinoma and YST but is also expressed in other GCT [51, 58]. SALL4 is not specific to GCT as it can also be expressed in carcinomas and sarcomas.

Although the sensitivity of AFP for YST is high, it is not a reliable marker for YST because of its low sensitivity [63]. Furthermore, AFP can be expressed in 60% of hepatoid adenocarcinomas of the lung [64], and might be expressed in scattered tumor cells or small foci in up to 30% of embryonal carcinoma.

Placental-like alkaline phosphatase (PLAP) has traditionally been the marker of choice for GCTs (mostly seminoma). However, because of its lack of sensitivity, generally high background staining, and the availability of newer antibodies, PLAP became less useful in the diagnosis of PMGCT. Interestingly, similar to CAM5.2, PLAP shows a strong dot-like paranuclear staining pattern in 92% of primary mediastinal seminomas [56].

Glypican 3 has recently been shown to be expressed in YST, choriocarcinoma and about one-third of immature teratoma but only rarely in embryonal carcinoma [51, 58]. Glypican 3 appears to be absent in seminoma.

Given that there is no single immunostain specific to a certain PMGCT, a panel of immunostains might be performed to distinguish a PMGCT from its mimickers in the mediastinum and to further subtype the PMGCT. The panel should be chosen based on morphologic features, clinical presentation (age, gender, serum markers) and the differential diagnosis.

Serum Markers

Serum markers might aid in the diagnosis of PMGCT. Increased levels of AFP and beta-HCG in the serum are frequently more sensitive than immunohistochemistry. For instance, AFP levels are almost always elevated in patients with YST. Beta-HCG is increased in patients with choriocarcinoma. Mild serum elevation of beta-HCG ($\leq$ 100 IU/L in adults, $\leq$ 25 IU/L in children, normal range, $\leq$ 5 IU/L) can be seen in up to one third of patients with pure seminoma while AFP levels are not elevated in the serum of patients with that tumor. Essentially, all patients with embryonal carcinoma have increased serum AFP levels, some also have increased levels of beta-HCG.

However, AFP and beta-HCG are not entirely specific for GCT. For instance, beta-HCG can be seen in 10–60% of lung adenocarcinomas [65, 66]. Lung carcinomas can also express AFP, and human placental lactogen [66, 67].

Cytogenetic Studies

i(12p) as evaluated by FISH studies or karyotyping is a useful marker for GCT in males [68]. In fact, abnormalities of chromosome 12p including 12p amplification and i(12p) have been reported in 87% and approximately 65% of mediastinal seminoma; i(12p) has been reported in 69% of PMGCT, respectively [45, 69].

i(12p) has also been shown to occur in the sarcomatous component of GCTs. Although helpful to separate seminoma from other non-GCT in the mediastinum, 12p abnormalities are not specific to mediastinal seminomas and can occur in other PMGCT or GCT elsewhere. For instance, 60% of YST in patients 8 years and older show i(12p) even though YST in children <8 years old do not harbor i(12p). Choriocarcinomas have also been described to harbor i(12p).

Overall, although the presence of i(12p) aids in the diagnosis of a GCT, its absence does not exclude such a tumor.

Differential Diagnosis of Primary Mediastinal Germ Cell Tumors

Features that might facilitate the distinction between PMGCT and their mimickers:

- Seminomas: Lymphocytic infiltrate; epithelioid cells with clear cytoplasm; non-necrotizing epithelioid granulomas; possible cyst formation; strong expression of OCT4; i(12p).
- Thymoma: Lobulated architecture; lack of OCT4 expression.
- Thymic carcinoma: Lack of OCT4 expression.
- NUT carcinoma: NUT expression; t(15;19) by FISH or RT-PCR. Pitfall: NUT can be expressed in some germ cell tumors, especially spermatocytic seminomas (Fig. 6.7).
- Metastatic carcinoma: Morphologic and immunophenotypic features suggestive of their origin.
- Synovial sarcoma: t(X;18) by FISH or RT-PCR.
- Lymphoma: Characteristic immunophenotype; B- or T-cell receptor rearrangement studies; lack of keratin expression. Pitfall: keratin might highlight residual thymic gland.

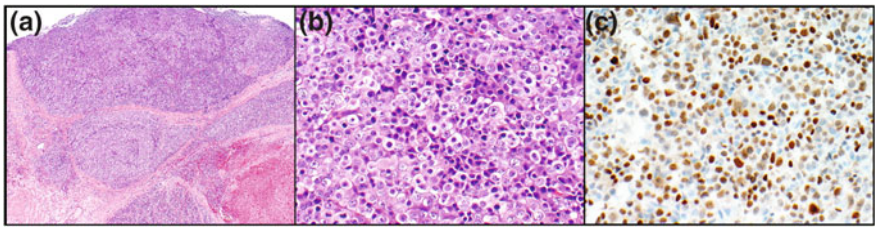

Fig. 6.7 Spermatocytic seminoma of testis. **a** This lobular neoplasm in general is comprised of 3 cell types. **b** a round cell with eosinophilic cytoplasm, small cells with dark nuclear chromatin and only scant cytoplasm and large, sometimes multinucleated giant cells with round, oval or indented nuclei (not seen in this figure). **c** At least a subset of the tumor cells stains with NUT. Magnification, × 40 (**a**), × 400 (**b**, **c**)

Morphologic patterns that might help to distinguish PMGCT from its mimickers [50]:

- Epithelial-lined cysts: Mature teratoma, seminoma, thymic cyst, enteric cyst, epidermal inclusion cyst, dermoid cyst, branchial cleft cyst, thyroglossal duct cyst, epidermoid cyst.
- Mixed epithelial and spindled pattern: Immature teratoma, YST, malignant mesothelioma, sarcomatoid carcinoma, synovial sarcoma, pleuropulmonary blastoma, congential peribronchial myofibroblastic tumor, pulmonary hamartoma, WHO type AB thymoma, spindle cell epithelial tumor with thymus-like differentiation (SETTLE), metastatic Wilms tumor.
- Poorly differentiated pattern: Embryonal carcinoma, seminoma, malignant mesothelioma, thymic carcinoma, lymphoma, NUT carcinoma, epithelioid angiosarcoma, lung adenocarcinoma, melanoma, carcinoma showing thymus-like differentiation (CASTLE).
- Papillary pattern: Embryonal carcinoma, YST, malignant mesothelioma, myxopapillary ependymoma.
- Clear cells: Seminoma, YST, thymic clear cell carcinoma, metastatic Muellerian clear cell carcinoma, metastatic renal cell carcinoma, clear cell type.

Key Points

- While morphologic, immunophenotypic and cytogenetic characteristics of PMGCT are largely identical to their gonadal counterpart, a few features are unique to the mediastinal location including dot-like staining pattern of CAM5.2 in primary mediastinal seminomas.
- As PMGCT have a different prognosis and require different treatment than other tumors in the mediastinum their correct diagnosis is critical. Given overlapping morphologic, immunophenotypic and serologic features of PMGCT and their mimickers in the mediastinum, the threshold for ordering immunostains and/or cytogenetic testing should be low.
- Although rare, metastatic GCT from the gonads should be excluded before making a diagnosis of a PMGCT.
- i(12p), as evaluated by FISH or karyotyping, is specific to GCT; however, its absence does not exclude such a diagnosis.
- Be aware that a biopsy might not harbor all components of a GCT and a mixed GCT and/or a sarcomatous or hematopathologic component might not be sampled. On the other hand, a biopsy might only contain a sarcomatous component and the more typical GCT component is missing.

References

1. Grosfeld JL, Skinner MA, Rescorla FJ, West KW, Scherer LR 3rd. Mediastinal tumors in children: experience with 196 cases. Ann Surg Oncol. 1994;1:121–7.
2. Davis RD Jr, Oldham HN Jr, Sabiston DC Jr. Primary cysts and neoplasms of the mediastinum: recent changes in clinical presentation, methods of diagnosis, management, and results. Ann Thorac Surg. 1987;44:229–37.
3. Jain KK, Bosl GJ, Bains MS, Whitmore WF, Golbey RB. The treatment of extragonadal seminoma. J Clin Oncol. 1984;2:820–7.
4. Schneider DT, Calaminus G, Koch S, Teske C, Schmidt P, Haas RJ, Harms D, Gobel U. Epidemiologic analysis of 1,442 children and adolescents registered in the German germ cell tumor protocols. Pediatr Blood Cancer. 2004;42:169–75.
5. Cushing B, Bhanot PK, Watts FB Jr, Hertzler JH, Brough AJ. Rhabdomyosarcoma and benign teratoma. Pediatr Pathol. 1983;1:345–8.
6. Levine GD. Primary thymic seminoma–a neoplasm ultrastructurally similar to testicular seminoma and distinct from epithelial thymoma. Cancer. 1973;31:729–41.
7. Moeller KH, Rosado-de-Christenson ML, Templeton PA. Mediastinal mature teratoma: imaging features. Am J Roentgenol. 1997;169:985–90.
8. Weidner N. Germ-cell tumors of the mediastinum. Semin Diagn Pathol. 1999;16:42–50.
9. Weissferdt A, Suster S, Moran CA. Primary mediastinal "thymic" seminomas. Adv Anat Pathol. 2012;19:75–80.
10. Cameron RB, Loehrer PJ, Thomas CR. Neoplasms of the mediastinum. In: DeVita VT, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. New York: Lippincott Williams & Wilkins; 2001.
11. Knapp RH, Hurt RD, Payne WS, Farrow GM, Lewis BD, Hahn RG, Muhm JR, Earle JD. Malignant germ cell tumors of the mediastinum. J Thorac Cardiovasc Surg. 1985;89:82–9.
12. Recondo J, Libshitz HI. Mediastinal extragonadal germ cell tumors. Urology. 1978;11:369–75.
13. Kiffer JD, Sandeman TF. Primary malignant mediastinal germ cell tumors: a study of eleven cases and a review of the literature. Int J Radiat Oncol Biol Phys. 1989;17:835–41.
14. Nichols CR, Heerema NA, Palmer C, Loehrer PJ Sr, Williams SD, Einhorn LH. Klinefelter's syndrome associated with mediastinal germ cell neoplasms. J Clin Oncol. 1987;5:1290–4.
15. Dexeus FH, Logothetis CJ, Chong C, Sella A, Ogden S. Genetic abnormalities in men with germ cell tumors. J Urol. 1988;140:80–4.
16. Guibert N, Attias D, Pontier S, Berjaud J, Lavialle-Guillautreau V, Didier A. Mediastinal teratoma and trichoptysis. Ann Thorac Surg. 2011;92:351–3.
17. Lewis BD, Hurt RD, Payne WS, Farrow GM, Knapp RH, Muhm JR. Benign teratomas of the mediastinum. J Thorac Cardiovasc Surg. 1983;86:727–31.
18. Gunes S, Varon J, Walsh G. Mediastinal teratoma presenting as massive hemoptysis in an adult. J Emerg Med. 1997;15:313–6.
19. Nagi DK, Jones WG, Belchetz PE. Gynaecomastia caused by a primary mediastinal seminoma. Clin Endocrinol (Oxf) 1994;40:545–8; discussion 548–9.
20. Hasle H, Jacobsen BB, Asschenfeldt P, Andersen K. Mediastinal germ cell tumour associated with Klinefelter syndrome. A report of case and review of the literature. Eur J Pediatr. 1992;151:735–9.
21. Hasle H, Mellemgaard A, Nielsen J, Hansen J. Cancer incidence in men with Klinefelter syndrome. Br J Cancer. 1995;71:416–20.
22. Beresford L, Fernandez CV, Cummings E, Sanderson S, Ming-Yu W, Giacomantonio M. Mediastinal polyembryoma associated with Klinefelter syndrome. J Pediatr Hematol Oncol. 2003;25:321–3.
23. Volkl TM, Langer T, Aigner T, Greess H, Beck JD, Rauch AM, Dorr HG. Klinefelter syndrome and mediastinal germ cell tumors. Am J Med Genet A. 2006;140:471–81.

24. Aygun C, Slawson RG, Bajaj K, Salazar OM. Primary mediastinal seminoma. Urology. 1984;23:109–17.
25. Bokemeyer C, Nichols CR, Droz JP, Schmoll HJ, Horwich A, Gerl A, Fossa SD, Beyer J, Pont J, Kanz L, Einhorn L, Hartmann JT. Extragonadal germ cell tumors of the mediastinum and retroperitoneum: results from an international analysis. J Clin Oncol. 2002;20:1864–73.
26. Fossa SD, Aass N, Heilo A, Daugaard G, Skakkebaek NE, Stenwig AE, Nesland JM, Looijenga LH, Oosterhuis JW. Testicular carcinoma in situ in patients with extragonadal germ-cell tumours: the clinical role of pretreatment biopsy. Ann Oncol. 2003;14:1412–8.
27. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. WHO Classification of tumours of the lung, pleura, thymus and heart. Lyon: International Agency for Research on Cancer; 2015.
28. Stang A, Trabert B, Wentzensen N, Cook MB, Rusner C, Oosterhuis JW, McGlynn KA. Gonadal and extragonadal germ cell tumours in the United States, 1973–2007. Int J Androl. 2012;35:616–25.
29. Moran CA, Suster S. Primary germ cell tumors of the mediastinum: I. Analysis of 322 cases with special emphasis on teratomatous lesions and a proposal for histopathologic classification and clinical staging. Cancer. 1997;80:681–90.
30. Takeda S, Miyoshi S, Ohta M, Minami M, Masaoka A, Matsuda H. Primary germ cell tumors in the mediastinum: a 50-year experience at a single Japanese institution. Cancer. 2003;97:367–76.
31. Coskun U, Gunel N, Yildirim Y, Memis L, Boyacioglu ZM. Primary mediastinal yolk sac tumor in a 66-year-old woman. Med Principles Pract. 2002;11:218–20.
32. Shimizu J, Yazaki U, Kinoshita T, Tatsuzawa Y, Kawaura Y, Nonomura A. Primary mediastinal germ cell tumor in a middle-aged woman: case report and literature review. Tumori. 2001;87:269–71.
33. Peterson CM, Buckley C, Holley S, Menias CO. Teratomas: a multimodality review. Curr Probl Diagn Radiol. 2012;41:210–9.
34. Roma A, Varsegi M, Magi-Galluzzi C, Ulbright T, Zhou M. The distinction of bronchogenic cyst from metastatic testicular teratoma: a light microscopic and immunohistochemical study. Am J Clin Pathol. 2008;130:265–73.
35. Abell MR. Mediastinal cysts. AMA Arch Pathol. 1956;61:360–79.
36. Koss MN, Hochholzer L, O'Leary T. Pulmonary blastomas. Cancer. 1991;67:2368–81.
37. Nakatani Y, Dickersin GR, Mark EJ. Pulmonary endodermal tumor resembling fetal lung: a clinicopathologic study of five cases with immunohistochemical and ultrastructural characterization. Hum Pathol. 1990;21:1097–107.
38. Nakatani Y, Kitamura H, Inayama Y, Kamijo S, Nagashima Y, Shimoyama K, Nakamura N, Sano J, Ogawa N, Shibagaki T, Resl M, Mark EJ. Pulmonary adenocarcinomas of the fetal lung type: a clinicopathologic study indicating differences in histology, epidemiology, and natural history of low-grade and high-grade forms. Am J Surg Pathol. 1998;22:399–411.
39. Yousem SA, Wick MR, Randhawa P, Manivel JC. Pulmonary blastoma. An immunohistochemical analysis with comparison with fetal lung in its pseudoglandular stage. Am J Clin Pathol. 1990;93:167–75.
40. El-Domeiri AA, Hutter RV, Pool JL, Foote FW Jr. Primary seminoma of the anterior mediastinum. Ann Thorac Surg 1968;6:513–521.
41. Polansky SM, Barwick KW, Ravin CE. Primary mediastinal seminoma. Am J Roentgenol. 1979;132:17–21.
42. Brown K, Collins JD, Batra P, Steckel RJ, Kagan AR. Mediastinal germ cell tumor in a young woman. Med Pediatr Oncol. 1989;17:164–7.
43. Moran CA, Suster S, Przygodzki RM, Koss MN. Primary germ cell tumors of the mediastinum: II. Mediastinal seminomas—a clinicopathologic and immunohistochemical study of 120 cases. Cancer. 1997;80:691–8.
44. Moran CA, Suster S. Mediastinal seminomas with prominent cystic changes. A clinicopathologic study of 10 cases. Am J Surg Pathol. 1995;19:1047–53.

45. Sung MT, Maclennan GT, Lopez-Beltran A, Zhang S, Montironi R, Cheng L. Primary mediastinal seminoma: a comprehensive assessment integrated with histology, immunohistochemistry, and fluorescence in situ hybridization for chromosome 12p abnormalities in 23 cases. Am J Surg Pathol. 2008;32:146–55.
46. Friedman SJ, Belbel RL, Martin NJ. Extragonadal mediastinal seminoma. Mil Med. 1988;153:32–4.
47. Moran CA, Suster S, Perino G, Kaneko M, Koss MN. Malignant smooth muscle tumors presenting as mediastinal soft tissue masses. A clinicopathologic study of 10 cases. Cancer. 1994;74:2251–60.
48. Malagon HD, Valdez AM, Moran CA, Suster S. Germ cell tumors with sarcomatous components: a clinicopathologic and immunohistochemical study of 46 cases. Am J Surg Pathol. 2007;31:1356–62.
49. Sumerauer D, Vicha A, Zuntova A, Stejskalova E, Krskova L, Kabickova E, Kodet R, Eckschlager T. Teratoma in an adolescent with malignant transformation into embryonal rhabdomyosarcoma: case report. J Pediatr Hematol Oncol. 2006;28:688–92.
50. McKenney JK, Heerema-McKenney A, Rouse RV. Extragonadal germ cell tumors: a review with emphasis on pathologic features, clinical prognostic variables, and differential diagnostic considerations. Adv Anat Pathol. 2007;14:69–92.
51. Weissferdt A, Rodriguez-Canales J, Liu H, Fujimoto J, Wistuba II, Moran CA. Primary mediastinal seminomas: a comprehensive immunohistochemical study with a focus on novel markers. Hum Pathol. 2015;46:376–83.
52. Jung SM, Chu PH, Shiu TF, Wu HH, Kuo TT, Chu JJ, Lin PJ. Expression of OCT4 in the primary germ cell tumors and thymoma in the mediastinum. Appl Immunohistochem Mol Morphol. 2006;14:273–5.
53. Emerson RE, Ulbright TM. The use of immunohistochemistry in the differential diagnosis of tumors of the testis and paratestis. Sem Diagn Pathol. 2005;22:33–50.
54. Hattab EM, Tu PH, Wilson JD, Cheng L. OCT4 immunohistochemistry is superior to placental alkaline phosphatase (PLAP) in the diagnosis of central nervous system germinoma. Am J Surg Pathol. 2005;29:368–71.
55. Jones TD, Ulbright TM, Eble JN, Baldridge LA, Cheng L. OCT4 staining in testicular tumors: a sensitive and specific marker for seminoma and embryonal carcinoma. Am J Surg Pathol. 2004;28:935–40.
56. Suster S, Moran CA, Dominguez-Malagon H, Quevedo-Blanco P. Germ cell tumors of the mediastinum and testis: a comparative immunohistochemical study of 120 cases. Hum Pathol. 1998;29:737–42.
57. Leroy X, Augusto D, Leteurtre E, Gosselin B. CD30 and CD117 (c-kit) used in combination are useful for distinguishing embryonal carcinoma from seminoma. J Histochem Cytochem. 2002;50:283–5.
58. Liu A, Cheng L, Du J, Peng Y, Allan RW, Wei L, Li J, Cao D. Diagnostic utility of novel stem cell markers SALL4, OCT4, NANOG, SOX2, UTF1, and TCL1 in primary mediastinal germ cell tumors. Am J Surg Pathol. 2010;34:697–706.
59. Nakagawa K, Matsuno Y, Kunitoh H, Maeshima A, Asamura H, Tsuchiya R. Immunohistochemical KIT (CD117) expression in thymic epithelial tumors. Chest. 2005;128:140–4.
60. Pan CC, Chen PC, Chiang H. KIT (CD117) is frequently overexpressed in thymic carcinomas but is absent in thymomas. J Pathol. 2004;202:375–81.
61. Butnor KJ, Burchette JL, Sporn TA, Hammar SP, Roggli VL. The spectrum of Kit (CD117) immunoreactivity in lung and pleural tumors: a study of 96 cases using a single-source antibody with a review of the literature. Arch Pathol Lab Med. 2004;128:538–43.
62. Ferreiro JA. Ber-H2 expression in testicular germ cell tumors. Hum Pathol. 1994;25:522–4.
63. Ramalingam P, Malpica A, Silva EG, Gershenson DM, Liu JL, Deavers MT. The use of cytokeratin 7 and EMA in differentiating ovarian yolk sac tumors from endometrioid and clear cell carcinomas. Am J Surg Pathol. 2004;28:1499–505.

64. Haninger DM, Kloecker GH, Bousamra Ii M, Nowacki MR, Slone SP. Hepatoid adenocarcinoma of the lung: report of five cases and review of the literature. Mod Pathol. 2014;27:535–42.
65. Dirnhofer S, Freund M, Rogatsch H, Krabichler S, Berger P. Selective expression of trophoblastic hormones by lung carcinoma: neurendocrine tumors exclusively produce human chorionic gonadotropin alpha-subunit (hCGalpha). Hum Pathol. 2000;31:966–72.
66. Boucher LD, Yoneda K. The expression of trophoblastic cell markers by lung carcinomas. Hum Pathol. 1995;26:1201–6.
67. Arnould L, Drouot F, Fargeot P, Bernard A, Foucher P, Collin F, Petrella T. Hepatoid adenocarcinoma of the lung: report of a case of an unusual alpha-fetoprotein-producing lung tumor. Am J Surg Pathol. 1997;21:1113–8.
68. Bosl GJ, Motzer RJ. Testicular germ-cell cancer. N Engl J Med. 1997;337:242–53.
69. Chaganti RS, Rodriguez E, Mathew S. Origin of adult male mediastinal germ-cell tumours. Lancet. 1994;343:1130–2.
70. Lau SK, Chang KL. OCT4: a sensitive and specific immunohistochemical marker for metastatic germ cell tumors. Adv Anat Pathol. 2006;13:76–9.
71. Mills AF, Lanfranchi M, Wein RO, Mukand-Cerro I, Pilichowska M, Cowan J, Bedi H. NUT midline carcinoma: a case report with a novel translocation and review of the literature. Head Neck Pathol. 2014;8:182–6.
72. Iczkowski KA, Butler SL, Shanks JH, Hossain D, Schall A, Meiers I, Zhou M, Torkko KC, Kim SJ, MacLennan GT. Trials of new germ cell immunohistochemical stains in 93 extragonadal and metastatic germ cell tumors. Hum Pathol. 2008;39:275–81.
73. Looijenga LH, Stoop H, de Leeuw HP, de Gouveia Brazao CA, Gillis AJ, van Roozendaal KE, van Zoelen EJ, Weber RF, Wolffenbuttel KP, van Dekken H, Honecker F, Bokemeyer C, Perlman EJ, Schneider DT, Kononen J, Sauter G, Oosterhuis JW. POU5F1 (OCT3/4) identifies cells with pluripotent potential in human germ cell tumors. Cancer Res. 2003;63:2244–50.
74. Howitt BE, Brooks JD, Jones S, Higgins JP. Identification and characterization of 2 testicular germ cell markers, Glut3 and CyclinA2. Appl Immunohistochem Mol Morphol. 2013;21:401–7.
75. Santagata S, Ligon KL, Hornick JL. Embryonic stem cell transcription factor signatures in the diagnosis of primary and metastatic germ cell tumors. Am J Surg Pathol. 2007;31:836–45.
76. Nakamura H, Tsuta K, Tsuda H, Katsuya Y, Naka G, Iizuka T, Igari T. NUT midline carcinoma of the mediastinum showing two types of poorly differentiated tumor cells: a case report and a literature review. Pathol Res Pract. 2015;211:92–8.
77. Kao CS, Idrees MT, Young RH, Ulbright TM. Solid pattern yolk sac tumor: a morphologic and immunohistochemical study of 52 cases. Am J Surg Pathol. 2012;36:360–7.
78. Bode PK, Barghorn A, Fritzsche FR, Riener MO, Kristiansen G, Knuth A, Moch H. MAGEC2 is a sensitive and novel marker for seminoma: a tissue microarray analysis of 325 testicular germ cell tumors. Mod Pathol. 2011;24:829–35.
79. Lau SK, Weiss LM, Chu PG. D2-40 immunohistochemistry in the differential diagnosis of seminoma and embryonal carcinoma: a comparative immunohistochemical study with KIT (CD117) and CD30. Mod Pathol. 2007;20:320–5.
80. Parikh SA, French CA, Costello BA, Marks RS, Dronca RS, Nerby CL, Roden AC, Peddareddigari VG, Hilton J, Shapiro GI, Molina JR. NUT midline carcinoma: an aggressive intrathoracic neoplasm. J Thorac Oncol. 2013;8:1335–8.
81. Miettinen M, Wang Z, McCue PA, Sarlomo-Rikala M, Rys J, Biernat W, Lasota J, Lee YS. SALL4 expression in germ cell and non-germ cell tumors: a systematic immunohistochemical study of 3215 cases. Am J Surg Pathol. 2014;38:410–20.
82. Moran CA, Suster S. Primary mediastinal choriocarcinomas: a clinicopathologic and immunohistochemical study of eight cases. Am J Surg Pathol. 1997;21:1007–12.

83. Weissferdt A, Moran CA. Anaplastic thymic carcinoma: a clinicopathologic and immunohistochemical study of 6 cases. Hum Pathol. 2012;43:874–7.
84. Saad RS, Landreneau RJ, Liu Y, Silverman JF. Utility of immunohistochemistry in separating thymic neoplasms from germ cell tumors and metastatic lung cancer involving the anterior mediastinum. Appl Immunohistochem Mol Morphol. 2003;11:107–12.
85. Moch H, Oberholzer M, Dalquen P, Wegmann W, Gudat F. Diagnostic tools for differentiating between pleural mesothelioma and lung adenocarcinoma in paraffin embedded tissue. Part I: immunohistochemical findings. Virchows Arch A Pathol Anat Histopathol. 1993;423:19–27.
86. Suzuki S, Kurabe N, Ohnishi I, Yasuda K, Aoshima Y, Naito M, Tanioka F, Sugimura H. NSD3-NUT-expressing midline carcinoma of the lung: first characterization of primary cancer tissue. Pathol Res Pract. 2015;211:404–8.
87. Comin CE, Novelli L, Boddi V, Paglierani M, Dini S. Calretinin, thrombomodulin, CEA, and CD15: a useful combination of immunohistochemical markers for differentiating pleural epithelial mesothelioma from peripheral pulmonary adenocarcinoma. Hum Pathol. 2001;32:529–36.
88. Morice WG, Ferreiro JA. Distinction of basaloid squamous cell carcinoma from adenoid cystic and small cell undifferentiated carcinoma by immunohistochemistry. Hum Pathol. 1998;29:609–12.
89. Suster S, Moran CA. Spindle cell thymic carcinoma: clinicopathologic and immunohistochemical study of a distinctive variant of primary thymic epithelial neoplasm. Am J Surg Pathol. 1999;23:691–700.
90. Wick MR, Swanson PE, Manivel JC. Placental-like alkaline phosphatase reactivity in human tumors: an immunohistochemical study of 520 cases. Hum Pathol. 1987;18:946–54.
91. Cheville JC, Rao S, Iczkowski KA, Lohse CM, Pankratz VS. Cytokeratin expression in seminoma of the human testis. Am J Clin Pathol. 2000;113:583–8.
92. Rekhtman N, Ang DC, Sima CS, Travis WD, Moreira AL. Immunohistochemical algorithm for differentiation of lung adenocarcinoma and squamous cell carcinoma based on large series of whole-tissue sections with validation in small specimens. Mod Pathol. 2011;24:1348–59.
93. Carella R, Deleonardi G, D'Errico A, Salerno A, Egarter-Vigl E, Seebacher C, Donazzan G, Grigioni WF. Immunohistochemical panels for differentiating epithelial malignant mesothelioma from lung adenocarcinoma: a study with logistic regression analysis. Am J Surg Pathol. 2001;25:43–50.
94. Lau SK, Weiss LM, Chu PG. Differential expression of MUC1, MUC2, and MUC5AC in carcinomas of various sites: an immunohistochemical study. Am J Clin Pathol. 2004;122:61–9.
95. Comin CE, Dini S, Novelli L, Santi R, Asirelli G, Messerini L. h-Caldesmon, a useful positive marker in the diagnosis of pleural malignant mesothelioma, epithelioid type. Am J Surg Pathol. 2006;30:463–9.
96. Truong LD, Mody DR, Cagle PT, Jackson-York GL, Schwartz MR, Wheeler TM. Thymic carcinoma. A clinicopathologic study of 13 cases. Am J Surg Pathol. 1990;14:151–66.
97. Lau SK, Thomas P, Weiss LM. Immunohistochemical evaluation of CON6D/B5: a new CD30 monoclonal antibody. Appl Immunohistochem Mol Morphol. 2010;18:273–7.
98. Ordonez NG. The diagnostic utility of immunohistochemistry in distinguishing between epithelioid mesotheliomas and squamous carcinomas of the lung: a comparative study. Mod Pathol. 2006;19:417–28.
99. Pan CC, Chen PC, Chou TY, Chiang H. Expression of calretinin and other mesothelioma-related markers in thymic carcinoma and thymoma. Hum Pathol. 2003;34:1155–62.
100. Masai K, Tsuta K, Kawago M, Tatsumori T, Kinno T, Taniyama T, Yoshida A, Asamura H, Tsuda H. Expression of squamous cell carcinoma markers and adenocarcinoma markers in

primary pulmonary neuroendocrine carcinomas. Appl Immunohistochem Mol Morphol. 2013;21:292–7.
101. Folpe AL, Gown AM, Lamps LW, Garcia R, Dail DH, Zarbo RJ, Schmidt RA. Thyroid transcription factor-1: immunohistochemical evaluation in pulmonary neuroendocrine tumors. Mod Pathol. 1999;12:5–8.
102. Roden AC. Mediastinal germ cell tumors. In: Nogales FF, Jimenez RE, editors. The pathology and biology of germ cell tumors. Heidelberg, Germany: Springer Verlag; 2016.

NUT Carcinoma

7

Lucian R. Chirieac and Christopher A. French

Clinical Features of NUT Carcinoma

NUT carcinoma (NC) is a rare, aggressive cancer. It can affect any gender or age group and occurs equally in males and females from the neonatal period [1, 2] through the eighth decade of life [3, 4]. Fewer than one hundred cases have been reported. At sites outside of the lung NC may represent 4–18% of tumors otherwise diagnosed as poorly differentiated carcinomas or undifferentiated malignant neoplasms [2, 5, 6]. Based on one study, the prevalence of NC amongst primary pulmonary nonglandular carcinomas was less than 1% [7]. There is no known racial predilection.

The cell of origin is not known and no in situ epithelial component has ever been observed. The tumor is usually locally invasive and widely metastatic at diagnosis. Because NCs arise from various anatomical sites, they cannot be categorized by the same system of nomenclature as most other carcinomas, which are traditionally defined by the tissue of origin. Instead, NC is defined genetically by the presence of chromosomal rearrangements involving the *NUT* (aka *NUTM1*) gene [8]. NCs tend to arise from midline anatomical sites, most commonly the upper aerodigestive tract (50%) [9] and the mediastinum (41%) [10]. However, it has been diagnosed within such varied tissues as the parotid gland, pancreas, adrenal gland, subcutis, bladder, and iliac bone [2, 11–14]. Apart from these unique features, NC is best known for its devastating clinical course. NC is characterized by aggressive local invasion and

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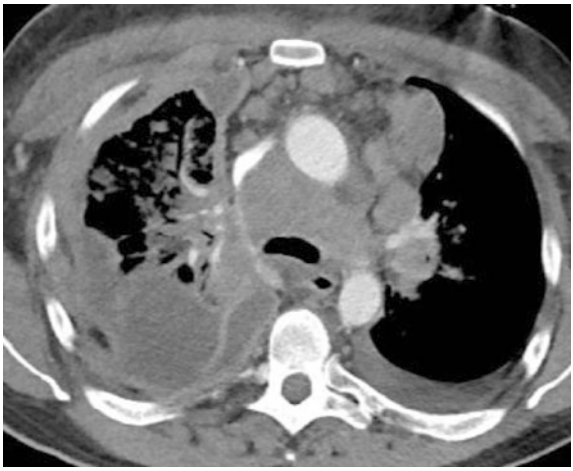

Fig. 7.1 A CT scan shows the appearance of a NUT carcinoma, as a hypoattenuating, heterogenously enhancing, necrotic mass with poorly defined, infiltrative borders

by lymphatic and hematogenous spread [2]. NC is often initially responsive to chemotherapy and radiation, but it invariably recurs rapidly and does not respond to subsequent therapeutic interventions. The median survival is only 6.7 months [4, 10], despite its frequent occurrence in previously healthy children or young adults without comorbid conditions. Thoracic NC usually presents at an advanced stage, with pleural effusions, pleuritic chest pain, nonproductive cough, weight loss, and shortness of breath [15, 16]. Thoracic NC may disseminate to bone, ovaries, liver, and brain [4, 12, 17–22]. Chest X-rays typically demonstrate extremely rapid tumor progression, with complete opacification of the thorax within 2–8 weeks from initial presentation [18]. By computed tomography (CT), NC appears as a hypoattenuating, heterogeneously enhancing, often extensively necrotic mass with poorly defined, infiltrative borders (Fig. 7.1) [15, 18, 23]. Given the age distribution of NC, it is unlikely that smoking plays a pathogenic role; this hypothesis is supported by the absence of a smoking history in many, but not all NC patients [13]. None of the cases tested to date have been associated with Epstein-Barr virus or with human papilloma virus infection [6, 13]. NC has been encountered in many parts of the developed world but is under-recognized in many developing countries.

It was in this rare cancer that the new class of bromodomain (BET) inhibitors were originally developed. BET inhibitors target the chromatin-binding bromdomains of BRD4 (and all other BET proteins) and thus directly inhibit the BRD4-NUT oncoprotein [24]. Clinical use of these inhibitors has demonstrated efficacy in NC [25], and multiple trials are ongoing enrolling NC patients in the United States and Europe. With the development of targeted therapy for NC, there is increased urgency for the early detection and diagnosis of this aggressive cancer.

Histopathology

The histopathology of NC is characteristic, but not diagnostic. The most common appearance is that of a poorly differentiated carcinoma with focal, abrupt squamous differentiation (Fig. 7.2). In contrast to many other poorly differentiated carcinomas, which consist of highly pleomorphic large cells, NC cells are usually medium sized, round, and often monomorphic in appearance (Fig. 7.3). Overt areas of squamous differentiation are seen in approximately half of cases [8] but may not always be present, particularly in small biopsies. A peculiar feature seen often in NC is a brisk neutrophilic infiltrate not associated with necrosis (Fig. 7.4). Well documented NC with unequivocal features of adenocarcinoma have not been seen. The histopathologic features of NC overlap with those of several other poorly differentiated cancers, including poorly differentiated squamous cell carcinoma, sinonasal undifferentiated carcinoma [5], Ewing sarcoma, Epstein-Barr virus-associated nasopharyngeal carcinoma, thymic carcinoma, neuroblastoma, pancreatoblastoma [12], and even primary salivary gland carcinoma (Fig. 7.5) [26]. NC is commonly misdiagnosed; it has even been mistaken for acute leukemia (due to the occasional expression of CD34) [2]. Also contributing to the failure to diagnose NC is poor awareness of the disease among clinicians and pathologists, its rarity, and until recently, the absence of widely available diagnostic tests. To counter the lack of awareness of NC among pathologists and oncologists, an Internet-based international NC registry (http://www.NCRegistry.org) has been established. This registry provides access to (a) pathologic review, (b) updated information about the disease, (c) treatment guideline suggestions, (d) a repository for clinical data, and (e) educational information for physicians and patients about this disease.

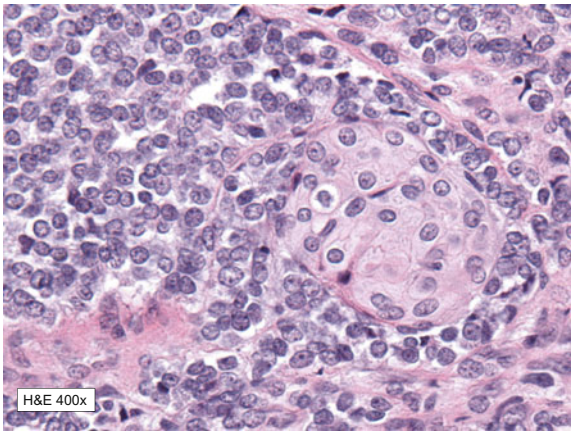

Fig. 7.2 The most common appearance of NUT carcinoma is that of a poorly differentiated carcinoma with focal abrupt squamous differentiation, present on the *right side* of the micrograph

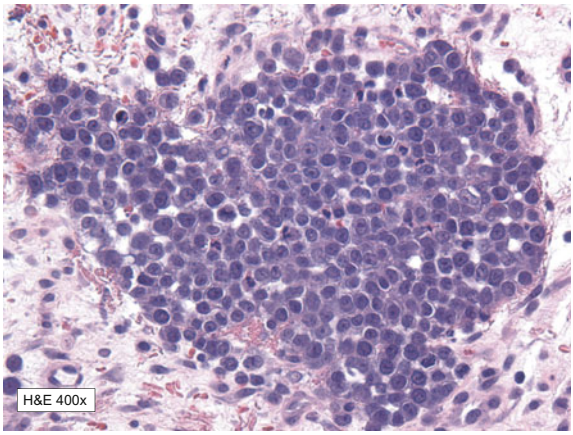

Fig. 7.3 NUT carcinomas cells are usually medium sized, round, and show a characteristic monomorphic appearance

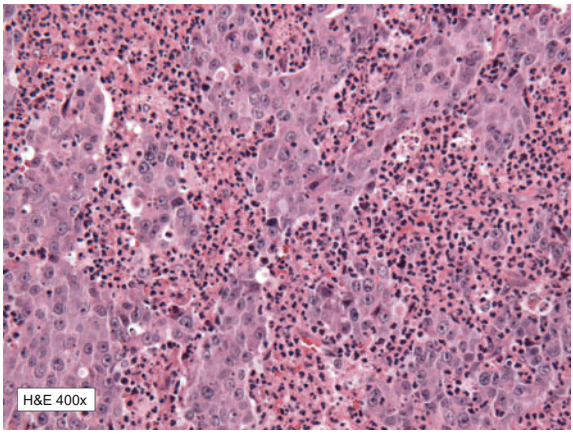

Fig. 7.4 A peculiar feature seen commonly in NUT carcinoma is the presence of a brisk neutrophilic infiltrate

Cytology

NUT carcinoma has a cytopathologic appearance that is nonspecific and mimics other primitive small round cell tumors or basaloid neoplasms [27–30]. Samples are highly cellular with monotonous, primitive-appearing small-to-mid-sized cells distributed most often singly and only occasionally in groups (Fig. 7.6). Vacuolated cytoplasm, corresponding with intracytoplasmic glycogen, is frequently seen, creating artifactual separation of cells and imparting a "fried-egg"-like appearance (Figs. 7.7 and 7.8) [27, 28, 31]. Chromatin ranges from open and pale, to hyperchromatic and neuroendocrine-like (Figs. 7.9 and 7.10) [32]. Mitoses, necrotic debris, and crush artifact are common [28, 33]. Overall, the cytologic characteristics overlap considerably with other poorly to undifferentiated carcinomas.

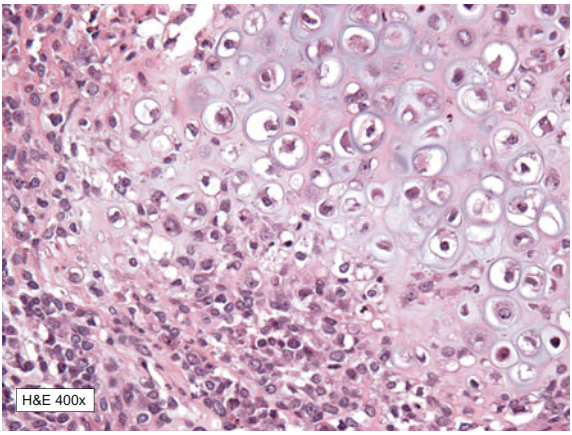

Fig. 7.5 This photomicrograph shows a NUT carcinoma originating in the parotid gland. Initially this tumor was thought to be a carcinoma ex pleomorphic adenoma because of the chondroid differentiation shown in this photomicrograph (i.e., originating from a pleomorphic adenoma)

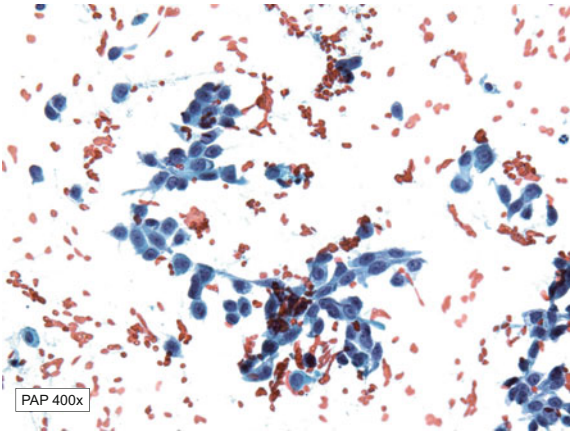

Fig. 7.6 Cytology sample from a patient with NUT carcinoma showing monomorphic, primitive-appearing small cells most often single and less commonly in groups

Macroscopy

NCs often present at advanced stages and therefore are not frequently amenable to surgical resection. NC typically grows as a large mass extending into hilar structures or along the pleura and chest wall (Fig. 7.11) [17]. NC has a fleshy, tan-white cut surface with or without prominent geographic necrosis.

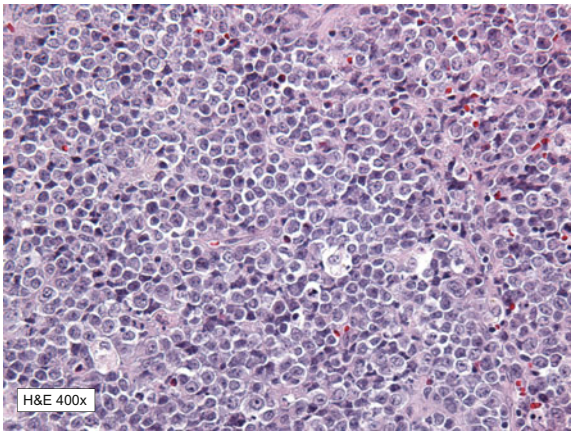

Fig. 7.7 Vacuolated cytoplasm with intracytoplasmic glycogen showing the artifactual separation of cells (fried egg appearance)

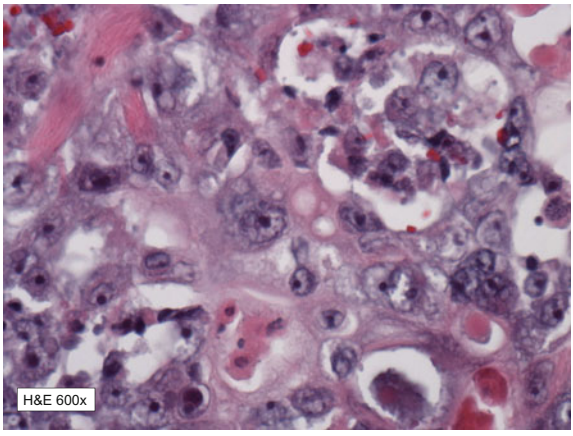

Fig. 7.8 High power magnification showing the fried egg appearance

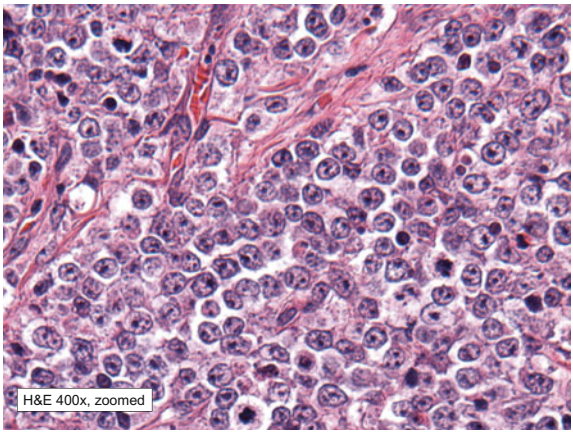

Fig. 7.9 NUT carcinoma cells, example of a pale open chromatin

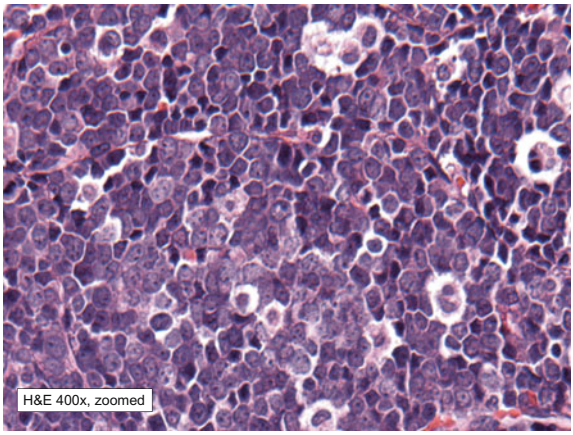

Fig. 7.10 Hyperchromatic, neuroendocrine-like chromatin, with similar appearance as in high grade neuroendocrine carcinomas

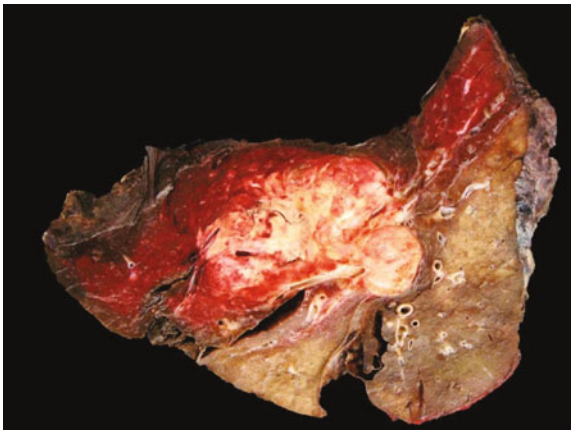

Fig. 7.11 Sagittal section from a pneumonectomy specimen of NUT carcinoma, typically growing as a large mass extending into other structures

Histopathologic Features in Biopsy Specimens

NUT carcinoma typically presents as sheets and nests of undifferentiated cells with a monomorphic appearance. The nuclei have irregular contours and granular to open chromatin (Figs. 7.9 and 7.10). The characteristic presence of abrupt foci of keratinization (Fig. 7.2) could be absent in small biopsy specimens [11, 16, 34]. Tumor cells infiltrate and expand the interstitium and may appear contiguous with bronchial epithelium (Fig. 7.12) [17]. Prominent geographic necrosis might be present (Fig. 7.13).

Tumor cells may be associated with a reactive pneumocyte proliferation, leading to diagnostic consideration of an adenosquamous carcinoma.

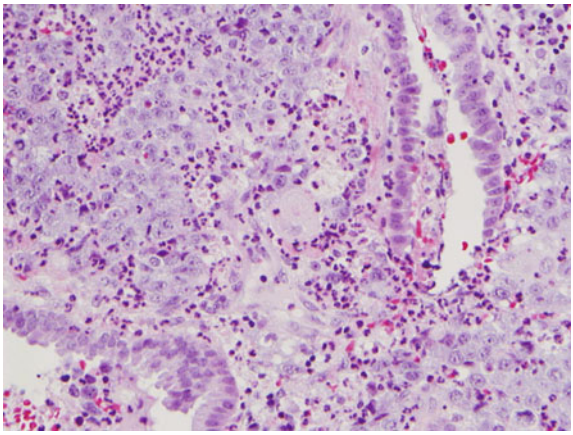

Fig. 7.12 Endobronchial biopsies from patients with NUT carcinoma show tumor cells infiltrating and expanding the interstitial spaces under the bronchial epithelium

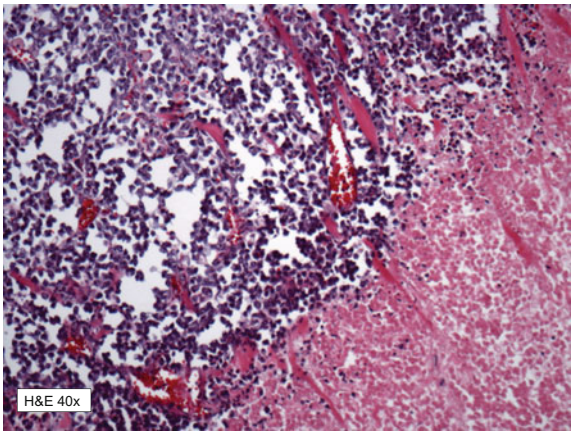

Fig. 7.13 A NUT carcinoma with small monomorphic cells (*left side*) and prominent geographic necrosis (*right side*)

Diagnosis

The diagnosis of NC depends on the demonstration of *NUT* (aka *NUTM1*) gene rearrangement or mis-expression. Although cytogenetic demonstration of a t(15;19) by karyotyping is sufficient for a presumptive diagnosis of NC, most diagnoses are based on formalin-fixed, paraffin-embedded (FFPE) tissues because few suspected carcinomas are submitted for karyotyping. To fill this diagnostic need, one of the authors developed a fluorescence in situ hybridization (FISH) assay that uses dual-color, break-apart bacterial artificial chromosome probes flanking the *NUT* and *BRD4* loci (Fig. 7.14) [35–37]. This assay can be used on virtually any specimen preparation, including frozen tissue, acetic acid-fixed cytogenetic preparations, thin (4–5 μm) sections of FFPE tissues or disaggregated cells, and air-dried or

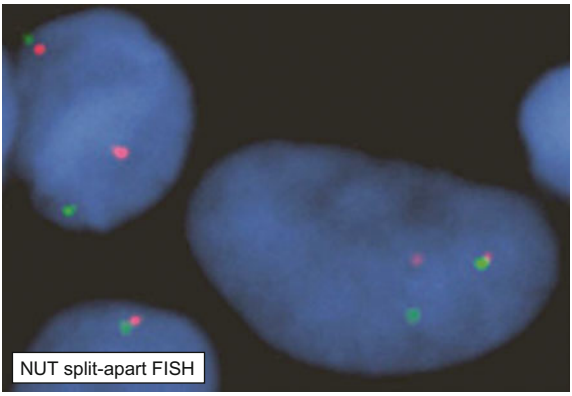

Fig. 7.14 Florescent in situ hybridization (FISH) using a dual color, break-apart probes flanking the NUT, and BRD4 loci. The typical translocation of a NUT carcinoma would result in separating (breaking apart) the probes with two distinctive separate signals: *red* and *green*

ethanol-fixed slides. Because this approach works on archival, formalin-fixed tissue, retrospective analysis can be performed on samples that are decades old [2].

If fresh or frozen tissue is available, reverse-transcriptase polymerase chain reaction can be employed by use of primers flanking the known *BRD4* and *NUT* break points [38]. However, this method overlooks *NUT*-variant fusion genes. To develop a diagnostic test for NC that can be used routinely in the community, a monoclonal antibody to NUT (clone C52B1, Cell Signaling Technologies, Danvers, MA) that detects NUT expression by immunohistochemistry was developed by one of the authors (CAF, Fig. 7.15) [39]. NUT expression is normally restricted to post-meiotic spermatids of the testes (Fig. 7.16) [40]. In a study that included a large number of control tissues, predominantly other forms of carcinoma, nuclear reactivity with this antibody was 100% specific and 87% sensitive for the diagnosis of NC when present in greater than 50% of cells [41]. The nuclear reactivity with the NUT antibody in NC frequently, though not invariably, displayed a speckled pattern of staining (Fig. 7.17). In this same study, the authors also observed NUT nuclear staining in a large percentage of germ cell tumors (seminomas, dysgerminomas, and embryonal carcinomas), though the staining was weak, not speckled, and present in less than 10% of cells.

Immunohistochemistry

Most cases of NC have nuclear expression for p63/p40 consistent with squamous differentiation (Fig. 7.18). Broad spectrum cytokeratins are positive in the majority of cases (Fig. 7.19), although rare cases are negative [6, 33]. The other epithelial markers such as EMA, BerEP-4, CEA are expressed variably in NCs. Occasionally

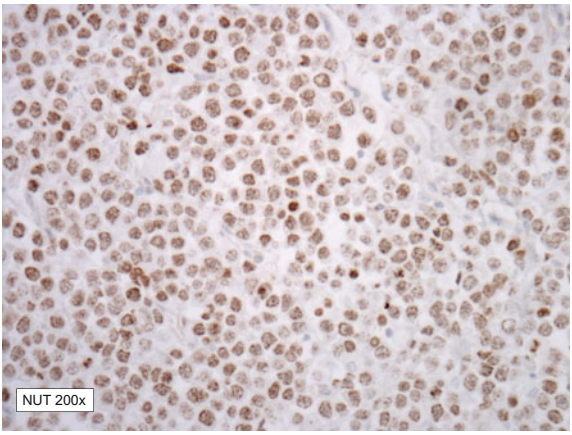

Fig. 7.15 Immunohistochemistry with a monoclonal antibody for NUT showing diffuse positivity for the antibody

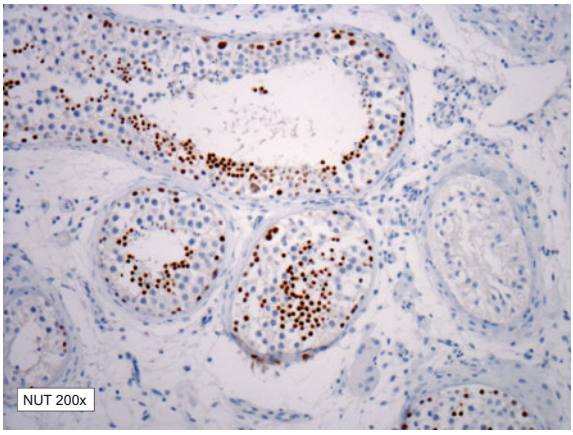

Fig. 7.16 NUT expression is normally restricted to post-meiotic spermatids of the testes

NCs can stain for chromogranin, synaptophysin, or even TTF-1 (Fig. 7.20) [17]. NCs are often positive for CD34, which may lead to a misdiagnosis of acute leukemia [2]. Germ cell, lymphoid, and myeloid markers are negative.

Differential Diagnosis

Since NC potentially look like any other poorly differentiated neoplasm, testing for NUT expression by immunohistochemistry should be considered in all poorly differentiated carcinomas that lack glandular differentiation or specific etiology [34]. NC may be misdiagnosed as squamous cell carcinoma, undifferentiated

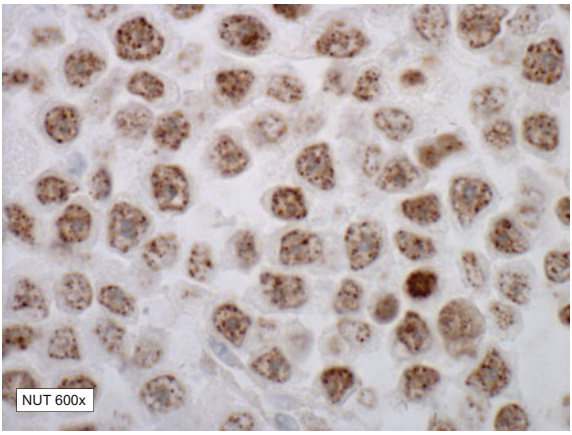

Fig. 7.17 Characteristic-speckled pattern of staining of NUT carcinoma cells (with the clone C52)

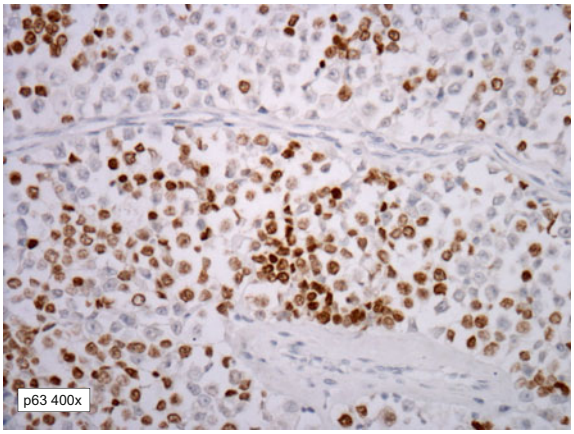

Fig. 7.18 NUT carcinoma cells positive for p63, consistent with squamous differentiation

carcinoma, small cell carcinoma, adenosquamous carcinoma, Ewing sarcoma, metastatic germ cell tumor, and acute leukemia [4, 35].

Summary

NC is a genetically defined, highly aggressive, and incurable squamous cell carcinoma associated with chromosomal rearrangements of *NUT*, most commonly resulting in *BRD4-NUT* fusion oncogenes or, less commonly, *BRD3-NUT*, *NSD3-NUT* or *NUT*-variant fusion oncogenes. Once a difficult diagnosis to make, NC is now diagnosable in most cases by immunohistochemical staining with an anti-NUT

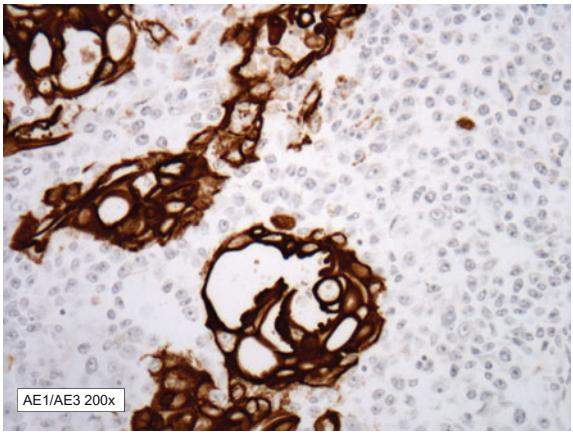

Fig. 7.19 NUT carcinoma cells positive for expressing broad spectrum cytokeratins in the majority of cases

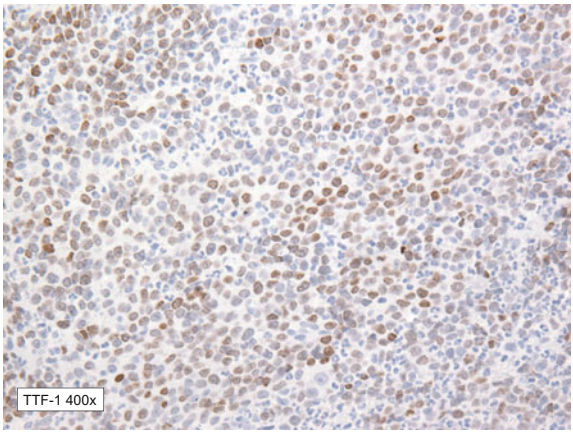

Fig. 7.20 Occasionally NUT carcinoma cells have nuclear TTF-1 expression

monoclonal antibody. Given the emergence of promising targeted therapy for this otherwise incurable cancer, there is an urgent need for increased awareness and early diagnosis of NC. Since NC resembles other poorly differentiated neoplasms, testing for NUT expression by immunohistochemistry should be considered in all poorly differentiated carcinomas with p63 or p40 nuclear expression that lack glandular differentiation or specific etiology.

References

1. Shehata BM, Steelman CK, Abramowsky CR, Olson TA, French CA, Saxe DF, et al. NUT mid line carcinoma in a newborn with multiorgan disseminated tumor and a 2-year-old with a pancreatic/hepatic primary. Pediatr Dev Pathol. 2010;13(6):481–5. PubMed PMID: WOS: 000288185300008. English.

2. French CA, Kutok JL, Faquin WC, Toretsky JA, Antonescu CR, Griffin CA, et al. Midline carcinoma of children and young adults with NUT rearrangement. J Clin Oncol Official J Am Soc Clin Oncol. 2004;22(20):4135–9.
3. Stelow EB, Bellizzi AM, Taneja K, Mills SE, LeGallo RD, Kutok JL, et al. NUT rearrangement in undifferentiated carcinomas of the upper aerodigestive tract. Am J Surg Pathol. 2008;32A(6):828–34. PubMed PMID: WOS:000256553000003. English.
4. Bauer DE, Mitchell CM, Strait KM, Lathan CS, Stelow EB, Luer SC, et al. Clinicopathologic features and long-term outcomes of NUT midline carcinoma. Clin Cancer Res Official J Am Assoc Cancer Res. 2012;18(20):5773–9. PubMed PMID: 22896655. Pubmed Central PMCID: 3473162.
5. Stelow EB, Bellizzi AM, Taneja K, Mills SE, Legallo RD, Kutok JL, et al. NUT rearrangement in undifferentiated carcinomas of the upper aerodigestive tract. Am J Surg Pathol. 2008;32(6):828–34.
6. Evans AG, French CA, Cameron MJ, Fletcher CD, Jackman DM, Lathan CS, et al. Pathologic characteristics of NUT midline carcinoma arising in the mediastinum. Am J Surg Pathol. 2012;36(8):1222–7. PubMed PMID: 22790861. Pubmed Central PMCID: 3396884.
7. Sholl LM, Nishino M, Pokharel S, Mino-Kenudson M, French CA, Janne PA, et al. Primary pulmonary NUT midline carcinoma: clinical, radiographic, and pathologic characterizations. J Thorac Oncol Official Publ Int Assoc Study Lung Cancer. 2015;10(6):951–9. PubMed PMID: 26001144. Pubmed Central PMCID: 4443847.
8. French CA, Kutok JL, Faquin WC, Toretsky JA, Antonescu CR, Griffin CA, et al. Midline carcinoma of children and young adults with NUT rearrangement. J Clin Oncol. 2004;22 (20):4135–9. PubMed PMID: WOS:000224573400015. English.
9. Chau NG, Hurwitz S, Mitchell CM, Aserlind A, Grunfeld N, Kaplan L, et al. Intensive treatment and survival outcomes in NUT midline carcinoma of the head and neck. Cancer. 2016. PubMed PMID: 27509377.
10. French CA. Demystified molecular pathology of NUT midline carcinomas. J Clin Pathol. 2010;63(6):492–6. PubMed PMID: WOS:000277941500004. English.
11. den Bakker MA, Beverloo BH, van den Heuvel-Eibrink MM, Meeuwis CA, Tan LM, Johnson LA, et al. NUT midline carcinoma of the parotid gland with mesenchymal differentiation. Am J Surg Pathol. 2009;33(8):1253–8.
12. Shehata BM, Steelman CK, Abramowsky CR, Olson TA, French CA, Saxe DF, et al. NUT midline carcinoma in a newborn with multiorgan disseminated tumor and a 2-year-old with a pancreatic/hepatic primary. Pediatr Dev Pathol Official J Soc Pediatr Pathol Paediatr Pathol Soc. 2010;13(6):481–5. PubMed PMID: 20017639.
13. French CA. Pathogenesis of NUT midline carcinoma. Annu Rev Pathol. 2012;7:247–65.
14. Mertens F, Wiebe T, Adlercreutz C, Mandahl N, French CA. Successful treatment of a child with t (15;19)-positive tumor. Pediatr Blood Cancer. 2007;49(7):1015–7.
15. Nelson BA, Lee EY, French CA, Bauer DE, Vargas SO. BRD4-NUT carcinoma of the mediastinum in a pediatric patient: multidetector computed tomography imaging findings. J Thorac Imaging. 2010;25(3):W93–6.
16. Lee AC, Kwong YI, Fu KH, Chan GC, Ma L, Lau YL. Disseminated mediastinal carcinoma with chromosomal translocation (15;19). A distinctive clinicopathologic syndrome. Cancer. 1993;72(7):2273–6.
17. Tanaka M, Kato K, Gomi K, Yoshida M, Niwa T, Aida N, et al. NUT midline carcinoma: report of 2 cases suggestive of pulmonary origin. Am J Surg Pathol. 2012;36(3):381–8.
18. Polsani A, Braithwaite KA, Alazraki AL, Abramowsky C, Shehata BM. NUT midline carcinoma: an imaging case series and review of literature. Pediatr Radiol. 2012;42(2):205–10.
19. Vargas SO, French CA, Faul PN, Fletcher JA, Davis IJ, Dal Cin P, et al. Upper respiratory tract carcinoma with chromosomal translocation 15;19: evidence for a distinct disease entity of young patients with a rapidly fatal course. Cancer. 2001;92(5):1195–203.
20. Engleson J, Soller M, Panagopoulos I, Dahlen A, Dictor M, Jerkeman M. Midline carcinoma with t (15;19) and BRD4-NUT fusion oncogene in a 30-year-old female with response to

docetaxel and radiotherapy. BMC Cancer. 2006;6:69. PubMed PMID: 16542442. Pubmed Central PMCID: 1456975.
21. Ball A, Bromley A, Glaze S, French CA, Ghatage P, Kobel M. A rare case of NUT midline carcinoma. Gynecol Oncol Case Rep. 2012;3:1–3. PubMed PMID: 24371650. Pubmed Central PMCID: 3862205.
22. Puliyel MM, Mascarenhas L, Zhou S, Sapra A, Dal Cin P, French CA, et al. Nuclear protein in testis midline carcinoma misdiagnosed as adamantinoma. J Clin Oncol Official J Am Soc Clin Oncol. 2014. PubMed PMID: 24470009.
23. Stelow EB, French CA. Carcinomas of the upper aerodigestive tract with rearrangement of the nuclear protein of the testis (NUT) gene (NUT midline carcinomas). Adv Anat Pathol. 2009;16(2):92–6.
24. Filippakopoulos P, Qi J, Picaud S, Shen Y, Smith WB, Fedorov O, et al. Selective inhibition of BET bromodomains. Nature. 2010;468(7327):1067–73. PubMed PMID: 20871596. Pubmed Central PMCID: 3010259.
25. Stathis A, Zucca E, Bekradda M, Gomez-Roca C, Delord JP, de La Motte Rouge T, et al. Clinical response of carcinomas harboring the BRD4-NUT oncoprotein to the targeted bromodomain inhibitor OTX015/MK-8628. Cancer Discovery. 2016;6(5):492–500. PubMed PMID: 26976114. Pubmed Central PMCID: 4854801.
26. den Bakker MA, Beverloo BH, van den Heuvel-Eibrink MM, Meeuwis CA, Tan LM, Johnson LA, et al. NUT midline carcinoma of the parotid gland with mesenchymal differentiation. Am J Surg Pathol. 2009;33(8):1253–8. PubMed PMID: WOS:000268850 300019. English.
27. Bishop JA, French CA, Ali SZ. Cytopathologic features of NUT midline carcinoma: a series of 26 specimens from 13 patients. Cancer Cytopathol. 2016;n/a–n/a.
28. Bellizzi AM, Bruzzi C, French CA, Stelow EB. The cytologic features of NUT midline carcinoma. Cancer. 2009;117(6):508–15.
29. Policarpio-Nicolas MLC, de Leon EMB, Jagirdar J. Cytologic Findings of NUT midline carcinoma in the hilum of the lung. Diagn Cytopathol. 2015;43(9):739–42. PubMed PMID: WOS:000359703200014. English.
30. Kuroda S, Suzuki S, Kurita A, Muraki M, Aoshima Y, Tanioka F, et al. Cytological features of a variant NUT midline carcinoma of the lung harboring the NSD3-NUT fusion gene: a case report and literature review. Case Rep Pathol. 2015;2015:572951. PubMed PMID: 25685583. Pubmed Central PMCID: 4320876.
31. Wartchow EP, Moore TS, French CA, Mierau GW. Ultrastructural features of NUT midline carcinoma. Ultrastruct Pathol. 2012;36(4):280–4.
32. Bishop JA, French CA, Ali SZ. Cytopathologic features of NUT midline carcinoma: a series of 26 specimens from 13 patients. Cancer Cytopathol. 2016. PubMed PMID: 27400194.
33. Zhu B, Laskin W, Chen Y, French CA, Cameron MJ, Nayar R, et al. NUT midline carcinoma: a neoplasm with diagnostic challenges in cytology. Cytopathol Official J Brit Soc Clin Cytol. 2011;22(6):414–7.
34. Stelow EB. A review of NUT midline carcinoma. Head Neck Pathol. 2011;5(1):31–5. PubMed PMID: 21221870. Pubmed Central PMCID: 3037455.
35. French CA, Ramirez CL, Kolmakova J, Hickman TT, Cameron MJ, Thyne ME, et al. BRD-NUT oncoproteins: a family of closely related nuclear proteins that block epithelial differentiation and maintain the growth of carcinoma cells. Oncogene. 2008;27(15):2237–42. PubMed PMID: WOS:000254621300014. English.
36. French CA, Miyoshi I, Aster JC, Kubonishi I, Kroll TG, Dal Cin P, et al. BRD4 bromodomain gene rearrangement in aggressive carcinoma with translocation t (15;19). Am J Pathol. 2001;159(6):1987–92. PubMed PMID: WOS:000172457400003. English.
37. Schwartz BE, Hofer MD, Lemieux ME, Bauer DE, Cameron MJ, West NH, et al. Differentiation of NUT midline carcinoma by epigenomic reprogramming. Cancer Res. 2011;71(7):2686–96. PubMed PMID: WOS:000289057600029. English.

38. Engleson J, Soller M, Panagopoulos I, Dahlen A, Dictor M, Jerkeman M. Midline carcinoma with t (15;19) and BRD4-NUT fusion oncogene in a 30-year-old female with response to docetaxel and radiotherapy. BMC Cancer. 2006;6. PubMed PMID: WOS:000237264000001. English.
39. Haack H, Johnson LA, Fry CJ, Crosby K, Polakiewicz RD, Stelow EB, et al. Diagnosis of NUT midline carcinoma using a NUT-specific monoclonal antibody. Am J Surg Pathol. 2009;33(7):984–91. PubMed PMID: WOS:000268043400003. English.
40. French CA, Miyoshi I, Kubonishi I, Grier HE, Perez-Atayde AR, Fletcher JA. BRD4-NUT fusion oncogene: a novel mechanism in aggressive carcinoma. Cancer Res. 2003;63(2):304–7.
41. Haack H, Johnson LA, Fry CJ, Crosby K, Polakiewicz RD, Stelow EB, et al. Diagnosis of NUT midline carcinoma using a NUT-specific monoclonal antibody. Am J Surg Pathol. 2009;33(7):984–91. PubMed PMID: 19363441. Pubmed Central PMCID: 2783402.

Lymphomas of the Thymus and Mediastinum

8

Philipp Ströbel and Alexander Marx

Introduction

Thymic B cells are a unique population of B lymphocytes that reside at the cortico-medullary junction of the thymus. They develop within the thymus from B lineage-committed progenitors and are not recirculating peripheral B cells [2–4]. Activation of STAT5 has been shown to be essential for B lineage commitment and proliferation and expansion of thymic B cells [5]. Thymic B cells have a highly activated phenotype [6, 7], and constitutive CD5 expression is one of their most distinctive features [8]. Activation through CD40 results in a high efficiency of antigen presentation, suggesting that thymic B cells play an important role in negative selection (i.e., elimination) of autoreactive thymocytes [7, 9]. There is evidence that thymic B cells, in contrast to other lymphoid cells, such as NK cells and lymphoid dendritic cells, are exported from the thymus. Thus, the thymus contributes not only to the formation of peripheral T cell, but also B-cell pools [4].

Especially in small mediastinal biopsies, consideration of epidemiology and clinical background are of vital importance in directing the pathologist in the optimal use of the available material. In children and young adults, where lymphomas account for approximately 12% of cases, the major differential diagnoses

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include neurogenic and germ cell tumors. Germ cell tumors with production of alpha-fetoprotein (AFP) or beta-chorionic-gonadotropin (HCG) can be safely diagnosed based on laboratory tests and imaging and biopsy is only needed in equivocal or non-secretory cases. Rapid onset of symptoms (such as airway compromise or pleural effusions), presentation as a medical emergency and elevated lactate dehydrogenase (LDH) levels especially in a child or young adult are highly suggestive of either a non-seminomatous germ cell tumor or a lymphoblastic lymphoma. In adults over 40 years, the most frequent entities (60%) are thymomas, thymic carcinomas, and endocrine tumors, while lymphomas account for only about 25–30% of cases. Paraneoplastic symptoms such as myasthenia gravis, pure red cell aplasia or hypogammaglobulinemia (Good syndrome) are virtually diagnostic for thymoma, while fever and night sweats are more suggestive of a lymphoma. Whereas exact subtyping of a thymoma in a biopsy is often not possible (nor required for the clinical management of the patient), the pathologist is expected to render a definitive diagnosis in the case of a lymphoma.

Although the differential diagnosis of mediastinal lymphomas is exhaustive in theory, the most frequent problems encountered in daily practice will be the following:

- the distinction between T-LBL, thymoma, and other small cell tumors (small neuroendocrine carcinoma, small round cell sarcomas)
- the distinction between lymphomas with frequent sclerosis (NS-CHL, PMBL, and gray zone lymphoma) from other sclerotic lesions, both reactive and neoplastic (e.g. sclerosing mediastinitis, germ cell tumors etc.) and, finally
- the distinction between NS-CHL, PMBL, and gray zone lymphoma, once the diagnosis of a mediastinal B-cell lymphoma has been established

Immunohistochemistry and Other Ancillary Studies It is prudent to perform a stepwise approach that can be slightly modified depending on the clinical information and the patient's age. One probate method is to order an H&E stain and as many unstained slides as possible for later immunohistochemical or molecular procedures, as required.

Take Home Messages

- The likelihood to diagnose a mediastinal lymphoma and the differential diagnosis are heavily influenced by the patient's demographic. The diagnostic approach should therefore always take the patient's age, clinical presentation, and laboratory parameters into account.
- Only nodular sclerosing Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, mediastinal gray zone lymphoma and T-lymphoblastic lymphoma are more frequently encountered in the mediastinum.
- In contrast to the management of epithelial tumors, where exact subtyping is usually not required, the pathologist is expected to render a definitive (final) diagnosis in the biopsy of a lymphoma.

- In sclerotic and cystic lesions, the underlying disease may not be sufficiently represented in a biopsy. In these situations, after careful examination of multiple sections of the biopsy, it is prudent not to render a definitive diagnosis and to recommend a repeat biopsy.

B-cell Lymphomas of the Thymus and Mediastinum

Primary Mediastinal Large B-cell Lymphoma (PMBL)

Definition and Terminology PMBL is an aggressive large B-cell lymphoma with distinctive clinical presentation and immunoprofile and a typical morphology, although PMBL cannot be reliably diagnosed on morphology alone. Since other large cell lymphomas can also involve the mediastinum, a definite diagnosis of PMBL requires clinical information (absence of widespread extrathoracic lymph node and bone marrow involvement).

Epidemiology PMBL accounts for 2–4% of all Non-Hodgkin lymphomas. It is mainly a disease of young adults (median 35 years) with a 2:1 predilection for females. Patients are considerably younger than patients with other diffuse large cell lymphomas (DLBCLs) [10].

Etiology and Pathogenesis PMBL is thought to arise from thymic B-cells [11], and virtually all patients present with a mass in the anterior mediastinum. The etiology of PMBL is unknown. There is no association with EBV infection. One study analyzing familial PMBL reported a variant of the mixed lineage leukemia (*MLL)* gene as potentially predisposing. The genetic and gene expression profile of PMBL (e.g., amplifications on chromosome 9p24.1 [*PDL1* and *-2* gene locus], chromosomal translocations involving the MHC class II transactivator (*CIITA*) gene on chromosome 16p13, or perturbation of the NFkB and JAK-STAT signaling pathway) are distinctly different from other DLBCL, but show considerable overlap with mediastinal Hodgkin lymphoma [12–15] and mediastinal gray zone lymphoma [16]. Since many PMBLs show downregulation of MHC molecules and overexpression of negative regulators of T-cell activation PDL-1 and -2 [14, 15, 17, 18], these alterations are believed to result in the immune escape of the tumor.

Clinical Considerations and Prognosis Most patients present with symptoms related to a bulky anterior mediastinal mass, such as superior vena cava syndrome, dyspnea, and pleural or pericardial effusions. Gene expression profiling suggests that rare cases of PMBL can present without mediastinal involvement [19]. Drenching night sweats, fatigue and fever as well as skin rashes or itching may be present. Lactate dehydrogenase is usually markedly elevated [10]. Infiltration of other intrathoracic organs such as lung, pleura, or chest wall is frequent. Supraclavicular lymph nodes are often involved. At progression, PMBL frequently

involves extranodal tissues, such as the kidney or the CNS, but widespread lymph node or bone marrow involvement are distinctly rare even in advanced cases [10]. Compared to other DLBCL, PMBL has a more favorable prognosis with a 5-year survival rate of 64% versus 46% for other DLBCL patients [14].

Histomorphology PMBL grows in sheets or clusters of large (2–5 times the size of a small lymphocyte) blastic cells with clear or pale eosinophilic cytoplasm. Most tumor cells are mononuclear, but intermingled Hodgkin/Reed–Sternberg cells may occur (Fig. 8.1a–c). A distinctive, but not invariable feature that is mainly found if the thymus is involved is presence of irregular fibrosis that can either be dense or more delicate creating an alveolar-like pattern (Fig. 8.1d–f). These features are of no prognostic relevance [10].

Immunohistochemistry and Other Ancillary Studies The key immunohistochemical findings are summarized in Table 8.1. PMBL shows diffuse expression of B-cell markers such as PAX5 (strong), OCT2, BOB.1, CD19, CD20, or CD79a, but surface immunoglobulins and light chains are not expressed. CD30 is present in >80% of cases, but usually weak and more focal than in Hodgkin lymphoma. Many tumors (>75%) express CD23 and p63. CD15 is negative (Fig. 8.2) [20]. Clonality assays show monoclonal immunoglobulin rearrangements with a post-germinal center phenotype (Ig-class switch, somatic hypermutation) [21].

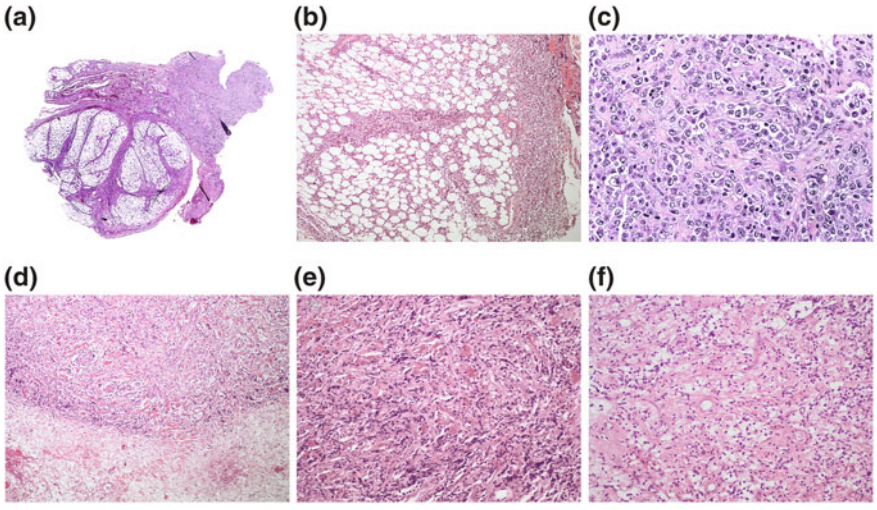

Fig. 8.1 H&E morphology of primary mediastinal large B cell lymphoma. **a+b** Low power view showing solid as well as diffuse infiltrative tumor areas. **b** Higher magnification shows interstitial infiltration of fat cells by a tumor with clear cell morphology. At this magnification, one possible differential diagnosis would be mediastinal seminoma. **c** High power magnification shows large tumor cells with more basophilic cytoplasm growing in solid nests with some interstitial matrix. Some tumor cells share similarities with Hodgkin cells. **d–f** Typical dense fibrosis found in many cases. Some cases **(f)** show a slight inflammatory background, which is however quite different from the distinct and dense inflammatory background seen in Hodgkin lymphoma

Table 8.1 Informative immunohistochemical markers in the differential diagnosis of large B cell lymphomas in the mediastinum

	PMBL	MGZL	NS-CHL	DLBCL
CD20	++	+/++	–/(+)	++
PAX5	++	++	(+)	++
BOB.1	++	++	–/(+)	++
OCT2	++	++	∓	++
MAL	60–70%	30–40%	20%	–
CD30	(+)/+	++	++Golgi pattern	∓
CD15	–	+	+ (>75%)	–
s-Immunoglobulins	–	–	–	++
CD45	++	∓	–	++
HLA class 1 and 2	–	∓/++	–	++
LMP	–	∓	∓(<25%)	–

PMBL Primary mediastinal large B-cell lymphoma, *MGZL* Mediastinal gray zone lymphoma, *NS-CHL* Mediastinal Hodgkin lymphoma, *DLBCL* Diffuse large B-cell lymphoma (Refs. [16, 20, 22, 23])

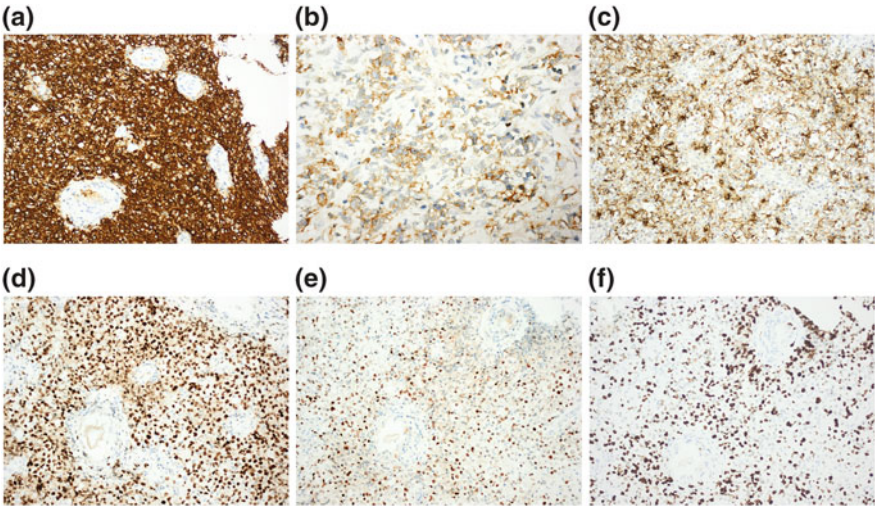

Fig. 8.2 Immunohistochemical features of primary mediastinal large B cell lymphoma. **a** Strong and diffuse expression of CD20, **b** Weak and focal expression of CD30, **c** moderate expression of CD23, **e** diffuse nuclear expression of OCT2, **d** nuclear expression of p63, **e** high proliferation index (ki67)

Differential Diagnosis and Pitfalls Major differential diagnoses include mediastinal involvement of a nodal diffuse large B-cell lymphoma, mediastinal Hodgkin lymphoma, and mediastinal gray zone lymphoma. The distinction between these entities is important, since there are major differences in treatment and prognosis.

Clinical information on presence of widespread extramediastinal dissemination should be obtained to rule out DLBCL. A background of inflammatory cells that is typical of Hodgkin lymphoma is absent in PMBL.

Pitfalls Remnants of an infiltrated thymus (e.g., Hassall corpuscles) and residual keratin-positive epithelial cells can mimic a thymoma or thymic carcinoma. On the other hand, some thymic carcinomas, including rare variants of lymphoepithelioma-like carcinoma, can have clear cell features with or without a rich inflammatory background that may even contain eosinophils, and may show weak or only focal keratin expression. In mediastinal lymph nodes involved by PMBL, the infiltration pattern may be carcinoma-like with colonization of the marginal sinus, a feature that is also seen in anaplastic large T-cell lymphomas (ALCL). It is important to remember that both PMBL and many carcinomas (as well as thymomas) express p63. Mediastinal germ cell tumors (especially seminomas) can have a clear cell morphology, and embryonal carcinomas express CD30 and p63.

Suggested Strategy to Confirm PMBL in a Small Biopsy If PMBL is suspected on morphology, the initial set of stainings should include CD5, CD15, CD20, CD30, CD23, p63, BOB.1/PAX5, LMP, ki67. Depending on the context, additional markers should include keratin (epithelial tumors), S100 (neurogenic tumors and melanoma), and SALL4 (germ cell tumors). Clonality assays are usually not required for diagnosis.

Take Home Messages

- PMBL occurs predominantly in young females and is usually restricted to the mediastinum and supraclavicular lymph nodes.
- Although PMBL, mediastinal Hodgkin lymphoma and mediastinal gray zone lymphomas are related diseases, their distinction is relevant due to differences in treatment and prognosis.
- The morphology and immunophenotype of PMBL, in the appropriate clinical setting, are sufficiently specific to render a definite diagnosis in most cases and molecular studies are usually not required.
- Rare cases with morphological and immunohistochemical features intermediate between PMBL and Hodgkin lymphoma fall into the “gray zone” category.

Mediastinal Hodgkin Lymphoma (NS-CHL)

Definition and Terminology Mediastinal Hodgkin lymphoma is a monoclonal B-cell neoplasm arising in the thymus, the mediastinal lymph nodes, or both. Its histology is characterized by Reed–Sternberg cells and their variants in a rich inflammatory background [24]. For unknown reasons, virtually all mediastinal cases belong to the nodular sclerosis subtype (NS-CHL).

Epidemiology NS-CHL is by far the most frequent mediastinal lymphoma and accounts for up to 70% of cases. Like primary mediastinal large B-cell lymphoma (PMBL), it is mainly a disease of young adults with a 2:1 female predominance. NS-CHL is most common among Caucasians in industrialized countries [25].

Etiology and Pathogenesis NS-CHL is thought to arise from thymic germinal center B cells [26] that have escaped apoptosis. The major molecular pathways thought to contribute to the pathogenesis of NS-CHL (NFkB and JAK-STAT signaling, evasion from apoptosis, impaired MHC class II regulation) are shared with PMBL and both diseases are closely related on gene expression [14, 26]. The etiology of NS-CHL is unknown. Only a minority of cases (10–25%) is associated with EBV [27, 28].

Clinical Considerations and Prognosis The clinical presentation of NS-CHL is very similar to PMBL. Most cases are in Ann-Arbor [29] stage II with a mediastinal mass (thymus and mediastinal lymph nodes) and supraclavicular or lower cervical lymph nodes. Infiltration of lung, pericardium or chest wall is possible. B symptoms (fatigue, fever, and night sweats) are often associated with higher clinical stage and increased risk of disseminated disease and are therefore considered risk factors [30]. With modern treatment, Hodgkin lymphoma is curable in at least 80% of patients [30].

Histomorphology The diagnosis of NS-CHL requires the identification of multinucleated Reed–Sternberg (RS) cells or their variants (the mononuclear Hodgkin cells, the so-called "mummified" RS cells and lacunar cells). Detection of RS cells may sometimes require multiple sections. RS cells represent the neoplastic cell population in Hodgkin lymphoma and are typically accompanied by a rich background of mixed inflammatory cells including T cells, eosinophils, plasma cells, histiocytes, and granulocytes. In addition to the cellular component, there is variable fibrosis. Involvement of the thymus by NS-CHL often results in multilocular cystic changes (Fig. 8.3). The thymic epithelium is usually destroyed, but NS-CHL can rarely also evoke pseudoepitheliomatous hyperplasia.

Immunohistochemistry and Other Ancillary Studies CD30 is the most important screening marker for NS-CHL and typically shows moderate to strong membranous staining with paranuclear accentuation of the Golgi area. CD15 is positive in at least 75% of cases and, if present, is a strong argument in favor of HL [20]. PAX5 is a very useful marker to confirm the B-cell lineage in the $\geq 80\%$ of cases that are negative for CD20. Expression of PAX5 in RS and Hodgkin cells is typically weaker than in small reactive B cells and Non-Hodgkin lymphomas (including PMBL) (Fig. 8.4). In line with the concept that the regulation of the immunoglobulin machinery is disturbed in HL, the transcription factors BOB.1 and OCT2 are often negative [20]. In the inflammatory background, T cells usually outnumber B cells and T-cell markers such as CD3 or CD5 may show rosetting around the neoplastic RS cells.

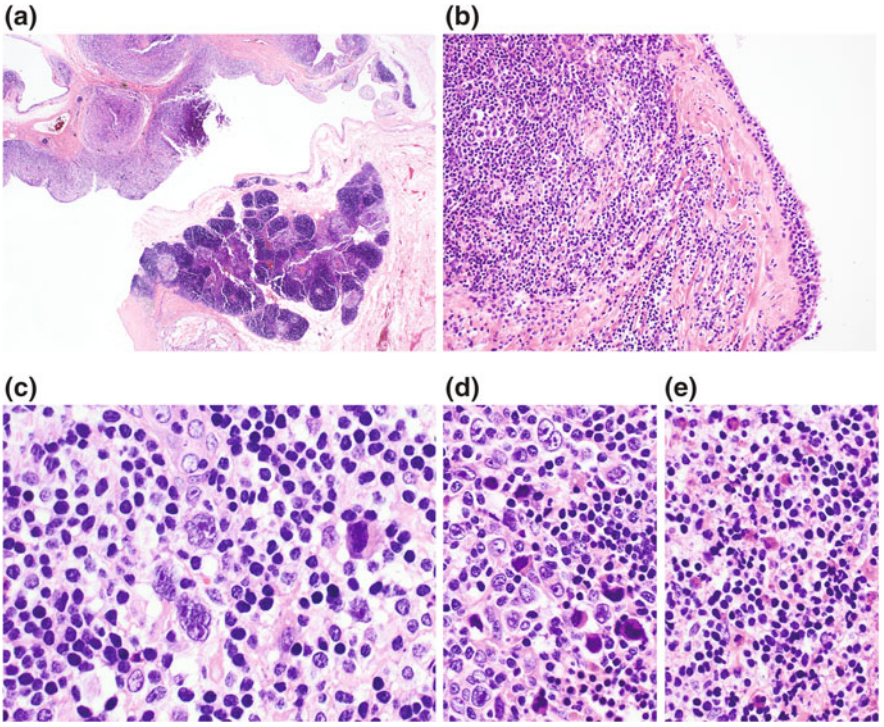

Fig. 8.3 H&E morphology of mediastinal Hodgkin lymphoma. **a** Low power view showing nodular tumor infiltrates (corresponding to a nodular sclerosis pattern) with marked secondary cystic changes in the upper portion. Lower half of the image shows a well-preserved thymic remnant with some cholesterol granulomas next to it. **b** Higher magnification shows the cyst wall covered by a ciliated epithelium next to tumor infiltrates. **c** High power view showing multinuclear Reed–Sternberg cells and one mummified cell with condensed nuclear chromatin. **d** Numerous mummified cells next to several mononuclear Hodgkin- and multinuclear Reed–Sternberg cells. **e** Dense mixed inflammatory background with numerous eosinophils

Differential Diagnosis and Pitfalls In addition to PMBL and mediastinal gray zone lymphoma (Table 8.1), the differential diagnosis also includes T cell/histiocyte-rich large B-cell lymphoma (THRLBCL) [31] and ALK+ anaplastic large T-cell lymphoma [32]. The tumor cells in THRLBCL may resemble Reed–Sternberg and Hodgkin cells, but are CD30 and CD15 negative. In addition, the inflammatory background in THRLBCL is mainly composed of T cells and macrophages without eosinophils and is distinctly different from Hodgkin lymphoma. Anaplastic large T-cell lymphoma (ALCL) with/without ALK expression can be a differential diagnosis [32], but the immunophenotype (CD30+, ALK±, CD4+ CD5+, perforin+, PAX5 negative, CD15 usually negative) is sufficiently different from Hodgkin

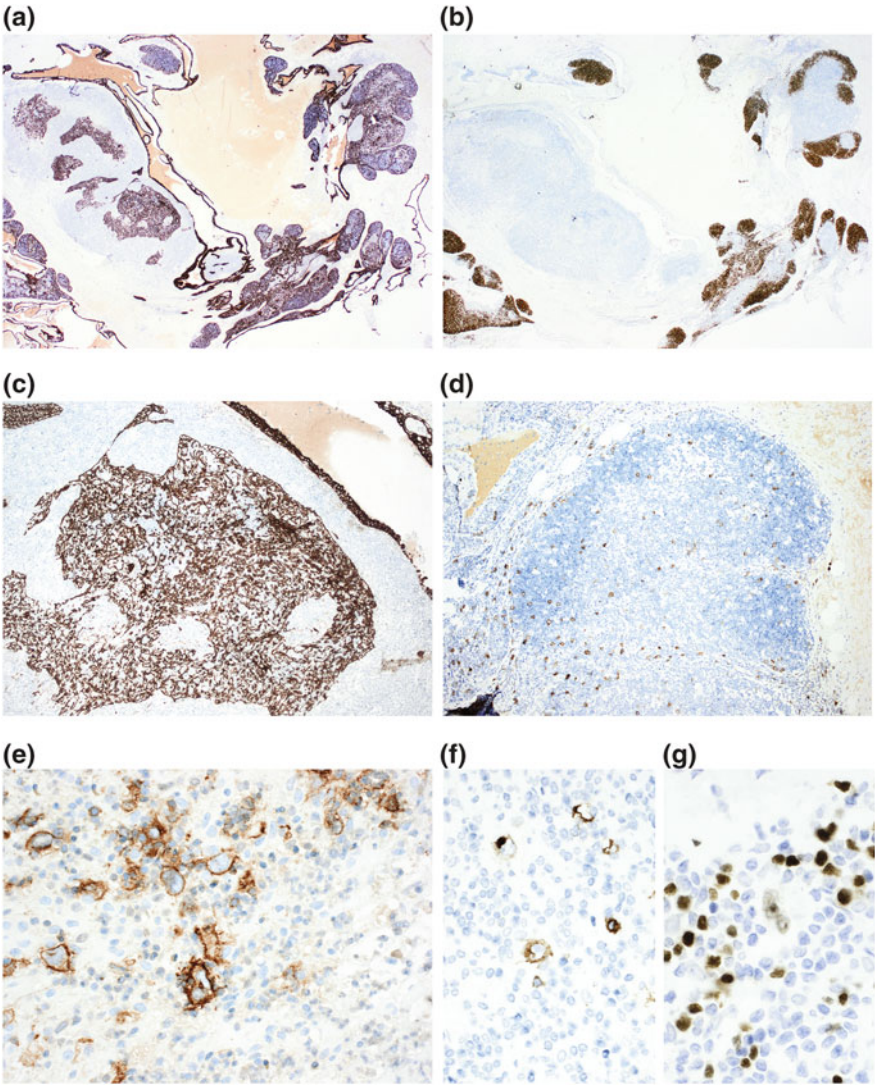

Fig. 8.4 Immunohistochemical features of mediastinal Hodgkin lymphoma. **a** Keratin staining at low power magnification shows massive cystic changes with normal thymic remnants to the right and nodular tumor infiltrates with some residual epithelial structures to the left. **b** TdT staining at low power magnification of the same area shows strong demarcation of normal thymic cortex, with depletion of immature T cells in the areas colonized by the lymphoma. **c** Detail of (**a**) showing colonization and destruction of the epithelial thymic meshwork by the lymphoma. **d** CD30 staining showing incipient colonization of a thymic lobule by Hodgkin cells. **e** CD30 staining in an established tumor area shows strong membranous staining. In this image, the typical Golgi accentuation of the staining is not obvious. **f** moderate expression of CD15. **g** Nuclear Pax5 staining with characteristic attenuation in tumor cells compared to the surrounding non-neoplastic reactive B cells

lymphoma (CD30+, CD15+, PAX5+, CD4/CD5 negative, perforin negative) to allow for a safe distinction. Of note, 5% of otherwise classical Hodgkin (and ALK-negative) lymphomas show aberrant expression of T-cell antigens (usually CD2, CD3, or CD4) [33, 34], a feature considered an adverse prognostic factor [35].

Apart from lymphomas and soft tissue tumors (such as solitary fibrous tumors or inflammatory myofibroblastic tumors) or desmoplastic mesothelioma, the differential diagnosis also includes sclerosing mediastinitis with or without a granulomatous component. Sclerosing mediastinitis is not a single entity, but rather a group of infectious and noninfectious inflammatory conditions. The epidemiology is similar to Hodgkin lymphoma, since many patients are young females. The most important underlying conditions are histoplasmosis and mycobacteria, IgG4-related disease, sarcoidosis and pharmacologic substances such as methysergid. Suitable bacterial (such as PAS, Grocott, or fast-acid) and immunohistochemical stainings (IgG/IgG4) are therefore advisable if sclerosing mediastinitis is suspected.

Pitfalls As illustrated in Fig. 8.3, NS-CHL with infiltration of the thymus frequently induces massive cystic changes with and without dense fibrosclerosis, features that are also seen in mediastinal seminoma. Since these secondary changes can be sharply separated from the neoplastic infiltrates, it is easy to miss the tumor on small biopsies. The acquired cysts can be lined by squamous nonkeratinizing, but also columnar or ciliated epithelium and may mimic various benign cystic lesions. The rare lymphoma-induced pseudoepitheliomatous hyperplasia can be mistaken for thymoma on small biopsies.

Suggested Strategy to Confirm NS-CHL in a Small Biopsy Immunohistochemical stainings should include CD5, CD15, CD20, CD30, PAX5, and LMP. CD15 and LMP, if positive, have a high predictive value for NS-CHL [20]. A high level of suspicion is mandatory in cases with multiple cysts, epithelial hyperplasia, or granulomas.

Take Home Messages

- NS-CHL is the most frequent mediastinal lymphoma with a predilection for young females (similar to PMBL)
- Virtually all cases are of the nodular sclerosis subtype
- NS-CHL can induce massive cystic change in the thymus which may obscure the underlying lymphoma
- CD30, CD15, CD20, PAX5, and CD5 are the most relevant immunohistochemical markers required for the diagnosis
- In cases with extensive sclerosis, the differential diagnosis also comprises non-neoplastic conditions such as sclerosing mediastinitis.

B-cell Lymphoma, Unclassifiable, with Features Intermediate Between Diffuse Large B-cell Lymphoma and Classical Hodgkin Lymphoma (Mediastinal Gray Zone Lymphoma)

Definition and Terminology Mediastinal gray zone lymphoma (MGZL) is a B-cell lymphoma with clinical, morphological and immunohistochemical features that overlap with mediastinal Hodgkin lymphoma (NS-CHL) and primary mediastinal large B-cell lymphoma (PMBL). Some tumors simultaneously show areas corresponding to NS-CHL, PMBL and MGZL, others show heterogeneity e.g. between thymus and affected lymph nodes, suggesting that NS-CHL, MGZL, and PMBL represent related tumors within a disease spectrum.

Epidemiology Like NS-CHL and PMBL, mediastinal gray zone is predominantly a disease of young adults, but occurs more frequently in males [22, 36].

Etiology and Pathogenesis The etiology of MGZL is unknown. MGZL shares many key molecular features with NS-CHL and PMBL, such as alterations at the 9p24.1 (the *Jak2/PDL2* gene locus), amplifications at 2p16.1 (the *REL/BCL11A* gene locus), or rearrangements of the *CIITA* gene locus at 16p13.13 [22]. The epigenetic profile of MGZL shows both overlapping and divergent alterations in MGZL, NS-CHL, and PMBL, while MGZL and extramediastinal diffuse large B-cell lymphoma are distinctly different [37]. Only 5–10% of MGZL are associated with EBV infection [16].

Clinical Considerations and Prognosis The clinical presentation is not different from NS-CHL or PMBL. Symptoms (dyspnea, pericardial and pleural effusions, etc.) are frequently related to a bulky anterior mediastinal mass. Genetic data suggest that tumors with features corresponding to MGZL can occur at other sites without mediastinal involvement [22]. In contrast to PMBL, extrathoracic parenchymal organs (such as kidney or CNS) are rarely involved as tumors progress [38].

Histomorphology The majority of cases resembles NS-CHL, but with unusual features, such as sheeting out of Hodgkin and Reed–Sternberg (RS) cells. The inflammatory background is usually less pronounced than in NS-CHL. Most of the remaining cases resemble PMBL, but show numerous Hodgkin/RS or lacunar cells (Fig. 8.5) [16].

Immunohistochemistry and Other Ancillary Studies The B-cell program is often retained with co-expression of CD20 and CD30 (often strong and with Golgi pattern). Transcription factors PAX5, OCT2, or BOB.1 are usually positive and thus more closely resemble PMBL than NS-CHL. CD15 is expressed in the majority of cases (Fig. 8.5) [16].

Differential Diagnosis and Pitfalls The differentiation of MGZL from NS-CHL and PMBL is important, since the behavior of MGZL is more aggressive and the outcome is worse. Apart from this distinction, the same differential diagnoses (including seminomas and carcinomas) apply.

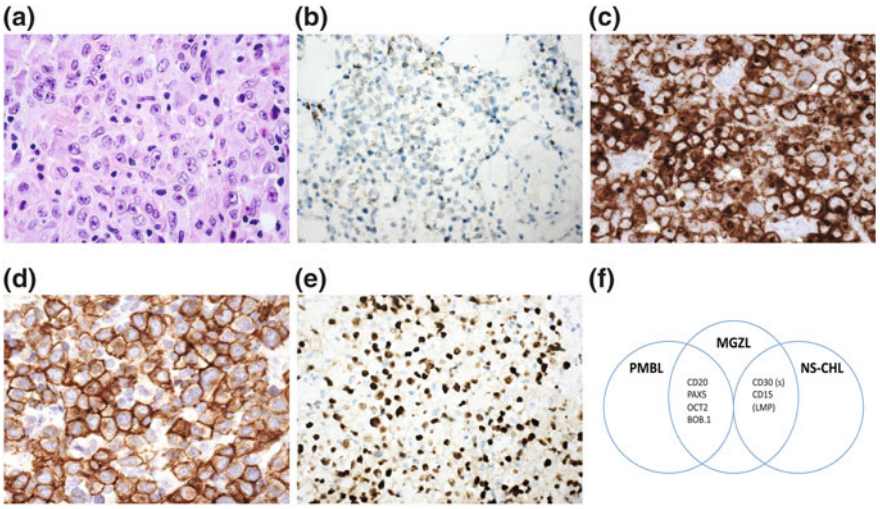

Fig. 8.5 H&E morphology and immunohistochemical features of mediastinal gray zone lymphoma. **a** Sheets of large polymorphic tumor cells with some resemblance towards Hodgkin and Reed–Sternberg cells. No inflammatory background. **b** In this example, there was subtotal loss of CD20 expression. **c** Strong and diffuse expression of CD30 with prominent Golgi pattern. **d** Strong expression of CD15, **e** strong, but variable nuclear expression of OCT2 (a similar pattern would be expected for PAX5). **f** Overlapping immunohistochemical features between primary mediastinal large B cell lymphoma (PMBL), mediastinal grey zone lymphoma (MGZL), and nodular sclerosis Hodgkin lymphoma (NS-CHL)

Take Home Messages

- Mediastinal gray zone lymphomas (MGZL) represent a spectrum of morphological and immunophenotypic features that are intermediate between classical Hodgkin lymphoma (NS-CHL) and primary mediastinal large B-cell lymphoma (PMBL).
- In contrast to NS-CHL and PMBL, MGZL is more common in young men.
- Sheeting out of Hodgkin and Reed–Sternberg cells and co-expression of CD20 and CD30 are typical histological and immunohistochemical findings.

Extranodal Marginal Zone Lymphoma (MALT Lymphoma) of the Thymus and Mediastinum

Definition and Terminology Extranodal marginal zone lymphoma (MALT lymphoma) of the thymus is an indolent mature B-cell lymphoma composed of small monocytoid lymphocytes and plasma cells that infiltrate and destroy the thymic

epithelium. IgA expression is a distinctive feature of most thymic MALT lymphomas.

Epidemiology Thymic MALT lymphoma is rare with less than 100 cases reported in the english literature [39–45]. Females are three times more frequently affected than males. The typical patient is an Asian female aged 40–60 years. The disease is highly unusual in children and adolescents [46].

Etiology and Pathogenesis Many patients have a history of long standing autoimmune disease, usually Sjögren syndrome (by far most frequent), rheumatoid arthritis, or systemic lupus erythematosus [39, 47, 48]. Rare cases develop in a micronodular thymoma [49], which should therefore always be checked for monoclonal B-cell populations. The chromosomal alterations found in thymic MALT lymphomas are similar to those in other autoimmunity-driven MALT lymphomas, such as thyroid or salivary gland lymphomas [48]. About 50% of cases show trisomy 3 (an alteration also found in many other MALT lymphomas), whereas translocations involving the *MALT1* and *IGH* gene are absent [48]. There is evidence that silencing of tumor suppressor genes (such as *p14/ARF*, *CDH1*, and *TIMP3*) through methylation is involved in the pathogenesis of thymic MALT lymphoma.

Clinical Considerations and Prognosis Most cases are incidental findings in elderly patients with long standing Sjögren syndrome. Some patients complain of chest pain or shortness of breath, which can either be due to the mediastinal mass or to infiltration of the lung [43]. Some patients show amyloid deposition [50]. Lymph nodes of the head and neck, axilla or mediastinum can be involved [51]. Most patients have increased IgA and restricted light chains in their serum. The prognosis of thymic MALT lymphoma is excellent. Patients with low-stage disease can be cured by surgical resection, patients with higher stage disease may require chemo- or radiotherapy.

Histomorphology On macroscopy, many cases show prominent cystic change. At low-power magnification, there is effacement of the normal lobular structure of the thymus. The neoplastic lymphocytes are monotonous and have a moderate amount of pale cytoplasm that is more pronounced around the so-called lymphoepithelial lesions (i.e., infiltration and destruction of thymic epithelium by the lymphoma) and cysts. Plasma cells are seen intermingled or in aggregates and usually show immunohistochemical light chain restriction (Fig. 8.6a–c).

Immunohistochemistry and Other Ancillary Studies Tumor cells are positive for CD19, CD20, or CD79a and negative for CD5, CD10, or CD23. CD23 highlights effaced or colonized meshworks of follicular dendritic cells [49]. The plasma cells express CD138 and usually show light chain restriction. Strikingly, more than 70% of thymic MALT lymphomas express IgA, which discriminates them from non-thymic MALT lymphomas, which typically express IgM or IgG, and only rarely IgA [39, 52]. Cytokeratins are very helpful in highlighting the lymphoepithelial lesions (Fig. 8.6).

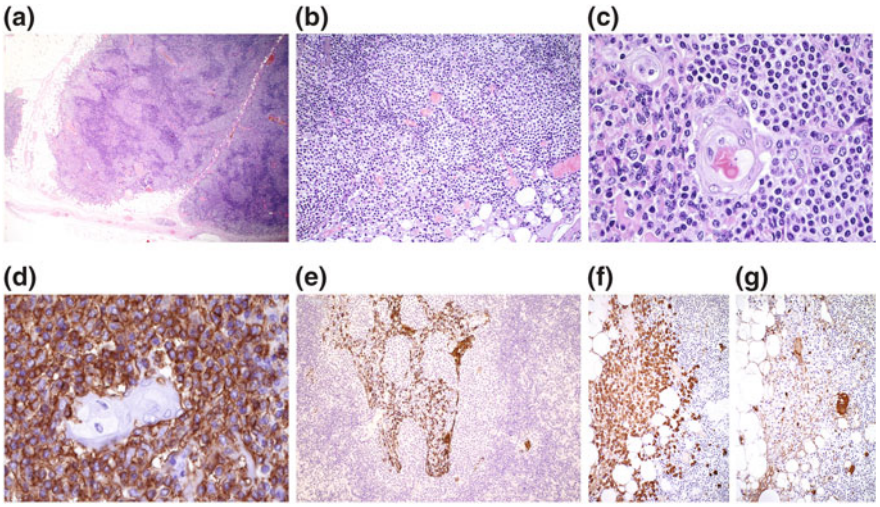

Fig. 8.6 H&E morphology and immunohistochemical features of extranodal marginal zone lymphoma of the thymus. **a** Low power view shows vaguely nodular infiltrates that efface the lobular structure of the thymus. **b** Higher magnification reveals monotonous lymphocytic infiltrates with pale cytoplasm. **c** Small monotonous lymphocytes surrounding residual Hassal corpuscles. Few scattered plasmacytes and extracellular deposition of homogenous eosinophilic material (eventually AL-amyloid). **d** Tumor cells but not the residual Hassal corpuscle show strong and diffuse expression of CD20. **e** Keratin staining highlights massive colonization and destruction of the thymic epithelial meshwork (lymphoepithelial lesions). **f**, **g** kappa and lambda staining showing unequivocal monotypic light chain restriction in many instances

Differential Diagnosis and Pitfalls Thymic follicular hyperplasia is a differential diagnostic consideration, since MALT lymphomas can also harbor reactive lymphoid follicles (Fig. 8.7a–c). Most patients with thymitis have myasthenia gravis (MG), which is a helpful clinical discriminator (of note, some MG patients may also have Sjögren disease [53]). In thymic follicular hyperplasia, there are no lymphoepithelial lesions and usually no cysts, and the B cells do not show light chain restriction. A much more challenging differential diagnosis is a recently described entity, the so-called thymic hyperplasia with lymphoepithelial sialadenitis-like features (TH-LESA) (Fig. 8.7g–j) [54]. The clinical setting is different, since men and women are equally affected and there is no association with autoimmune disease [54]. Low power magnification strikingly resembles MALT lymphoma with prominent cystic change and (often "incomplete" or equivocal) lymphoepithelial lesions. However, monocytoid B cells are absent, light chain expression is polytypic and molecular tests do not show monoclonal B-cell receptor rearrangements. Progression into MALT lymphoma has not been reported.

While rarely observed in the thymus, most other B-cell lymphomas that have been described either in the thymus or the mediastinal lymph nodes (bona fide primary

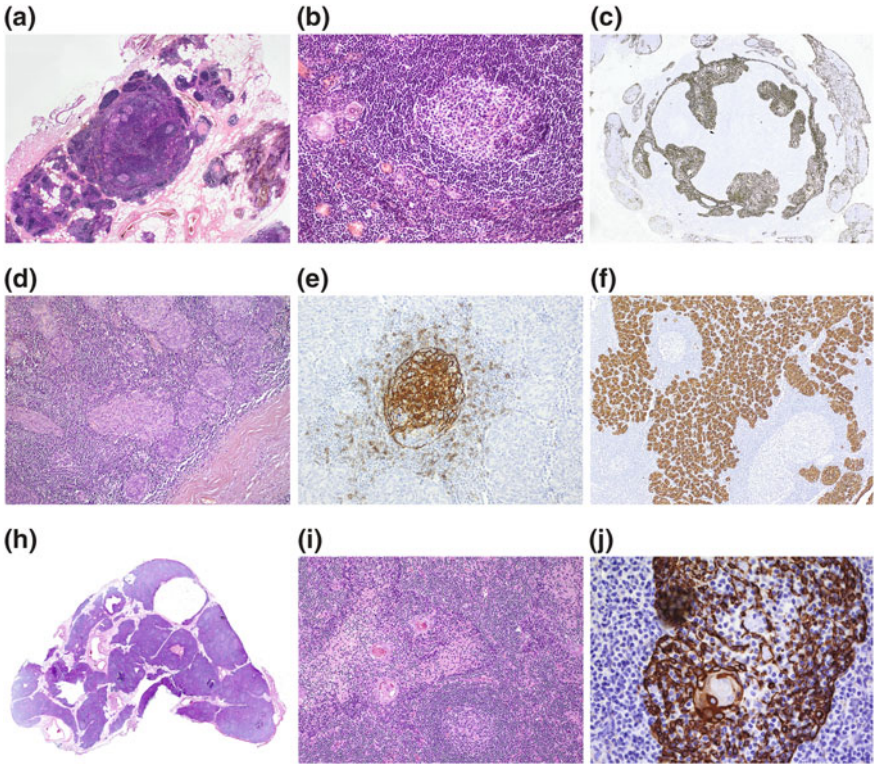

Fig. 8.7 Histological mimics of marginal zone lymphoma of the thymus. **a–c** Thymic lymphofollicular hyperplasia (thymitis) in a young female with myasthenia gravis. **a** Low power view showing so-called lymph node like transformation of a medullary area by numerous lymphoid follicles. **b** Detail of the same case showing reactive lymphoid follicle with germinal centre in the vicinity of several Hassal corpuscles. **c** Keratin stain (low power view) shows massive distention and condensation, but not destruction, of the medullary epithelial meshwork, while the thymic cortex seems uninvolved. **d–f** Micronodular thymoma with lymphoid stroma (MNT). Tumor grows in multiple small epithelial nodules with bland spindle cell morphology resembling type A thymoma, surrounded by a dense lymphoid stroma (**d**) that may contain numerous lymphoid follicles. Of note, some MNT have been shown to contain monoclonal B cell populations and rarely overt lymphomas including MALT lymphoma. **e** CD23 staining in this case shows regular meshwork of follicular dendritic cells with no evidence of colonization. **f** Low power view of keratin staining highlights multiple epithelial nodules surrounded by a dense lymphoid stroma that contains several lymphoid follicles. **h–j** So-called thymic hyperplasia with lymphoepithelial sialadenitis-like (LESA) features in a 45 years old male patient without autoimmune symptoms. **h** Low power view showing dense lymphoid infiltrates with effacement of thymic lobular structures and several cysts. At this magnification, the picture is indistinguishable from thymic MALT lymphoma. **i** Higher magnification shows condensed and seemingly colonized epithelial structures with a few Hassal corpuscles and surrounding lymphofollicular stroma. Again, the morphology is indistinguishable from thymic MALT lymphoma. However, the typical pale cytoplasm seen in most MALT lymphomas is absent. **j** Keratin stain reveals equivocal epithelial colonization by the lymphocytes. In this situation, B clonality assays are mandatory to safely rule out a lymphoma. At extended follow-up, the patient was well without evidence of disease

mediastinal lymphomas) include follicular lymphoma [49], nodal marginal zone lymphoma, diffuse large B-cell lymphoma, and Burkitt lymphoma.

Specific Considerations in Small Biopsies Cystic change in a "clear cell" monotonous lymphocytic background is an important diagnostic clue. The major differential diagnosis in this setting is thymic hyperplasia with lymphoepithelial sialadenitis-like features. Immunohistochemistry should be directed to demonstrate lymphoepithelial lesions (keratin), a prominent monotypic B-cell population (CD5, CD20), and plasma cells with expression of IgA or IgG and kappa or lambda light chain restriction. Molecular B-cell clonality assays are not mandatory in cases with unequivocal light chain restriction on immunohistochemistry, but can be helpful in more difficult cases.

Take Home Messages

- The clinical background information (older adults, often Asian females with a history of Sjögren syndrome) is an important clue to the diagnosis. This setting is different from the typical patient with thymic follicular hyperplasia (young females with myasthenia gravis)
- Cystic change of the thymus is frequent in MALT lymphoma and rare in thymic follicular hyperplasia
- Demonstration of unequivocal lymphoepithelial lesions (keratin stain) and of a partially clear cell lymphoplasmacellular infiltrate with light chain restriction (CD20 or CD79a, CD138, kappa, lambda) are morphological key features. IgA expression, when present, supports a thymic origin of the lymphoma. Clonality assays may be necessary for the distinction of MALT lymphoma from its closest mimic, thymic hyperplasia with lymphoepithelial sialadenitis-like features.

T-cell Lymphomas of the Thymus and Mediastinum

General Remarks

T-Lymphoblastic Lymphoma (T-LBL)

Definition and Terminology T-lymphoblastic lymphoma (T-LBL) is a rare aggressive neoplasm of T-cell-precursors. The term lymphoblastic lymphoma is based on the clinical presentation and describes a mediastinal disease with a predominantly nodal distribution and with no or minimal bone marrow involvement at diagnosis (85% of cases). By convention, the 15% of cases with an identical morphology, but with more than 25% bone marrow involvement or leukemic spread into the peripheral blood are termed T-lymphoblastic leukemia (T-ALL).

Epidemiology T-LBL is rare and accounts for only 1–2% of all non-Hodgkin lymphomas. It is mainly a disease of adolescents and young adults and occurs more

frequently in males than in females. T-LBL appears to be somewhat more frequent in developing countries [55].

Etiology and Pathogenesis The etiology of T-LBL is unknown. Persons with constitutional mismatch repair deficiency (CMMRD), a rare genetic disorder with inherited bi-allelic (homozygous) mutations of one of the mismatch repair genes *MLH1*, MSH2, PMS2, or MSH6 are at high risk to develop T-LBL [56]. The pathogenesis of T-LBL/T-ALL has been extensively studied and the key molecular events are well known [57–59]. Tumors are thought to arise from transformed hematopoietic progenitors primed toward the T-cell lineage. The core oncogenic program in T-LBL and T-ALL is constitutive activation of NOTCH signaling, together with loss of the tumor suppressor genes *p16/INK4A* and *p14/ARF* at the chromosome 9p21 gene locus. In addition, there are numerous chromosomal translocations, which usually place oncogenic transcription factors involved in cell cycle signaling, cell growth and proliferation, chromatin remodeling, T-cell differentiation, and self-renewal, under the control of strong T-cell-specific enhancers [58]. Many of these transcription factors play important roles at specific stages of early T-cell development. The most frequent of these (often mutually exclusive) translocations involve the *T-cell receptor alpha–delta* gene loci and multiple partner genes, including *HOX* genes (*TLX 1* and *3*), *MYC*, *TAL1*, *LMO1* and *2*, and *LCK*.

Clinical Considerations and Prognosis The onset of symptoms (related to a mass lesion in the mediastinum and/or pleural or pericardial effusions) is usually acute and often presents as a medical emergency. The prognosis of T-LBL with modern therapy is comparable to that of B-lymphoblastic lymphomas/B-ALL with a 5-year overall survival rate of 80–90% in children and 45–55% in adults. As central nervous system (CNS) relapse is common, CNS prophylaxis with high-dose chemotherapy and intrathecal therapy is standard [60]. Molecular subtyping does not appear to have major impact on outcome and has currently no role in clinical practice. T-LBL of the mediastinum can relapse as dendritic cell tumors [61, 62], e.g., Langerhans cell histiocytosis, which carry the same T-cell receptor rearrangement as the initial lymphoma.

Histomorphology T-LBL shows extensive and destructive growth with infiltration and destruction of the thymus, although occasional remnant Hassall corpuscles may give the false impression of preserved epithelial structures (Fig. 8.8a, b, and f). Another typical and important feature is effacement of the typical lobular structures of the thymus with diffuse interstitial infiltration of the peri-thymic fat (Fig. 8.8d). Here, the tumor cells often grow in a string-of-pearls or streaming pattern (Fig. 8.8c). Importantly, the growth pattern in affected lymph nodes can sometimes be quite different, as tumor cells grow in a multinodular or pseudofollicular pattern that may mimic follicular lymphoma. On cytology, T-LBL consists of small to medium-sized lymphocytes with round or slightly irregular nuclei and small nucleoli, that may be vulnerable and cause smear artefacts. Mitotic and apoptotic figures (in contrast to the normal thymus or thymomas) are numerous (Fig. 8.9).

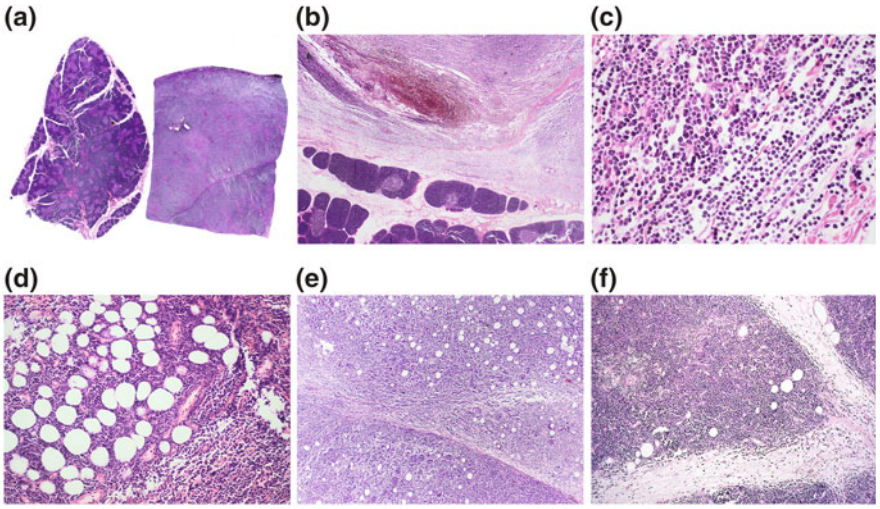

Fig. 8.8 H&E morphology of T-lymphoblastic lymphoma. **a** Low power view shows diffuse tumor infiltration with loss of the lobular structures seen in the adjacent sample of a normal juvenile thymus. **b** Another example where diffuse tumor infiltrates (upper half) abut on an unaffected region of the thymus. **c** Typical streaming (string-of pearls) pattern of tumor cells. Slight nuclear irregularities can be seen. **d** Characteristic septal infiltration pattern of the mediastinal fat. **e** Effacement of lobular thymic structures is an important clue. **f** Sometimes, lobular structures are seemingly preserved, as in this example, but the separation into cortex and medullar is completely lost due to tumor infiltration. The single Hassal corpuscle in the center of the lobule is a surviving epithelial remnant and may lead to a misdiagnosis of thymic hyperplasia or thymoma

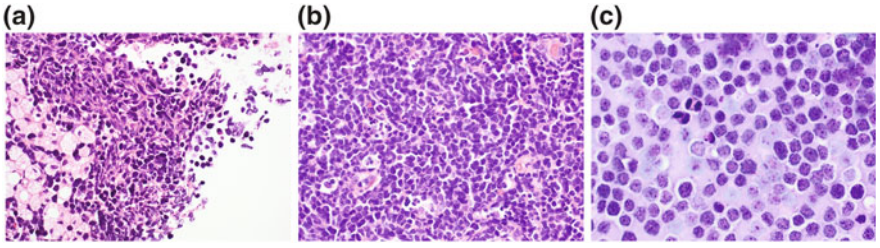

Fig. 8.9 Cytologic features of T-lymphoblastic lymphoma. **a** Highly irregular lymphocytes with hyperchromatic and polygonal nuclei next to foam cells (*macrophages*). Foam cells are nonspecific and can also occasionally be seen in thymomas and other mediastinal pathologies. **b** In addition to the irregular nuclear features, there are numerous apoptoses and mitoses, resulting in a starry-sky pattern. **c** Cytologic specimen again highlights the irregular nuclear contour and the speckled chromatin of the neoplastic lymphocytes as well as several apoptoses and mitoses

The cytologic atypia and the variability of the tumor cells contrasts with the regular features of non-neoplastic lymphocytes in the normal thymus or in thymomas and may be a diagnostic clue in small biopsies (Fig. 8.10).

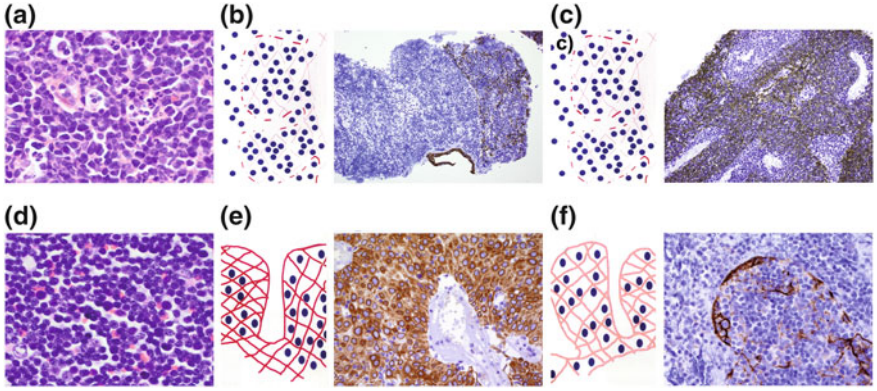

Fig. 8.10 Comparison between cytological and immunohistochemical features of T-lymphoblastic lymphoma (**a**–**c**) and thymoma (**d**–**f**). Direct comparison of T-LBL (**a**) and thymoma (**d**) highlights the fundamental cytological differences between the two conditions. The striking nuclear irregularities and multiple apoptoses and mitoses in T-LBL are in stark contrast to the rather monotonous non-neoplastic immature lymphocytes in thymomas. It is unusual to see many mitoses or apoptoses in a thymoma. The epithelial meshwork of the thymus (highlighted by keratin stainings) is destroyed T-LBL (**b**), but increased in thymomas (such as in this type B3 thymoma) (**e**). However, there are some important caveats and pitfalls to this important general rule. **c** Occasionally, T-LBL infiltrates generate ‚rhythmic' patterns that may mimic epithelial hyperplasia and may be somewhat difficult to differentiate e.g. from patterns seen in some type AB thymomas. A very important pitfall are thymomas with loss of keratin expression (**f**). In this example of a type B2 thymoma, the epithelial meshwork is preserved (as could be demonstrated e.g. by E-cadherin stains), but loss of keratin expression strikingly resembles the destructive colonization pattern of T-LBL. Therefore, use of several epithelial markers is recommended to assess the integrity of the thymic epithelial cell meshwork

Immunohistochemistry and Other Ancillary Studies The vast majority of T-LBL cases are diffusely positive for TdT. TdT is the most sensitive and specific marker to indicate the immature nature of the lymphocytes and should always be included [63]. Other markers, such as CD99, CD34, or CD1a are all expressed also in other cell types and should be interpreted with more caution (Fig. 8.11). Only CD3 is considered T-cell specific, whereas the expression of CD2, CD5, CD4, or CD8 is variable. Aberrant expression of CD79a or the myeloid antigens CD13 or CD33 is observed in 10–30% of cases and does not influence the diagnosis of T-LBL. In contrast, expression of CD19, PAX5, or myeloperoxidase is considered specific of B-cell or myeloid differentiation and results in the diagnosis of mixed phenotype lymphoma/leukemia [63]. T-LBL can be further subdivided into different stages of T-cell maturation, and this has some clinical and prognostic relevance [64]. In practice, the most reproducible distinction in paraffin material is between "immature" cortical (encompassing pro-/pre T-LBL) and "mature" (medullary) non-cortical T-LBL, based on presence of CD1a in cortical versus absence in non-cortical subtypes [63].

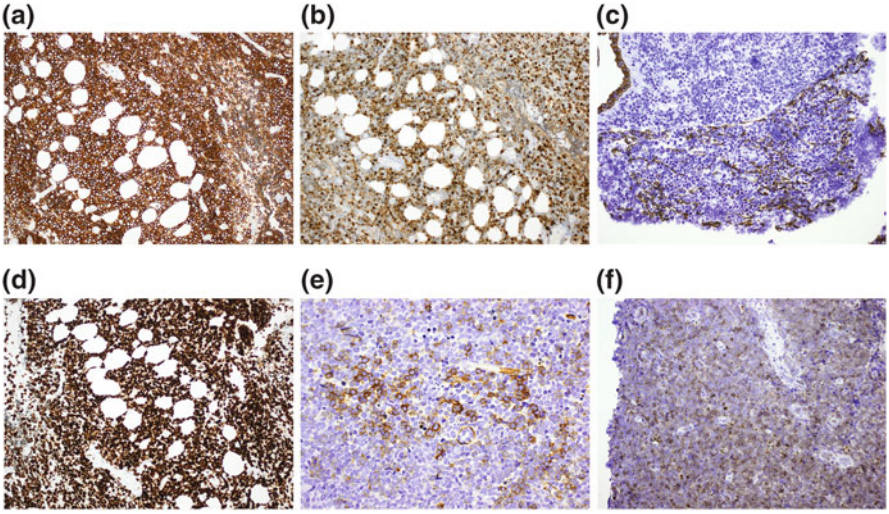

Fig. 8.11 Immunohistochemical features of T-lymphoblastic lymphoma. (**a**) CD3 is the recommended marker to determine T-cell lineage. Its expression is however variable and not always as strong and diffusely positive as in this example. **b** Nuclear expression of TdT is the most sensitive and specific marker to demonstrate the precursor T cell phenotype (caveats mentioned in the text). Of note, expression of TdT *per se* is not an indication of malignancy, as most thymocytes in a normal thymic cortex and in thymomas are also TdT positive. **c** As discussed in Fig. 8.10, keratin stains to demonstrate destruction of the thymic epithelial meshwork are among the most important immunohistochemical clues to the diagnosis of T-LBL. **d** Like TdT, ki67 *per se* is useless in the distinction between T-LBL, thymoma, and normal thymic cortex, since immature thymocytes (both neoplastic and non-neoplastic) show a proliferation rate of nearly 100%. **e** Expression of CD34 is possible and not an indication of myeloid differentiation. **f** Weak to moderate expression of CD1a would help to assign this case to the 'immature/cortical' subtype of T-LBL

The vast majority of cases show clonal rearrangement of the *T-cell receptor* genes, but simultaneous presence of *IGH* gene rearrangements can be found in approximately 20% of cases [65].

Differential Diagnosis and Pitfalls Due to its profound (and virtually diametrically opposed) therapeutic consequences, the distinction between type B1/B2 thymoma and T-lymphoblastic lymphoma in needle biopsies is one of the most challenging in mediastinal pathology. Many type-B1 thymomas occur in younger patients, do not show pronounced lobular structures and have low epithelial cell content. The clinical context of T-LBL (typically a young man with acute onset, elevated LDH, and severe symptoms) is in sharp contrast to the typical presentation of a thymoma (elderly patients of both sexes with symptoms gradually developing over extended time periods), and is already an important diagnostic clue. The cytological atypia and increased mitotic rate, the effacement of lobular structures and interstitial infiltration of peri-thymic fat (especially in the presence of a string-of-pearls or streaming pattern) are features of T-LBL and usually not seen in thymoma. Keratin stains are important for the demonstration of destroyed epithelial

thymic structures (in contrast to increased epithelial cell content in thymomas). A potential pitfall is the rare thymomas with lost expression of one or several keratins [66] (Fig. 8.10f). A panel of epithelial markers including e.g. p63 is therefore required to demonstrate preserved epithelial structures in some cases. Ki67 staining is useless or even misleading, since the immature lymphocytes both in the normal thymus and in thymomas usually show a ki67-index close to 100%. New antibodies, e.g., against NOTCH1 intracellular domain 1, have shown constitutive overexpression in T-LBL but not in thymomas and appear very useful to discriminate between these two entities [67]. Clonality assays are a helpful tool in equivocal cases.

There are a number of variants that merit consideration.

T-LBL cases with increased eosinophils appear to be a specific variant. Patients present with lymphoblastic lymphoma and a concomitant myeloproliferative disorder in the bone marrow, often with increased eosinophils. These cases harbor a t (8;13)(p11;q11–12) translocation that leads to activation of *FGFR1* [68]. Recognition of this variant is important, since there is a high risk for early relapses, often as acute myeloid leukemia or as myeloproliferative disease.

Rare cases of T-LBL are negative for TdT [69] and express myeloid markers (CD33 and HLA-DR) in addition to CD3. These cases belong to a clinical high-risk group. A small subset also expresses CD117, which appears to be associated with activating *FLT3* mutations [70].

Although TdT is highly specific for immature T- and B cells (which are usually only seen in lymphoblastic T- and B-cell lymphomas and in thymomas), rare nonhematopoietic tumors such as follicular dendritic cell (FDC) tumors [71] or Merkel cell carcinomas may also express TdT [72]. Advanced follicular lymphomas [73] and so-called double- and triple-hit lymphomas can present with features suggestive of immaturity, including TdT expression, and may create diagnostic challenges [74].

Finally, in lymph nodes with and without Castleman's disease, there are indolent proliferations of immature, TdT-positive T-lymphoblasts (iT-LBP) that do not show morphologic atypia and are polyclonal on PCR [75]. The follicular structure of the lymph node is usually maintained. Unlike T-LBL, these expansions are clinically indolent and do not require treatment.

Take Home Messages

- T-LBL is a challenging diagnosis that usually presents as a medical emergency in young adults.
- The most difficult differential diagnosis is type B1/B2 thymoma. Thymoma with loss of keratin expression is a pitfall. New antibodies directed against components of the NOTCH signaling pathway appear useful for this distinction.
- An initial set of immunohistochemical stainings should include TdT, keratin, CD3, MPO, and CD79a. In CD79a positive cases, CD19 or Pax5 should be added to rule out B-cell lineage differentiation.

- In cases where the diagnosis of T-LBL has been established, an extended immunohistochemical panel should include CD1a (to distinguish between the clinically relevant cortical vs. non-cortical T-LBL subgroups), CD56 (to detect cases with immature NK cells), and CD117 (as an indication for a *FLT3* mutation).
- Presence of eosinophils should be reported and should prompt assessment of the bone marrow and *FGFR1* status.

Mature T- and NK-cell Lymphomas

Definition and Terminology Mature T-cell lymphomas are extremely rare in the thymus and usually reflect mediastinal involvement of an advanced peripheral lymphoma. Among these, anaplastic large cell lymphoma (ALCL) is notable, since it may mimic carcinoma, melanoma, and B-cell lymphomas including Hodgkin lymphoma, and may thus cause differential diagnostic problems.

Epidemiology and Pathogenesis ALK+ ALCL is the most frequent mature T-cell lymphoma in children and accounts for 10–20% of pediatric lymphomas, whereas adult cases are more frequently ALK-negative. ALK overexpression is the result of various chromosomal translocations that show some correlation with the subcellular staining pattern of ALK.

Histomorphology ALCL is notorious for a variety of growth patterns that may closely mimic other tumors. The only constant feature of all ALCL variants are the so-called hallmark cells; large lymphoid cells with abundant cytoplasm and pleomorphic, horseshoe- or kidney-shaped nuclei (Fig. 8.12). Some multinuclear cells may mimic lacunar Reed–Sternberg cells, others show epithelioid (or even signet ring) morphology with basophilic cytoplasm. In affected lymph nodes, there is a tendency to grow in the lymph node sinuses, much like carcinomas and melanomas. Some cases show atypical giant cells or spindle cells and thus simulate soft tissue sarcomas. Others have a histiocyte-rich background or grow in tumor nodules surrounded by broad fibrotic bands, thus simulating T-cell/histiocyte-rich B-cell lymphoma or Hodgkin's lymphoma.

Immunohistochemistry and Other Ancillary Studies Tumor cells are positive for CD30 and often express EMA. CD3 expression is lost in a substantial number of cases especially in ALK+ cases (Fig. 8.12b). Most cases are CD4 positive, only occasional cases express CD8. Cytotoxic markers, such as TIA or perforin, are usually positive. Few cases can express CD15, but EBV markers (LMP and EBER) are consistently negative. CD25 can be strongly expressed, but is not particularly helpful in the differential diagnosis. Especially in children and young adolescents, the majority of

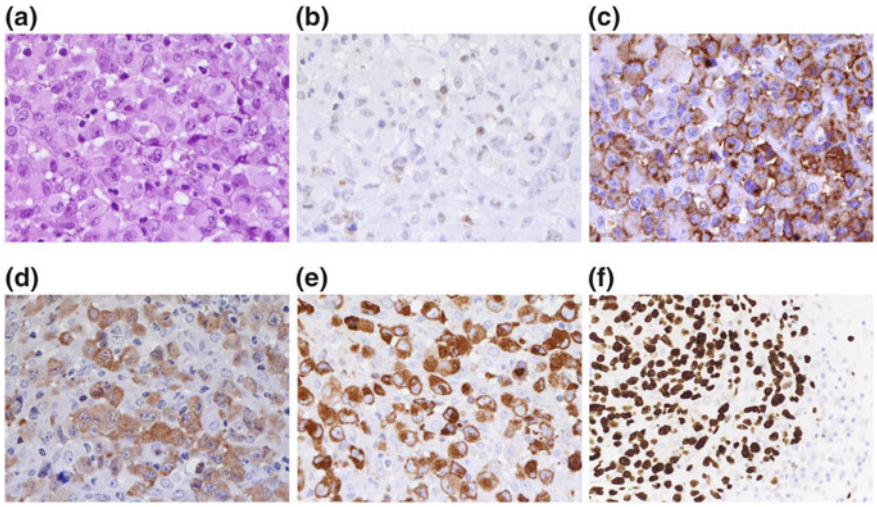

Fig. 8.12 Morphological and immunohistochemical features of anaplastic large cell lymphoma. **a** H&E stain shows large epitheloid tumor cells including numerous 'hallmark cells' with horseshoe- or kidney-shaped nuclei. Many cases are initially misinterpreted as carcinomas or melanomas. Expression of EMA may further add confusion. **b** Loss of one or several T cell antigens, including CD3 (this image) or CD45, is found in >50% of cases. Therefore, a panel of T cell specific antibodies is usually mandatory. **c** Expression of CD30 is strong and shows a Golgi pattern. The image shows several cells that resemble Hodgkin or Reed–Sternberg cells. **d** The staining pattern of ALK depends on the underlying gene fusion partner. This example shows cytoplasmic staining which can be found in a number of different translocations. **e** Expression of cytotoxic molecules, such as perforin is an important feature and helpful in the distinction e.g. from Hodgkin lymphoma. **f** The ki67 index is usually high

cases will be ALK positive. Depending on the underlying translocation, the staining can be membranous, cytoplasmic, or cytoplasmic and nuclear (Fig. 8.12e).

Molecular clonality assays are very helpful especially in ALK-negative cases and will show clonal T-cell receptor (TCR) rearrangements in about 90% of cases.

Differential Diagnosis and Pitfalls By histomorphology, ALCL is frequently initially mistaken for metastatic carcinoma or melanoma. The frequent antigen loss of CD3 may cause further confusion, if CD3 is the only T-cell marker used. It is, therefore, prudent to include CD30 and ALK (along with keratin, S100 and MelanA) in the first screening panel of antibodies when dealing with a large cell mediastinal neoplasm. ALK is not specific for ALCL and can also be found in non-small cell lung cancers (4%), and in inflammatory myofibroblastic tumors (IMT). If a lymphoma is to be excluded, the panel should further include CD45 (variable in ALCL), CD2 or CD5, CD4, CD8, EMA, CD79a, PAX5, and cytotoxic markers such as perforin or TIA.

As pointed out, there is considerable morphologic and immunohistochemical overlap with Hodgkin lymphoma (nodular sclerosing growth pattern, presence of Reed–Sternberg-like cells, expression of CD30 and occasionally CD15, usually negative for CD45, frequently negative for CD3). However, expression of ALK (if present), CD4, cytotoxic markers, and EMA, and negative stain for PAX5 and LMP/EBER in ALCL, along with TCR clonality assays allow for a safe distinction.

In ALK-negative ALCL cases, the distinction from CD30+ peripheral T-cell lymphomas, not otherwise specified (NOS), is sometimes arbitrary and rests mainly on the presence of hallmark cells and (except for absence of ALK) otherwise typical immunohistochemical features of ALCL.

Take Home Messages

- Anaplastic large cell lymphoma (ALCL) is a rare, but notorious pitfall that is often initially mistaken for a carcinoma, melanoma, or Hodgkin's lymphoma. The clinical background information is not necessarily helpful, since all of these tumors can involve the thymus and mediastinum in the course of the disease.
- ALK staining is essential to recognize the majority of cases. Most ALCL in children and young adults are ALK positive, whereas many cases in adults are ALK-negative.
- By morphology and immunohistochemistry, the differential diagnosis between ALCL and Hodgkin lymphoma is the most challenging. ALK, EMA, CD4, cytotoxic markers, PAX5, and LMP/EBER are the best markers for this distinction.
- The distinction between ALK-negative ALCL and CD30+ peripheral T-cell lymphoma (NOS) is sometimes somewhat arbitrary and rests mainly on the morphology and otherwise typical immunohistochemical features.

References

1. Moldenhauer G, et al. AID expression identifies interfollicular large B cells as putative precursors of mature B-cell malignancies. Blood. 2006;107(6):2470–3.
2. Isaacson PG, Norton AJ, Addis BJ. The human thymus contains a novel population of B lymphocytes. Lancet. 1987;2(8574):1488–91.
3. Nango K, et al. Ontogeny of thymic B cells in normal mice. Cell Immunol. 1991;133(1):109–15.
4. Akashi K, et al. B lymphopoiesis in the thymus. J Immunol. 2000;164(10):5221–6.
5. Goetz CA, et al. Restricted STAT5 activation dictates appropriate thymic B versus T cell lineage commitment. J Immunol. 2005;174(12):7753–63.
6. Inaba M, et al. Activation of thymic B cells by signals of CD40 molecules plus interleukin-10. Eur J Immunol. 1995;25(5):1244–8.

7. Ferrero I, et al. Functional and phenotypic analysis of thymic B cells: role in the induction of T cell negative selection. Eur J Immunol. 1999;29(5):1598–609.
8. Inaba M, et al. Functional analyses of thymic CD5 + B cells. Responsiveness to major histocompatibility complex class II-restricted T blasts but not to lipopolysaccharide or anti-IgM plus interleukin 4. J Exp Med. 1990;171(1):321–6.
9. Perera J, Huang H. The development and function of thymic B cells. Cell Mol Life Sci. 2015;72(14):2657–63.
10. Cazals-Hatem D, et al. Primary mediastinal large B-cell lymphoma. A clinicopathologic study of 141 cases compared with 916 nonmediastinal large B-cell lymphomas, a GELA ("Groupe d'Etude des Lymphomes de l'Adulte") study. Am J Surg Pathol. 1996;20(7):877–88.
11. Csernus B, et al. Mutational analysis of IgVH and BCL-6 genes suggests thymic B-cells origin of mediastinal (thymic) B-cell lymphoma. Leuk Lymphoma. 2004;45(10):2105–10.
12. Steidl C, et al. MHC class II transactivator CIITA is a recurrent gene fusion partner in lymphoid cancers. Nature. 2011;471(7338):377–81.
13. Joos S, et al. Primary mediastinal (thymic) B-cell lymphoma is characterized by gains of chromosomal material including 9p and amplification of the REL gene. Blood. 1996;87 (4):1571–8.
14. Rosenwald A, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. J Exp Med. 2003;198(6):851–62.
15. Green MR, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood. 2010;116(17):3268–77.
16. Traverse-Glehen A, et al. Mediastinal gray zone lymphoma: the missing link between classic Hodgkin's lymphoma and mediastinal large B-cell lymphoma. Am J Surg Pathol. 2005;29 (11):1411–21.
17. Mottok A, et al. Genomic alterations in CIITA are frequent in primary mediastinal large B cell lymphoma and are associated with diminished MHC class II expression. Cell Rep. 2015;13 (7):1418–31.
18. Moller P, et al. The primary mediastinal clear cell lymphoma of B-cell type has variable defects in MHC antigen expression. Immunology. 1986;59(3):411–7.
19. Yuan J, et al. Identification of primary mediastinal large B-cell lymphoma at nonmediastinal sites by gene expression profiling. Am J Surg Pathol. 2015;39(10):1322–30.
20. Hoeller S, et al. BOB.1, CD79a and cyclin E are the most appropriate markers to discriminate classical Hodgkin's lymphoma from primary mediastinal large B-cell lymphoma. Histopathology. 2010;56(2):217–28.
21. Leithauser F, et al. Isotype-switched immunoglobulin genes with a high load of somatic hypermutation and lack of ongoing mutational activity are prevalent in mediastinal B-cell lymphoma. Blood. 2001;98(9):2762–70.
22. Eberle FC, et al. Gray zone lymphoma: chromosomal aberrations with immunophenotypic and clinical correlations. Mod Pathol. 2011;24(12):1586–97.
23. Pileri SA, et al. Primary mediastinal B-cell lymphoma: high frequency of BCL-6 mutations and consistent expression of the transcription factors OCT-2, BOB.1, and PU.1 in the absence of immunoglobulins. Am J Pathol. 2003;162(1):243–53.
24. Eberle FC, Mani H, Jaffe ES. Histopathology of Hodgkin's lymphoma. Cancer J. 2009;15 (2):129–37.
25. Clavel J, et al. Hodgkin's disease incidence and survival in European children and adolescents (1978–1997): report from the automated cancer information system project. Eur J Cancer. 2006;42(13):2037–49.
26. Savage KJ, et al. The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin lymphoma. Blood. 2003;102(12):3871–9.

27. Glaser SL, et al. Epstein-Barr virus-associated Hodgkin's disease: epidemiologic characteristics in international data. Int J Cancer. 1997;70(4):375–82.
28. Harris NL. The many faces of Hodgkin's disease around the world: what have we learned from its pathology? Ann Oncol. 1998;9(Suppl 5):S45–56.
29. Lister TA, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: cotswolds meeting. J Clin Oncol. 1989;7(11):1630–6.
30. Hoppe RT, et al. Hodgkin lymphoma, version 2.2015. J Natl Compr Canc Netw. 2015;13 (5):554–86.
31. Xu J, Wu X, Reddy V. T cell/histiocyte-rich large B cell lymphoma of the thymus: a diagnostic pitfall. Case Rep Hematol. 2016;2016:2942594.
32. Vassallo J, et al. ALK-positive anaplastic large cell lymphoma mimicking nodular sclerosis Hodgkin's lymphoma: report of 10 cases. Am J Surg Pathol. 2006;30(2):223–9.
33. Falini B, et al. Expression of lymphoid-associated antigens on Hodgkin's and Reed-Sternberg cells of Hodgkin's disease. An immunocytochemical study on lymph node cytospins using monoclonal antibodies. Histopathology. 1987;11(12):1229–42.
34. Tzankov A, et al. Rare expression of T-cell markers in classical Hodgkin's lymphoma. Mod Pathol. 2005;18(12):1542–9.
35. Venkataraman G, et al. Aberrant T-cell antigen expression in classical Hodgkin lymphoma is associated with decreased event-free survival and overall survival. Blood. 2013;121 (10):1795–804.
36. Wilson WH, et al. A prospective study of mediastinal gray-zone lymphoma. Blood. 2014;124 (10):1563–9.
37. Eberle FC, et al. Methylation profiling of mediastinal gray zone lymphoma reveals a distinctive signature with elements shared by classical Hodgkin's lymphoma and primary mediastinal large B-cell lymphoma. Haematologica. 2011;96(4):558–66.
38. Dunleavy K, et al. Gray zone lymphoma: better treated like hodgkin lymphoma or mediastinal large B-cell lymphoma? Curr Hematol Malig Rep. 2012;7(3):241–7.
39. Inagaki H, et al. Primary thymic extranodal marginal-zone B-cell lymphoma of mucosa-associated lymphoid tissue type exhibits distinctive clinicopathological and molecular features. Am J Pathol. 2002;160(4):1435–43.
40. Isaacson PG, et al. Low-grade B-cell lymphoma of mucosa-associated lymphoid tissue arising in the thymus. A thymic lymphoma mimicking myoepithelial sialadenitis. Am J Surg Pathol. 1990;14(4):342–51.
41. Lorsbach RB, et al. Primary marginal zone lymphoma of the thymus. Am J Clin Pathol. 2000;113(6):784–91.
42. Sugimoto KJ, et al. IgG3 subclass-positive primary thymic MALT lymphoma without trisomy 3 and trisomy 18: report of a case and review of literature. Int J Clin Exp Pathol. 2014;7 (12):8980–7.
43. Muramatsu T, et al. Thymic and pulmonary mucosa-associated lymphoid tissue lymphomas. Ann Thorac Surg. 2013;95(3):e69–70.
44. Takino H, et al. Thymic extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue: a gene methylation study. Leuk Lymphoma. 2013;54(8):1742–6.
45. Fujimoto M, et al. Coexistence of Epstein-Barr virus-associated lymphoproliferative disorder and marginal zone B-cell lymphoma of the thymus in a patient with rheumatoid arthritis treated with methotrexate. Histopathology. 2012;61(6):1230–2.
46. Naithani R, et al. Thymic mucosa-associated lymphoid tissue lymphoma in an adolescent girl. J Pediatr Hematol Oncol. 2012;34(7):552–5.
47. Kang LY, Ho SP, Chou YP. Primary thymic mucosa-associated lymphoid tissue lymphoma with multiple thin walled lung cysts: case report and literature review. Chin J Cancer Res. 2013;25(3):354–7.
48. Kominato S, et al. Characterization of chromosomal aberrations in thymic MALT lymphoma. Pathol Int. 2012;62(2):93–8.

49. Strobel P, et al. Micronodular thymoma: an epithelial tumour with abnormal chemokine expression setting the stage for lymphoma development. J Pathol. 2005;207(1):72–82.
50. Moriyama E, et al. Low-grade B-cell lymphoma of mucosa-associated lymphoid tissue in the thymus of a patient with pulmonary amyloid nodules. Jpn J Clin Oncol. 2000;30(8):349–53.
51. Ota H, Kawai H, Tsubasa M. Thymic mucosa-associated lymphoid tissue lymphoma involving lymph nodes. Int J Surg Case Rep. 2013;4(3):250–2.
52. Harris NL, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the international lymphoma study group. Blood. 1994;84(5):1361–92.
53. Tellez-Zenteno JF, et al. Associated conditions in myasthenia gravis: response to thymectomy. Eur J Neurol. 2004;11(11):767–73.
54. Weissferdt A, Moran CA. Thymic hyperplasia with lymphoepithelial sialadenitis (LESA)-like features: a clinicopathologic and immunohistochemical study of 4 cases. Am J Clin Pathol. 2012;138(6):816–22.
55. Toren A, Ben-Bassat I, Rechavi G. Infectious agents and environmental factors in lymphoid malignancies. Blood Rev. 1996;10(2):89–94.
56. Ripperger T, Schlegelberger B. Acute lymphoblastic leukemia and lymphoma in the context of constitutional mismatch repair deficiency syndrome. Eur J Med Genet. 2016;59(3):133–42.
57. Armstrong SA, Look AT. Molecular genetics of acute lymphoblastic leukemia. J Clin Oncol. 2005;23(26):6306–15.
58. Van Vlierberghe P, Ferrando A. The molecular basis of T cell acute lymphoblastic leukemia. J Clin Invest. 2012;122(10):3398–406.
59. Hnisz D, et al. Activation of proto-oncogenes by disruption of chromosome neighborhoods. Science. 2016;351(6280):1454–8.
60. Portell CA, Sweetenham JW. Adult lymphoblastic lymphoma. Cancer J. 2012;18(5):432–8.
61. Feldman AL, et al. Clonal relationship between precursor T-lymphoblastic leukaemia/lymphoma and Langerhans-cell histiocytosis. Lancet Oncol. 2005;6(6):435–7.
62. Yokokawa Y, et al. Unique clonal relationship between T-cell acute lymphoblastic leukemia and subsequent Langerhans cell histiocytosis with TCR rearrangement and NOTCH1 mutation. Genes Chromosom Cancer. 2015;54(7):409–17.
63. Oschlies I, et al. Diagnosis and immunophenotype of 188 pediatric lymphoblastic lymphomas treated within a randomized prospective trial: experiences and preliminary recommendations from the European childhood lymphoma pathology panel. Am J Surg Pathol. 2011;35(6):836–44.
64. Burkhardt B. Paediatric lymphoblastic T-cell leukaemia and lymphoma: one or two diseases? Br J Haematol. 2010;149(5):653–68.
65. Pilozzi E, et al. Gene rearrangements in T-cell lymphoblastic lymphoma. J Pathol. 1999;188(3):267–70.
66. Adam P, et al. Thymoma with loss of keratin expression (and giant cells): a potential diagnostic pitfall. Virchows Arch. 2014;465(3):313–20.
67. Jegalian AG, Bodo J, Hsi ED. NOTCH1 intracellular domain immunohistochemistry as a diagnostic tool to distinguish T-lymphoblastic lymphoma from thymoma. Am J Surg Pathol. 2015;39(4):565–72.
68. Xiao S, et al. FGFR1 is fused with a novel zinc-finger gene, ZNF198, in the t(8;13) leukaemia/lymphoma syndrome. Nat Genet. 1998;18(1):84–7.
69. Zhou Y, et al. Absence of terminal deoxynucleotidyl transferase expression identifies a subset of high-risk adult T-lymphoblastic leukemia/lymphoma. Mod Pathol. 2013;26(10):1338–45.
70. Paietta E, et al. Activating FLT3 mutations in CD117/KIT(+) T-cell acute lymphoblastic leukemias. Blood. 2004;104(2):558–60.
71. Hartert M, et al. A follicular dendritic cell sarcoma of the mediastinum with immature T cells and association with myasthenia gravis. Am J Surg Pathol. 2010;34(5):742–5.
72. Bernd HW, et al. Expression of terminal desoxynucleotidyl transferase in Merkel cell carcinomas. Histopathology. 2007;50(5):676–8.

73. Geyer JT, et al. Lymphoblastic transformation of follicular lymphoma: a clinicopathologic and molecular analysis of 7 patients. Hum Pathol. 2015;46(2):260–71.
74. Moench L, et al., Double- and triple-hit lymphomas can present with features suggestive of immaturity, including TdT expression, and create diagnostic challenges. Leuk Lymphoma 2016;1–10.
75. Ohgami RS, et al. Indolent T-lymphoblastic proliferation (iT-LBP): a review of clinical and pathologic features and distinction from malignant T-lymphoblastic lymphoma. Adv Anat Pathol. 2013;20(3):137–40.

Non-neoplastic/Inflammatory Lesions in the Mediastinum

9

Eunhee S. Yi

Cystic Diseases Involving the Mediastinum

Various types of cystic diseases can occur in the mediastinum [1]. About half of the patients affected by mediastinal cysts may be asymptomatic and the cystic lesions are found incidentally on chest X-rays or CT scans performed for other reasons. The symptoms are usually due to compression and/or invasion of adjacent structures and include chest pain, cough, and dyspnea. The superior vena cava syndrome is generally an indication of malignancy and would be an atypical finding for benign mediastinal cysts. Many benign and malignant lesions may show similar radiographic and computed tomography (CT) scan appearances, which lead to a surgical exploration in many cases [1]. It would be highly unusual for the patients with mediastinal cysts to undergo a core biopsy for diagnosis. However, a specific diagnosis might be possible by a core biopsy in some cases with a histopathologic examination of the lining cells and the wall contents along with careful clinical and radiologic correlations. Cytologic features that might be suggestive of a mediastinal cyst as might be seen on fine needle aspirations are described in another chapter.

The distribution of cysts and other benign lesions within the mediastinal compartments are illustrated in Table 9.1.

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Table 9.1 Predilection sites for mediastinal lesions in mediastinal compartments

	Non-neoplastic
Prevascular	Thymic cyst True thymic hyperplasia Thymic follicular hyperplasia Thyroid goiter Parathyroid hyperplasia Fibrosing mediastinitis Castleman disease
Visceral	Pericardial cyst Bronchogenic cyst
Paravertebral	Esophageal cyst Gastric, enteric, or gastroenteric cysts

Foregut Cysts

During the embryogenesis, a small bud or diverticulum of the foregut may be separated and become mediastinal cysts that are referred to as foregut cysts. They are surrounded by lining epithelial cells of endodermal and wall of mesodermal origin that normally would have developed into trachea, bronchi, esophagus, stomach, or intestine. These cysts usually do not communicate with tracheobronchial tract or the esophageal lumens. Malignancy may occur in a background of foregut cysts, though very rare, usually in the form of adenocarcinoma [2]. While most patients with bronchogenic, esophageal and enteric cysts are asymptomatic, gastric, and gastroenteric cysts may cause severe symptoms in the affected patients due to peptic ulcer or even present with a life-threatening complication associated with perforation.

Bronchogenic (Bronchial) Cysts

Bronchogenic or bronchial cysts can occur anywhere along the tracheobronchial tree. They are most frequently found in the location posterior to the carina but rarely in the lower portion of the visceral mediastinum, just above the diaphragm [3]. Barium study or CT scan should be helpful in finding the lesion that could be missed by plain chest X-ray. Bronchogenic cysts are usually unilocular and contain clear or gelatinous fluid. Average diameter of the cysts is 3–4 cm and the lining epithelium is respiratory type (i.e., ciliated columnar epithelium) with variable degree of squamous metaplasia (Fig. 9.1). The cyst wall also may contain cartilage, smooth muscle, bronchial glands, and nerve fibers, as in the normal bronchial wall.

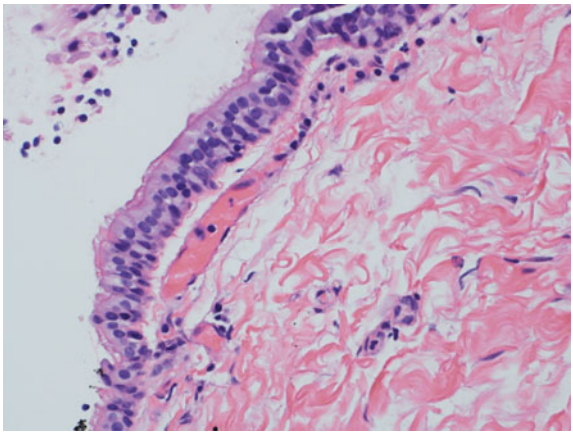

Fig. 9.1 Bronchogenic cyst lined by respiratory type mucosa with long cilia (HE, 200× original magnification)

Esophageal Cysts

Most esophageal cysts are found within the wall of the lower half of the esophagus. The lining epithelium is diverse and may be squamous, ciliated columnar, or mixed (showing both types). Distinction from bronchogenic cysts can be difficult and even impossible, but the presence of two layers of smooth muscle helps to confirm the diagnosis of esophageal cysts.

Gastric, Enteric, and Gastroenteric Cysts

The paravertebral area in the paravertebral mediastinum is the most common location for these cysts that are often attached to or embedded within the esophageal wall [1]. Nearly all cases are associated with vertebral malformations. The gastric variety is made up of the same coats as the stomach, whereas the enteric type simulates the normal small intestinal wall. Nerve fibers and ganglia are often found in the wall. Gastroenteric cyst refers to the combined form of gastric and enteric cysts.

Pericardial Cysts

Most pericardial cysts (also known as coelomic cysts) are located at the right cardiophrenic angle but also can be seen in the left heart border and the prevascular and paravertebral mediastinum. Pericardial cysts are lined by mesothelial cells that should be positive for keratins as well as mesothelial markers. The cyst wall may show sparse inflammatory infiltrates and mild fibrosis. Xanthomatous changes and reactive mesothelial hyperplasia may occur. Differential diagnosis includes

lymphangioma, bronchogenic cysts, and pseudocysts. If a core biopsy of the cyst shows the mesothelial lining cells, the diagnosis of pericardial cyst can be made.

Take home messages

1. Location of the cysts on imaging study and types of the lining epithelium will be crucial in the classification of mediastinal cysts.
2. Immunohistochemical stainings for keratins are positive in the lining cells of all types of foregut cysts and pericardial cysts. Mesothelial markers including calretinin, WT-1, and D2-40 are positive in the lining cells of pericardial cysts but negative in foregut cysts.
3. Reactive changes with cytologic atypia may be seen and should not be mistaken as malignancy.

Thymic Cysts

There are two types of thymic cysts: unilocular and multilocular. Unilocular thymic cysts are thought to be developmental origin and likely arise from remnants of the third branchial pouch [4]. They tend to be small and can be found anywhere along a line extending from the angle of the mandible to the manubrium sternum (i.e., along the migration route of the thymus during the development), though present more often in the neck than in the mediastinum. The cyst wall is thin and translucent without inflammation. The epithelial lining is flattened, cuboidal, columnar, or rarely squamous. In contrast to the developmental nature of unilocular thymic cysts, multilocular thymic cysts are thought to be an acquired process, likely representing a reactive or secondary change due to other lesions within the thymus or other adjacent organs, given the inflammation and fibrosis present in nearly all cases [5]. Multilocular thymic cysts might be identified as an incidental microscopic finding. However, they can also present as a large tumor-like mass with adhesion to other mediastinal structures, mistaken as a malignant process at the time of surgery. The lining cells of multilocular thymic cysts may be also flat, cuboidal, ciliated columnar, or squamous as in unilocular thymic cysts. Multilocular thymic cysts may also show denuded areas lacking the lining cells or a highly proliferative appearance with the features of pseudoepitheliomatous hyperplasia. Nonspecific reactive changes are very common including cholesterol granulomas, mixed inflammatory infiltrates, and numerous lymphoid follicles. A multilocular thymic cyst is postulated to be formed by acquired cystic dilation of medullary epithelial structures, which is probably induced by an inflammatory reaction within the thymic parenchyma (Fig. 9.2). The initial thymic inflammation could be idiopathic without any cause, but there might be a specific etiology (e.g., HIV infection, autoimmune disease, etc.) [6]. Also, one should remember that the histopathologic features of multilocular thymic cysts are often seen in the thymuses harboring nodular sclerosis Hodgkin lymphoma or seminoma. Other tumors such as

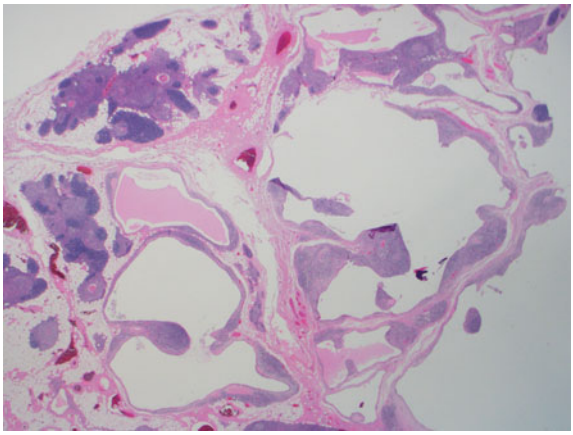

Fig. 9.2 Multilocular thymic cysts with variable sized cystic spaces lined by medullary thymic epithelial cells (HE, 40×)

thymoma, non-Hodgkin lymphoma, mature teratoma, and yolk sac tumor may be also associated with multilocular thymic cysts, though less common. Therefore, a thorough clinical and radiologic correlation is needed to rule out the neoplastic process in the vicinity when a diagnosis of multilocular thymic cysts is made. Main histopathologic differential diagnosis of multilocular thymic cysts include cystic degeneration of thymus and cystic lymphangioma [7]. Rarely, squamous cells carcinomas, basaloid carcinomas, and neuroendocrine carcinomas may be seen in a background of multilocular thymic cysts with the intimate connection between the lining and the carcinoma, suggesting their causal relationship [8–11]. A core biopsy can provide with the diagnosis of multilocular thymic cysts. However, sampling is always an issue and one has to be always mindful about the adjacent cancer.

Take home messages

1. Multilocular thymic cyst is an acquired condition while unilocular thymic cyst tends to be considered congenital. Both types of thymic are characterized by the presence of thymic tissue within the cyst wall and can be lined by flat, squamous, or columnar epithelial cells.
2. Diagnostic pitfalls: clinical consideration and careful evaluation of previous or current history of malignancy is important because thymic cysts can be associated with other tumors in the vicinity or away from the thymus.

Ectopic Tissues

Ectopic parathyroid or thyroid tissue can be seen in the mediastinum (Fig. 9.3) and gives rise to a benign or malignant process. Sebaceous glands or salivary gland tissue may be seen in the mediastinum, though extremely rare. Accordingly,

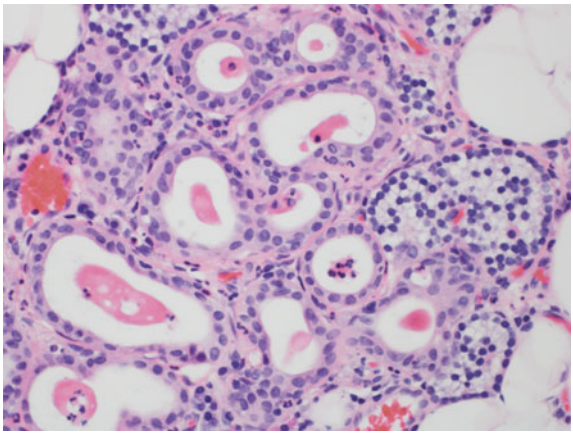

Fig. 9.3 Ectopic thyroid and parathyroid tissues present incidentally identified in a mediastinal biopsy (HE, 200×)

these tissues can be encountered in a needle biopsy or fine needle aspiration that can provide with a definite diagnosis.

Take home messages Diagnosis of ectopic tissue can be made by a recognition of cell types on hematoxylin and eosin (HE) stain but appropriate immunostains can be helpful to confirm (e.g., TTF-1 and thyroglobulin stains for thyroid; chromogranin and parathyroid hormone stains for parathyroid tissue).

Fibroinflammatory Mediastinal Diseases

Acute Mediastinitis

Acute mediastinitis refers to acute inflammation of the tissues in the mediastinum, usually due to bacterial infection associated with a rupture of mediastinal organs, especially esophagus. The diagnosis is typically made on clinical and radiologic ground without biopsy. In the past, acute mediastinitis usually arose from either perforation of the esophagus or from contiguous spread of odontogenic or retropharyngeal infections. However, most cases of acute mediastinitis in modern practice are iatrogenic due to complications of endoscopic or surgical procedures. Acute mediastinitis may progress rapidly and becomes a medical emergency. Treatment usually involves aggressive intravenous antibiotic therapy and hydration. Surgical intervention might be needed for the cases that develop abscesses or discrete fluid collections.

Chronic (Fibrosing) Mediastinitis

Chronic mediastinitis refers to chronic inflammation with granulomas and/or severe fibrosis, typically affecting the anterior mediastinum (Fig. 9.4). This term is often used interchangeably with fibrosing mediastinitis (also known as sclerosing

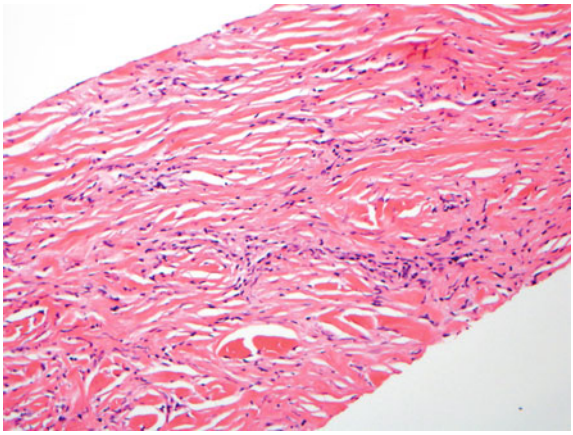

Fig. 9.4 Fibrosing mediastinitis in a mediastinal biopsy, characterized by keloid-type of refractile collagen deposition with mild inflammatory infiltrate (HE, 200×)

mediastinitis), a rare condition characterized by an aggressive fibroinflammatory process involving the mediastinum [12–17]. Fibrosing mediastinitis affects predominantly young adults with a slight male predominance [17]. It frequently causes compression of airways or blood vessels in the mediastinum, which may result in superior vena cava syndrome. Pulmonary edema or pulmonary venous infarct may occur due to the obstruction of pulmonary veins. Clinical and radiologic features of fibrosing mediastinitis may mimic a malignancy. Treatment for fibrosing mediastinitis is somewhat controversial, and may include steroids or surgical decompression of affected vessels or other vital structures.

A specific etiology cannot be demonstrated in many instances of fibrosing mediastinitis. However, it has been postulated that some cases might be an abnormal immunologic response to various infection, such as histoplasmosis, especially in the endemic areas of such infection [18–24]. A study of 38 fibrosing mediastinitis cases reported that histoplasmosis and mycobacterial infection were implicated in 26 and 12 cases, respectively [25]. Fibrosing mediastinitis cases due to nocardiosis or radiation therapy have been also reported [26].

Morphologic heterogeneity of fibrosing mediastinitis was addressed in a study of 30 cases with idiopathic fibrosing mediastinitis [24]. Three distinct groups (stages) were described: Stage I, edematous fibromyxoid tissue with numerous spindle cells, eosinophils, mast cells, lymphocytes, plasma cells, and thin-walled blood vessels; stage II, thick glassy bands of haphazardly arranged collagen with focal interstitial spindle cells, lymphocytes, and plasma cells; stage III, dense acellular collagen with scattered lymphoid follicles and occasional dystrophic calcification. These findings suggested that "sclerosing mediastinitis" may represent the final stage of an evolving, dynamic process with different morphologic appearances akin to abnormal wound healing [24]. Fibrosing mediastinitis can be seen in association with one or more of idiopathic fibroinflammatory conditions, such as retroperitoneal fibrosis, sclerosing cholangitis, Riedel's struma, and inflammatory pseudotumor of the orbit [24]. Importantly, one should always keep in mind that any given biopsy with only fibrosis and chronic inflammation may represent a nonspecific reactive change to

some neoplastic disorders in the vicinity, especially nodular sclerosis type of Hodgkin lymphoma. Thus, a careful clinical and radiologic correlation is required whenever a diagnosis of fibrosing mediastinitis is made.

IgG4-Related Disease Involving Mediastinum

Immunoglobulin(Ig)G4-related disease (IgG4-RD) is a chronic fibroinflammatory condition of unknown etiology characterized by tumefactive/infiltrative fibrosis and lymphoplasmacytic infiltrates involving a single or several anatomic sites and often with an elevated IgG4 serum level [27]. Autoimmune pancreatitis is the originally described organ manifestation of IgG4-RD [28]. Many other anatomic sites have been reported since, including mediastinum, as well as salivary and lacrimal glands, lymph nodes, spleen, lung, pleura, breast, liver, bile ducts, gallbladder, retroperitoneum, kidney, prostate, paravertebral space, meninges, and peripheral nerves and arteries [15].

Mediastinal lymphadenopathy is one of the most frequent extrapancreatic diseases manifests in patient with IgG4-RD [29, 30]. There has been a single case report of fibrosing mediastinitis attributed to IgG4-RD in the literature; this was a Japanese patient who had a clinical and radiographic presentation consistent with idiopathic immune-mediated fibrosing mediastinitis but demonstrated histopathological changes typical of IgG4-RD with an elevated serum IgG4 level and responded favorably to glucocorticoid therapy [31]. Fibrosis within the mediastinum without compression of mediastinal structure has been reported in the context of patients with other disease manifestations of IgG4-RD [32–34]. It has been also postulated that a subset of fibrosing mediastinitis cases may belong in the IgG4-RD spectrum due to overlapping histopathologic features between histoplasmosis/granulomatous disease associated fibrosing mediastinitis and IgG4-RD (Fig. 9.5). Recently, the use of chest CT has reduced the need for routine surgical biopsies to establish a diagnosis of fibrosing mediastinitis. As endoscopic needle biopsies in the pancreas have been very successful for the diagnosis of IgG4-RD, transbronchoscopic ultrasound-guided needle biopsies might prove to be useful as well [35–37]. Similar histopathologic criteria for diagnosis of IgG4-RD may be used in this setting with IgG4 and IgG immunostainings as well as a careful clinical and serologic evaluation. Such an approach would be very helpful to identify a patient population to prospectively evaluate the treatment effects of glucocorticoids and/or other immunosuppressive agents such as rituximab in fibrosing mediastinitis patients who have the features of IgG4-RD.

Noh et al reported a case presenting with recurrent superior vena syndrome caused by IgG4-RD invading the trachea and superior vena cava in the mediastinum [38]. Microscopic examination of the mass revealed a marked increase in lymphoid follicles, fibrosclerotic stroma and heavy plasmacytic infiltrates that were positive for IgG4 staining. Sakamoto et al reported 11 cases with inflammatory aortic aneurysm and inflammatory pericarditis as well as retroperitoneal fibrosis, suggesting a role of IgG4-RD in these settings [32]. Isolated diffuse thymic fibrosis

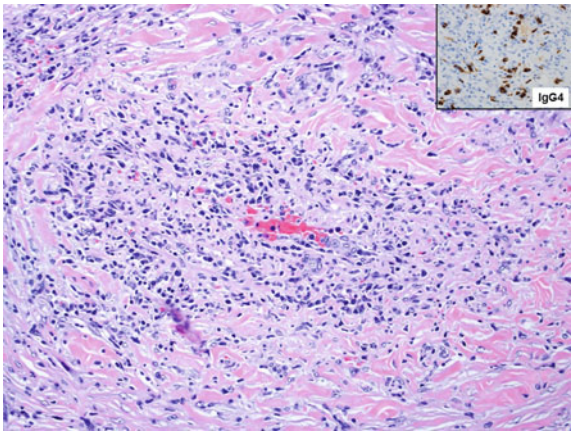

Fig. 9.5 IgG4-related disease involving the mediastinum with obliterative phlebitis due to lymphoplasmacytic infiltrates (HE, 200×) containing increased IgG4-positive plasma cells (*inset* anti-IgG4 immunostaining, 400×)

was reported by Shilo et al in the absence of any primary thymic lesion; they suggested that diffuse thymic fibrosis might be associated with IgG4-RD, given the morphologic similarities in their six such cases [39]. However, only one of their cases showed an increase in IgG4-positive cells and the association with IgG4-RD remains uncertain.

Take home messages

1. Acute mediastinitis shows severe acute inflammation and is usually of iatrogenic origin.
2. Chronic mediastinitis, often referred to as fibrosing or sclerosing mediastinitis, is characterized by chronic inflammation, granulomas in some cases, and keloid-like fibrosis, which could result in mass-like lesion, superior vena cava syndrome or compression of large vessels in the mediastinum.
3. IgG4-related disease is diagnosed based on the constellation of clinical features and pathologic findings including storiform fibrosis, obliterative phlebitis, and heavy plasmacytic infiltrates containing increased IgG4-positive cells (>20/high power field in hot spot in needle biopsies; >40% in IgG4/IgG).
4. Immunohistochemistry: IgG4 and IgG are required to examine the absolute counts of IgG4-positive cells and IgG4/IgG ratio in the diagnosis of IgG4-related disease based on needle biopsy. Kappa and lambda immunostains or in situ hybridization studies are often needed to exclude a clonal population with light chain restriction in the cases with heavy plasmacytic infiltrates. Immunohistochemical stains for Hodgkin or non-Hodgkin lymphoma should be considered to rule out such diagnoses whenever appropriate.
5. Diagnostic pitfalls: These diagnoses based on needle biopsy would be very difficult and should be made with extreme caution; a possibility of other lesions in the vicinity, especially various neoplasms (e.g., thymic neoplasm, hematolymphoid malignancy and germ cell tumor, etc.), should be carefully excluded by radiologic and clinical as well as histopathologic evaluations.

Castleman Disease

Castleman disease, also known as angiofollicular lymph node hyperplasia or giant lymph node hyperplasia, was first described in 1956 [40]. Castleman disease is a rare lymphoproliferative disorder and encompasses two clinical variants including unicentric and multicentric Castleman diseases [41]. There are two histopathologic subtypes: hyaline vascular and plasma cell types [42]. Recently, plasma cell type has been further divided into human herpesvirus (HHV)-8 negative and HHV-8 positive groups, based on the presence or absence of HHV-8 that is also associated with other conditions including Kaposi sarcoma and primary effusion lymphoma. HHV-8 infection is strongly associated with multicentric Castleman disease and is responsible for most HIV-positive multicentric Castleman disease and half of HIV-negative multicentric Castleman disease [43–45]. Patients affected by multicentric Castleman disease are at an increased risk of lymphoma and other related neoplasms including Kaposi sarcoma [43, 46, 47]. Follicular dendritic sarcoma occurs in association with Castleman disease in a small proportion of cases, usually hyaline vascular type [48]. In these cases, either the Castleman disease precedes the follicular dendritic cell sarcoma or the two lesions occur simultaneously.

Castleman disease is characterized by abnormal follicles with polyclonal B-cells and T-cells without aberrant immunophenotype, resulting in the involvement of one or more sites. Three different histopathological variants can be seen, which may occur in both unifocal and multifocal Castleman disease: 1. hyaline vascular type, 2. HHV-8 negative plasma cell variant, and 3. HHV-8 positive plasma cell variant. Hyaline vascular type Castleman disease is the most common variant and accounts for ~70–80% of Castleman disease [41, 49]. It occurs usually as a solitary mass in the chest. Multiple abnormal follicles with atrophic and hyalinized germinal centers are enclosed within a mantle zone of small lymphocytes (Fig. 9.6). Germinal centers are depleted of lymphocytes, with residual dendritic cells arranged concentrically in an onion-skin appearance (Fig. 9.4). Small blood vessels with tight

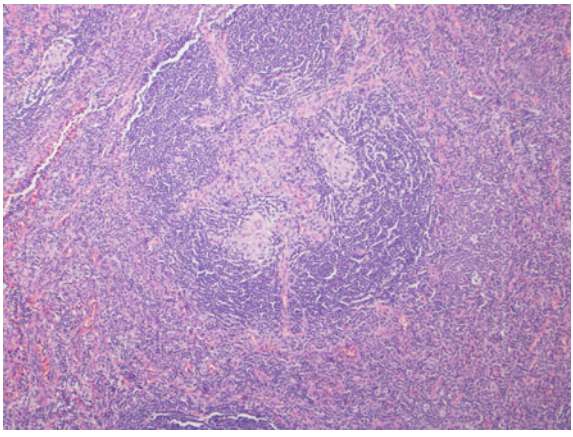

Fig. 9.6 Castleman disease, hyaline vascular type, characterized by atrophic germinal center, and "lollipop" blood vessel across mantle zone (HE, 100×)

aggregates of dendritic cells are seen in the interfollicular spaces. Often, a characteristic feature called lollipop lesions is seen, resulting from the presence of a sclerotic blood vessel into an atrophic germinal center. HHV-negative plasma cell variant Castleman disease consists of germinal center hyperplasia formed mainly of B-cell, and expansion of mantle zone. The lymph node architecture is conserved. Germinal centers reveal typical reactive features and interfollicular areas are hypervascularized. HHV-positive plasma cell variant Castleman disease shows polyclonal plasmablasts in the mantle zone of lymphoid follicle, which distinguishes it from HHV-8 negative plasma cell variant Castleman disease. Plasmablasts are HHV-8 infected B-cells. HHV-8 infected cells are detected by IHC with LANA-1 antibody [47]. In about two-thirds of samples, Kaposi sarcoma may be found in the same involved lymph node. In general, excisional biopsy of a lymph node or a mass is needed to reach the definite diagnosis of Castleman disease with confidence. However, core biopsy might offer sufficient diagnostic features to reach the diagnosis.

Take home messages

1. Diagnostic features: Hyaline vascular type is characterized by multiple abnormal follicles with atrophic and hyalinized germinal centers. Onion-skin appearance of atrophic germinal centers with lollipop lesions can be seen.
2. Immunohistochemistry: HHV8 immunostain is needed to subtype the plasma cell variant Castleman diseases. CD3, CD20, CD10 or BCL-6, CD1a, and other expanded panel may be useful to highlight the immunoarchitecture of lymphoid follicle and interfollicular cells.
3. Pitfalls of diagnosis in a small biopsy: Diagnosis of Castleman disease would be very difficult on a small needle biopsy, if not impossible, given the overlapping features with other neoplastic and reactive hematolymphoid lesions. Bigger sample should be requested whenever appropriate.

Sarcoidosis

Sarcoidosis is a relatively common cause of thoracic lymphadenopathy in young adults and can be distinguished from other causes by the multiple and symmetrical enlargement of lymph nodes. Transbronchial needle aspiration has been proven to be a safe and effective method of identifying the characteristic exuberant non-necrotizing granulomas to reach a diagnosis of sarcoidosis [50, 51]. However, performing appropriate special stains for microorganisms and correlating with microbiologic culture study would be prerequisite to exclude an infectious process in the diagnosis of sarcoidosis. Sarcoidosis has been well recognized as a great mimicker and could masquerade as various other conditions including metastatic cancer [52].

Take home messages

1. Morphologic features for diagnosis: Exuberant non-necrotizing tight epithelioid granulomas are apparent even in a small biopsy such as percutaneous or transbronchial needle biopsies and transbrochial forcep or cryobiopsies. Occasional necrotizing granulomas may be seen, though less common.
2. Special stains: Stains for fungi, mycobacteria, and other microorganisms are required.
3. Diagnostic pitfalls: Infection is always in the differential diagnosis even when there is no stainable microorganism. Thus, a thorough correlation with microbiologic culture study and other clinical manifestations would be important.

Summary

There are a number of developmental or acquired mediastinal lesions that are subjected to small biopsies. It is extremely difficult to reach a definite diagnosis of non-neoplastic/inflammatory mediastinal lesions based on those small biopsies and cytology specimens partly due to the nonspecific nature of their findings typically seen in those specimens. While many lesions are found incidentally during a procedure for unrelated thoracic condition, fibrosing mediastinitis might mimic a malignancy on radiological as well as pathologic examination. IgG4-related disease has been shown to involve the mediastinum and may have some overlapping findings with fibrosing mediastinitis. More studies are required, however, to characterize the true nature of this rare disease. Sampling issue has to be always considered during the interpretation of small biopsies; for example, the changes reminiscent of fibrosing mediastinitis can be seen in the tissues around malignant neoplasms especially nodular sclerosis type of Hodgkin lymphoma; multilocular thymic cysts are seen around thymomas as well as many other malignant tumors. Thus, one should always question whether the observed findings account for the real lesion or simply represent a nonspecific reactive change at the periphery of the targeted lesion that is missed. The importance of careful clinical and radiologic correlation cannot be overemphasized in the evaluation of small biopsies from any mediastinal lesions.

References

1. Wick MR. Cystic lesions of the mediastinum. Semin Diagn Pathol. [Review]. 2005;22 (3):241–53.
2. Olsen JB, Clemmensen O, Andersen K. Adenocarcinoma arising in a foregut cyst of the mediastinum. Ann Thorac Surg. [Case Reports Review]. 1991;51(3):497–9.
3. St-Georges R, Deslauriers J, Duranceau A, Vaillancourt R, Deschamps C, Beauchamp G, et al. Clinical spectrum of bronchogenic cysts of the mediastinum and lung in the adult. Ann Thorac Surg. 1991;52(1):6–13.

4. Ratnesar P. Unilateral cervical thymic cyst. J Laryngol Otol. 1971;85(3):293–8.
5. Izumi H, Nobukawa B, Takahashi K, Kumasaka T, Miyamoto H, Yamazaki A, et al. Multilocular thymic cyst associated with follicular hyperplasia: clinicopathologic study of 4 resected cases. Hum Pathol. [Case Reports]. 2005;36(7):841–4.
6. Mishalani SH, Lones MA, Said JW. Multilocular thymic cyst. A novel thymic lesion associated with human immunodeficiency virus infection. Arch Pathol Lab Med. [Case Reports]. 1995;119(5):467–70.
7. Pannell TL, Jolles H. Adult cystic mediastinal lymphangioma simulating a thymic cyst. J Thorac Imaging. [Case Reports]. 1991;7(1):86–9.
8. Leong AS, Brown JH. Malignant transformation in a thymic cyst. Am J Surg Pathol. [Case Reports]. 1984;8(6):471–5.
9. Moran CA, Suster S. "Ancient" (sclerosing) thymomas: a clinicopathologic study of 10 cases. Am J Clin Pathol. 2004;121(6):867–71.
10. Moran CA, Suster S. Cystic well-differentiated neuroendocrine carcinoma (carcinoid tumor): a clinicopathologic and immunohistochemical study of two cases. Am J Clin Pathol. 2006;126(3):377–80.
11. Rakheja D, Weinberg AG. Multilocular thymic cyst associated with mature mediastinal teratoma: a report of 2 cases. Arch Pathol Lab Med. [Case Reports]. 2004;128(2):227–8.
12. Cheuk W, Chan JK. IgG4-related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity. Adv Anat Pathol. [Review]. 2010;17(5):303–32.
13. Kamisawa T, Okamoto A. IgG4-related sclerosing disease. World J Gastroenterol. [Editorial Review]. 2008;14(25):3948–55.
14. Khosroshahi A, Stone JH. A clinical overview of IgG4-related systemic disease. Curr Opin Rheumatol. [Editorial Review]. 2011;23(1):57–66.
15. Zen Y, Nakanuma Y. IgG4-related disease: a cross-sectional study of 114 cases. Am J Surg Pathol. 2010;34(12):1812–9.
16. Ebbo M, Daniel L, Pavic M, Seve P, Hamidou M, Andres E, et al. IgG4-related systemic disease: features and treatment response in a French cohort: results of a multicenter registry. Medicine (Baltimore). [Multicenter Study]. 2012;91(1):49–56.
17. Khosroshahi A, Deshpande V, Stone JH. The Clinical and Pathological Features of IgG(4)-Related Disease. Curr Rheumatol Rep. [Review]. 2011;13(6):473–81.
18. Mathisen DJ, Grillo HC. Clinical manifestation of mediastinal fibrosis and histoplasmosis. Ann Thorac Surg. 1992;54(6):1053–7; discussion 7–8.
19. Mole TM, Glover J, Sheppard MN. Sclerosing mediastinitis: a report on 18 cases. Thorax. 1995;50(3):280–3.
20. Devaraj A, Griffin N, Nicholson AG, Padley SP. Computed tomography findings in fibrosing mediastinitis. Clin Radiol. [Review]. 2007;62(8):781–6.
21. Rossi SE, McAdams HP, Rosado-de-Christenson ML, Franks TJ, Galvin JR. Fibrosing mediastinitis. Radiographics. [Review]. 2001;21(3):737–57.
22. Dunn EJ, Ulicny KS, Jr., Wright CB, Gottesman L. Surgical implications of sclerosing mediastinitis. A report of six cases and review of the literature. Chest. [Case Reports Review]. 1990;97(2):338–46.
23. Dozois RR, Bernatz PE, Woolner LB, Andersen HA. Sclerosing mediastinitis involving major bronchi. Mayo Clin Proc. 1968;43(8):557–69.
24. Flieder DB, Suster S, Moran CA. Idiopathic fibroinflammatory (fibrosing/sclerosing) lesions of the mediastinum: a study of 30 cases with emphasis on morphologic heterogeneity. Mod Pathol. 1999;12(3):257–64.
25. Goodwin RA, Nickell JA, Des Prez RM. Mediastinal fibrosis complicating healed primary histoplasmosis and tuberculosis. Medicine (Baltimore). 1972;51(3):227–46.
26. Rankin RS, Westcott JL. Superior vena cava syndrome caused by Nocardia mediastinitis. Am Rev Respir Dis. 1973;108(2):361–3.
27. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med. [Review]. 2012;366(6):539–51.

28. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med. [Research Support, Non-U.S. Gov't]. 2001;344(10):732–8.
29. Naitoh I, Nakazawa T, Ohara H, Ando T, Hayashi K, Tanaka H, et al. Clinical significance of extrapancreatic lesions in autoimmune pancreatitis. Pancreas. [Research Support, Non-U.S. Gov't]. 2010;39(1):e1–5.
30. Tsushima K, Tanabe T, Yamamoto H, Koizumi T, Kawa S, Hamano H, et al. Pulmonary involvement of autoimmune pancreatitis. Eur J Clin Invest. [Comparative Study]. 2009;39 (8):714–22.
31. Inoue M, Nose N, Nishikawa H, Takahashi M, Zen Y, Kawaguchi M. Successful treatment of sclerosing mediastinitis with a high serum IgG4 level. Gen Thorac Cardiovasc Surg. [Case Reports]. 2007;55(10):431–3.
32. Sakamoto A, Nagai R, Saito K, Imai Y, Takahashi M, Hosoya Y, et al. Idiopathic retroperitoneal fibrosis, inflammatory aortic aneurysm, and inflammatory pericarditis–retrospective analysis of 11 case histories. J Cardiol. [Research Support, Non-U.S. Gov't]. 2012;59(2):139–46.
33. Taniguchi T, Kobayashi H, Fukui S, Ogura K, Saiga T, Okamoto M. A case of multifocal fibrosclerosis involving posterior mediastinal fibrosis, retroperitoneal fibrosis, and a left seminal vesicle with elevated serum IgG4. Hum Pathol. [Case Reports Comment Letter]. 2006;37(9):1237–9; author reply 9.
34. Zen Y, Sawazaki A, Miyayama S, Notsumata K, Tanaka N, Nakanuma Y. A case of retroperitoneal and mediastinal fibrosis exhibiting elevated levels of IgG4 in the absence of sclerosing pancreatitis (autoimmune pancreatitis). Hum Pathol. [Case Reports]. 2006;37 (2):239–43.
35. Sherrick AD, Brown LR, Harms GF, Myers JL. The radiographic findings of fibrosing mediastinitis. Chest. 1994;106(2):484–9.
36. Sah RP, Chari ST. Serologic issues in IgG4-related systemic disease and autoimmune pancreatitis. Curr Opin Rheumatol. [Review]. 2011;23(1):108–13.
37. Levy MJ, Wiersema MJ, Chari ST. Chronic pancreatitis: focal pancreatitis or cancer? Is there a role for FNA/biopsy? Autoimmune pancreatitis. Endoscopy. [Review]. 2006;38 Suppl 1: S30–5.
38. Noh D, Park CK, Kwon SY. Immunoglobulin G4-related sclerosing disease invading the trachea and superior vena cava in mediastinum. Eur J Cardiothorac Surg. [Case Reports]. 2014;45(3):573–5.
39. Shilo K, Mani H, Deshpande C, Ozbudak IH, Travis WD, Galvin JR, et al. Diffuse thymic fibrosis: histologic pattern of injury or distinct entity? Am J Surg Pathol. 2010;34(2):211–5.
40. Castleman B, Iverson L, Menendez VP. Localized mediastinal lymphnode hyperplasia resembling thymoma. Cancer. 1956;9(4):822–30.
41. Herrada J, Cabanillas F, Rice L, Manning J, Pugh W. The clinical behavior of localized and multicentric Castleman disease. Ann Intern Med. 1998;128(8):657–62.
42. Casper C. The aetiology and management of Castleman disease at 50 years: translating pathophysiology to patient care. Br J Haematol. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, P.H.S. Review]. 2005;129(1):3–17.
43. Hillier JC, Shaw P, Miller RF, Cartledge JD, Nelson M, Bower M, et al. Imaging features of multicentric Castleman's disease in HIV infection. Clin Radiol. 2004;59(7):596–601.
44. Borie R, Cadranel J, Guihot A, Marcelin AG, Galicier L, Couderc LJ. Pulmonary manifestations of human herpesvirus-8 during HIV infection. Eur Respir J. [Review]. 2013;42(4):1105–18.
45. Menter T, Schlageter M, Bastian L, Haberthur R, Ratz Bravo AE, Tzankov A. Development of an Epstein-Barr virus-associated lymphoproliferative disorder in a patient treated with azacitidine for chronic myelomonocytic leukaemia. Hematol Oncol. [Case Reports]. 2014; 32(1):47–51.

46. Dupin N, Diss TL, Kellam P, Tulliez M, Du MQ, Sicard D, et al. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. Blood. [Research Support, Non-U.S. Gov't]. 2000;95(4):1406–12.
47. Du MQ, Liu H, Diss TC, Ye H, Hamoudi RA, Dupin N, et al. Kaposi sarcoma-associated herpesvirus infects monotypic (IgM lambda) but polyclonal naive B cells in Castleman disease and associated lymphoproliferative disorders. Blood. [Research Support, Non-U.S. Gov't]. 2001;97(7):2130–6.
48. Chan JK, Tsang WY, Ng CS, Tang SK, Yu HC, Lee AW. Follicular dendritic cell tumors of the oral cavity. Am J Surg Pathol. [Case Reports Review]. 1994;18(2):148–57.
49. Cronin DM, Warnke RA. Castleman disease: an update on classification and the spectrum of associated lesions. Adv Anat Pathol. [Historical Article Review]. 2009;16(4):236–46.
50. Eom JS, Mok JH, Lee MK, Lee K, Kim MJ, Jang SM, et al. Efficacy of TB-PCR using EBUS-TBNA samples in patients with intrathoracic granulomatous lymphadenopathy. BMC Pulm Med. 2015;15:166.
51. Govender P, Berman JS. The Diagnosis of Sarcoidosis. Clin Chest Med. [Review]. 2015;36 (4):585–602.
52. Altinkaya M, Altinkaya N, Hazar B. Sarcoidosis mimicking metastatic breast cancer in a patient with early-stage breast cancer. Ulus Cerrahi Derg. 2016;32(1):71–4.

Soft Tissue Tumors of the Mediastinum

10

Narasimhan P. Agaram

Introduction

Soft tissue tumors of the mediastinum are rare. Their estimated incidence is between 2 and 6% of mediastinal neoplasms [1–3]. Because of their rarity, most mesenchymal tumors in the mediastinum have been reported as case reports or small series. Mediastinal sarcomas may either occur de novo or rarely as "somatic-type" malignancy in a mediastinal germ cell tumor. Development of a sarcomatous component has been reported to occur more frequently in mediastinal germ cell tumors than in other sites [4]. The two most common sarcomas developing in mediastinal germ cell tumors are rhabdomyosarcoma and angiosarcoma. In addition, sarcomatous areas as part of a thymic sarcomatoid carcinoma may sometimes be a diagnostic consideration [5, 6]. This chapter will emphasize on the primary mesenchymal tumors of the mediastinum.

Lipomatous Tumors

Lipomatous tumors are one of the most common tumors in the mediastinum. Although they could be located in any compartment, they usually occur in the anterior mediastinum.

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Lipoma

Lipomas usually present between the ages of 40 and 60 years and are rare in children. The most common sites are the subcutaneous tissue and deep soft tissues. They usually present as a large painless soft tissue mass, except when they compress the adjacent structures including the lung. Imaging studies show a homogeneous soft tissue that demonstrates fat saturation. Conventional lipomas are characterized histologically by lobules of mature adipocytes (Fig. 10.1) [7]. A thorough examination of the resected lipoma should be performed to rule out the possibility of thymic tissue within the lesion, features that represent a thymolipoma [8]. This may be rather difficult on biopsy material. The differential diagnosis of lipoma includes lipomatosis, a non-neoplastic, nonencapsulated proliferation of mature adipose tissue seen in patients with steroid use, Cushing disease or obesity [9, 10]. Imaging studies may be helpful in this regard.

Lipoma Variants

Angiolipoma is an adipocytic tumor composed of proliferation of vascular channels, mostly capillaries, in adipose tissue. Focally, the vascular lumens show microthrombi, a helpful feature in the diagnosis. These tumors have been rarely described in the mediastinum [11, 12].

Spindle cell and pleomorphic lipomas have been rarely reported in the mediastinum [13, 14]. Spindle cell lipomas are characterized by spindle cells arranged in parallel clusters between the adipocytes and associated with thick collagen bundles. Mast cells are frequently noted in between the spindle cells (Fig. 10.2). Pleomorphic lipomas are clinically similar to spindle cell lipoma. They are characterized by the presence of a variable number of cells with enlarged nuclei, including floret cells, in close association with adipocytes and collagen bundles. Immunohistochemical stain

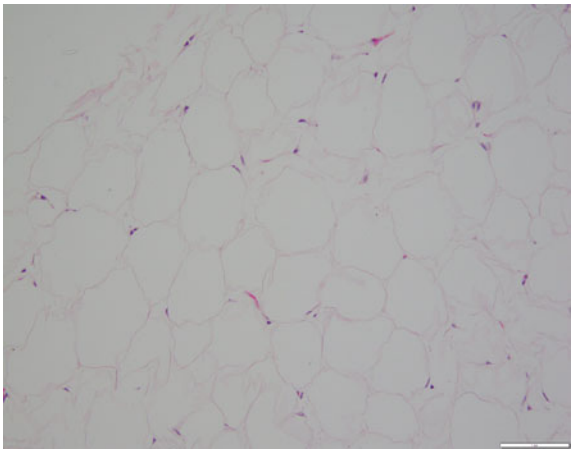

Fig. 10.1 Lipoma with mature adipose tissue and uniform-sized adipocytes (H & E, 200×)

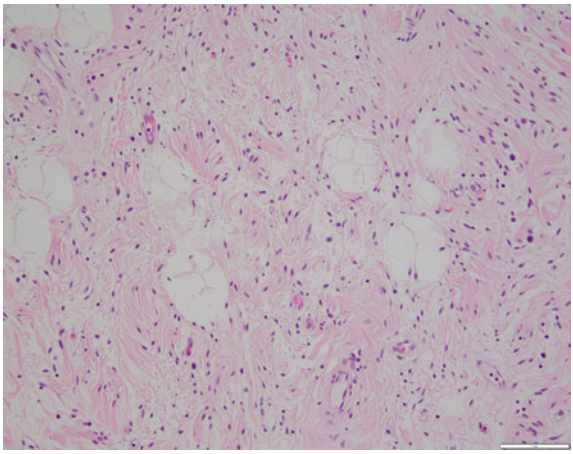

Fig. 10.2 Spindle cell lipoma showing bland spindle cells amidst long ropy collagenous bundles with admixed adipose tissue. Note the scattered mast cells (H & E, 200×)

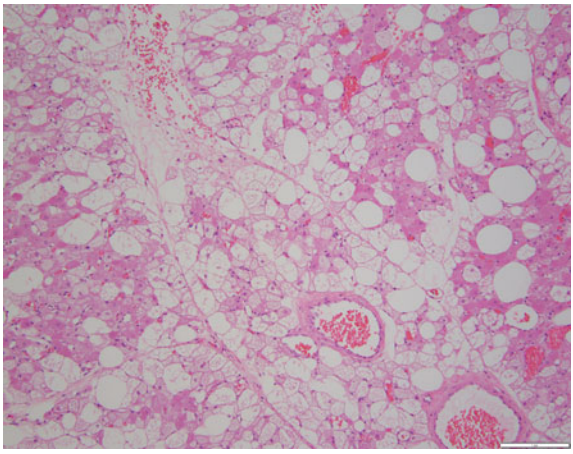

Fig. 10.3 Hibernoma showing lobulated adipocytic neoplasm composed of adipocytes with multi vacuolated to granular cytoplasm resembling 'brown fat' (H & E, 100×)

for CD34 highlights the spindle cells and is helpful in the diagnosis of these lesions, especially on biopsy material.

Hibernoma is a benign tumor composed of brown fat with granular, multivacuolated cytoplasm. It is more common around the third and fourth decades of life and there is a slight male predominance. The more frequent sites of involvement are the subcutaneous tissue in the thigh, trunk, upper extremity, and head and neck. Hibernomas show adipocytes with pale to variably eosinophilic multivacuolated cytoplasm. Mitotic figures or atypia are unusual (Fig. 10.3) [15].

Other rare lipoma variants reported in the mediastinum include myelolipoma which shows hematopoietic elements admixed with mature adipose tissue [16, 17].

Liposarcoma

Liposarcomas are the most common mesenchymal malignant tumors of the mediastinum. A majority of them occur in the anterior mediastinum and in association with the thymus, although tumors have been described in the posterior mediastinum as well [18–21].

Well-Differentiated/Dedifferentiated Liposarcoma

They represent 40% of all liposarcomas with a peak incidence in the sixth decade of life and equally affect men and women. The prognosis is related to the resectability of the lesion. These lesions range from small to very large in size and are usually asymptomatic. Histologically, they can be subdivided into lipoma-like, sclerosing, inflammatory, and spindle cell types. The most common type is the lipoma-like variant, which is characterized by a proliferation of adipocytes with prominent cellular septae. Histological sections show adipocytes and stromal cells with focal nuclear atypia associated with hyperchromasia. Mono- or multivacuolated lipoblasts might be also seen (Fig. 10.4) [7]. Nuclear immunoreactivity for MDM2 and/or CDK4 is usually seen and is a good diagnostic test on small biopsy specimens.

Dedifferentiated liposarcoma is defined as the transition from a well-differentiated liposarcoma to non-lipogenic sarcoma of variable histological grade. There is no sex predilection. Histologically, it is characterized by the presence of a sarcoma, usually high grade, in close association with a well-differentiated liposarcoma component. The most common histological appearances of the

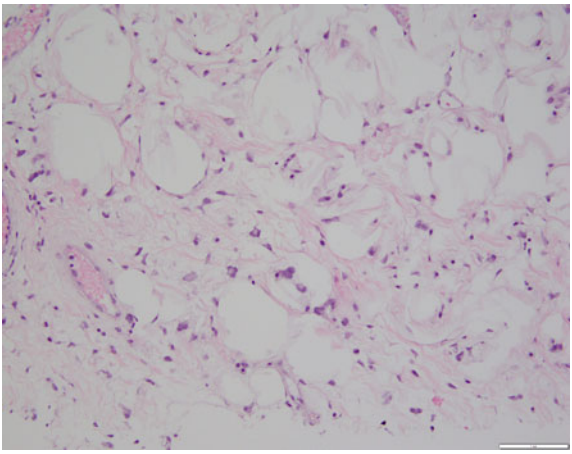

Fig. 10.4 Well-differentiated liposarcoma showing scattered large atypical cells in the septa of adipose tissue (H & E, 200×)

non-lipogenic sarcoma are a pleomorphic sarcoma and intermediate to high-grade myxofibrosarcoma. There are also cases of low-grade dedifferentiation characterized by a uniform population of spindle cells with mild nuclear atypia as well as lesions with heterologous differentiation such as myoid or chondroid differentiation.

Myxoid Liposarcoma

Myxoid liposarcoma is the second most common type of liposarcoma. The peak age incidence is in the fourth and fifth decades of life, but it can occur in patients younger than 20 years old. Histologically, myxoid liposarcoma is characterized by a uniform population of round to oval-shaped cells and a variable number of small signet ring lipoblasts which are present in a myxoid stroma associated with a vascular network with a "chicken-wire" appearance (Fig. 10.5a). Usually, myxoid liposarcomas do not show nuclear pleomorphism, giant cells, abundant spindle cells, or increased mitotic activity. The round cell component contains solid sheets of small round cells with high nuclear-to-cytoplasmic (N/C) ratio, conspicuous nucleoli, and no myxoid stroma (Fig. 10.5b). Tumors with at least 5% round cell component are usually associated with a poor prognosis. The demonstration of the specific translocation t(12;16)(q13;p11) of myxoid liposarcoma by FISH and/or the identification of the fusion gene product *FUS-DDIT3* (CHOP) can help to establish the diagnosis [7, 22].

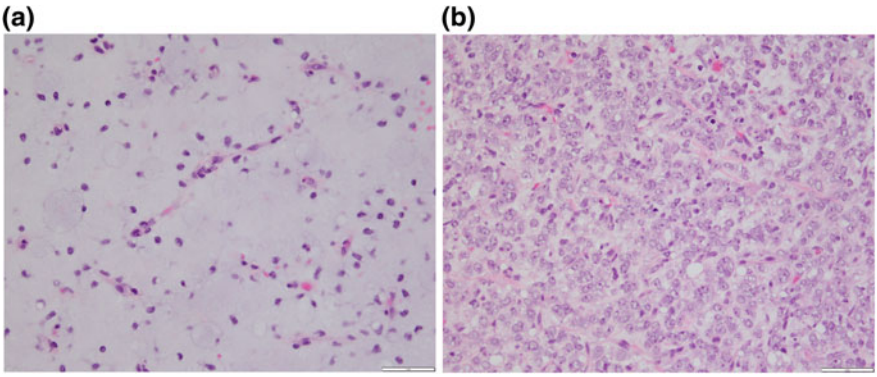

Fig. 10.5 **a** Myxoid liposarcoma showing small ovoid nuclei in a predominantly myxoid background with branching capillary vascularity. Note the small univacuolated lipoblasts in the *lower right* of the image. (H & E, 400×). **b** Round cell liposarcoma showing sheets of medium sized cells with round nuclei with open chromatin and minimal cytoplasm (H & E, 400×)

Pleomorphic Liposarcoma

Pleomorphic liposarcoma is a high-grade sarcoma characterized by the presence of lipoblasts in the absence of a well-differentiated component or a component with a different line of differentiation. It is the least common type of liposarcoma, occurs mostly in patients older than 50 years old, and has no definite sex predilection. Histologically, pleomorphic liposarcomas are characterized by a population of pleomorphic spindle cells with pleomorphic, multivacuolated lipoblasts [7]. A more recently described variant of liposarcoma that occurs in children and young adults and has a predilection for the mediastinum has been termed as pleomorphic myxoid liposarcoma [18]. This tumor shows areas similar to low-grade myxoid liposarcoma with other areas showing increased cellularity, hyperchromatic cells, and pleomorphic lipoblasts. These tumors are highly aggressive with a metastatic rate of approximately 50% and an overall tumor-related mortality ranging from 40 to 50%.

Fibrous Tumors

Fibromatosis

Fibromatoses are tumors characterized by infiltrative growth but with benign-appearing cellular features. Occurring at almost every site of the body, mediastinal fibromatoses have been reported. These tumors are often very aggressive locally, but rarely metastatic. Fibromatosis occurs in both childhood and adult life. Fibromatoses of adulthood can be superficial or deep, usually slow growing and painless. Abdominal fibromatosis or desmoid tumors are more common in women of childbearing age and may be associated with pregnancy. Histologically, cellular areas of the tumor show myofibroblastic spindle cell proliferation with monomorphic cells arranged in streaming pattern. No atypia or mitotic activity is noted (Fig. 10.6). Varying amounts of collagen can be identified with some tumors being predominantly collagenous. Recent genetic studies have identified *Beta-catenin* mutations as the genetic hallmark of fibromatosis. This results in the nuclear expression of Beta-catenin by immunohistochemistry, a finding that is extremely useful to distinguish this tumor from a hypertrophic scar [23–25]. Although this tumor has been managed in different ways including surgery, radiation, chemotherapy, hormonal therapy, etc., with limited success, novel therapies using targeted kinase inhibitors such as Sorafenib have recently shown some benefit [26].

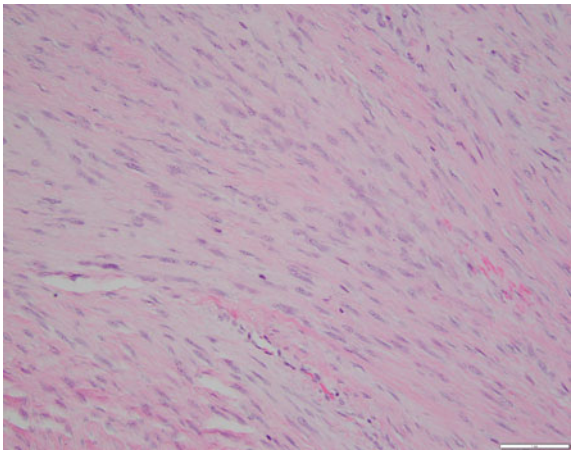

Fig. 10.6 Desmoid-type fibromatosis showing uniform myofibroblastic spindle cells in a streaming pattern (H & E, 200×)

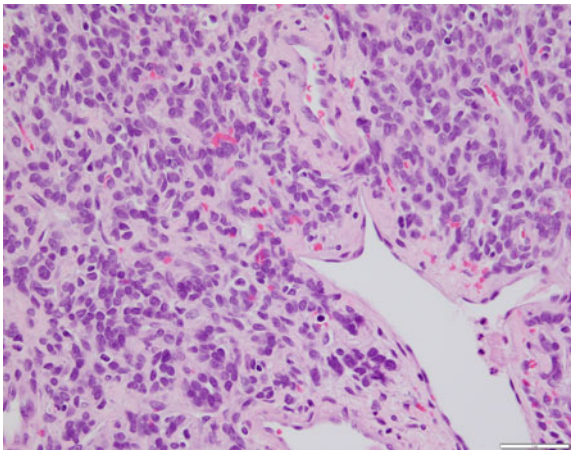

Fig. 10.7 Solitary fibrous tumor composed of plump spindle cells in a haphazard pattern of arrangement with 'staghorn' branching vascularity noted in the background (H & E, 200×)

Solitary Fibrous Tumor

Extrapleural solitary fibrous tumors (SFT) are uncommon tumors that occur in almost any organ site and affects equally men and women. In some circumstances of mediastinal SFTs it may be questionable if the tumor is arising from the pleura or if the tumor is truly extrapleural [7, 27]. Histologically, the tumors have a patternless architecture characterized by hypocellular and hypercellular areas associated with hemangiopericytoma-like branching vessels. The tumors are composed of ovoid to spindle-shaped cells with scant cytoplasm (Fig. 10.7). The criteria for malignancy are high mitotic count (>4 mitoses per 10 high power fields), high cellularity, pleomorphism and necrosis. All cases are immunoreactive for CD34. Recently, nuclear staining of STAT6 resulting from *NAB2-STAT6* gene fusion has been shown to be a more specific marker for SFT [28, 29]. It is important to note

that STAT6 positivity has also been reported in dedifferentiated liposarcomas. So in cases of lipomatous SFT that shows a component of adipose tissue, dedifferentiated liposarcoma may be one of the differential diagnoses [30]. In such circumstances, other stains for MDM2 and CDK4 might be helpful. It has been suggested that mediastinal SFTs more frequently show aggressive behavior compared to non-mediastinal SFTs [31].

Angiomatoid Fibrous Histiocytoma

Angiomatoid malignant fibrous histiocytoma is a rare, low-grade malignant mesenchymal neoplasm that affects mostly the extremities of children and young adults. It is believed to have a partially myoid phenotype. Histologically, it is characterized by the presence of a multinodular proliferation of eosinophilic, histiocytoid or myoid cells, pseudoangiomatoid spaces, thick fibrous capsule, and pericapsular lymphoplasmacytic infiltrate. Immunohistochemical results are most consistent with myofibroblastic differentiation with desmin positivity in half of the cases. The most frequent genetic abnormality is t(2;22) translocation resulting in the fusion of *EWSR1* and *CREB1* genes. Other variant fusions reported include *FUS-ATF1* and *EWSR1-ATF1* [7, 32].

Low-Grade Fibromyxoid Sarcoma

This is a distinctive neoplasm characterized by bland spindle cells arranged in a whorling pattern and curvilinear vessels, which are associated with extensive areas of collagenized and myxoid zones. Cytological features include clusters of bland spindle and round/polygonal cells embedded in a collagenous and myxoid matrix along with dissociated, uniform, or slightly/moderately pleomorphic spindle cells, bare nuclei and fragments of collagen and myxoid tissue in varying proportions [33, 34]. At a molecular level, these lesions demonstrate *FUS-CREB3L2* or *FUS-CREB3L1* gene fusion [7, 35, 36].

Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumor (IMT) is a tumor composed of myofibroblastic spindle cells and a variably dense nonneoplastic inflammatory component. It has been reported in many sites, predominantly in young adults and children [37]. Bona fide mediastinal IMTs are rare with few cases reported [38–41]. They appear to arise mostly in young adults (range 13–72; median age 34) with a slight female predominance (male:female = 5:8). Histologically, IMT is an infiltrative tumor composed of myofibroblastic cells admixed with an inflammatory infiltrate of lymphocytes, plasma cells, and eosinophils. Multifocality is not uncommon in IMT. Cytoplasmic expression of ALK protein is detectable in about half of the cases and

correlates well with presence of *ALK* gene rearrangements. Recent genetic studies have identified other genetic abnormalities in the *ROS1*, *RET,* and *PDGFRB* genes [42, 43]. The biological behavior of IMT is variable and recurrences are common, but distant metastasis is rare. Similar to non-mediastinal sites, treatment rests mainly on complete local excision. Patients with *ALK*-rearranged IMT are potential candidates for treatment with specific inhibitors.

Vascular Tumors

Hemangioma

Hemangiomas are common benign vascular neoplasms which can present in almost any body location and at any age. Mediastinal hemangioma may originate in the soft tissue of the mediastinum or may arise in the thymus. Tumor size can range from a few centimeters to 20 cm. They are characterized histologically by a proliferation of thin-walled vascular channels lined by bland endothelial cells. Both capillary and cavernous hemangioma subtypes can be seen. Associated histological features described include adipose metaplasia, fibrosis, smooth muscle overgrowth and inflammation [44]. Surgical resection is curative in most cases.

Epithelioid Hemangioma

Epithelioid hemangioma, also known as angiolymphoid hyperplasia with eosinophilia, is a rare benign vascular lesion. Although the most common sites are the skin and subcutaneous tissue of the head and neck region, it can rarely be seen in the deep soft tissue. The histological sections show a central area of proliferating blood vessels surrounded by a cellular infiltrate composed of lymphoid cells and eosinophils. The vascular proliferation is lined by endothelial cells with an epithelioid or histiocytoid appearance [7]. Recent studies have identified *FOS* gene-related fusions in a subset of these tumors [45].

Lymphangioma

Lymphangiomas are benign cavernous vascular lesions composed of dilated lymphatic channels most common in early childhood; they have been associated with Turner syndrome. The most common sites of the cystic type are the neck, axilla, and groin, while the cavernous types are most common in the mouth, upper trunk, and limbs. Lymphangiomas are more commonly seen in the anterior mediastinum [46, 47]. Histologically, these lesions are characterized by the presence of thin-walled, lymphatic vessels of different sizes lined by flat endothelium and surrounded by a lymphocytic infiltrate.

Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma (EHE) is a vascular tumor with metastatic potential. This tumor is rare and can occur at any age and usually in the deep soft tissue of extremities. Mediastinal involvement has been reported [48]. It is characterized histologically by a cellular proliferation composed of short nests and strands of round epithelioid cells embedded in myxohyaline stroma. These cells show intracytoplasmic lumina containing erythrocytes. The cells are bland with little or no mitotic activity. No distinct vascular formation is identified (Fig. 10.8). Immunohistochemical studies for vascular markers such as CD31 and ERG are required to distinguish epithelioid vascular lesions from carcinomas [7]. Angiosarcomas demonstrate a higher degree of atypia than hemangioendotheliomas. A t(1;3)(p36.3;q25) has been described in EHE resulting in a fusion of *WWTR1*(3q25) and *CAMTA1*(1p36) genes, suggesting a possible role as diagnostic marker [49]. A subset of EHE has been shown to have the *YAP1-TFE3* gene fusion. These cases show strong positivity of the TFE3 stain by immunohistochemistry [50].

Angiosarcoma

Angiosarcomas are malignant tumors composed of cells with morphological and phenotypical features of endothelial cells. The most common sites for angiosarcomas of soft tissue are deep muscles of lower extremities, arm, trunk, and head and neck. Few cases have been reported in the mediastinum [51]. They have been associated with coagulopathies, patients with Klippel-Trenaunay and Maffucci syndromes, and following radiation for other malignancies. The most common morphologies include spindle and epithelioid cell morphologies. These morphologies can coexist and might show predominance of one subtype. The spindle

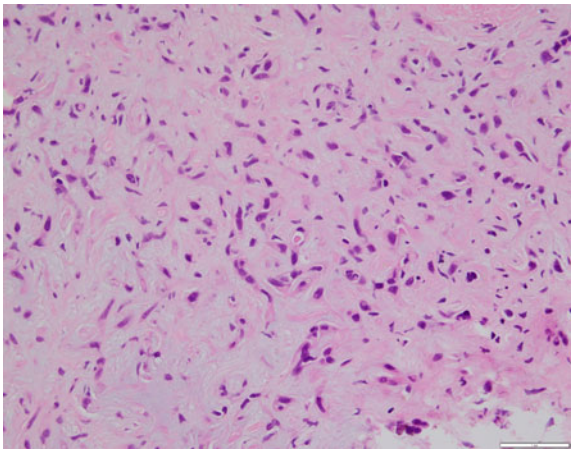

Fig. 10.8 Epithelioid hemangioendothelioma composed of cords of epithelioid cells in a partially myxoid matrix. Note that some cells show intracytoplasmic lumen with red blood cells (H & E, 200×)

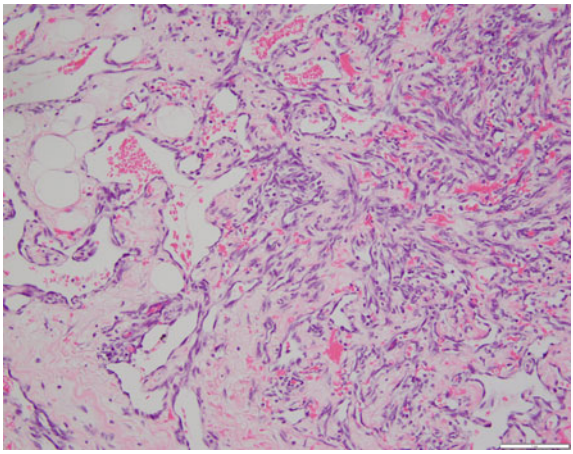

Fig. 10.9 Angiosarcoma showing vascular neoplasm composed of interanastomosing vascular channels line by atypical endothelial cells. (H & E, 200×)

cell morphology resembles fibrosarcoma or Kaposi sarcoma. The epithelioid cells are represented by large polygonal cells with a high N/C ratio and eosinophilic or amphophilic cytoplasm. The neoplastic cells form rudimentary vascular channels, which are irregular in shape and infiltrate soft tissue (Fig. 10.9). The main differential diagnosis of the spindle cell angiosarcomas is with other types of sarcomas, while the main differential diagnosis of epithelioid angiosarcoma is adenocarcinoma and other epithelioid malignant neoplasms. Immunohistochemical stains for vascular markers such as CD31 and ERG are helpful in achieving the correct diagnosis. Special care must be taken in the interpretation of cytokeratin in epithelioid angiosarcomas since these lesions can express keratin markers. Vascular markers must be part of the immunohistochemical panel to avoid a misdiagnosis [7]. No consistent recurrent chromosomal abnormality has been identified in angiosarcomas. *KDR (VEGFR)* mutations have been seen in a subset of angiosarcoma [52]. Amplification of *MYC* gene on 8q24 is seen in radiation-induced and lymphedema-associated angiosarcoma [53].

Smooth Muscle Tumors

Leiomyoma

These benign smooth muscle tumors are frequently found in the uterus. They also occur in the gastrointestinal tract and the skin and subcutaneous tissue. Smooth muscle tumors of superficial origin often have a vascular component (angioleiomyomas) and present with pain. Primary mediastinal leiomyomas are extremely rare [54]. Tumors histologically show bland appearing smooth muscle bundles with no significant atypia, mitoses or necrosis. Degenerative changes such as sclerosis, hemorrhage, cystic change, and calcification can be present. Tumor cells are positive for SMA, Desmin and h-Caldesmon and are negative for S-100.

Leiomyosarcoma

This malignant smooth muscle tumor is found in adulthood, most frequently in the retroperitoneum, but also in association with blood vessels such as the pulmonary artery or vena cava. They rarely occur in the mediastinum and can involve the posterior mediastinum [55, 56]. Malignant smooth muscle tumors are characterized by increased mitoses, cytologic atypia, and necrosis.

Low-grade leiomyosarcoma may be less cellular with nuclear atypia and coarse chromatin more difficult to identify. Cells may palisade similar to neurogenic tumors. It may not be possible to make a diagnosis of malignancy with accuracy in these cases, which may have to be considered suspicious for malignancy or labeled as atypical. High-grade leiomyosarcoma show significant pleomorphism with necrosis and markedly abnormal-appearing cells (Fig. 10.10). Leiomyosarcoma express SMA, Desmin and h-Caldesmon in a majority of cases. Genetically, soft tissue leiomyosarcomas have a complex karyotype with genomic instability [57].

Pericytic (Perivascular) Tumors

Glomus Tumor

Glomus tumors are uncommon and only rarely involve the mediastinum [58–61]. They are composed of cells that resemble the modified smooth muscle cells of a glomus body. Most of these tumors are present in the distal extremities, especially in subungual region, hand, wrist, and foot. They can occur in deep soft tissue or viscera and most malignant glomus tumors are present in these locations. Familial glomus tumors have been reported and have an autosomal dominant pattern of inheritance. Histologically, the tumors are composed of small uniform round cells

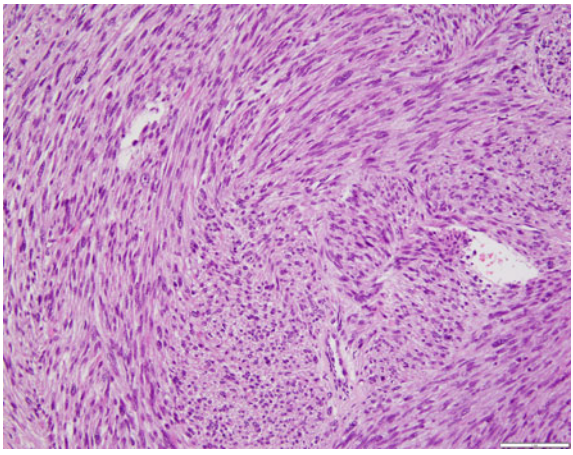

Fig. 10.10 Leiomyosarcoma composed of spindle cells with plump elongated nuclei arranged in intersecting fascicles. Note the scattered large atypical cells (H & E, 200×)

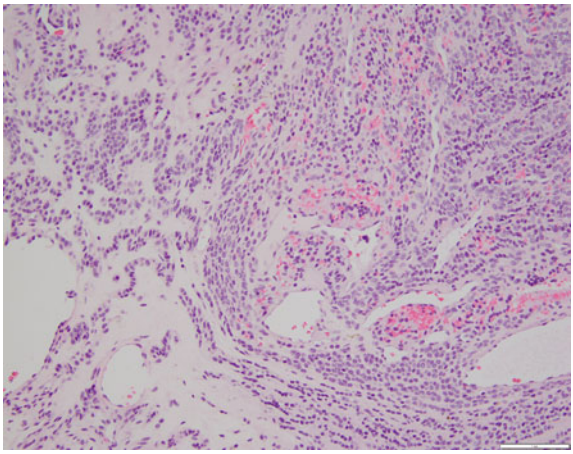

Fig. 10.11 Glomus tumor showing proliferation of monomorphous cells with round to ovoid nuclei arranged in a perivascular pattern (H & E, 200×)

with a round nuclei and amphophilic to lightly eosinophilic cytoplasm, arranged around vessels (Fig. 10.11). Each cell is surrounded by a basement membrane, which can be seen by PAS stain. The neoplastic cells are immunoreactive for SMA and h-Caldesmon, while negative for CD34, cytokeratin, and S-100. Occasionally, features of malignancy, such as increased cellularity with cytologic atypia, increased mitotic activity and necrosis may be appreciated [7]. Recent studies have shown gene fusions involving the miR143 and *NOTCH* genes [62].

Skeletal Muscle Tumors

Rhabdomyoma

Rhabdomyoma is most commonly found in the head and neck area of adults and is infrequent in the mediastinum. The tumor histologically resembles regenerating muscle with large polygonal cells. The nuclei may vary in appearance with cytoplasmic inclusion often found. Mitoses are uncommon. The cytoplasm is dense and cross-striations can be seen. Fetal rhabdomyoma often occurs in association with basal cell nevus syndrome, caused by loss of functional mutations of the *PTCH1* gene [7].

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is the most common soft tissue tumor of childhood and is classified into embryonal RMS, alveolar RMS, spindle cell/sclerosing RMS and pleomorphic RMS. Head and neck and orbit are the most common locations. Primary mediastinal rhabdomyosarcomas are exceedingly rare [63]. According to NCI

criteria embryonal RMS is considered a favorable subtype over alveolar rhabdomyosarcoma. Pleomorphic RMS is the rarest type and may be difficult to distinguish from other high-grade sarcomas such as malignant fibrous histiocytoma.

Embryonal RMS shows a combination of primitive round cells with other forms of rhabdomyoblasts such as strap cells. The cells of embryonal RMS are "small round blue cells" and must be distinguished from the other small round blue tumor cells occurring in childhood such as Ewing sarcoma (ES)/primitive neuroectodermal tumor (PNET). When cytoplasmic cross-striations are found they serve as a clue to the correct classification of this tumor. Myxoid stroma is seen in the background. The botryoid subtype of embryonal RMS, found in bladder and vagina of children, is characterized by abundant myxoid stroma and a denser, more cellular subepithelial area.

Alveolar RMS shows a relatively uniform population of round cells with eccentrically located nuclei and cytoplasmic vacuoles (Fig. 10.12). Pleomorphic RMS usually occurs in adults in the sixth to seventh decades of life and occurs more frequently in men. The tumors show high-grade sarcoma morphology, are rich in mitotic figures, and have bizarre shapes and atypical nuclei. Cytoplasmic cross-striations may be found in some cells. RMSs are positive for desmin, MyoD1, and myogenin. Molecular studies can be useful in alveolar RMS which show a t (2;13) (q35;q14) or a variant translocation t(1;13) (p36;q14) resulting in the fusion of the *FOXO1* gene with either the *PAX3* or the *PAX7* genes. Embryonal and pleomorphic RMS do not show a consistent cytogenetic abnormality [7].

The differential diagnosis of mediastinal RMS includes germ cell tumors with RMS as a secondary somatic malignancy, a scenario more common than a primary RMS. Identification of a germ cell tumor component by immunohistochemical stains will help in distinguishing these tumors.

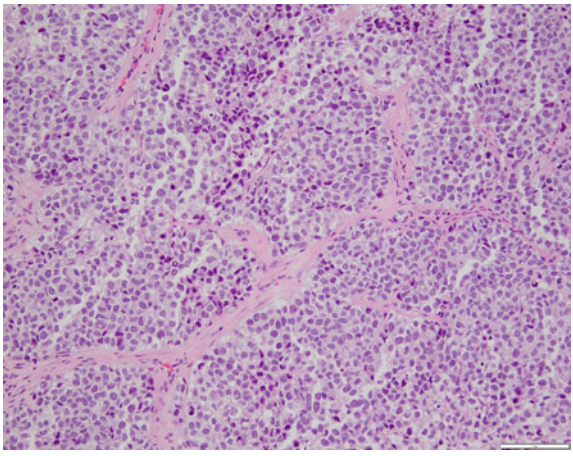

Fig. 10.12 Alveolar rhabdomyosarcoma showing primitive, small- to medium-sized cells with round nuclei, arranged in a nested pattern. (H & E, 100×)

Nerve Sheath Tumors and Tumors Derived from the Autonomic Nervous System

Neural tumors are the most common mesenchymal tumors in the mediastinum with an estimated incidence of 12–19% of all mediastinal tumors [60, 64]. Neural mediastinal tumors may be categorized into tumors of nerve sheath—schwannian derivation, which are predominantly seen in adults, those of the autonomic (neuronal–ganglionic/sympathetic–parasympathetic) nervous system, which are much more common in the pediatric age group and those which are thought to arise from embryonic remnants of the neural tube, such as ependymoma [60].

Schwannomas are the most common of the mediastinal neural tumors and arise from spinal nerves. They are more often seen in the posterior mediastinum. Symptomatic cases present with chest pain, cough, or compression symptoms, in particular in tumors extending through spinal foramina. They are most common in young- to middle-aged adults. They are circumscribed encapsulated tumors which show compact areas of spindle cells (Antoni A) showing occasional palisading (Verocay bodies) and loosely arranged areas (Antoni B) (Fig. 10.13). Areas of cystic degeneration and degenerative ('ancient') changes may be seen. Lesional cells are strongly positive for S100. Surgical removal is curative with extremely low recurrence rates. The cellular variant of schwannoma, which may be mistaken for a malignant tumor owing to its increased cellularity and lack of Verocay bodies, is particularly common in the mediastinum [65]. Its benign behavior has been confirmed in several series.

Neurofibroma, similar to schwannoma, occurs mainly in the paravertebral mediastinum. 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. Histologically, the tumor shows loosely arranged spindle cells that diffusely infiltrate the nerve. The cells have round, ovoid,

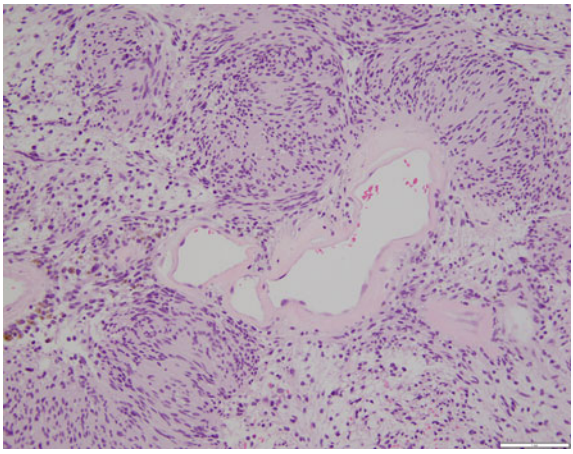

Fig. 10.13 Schwannoma composed of elongated spindle cells in fascicles with areas of nuclear palisading (Verocay bodies). Note the centrally dilated vessels with perivascular hyalinization (H & E, 200×)

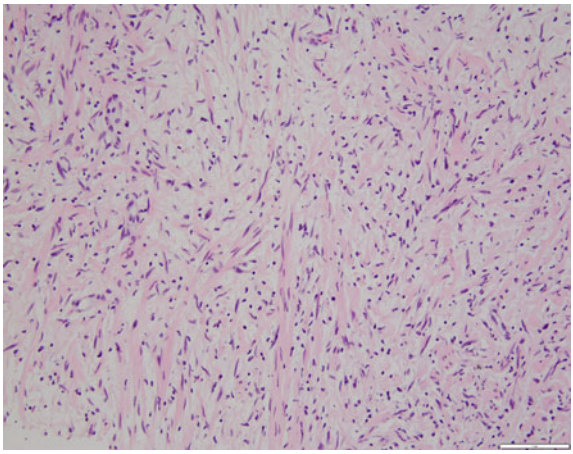

Fig. 10.14 Neurofibroma composed of spindle cells with thin wavy nuclei in a background of collagen fibrils (*shredded carrot* appearance). (H & E, 200×)

or comma shaped nuclei and are separated by collagen fibrils (Fig. 10.14). Some tumors show degenerative nuclear changes. Lesional cells are strongly positive for S100. Plexiform neurofibroma is pathognomonic for NF1 and carries a risk of transformation to malignant peripheral nerve sheath tumor (MPNST).

Malignant peripheral nerve sheath tumors (MPNST) are high-grade sarcomas which typically arise in association with larger nerve trunks and carry a poor prognosis. MPNST, in particular those arising in NF1-associated neurofibromas, can occur in young patients. Similar to other nerve sheath tumors, mediastinal MPNST is typically located in the posterior compartment, although cases may also arise in the prevascular mediastinum [66, 67]. Histologically, typical cases are composed of primitive appearing spindle cells in a fascicular growth pattern with alternating hypercellular and hypocellular areas. Geographic areas of necrosis can be found. Occasionally, MPNSTs can show significant pleomorphism (Fig. 10.15). Immunohistochemical stain for S100 is positive in less than half of the cases. Complete surgical resection may provide a cure, but overall, these are aggressive neoplasms with high rates of local recurrence and metastases [7]. Variants of MPNST, which have also been reported in the mediastinum, may show divergent mesenchymal differentiation with components of skeletal muscle (rhabdomyosarcoma, the so-called Triton tumor), osteosarcoma, and chondrosarcoma [68]. MPNST, including the Triton tumor variant, has been reported as a somatic component of mediastinal germ cell tumors [69].

Granular cell tumor shows differentiation along neuroectodermal lines and shares similarities with Schwann cells. They typically occur in the paravertebral mediastinum, in keeping with its proposed neuroectodermal/neural derivation. Few cases of granular cell tumor have been reported in the mediastinum, including cases with malignant behavior or atypical features suggestive of malignant granular cell tumor [70–73]. Histologically, this tumor shows nests and trabeculae of large, oval to round cells with intensely eosinophilic, granular cytoplasm. Cell borders are indistinct,

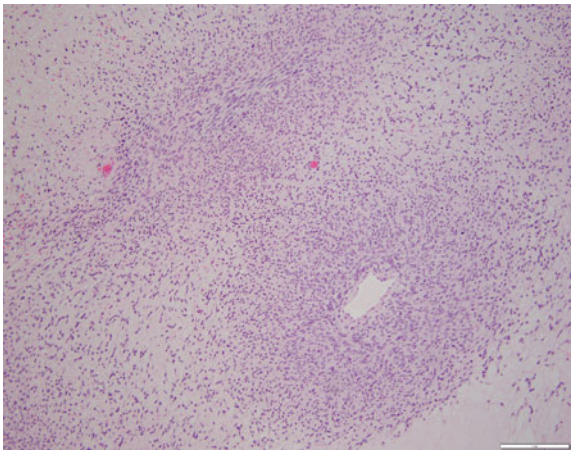

Fig. 10.15 Malignant peripheral nerve sheath tumor showing *light* and *dark* areas with primitive round to spindle cells in fascicles. Tumor cells show perivascular viability with areas of geographic necrosis (H & E, 100×)

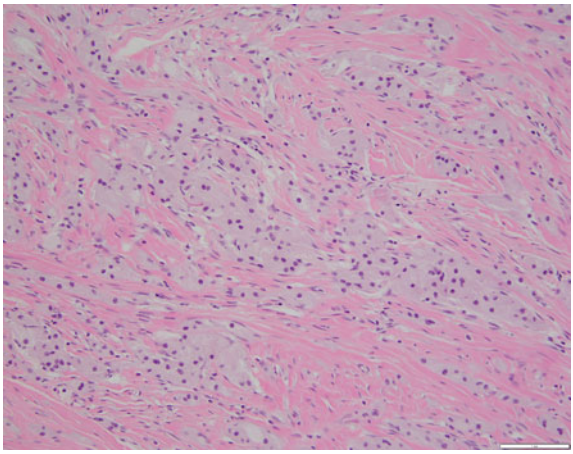

Fig. 10.16 Granular cell tumor showing nests and trabeculae of large, oval to round cells with eosinophilic, granular cytoplasm. (H & E, 200×)

producing a syncytial appearance (Fig. 10.16). Benign mediastinal granular cell tumor occur twice as frequently in females as in males; malignant granular cell tumors are equally distributed in males and females. Benign granular cell tumor are seen in young- to middle-aged adults (range 11–53 years, median age 27 years) with an average size of 4 cm and are often discovered incidentally. Malignant granular cell tumors are symptomatic, occur in older individuals (range 59–66 years, median age 63 years) and are larger (range 5.4–15 cm, average size 10.3 cm).

Paraganglioma

Paragangliomas located in the paravertebral compartment derive from the sympathetic chain, are situated in the costovertebral sulcus and secrete catecholamines in up to 50% of cases, resulting in systemic symptoms ('extraadrenal

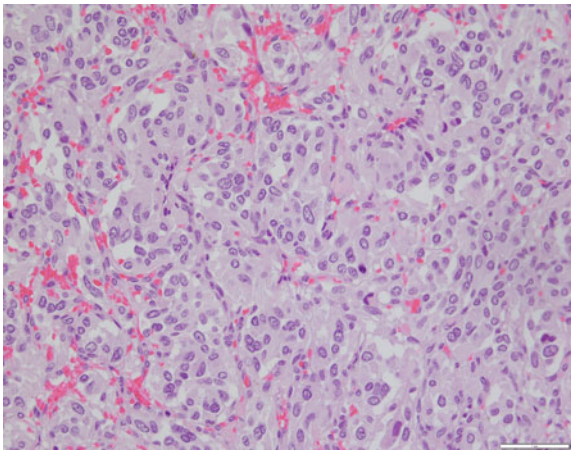

Fig. 10.17 Paraganglioma showing plump epithelioid cells in a characteristic nested 'Zell ballen' pattern with nests surrounded by spindle-shaped sustentacular cells (H & E, 400×)

pheochromocytoma'). Mediastinal paragangliomas occur over a wide age range; those located in the prevascular mediastinum are slightly more common in females, whilst paravertebral paragangliomas have slightly more frequently been reported in young adult males [74]. Histologically, they show typical nested (Zellballen) pattern of arrangement with the interspersed sustentacular cells (Fig. 10.17). The biological behavior of these tumors cannot reliably be predicted based on morphological features. Up to a quarter of cases may metastasize [75].

Synovial Sarcoma

Synovial sarcoma is a spindle cell tumor with variable epithelial differentiation and specific chromosomal alteration t(X;18) (p11;q11) resulting in *SS18-SSX* gene fusion. It occurs mainly in young adults with equal sex predilection. It commonly arises in deep soft tissue of the extremities, adjacent to joints and tendon sheaths; however, any site can be involved and tumors have been reported in the mediastinum [76–78]. Histologically, synovial sarcoma can be classified as monophasic or biphasic. The biphasic synovial sarcoma is composed of epithelial and spindle cells in varying proportions. The epithelial cells are ovoid and have abundant cytoplasm. They might form glands, papillary structures, or cords and nests. The spindle cell component is represented by a uniform population of small ovoid nuclei and small nucleoli (Fig. 10.18a). In the absence of the epithelial cells, the synovial sarcoma is classified as monophasic, and is composed of spindle cells in cellular sheets or fascicles with hemangiopericytomatous pattern (Fig. 10.18b). Areas of fibrosis and calcifications might also be noted. Areas of necrosis, high mitotic count, hypercellularity, and rhabdoid appearance might indicate a poorly differentiated synovial sarcoma, which is associated with a worse prognosis. About 90% of the synovial sarcomas express EMA and cytokeratin in the epithelial component,

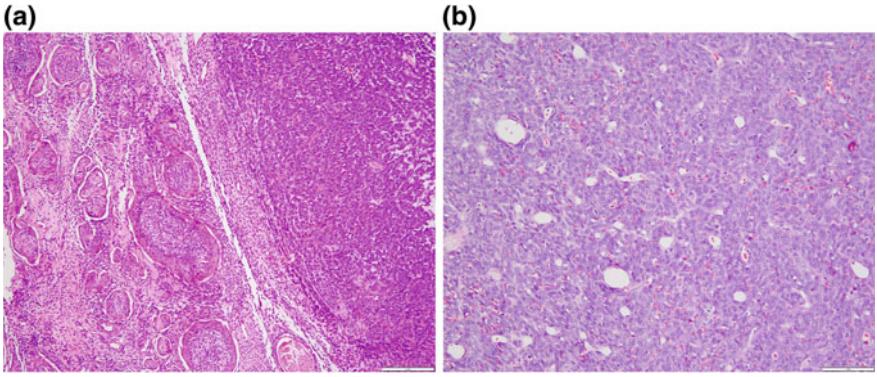

Fig. 10.18 **a** Biphasic synovial sarcoma showing distinctly epithelioid and spindle cell areas (H & E, 100×). **b** Monophasic synovial sarcoma showing uniform population of primitive appearing ovoid to spindle cells with minimal cytoplasm (H & E, 200×)

while BCL-2 expression is noted in the spindle component. Although not specific for synovial sarcoma, nuclear staining for the transcriptional co-repressor TLE1 is seen in most tumors. Molecular confirmation of synovial sarcoma can be performed using FISH for *SS18* gene rearrangemnet or RT-PCR study to prove the presence of the characteristic t(X;18)(p11;q11) translocation [7].

Undifferentiated Sarcoma

High-grade undifferentiated pleomorphic sarcomas (UPS) were previously often classified as malignant fibrous histiocytoma (MFH). A series of 34 so-called MFH cases in the mediastinum were reviewed by Murakawa et al. [79], and further individual case reports have been published. As in other soft tissue sites, these tumors are seen over a wide age range but mainly in older adults, with an equal gender distribution. These tumors can have a spectrum of morphologies the most common of which would be spindle cells arranged in fascicles with pleomorphic nuclei. Epithelioid, round cell and giant cell rich morphology can also be seen in some tumors. Most tumors show increased mitotic activity and evidence of necrosis in keeping with the high-grade behavior of these tumors. The diagnostic feature includes a lack of evidence of differentiation to any of the well recognized lines of differentiation, as detected by immunohistochemistry. As would be expected, these tumors have a poor prognosis despite therapeutic intervention.

Take home message:

– Primary soft tissues of the mediastinum are rare and can occur at any compartment of the mediastinum.

- Biopsy diagnosis of soft tissue tumor should follow the same protocol for handling and evaluating soft tissue tumors from other sites.
- Tissue utilization should be appropriately performed when dealing with small biopsy specimens, since the diagnosis of soft tissue tumor often requires molecular diagnosis.

References

1. Dubashi B, Cyriac S, Tenali SG. Clinicopathological analysis and outcome of primary mediastinal malignancies—a report of 91 cases from a single institute. Ann Thorac Med. 2009;4(3):140–2.
2. Pachter MR, Lattes R. Mesenchymal tumors of the mediastinum. I. Tumors of fibrous tissue, adipose tissue, smooth muscle, and striated muscle. Cancer. 1963;16:74–94.
3. den Bakker MA, Marx A, Mukai K, Strobel P. Mesenchymal tumours of the mediastinum-part I. Virchows Archiv: Int J Pathol. 2015;467(5):487–500.
4. Malagon HD, Valdez AM, Moran CA, Suster S. Germ cell tumors with sarcomatous components: a clinicopathologic and immunohistochemical study of 46 cases. Am J Surg Pathol. 2007;31(9):1356–62.
5. Okudela K, Nakamura N, Sano J, Ito T, Kitamura H. Thymic carcinosarcoma consisting of squamous cell carcinomatous and embryonal rhabdomyosarcomatous components. Report of a case and review of the literature. Pathol Res Pract. 2001;197(3):205–10.
6. Suster S, Moran CA, Chan JK. Thymoma with pseudosarcomatous stroma: report of an unusual histologic variant of thymic epithelial neoplasm that may simulate carcinosarcoma. Am J Surg Pathol. 1997;21(11):1316–23.
7. Fletcher CD, Bridge J, Hogendoorn P, Mertens F. WHO classification of tumours of soft tissue and bone. Lyon: IARC Press; 2013.
8. Damadoglu E, Salturk C, Takir HB, Ertugrul M, Yilmaz A, Atasalihi A, et al. Mediastinal thymolipoma: an analysis of 10 cases. Respirology. 2007;12(6):924–7.
9. Dhawan SS, Khouzam R. Atypical mediastinal lipomatosis. Heart Lung: J Crit Care. 2007;36 (3):223–5.
10. Nguyen KQ, Hoeffel C, Le LH, Phan HT. Mediastinal lipomatosis. South Med J. 1998;91 (12):1169–72.
11. Choi JY, Goo JM, Chung MJ, Kim HC, Im JG. Angiolipoma of the posterior mediastinum with extension into the spinal canal: a case report. Korean J Radiol. 2000;1(4):212–4.
12. Negri G, Regolo P, Gerevini S, Arrigoni G, Zannini P. Mediastinal dumbbell angiolipoma. Ann Thorac Surg. 2000;70(3):957–8.
13. La Mantia E, Franco R, Rocco R, Rocco G. Spindle cell lipoma: a rare tumor of the mediastinum. J Thorac Dis. 2013;5(4):E152–4.
14. Oaks J, Margolis DJ. Spindle cell lipoma of the mediastinum: a differential consideration for liposarcoma. J Thorac Imaging. 2007;22(4):355–7.
15. Ahn C, Harvey JC. Mediastinal hibernoma, a rare tumor. Ann Thorac Surg. 1990;50(5): 828–30.
16. Ema T, Kawano R. Myelolipoma of the posterior mediastinum: report of a case. Gen Thorac Cardiovasc Surg. 2014;62(4):241–3.
17. Franiel T, Fleischer B, Raab BW, Fuzesi L. Bilateral thoracic extraadrenal myelolipoma. Eur J Cardio-thorac Surg: Official J Eur Assoc Cardio-thorac Surg. 2004;26(6):1220–2.
18. Alaggio R, Coffin CM, Weiss SW, Bridge JA, Issakov J, Oliveira AM, et al. Liposarcomas in young patients: a study of 82 cases occurring in patients younger than 22 years of age. Am J Surg Pathol. 2009;33(5):645–58.

19. Hahn HP, Fletcher CD. Primary mediastinal liposarcoma: clinicopathologic analysis of 24 cases. Am J Surg Pathol. 2007;31(12):1868–74.
20. Ortega P, Suster D, Falconieri G, Zambrano E, Moran CA, Morrison C, et al. Liposarcomas of the posterior mediastinum: clinicopathologic study of 18 cases. Mod Pathol: Official J U S Can Acad Pathol Inc. 2015;28(5):721–31.
21. Boland JM, Colby TV, Folpe AL. Liposarcomas of the mediastinum and thorax: a clinicopathologic and molecular cytogenetic study of 24 cases, emphasizing unusual and diverse histologic features. Am J Surg Pathol. 2012;36(9):1395–403.
22. Bonnette P, Jouan J, Colchen A, Epardeau B, Grapin D, Grapin JP. Myxoid liposarcoma of the mediastinum. Rev Mal Respir. 2000;17(1):109–11.
23. Fujinaga K, Sakamoto S, Sawada Y, Tanaka J, Mizumoto T. Recurrent mediastinal desmoid tumor treated by surgical resection; report of a case. Kyobu geka Jpn J Thorac Surg. 2012;65(3):252–4.
24. Ko SF, Ng SH, Hsiao CC, Hsieh CS, Lin JW, Huang CC, et al. Juvenile fibromatosis of the posterior mediastinum with intraspinal extension. AJNR Am J Neuroradiol. 1996;17(3):522–4.
25. Nakagiri T, Koseki M, Nakamoto K, Taniyama K. Paraesophageal mediastinal desmoid tumor: case report. Gen Thorac Cardiovasc Surg. 2007;55(3):125–9.
26. Gounder MM, Lefkowitz RA, Keohan ML, D'Adamo DR, Hameed M, Antonescu CR, et al. Activity of Sorafenib against desmoid tumor/deep fibromatosis. Clin Cancer Res: Official J Am Assoc Cancer Res. 2011;17(12):4082–90.
27. Eguchi T, Ito N, Makiuchi A, Yoshida K. A solitary fibrous tumor arising from the thymus. Interact CardioVasc Thorac Surg. 2010;11(3):362–3.
28. Chmielecki J, Crago AM, Rosenberg M, O'Connor R, Walker SR, Ambrogio L, et al. Whole-exome sequencing identifies a recurrent NAB2-STAT6 fusion in solitary fibrous tumors. Nat Genet. 2013;45(2):131–2.
29. Robinson DR, Wu YM, Kalyana-Sundaram S, Cao X, Lonigro RJ, Sung YS, et al. Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing. Nat Genet. 2013;45(2):180–5.
30. Guillou L, Gebhard S, Coindre JM. Lipomatous hemangiopericytoma: a fat-containing variant of solitary fibrous tumor? Clinicopathologic, immunohistochemical, and ultrastructural analysis of a series in favor of a unifying concept. Hum Pathol. 2000;31(9):1108–15.
31. Witkin GB, Rosai J. Solitary fibrous tumor of the mediastinum. A report of 14 cases. Am J Surg Pathol. 1989;13(7):547–57.
32. Asakura S, Tezuka N, Inoue S, Kihara N, Fujino S. Angiomatoid fibrous histiocytoma in mediastinum. Ann Thorac Surg. 2001;72(1):283–5.
33. Domanski HA, Mertens F, Panagopoulos I, Akerman M. Low-grade fibromyxoid sarcoma is difficult to diagnose by fine needle aspiration cytology: a cytomorphological study of eight cases. Cytopathol: Official J Br Soc Clin Cytol. 2009;20(5):304–14.
34. Lindberg GM, Maitra A, Gokaslan ST, Saboorian MH, Albores-Saavedra J. Low grade fibromyxoid sarcoma: fine-needle aspiration cytology with histologic, cytogenetic, immunohistochemical, and ultrastructural correlation. Cancer. 1999;87(2):75–82.
35. Galetta D, Cesario A, Margaritora S, Granone P. Primary mediastinal hyalinizing spindle cell tumor with giant rosettes. Ann Thorac Surg. 2004;77(6):2206–9.
36. Takanami I, Takeuchi K, Naruke M. Low-grade fibromyxoid sarcoma arising in the mediastinum. J Thorac Cardiovasc Surg. 1999;118(5):970–1.
37. Coffin CM, Watterson J, Priest JR, Dehner LP. Extrapulmonary inflammatory myofibroblastic tumor (inflammatory pseudotumor). A clinicopathologic and immunohistochemical study of 84 cases. Am J Surg Pathol. 1995;19(8):859–72.
38. Chen M, Yang J, Zhu L, Zhou C, Zhao H. Primary intrathoracic liposarcoma: a clinicopathologic study and prognostic analysis of 23 cases. J Cardiothorac Surg. 2014;9:119.
39. Makimoto Y, Nabeshima K, Iwasaki H, Ishiguro A, Miyoshi T, Shiraishi T, et al. Inflammatory myofibroblastic tumor of the posterior mediastinum: an older adult case with

anaplastic lymphoma kinase abnormalities determined using immunohistochemistry and fluorescence in situ hybridization. Virchows Archiv: Int J Pathol. 2005;446(4):451–5.
40. Ramachandra S, Hollowood K, Bisceglia M, Fletcher CD. Inflammatory pseudotumour of soft tissues: a clinicopathological and immunohistochemical analysis of 18 cases. Histopathology. 1995;27(4):313–23.
41. Yamaguchi M, Yoshino I, Osoegawa A, Kameyama T, Tagawa T, Fukuyama S, et al. Inflammatory myofibroblastic tumor of the mediastinum presenting as superior vena cava syndrome. J Thorac Cardiovasc Surg. 2003;126(3):870–2.
42. Antonescu CR, Suurmeijer AJ, Zhang L, Sung YS, Jungbluth AA, Travis WD, et al. Molecular characterization of inflammatory myofibroblastic tumors with frequent ALK and ROS1 gene fusions and rare novel RET rearrangement. Am J Surg Pathol. 2015;39(7): 957–67.
43. Lovly CM, Gupta A, Lipson D, Otto G, Brennan T, Chung CT, et al. Inflammatory myofibroblastic tumors harbor multiple potentially actionable kinase fusions. Cancer Discov. 2014;4(8):889–95.
44. Moran CA, Suster S. Mediastinal hemangiomas: a study of 18 cases with emphasis on the spectrum of morphological features. Hum Pathol. 1995;26(4):416–21.
45. Huang SC, Zhang L, Sung YS, Chen CL, Krausz T, Dickson BC, et al. Frequent FOS gene rearrangements in epithelioid hemangioma: a molecular study of 58 cases with morphologic reappraisal. Am J Surg Pathol. 2015;39(10):1313–21.
46. Oshikiri T, Morikawa T, Jinushi E, Kawakami Y, Katoh H. Five cases of the lymphangioma of the mediastinum in adult. Ann Thorac Cardiovasc Surg: Official J Assoc Thorac Cardiovasc Surg Asia. 2001;7(2):103–5.
47. Park JG, Aubry MC, Godfrey JA, Midthun DE. Mediastinal lymphangioma: mayo clinic experience of 25 cases. Mayo Clin Proc. 2006;81(9):1197–203.
48. Suster S, Moran CA, Koss MN. Epithelioid hemangioendothelioma of the anterior mediastinum. Clinicopathologic, immunohistochemical, and ultrastructural analysis of 12 cases. Am J Surg Pathol. 1994;18(9):871–81.
49. Errani C, Zhang L, Sung YS, Hajdu M, Singer S, Maki RG, et al. A novel WWTR1-CAMTA1 gene fusion is a consistent abnormality in epithelioid hemangioendothelioma of different anatomic sites. Genes Chromosom Cancer. 2011;50(8):644–53.
50. Antonescu CR, Le Loarer F, Mosquera JM, Sboner A, Zhang L, Chen CL, et al. Novel YAP1-TFE3 fusion defines a distinct subset of epithelioid hemangioendothelioma. Genes Chromosom Cancer. 2013;52(8):775–84.
51. Weissferdt A, Kalhor N, Suster S, Moran CA. Primary angiosarcomas of the anterior mediastinum: a clinicopathologic and immunohistochemical study of 9 cases. Hum Pathol. 2010;41(12):1711–7.
52. Antonescu CR, Yoshida A, Guo T, Chang NE, Zhang L, Agaram NP, et al. KDR activating mutations in human angiosarcomas are sensitive to specific kinase inhibitors. Cancer Res. 2009;69(18):7175–9.
53. Guo T, Zhang L, Chang NE, Singer S, Maki RG, Antonescu CR. Consistent MYC and FLT4 gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical vascular lesions. Genes Chromosom Cancer. 2011;50(1):25–33.
54. Shaffer K, Pugatch RD, Sugarbaker DJ. Primary mediastinal leiomyoma. Ann Thorac Surg. 1990;50(2):301–2.
55. Van Schil PE, Colpaert CG, Van Look R, Van Oosterom AT, Van marck EA, Reher SW, et al. Primary mediastinal leiomyosarcoma. Thorac Cardiovasc Surg. 1993;41(6):377–8.
56. Auliac JB, Cuvelier A, Peillon C, Louvel JP, Metayer J, Muir JF. Mediastinal leiomyosarcoma. Rev Mal Respir. 1999;16(2):210–3.
57. Agaram NP, Zhang L, LeLoarer F, Silk T, Sung YS, Scott SN, et al. Targeted exome sequencing profiles genetic alterations in leiomyosarcoma. Genes Chromosom Cancer. 2015.
58. Boor A, Jurkovic I, Janik M, Vajo J, Kocan P, Ponist J, et al. Benign glomus tumor of the superior posterior mediastinum. Cesk Patol. 2000;36(4):156–9.

59. Brindley GV Jr. Glomus tumor of the mediastinum. J Thorac Surg. 1949;18(3):417–20.
60. den Bakker MA, Marx A, Mukai K, Strobel P. Mesenchymal tumours of the mediastinum-part II. Virchows Archiv: Int J Pathol. 2015;467(5):501–17.
61. Gaertner EM, Steinberg DM, Huber M, Hayashi T, Tsuda N, Askin FB, et al. Pulmonary and mediastinal glomus tumors–report of five cases including a pulmonary glomangiosarcoma: a clinicopathologic study with literature review. Am J Surg Pathol. 2000;24(8):1105–14.
62. Mosquera JM, Sboner A, Zhang L, Chen CL, Sung YS, Chen HW, et al. Novel MIR143-NOTCH fusions in benign and malignant glomus tumors. Genes Chromosom Cancer. 2013;52(11):1075–87.
63. Suster S, Moran CA, Koss MN. Rhabdomyosarcomas of the anterior mediastinum: report of four cases unassociated with germ cell, teratomatous, or thymic carcinomatous components. Hum Pathol. 1994;25(4):349–56.
64. Gale AW, Jelihovsky T, Grant AF, Leckie BD, Nicks R. Neurogenic tumors of the mediastinum. Ann Thorac Surg. 1974;17(5):434–43.
65. Fletcher CD, Davies SE, McKee PH. Cellular schwannoma: a distinct pseudosarcomatous entity. Histopathology. 1987;11(1):21–35.
66. Ducatman BS, Scheithauer BW, Piepgras DG, Reiman HM, Ilstrup DM. Malignant peripheral nerve sheath tumors. A clinicopathologic study of 120 cases. Cancer. 1986;57(10):2006–21.
67. Koezuka S, Hata Y, Sato F, Otsuka H, Makino T, Tochigi N, et al. Malignant peripheral nerve sheath tumor in the anterior mediastinum: a case report. Mol Clin Oncol. 2014;2(6):987–90.
68. Ducatman BS, Scheithauer BW. Malignant peripheral nerve sheath tumors with divergent differentiation. Cancer. 1984;54(6):1049–57.
69. Moran CA, Suster S. Primary germ cell tumors of the mediastinum: I. Analysis of 322 cases with special emphasis on teratomatous lesions and a proposal for histopathologic classification and clinical staging. Cancer. 1997;80(4):681–90.
70. Nakao M, Hishida T, Ishii G, Yoshida J, Nishimura M, Nagai K. Malignant granular cell tumor of the posterior mediastinum with dissemination. Asian Cardiovasc Thorac Ann. 2012;20(1):71–3.
71. Harrer WV, Patchefsky AS. Malignant granular-cell myoblastoma of the posterior mediastinum. Chest. 1972;61(1):95–6.
72. De Luca G, Luciano A, Benincasa G, Sessa R, Petteruti F. Giant malignant granular cell tumor (GCT) of the posterior mediastinum. J Thorac Oncol: Official Publ Int Assoc Study Lung Cancer. 2013;8(8):1107–8.
73. Machida E, Haniuda M, Eguchi T, Kurai M, Yamanda T, Amano J, et al. Granular cell tumor of the mediastinum. Intern Med. 2003;42(2):178–81.
74. Moran CA, Suster S, Fishback N, Koss MN. Mediastinal paragangliomas. A clinicopathologic and immunohistochemical study of 16 cases. Cancer. 1993;72(8):2358–64.
75. Lamy AL, Fradet GJ, Luoma A, Nelems B. Anterior and middle mediastinum paraganglioma: complete resection is the treatment of choice. Ann Thorac Surg. 1994;57(1):249–52.
76. Katakura H, Fukuse T, Shiraishi I, Hayatsu E, Nishijo K, Toguchida J, et al. Mediastinal synovial sarcoma. Thorac Cardiovasc Surg. 2009;57(3):183–5.
77. Salah S, Salem A. Primary synovial sarcomas of the mediastinum: a systematic review and pooled analysis of the published literature. ISRN Oncol. 2014;2014:412527.
78. Trupiano JK, Rice TW, Herzog K, Barr FG, Shipley J, Fisher C, et al. Mediastinal synovial sarcoma: report of two cases with molecular genetic analysis. Ann Thorac Surg. 2002;73(2):628–30.
79. Murakawa T, Nakajima J, Fukami T, Tanaka M, Takeuchi E, Takamoto S. Malignant fibrous histiocytoma in the anterior mediastinum. Jpn J Thorac Cardiovasc Surg: Official Publ Jpn Assoc Thorac Surg (Nihon Kyobu Geka Gakkai zasshi). 2001;49(12):722–7.

Summary

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Andre L. Moreira and Anja C. Roden

The mediastinum represents the central portion of the thoracic cavity. It is shared by many organs and tissues. Although primary tumors of the mediastinum are rare, any of the organs in the mediastinum can give rise to either benign or malignant tumors. The site is also often affected by metastatic diseases and inflammatory processes. Needless to say that the diagnosis of mediastinal lesions is challenging, not only for their rare occurrence, but also for the relative lack of experience many physicians, including pathologists, have with the diagnosis and clinical management of these lesions. This challenging issue becomes even more relevant when small biopsies including cytological specimens are used to establish a histological diagnosis. Luckily, a great number of mediastinal tumors do not require an initial histological diagnosis. In many cases, if a tumor is deemed to be amenable for surgical resection, surgery is the first line of therapy and the surgical specimen becomes the main diagnostic material. In the chapter on radiologic features, we learned that often the diagnosis of mediastinal masses can be suggested by characteristic imaging features with certain degree of confidence such as in teratomas, for example. However, in other cases, in the presence of common features of certain tumors in association with specific clinical information, a presumptive diagnosis can be reliably offered. A radiographic approach based on localization to a specific compartment and key imaging features can facilitate further evaluation of patients. This same approach to localization of the lesion is also useful to the pathologist evaluating biopsies of the

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mediastinum, since there is a good correlation between site of disease and the differential diagnosis.

For example, a patient who presents with a prevascular mediastinal mass and myasthenia gravis, thymoma and thymic hyperplasia should be included in the differential diagnosis. A prevascular mediastinal mass in a young man with elevated serum levels of alpha-fetal protein should prompt a presumptive diagnosis of germ cell tumor.

Biopsies are often procured in non-surgical cases in order to establish the diagnosis or in atypical presentations when the clinical information leads only to a differential diagnosis. For instance, a prevascular mass and lymphadenopathy can be seen in inflammatory conditions, thymic carcinoma, and lymphoma. Therefore, a multidisciplinary approach to mediastinal lesions is essential for patient management. In these situations, histological diagnosis is critical for the development of a treatment strategy.

In the chapter on biopsy techniques, we learned that mediastinal biopsies can be performed using minimally invasive technologies that allow easy access to all mediastinal compartments and that these procedures are slowly replacing surgical ones. However, the latter must still be performed in certain cases when a smaller biopsy fails to obtain adequate diagnostic tissue. Mediastinal biopsies are safe, regardless of the approach utilized. Most of the diagnostic failure in small biopsies, including cytology specimens, occurs in benign lesions such as mediastinal cysts and inflammatory conditions. Biopsies of the former may be interpreted as non-diagnostic because only benign structures are encountered and therefore, interpreted as contaminants and not diagnostic components of the lesion; and for inflammatory conditions, changes reminiscent of fibrosing mediastinitis can be seen around malignant neoplasms especially nodular sclerosis type of Hodgkin lymphoma; multilocular thymic cysts are seen around thymomas as well as many other malignant tumors.

The most important approach for a diagnosis on a biopsy is to have a firm understanding of the differential diagnosis and to be able to correlate the findings with clinical information. Failure to perform clinical, radiographic, and pathological correlations can lead to erroneous diagnosis and inadequate clinical management plan.

Another major pitfall emphasized in this book is metastatic disease. It is true that metastatic carcinomas from other organs are much more common than primary mediastinal lesions, especially in visceral mediastinum, where metastases to hilar lymph nodes are prevalent with an estimated incidence ranging from 15 to 43% [1, 2]. Fine needle aspiration biopsies are better accepted in the documentation of suspected metastatic disease to the mediastinum in the setting of a known primary tumor. As discussed above, most mediastinal tumors are resectable, whereas biopsies are procured in atypical presentations, when lymphomas are the presumptive diagnosis and in cases of disseminated disease. Therefore, when a clinical

history of a mediastinal mass, even if remote, is discovered, primary mediastinal tumors should enter the differential diagnosis. This pitfall is particularly important for thymomas where metastases often maintain the same morphologic and cytologic features of the primary tumor [3] but can be easily considered as metastatic carcinoma to a lymph node given the classical dual population of lymphocytes and clusters of epithelial cells.

Other key problems well discussed in the chapter on thymomas, thymic carcinomas, and thymic hyperplasia as well as in the chapter on cytology of mediastinal lesions is the sampling nature of biopsies. This is very relevant when a biopsy comes from the prevascular space due to the high degree of microscopic similarity between normal thymus, thymic hyperplasia, T cell-rich thymomas (WHO type B1), and T-lymphoblastic lymphoma; histological heterogeneity across individual type B thymomas; morphological overlap between spindle cell lesions with thymic epithelial, neuroendocrine, mesenchymal, and dendritic cell differentiation; and inflammatory conditions that may be associated with neoplasms such as granulomatous reaction. Therefore, the use of immunohistochemical stains and molecular techniques are often necessary for the establishment of the diagnosis. This is particularly important in cases of poorly differentiated neoplasms.

Poorly differentiated, non-keratinizing thymic squamous cell carcinoma can be recognized only by immunohistochemical detection of p63/p40; expression of CK5/6, and positivity for CD5 and CD117 positivity, which is seen in approximately 60% of cases. Positivity for immunohistochemical marker in large cell neuroendocrine carcinomas can be unevenly distributed and might not be detected in small biopsies; NUT carcinoma is a genetically defined, highly aggressive, and currently incurable carcinoma associated with chromosomal rearrangements of *NUT* which can be diagnosed only by immunohistochemical stains and/or molecular techniques, since morphological features are not reliable. Other differential diagnostic challenges comprise embryonal carcinoma (CD30+, OCT3/4+, SALL4+), seminoma (that can be keratin+ and CD117+ but is OCT3/4+ and SALL4+), melanoma, large cell lymphoma, and metastasis.

As it is for any biopsy material, tissue conservation approaches when using ancillary test are an important safeguard in the way we currently practice pathology.

Therefore, given the diversity of mediastinal abnormalities and lesions, and the fact that metastases from tumors that have originated elsewhere in the body are common occurrences in the mediastinum, the acquisition of a tissue sample, correlation with tumor location within the mediastinum, and a multidisciplinary approach to its interpretation is of paramount importance in establishing the correct diagnosis.

We hope you have enjoyed this book and that we may have been able to offer a practical approach to mediastinal tumor and inflammatory conditions!

References

1. Dziedzic D, Peryt A, Malgorzata S, Langfort R, Orlowski T. Evaluation of the diagnostic utility of endobronchial ultrasound-guided trans bronchial needle aspiration for metastatic mediastinal tumors. Endos Ultrasound. 2016;5:173–7.
2. Wakely PE Jr. Cytopathology-histology of mediastinum: epithelial, lymphoproliferative, and germ cell neoplasms. Ann Diagn Pathol. 2002;6:30–43.
3. Wakely PE Jr. Fine Needle aspiration in the diagnosis of thymic epithelial neoplasm. Hematol Oncol Clin North Am. 2008;22:433–42.

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