Thymoma

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Despite being the most common epithelial tumor in the anterior mediastinum, thymomas have been the subject of much controversy in terms of classification, staging, and clinical outcomes. This controversy derives in part from the fact that thymomas are uncommon tumors, as mediastinal pathology is unusual in general. Therefore, most publications regarding thymomas comprise small series of cases in which the authors have proposed their own views about classification, staging, or clinical behavior. In more recent times, some issues around thymomas have been resolved, but nevertheless, it is important to highlight that the published literature is rather empiric at best with little detail and with a wide spectrum of disparity in terms of pathology.

Publications dating back to the 1950s identified several neoplasms that were incorrectly grouped among cases of thymoma, such as granulomatous thymoma—currently Hodgkin lymphoma, and seminomatous thymoma—now seminoma. The period of time between 1950 and 2000 saw some advancement in terms of proper classification for tumors that do not belong to the thymoma family but other publications on the topic of classification have not provided clarity regarding the difference between thymoma and thymic carcinoma. At this point, it is important to clarify that thymoma is not the benign counterpart of thymic carcinoma nor is thymic carcinoma the malignant form of thymoma. Both conditions, thymoma and thymic carcinoma, represent unique clinicopathological entities, which require proper delineation not only for diagnostic purposes but also for prognosis, treatment, and outcomes. It has been only in the last 30 years that the distinctions have been clarified to some extent. Nevertheless, terms such as "malignant thymoma," are still prevalent in some of the literature, making it difficult to discern whether that term refers to invasive thymoma or thymic carcinoma. In any case, such terminology should be abandoned and the preferred terms of thymoma and thymic carcinoma should be employed.

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Epidemiological Features

It is difficult to estimate the true incidence and prevalence of thymomas. On the one hand, most databases collect cases that are considered malignant and for some the diagnosis of thymoma may fall into the benign category. On the other hand, thymomas are often included in the same category of thymic carcinoma, which also likely contaminates the true incidence of these tumors. Pfizzer and Engels [1] using the National Cancer Institute's Surveillance Epidemiology and End Results (SEERS) provided their results in a study in 2003 in which the authors were able to gather information from nine cities in the USA from the years 1973–1998. The author identified 849 cases of what was termed "malignant thymoma" giving an approximate incidence of 0.15 per 100,000 person-years with a mean age at diagnosis of 56 years; 11% of these tumors occurred in patients under 35 years. The authors also identified a decrease in patients over 77 years. Thymomas appear to have a higher incidence in men than in women and 0.12, 0.20, 0.29/10000 person-year among whites, Blacks, and other races, respectively. In a different study on rare thoracic cancers, the authors provided an incidence for thymic epithelial tumors of 1.7 per million per year, with the so-called malignant thymomas the most common at 1.4 per

C. A. Moran et al. (eds.), *The Thorax*, https://doi.org/10.1007/978-3-031-21040-2_3

million per year [2]. In addition, it has been stated that thymoma patients may be at higher risk of developing B-cell lymphomas and sarcomas [3].

Clinical Features

The association of thymomas with numerous autoimmune diseases has been extensively reported in the literature [4–15]. The closest association has been with myasthenia gravis (MG), with thymomas present in 10–15% of patients with MG. Other studies have documented the presence of thymoma in approximately 21% of patients with immunological disorders [16]. More recently, in a large study of more than 1400 cases of thymoma [17], the authors identified an association with MG in 17%, with other immunological disorders in 3.8%, and with other types of neoplasia in 6.8%. The clinical symptoms of patients with thymoma are variable and depend on the underlying conditions associated with the tumor. Table 3.1 illustrates the numerous clinical entities that may be associated with thymomas. Nevertheless, it is also important to highlight that in approximately 50% of cases, patients may present with non-specific symptoms or with no symptoms at all and their mediastinal mass may be discovered incidentally during a routine chest radiograph.

Table 3.1 Clinical and neoplastic diseases associated with thymoma[a]

Autoimmune, non-autoimmune diseases, and paraneoplastic syndromes
• Myasthenia gravis
• Sjögren syndrome
• Pemphigus vulgaris
• Guillain-Barré syndrome
• Polymyalgia rheumatica
• Lupus erythematosus
• Polymyositis
• Hashimoto thyroiditis
• Rheumatoid arthritis
• Limbic encephalitis
• Neuromyotonia
• Stiff person syndrome
• Myotonic dystrophy
• Mixed connective tissue diseases
• Myocarditis
• Graft-versus-host disease
• Hypogammaglobulinemia
• Pure red cell aplasia
• Intestinal pseudo-obstruction
• Paroxysmal nocturnal hematuria
• Acrokeratosis
• Lichen planus
• Conjunctivitis
• Cancer-associated retinopathy
• Glomerulonephritis
• Thalassemia
Neoplastic diseases of different organ systems
• Thyroid carcinoma
• Cholangiocarcinoma
• Breast carcinoma
• Lung carcinoma
• Gastrointestinal carcinoma (gastric, esophagus, colon)
• Hepatic carcinoma
• Genitourinary carcinoma (kidney, prostate, bladder)
• Endometrial carcinoma
• CNS malignancies
• Malignant Lymphoproliferative disorders (lymphoma, myeloma)

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*The plethora of clinical conditions that have been associated with thymoma is extensive and it is possible that this table is incomplete

Diagnostic Imaging

Thymic epithelial neoplasms such as thymoma, thymic carcinoma, and thymic neuroendocrine neoplasms can present as homogeneous or heterogeneous, solid or solid/cystic, well-circumscribed or irregular masses, predominantly in the prevascular/anterior mediastinum (Figs. 3.1, 3.2, and 3.3). Thymoma should be strongly considered when a predominantly homogeneous prevascular/anterior mediastinal mass is encountered in a patient over 40 years old with symptoms related to myasthenia gravis, Diamond-Blackman syndrome/pure red cell aplasia, aplastic anemia, or hypogammaglobulinemia [18]. Larger masses with irregular margins, necrosis, cystic change, hemorrhage, local invasion, or with evidence of advanced disease including pleural and or pericardial nodules, pleural effusion, or distant metastasis suggest invasive thymoma, thymic carcinoma, or thymic neuroendocrine neoplasm.

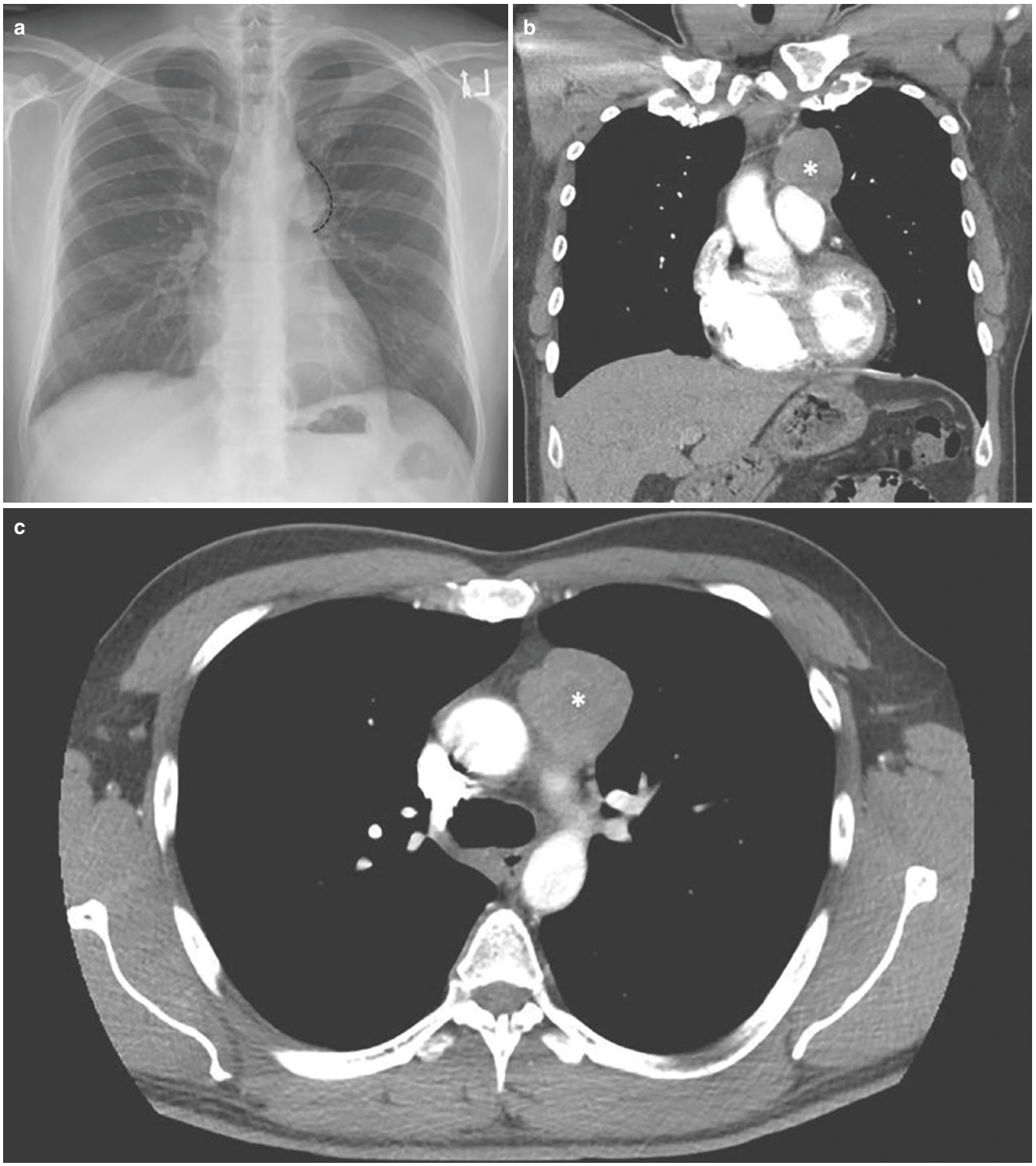

Fig. 3.1 Thymoma 1. (**a**) Frontal chest radiograph shows a mass (outlined by dashed line) in the aorto-pulmonic window. Contrast-enhanced computed tomography coronal (**b**) and axial (**c**) images show a weakly enhancing anterior mediastinal mass (asterisk) with soft-tissue attenuation without invasion of regional structures

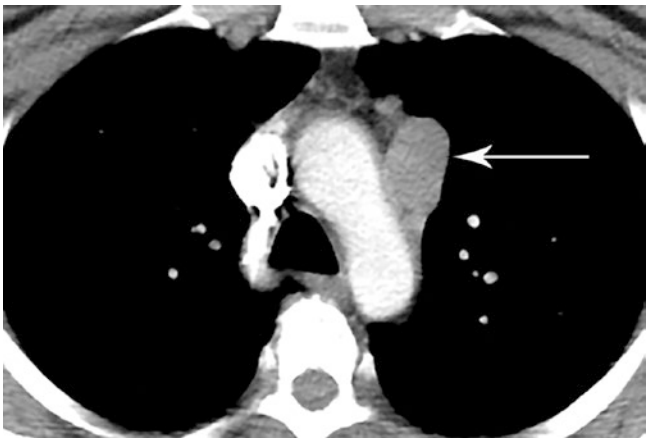

Fig. 3.2 Thymoma—Contrast-enhanced CT shows left anterior mediastinal mass (arrow)

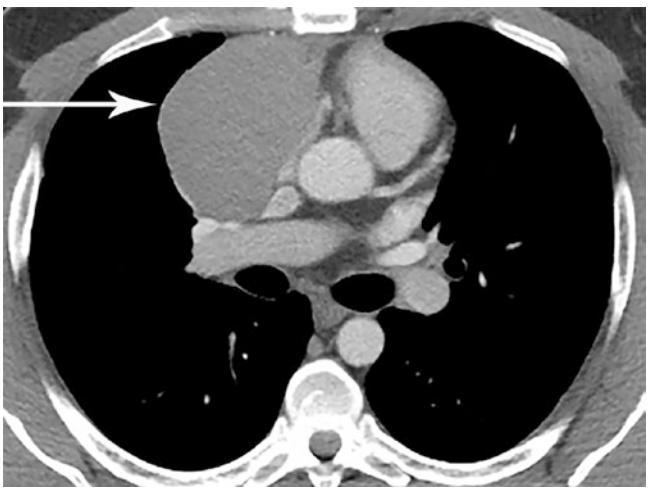

Fig. 3.3 Thymoma—Contrast-enhanced CT shows soft tissue mass in the right anterior mediastinum (arrow) with mass effect compressing the right atrium more consistent with an invasive thymoma

Histological Classification

Over the last century the histological classification of thymomas has been a point of contention with little agreement. This is partially due to early misunderstandings about the tumor and the unfortunate practice of labeling every tumor originating from the anterior mediastinum as a thymoma [19]. Therefore, prior to 1961 there were numerous points of view regarding the histological classification of thymomas [20–30]. After 1961, many of these misconceptions were clarified in some measure. Table 3.2 depicts the most commonly used histological classifications with the corresponding World Health Organization (WHO) translation.

Bernatz et al. [31] in 1961 described 138 thymoma cases (96 surgical resections) and outlined what has become the traditional histological classification of thymomas. The authors classified thymomas based on the proportional presence of lymphocytes into lymphocyte-rich or epithelial-rich tumors. For those tumors with approximately equal number of lymphocytes and epithelial cells, the term mixed or reticuloepitheial thymomas was used. In addition, the authors considered separately a group of tumors in which the cells had a fusiform appearance and called those tumors spindle cell thymomas. The authors found that thymomas rarely metastasize to distant organs but rather invade by local extension into the mediastinal organs. In addition, it was noted that patients with invasive thymomas had a shorter survival compared to those with noninvasive tumors. Recurrence in cases of noninvasive thymoma (encapsulated thymoma) has been reported in no more than 2% of thymomas [32]. In 1973, Bernatz et al. [33] provided their experience with 181 cases, in which the authors identified only two patients with distant metastasis (liver). Crucially, the authors established that all thymoma tumors have the potential to be invasive, regardless of the histological features of the tumor. Salyer and Eggleston [34] in a report of 65 cases confirmed that the single most important parameter in predicting clinical outcome is the capsular integrity of the tumor. Furthermore, their data showed that there is histological heterogeneity of thymomas, histological classification is rather subjective, the histological examination of multiple sections is required, and that histology and invasiveness of the tumors do not necessarily correlate. Additional series of reported cases also stress that invasiveness of the tumor is more important than histology of the tumor in assessing clinical outcome [35–37]. Also note that some authors have used the designation of "malignant thymoma" for cases of invasive thymoma, incorrectly implying that encapsulated thymomas are benign tumors [38]. The description of some cases raises the possibility that "malignant thymoma" may have also included some thymic carcinomas.

In 1985, Marino and Muller-Hermelink [39] reported a series of 58 cases of thymoma and 13 cases of thymic carcinoma that the authors identified over a period of 16 years. In contrast to the series published by Bernatz et al. [31, 33] and previous assessments by Salyer and Eggleston [34] regard-

Table 3.2 Camparison among the different histological classifications of thymoma with the corresponding WHO translator

Bernatz	Marino-Muller-Hermelink	Suster-Moran	WHO translator
Lymphocyte-rich	Cortical thymoma	Thymoma	B1 type
Mixed (equal proportion of lymphocytes and epithelial cells)	Cortical thymoma	Thymoma	B2 type
Epithelial-rich	Well-differentiated thymic carcinoma	Atypical thymoma	B3 type
Spindle cell	Medullary thymoma	Thymoma	A type

ing the heterogeneity of thymomas, Marino and Muller-Hermelink advanced the so-called histogenetic classification of thymomas, using biopsy material only, and drawing an analogy with the normal anatomy of the thymus. They designated thymoma tumors as cortical thymoma, medullary thymoma, and mixed thymoma (in which cortical and medullary differentiation were present). Important questions arise from this study, including the ability to differentiate cortical and medullary tumors in small biopsies. Further, the authors stated that medullary thymoma (spindle cell thymoma) neoplasms were benign based on only three cases/biopsies.

This classification of thymomas correlates with their counterpart in the Bernatz [31, 33] histological classification, with one exception: predominantly epithelial thymomas. In 1992, Kirchner et al. [39] reported 26 cases with similar features as those described by Bernatz but which Kirchner et al. interpreted as "well differentiated thymic carcinoma."

Although semantics may play some role in the descriptions and names of the different histological groups in these two classification systems, there are other concerning issues:

- The histogenetic classification assumes that cortical thymomas originate from epithelial cells of the cortex while medullary thymomas from epithelial cells from the medulla—this particular issue has not been proven up to now, even by the proponents of such classification [40]. In addition, further studies attempting to correlate this new approach have failed in providing consistency [41, 42].
- Spindle cell (medullary) thymomas are assumed to be benign tumors with limited data.
- The histological features of the tumor are assumed able to predict the clinical outcome of patients with thymomas.

Later studies on thymomas have nevertheless endorsed this classification schema, including the idea that spindle cell (medullary) thymomas are benign, even though in most of these studies, the number of such tumors is very limited [43–50]. Lewis et al. [51] reported 283 cases of thymoma in which the authors estimated an overall survival rate of 67% and 53% at 5 and 10 years, respectively. In addition, the authors stated that thymomas rarely metastasize outside of the thoracic cavity.

In 1995, the WHO provided a translator for the different classification schemas (Bernatz and Marino-Muller Hermelink), using letters and numbers to designate the different histological groups, in an effort to address the different histological schemas presented in the literature and the lack of uniformity. In 1999, the WHO [52] stated that the use of letters and numbers is noncommittal terminology and does not represent a new classification. Some authors have proposed that the extent of the tissue sampling may affect the final histopathological classification [53].

In 1999, a different proposal was put forward in which the authors [54] classified thymic neoplasms into three categories: (1) thymoma, which includes all thymomas containing lymphocytes and spindle cells, (2) atypical thymoma, predominantly epithelial thymomas or well differentiated thymic carcinomas, and (3) thymic carcinoma. However, in this proposal, the authors place more emphasis on the staging of the tumor rather than the histological subtyping. This classification schema has been validated by different studies with large numbers of cases, including a multi-institutional study [17, 55–57]. A correlation with the letters and numbers previously proposed by the WHO found no meaningful clinical correlation. Further, a study of more than 200 cases of invasive thymomas showed that spindle cell thymomas (WHO type A) account for approximately 19% of all cases of invasive thymoma and that the tumor can invade other structures such as lung and thyroid [58].

Pathological Staging

Just as the nomenclature and histological classification of thymomas has been controversial over the last decades, so is the staging of these tumors. The most recent proposed staging system for thymomas uses TNM categories. The TNM system is well known and includes primary tumor size, nodal involvement, and distant metastasis, and is commonly employed for other neoplasms. In a recent review of the different staging systems used over the years [59], several issues were identified with regard to the new TNM system. Table 3.3 provides a comparison of the three most common staging systems and their differences.

In contrast to other tumors, the T descriptor for the staging of thymomas does not use the size of the tumor. The authors of the TNM approach to thymomas have defined the T factor borrowing from the experience of two older, well-documented staging systems—modified Masaoka staging and Moran staging. In this context, the designations TX, cannot assess tumor, and T0, no tumor present, are less applicable in the case of baseline staging. Also, thymomas rarely metastasize to lymph nodes (in the largest series of cases, this feature was not observed), and uncommonly implant outside of the thorax, meaning that the N and M descriptors at initial staging almost invariably correspond to N0 and M0 [60, 61]. The natural history of tumor progression is by direct extension into adjacent structures rather than with separate nodules. In the new TNM system, involvement of nearby organs such as the pericardium and blood vessels has been designated as M disease. It should be noted that metastatic pleural deposits from thymoma can occur even years after tumor resection.

In order to understand and to place the TNM in perspective, it is essential to understand and know the Masaoka and

Table 3.3 Staging systems for thymoma

TNM	Definition	Mazaoka/Koga	Moran
TX	Primary tumor cannot be assessed	N/A	N/A
T0	No evidence of primary tumor	N/A	Encapsulated thymoma (**Stage 0**)
T1	Encapsulated tumor	**Stage I**	Minimally invasive thymoma without involvement of any adjacent structure (**Stage I**)
T1a	No mediastinal pleural involvement	N/A	N/A
T1b	Direct invasion of mediastinal pleura	**Stage II**	**Stage IIA** (innominate vein, mediastinal pleura, lung)
T2	Direct invasion of pericardium	**Stage III**	**Stage IIB** (pericardium)
T3	Invasion into lung, brachiocephalic vein, SVC, phrenic nerve, chest wall, extrapericardial pulmonary artery or veins	**Stage III**	
T4	Invasion into aorta, arch vessels, pulmonary artery, myocardium, trachea, esophagus	**Stage III**	**Stage IIC** (great vessels and heart)
M1a, b		**Stage IVa—**Pleural, pericardial dissemination **Stage IVb—**Lymphogenous or Hematogenous dissemination	**Stage III—**Metastatic disease **IIIA**—Intrathoracic structure Diaphragm (drop metastasis) Lymph nodes **IIIB**—Extra-thoracic

Moran staging systems. Both systems employ the well-documented feature of capsular integrity for the early stages while invasive tumors correlate with later stages. Also, both systems address the metastatic potential of thymomas with proper designation for tumors within and outside of the thoracic cavity. One important difference is that in Masaoka stages I and II, the clinical outcome is similar. The Moran staging system uses stage 0 for a completely encapsulated tumor and Stage I for a minimally invasive tumor, separating the tumors based on the extent of disease: limited versus invasive. (Figures 3.4, 3.5, 3.6, 3.7, 3.8, and 3.9) provide a schematic perspective of how to approach the staging of thymomas. Since TNM schema uses similar definitions as those proposed by Masaoka and Moran, the outcomes may be similar. However, in some regards it may be less accurate as tumor invasion of the adjacent organs is generally not considered metastatic disease. In addition, the separation of great vessel invasion into two different T categories by the TNM system is not associated with any specific clinical significance.

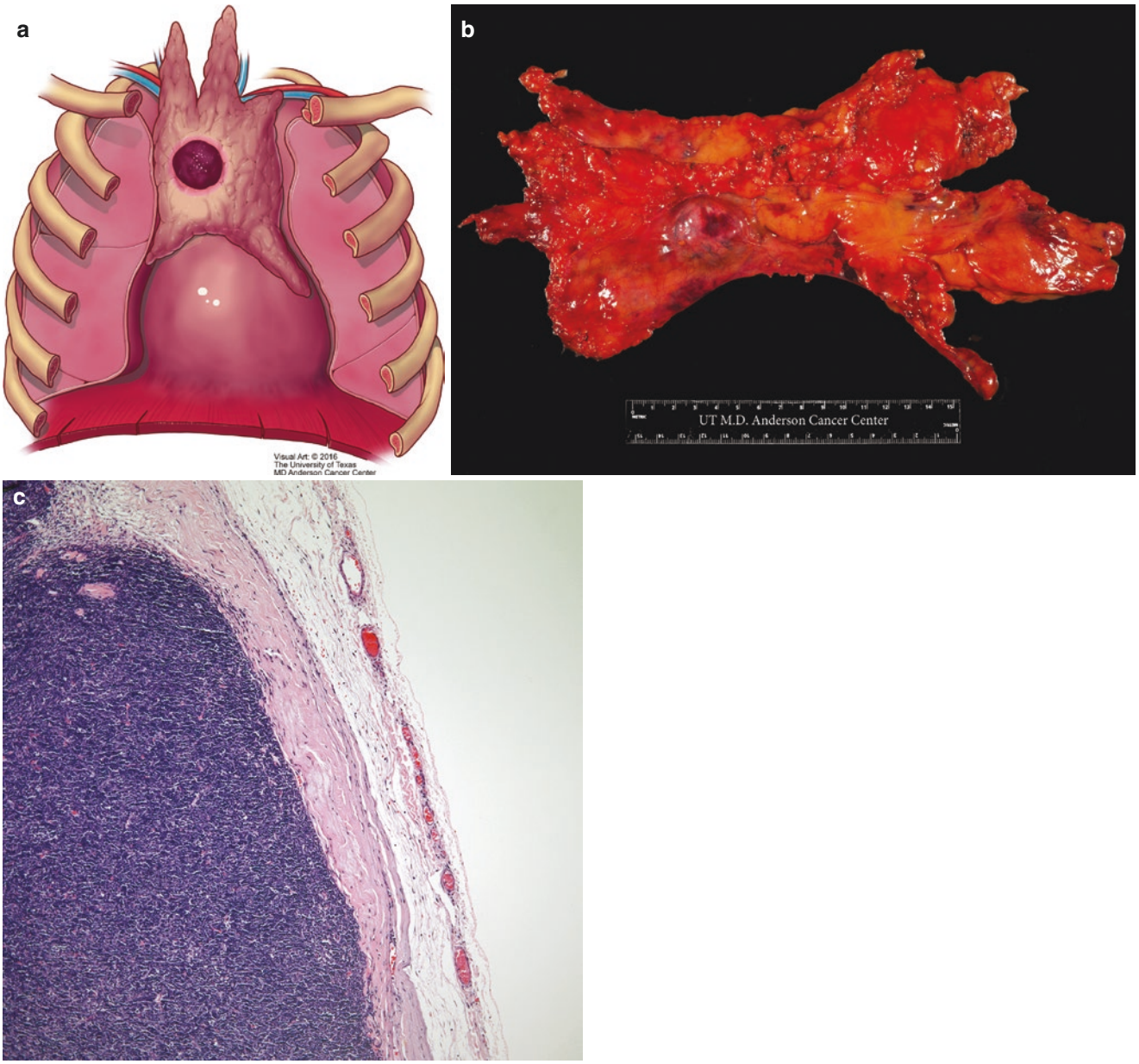

Fig. 3.4 Pathological staging using the Moran schema: (**a**) Stage 0—Limited disease—encapsulated thymoma, (**b**) Gross illustration of a resected encapsulated thymoma, (**c**) Histologically the tumor is encapsulated (with permission from Dr. Moran, copyright ©2016)

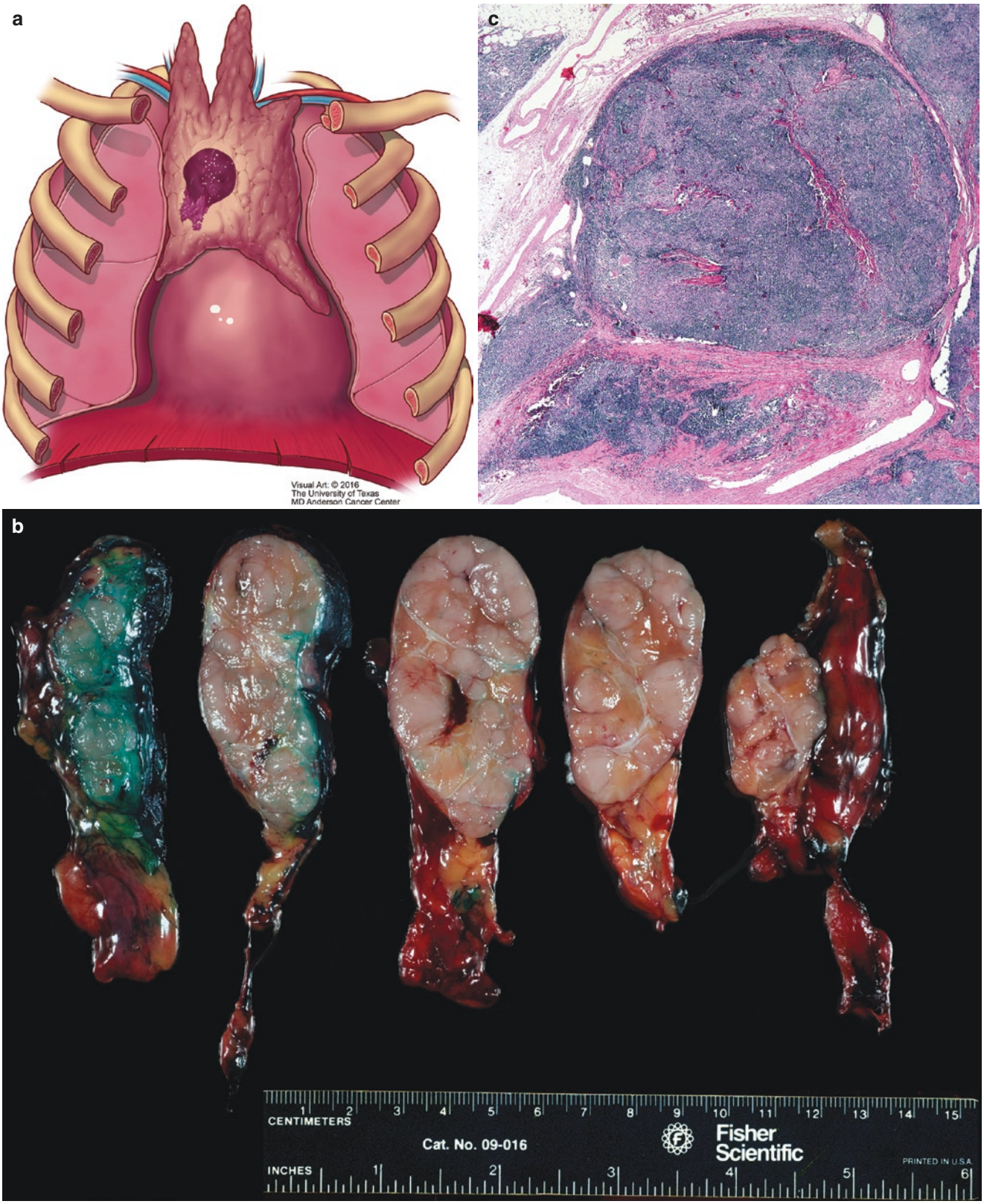

Fig. 3.5 Stage I—Limited disease—(**a**) Minimally invasive thymoma, (**b**) Gross illustration of a resected minimally invasive thymoma, (**c**) tumors has transgression of the fibrous capsule (with permission from Dr. Moran, copyright ©2016)

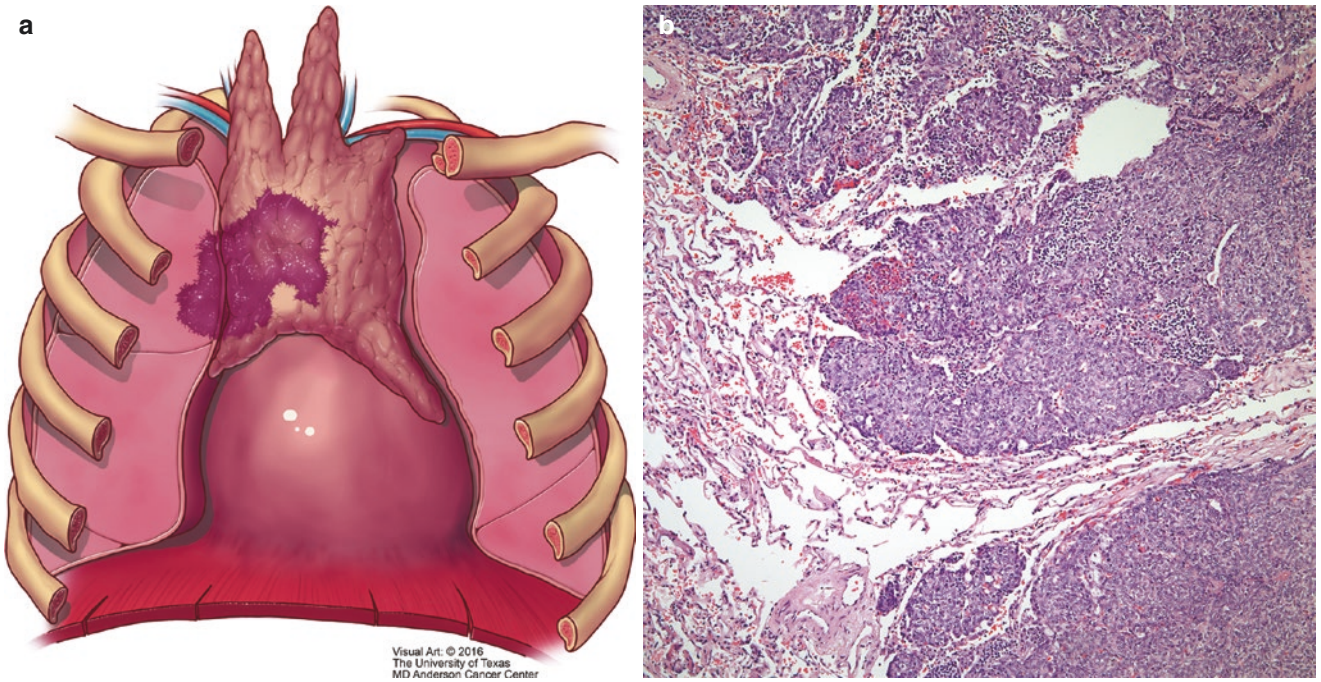

Fig. 3.6 Stage IIA—invasive disease—(**a**) tumor invades pleural and lung, (**b**) histologically proven invasion of the lung parenchyma (with permission from Dr. Moran, copyright ©2016)

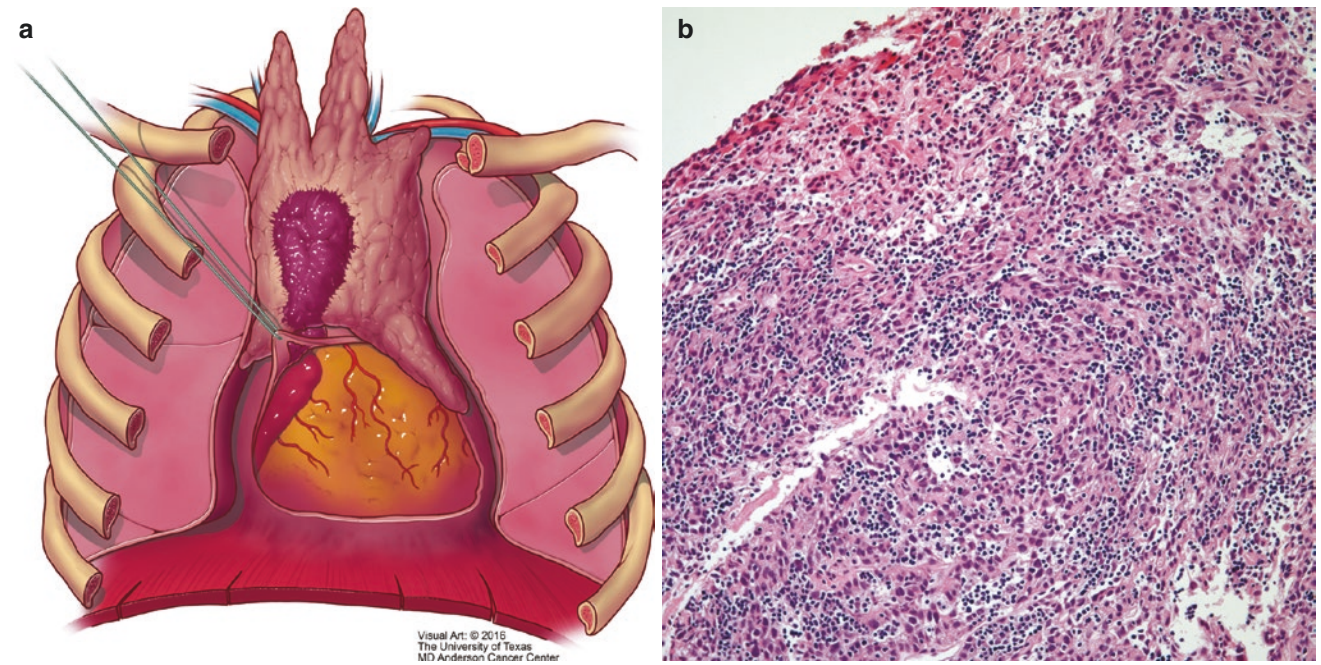

Fig. 3.7 Stage IIB—Invasive disease—(**a**) tumor invades pericardium, (**b**) Histologically proven pericardial invasion (with permission from Dr. Moran, copyright ©2016)

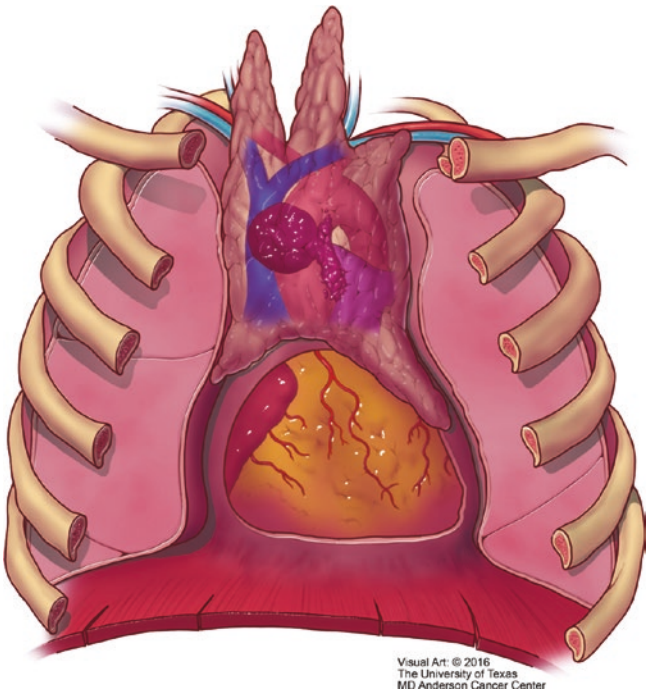

Fig. 3.8 Stage IIC—invasive disease—Schematic illustration of tumor invading the great vessels (with permission from Dr. Moran, copyright ©2016)

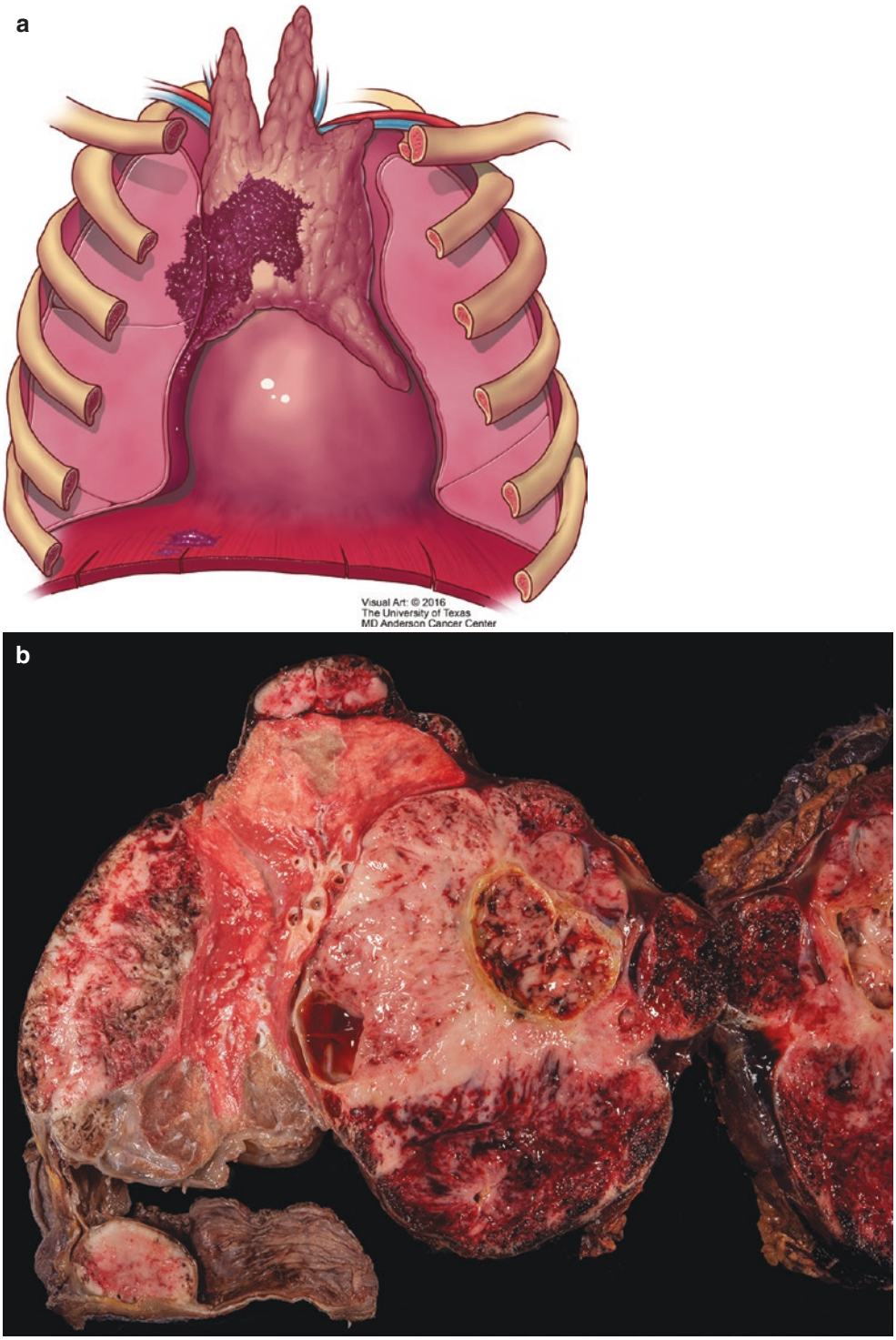

Fig. 3.9 Stage IIIA—(**a**) Metastatic disease the so-called "drop metastasis" as tumor involves diaphragm, (**b**) Gross specimen of such occurrence, note the presence of tumor in the diaphragmatic muscle (with permission from Dr. Moran, copyright ©2016)

Pathological Features

Grossly, thymomas varied in size and shape. The tumors may show an infiltrative border or may be well circumscribed. In addition, thymomas may have cystic changes or be solid; areas of hemorrhage and or necrosis may also be present. Regarding size, these tumors may be over or under 10 cm in greatest diameter. However, it is important to highlight that size does not correlate with invasiveness or with any type of histology (Figs. 3.10 and 3.11).

Histologically, all classifications employ the progressive loss of lymphocytes in order to provide a particular designation or letter and number to that specific type of thymoma (see Table 3.2). Thymomas are a very heterogeneous group of tumors with different growth patterns that have been reported in the literature [62–85]. Table 3.4 lists the various

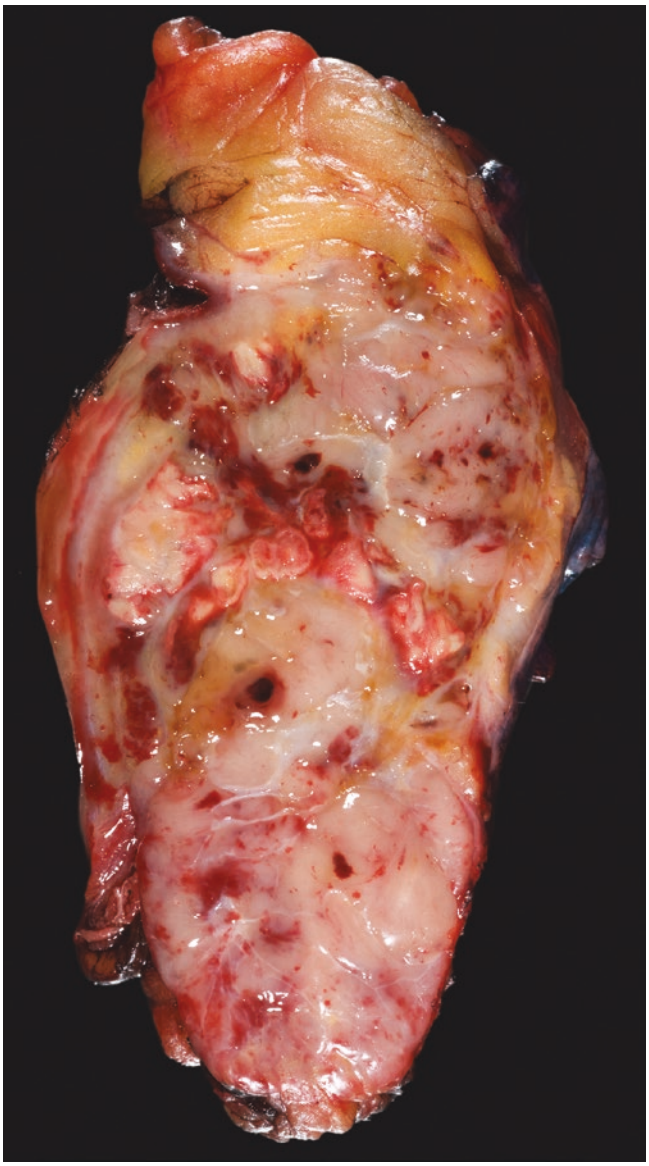

Fig. 3.10 Gross specimen of a thymoma, note the solid and lobulated appearance of the tumor

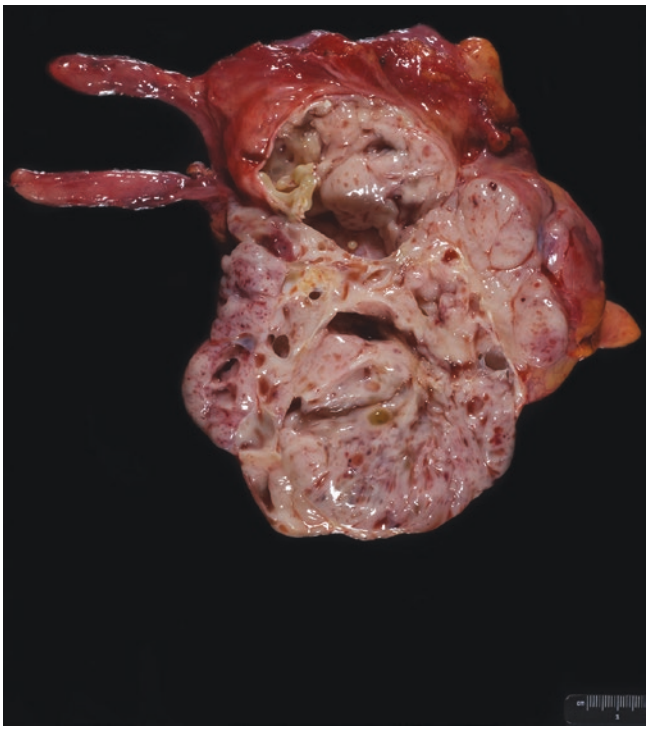

Fig. 3.11 Gross specimen of a thymoma showing prominent cystic changes

Table 3.4 Different growth patterns associated with thymomas[a]

Lymphocytic thymomas (WHO type B1, B2)
Spindle cell thymomas (WHO type A)
Atypical (WHO type B3)
Atypical thymoma with pseudosarcomatous stroma (WHO type metaplastic thymoma)
Combined thymoma and thymic carcinoma
Mixed histologies
Plasma cell rich
Rhabdomyomatous
Necrotic and hemorrhagic
Mucinous
Desmoplastic
Glandular
Signet ring cell-like
Micronodular with B-cell hyperplasia
Cystic and cystic micronodular
Neuroendocrine morphology
Papillary
Ancient changes (sclerosing thymoma)
Adenomatoid
Giant cells
Other unusual features
Myxoid/edematous
Hydropic-like changes
Alveolar
Angiomatous
Sebaceous
Microvesicular
Synovial sarcoma-like
Neural-like

*modified from the original in Mediastinal Pathology by Kahor N and Moran CA, Springer 2–19)

growth patterns found to be associated with thymomas (Figs. 3.12, 3.13, 3.14, 3.15, 3.16, 3.17, 3.18, 3.19, 3.20, 3.21, 3.22, and 3.23). Although the most common subtypes of thymoma are those with a lymphocytic component, removing more than five sections from a tumor specimen raises the possibility of a mixed histology lesion greater than 50%. Therefore, if a tumor is properly sampled and more than 50% of the tumors have mixed histology, relying upon a specific histological classification may be less useful [53, 56]. Also, importantly, histologic subtype does not correlate with invasiveness or size. Therefore, staging becomes the single most important factor in predicting clinical outcome.

The immunohistochemical stains that are often used as an aid in the diagnosis of thymoma include keratin 5/6, p63, and

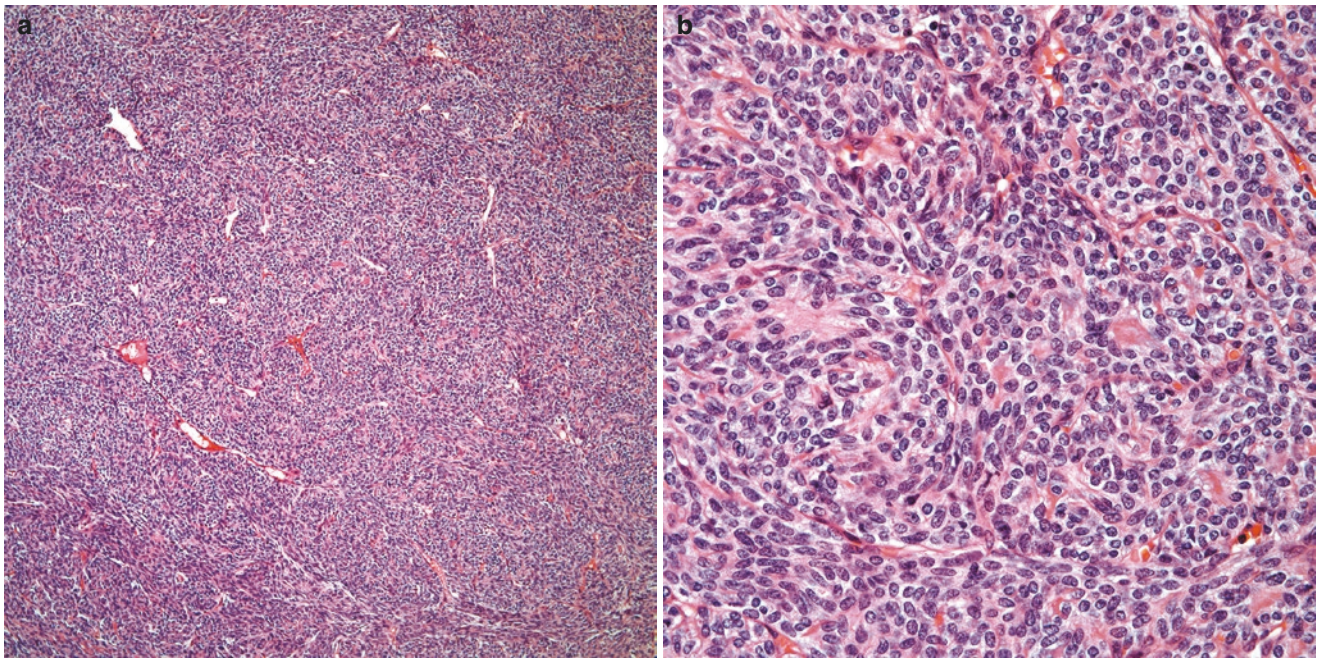

Fig. 3.12 (**a**) Low power of a spindle cell thymoma, (**b**) spindle cells with bland appearance and lack of atypia or mitotic activity (Spindle cell thymoma in the Bernatz classification, Medullary thymoma in the Marino-Muller-Hermelink classification, type A in the WHO translator)

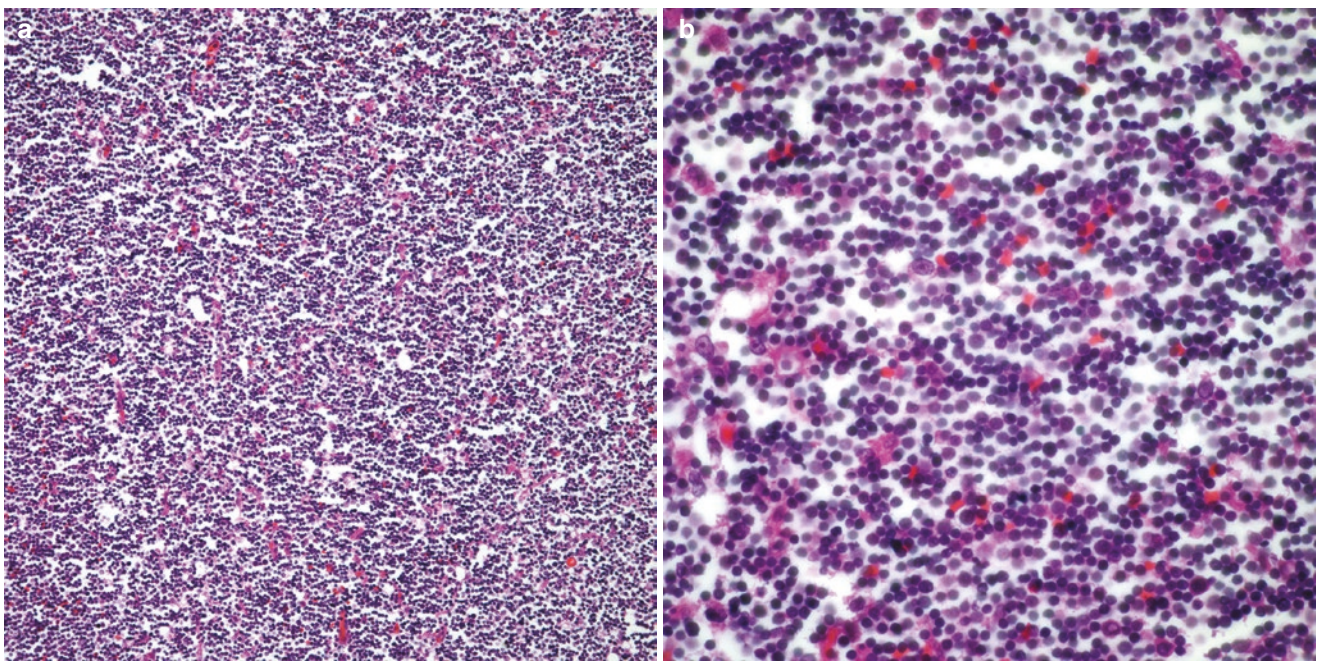

Fig. 3.13 (**a**) Thyoma with prominent lymphocytic component, (**b**) higher magnification showing more lymphocytes than epithelial cells (Lymphocyte rich in Bernatz classification; Cortical thymoma in Marino-Muller-Hermelink classification, B1 in the WHO translator)

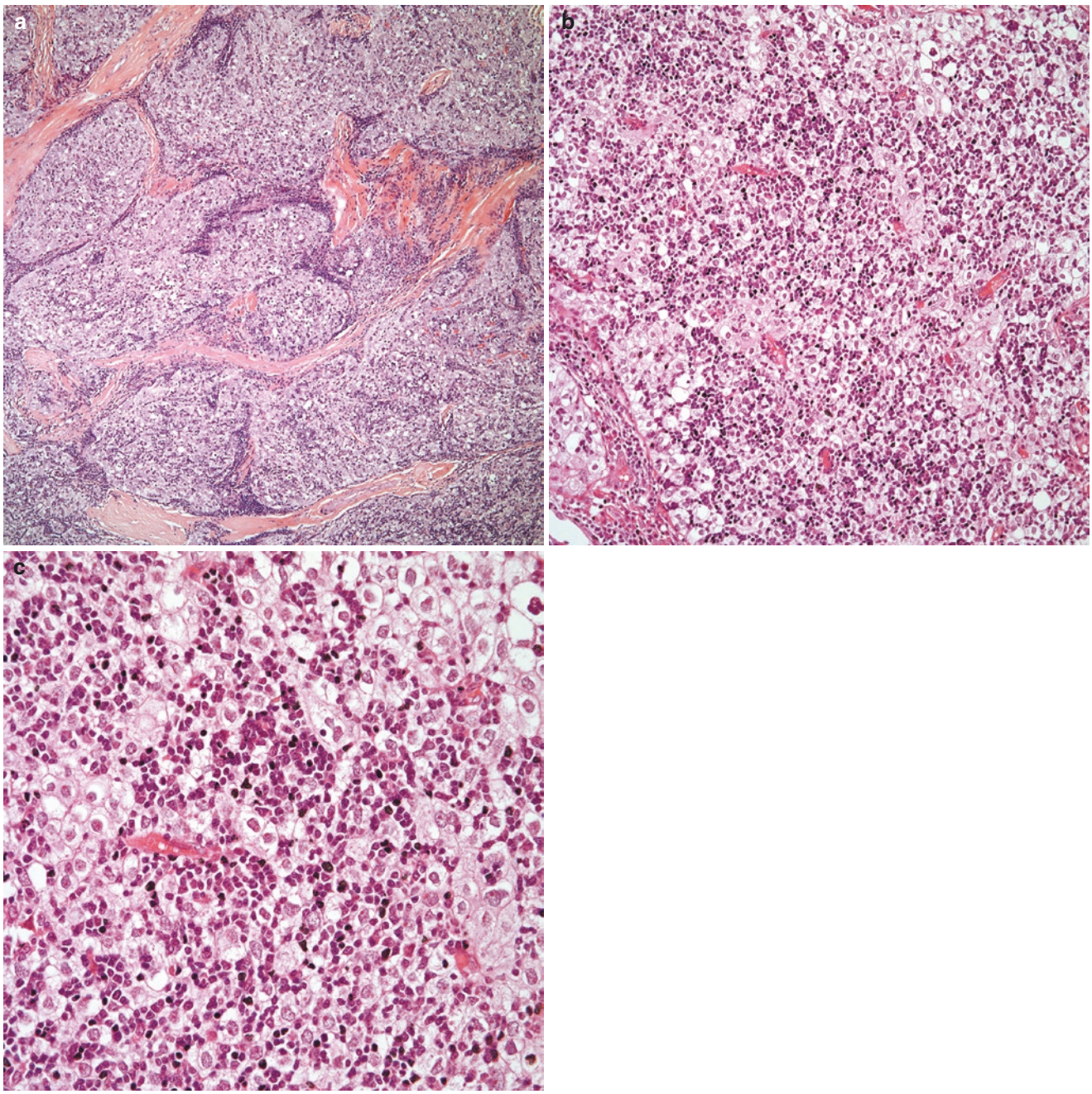

Fig. 3.14 (**a**) Low power view of a thymoma showing lobulation, (**b**) epithelial cells mixed with lymphocytes, (**c**) higher magnification showing approximately equal components of lymphocytes and epithelial cells (Mixed thymoma in Bernatz classification, Cortical thymoma in Marino-Muller-Hermelink classification, type B2 in the WHO translator)

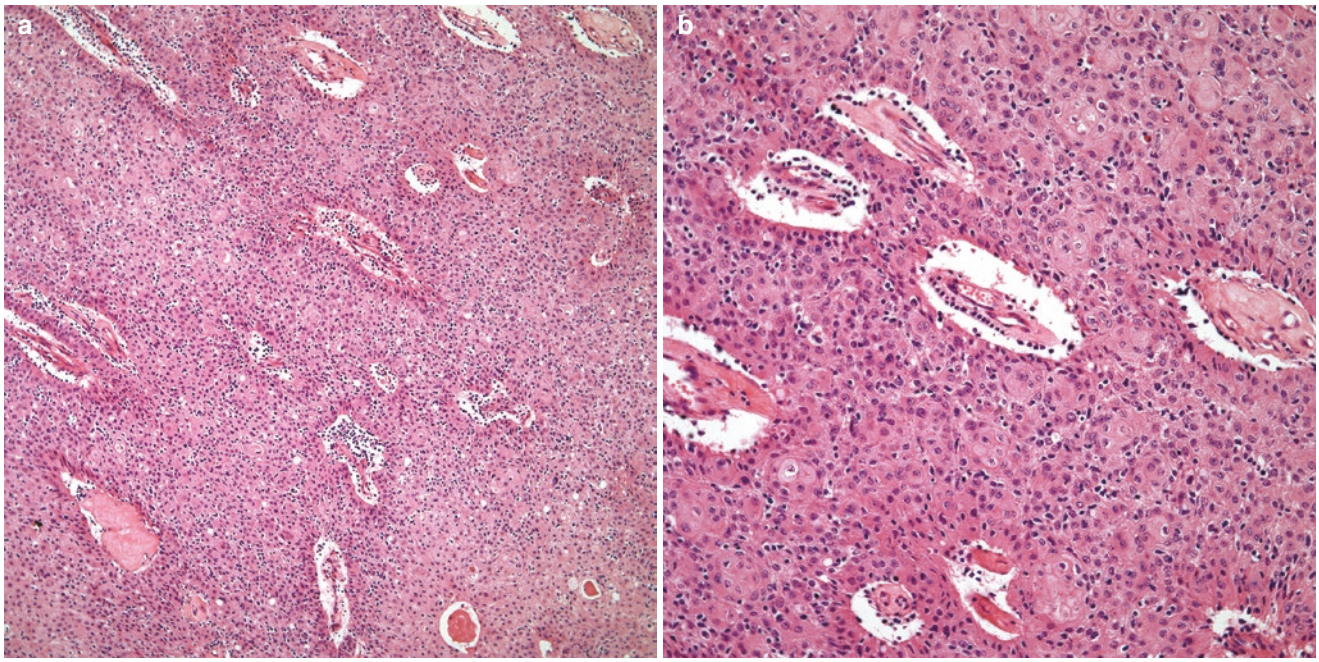

Fig. 3.15 (**a**) Atypical Thymoma showing prominent epithelial component, (**b**) higher magnification showing epithelial cells with perivascular spaces (Predominantly epithelial thymoma in Bernatz classification; Well-differentiated thymic carcinoma in the Muller-Hermelink classification, Type B3 in the WHO translator)

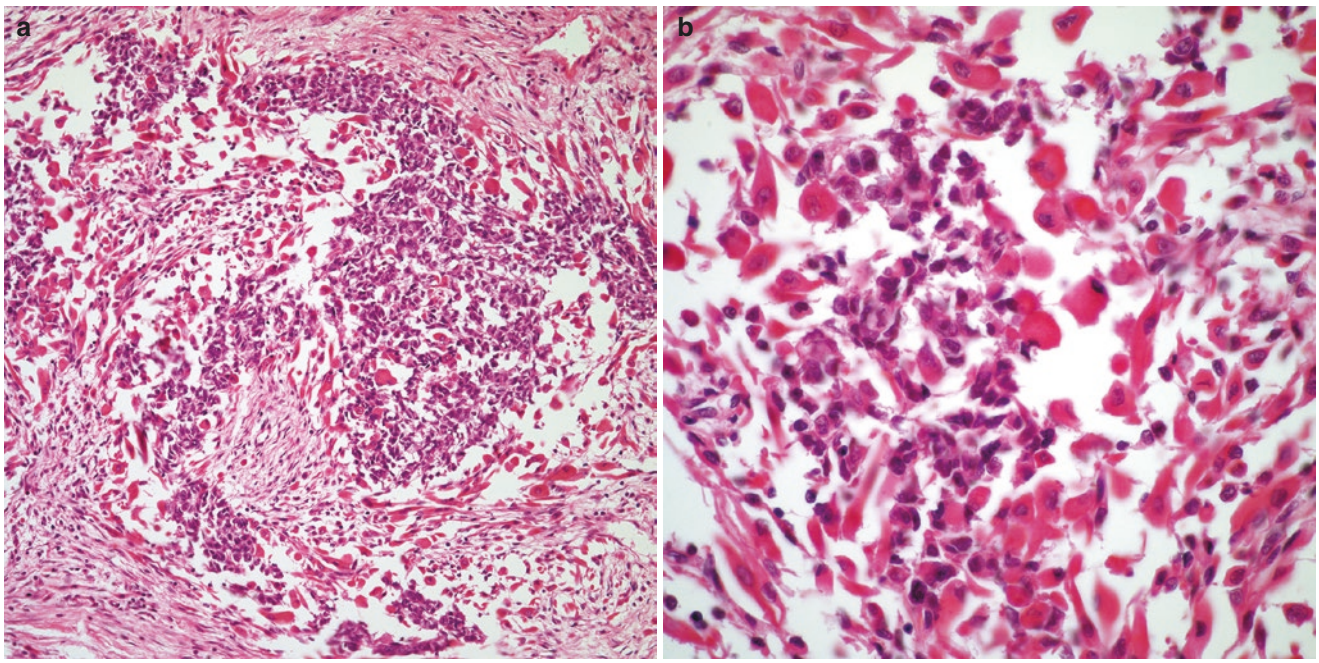

Fig. 3.16 (**a**) Thymoma with prominent muscle component, (**b**) higher magnification showing epithelial cells and myoid component

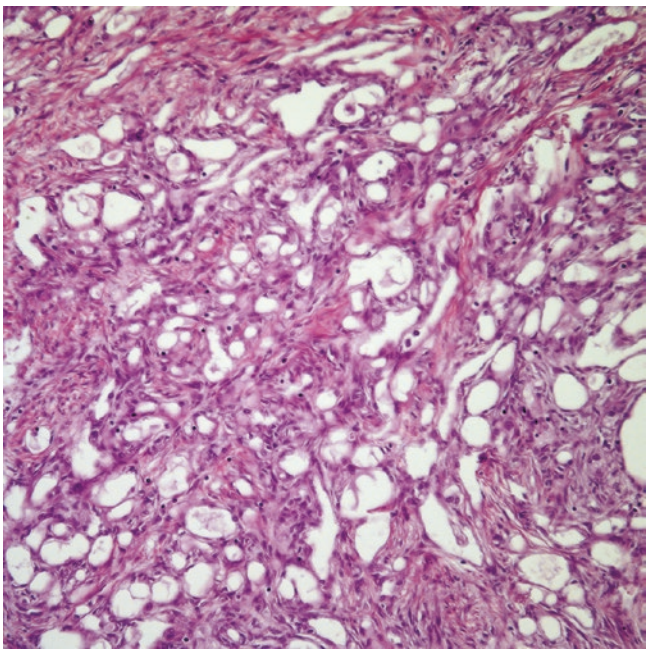

Fig. 3.17 Thymoma with prominent adenomatoid features

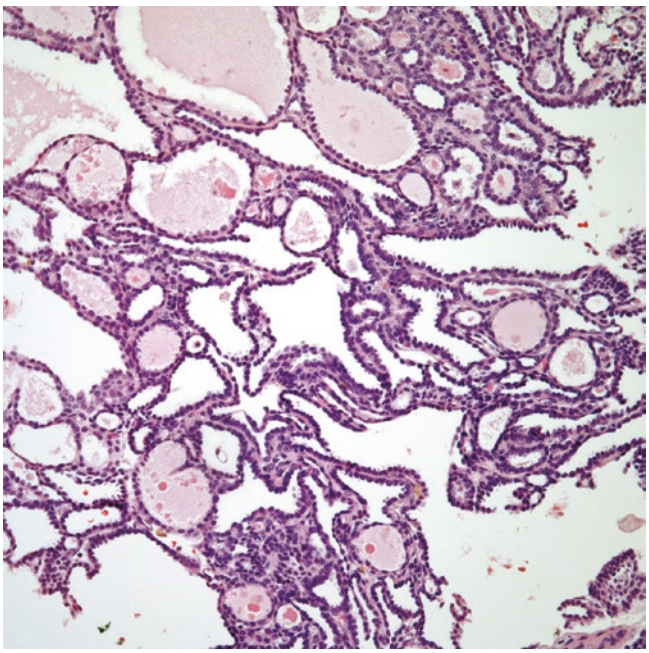

Fig. 3.19 Thymoma with prominent glandular and papillary features

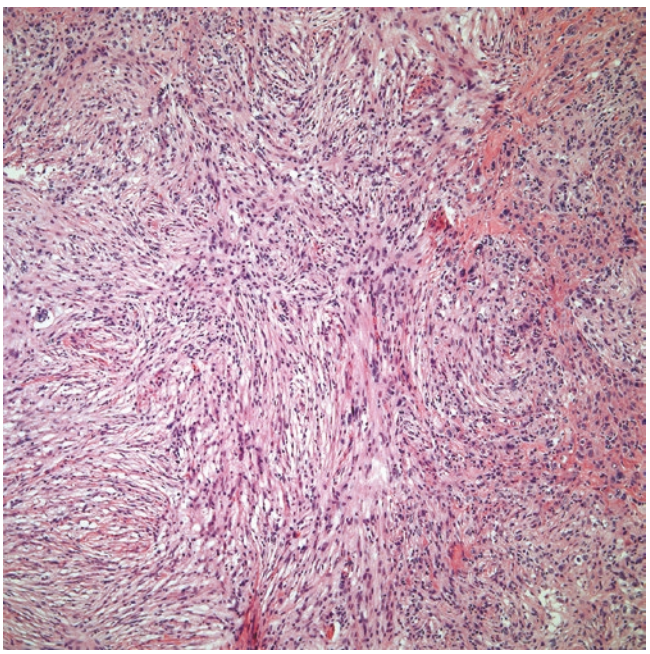

Fig. 3.18 Thymoma with pseudosarcomatous stroma (WHO type metaplastic thymoma; Metaplastic carcinoma by Muller-Hermelink)

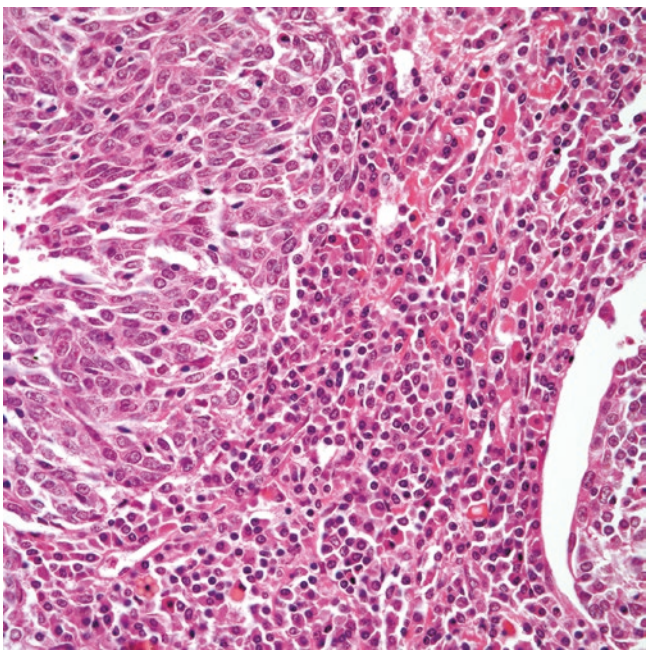

Fig. 3.20 Thymoma with prominent plasma cell component

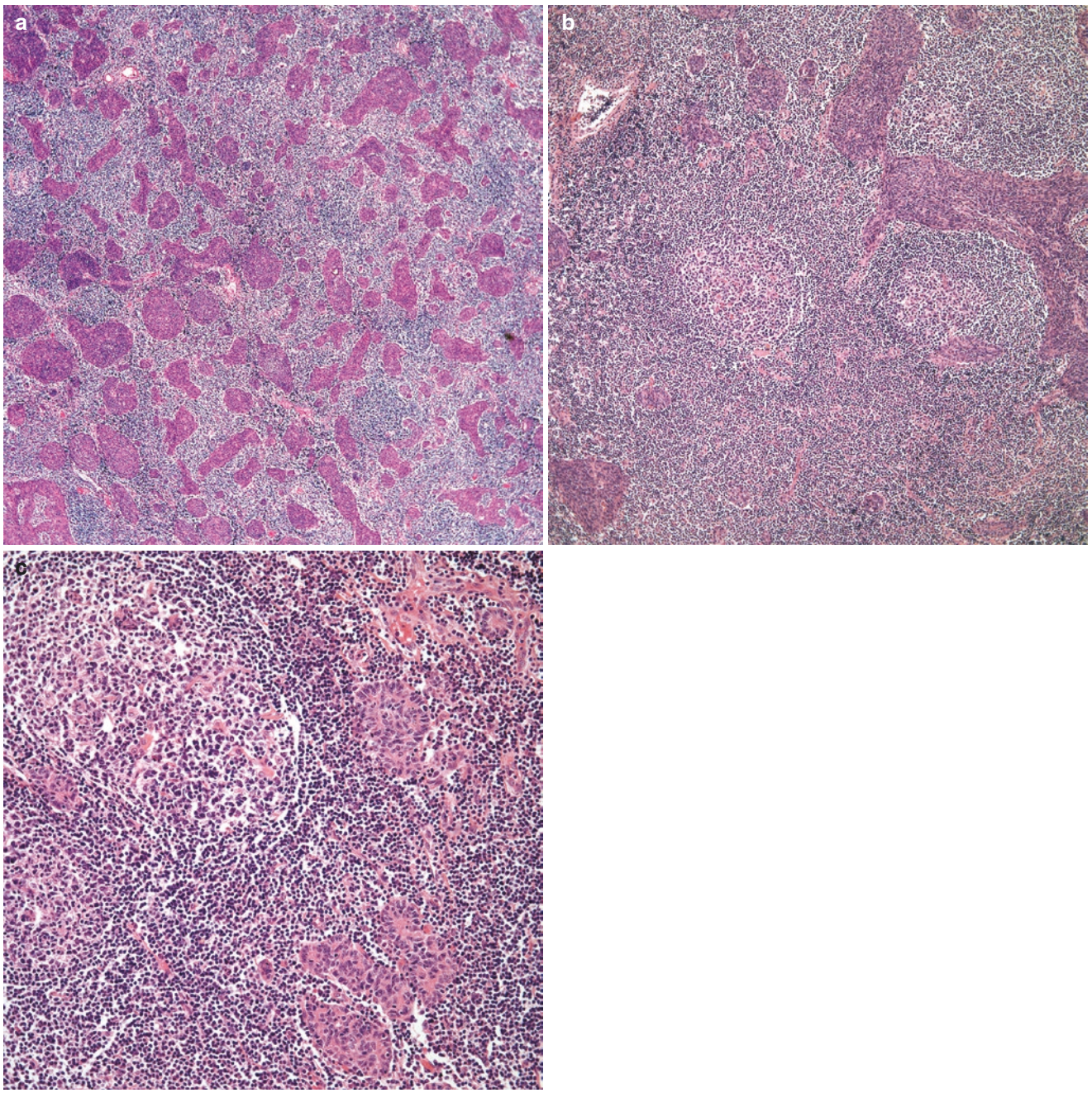

Fig. 3.21 (**a**)Micronodular thymoma with B-cell lymphoid hyperplasia, (**b**) Epithelial cells and germinal centers, (**c**) Germinal centers associated with small islands of spindle cell thymoma

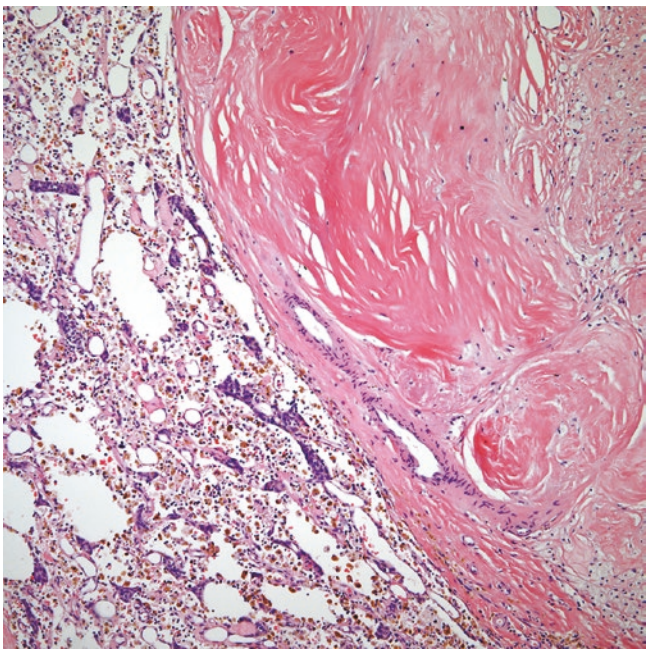

Fig. 3.22 Thymoma with ancient changes (sclerosing thymoma)

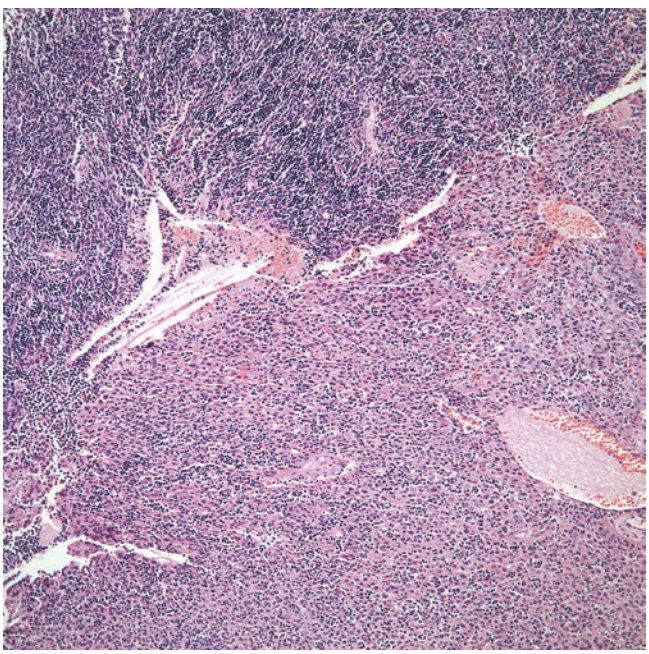

Fig. 3.23 Thymoma showing mixed histologies—atypical and conventional thymoma. The occurrence of thymomas with mixed histologies is observed in more than 50% of all thymoma cases

p40, which are commonly positive in the epithelial component of the tumor. In cases in which there is lymphocytic component, the use of B and T cell lymphoid markers (CD-20, CD3, Tdt) may also help in the diagnosis, as those stains will highlight the lymphocytic component.

Clinical Outcome

The clinical outcome in patients with thymoma is closely linked to the pathological stage at the time of diagnosis. In tumors that are encapsulated or minimally invasive, it is possible that only surgical resection offers a good clinical outcome while in those patients with invasive disease other treatment options such as radiation therapy and/or chemotherapy become possible alternatives [86–93].

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