Thymic Epithelial Tumor

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Thymic epithelial tumors are rare malignancies of thymic origin and include thymoma, thymic carcinoma, and thymic neuroendocrine tumors.

3.1 Epidemiology

Thymic epithelial tumors are rare malignant tumors that account for 0.2–1.5% of all malignancies, 20% of adult mediastinal tumors, and 47% of anterior mediastinal tumors. They may be related to EB virus infection, ionizing radiation, and genetic genes.

Thymoma is the most common primary malignancy of the anterior mediastinum and the most common thymic epithelial tumor. The incidence of thymoma is 1–5 cases per million people per year in the United States, but the incidence of Asian and African Americans is higher than that of Hispanics and whites. Men and women are equally affected. The incidence of thymoma increases with advancing age, patients older than 40 years are most commonly affected, although the incidence starts to decline after the age of 60 years. Thymoma is slow-growing neoplasms that may exhibit aggressive behavior, such as invasion of adjacent structures and involvement of the pleura and pericardium, but distant metastases rarely occur.

Thymic carcinoma represents approximately 20% of thymic epithelial tumors. The average age of patients at presentation is 50 years. Contrary to thymoma, thymic carcinoma tends to show aggressive features such as local invasion, intrathoracic lymphadenopathy, and distant metastases. 50–65% of patients have distant metastases at diagnosis.

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Neuroendocrine tumor is the least common, accounting for 2–5% of all such lesions. Most neuroendocrine tumors of thymic origin are carcinoids. Approximately 0.4% of all carcinoids come from the thymus. Similar to thymic carcinoma, thymic neuroendocrine tumors may demonstrate aggressive behavior such as invasion of adjacent structures and mediastinal lymph node involvement, the latter of which is present in 50% of patients at diagnosis.

3.2 Classification

Historically, many staging systems have been used for thymic epithelial tumors, including both non-TNM based and TNM based. Due to the diversity of thymic epithelial tumor morphology, the heterogeneity of tumor cells, and the lack of simple and effective classification of observation indicators, there is no unified basis for its classification method. At least 15 different stage classification systems have been proposed and used clinically to varying degrees, most of which have been derived from data on small groups of patients. The most widely used staging classification is the Masaoka-Koga staging system.

In the 1960s, thymomas were classified as non-invasive and invasive. Historically, the morphologic classification has been the most widely accepted during the past several decades. Thymomas were divided by these authors, based on their relative proportion of epithelial cells to lymphocytes and on the shape of the epithelial cells. In 1961, Bernatz et al. classified thymoma into four basic histopathologic variants: lymphocyte-predominant, epithelial-predominant, lymphoepithelial (mixed), and spindle cell thymoma. This classification essentially constituted a variation of a similar formula proposed by Lattes and Jonas 4 years earlier, in which thymomas were also divided into 4 variants (predominantly lymphocytic, predominantly epithelial, and predominantly spindle cell). However, it also included a category of rosette-forming thymoma. The Bernatz et al. classification

S. Zhang (ed.), *Diagnostic Imaging of Mediastinal Diseases*, https://doi.org/10.1007/978-981-15-9930-9_3

and variants thereof have come to be known collectively as the traditional classification of thymoma.

The first staging system was proposed by Bergh et al. [1] which differentiated thymoma according to the presence of symptoms, the tumor extent and histology, and designed a three-stage classification system. Stage I thymoma is intact capsule or growth within the capsule. Stage II thymoma is pericapsular growth into the mediastinal fat tissue. Stage III thymoma is invasive growth into the surrounding organs, intrathoracic metastases, or both. A complete tumor resection (R0), (commonly observed in stages I and II), was associated with a longer survival. Postoperative radiotherapy was offered to incompletely resected patients and mostly stage II and III ones. Minor modifications were made to the Bergh staging system by Wilkins and Castleman in 1979 [2], including mediastinal pleura or pericardial invasion in stage II. Tumor invasiveness was demonstrated as an adverse prognostic factor, and it may guide postoperative radiotherapy. The completeness of resection was proposed as the strongest prognostic factor. In a series study of 103 patients with thymoma, the 10-year survival rates were 67% for encapsulated tumors and 40% for invasive lesions. There are some disadvantages for this system: the actual site of intrathoracic metastasis, inadequate description of invasion, too broad classification of stage III, and lack of representation of lymphogenous or hematogenous metastasis.

Despite apparently good reproducibility among pathologists for applying the traditional histopathologic classification of thymoma, the various types did not show good correlation with the clinical behavior of the tumors and, therefore, were not very useful for prognostication. In 1978, the encapsulated tumors were proposed as benign by Levine and Rosai and that all invasive tumors should be regarded as malignant [3]. The malignant thymoma was further proposed to be subclassified into two types: I— invasive tumors showing the same morphologic features as benign thymoma; II—for tumors displaying overt cytologic features of malignancy (also designated as thymic carcinoma). The Levine and Rosai proposal gained wide acceptance [3], which was used for many years, often in combination with the traditional nomenclature for the various morphologic subtypes of thymoma.

Two additional approaches to the classification of thymoma were introduced in 1985. Marino and Muller-Hermelink based on the light microscopical features of normal thymic epithelial cells [4], human thymoma was divided into different types, namely cortical, medullary, and mixed types. In their retrospective study of 58 thymomas and 13 thymic carcinomas, they found malignant invasive character and the occurrence of myasthenia gravis is related to the neoplastic proliferation of the cortical epithelial cells. The tumors composed of cells were thought to be derived from the medulla or of mixed cortical-medullary types that were not associated with invasion or metastases. This classification subsequently was modified by Kirchner and Muller-Hermelink to include 2 additional categories [5], the predominantly cortical thymoma (later renamed organoid) and the well-differentiated thymic carcinoma in 1989. The value of this new classification resided in facilitating the correlation between these various morphologic types of thymoma and invasiveness.

In 1985, Verley and Hollmann published the 1955–1982 Marie Lannelongue Hospital (Paris, France) experience on surgical management of 200 thymoma [6]. They compared clinical stages and histologic types in different aspects, including survival. Clinical stages were defined as follows: Stage I—no invasiveness, total excision; Stage II—localized invasiveness (no more than two mediastinal structures); Stage III—largely invasive, with or without distant tumorous grafts, lymph node deposits, or metastases. Four histologic types included spindle cell thymoma, lymphocyte-rich thymoma, differentiated epithelial thymoma (roughly corresponding to epithelial-rich thymoma according to the traditional classification), and undifferentiated epithelial thymoma (corresponding to thymic carcinoma). Histologic typing indicated a good correlation between the degree of differentiation of the tumors and prognosis. They pointed out that although invasiveness often paralleled histologic typing, they both seemed to represent distinct and independent parameters with separate prognostic significance. The associated syndromes were no longer an adverse factor in the prognosis of thymoma.

The clinical course of thymoma was firstly highlighted by Masaoka [7], usually indolent, which may be characterized by local invasion, infiltration, and finally by distant spread with lymphogenous/hematogenous metastases. The four-stage system proposed by Masaoka in 1981 was based on the Osaka University experience with 93 thymoma patients during 1954–1979. Establishing a correct stage at the beginning of the treatment was suggested to be helpful for selecting the appropriate therapy and improve survival. One of the main prognostic factors is invasiveness, along with the completeness of surgical resection. Clinical stages were defined: Stage I—macroscopically encapsulated and microscopically no capsular invasion; Stage II—(1) macroscopic invasion into surrounding fatty tissue of mediastinal pleura, or (2) microscopic invasion into capsule; Stage III—macroscopic invasion into neighboring organ; Stage IVa—pleural or pericardial dissemination; Stage IVb—lymphogenous or hematogenous metastasis. Koga et al. proposed a revised Masaoka staging system in 1994. The stages were as follows: Stage I—grossly and microscopically completely encapsulated; Stage II—(1) microscopic transcapsular invasion, or (2) macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent but not breaking through mediastinal pleura or pericardium; Stage III—macroscopic invasion

of neighboring organ (i.e., pericardium, great vessel, or lung); Stage IVa—pleural or pericardial dissemination; Stage IVb—lymphatic or hematogenous metastasis. According to the Masaoka-Koga system, survival curves demonstrated no significant difference between stages I and II, and between stages III and IV either. Tumor-related death and recurrences were more frequent in advanced stages. A simplified our-staged staging system was concluded to only differentiate between invasive (stage III/IV) and noninvasive (stage I/II) thymomas. The Masaoka-Koga staging system is still the most commonly used and the International Thymic Malignancy Interest Group (ITMIG) had established it as the unified staging system for use in 2011 until publication of the eighth edition of AJCC/UICC staging manuals. There are limitations of the Masaoka-Koga staging system, including lack of survival difference between stages I and II disease, stage III disease involving invasion of a large range of structures, and a predominantly pathologic staging system that is difficult to apply to clinical staging.

The first classification system developed by the World Health Organization (WHO) Consensus Committee in 1999 classified thymomas into six separate subtypes (A, AB, B1, B2, B3, and C) based on morphologic features of the neoplastic epithelial cells and the lymphocyte–epithelial cell ratio. There are two major types of thymoma, depending on whether the neoplastic epithelial cells and their nuclei showed a spindle or oval shape (designated type A) or a round epithelioid appearance (designated type B). Type AB is designated for tumors that show a combination of these 2 cell types. Based on the proportional increase (in relation to the lymphocytes) and emergence of atypia of the neoplastic epithelial cells, type B thymomas were subdivided further into 3 subtypes, designated B1, B2, and B3. Type C thymoma was regarded as a tumor showing overt cytologic features of malignancy (i.e., thymic carcinoma). Therefore, the morphologic basis for this classification was essentially similar to that of the traditional classification presented more than 40 years earlier. A revised scheme published in 2004 relocated type C (thymic carcinoma) to a separate category. In 2015, the WHO classification of thymic tumors corrected the view that thymoma is a benign tumor. Except for micronodular and microscopic thymomas, all major thymoma subtypes can behave in a clinically aggressive fashion and therefore should no longer be called benign tumors, irrespective of tumor stage. The high- and low-risk groups were divided according to type, B2, and B3 or types A, AB, and B1.

Yamakawa et al. translated the Masaoka system into a tumor, node, metastasis (TNM) system in 1991 (based on 207 patients). There is no modification for the T descriptor followed the Masaoka criteria. Anterior mediastinal lymph nodes around the thymus were deemed the primary lymph nodes in thymoma, and classified as N1. Finally, tumors were classified M0 or M1 according to the absence/presence of hematogenous spread. Prognosis correlating to size was not found. Tsuchiya et al. evaluated the utility of the Yamakawa/Masaoka TNM and staging system and proposed a modification proposed based on experience with 16 thymic carcinomas in 1994 [8]. Although the N descriptor was the same as that of the Yamakawa system, tumors penetrating through the mediastinal pleura or pericardium were classified as T3 category. A much greater role for nodal involvement was considered in this stage grouping. A wide separation in the survival curves was found between stages I and III–IV and between stages III and IV, although this was not statistically significant in the small series. World Health Organization (WHO) proposed another TNM-based classification in 2004. The definition of lymph node categories is the same as that of the other TNM systems. However, the pertinence of nodal grouping from N1 to N3 has not been studied. The main determinants of the T descriptor are tumor invasion through the capsule and into the neighboring organs/structures. Invasion may be assessed by the surgeon during intervention, or histologically by the pathologist.

Bedini et al. proposed a modified TNM system in 2005 (based on a sophisticated analysis of 127patients) [9], which was named the Istituto Nazionale Tumori system. They proposed three-stage groupings: stage I (locally restricted disease) essentially includes Masaoka stages I and II with the exception of mediastinal pleural involvement, stage II (locally advanced disease) includes tumors invading local structures or involving intrathoracic lymph nodes, and stage III (systemic disease) involving cervical nodes or distant extrathoracic sites.

Weissferdt and Moran proposed a 3-stage TNM classification for thymic carcinoma based on 33 patients in 2012 [10]. Classification of T1 as a tumor confined to the thymus, T3 as direct extension outside the chest, limiting node categories to intrathoracic and grouping any T3, N1, or M1 as stage III are the major features.

The ITMIG and the International Association for the Study of Lung Cancer (IASLC) set out to accomplish a staging system for thymic epithelial tumors, and subsequently joined forces in 2010, partnering to create a Thymic Domain of the Staging and Prognostic Factors Committee (TD-SPFC). ITMIG and IASLC created a collaborative worldwide database involving 105 institutions and 10,808 patients. The IASLC/ITMIG staging system, which has been included in the official eighth edition of AJCC/UICC staging manuals, is based on TNM descriptors. The T stage is derived from Masaoka-Koga staging and is defined by the highest level of invasion of $\geq$1 structure, with an overall decreased emphasis on tumor encapsulation. The T component was proposed to be divided into four categories by the committee, representing levels of invasion. T1 includes tumors localized to the thymus: T1a is anterior mediastinal fat, and regardless of

capsular invasion, up to and including infiltration through the mediastinal pleura (T1b). Invasion of the pericardium is designated as T2. T3 includes tumors with direct involvement of lung, chest wall, phrenic nerve, brachiocephalic vein, superior vena cava, or hilar (extrapericardial) pulmonary vessels. Invasion of thoracic aorta, arch vessels, main pulmonary artery, trachea, esophagus, or myocardium is designated as T4. Nodal involvement is divided into no lymph node metastasis (N0), involvement of anterior (perithymic) lymph nodes (N1), and involvement of deep intrathoracic or cervical lymph nodes (N2). Metastases can involve pleural or pericardial nodules (M1a) or intraparenchymal pulmonary nodules or metastases to distant sites (M1b). Stage groups I to IIIB are decided by the T component, whereas stage IVA/B groups are decided by the N and/or M component.

3.3 Clinical Features

The most common symptoms of thymomas described at clinical presentation include those related to local effects of malignant tumors, including compression and invasion of adjacent structures, which can lead to diaphragmatic paralysis, dysphagia, or superior vena cava syndrome. One-third of patients report chest pain, dyspnea, or cough. Due to the release of hormones, antibodies, and cytokines by the neoplasm, patients may present with systemic symptoms and paraneoplastic syndromes. The most common paraneoplastic syndrome associated with thymoma is myasthenia gravis; 30–50% of patients with thymoma have signs and symptoms of myasthenia gravis, compared to only 10–15% of patients with myasthenia gravis have thymoma. Hypogamma globulinemia and pure red cell aplasia are other important paraneoplastic syndromes, accounting for 10% and 5% of cases, respectively. Various autoimmune diseases may be associated with thymoma, including polymyositis, systemic lupus erythematosus, and myocarditis.

The most common symptoms of thymic carcinomas described at clinical presentation include those related to local effects of the tumor, mainly compression and invasion of adjacent structures. In contrast to thymomas, paraneoplastic syndromes rarely accompany thymic carcinomas.

3.4 Radiographic Features

CT is important in differentiating thymic epithelial tumor from other malignant and nonmalignant conditions, identifying the need for pretreatment biopsy, and assessing surgical resectability. The assessable CT imaging features included the following data on the primary mass and its surrounding structures: mass location; size in the *x*, *y*, and *z* axis; contour (smooth or irregular, single lobulated or multi-lobulated); internal density (homogenous or heterogeneous); calcifications; infiltration of surrounding fat; tumor abutting of an adjacent mediastinal structure (≥50% or <50%); and direct vascular endoluminal invasion. It also includes the following information about surrounding structures: adjacent lung abnormalities, pleural effusion (without, unilateral or bilateral), pleural nodule, mediastinal lymphadenopathy, phrenic nerve involvement (consistent with elevated hemidiaphragm evaluated on the coronal reconstruction images), and pulmonary nodules.

Thymic epithelial tumor is usually manifested as a well-defined soft tissue mass, which mostly extends to one side of the anterior mediastinum (Fig. 3.1), occasionally protruding to central location (Fig. 3.2). The pericardium is also a more common site of thymic epithelial tumor, which can exist alone (Fig. 3.3), more often draping alongside the heart (Fig. 3.4). A small number of thymic epithelial tumors are located in the neck (Fig. 3.5) or other locations in the medi-

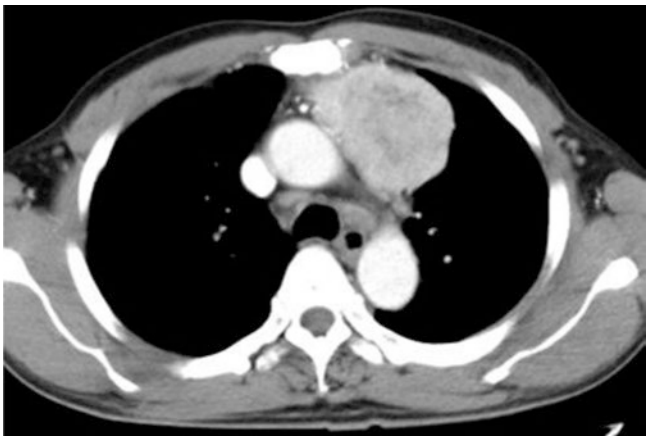

Fig. 3.1 A 57-year-old man with type B2 thymoma in the left anterior mediastinum

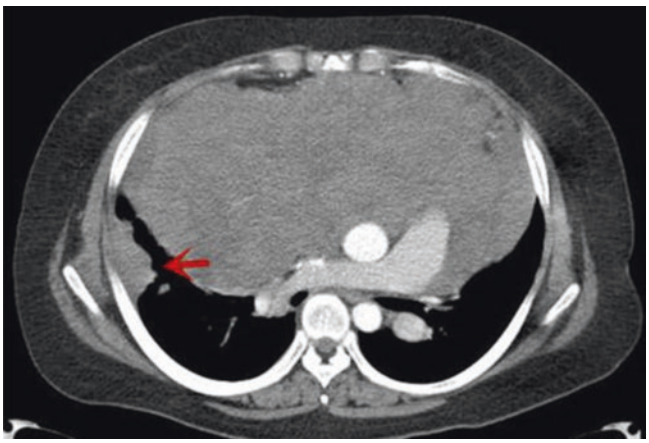

Fig. 3.2 A 28-year-old woman with a huge type B2 thymoma with right pleural metastasis (red arrow)

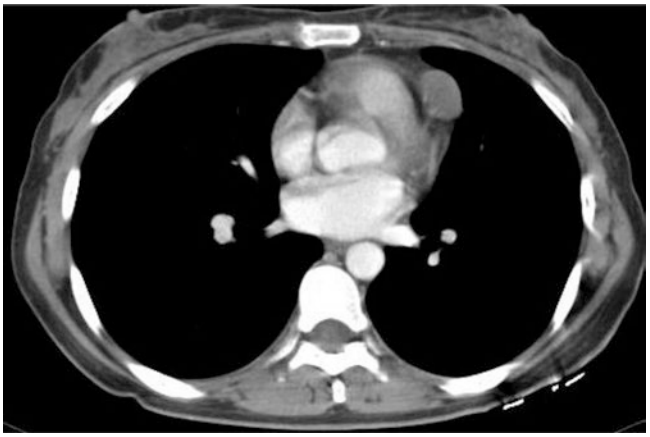

Fig. 3.3 A 34-year-old woman with type B2 thymoma adjacent to the left pericardium

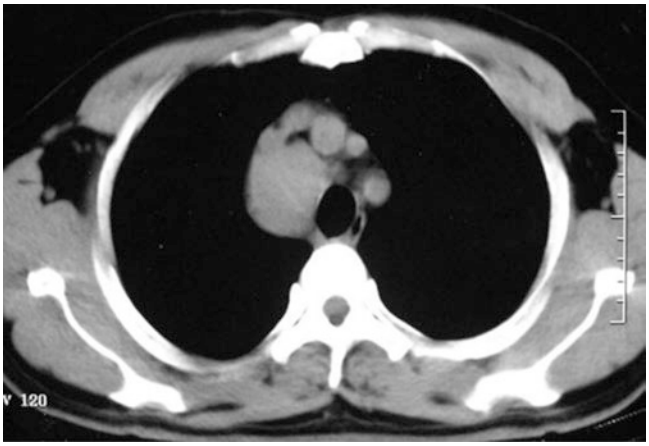

Fig. 3.6 A 50-year-old woman with thymoma in the middle mediastinum

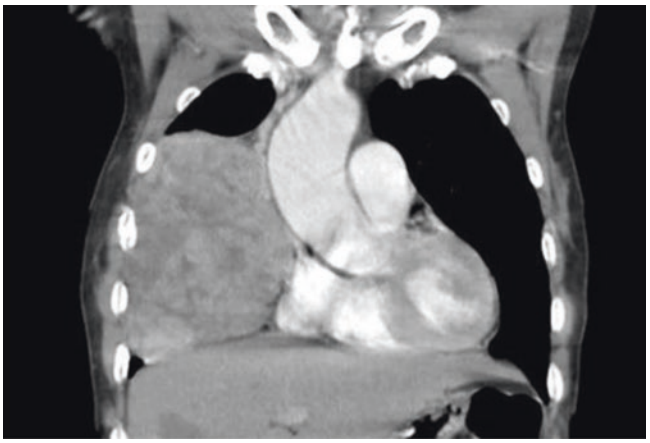

Fig. 3.4 A 50-year-old woman with type AB thymoma, draping alongside the heart

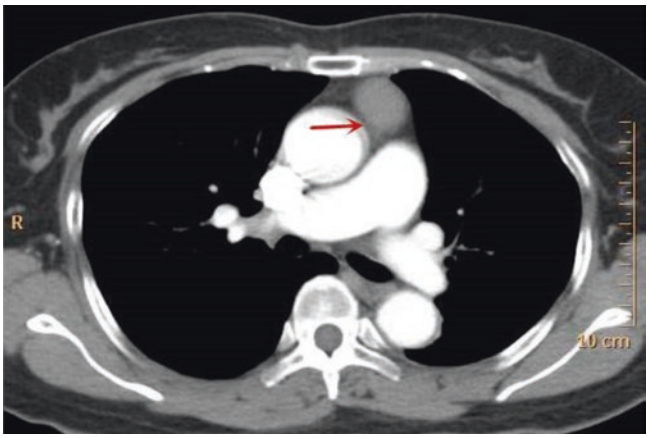

Fig. 3.7 A 59-year-old woman with type B1 thymoma. Chest CT showed a complete capsule and clear mediastinal fat plane (red arrow)

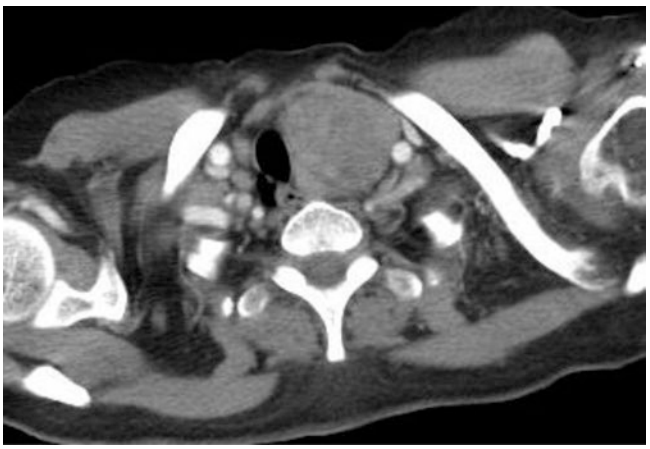

Fig. 3.5 A 60-year-old woman with type A thymoma in the neck

astinum (Fig. 3.6). The size of thymic epithelial tumor is mostly below 10 cm, and rare above 15 cm.

The tumor size, contour, internal density, and infiltration of surrounding fat differed between low- and high-risk thymomas. Lobulated morphology is more typical of high-risk thymomas and round or oval morphology is more typical of low-risk thymomas. Low-risk thymomas have a smooth and regular margin due to a complete capsule, and without infiltration of surrounding mediastinal fat (Fig. 3.7). High-risk thymomas and thymic carcinomas are highly invasive, which often invade the capsule and infiltrate the surrounding fat (Fig. 3.8). Type B3 thymoma (Fig. 3.9) and thymic carcinoma (Fig. 3.10) have a high incidence of necrosis and cystic changes, which may be caused by rapid growth.

Calcifications of any pattern, including curvilinear, punctate, or coarse, have been associated with more advanced thymic epithelial tumors. Type A thymoma has rare calcification in the parenchyma (Fig. 3.11), and may have calcification in the capsule (Fig. 3.12). Multiple punctate calcifications and microcalcifications are more common in type B thymoma, especially types B2 and B3. Calcifications are mostly at the edge of low-risk thymomas, which can be eggshell-like. Calcifications in the high-risk thymomas and thymic carcinomas mostly occur in the non-marginal parts. Calcifications cannot distinguish between benign and malignant thymic epithelial tumors.

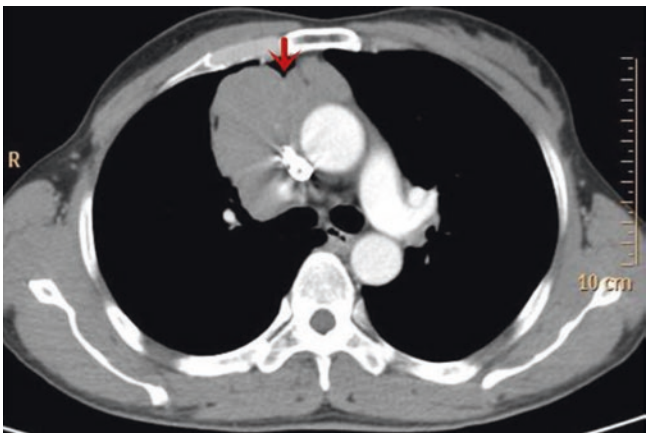

Fig. 3.8 A 42-year-old man with type B2 thymoma. Chest CT showed a lobulated tumor (red arrow) extending into the surrounding fat

The degree of tumor enhancement can reflect the blood supply of the tumor. Thymic epithelial tumor is generally mild-to-moderate enhancement, but a few are rich in blood supply. The degree of individual enhancement can even be similar to Castleman's disease (Fig. 3.13). It has been reported in literature that the enhancement of type A and AB thymomas is significantly higher than that of type B thymoma. It may be because type B thymoma is rich in lymphocytes, while type A and AB thymoma are rich in epithelial cells.

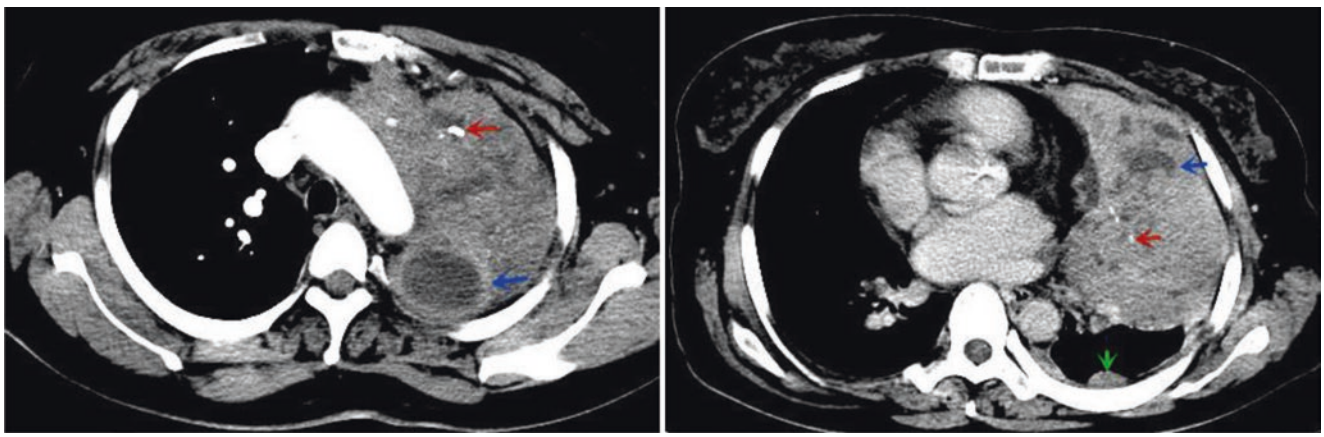

Fig. 3.9 A 42-year-old woman with type B3 thymoma. The tumor grew alongside the heart. Necrosis and cystic changes (blue arrows), calcifications (red arrows) are seen in the mass, and metastatic nodules (green arrows) are seen in the pleura

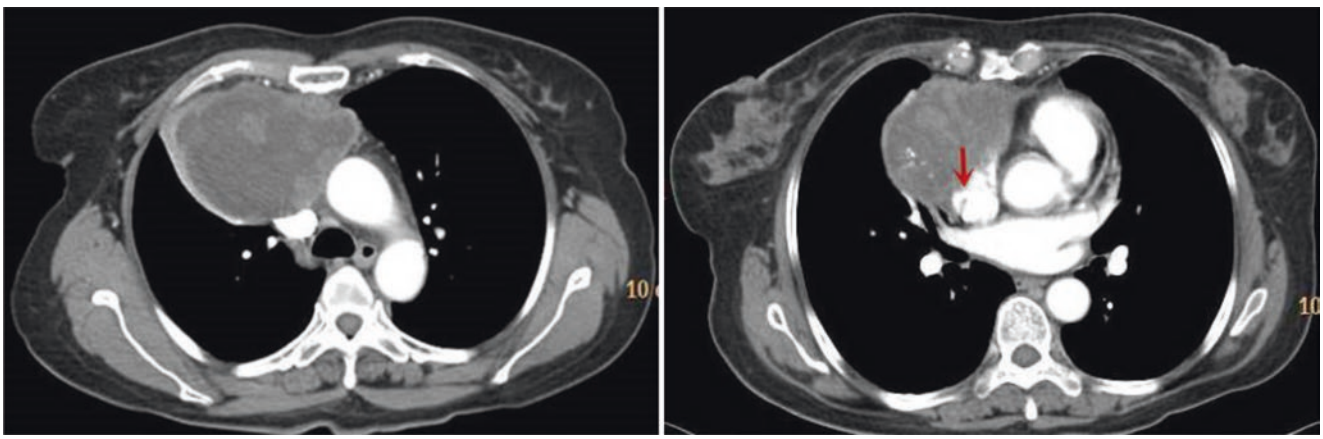

Fig. 3.10 A 55-year-old woman with thymic squamous cell carcinoma. Chest CT showed a large area of necrosis and calcifications within the lesion invading into the superior vena cava (red arrow)

The vast majority of thymomas can be seen separated on pathological specimens. With the increase of invasiveness, the septum will gradually become insignificant. The characteristics of multiple nodules with fibrous septa are more common in type A (Fig. 3.14) and AB thymomas (Fig. 3.15), especially type AB thymoma, with a high specificity.

Invasion of large cardiac vessels, pleural or pericardial nodules (Fig. 3.16), pleural effusion or pericardial effusion (Fig. 3.17), and mediastinal lymphadenopathy are all signs of aggressive thymic epithelial tumor, suggesting high-risk thymoma and thymic carcinoma. Its appearance means that the stage of thymoma is stage III or IV, and the prognosis is poor. Enlarged mediastinal lymph nodes (Fig. 3.18) suggest a high probability of thymic carcinoma. The presence of nerve (more common phrenic nerve) involvement (Fig. 3.19), also prompted the diagnosis of thymic carcinoma.

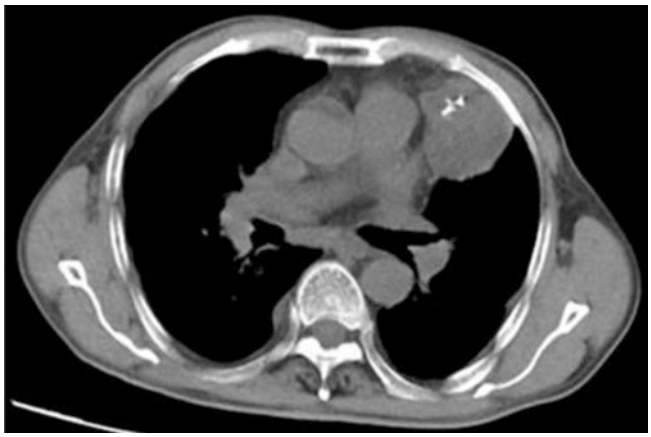

Fig. 3.11 Type A thymoma with intraparenchymal calcifications in a 64-year-old man

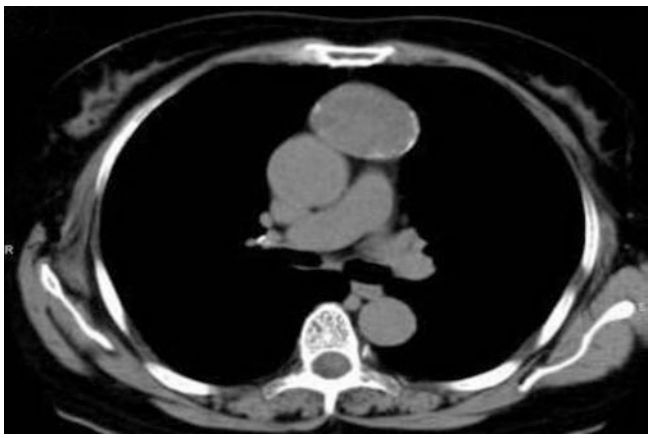

Fig. 3.12 Type A thymoma with capsular calcifications in a 65-year-old woman

3.5 Differential Diagnosis

Thymic epithelial tumor needs to be differentiated from thymic hyperplasia, thymic cyst, mediastinal germ cell-derived tumor and lymphoma.

Thymus hyperplasia usually occurs under the age of 20 years, showing diffuse enlargement of the thymus. Bipyramidal morphology and gross intercalated fat or "marbling" were 100% specific to thymic hyperplasia.

Thymic cyst has been described as typically thin-walled lesion and water attenuation on CT, although potentially more hyperdense when they contain internal hemorrhage. Ackman et al. [11] study shows that if a thymic lesion is well-circumscribed, round, oval, or "hot water bottle"/saccular in configuration, and homogeneous attenuation, with an ROI $\leq$ 60 HU, the appearance of lesion may be a cyst, rather than a solid or mixed cystic and solid thymic lesion. In such cases, a simple thymic cyst from a complex cystic or solid thymic lesion could be distinguished by a thymic MRI, in order to prevent unnecessary diagnostic intervention.

Malignant germ cell tumors are more common in children and adolescent patients, and AFP or β-HCG is often elevated. Multiple components are found in mature cystic teratoma.

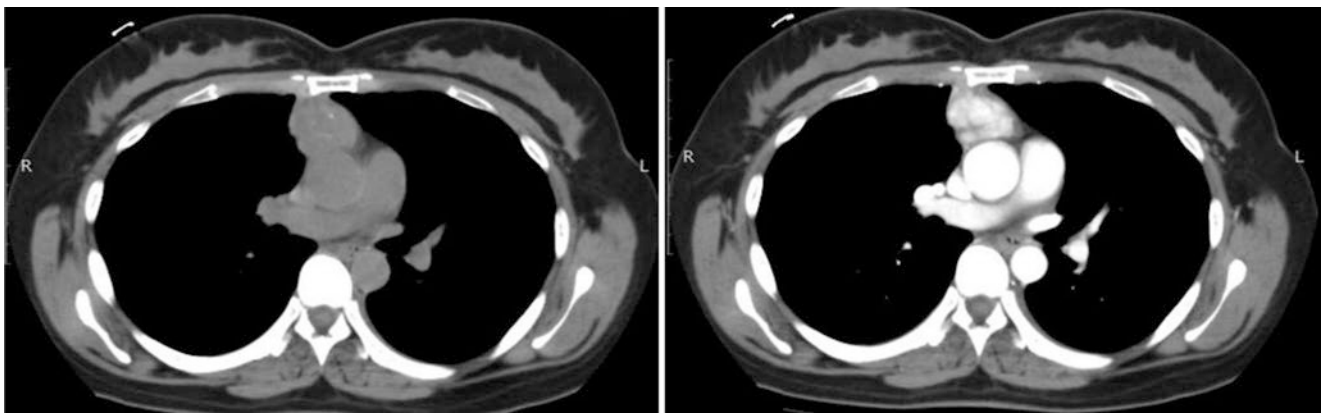

Fig. 3.13 A 44-year-old woman with type B3 thymoma. The enhancement is similar to that of blood vessels

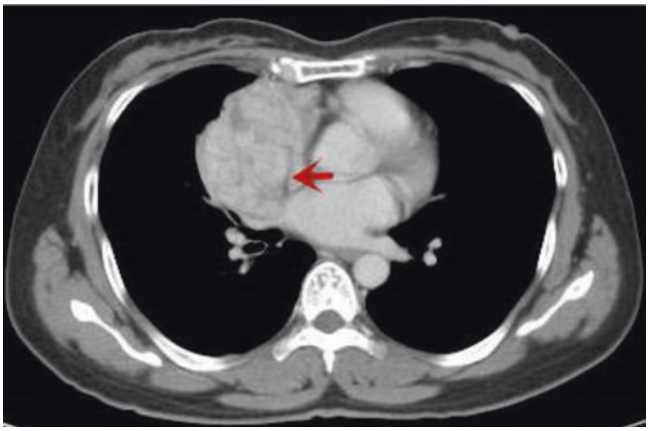

Fig. 3.14 Type A thymoma with fibrous septa (red arrow) in a 40-year-old woman

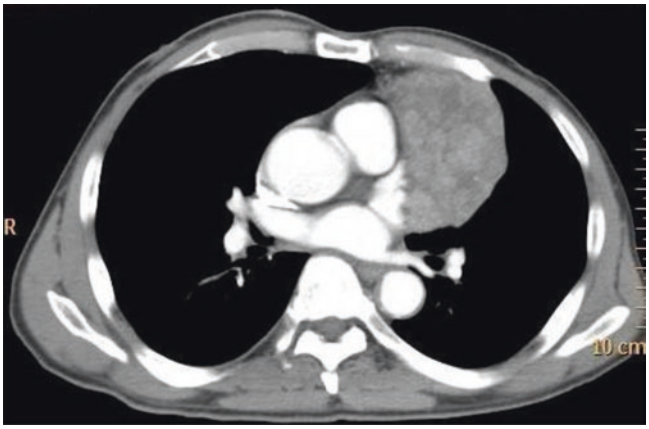

Fig. 3.15 Type AB thymoma with fibrous septa in a 62-year-old man

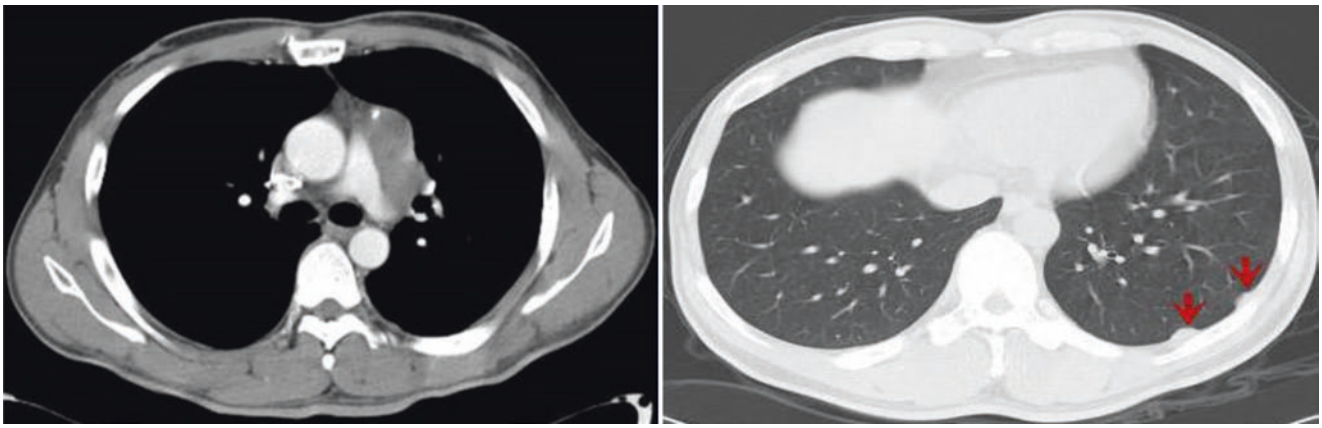

Fig. 3.16 Type B2 thymoma with pleural metastases (red arrow) in a 38-year-old man

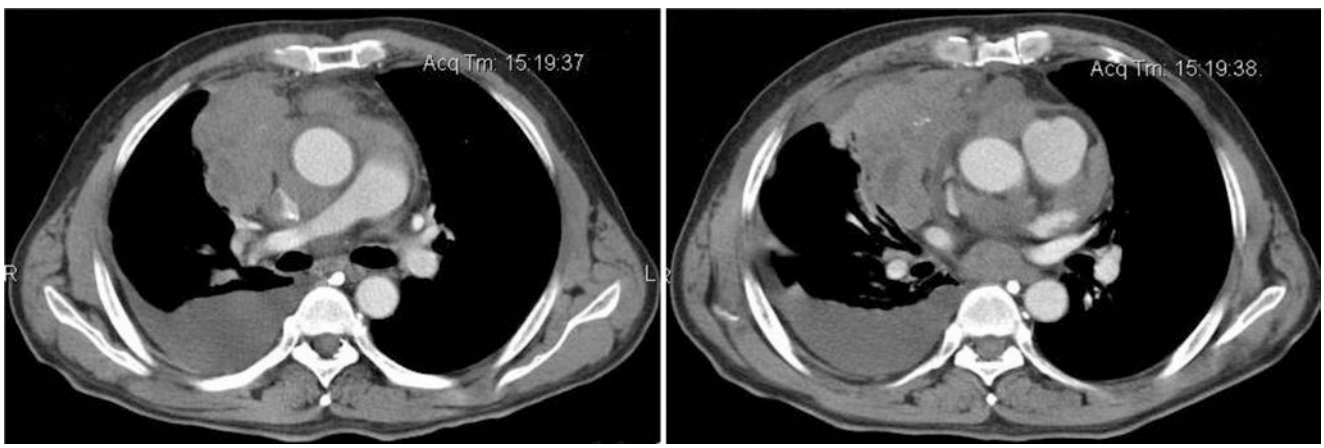

Fig. 3.17 Type B3 thymoma with microcalcifications, pleural effusion, and pericardial implantation in a 38-year-old man

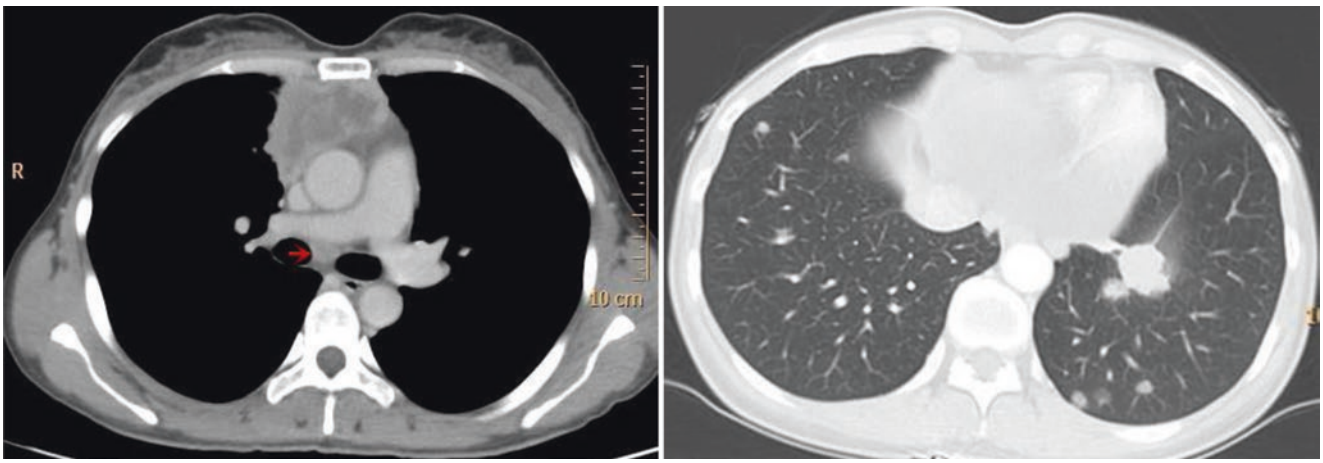

Fig. 3.18 Thymic squamous cell carcinoma with mediastinal lymph node metastasis (red arrow) and double lung metastasis in a 42-year-old woman

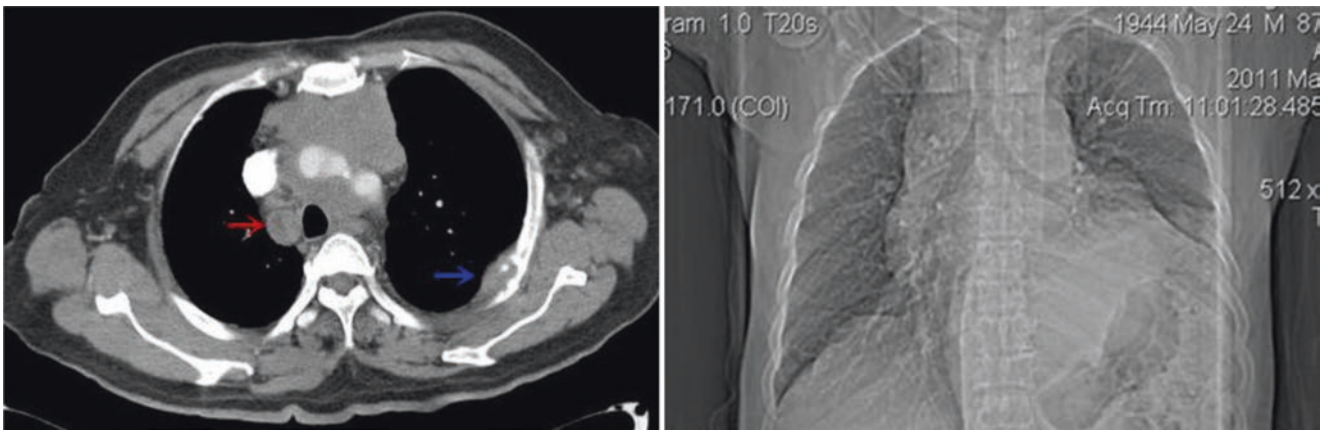

Fig. 3.19 Thymic squamous cell carcinoma with mediastinal lymph node metastasis (red arrow), rib metastasis (blue arrow), and left phrenic nerve paralysis (left diaphragmatic muscle elevation) in a 67-year-old man

Some teratomas do not contain fat and calcification components, which is easy to be misdiagnosed. Their characteristic lesions have a complete and uneven thickness of the cyst wall.

The age of onset of lymphoma is younger, often showing irregular low-density tumors. The finding of a round or oval, well-circumscribed, off-midline mass favors thymoma over lymphoma. In contrast, if the lesion is lobulated and/or multinodular, amorphous and midline or difficult to categorize as midline or off-midline, it is beneficial for the diagnosis of lymphoma, especially if lymphadenopathy is present. Lymphomas generally have no calcifications, and less enhanced than thymoma. Lymphoma usually involves multiple groups of lymph nodes and tends to fuse into groups. Except for the anterior mediastinal mass, most lymphomas have enlarged lymph nodes in the neck and other areas of the mediastinum.

3.6 Treatment

Surgical resection is the mainstay of treatment of thymomas, because the vast majority (90–95%) of these tumors is localized. Multimodality therapy, including radiation and/or chemotherapy, is considered as adjuvant therapy. For early and advanced stage thymoma, total thymectomy via standard median sternotomy is considered to be the standard treatment. With recent developments in thoracoscopic surgical instruments and practices, thoracoscopy surgery has been increasingly used for thymoma. Most patients with Masaoka stage I–II thymomas receive surgical treatment. Ten-year survival rates after resection for stages I and II thymomas are 90% and 70%, respectively. The majority of deaths result from unrelated causes. Ten-year survival for stages III and IVa is 55% and 35%, respectively. Survival rates improve if complete resection is achieved.

Thymoma is usually sensitive to radiotherapy, including postoperative adjuvant therapy, locally advanced, unresectable, and relapse treatment. Adjuvant radiotherapy after complete thymoma resection cannot reduce the recurrence rate and does not improve disease-free survival (PFS) and overall survival (OS). Patients with stage I need no radiotherapy after complete resection. Some of the studies showed no benefit for radiotherapy for stage II patients, but others pointed to a benefit. Adjuvant radiotherapy does not add any advantage for stage II thymoma which is completely resected; and it might be indicated for type B2/B3 lesions. For stages III and IV, postoperative radiotherapy plays a significant role in the management of thymoma. The National Cancer Network guidelines recommend postoperative radiotherapy for patients with stages II and above, and recommend 50–60 Gy for patients undergoing complete resection. The dose of postoperative radiotherapy for patients with incomplete resection should be greater than 60 Gy, and use 3D conformal radiotherapy or intensity-modulated radiotherapy. Preoperative radiotherapy for stages III and IVa thymomas can shrink the tumor and obtain surgery opportunities.

About 30% of patients present with advanced stage or relapsing tumors, which require administration of chemotherapy. Chemotherapy is mainly aimed at those patients with primarily non-resectable tumors, with advanced stages (stages III–IV considering the Masaoka or the ITMIG classifications) in the setting of multimodal therapeutic strategies, and is suitable for recurrent or refractory disease. The most popular and active regimens are cisplatin–anthracycline (CAP or ADOC) or cisplatin–etoposide combinations, which should be recommended for first-line chemotherapy of thymoma or thymic carcinoma. Other platinum combinations with taxanes seem suitable alternatives, mainly for second-line treatment or thymic carcinomas.

Immunotherapy with anti-PD-1/PDL-1 or other antibodies showed early promising data that need further confirmation, with special emphasis on immune-related toxicity.

3.7 Recurrence

After complete resection, the recurrence rate of thymoma is ranging from 5% to 50%. The ITMIG has defined a standard set of definitions for recurrence: (1) the term "recurrence" is appropriate if all disease has been potentially eradicated (R0 resection); (2) recurrences are classified as local (anterior mediastinum), regional (intrathoracic not contiguous with the thymus), and distant (intrapulmonary and extrathoracic); and (3) the freedom from recurrence outcome indicator should be used for any study on recurrence after R0 resection, and 5- and 10-year outcomes should be reported in every series.

The average disease-free time of recurrent patients was 5 years, and recurrence occurred 32 years after initial operation was also reported. The time to relapse was 10 years for patients of clinical stage I, and 3 years for patients of stages II, III, and IV.

Most recurrences are local and regional. 46%–80% of recurrent cases are found in the thoracic cavity, and then in the mediastinum and lungs, distant metastases occur in less than 5% of the cases. In the report of Detterbeck et al. [12], 58% of patients with recurrences involved the pleural space or the lung (most often as a nodule under the parietal pleura), the pericardium or mediastinum in 41%, bone in 10%, and liver in 8%.

According to the study of The Japanese Association for Chest Surgery, 862 patients had information on recurrence. Of these, 67 (7.8%) developed recurrence. The recurrence rates in stages I, II, III, and IV were 0.9%, 4.1%, 28.4%, and 34.3%, respectively. In thymic carcinoma, 51% of patients developed recurrence, whereas, in thymic carcinoid, 64% of patients had recurrence.

Recurrent thymoma is malignant and requires multimodal treatment. Surgery is the first choice for patients of recurrent thymoma. The overall survival rate of patients with recurrent thymoma undergoing surgery is significantly higher than that of patients with chemotherapy alone. Many literatures suggest that chemotherapy is the best choice for nonresectable recurrent thymoma. However, there is currently no well-accepted chemotherapy regimens yet.

Masaoka classification, WHO histology type, and complete resection are the main factors affecting the prognosis. Early recurrence (<40 months) is considered to be a negative prognostic factor, and local recurrence, single recurrence both predict better prognosis. For the patients with single-site recurrence, the 5- and 10-year survival rates of the patients with pleural dissemination are 90.6% and 66.9%, respectively, which indicate a more favorable survival compared with that observed in the patients with recurrence at the other sites.

3.8 Case Analysis

3.8.1 Case 1

A 49-year-old woman complained of chest tightness, chest pain, and blepharoptosis for 2 months.

Chest CT: An elliptical mass in the right anterior mediastinum with multiple calcifications and mild enhancement (Fig. 3.20).

[Diagnosis] Type A thymoma.

[Diagnosis basis] In a middle-aged female with lateral mass in the right mediastinum, the boundary between the mass and the surrounding structures was clear, and MPR

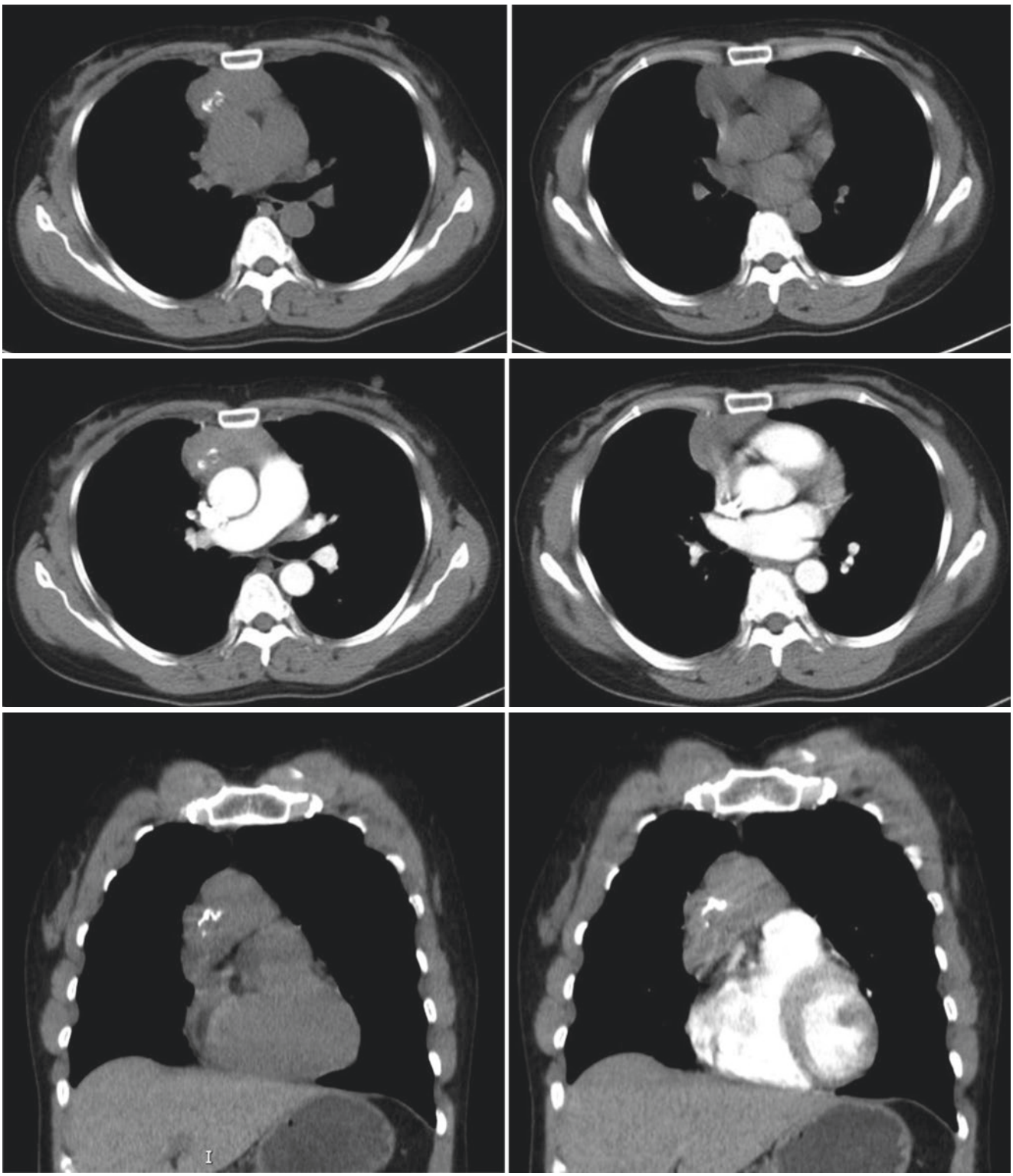

Fig. 3.20 Chest CT images of a 49-year-old woman complained of chest tightness, chest pain, and blepharoptosis for 2 months

reconstruction showed that the tumor grew alongside the heart. Combined with the patient's blepharoptosis, it is suggested to have myasthenia gravis and support the diagnosis of low-risk thymoma. Intraoperatively, the tumor size was about 6 × 4 × 5 cm and the capsule was intact. Pathologically, the tumor cells were fusiform, and a few lymphocytes were scattered among them, and fibrous septa were seen, which was consistent with type A thymoma (Fig. 3.21). Immunohistochemistry demonstrated positivity for CK19, CD5, and EMA, and negativity for TdT, CD3, CD20, HMB45, CD34, SMA, S-100, Desmin, and bcl-2 (Fig. 3.22).

[Analysis] Type A thymoma essentially was regarded as the equivalent of the spindle cell thymoma in the traditional classification and of medullary thymoma in the Marino and Muller Hermelink classification [4]. Type A thymoma is mainly composed of spindle or oval shape neoplastic thymic epithelial cells, lacking nuclear atypia, and accompanied by few or no lymphocytes.

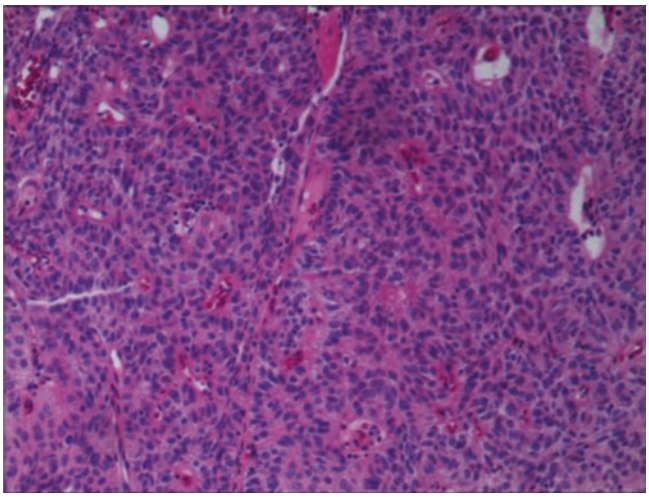

Fig. 3.21 Spindle or oval-shaped neoplastic thymic epithelial cells with a few lymphocytes

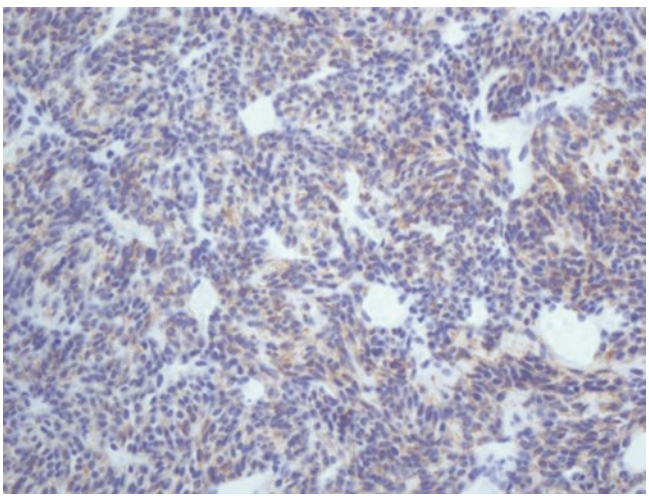

Fig. 3.22 Immunohistochemical staining was positive for CK19 (400×)

Type A thymoma is rare, accounting for 9% of thymic tumors. The vast majority of patients are stage I (80%), followed by stage II (17%) and stage III (3%), and only cases have been reported in stage IV. The average age of onset of type A thymoma is over 60 years, which is significantly higher than the average age of all thymoma (50 years).

Grossly, the tumors are encapsulated and the cut surface shows solid patterns. The solid elements can be composed of rubbery firm gray-white or brownish brittle tissue with or without focal calcification, lacking most of the organotypical features seen in conventional thymomas (e.g., a well-developed lobular architecture, prominent fibrous bands, and dilated perivascular spaces). Hemorrhage and/or necrosis are not a common feature of type A thymoma.

On imaging, fibrous septa is visible within the lesion (Fig. 3.23), which has few lobes, cystic changes (Fig. 3.24), and intra-parenchymal calcification. Hypogamma globulinemia and pure red blood cell aplastic anemia are more common in type A thymoma.

The obligatory criteria for type A thymoma are: occurrence of bland, spindle-shaped epithelial cells (at least focally); paucity or absence of immature (TdT+) T cells throughout the tumor. The optional criteria for type A thymoma are polygonal epithelial cells and CD20+ epithelial cells. The 2015 WHO classification first proposed the feasibility of cytological diagnosis of type A thymoma. It is considered that its sensitivity and specificity are acceptable, but other spindle cell tumors should be excluded, such as carcinoid tumors and low-grade sarcoma.

Type A thymoma is thought to originate from thymic medullary epithelial cells. Evidence supporting this hypothesis includes that their immunohistochemistry expresses CD20, cytokeratin, and metallothionein, as well as very few immature T cells. CD20 is a phosphorylated protein molecule. As a surface membrane protein of B lymphocytes, it is expressed only in pre-B lymphocytes, immature, mature, and activated B lymphocytes, but is lacking in plasma cells, pluripotent stem cells, and other tissues. There is no free CD20 in human serum. Therefore, CD20 is an important marker for identifying B lymphocytes or B-cell lymphoma. In 1992, Chilosi et al. found that thymic epithelial cells expressed CD20, which was positive for lymphocytes in the medulla or medulla differentiation zone in normal thymus and thymoma, and was focally distributed. CD20 is highly expressed in type A and AB thymoma epithelial cells, positively expressed in some lymphocytes, and mostly not expressed in type B thymoma epithelial cells. CD20 is negative in the epithelioid area and spindle cell area of metaplastic thymoma, which helps to distinguish it from type A thymoma.

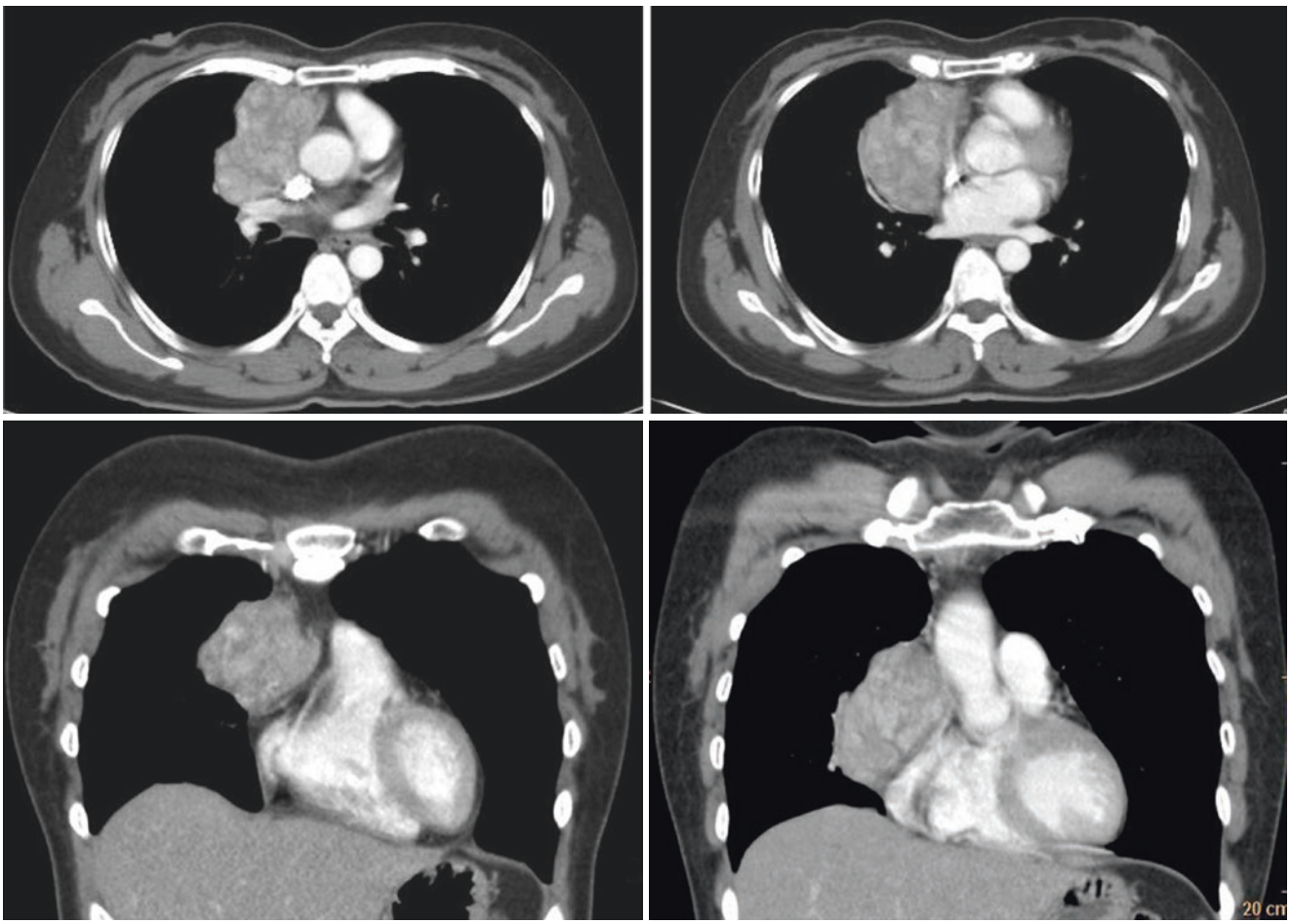

Fig. 3.23 Type A thymoma with fibrous septa in a 40-year-old woman

3.8.2 Case 2

A 59-year-old man complained of dry cough for 2 weeks.

Chest CT: A large mediastinal mass with associated elevation of the left hemidiaphragm (Fig. 3.25).

[Diagnosis] Atypical type A thymoma.

[Diagnosis basis] Intraoperatively, the tumor was mixed cystic and solid, without intact capsule and obvious surrounding fat gap, invading the parietal pleura and anterior segment of the left upper lobe. The tumor extensively and densely adheres to the thoracic aortic arch, pericardium, and superior vena cava. Pathology showed atypical type A thymoma. Immunohistochemistry demonstrated positivity for CKpan, CK19, CK5, and P63, and negativity for TdT, CD5, CD117, Syn, CgA, CD34, EMA, and SMA. The staining index for Ki-67 was about 5–10%.

[Analysis] Type A thymoma is regarded as an indolent tumor with a good prognosis. However, studies have shown that some type A thymomas show distant metastases or postoperative local recurrence. In 2015, atypical type A thymoma variant was categorized according to the WHO classification as a subtype of type A thymoma, characterized by moderate to severe nuclear atypia; increased mitotic activity (>4/2 mm^2); and signs of necrosis. Necrosis in particular appears to correlate with advanced stage, including metastasis (Fig. 3.26). Vladislav et al. [13] reviewed their cases and reported that atypical type A thymoma accounted for 3.8% (23/600) of the 600 cases of type A thymoma they had experienced. During the follow-up period (average, 49 months), approximately 43% of the cases had recurrence or metastases. The presence of necrosis correlates with both relapse and extrathoracic metastases but not with the stage of diagnosis. However, none of the other clinical or histological features of size, predominant nuclear shape, nuclear variability, and mitotic activity, were correlated with the outcome parameters (stage at diagnosis, presence or absence of relapse, and extrathoracic metastases).

Type A thymoma should be mainly distinguished from type AB thymoma, spindle cell B3 type thymoma, and spindle cell thymic carcinoma. The difference between type A and AB thymoma is whether the content of immature T cells is less or more. Any lymphocyte-dense areas or >10% tumor

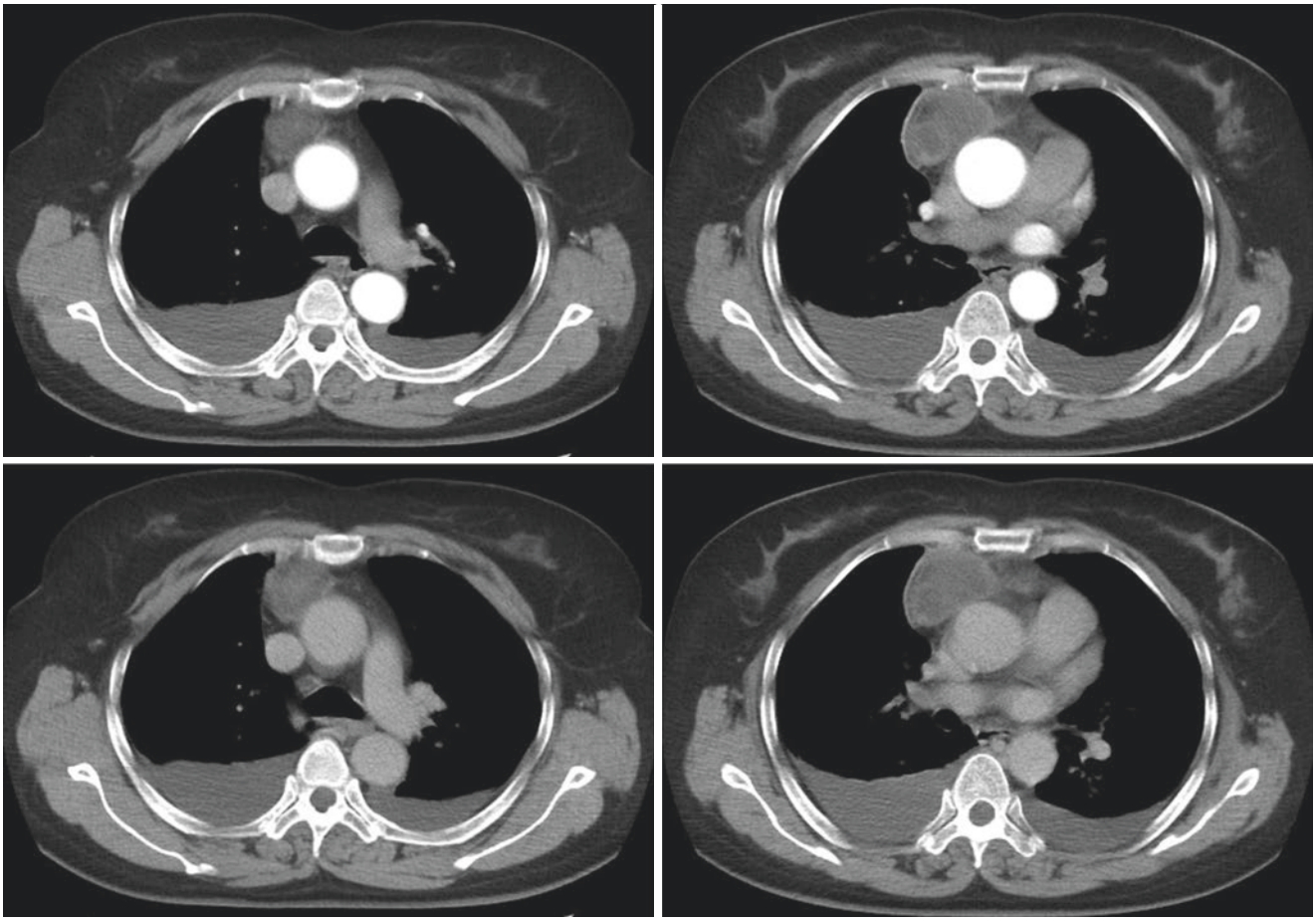

Fig. 3.24 A 54-year-old woman complained of shortness of breath, chest tightness, and chest pain for 1 week. Surgical pathology showed type A thymoma with extensive necrosis, hemorrhage and cystic changes, and no tumor infiltration in the capsule

areas with a moderate infiltrate of immature T cells should prompt classification as type AB thymoma. Type A and B3 thymoma was defined by an organotypic architecture and few or no lymphocytes. Type A thymoma had bland spindle or oval epithelial cells, without features to suggest spindle cell thymic carcinoma. Type B3 thymoma was composed of medium-sized round or polygonal cells with mild atypia.

Ki-67 is a well-known histological marker of proliferation used as an index of biological aggressiveness in various solid tumors. It has already been reported that Ki-67 labeling index (LI) correlates with the tumor aggressiveness in thymic epithelial neoplasm. Roden et al. [14] reported that mitotic activity differed between thymic carcinoma and type A or type B3 thymoma. Ki-67 LI in type A thymoma was 0.3–11.0% (median 3.0) and in thymic carcinoma was 12.2–43.3% (median 23.2%). In differentiating thymic epithelial neoplasms, Ki-67 LI is helpful, with Ki-67 LI <2% and ≥13.5% distinguishing type A thymoma and thymic carcinoma, respectively. Ki-67 LI in the case was 5–10%, which is similar to that of atypical type A thymoma.

3.8.3 Case 3

A 51-year-old man found a mediastinum mass for 1 month.

Chest CT: An elliptical mass in the right anterior mediastinum with obvious enhancement and necrotic or cystic components (Fig. 3.27).

[Diagnosis] Type AB thymoma.

[Diagnosis basis] A middle-aged male with a lobular mass in the anterior mediastinum, the contours of the mass were smooth. MPR shows that the tumor grows along the mediastinum and has no obvious invasion of the surrounding tissues, considering the diagnosis of low-risk thymoma. Contrast-enhanced CT images show multiple higher-density nodules and low-density septa (red arrows), suggesting that the possibility of type A or AB thymoma. The lesions have shallow lobes (blue arrows), necrosis, and obvious cystic changes, which more support the diagnosis of AB thymoma. Intraoperatively, the tumor was measured 11 × 8 × 6 cm, with a complete capsule (Fig. 3.28). Immunohistochemistry demonstrated positivity for CKpan, CK19, CK5/6, and

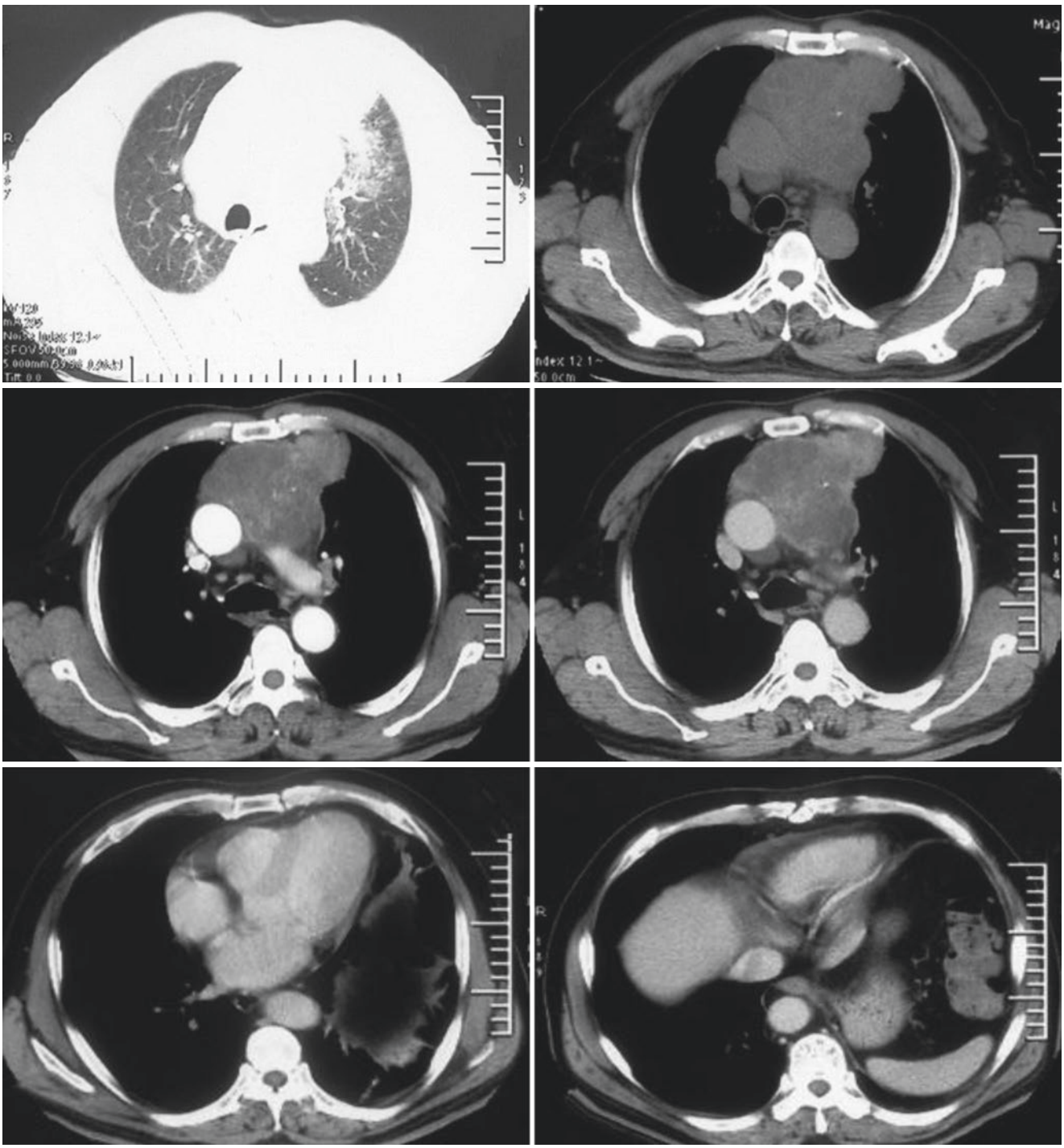

Fig. 3.25 Chest CT images of a 59-year-old man complained of dry cough for 2 weeks

CD20 in epithelial cells and CD3, CD5, and TdT in lymphocytes. The staining index for Ki-67 was about 30–40%. Pathology combined with immunohistochemistry, consistent with type AB thymoma (Fig. 3.29).

[Analysis] Most thymomas are lobulated and encapsulated, and larger tumors may have cystic lesions. Benign tumors usually have evident fibrous capsules composed of thymic epithelial cells with neoplastic proliferation and different numbers of nonneoplastic T lymphocytes.

The incidence of type AB thymoma is only lower than that of type B2 thymoma. Type AB thymoma is defined as a thymic epithelial neoplasm composed of a mixture of lymphocyte-poor type A-like components and lymphocyte-rich type B1-like components in the WHO histological clas-

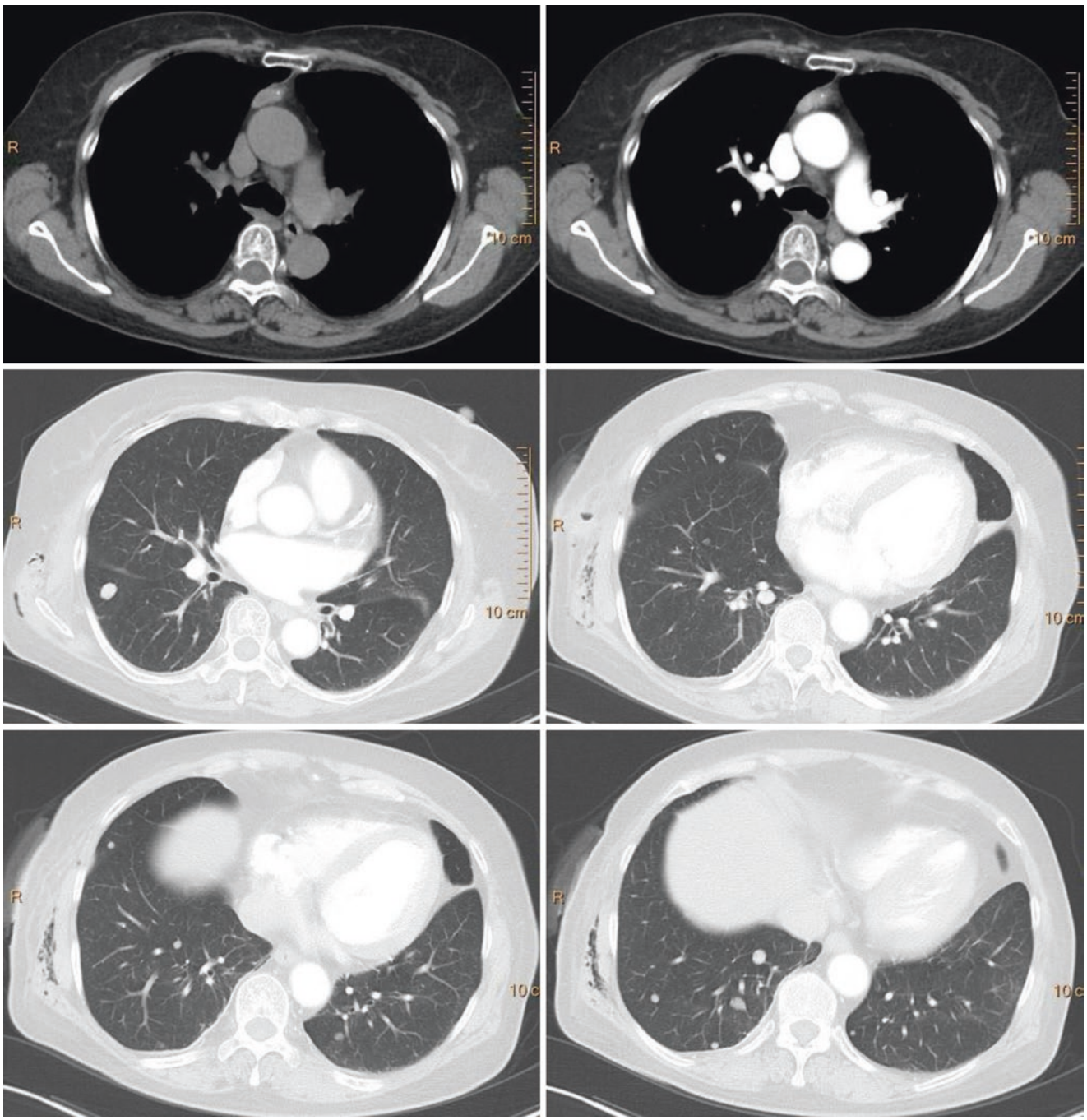

Fig. 3.26 Atypical type A thymoma variant with lung metastases in a 64-year-old woman

sification of thymoma published in 2004. In addition, it has been shown that all histological features of type A-like components can be seen in type A thymoma. Any lymphocyte dense areas (with crowded TdT+ cells that are "impossible to count" in "type B-like" areas) or more than 10% tumor areas with a moderate infiltrate of immature T cells should classification as type AB thymoma. The spindled epithelial cells of type A and AB thymoma are likewise pan-CK and p63 positive, and can also express CD20. Spindle cell thymoma with obvious TdT+/CD1a+/CD99+ positive lymphoid cell population points to type AB thymoma.

In a few cases, lymphocytes may be abundant throughout the tumor. Areas with typical spindled epithelial cells may be intimately admixed with lymphocyte-rich areas or may have a clear boundary with them. It is worth noting that a spectrum of epithelial cell morphologies ranging from (obligatory) spindle cells to polygonal epithelial cells was shown in the lymphocyte-rich areas, resembling those in type B1 or

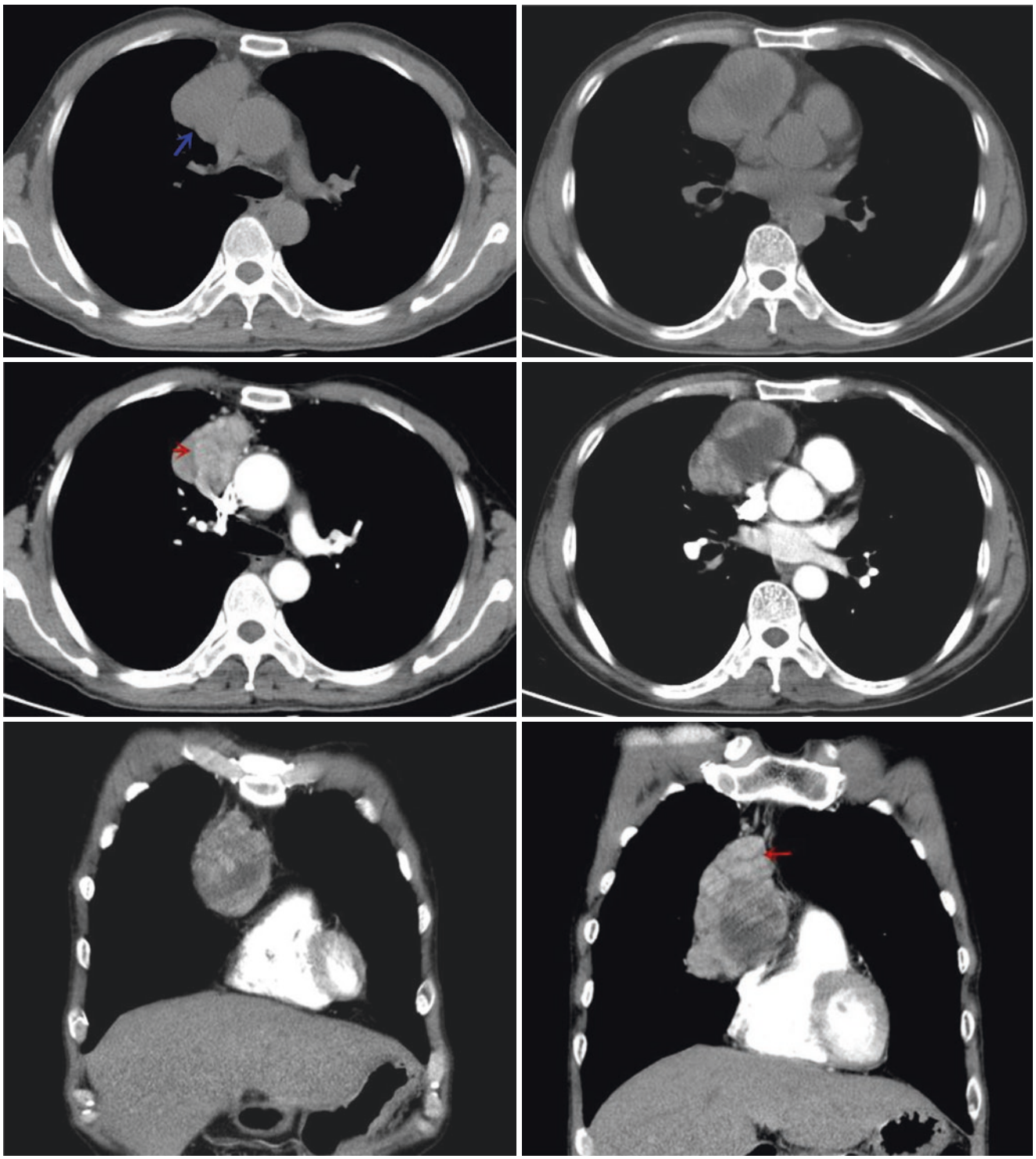

Fig. 3.27 Chest CT images of a 51-year-old man found a mediastinum mass for 1 month

B2 thymomas. Small-scale medullary differentiation as encountered in type B1 thymomas may also occur in the lymphocyte-rich regions of AB thymomas.

Type AB thymoma has clear margin and clear fat gap with the pericardium. The lobes are more common than type A thymoma, and calcification can be seen in the parenchyma (Fig. 3.30). Type AB thymoma is generally not accompanied by pleural implant nodules and pleural effusion. The multiple nodules are obvious enhancement and the line-like low-density septa are its biggest feature (Fig. 3.31), which is intact with the general specimen. The cut surface is multiple yellow-brown nodules, which are separated by white fiber

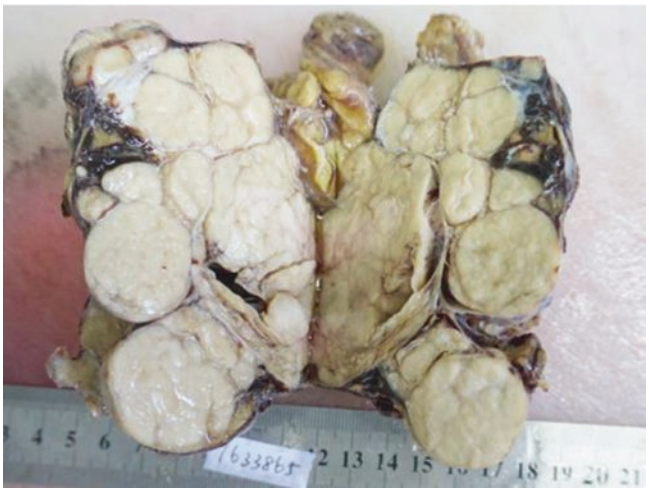

Fig. 3.28 On cut surface, the tumor had multiple white-colored nodules separated by fibrous bands without infiltrative growth

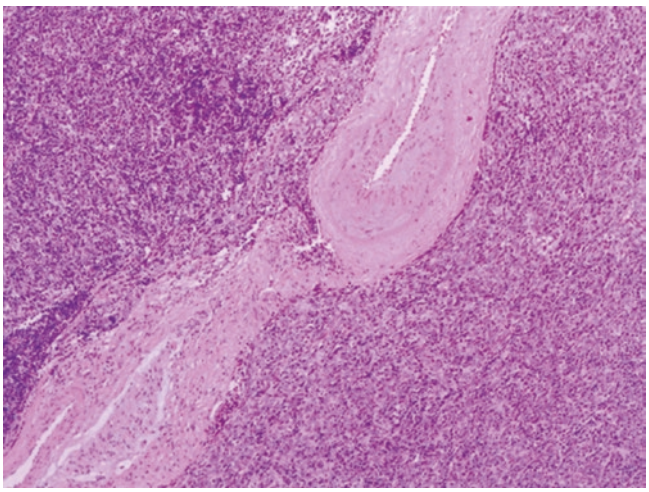

Fig. 3.29 Photomicrograph showing type AB thymoma, composed of spindle cell component and lymphocyte component

bands. The obvious enhancement characteristics of type AB thymoma are related to the ultrastructure of epithelial cells whose components are like cortex and medulla junction. This organoid thymic epithelial tumor has the characteristic that the blood supply of the junction structure of the cortex and medulla in the normal thymus is rich. This is inconsistent with the regularity that the degree of tumor enhancement increases with the change of malignant degree or grade, and also reflects the characteristics of this type of thymoma, which not only reflects the malignancy of the tumor, but also retains the histological classification. Some type AB thymomas exhibit capsular invasion or the formation of adhesions to surrounding structures. The invasive potential increases along with the pathological type from A to B3. Type A and AB thymoma rarely have extensive cystic changes. In this case, the cystic changes are obvious and special. These tumors rarely develop recurrence and distant metastases, and the 5- and 10-year survival rates of AB thymoma are 80–100%.

3.8.4 Case 4

A 72-year-old man complained of left ptosis, diplopia, and chest tightness for 1 month.

Chest CT: A soft tissue mass with nodular-like enhancement and line-like septa (Fig. 3.32).

[Diagnosis] Type AB thymoma with myasthenia gravis (ocular MG).

[Diagnosis basis] Chest CT showed a lateral growth mass in the left anterior mediastinum with clear borders, uniform density, obvious lobes (red arrows), middle enhancement, and low-density linear fiber septa, suggesting the diagnosis of type AB thymoma. Intraoperatively, the tumor was measured 7.5 × 6.5 × 4.0 cm, with a complete capsule. The cut surface was grayish-white, reddish, and slightly lobulated.

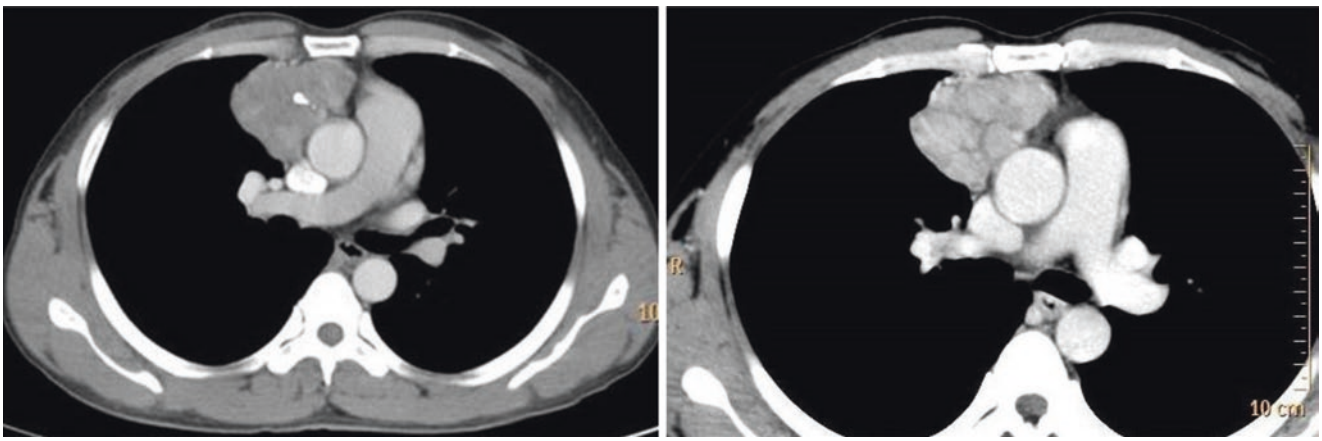

Fig. 3.30 A 50-year-old man with type AB thymoma. Chest CT showed a lobular mass in the anterior mediastinum. Calcification was visible in the parenchyma. Multiple nodules were obviously enhancement, and the septa were obvious

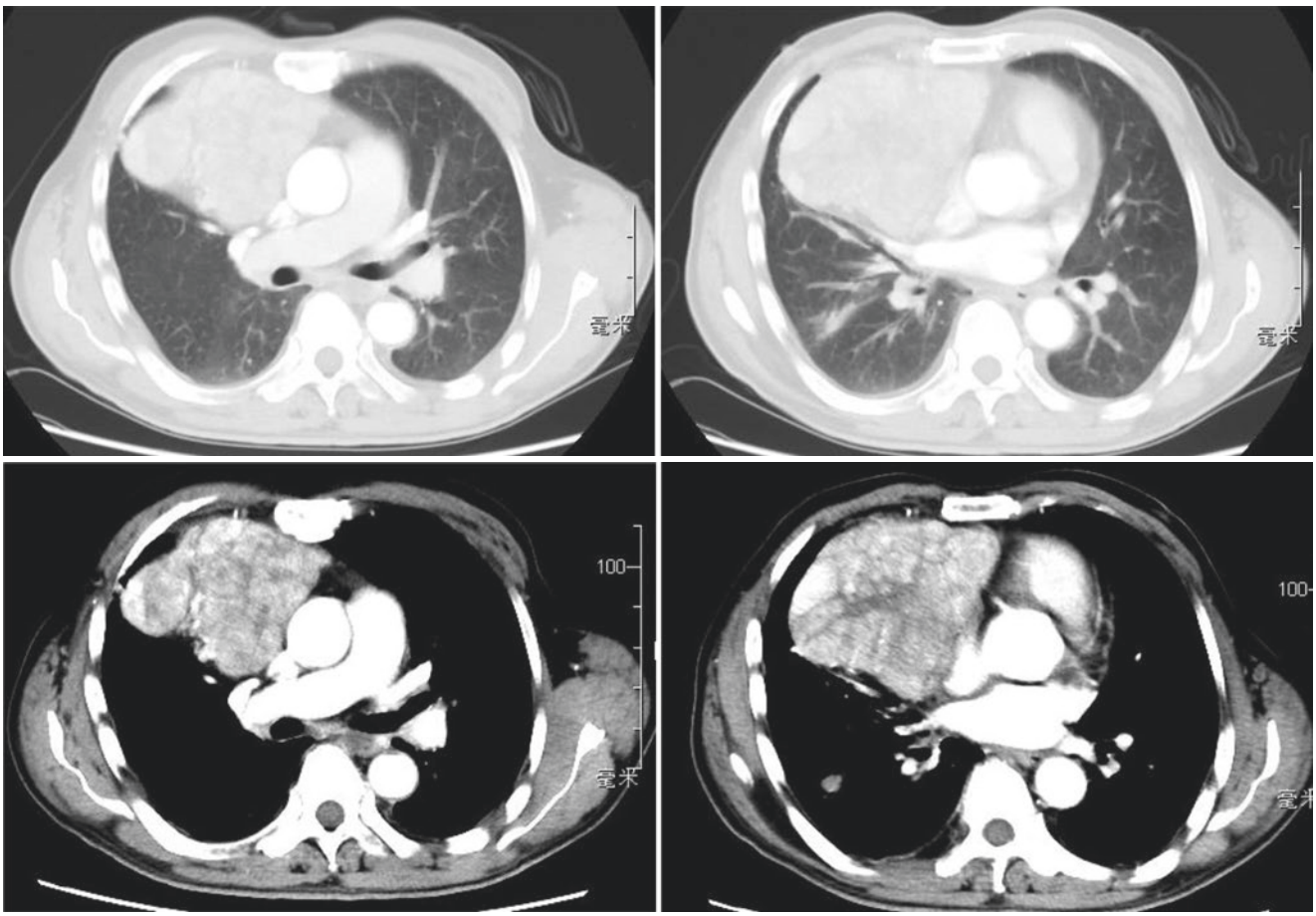

Fig. 3.31 A 40-year-old man with type AB thymoma in the anterior mediastinum. Chest CT showed a mass with multiple nodular enhancement and line-like low-density septa

Immunohistochemistry demonstrated positivity for CKpan, CK19, and Bcl-2 in epithelial cells and TDT, CD1a, CD20, CD7, and CD5 in lymphocytes. Pathology combined with immunohistochemistry, consistent with type AB thymoma.

[Analysis] Thymomas are tumors that appear to be originated from or show differentiation toward thymic epithelial cells, similar to the normal thymic histological architecture, such as discrete lobulation, perivascular spaces, and admixed immature T cells. One of the unique characteristics of thymomas is their frequent association with autoimmune diseases, especially myasthenia gravis (MG). Many reports indicate that 30–50% of patients with thymoma have MG, and conversely, 10–15% of MG patients have thymoma.

MG is characterized by autoantibodies against components of the neuromuscular junction and divided into several subgroups based on clinical features and the causative antibody. The symptoms that occurred most frequently in patients with MG were ptosis, diplopia, appendicular weakness, dysphonia, and dysphagia. MG-associated antibodies are the most important biomarkers in guiding MG diagnosis and helping to define MG subtypes. Anti-acetylcholine receptor (AChR) antibodies can be detected in 70% of all patients with MG. Antibodies against titin are mostly detected in patients with thymomatous myasthenia gravis (TMG) or late-onset MG, while anti-ryanodine receptor antibodies are presented in 70% of anti-AChR Ab positive MG (AChR-MG) and in 14% of patients with late-onset AChR-MG. Acetylcholine receptor antibodies associated with muscle fatigability and weakness are detected in most thymoma patients with MG. Approximately 95% and 70% of thymoma patients with MG have titin and ryanodine receptor autoantibodies, respectively.

A pathogenic model for the development of MG in thymoma has been described, which is based on evidence that there is very little intra-tumorous antibody production in thymoma and thymomas produce developing T-cells and export them to the periphery. It has been proposed that these exported T cells derived from thymoma circulate to organs and contribute to the pathogenesis of MG. The defect of thymocyte maturation within the tumor may partly lead to the development of autoreactive T-cells. These naïve T-cells are activated in the periphery and in turn aid autoantibody-producing B cells outside the thymoma. The production of autoreactive T-cells in thymomas may be partly due to inef-

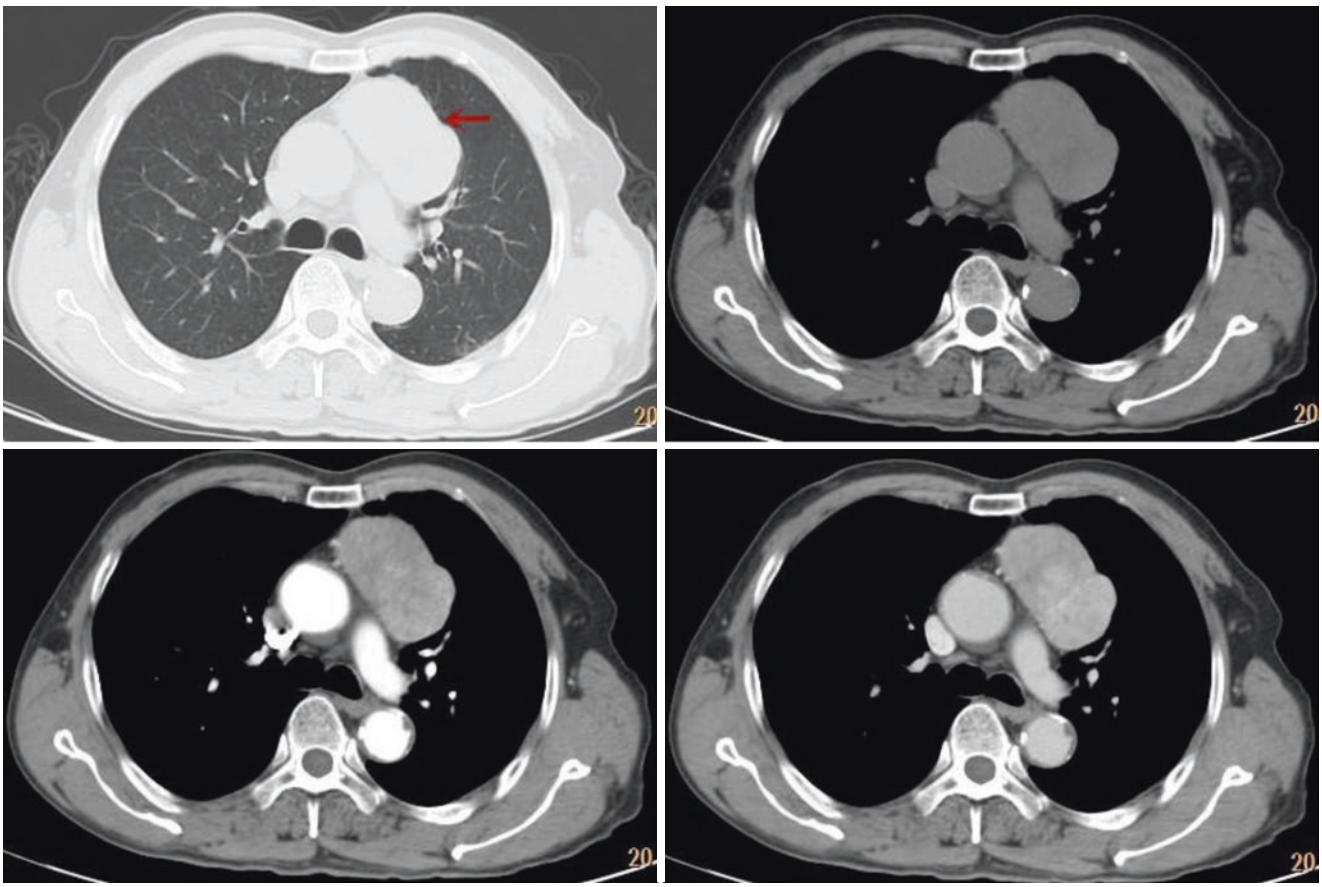

Fig. 3.32 Chest CT images of a 72-year-old man complained of left ptosis, diplopia, and chest tightness for 1 month

ficient generation of CD4+ CD25+ FOXP3+ regulatory T-cells.

Definitive treatment of thymoma is indicated for all patients with MG regardless of antibody status and MG type. Surgical resection of thymoma in patients with MG consists of complete resection of the thymus and the surrounding anterior mediastinal fat tissue. Surgical approaches include open transsternal and minimally invasive procedures. Less invasive approaches are reportedly associated with less morbidity and faster recovery. It is reported that the remission rate after thymectomy reached 80%. Myasthenia crisis is the most common reason for operative mortality. Other reasons are damaged airway, infection, and nerve palsies. Preoperative neurological assessment, CT scan, and pulmonary function test can reduce myasthenia crisis; operating during stable phase of myasthenia gravis, and low use of steroids and neuromuscular blockade during anesthesia. To stabilize myasthenia gravis, Pyridostigmine can be used for a month before surgery. Postoperative challenges occur during recovery and extubation. The management of myasthenia crisis involves ensuring airway safety and maintaining respiratory function.

The prognostic value of MG associated thymoma remains controversial in the different reports of literature. Previous studies showed that MG is an indicator of poor prognosis for thymoma. Worsened myasthenic symptoms or crisis may delay postoperative adjuvant treatment, reduce tolerance to radiotherapy or chemotherapy, and increase perioperative mortality. However, some experts pointed out that MG may be a positive prognostic factor, because thymoma can be diagnosed earlier due to MG symptoms, which can increase the R0 resection rate and improve prognosis. Others reported that having MG or not, did not show any statistical significance. This discrepancy is probably due to the wide range of clinical and pathogenic variants in MG patients.

3.8.5 Case 5

A 59-year-old woman complained of cough and sputum for 3 months.

Chest CT: A mass in the left superior mediastinum with a smooth and clear margin, measured 2.9 × 2.9 × 2.0 cm (Fig. 3.33).

[Diagnosis] TypeB1 thymoma.

[Diagnosis basis] Intraoperatively, the tumor was measured 2.5 × 2.0 × 2.0 cm, with a complete capsule and no external invasion. The pathology is a type B1 thymoma

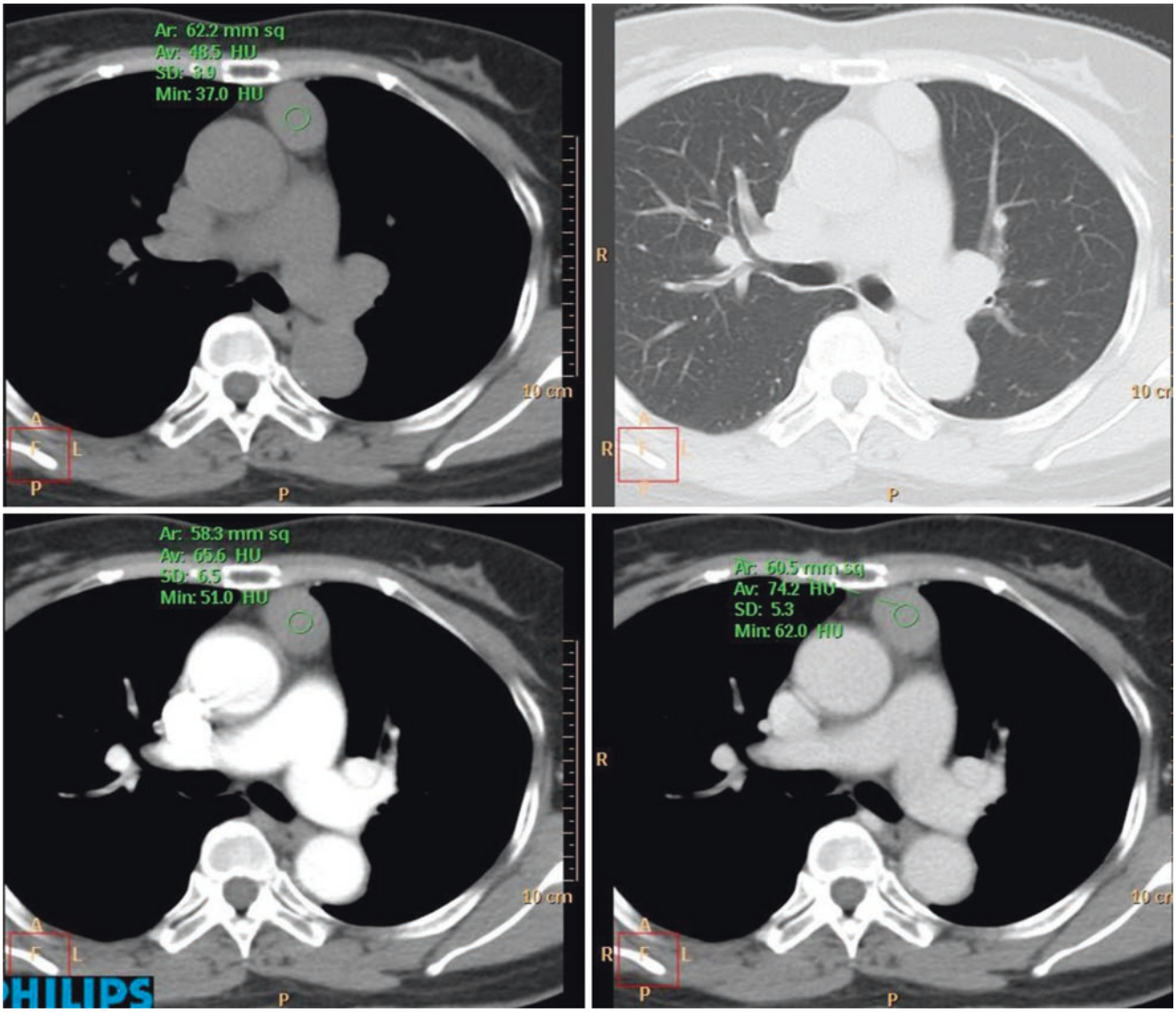

Fig. 3.33 Chest CT images of a 59-year-old woman complained of cough and sputum for 3 months

(Fig. 3.34). Immunohistochemistry demonstrated positivity for CD20, CD79a, CD3, CD45RO, and a small amount of CKpan epithelium cells (Fig. 3.35).

[Analysis] Type B1 thymoma was described as a tumor that was similar to the normal functional thymus in that it combined large expanses having an appearance almost indistinguishable from the normal thymic cortex admixed with areas resembling thymic medulla. In the traditional classification, these tumors were considered to correspond to lymphocyte-rich thymomas. It is also correlated to the predominantly cortical or organoid thymoma in the Kirchner and Muller-Hermelink classification [5]. The thymus-like architecture and cytology of B1 thymomas are highlighted as obligatory criteria, including abundance of immature T cells, areas of medullary differentiation (medullary islands); paucity of polygonal or dendritic epithelial cells without clustering (i.e., <3 contiguous epithelial cells). The optional criteria

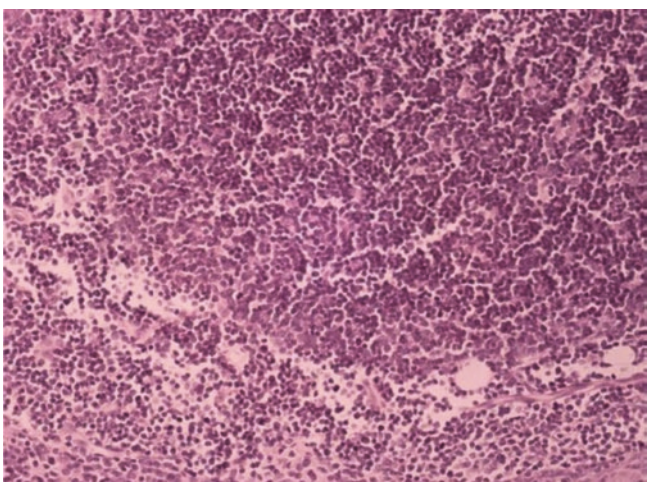

Fig. 3.34 Photomicrograph showing typeB1 thymoma, composed of a large number of small lymphocytes with a few epithelial cells

includes Hassall's corpuscles and perivascular spaces. As characteristic structures of the normal thymus, Hassall's corpuscles are commonly used as diagnostic features to identify the human thymus. The majority of studies consider that they come from epithelial cells of the thymic medulla. Typical Hassall's corpuscles are occasionally identified in areas with medullary differentiation of WHO type B1-3 thymoma; however, they are not identified in type A and AB thymoma. Immunohistochemical staining of keratin is diffusely distributed in a delicate network, which is an obligatory feature of type B1 thymoma.

Type B1 thymoma is rare, accounting for about 6–7% of thymoma. Tumors are round, elliptical or lobulated, with uniform density, calcification (Fig. 3.36), thick fibrous envelope, and irregular fibrous septa. In 53–58% of cases, the capsule is intact (stage I), and in 24–27% of cases, only the mediastinal fat is invaded (stage II). It is rare to invade the pleura, pericardium, large blood vessels, and adjacent organs. Metastasis is extremely rare. 91–94% of patients were surgically resected, postoperative recurrence rate was lower than 10%, and the 10-year survival rate was higher than 90%.

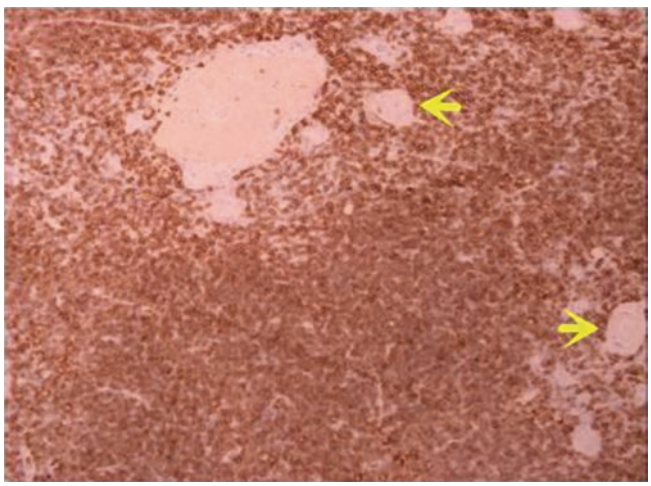

Fig. 3.35 CD3 stain, with sparing of Hassall's corpuscles (yellow arrow)

3.8.6 Case 6

A 59-year-old woman complained of left chest pain for 1 week.

Chest CT: A soft tissue mass next to the aortic arch, with regular contours, coarse calcification, and necrotic or cystic component (Fig. 3.37).

[Diagnosis] Type B2 thymoma.

[Diagnosis basis] An elderly woman with mediastinal lateral mass showed clearer border and coarse calcification, supporting the diagnosis of thymoma. The cystic changes were obvious and the MPR showed an elevation of the left diaphragm, the diagnosis of high-risk thymoma should be considered. Chest CT showed a small amount of pleural effusion and the pericardium was invaded. No exact soft tissue density nodules were found in the pericardium, which was more consistent with B2 thymoma than B3 thymoma. Intraoperatively, the large mass measured 10.0 × 9.0 × 8.0 cm located in the left anterior mediastinum. The capsule was incomplete, involving the left upper lobe and the pericardium. The phrenic nerve was wrapped and involved. Pathology suggested type B2 thymoma with invasion of lung tissue (Fig. 3.38). Immunohistochemistry demonstrated positivity for CKpan, Ck19, CD5, CD3, and TdT.

[Analysis] Type B2 thymoma is defined as a tumor in which the neoplastic epithelial component appears as scattered plump cells with vesicular nuclei and distinct nucleoli among a heavy population of lymphocytes by the WHO classification. Type B1 and B2 thymomas are, by definition, both lymphocyte-rich tumors. It may be difficult to improve their distinction from one another. Type B2 thymoma must display a higher number of polygonal (nonspindle) neoplastic epithelial cells. Those cells usually appear in clusters, defined as three or more contiguous

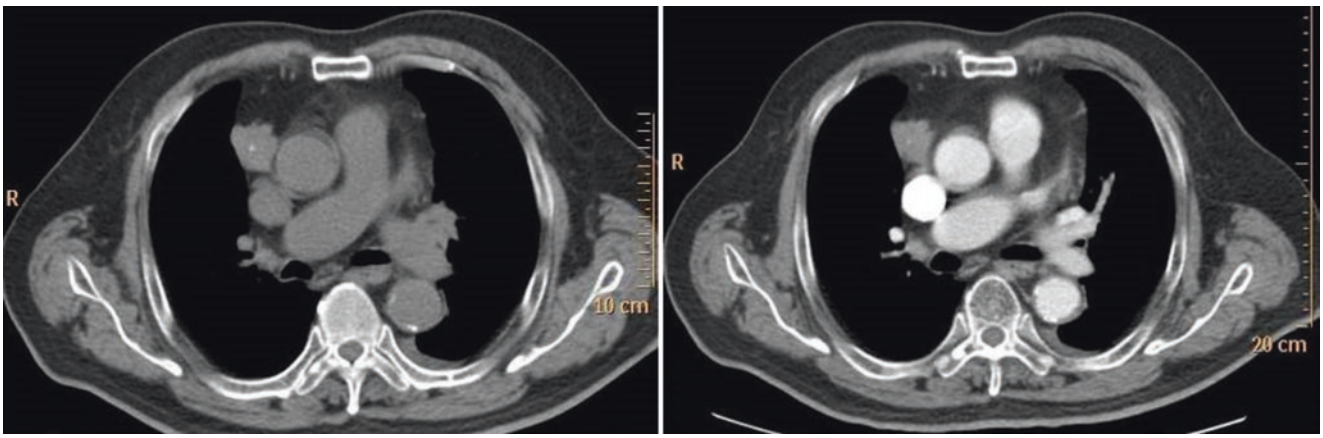

Fig. 3.36 An 80-year-old man with type B1 thymoma

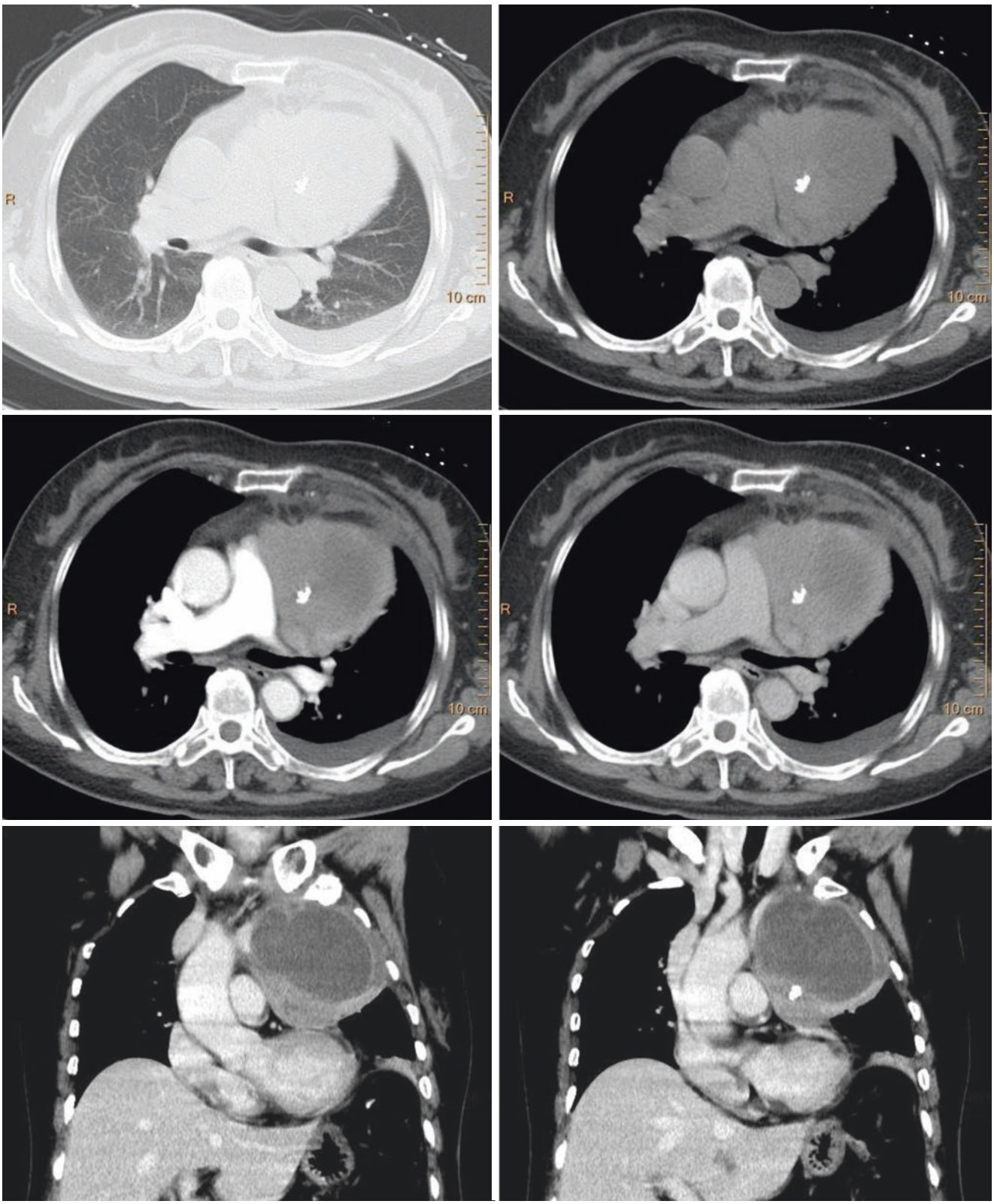

Fig. 3.37 Chest CT images of a 59-year-old woman complained of left chest pain for 1 week

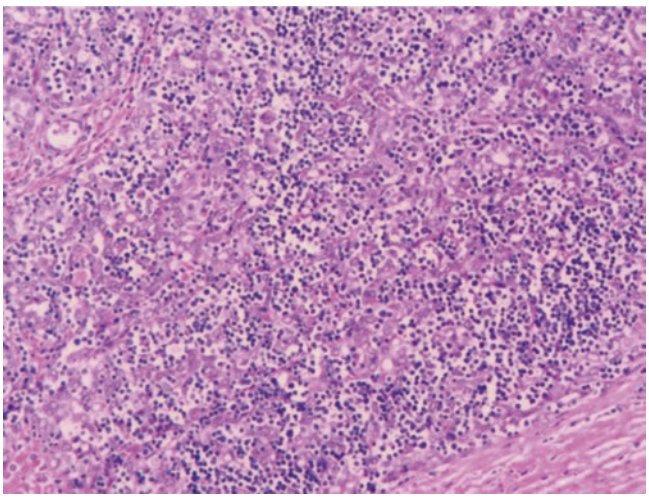

Fig. 3.38 Microscopically, the tumor presented multiple polygonal cells with large nuclei and prominent nucleoli, the number of neoplastic epithelial cells and lymphocytes were equal

epithelial cells. Medullary islands optionally appear in type B2 thymoma, whereas Hassall's corpuscles appear as optional feature usually in type B1 and rarely in B2 thymoma. Cytokeratin (and p40/p63) expression patterns may be helpful to differentiate type B1 from type B2 (and AB) thymoma.

The proportion of type B2 thymoma reported is about 20% for all thymomas. Type B2 thymoma has been shown to have a better prognosis than thymic carcinoma and worse than types A, AB, and B1. Compared with other subtypes, type B2 thymoma has a moderate aggressive nature. About half of patients were classified as stage III or IV at the first diagnosis. In contrast, most patients with type B3 thymoma and thymic carcinoma were at an advanced stage. Surgery is the mainstay treatment. The 5-year survival rate of type B2 thymoma was about 60–70%.

Type B2 thymoma is a high-risk thymoma, so imaging shows that the tumor is more lobed, with a large range of cystic changes and low-density areas (Fig. 3.39), which can

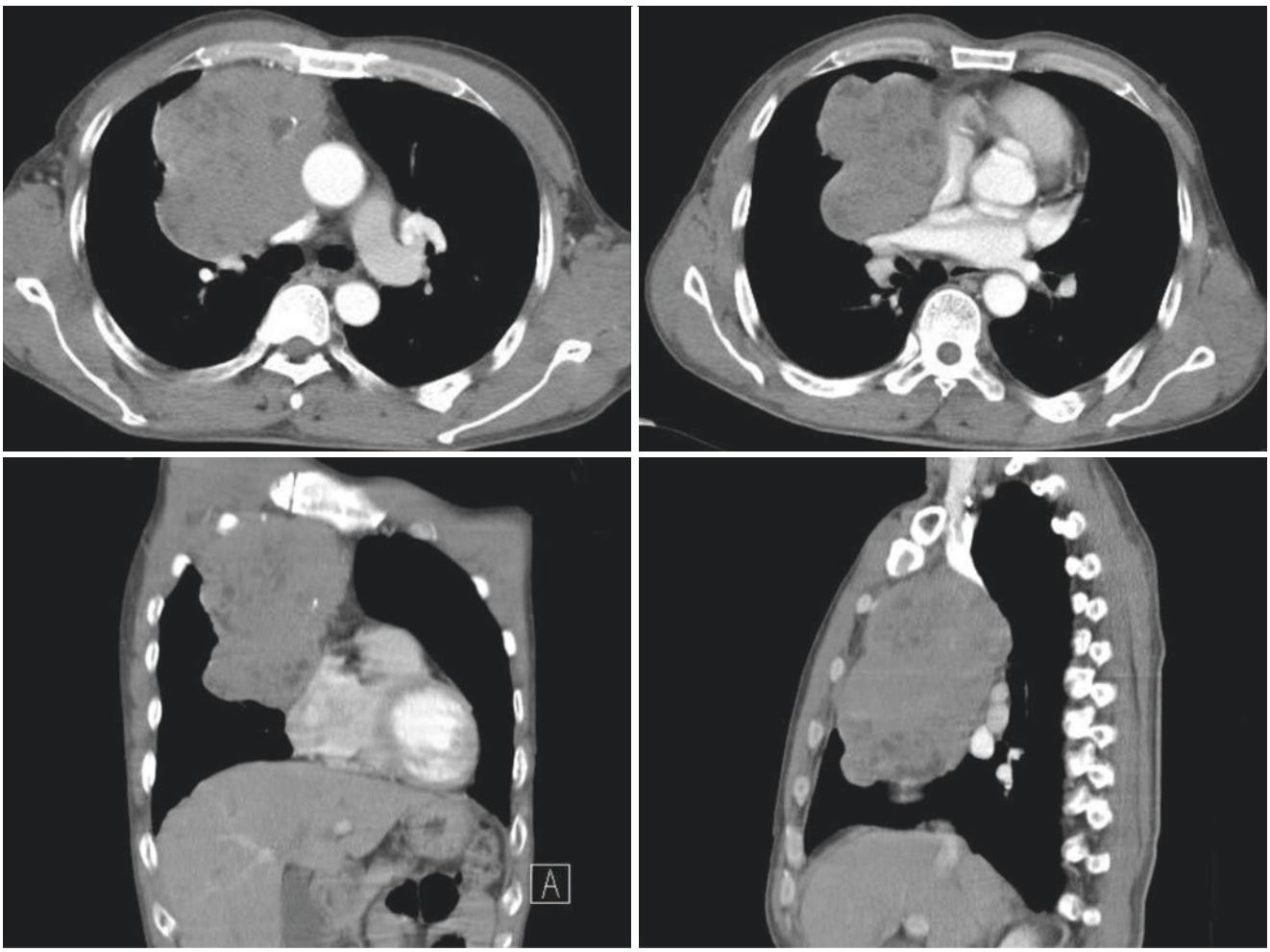

Fig. 3.39 A 56-year-old man with type B2 thymoma. Chest CT showed that the tumor invaded the capsule, and cystic changes, necrosis, and calcification were seen in the lesion

invade the pericardium (Fig. 3.40) and pleura (Fig. 3.41), the latter manifested as pleural nodules and pleural effusion.

3.8.7 Case 7

A 32-year-old man complained of weakness in both upper limbs and dysphagia for 2 months.

Chest CT: An irregular soft tissue mass was seen in the anterior superior mediastinum, with multiple nodules in both lungs (Fig. 3.42).

[Diagnosis] Type B3 thymoma.

[Diagnosis basis] An irregular soft tissue mass in the anterior mediastinum with pleura (blue arrow) and intrapulmonary metastases (red arrow), combined with myasthenia gravis symptoms, the diagnosis first considers B2 or B3 thymoma. The patient underwent pleural tumor biopsy, and immunohistochemistry demonstrated positivity forAE1/AE3, EMA, TdT, CD20 (scattered), CD5 (scattered), and CD99 (partial) and negativity for CD117, Calretinin, and TTF-1. Combined with the results of immunohistochemistry and pathology, the lesions were consistent with type B3 thymoma (Fig. 3.43). After a definite diagnosis, oral brompiroxamine was taken. Myasthenia gravis symptoms did not progress significantly.

[Analysis] Type B3 thymomas comprise round or polygonal epithelial cells with no or mild atypia. These tumors also contain small amounts of lymphocytes, and display sheet-like growth of the neoplastic epithelial cells. The epithelial cells usually exhibit a squamoid quality without intercellular bridges, and cellular palisading around perivascular spaces and along fibrous septa is often striking. Round to oval irregular nuclei are present with inconspicuous nucleoli in most cases, and the cytoplasm is eosinophilic to clear,

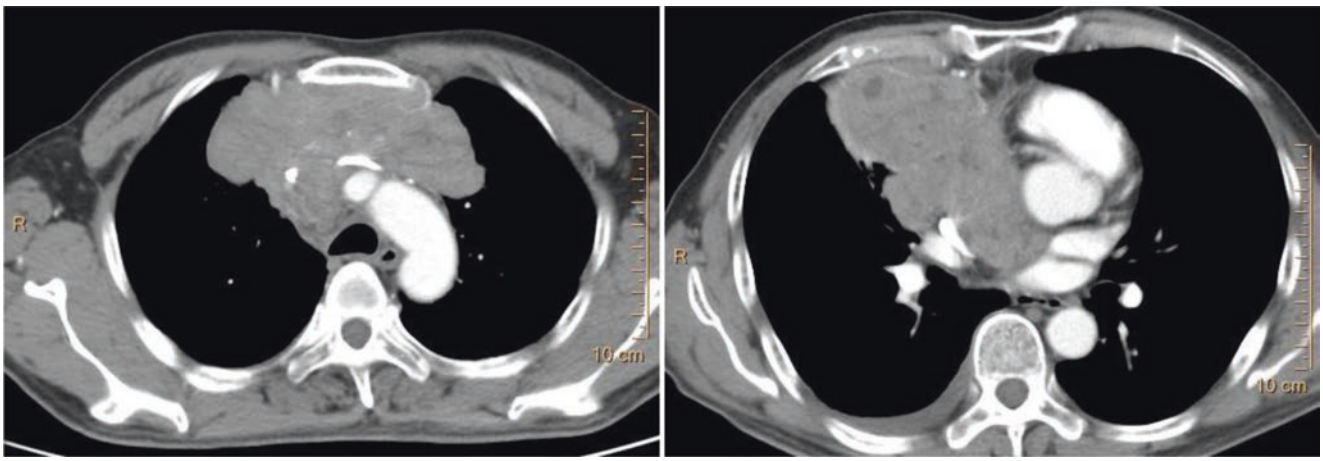

Fig. 3.40 A 66-year-old man with type B2 thymoma invading the pericardium

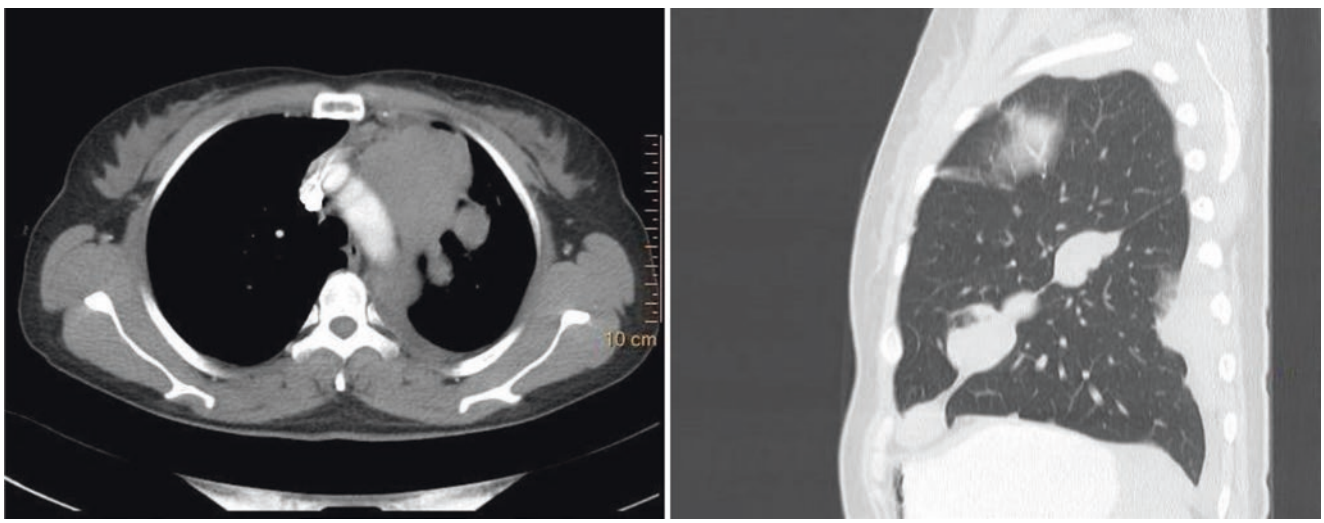

Fig. 3.41 A 39-year-old woman with type B2 thymoma, with interlobar pleural metastases and pleural effusion

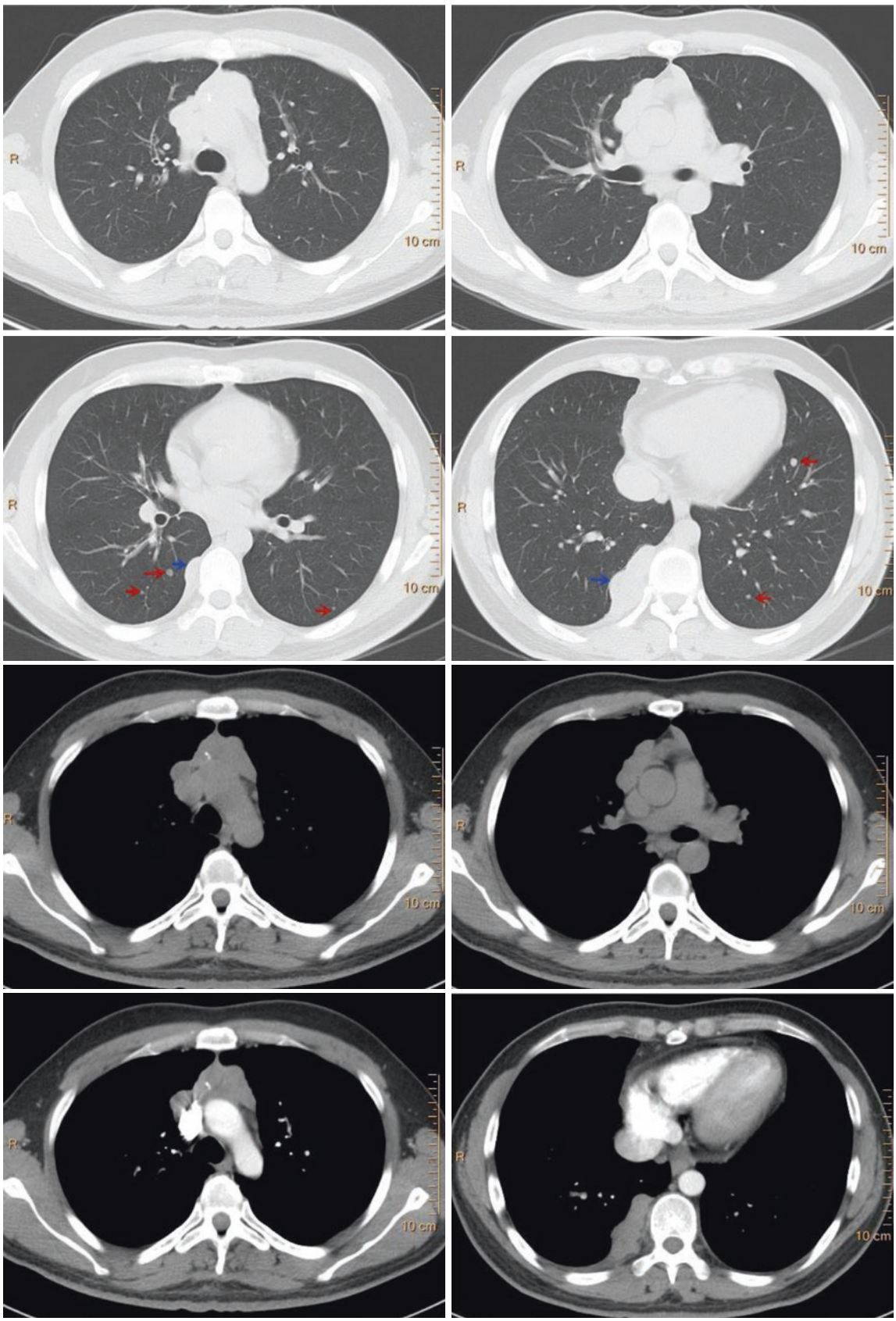

Fig. 3.42 Chest CT images of a 32-year-old man complained of weakness in both upper limbs and dysphagia for 2 months

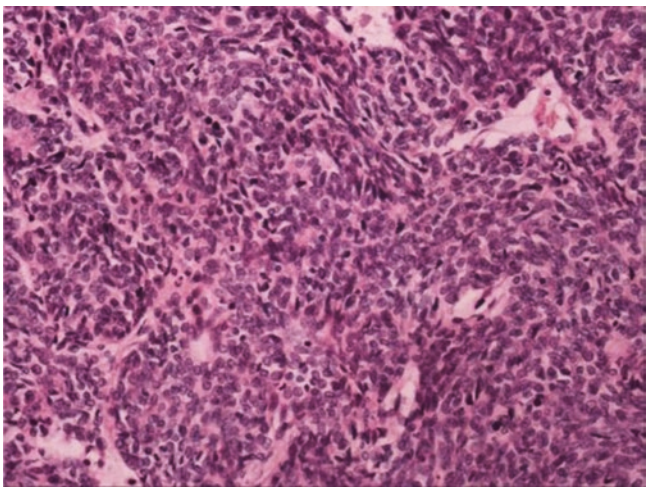

Fig. 3.43 The tumor cells are medium in size, arranged in a leaflet shape, and have few lymphocytes

resembling that of koilocytes. Tumor cells sometimes form spindles and fascicles, similar to those of type A thymomas, or may contain large vesicular nuclei and distinct nucleoli, similar to those of type B2 thymomas.

Type B3 thymoma is a tumor with few lymphocytes and abundant epithelium, but it is difficult to distinguish it from type B2 thymoma. Because of the lack of distinguishing markers, the differential diagnosis depends on the visual impression that type B2 thymomas appear blue on HE staining (because of the presence of many admixed lymphocytes), whereas type B3 thymomas appear pink (because of sheets of confluent tumor cells).

The distinction of type B3 thymoma from thymic squamous cell carcinoma (TSQCC) can be a challenge when rare tumors with a type B3 thymoma morphology show focal expression of "TSQCC-markers" (such as CD5 and CD117) and/or lack of "type B3 thymoma markers" (such as TdT+ T cells), or when tumors with a TSQCC morphology harbor (usually rare) TdT+ immature T cells. The fourth edition stated that tumors that look like type B3 thymoma on HE staining should be diagnosed as type B3 thymoma, while tumors with TSQCC morphology should be labeled as TSQCC, irrespective of immunohistochemistry.

Because of the potential heterogeneity of thymomas, caution should be exercised in subtyping thymomas on biopsies; ideally, subtyping of thymomas should be performed on the resection specimen.

3.8.8 Case 8

A 50-year-old man complained of cough and chest tightness for 4 months.

Chest CT: Irregular soft tissue mass in the right middle lobe and mediastinum, with right pleural effusion (Fig. 3.44).

[Diagnosis] Type B3 thymoma with pericardial, pleural, and lung metastases.

[Diagnosis basis] An irregular soft tissue mass occupies the right anterior mediastinum, with calcifications (red arrow) and no enlarged lymph nodes in the mediastinum, which does not support the diagnosis of lymphoma, and is considered to be thymic epithelial tumor. The tumor invades the pericardium and pleura. Ipsilateral pleural effusion and pleural nodules (black arrows) can be seen, supporting the diagnosis of high-risk thymoma. The tumor is slightly necrotic (green arrow) and clear soft tissue lesions (blue arrow) are seen in the pericardial cavity, so the diagnosis of type B3 thymoma needs to be considered. The patient underwent thoracoscopy, the tumor measured 10 × 8 × 5 cm located in the middle lobe of the right lung and mediastinum, with multiple metastatic nodules in the visceral and parietal pleura. Biopsy pathology showed type B3 thymoma. After 4 cycles of docetaxel and cisplatin chemotherapy, precise radiotherapy of thymic tumors and pleural metastases was performed. The patient's chest tightness and suffocation symptoms disappeared. A review of the chest CT one year later showed that the lesions were clearly absorbed (Fig. 3.45).

[Analysis] For many resected thymomas, histology is unique and diagnostic. However, accurate subtype can be improved by the judicious use of specific antibodies. In addition, immunohistochemistry can be helpful to distinguish thymomas from its mimickers in biopsies. When deciding on the B subtype (and possible relative proportions of subtypes), CK stains can be used to determine the density and pattern of the thymic epithelial network. A delicate network of CK-positive epithelial cells can be seen in B1 thymoma. B2 thymoma has a denser network of CK-positive epithelial cells than in the normal thymic cortex and/or clusters of epithelial cells. Sheets of CK-positive tumor cells define B3 thymoma. When evaluating the epithelial density of thymoma, p63 is a useful alternative method for CK staining because it has a similar staining profile and sometimes might be easier to interpret. As the CK profile of the epithelial cells overlaps considerably in B-type thymomas, CK subtyping is almost useless in routine diagnosis. CD3/TdT stains confirm the immature phenotype of the lymphoid population. Alternatively or complementary, CD1a and CD99 can be used.

Type B3 thymoma is considered to be a low-to-moderate malignant tumor, most of which are Masaoka stage II (15–38%) or stage III (38–66%), and stage I is rare (average 4.2%). Cases of pleural spread (stage IVa) or distant metastasis (stage IVb) account for 6–26% (average 15%). Complete surgical resection is the preferred treatment to achieve a cure in B3 cases. At the diagnosis, B3 thymomas are commonly not encapsulated and present an infiltrative border with extension to the mediastinal fat and the sur-

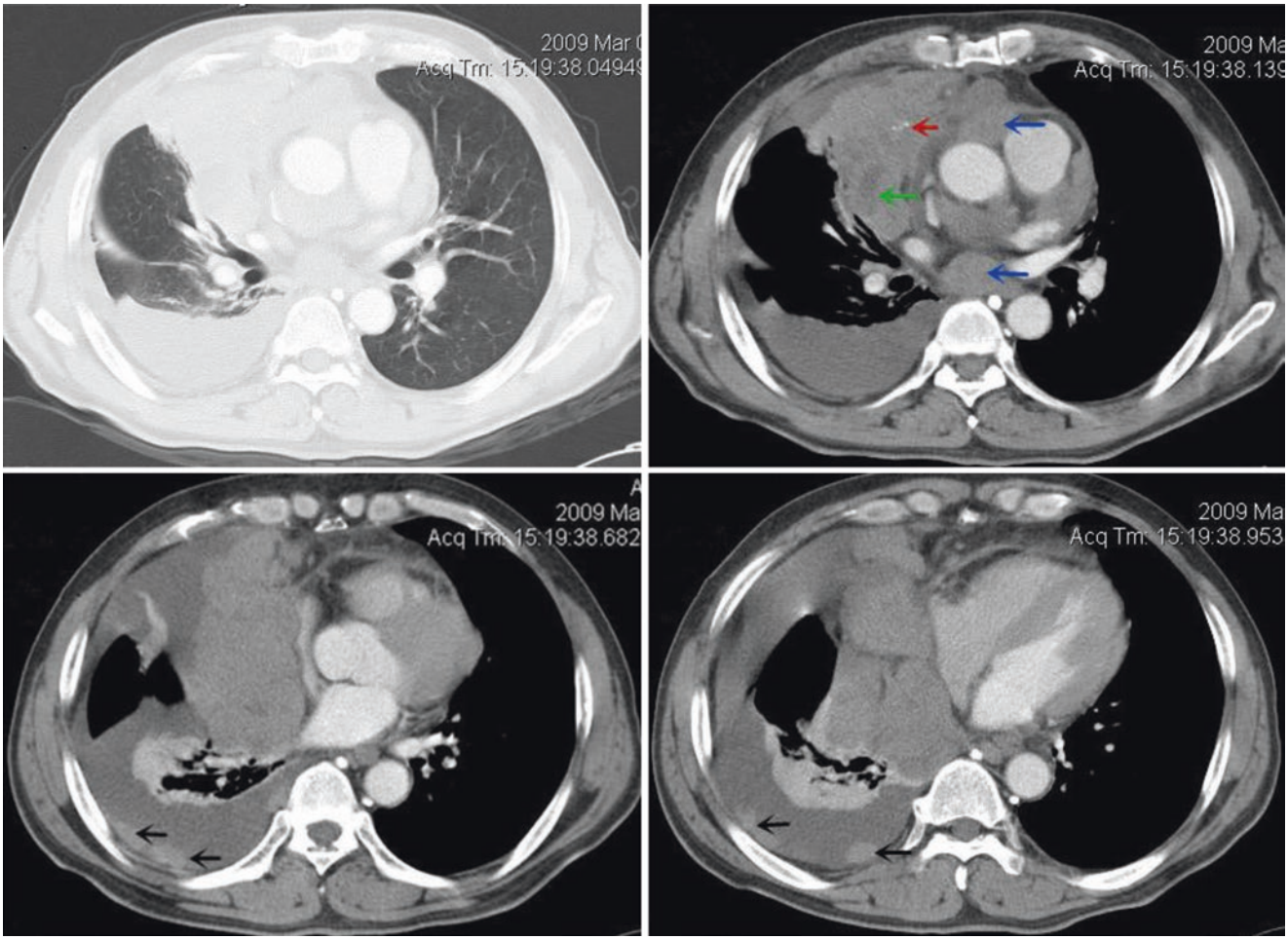

Fig. 3.44 Chest CT images of a 50-year-old man complained of cough and chest tightness for 4 months

rounding organs, about 60–90% of patients were staged as III or IV. Therefore, invasive B3 thymomas frequently require preoperative treatment in order to reduce tumor extension and increase resectability. Platinum-based regimens are used for first-line chemotherapy to treat these thymic epithelial tumors. Recently, there are reports on the expressions of various tumor-related genes that correlate with the chemosensitivity of several types of tumor and prognosis of affected patients. Type B3 thymomas complete resection was achieved in 92%. After surgery, 15–17% of B3 thymomas developed a local recurrence and 20% distant metastases. The 10-year survival rate was 50–70%, the 20-year survival was 36%. Among the other subtypes of thymoma, patients with type B3 thymoma have the worst prognosis. This finding may be due to the lower resectability of these patients' tumors compared to other types of patients. Furthermore, such low resectability is often associated with a high proportion of invasive tumors.

3.8.9 Case 9

A 78-year-old woman complained of cough for 5 months and left shoulder and back pain for half a month.

Chest CT: A mass with irregular contours and calcifications in the anterior mediastinum, locally invading sternum and pericardium (Fig. 3.46).

PET-CT: An irregular soft tissue mass measured 11.6 × 6.6 × 12.8 cm located in the left anterior mediastinum with abnormal radioactive concentration. The maximum SUV value was 8.6. The mass invaded the pericardium and surrounded the large blood vessels. The 2R and 4R areas in the mediastinum also showed enlarged lymph nodes with abnormal radioactive uptake, the maximum SUV value was 3.8 (Fig. 3.47).

[Diagnosis] Type B3 thymoma.

[Diagnosis basis] The patient underwent a biopsy of the anterior mediastinal tumor and the pathological diagnosis was type B3 thymoma.

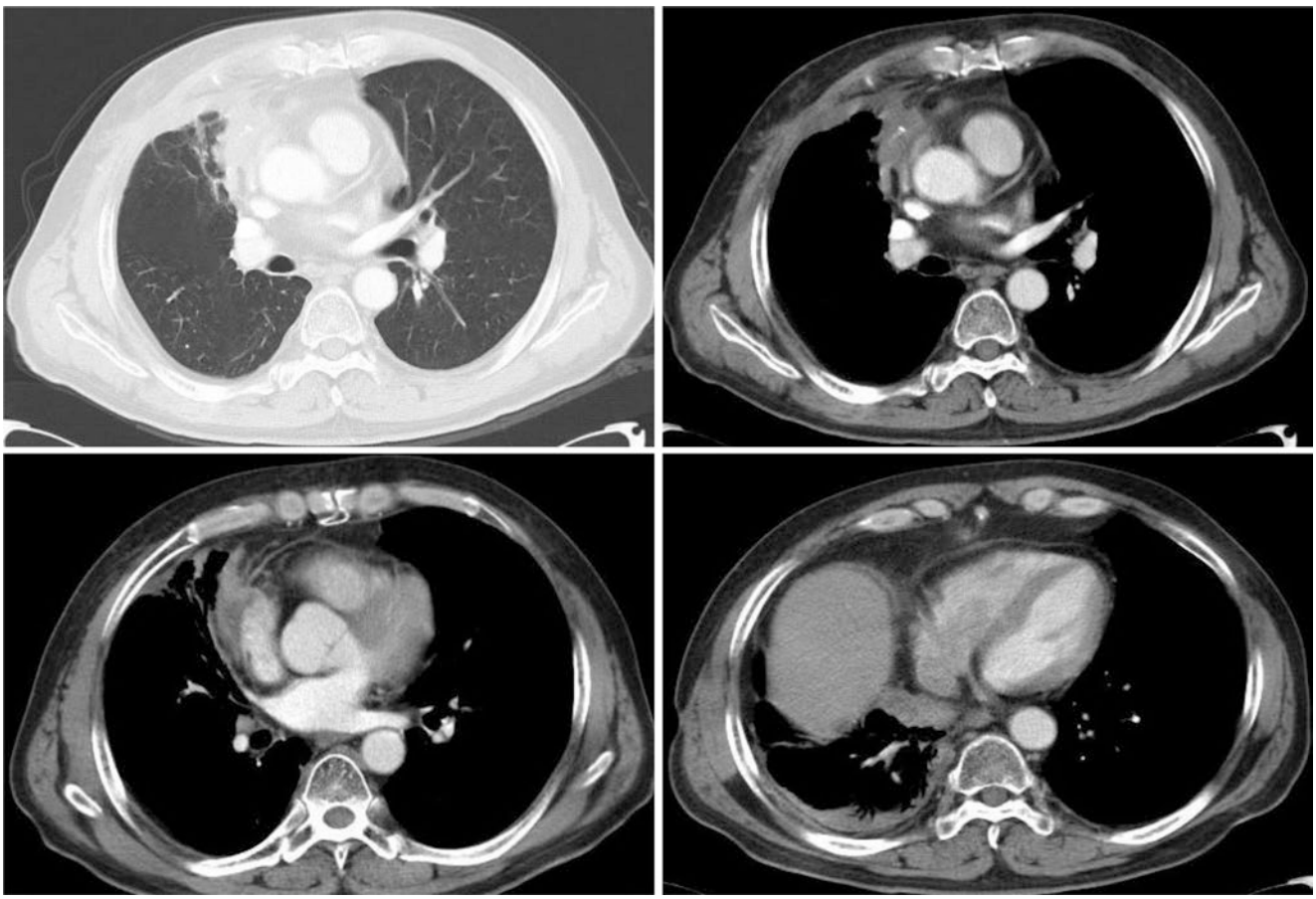

Fig. 3.45 After radiotherapy and chemotherapy, the lesion was absorbed

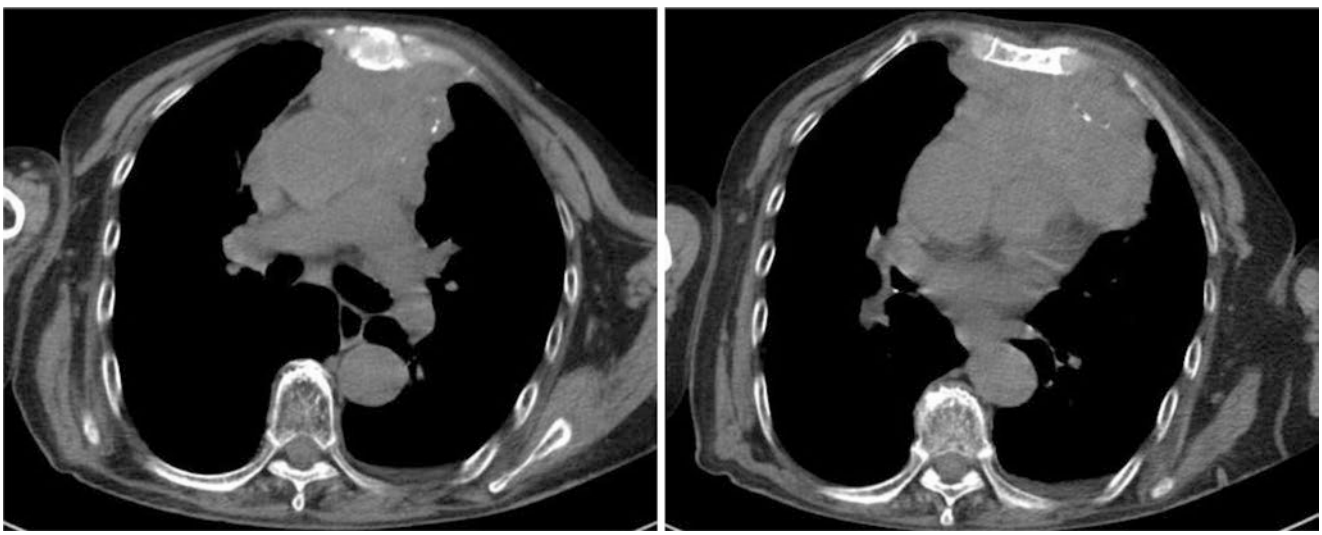

Fig. 3.46 Chest CT images of a 78-year-old woman complained of cough for 5 months and left shoulder and back pain for half a month

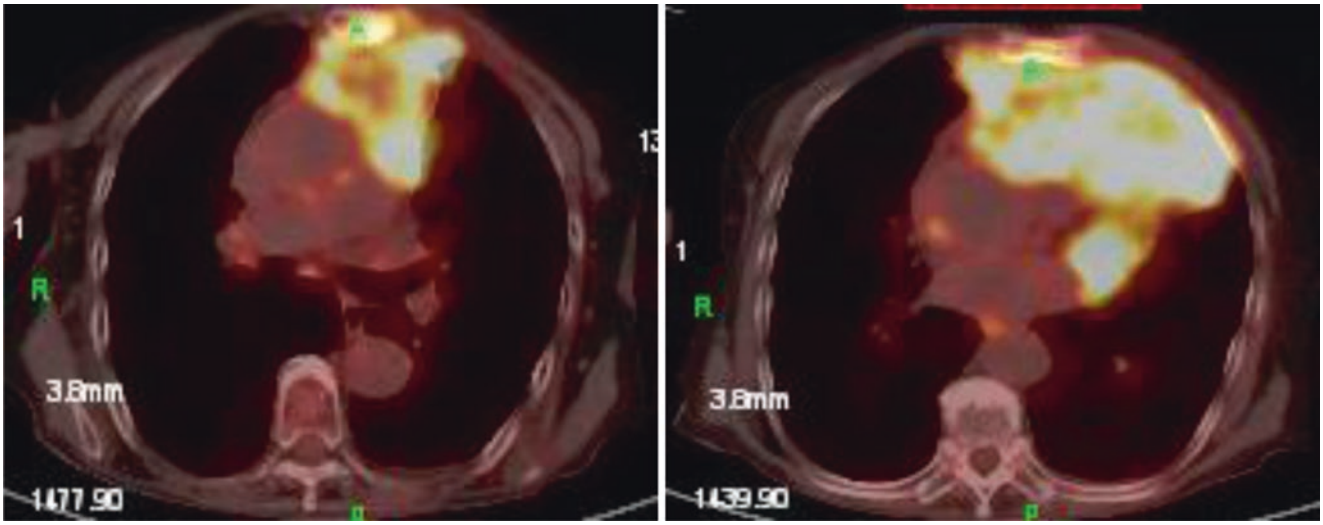

Fig. 3.47 PEC-CT shows an irregular soft tissue mass located in the left anterior mediastinum

[Analysis] The uptake of 18F-FDG on PET images is capable of indirectly predicting the aggressiveness of tumors by evaluating their biological activity, so it can provide information on tumor invasiveness, proliferative activity, and prognosis. 18F-FDG PET-CT also showed encouraging results in the characterization of thymic tumors. The uptake of 18F-FDG in thymus can be normal physiological uptake or can represent thymic hyperplasia, primary thymic tumors, lymphomatous involvement, or metastasis.

Liu et al. [15] firstly reported that thymomas have a high 18F-FDG uptake and suggested that 18F-FDG PET-CT is useful in the assessment of the invasiveness of thymomas, and may have the potential to differentiate thymomas from thymic hyperplasia. 18F-FDG PET-CT has shown promising results in distinguishing different histological subtypes and help in preoperative characterization of thymomas. The cellular uptake of 18F-FDG in thymic epithelial cells is mediated by glucose transporter (GLUT). Visual grading of uptake, SUVmax, uptake pattern, and contour of tumor on PET-CT can be used to distinguish histological subtypes. Sung et al. [16] studied 33 patients with thymic epithelial tumors, who underwent both integrated PET/CT and enhanced CT. 8 low-risk thymomas, 9 high-risk thymomas, and 16 thymic carcinomas can be considered as tumors. Clinicians found that the maximum SUVs of high- and low-risk thymomas are significantly lower than those of thymic carcinomas. Homogeneous 18F-FDG uptake within tumors was more frequently seen in thymic carcinomas than in high-risk thymomas or low-risk thymomas. Integrated PET/CT was found to be helpful for differentiating subgroups of thymic epithelial tumors, and staging the extent of the disease. On the contrary, Shibata et al. [17] reported that 18F-FDG PET-CT cannot differentiate among histopathological subtypes of thymoma. In addition, the SUV cut-offs shown in these studies show considerable overlap.

Toba et al. [18] reviewed thirty-three patients who underwent FDG-PET/CT before treatment. FDG uptake was often visually recognized in almost (100%) tumors. In the order of low- to high-risk thymomas to thymic carcinomas, a homogeneous pattern of FDG uptake was increasingly observed. SUVmax for thymic carcinomas was significantly higher than that for thymomas. In the differential diagnosis of thymic epithelial tumors, FDG uptake and SUVmax are very useful. Furthermore, the expressions of HIF-1α, Glut-1, and VEGF might be associated with malignancy of thymic epithelial tumors. In contrast, FDG uptake might be dependent on tumor size rather than Glut-1 overexpression.

Nakajo et al. [19] compared SUV-related and 6 texture parameters (entropy, homogeneity, dissimilarity, intensity variability, size-zone variability, and zone percentage) between 11 low-risk and 23 high-risk thymic epithelial tumors. Although the diagnostic performances of individual SUVmax and texture parameters were relatively low, combining these parameters can significantly increase diagnostic performance when differentiating between relatively large low- and high-risk 18F-FDG-avid thymic epithelial tumors.

Various factors may cause these differences. These factors include a smaller sample size, variation in acquisition/processing protocols, variability in tumor size along with factors that influence SUVmax (serum glucose, body weight, injection time, etc.). In spite of these variations, it is generally agreed that high-risk thymomas show higher 18F-FDG uptake (SUVmax) as compared to low-risk thymomas.

3.8.10 Case 10

A 59-year-old woman complained of palpitation and fatigue for 1 month. Her blood cell count showed severe anemia. She was diagnosed with pure red cell aplasia (PRCA) by bone marrow aspiration biopsy, which showed a marked decrease in the number of erythroblasts.

Chest CT: A solid tumor in the anterior mediastinum, protruded into the bilateral lung fields and separated on both sides (Fig. 3.48).

[Diagnosis] Type AB thymoma with PRCA.

[Diagnosis basis] A middle-aged woman has PRCA, so the anterior mediastinal lesion is likely to be thymoma. The patient was transfused with 8 units of packed red cells before surgery. She underwent extended thymothymectomy through median sternotomy. The tumor capsule was smooth, and the tumor and surrounding tissue were removed together (Fig. 3.49). The pathological diagnosis was type AB thymoma (Fig. 3.50).

[Analysis] The thymus plays an important role in immune function, mainly with T-cell development. After migrating to the thymic cortex from the bone marrow, T-cell progenitors undergo sequences of positive and negative selections ensuring their recognition of foreign antigens and tolerance of self-peptides. Neoplastic cells replace the normal epithelial cells in thymoma, and may disrupt T-cell maturation, and thus induct self-tolerance. This explains the great propensity of developing autoimmune disorders in thymoma, with the incidence reported being as high as 30%.

PRCA is defined as normocytic normochromic anemia, severe reticulocytopenia, a marked reduction or absence of erythroid precursors, and a normal granulopoietic or thrombopoietic system in the bone marrow. It has been demonstrated that PRCA etiology is based on several factors, including antibodies against marrow erythroid cells and erythropoietin. PRCA is classified as congenital and acquired. Acquired PRCA may be either a primary disorder or secondary to some other disorder or agent.

PRCA is the second most common paraneoplastic syndrome associated with thymoma. The first case of PRCA associated with thymoma was reported in 1930 by Polayes and Lederer. PRCA patients were associated with thymoma in approximately 20–50% of all cases, and approximately 2–5% of thymoma patients developed PRCA. The pathogen-

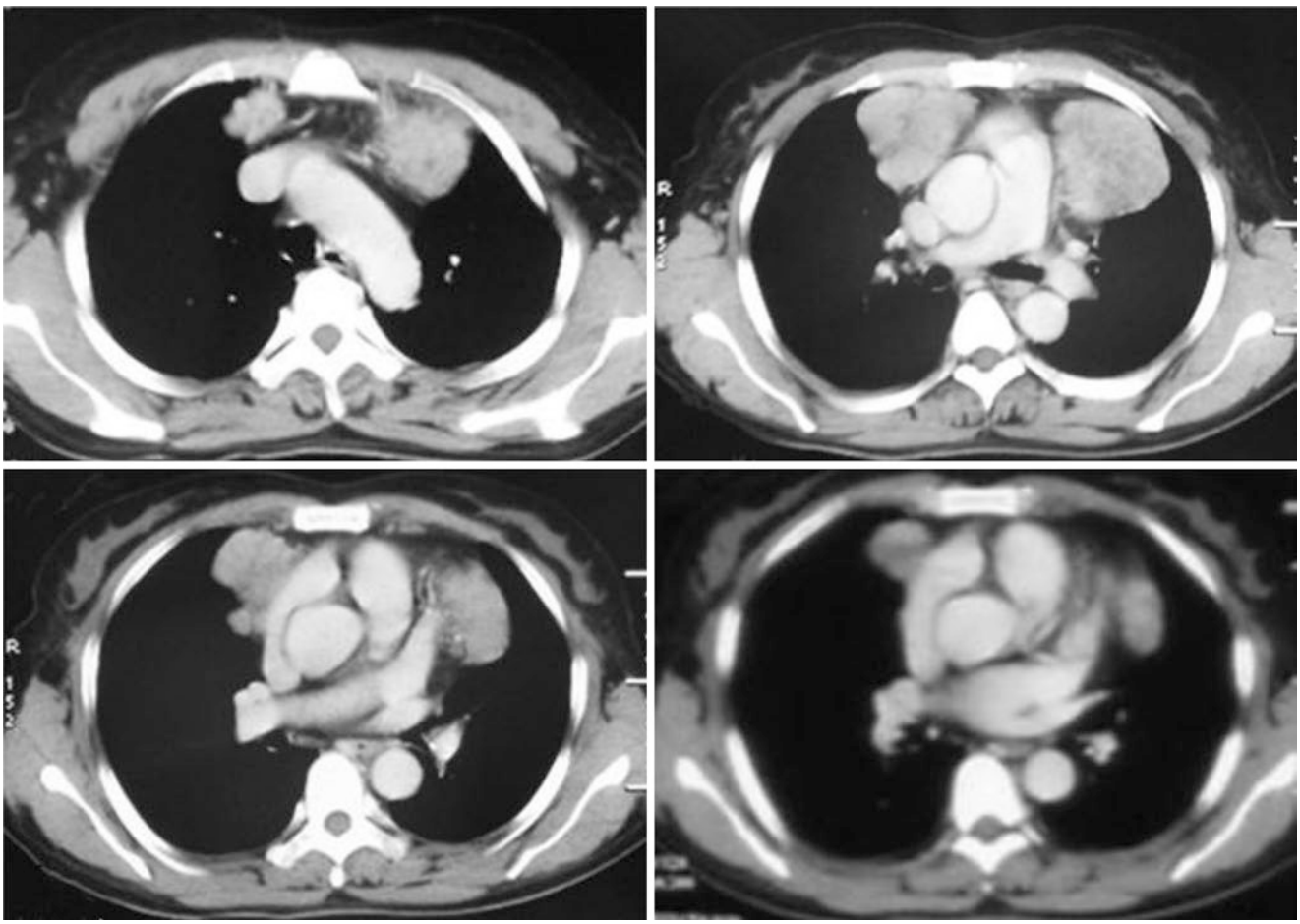

Fig. 3.48 Chest CT images of a 59-year-old woman complained of palpitation and fatigue for 1 month

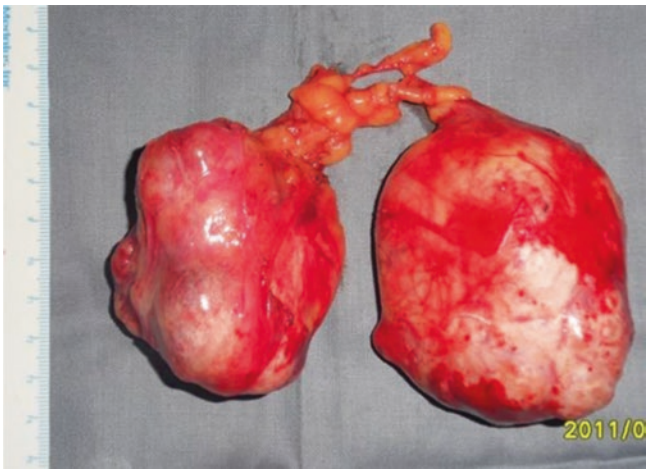

Fig. 3.49 Gross specimen

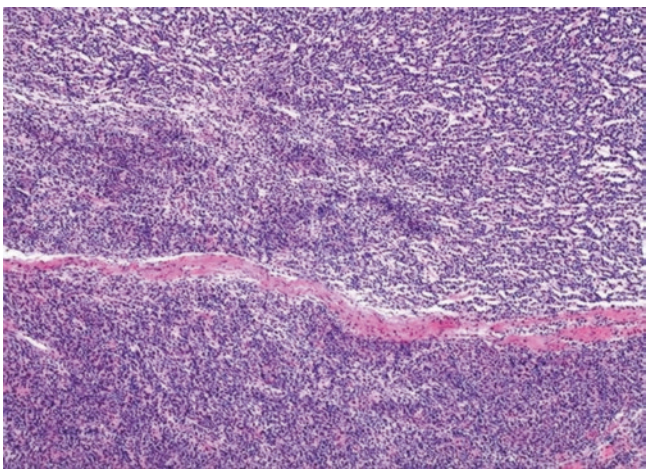

Fig. 3.50 Pathology of type AB thymoma

esis between acquired PRCA and thymoma is not well elucidated but might be a humoral immunity and T-cell clonal disorder. Bernard et al. [20] retrospectively analyzed 85 cases with thymoma and found that even if after thymectomy, there were 8% patients with autoimmune disease. Some authors thought that thymoma might enhance the sensitivity of the immune system and that immunological alteration of T or B cells could continue after thymectomy and possibly influence the maturation of erythroid cells in the bone marrow. Furthermore, autoreactive T cells produced by a thymoma were demonstrated to induce clinical autoimmune disease at a later time, even after resection of thymoma. Bernard et al. [20] found that the patients who presented with autoimmune disease after thymectomy tended to be younger than those who did not. However, gender and follow-up duration were significantly similar between the autoimmune disease group after thymectomy and the no autoimmune disease group after thymectomy, suggesting that pre-existing autoimmunity was not a risk factor for developing autoimmune manifestations after thymectomy.

Surgical resection of thymoma can treat thymoma-associated PRCA, but interestingly, a subset of patients develop thymoma-associated PRCA after thymectomy. Surgical resection of thymoma was demonstrated to be insufficient for normalization of erythropoiesis by Thompson and Steensma [21], but immunosuppressive therapy was effective as an adjuvant treatment. The therapeutic approach to PRCA typically includes immunosuppression, but specific pathogenic subtypes are associated with specific therapeutic approaches. With or without concurrent corticosteroids Cyclosporine A appears to be the single most effective immunosuppressive agent, compared with other therapeutic options like intravenous immunoglobulin, rituximab, alemtuzumab, and bortezomib. Without the removal of thymoma, immunosuppressive agents and glucocorticoids are ineffective for the treatment of PRCA.

3.8.11 Case 11

A 54-year-old man had a history of thymoma for more than 8 years and had undergone radiotherapy and chemotherapy. He was admitted to the hospital due to cough and sputum for more than 10 days and worsening with dyspnea for 4 days.

Chest CT: There were multiple soft tissue lesions in the anterior mediastinum, the pericardial area above the left and right atria, and the pericardial area outside the left ventricle; the two lungs are scattered with patches and ground glass shadows (Fig. 3.51).

[Diagnosis] Type B2 thymoma with Good syndrome.

[Diagnosis basis] A middle-aged male with thymoma relapse after 8 years of treatment, invading the pericardium, the diagnosis of type B2 thymoma is considered. His blood results revealed hypogammaglobulinemia: IgG (3.41 g/L, 7.00–16.00), IgA (0.32 g/L, 0.85–3.50), and IgM (0.18 g/L, 0.40–2.30). His CD4:CD8 ratio was also consistently low. A preliminary diagnosis was made as a Good syndrome in the setting of hypogammaglobulinemia and thymoma. The patient underwent puncture of pericardial tumor, confirmed as type B2 thymoma. Pulmonary infection considers pneumocystis pneumonia, confirmed by sputum smear and alveolar lavage.

[Analysis] Good syndrome (GS), which is classically defined as the triad of thymoma, immunodeficiency (absent peripheral B cells and T cell abnormalities), and hypogammaglobulinemia. This presentation pattern was first reported by Robert Good in 1954 [22]. Seven individuals who suffered from recurrent severe bacterial infections were identified by Good, who had both agammaglobulinemia and thymoma. It is hypothesized that the simultaneous occur-

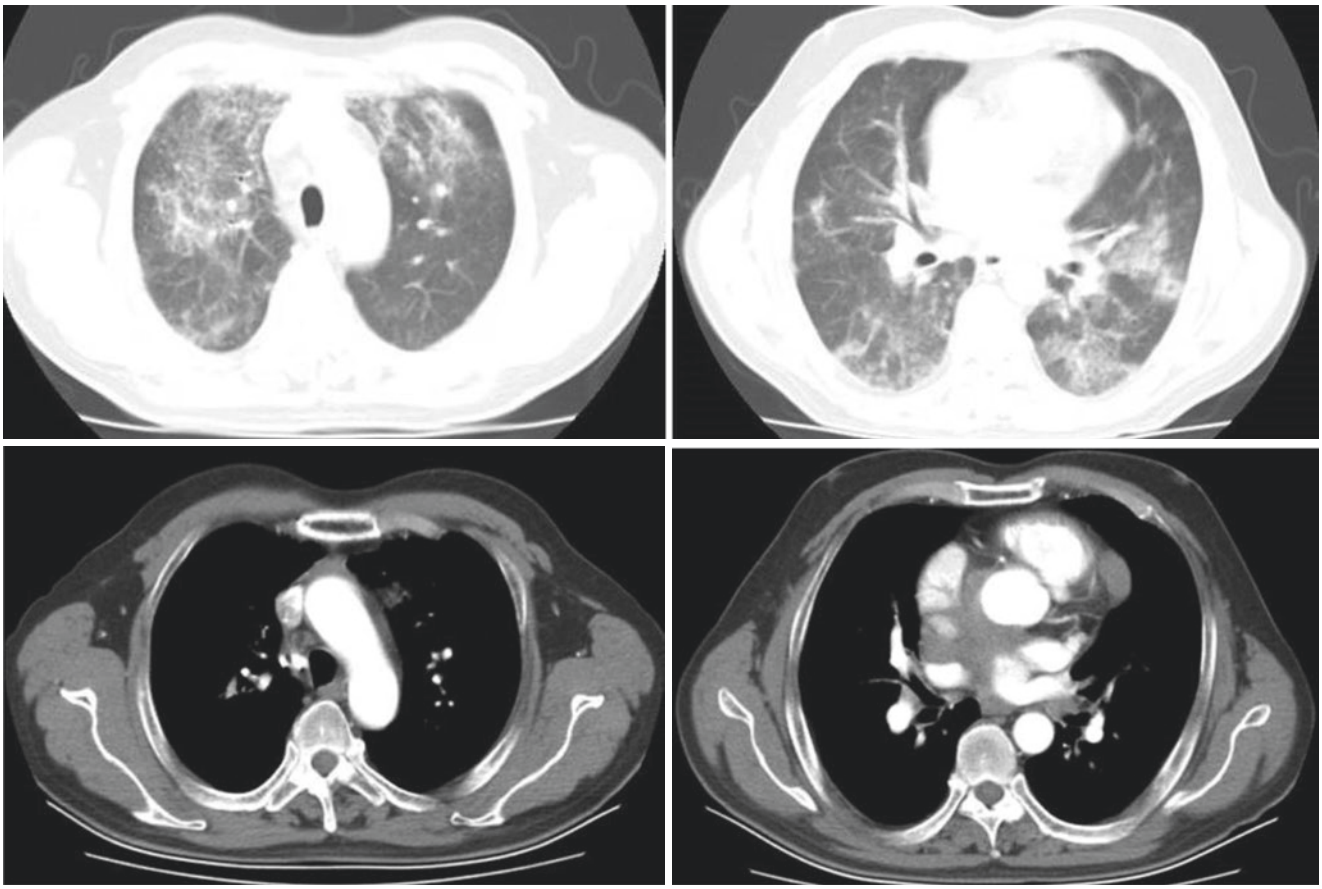

Fig. 3.51 Chest CT images of a 54-year-old man had a history of thymoma for more than 8 years

rence of thymoma and acquired agammaglobulinemia suggested that the thymus might play a role in immunological responsiveness including inhibition of antibody formation. Twenty adult patients who underwent thymectomy but did not experience hypogammaglobulinemia reversal were reported by Jeunet and Good in 1968 [23]. The simultaneous occurrence of two rare clinical conditions (hypogammaglobulinemia and thymoma) was later eponymously termed Good syndrome.

GS had previously been considered as a subset of common variable immunodeficiency (CVID). Later, it was reclassified as a separate entity (immunodeficiency with thymoma) by the International Union of Immunological Societies Scientific Committee in 1999. So far, there are no recognized diagnostic criteria.

GS fundamentally involves impairment in humoral immunity. B-lymphocyte deficiency can be seen in up to 87% of cases. However, the absence of peripheral blood B lymphocytes does not rule out the possibility that B lymphocytes could exist in lymphatic tissues, assuring some amount of immunoglobulin production, although it has been greatly reduced. In almost all patients, serum levels of IgG, IgA, and IgM were reduced, although there are reports of patients who have normal IgA or elevated IgM levels. Immunological features of GS include low peripheral B cells and hence hypogammaglobulinemia, CD4+ lymphopenia, and reversal of CD4: CD8 ratio. The proposed mechanisms of GS include a lack of interferon-like cytokines from thymic T cells to promote B cell growth and differentiation and impaired hemopoiesis from thymoma paraneoplastic phenomena. Patients with GS and thymoma may also have other associated autoimmune manifestations, which pure red cell aplasia and myasthenia gravis are most prominently.

GS is typically an adult onset of immunodeficiency, usually in the fourth or fifth decade of life. Patients with GS have an exceptional immunocompromised state with universal and variable impact of humoral and cell-mediated immunity, respectively. Therefore, the types of opportunistic infections faced are similar to those occurring in patients with CVID, X-linked agammaglobulinemia (XLA), and AIDS. Patients are susceptible to bacterial, viral, fungal, and opportunistic infections due to both humoral and cell-mediated immune deficiency. Patients with GS may present with recurrent pulmonary infections. However, their CD4 lymphopenia can also lead to opportunistic infections. Notably, opportunistic infections in GS are different from

patients with HIV in several ways: (1) compared with HIV, their CD4 counts are much higher (Cytomegalovirus retinitis is documented in patients with HIV with CD4 counts <50, but occurs in patients with GS at CD4 counts >300), (2) the most common opportunistic infections are Cytomegalovirus retinitis and colitis, and mucocutaneous candidiasis, and (3) there have been few documented cases of cryptococcus or systemic fungal infections, and toxoplasmosis and disseminated tuberculosis are rare in patients with GS. Chronic diarrhea is a common complication of GS patients, and its pathogenesis remains unclear. Gastrointestinal disorders could be due to pathogens such as *Giardia intestinalis*, *Salmonella* spp., *Campylobacter jejuni*, or Cytomegalovirus, bacterial overgrowth, or due to immune-mediated colitis, malabsorption, or villous atrophy. However, the cause of diarrhea remains unclear in most GS cases.

Retrospective case series suggest that GS has survival rates of 82% at 5 years and 68% at 10 years with a median survival of 14 years. For patients with viable negative margins, thymectomy is recommended. However, the immunologic abnormalities leading to immunodeficiency cannot be corrected after thymectomy. Treatment of the immunodeficiency includes immunoglobulin replacement, targeted antimicrobial prophylaxis, and appropriate vaccination with avoidance of live vaccines. The treatment of infection generally focuses on targeted antimicrobial therapy. In the case of recurrent pulmonary infections associated with hypogammaglobulinemia, intravenous immunoglobulin (IVIg) may be an effective prophylactic measure. IVIg has also been used to enhance the immune response in the case of Cytomegalovirus infection. Although the mechanistic explanation for this benefit is still unclear, it can also be effective in treating anti-acetylcholine receptor-associated myasthenia gravis. In some cases, such as patients with pneumocystis pneumonia, secondary prophylaxis could be considered.

3.8.12 Case 12

A 34-year-old woman complained of chest pain for more than 4 months.

Chest CT: Oval soft tissue mass adjacent to the left pericardium, and lesions in the left upper lobe, lower lobe, and right middle lobe were seen (Fig. 3.52).

[Diagnosis] Thymoma with lung adenocarcinoma.

[**Diagnosis basis**] Intraoperatively, the mediastinal tumor was type B2 thymoma, which invaded the lung tissue; the ground glass lesion of the lower lobe of the left lung was adenocarcinoma in situ, and the remaining lesions were well-differentiated adenocarcinoma. No lymph node metastasis was found in the 10 groups of lymph node areas.

[Analysis] Various tissue types and stages of thymoma can metastasize, mostly local infiltration or intrathoracic metastasis. Thymoma can still increase the risk of malignant tumors outside the thymus. Multiple studies have shown that about 17–28% of thymoma patients can develop a second primary malignant tumor at the same time or later, the cause may be related to genetic susceptibility and immune disorders. The risk of developing non-Hodgkin's lymphoma 5–9 years after diagnosis of thymoma is as high as 7.1 times. In addition, patients with thymoma and myasthenia gravis are prone to extra-thymic malignancies. The most common second primary malignant tumor is lung cancer (Fig. 3.53). As the incidence of lung cancer has increased in recent years, the probability of thymoma with lung cancer may also increase. Other common tumors include thyroid cancer, gastrointestinal cancer, prostate cancer, and lymphoma. Brain tumor, sarcoma, and leukemia are relatively rare.

3.8.13 Case 13

An 18-year-old man's physical examination revealed mediastinal mass.

Chest CT: A well-circumscribed homogeneous minimally enhancing anterior mediastinal mass with fat attenuation (blue arrow) (Fig. 3.54).

[Diagnosis] Lipofibroadenoma of the thymus.

[**Diagnosis basis**] The patient performed a thymothymectomy via a median sternotomy. The histopathological diagnosis was a lipofibroadenoma of the thymus.

[Analysis] Lipofibroadenoma is an unusual thymic tumor resembling fibroadenoma of the breast. It is categorized under "rare thymomas" in the WHO classification composed of thymic elements, mature adipose tissue, and fibrosis. It accounts for 6–17% of all thymomas occurring predominantly in the age group of 40–50 years. It is commonly associated with myasthenia gravis. However, its association with hypogammaglobulinemia and pure red cell aplasia is rare.

Lipofibroadenoma commonly appears in the anterosuperior mediastinum. However, it has also been described in the neck, pleura, or lung. Patients usually have localized symptoms such as cough, dyspnea, and pain. It usually appears radiographically as a smooth-edged lesion.

Pathology is still the gold standard for the diagnosis of lipofibroadenoma, and the classic histological features are that thymic epithelial cells which are arranged as crack structure under the background of fibrous tissue. Lymphocytes are infiltrated in the crack and fat cells are distributed as individuals or groups. In rare cases, thymic corpuscle could be found. Epithelial cells are positive for AE1/AE3, CK19 and the lymphocytes are immunostained with CD3 and CD20, which were used to make the diagnosis of lipofibroadenoma.

The differential diagnosis includes thymolipoma, sclerosing thymoma, and fibroadenoma. Like lipofibroadenomas,

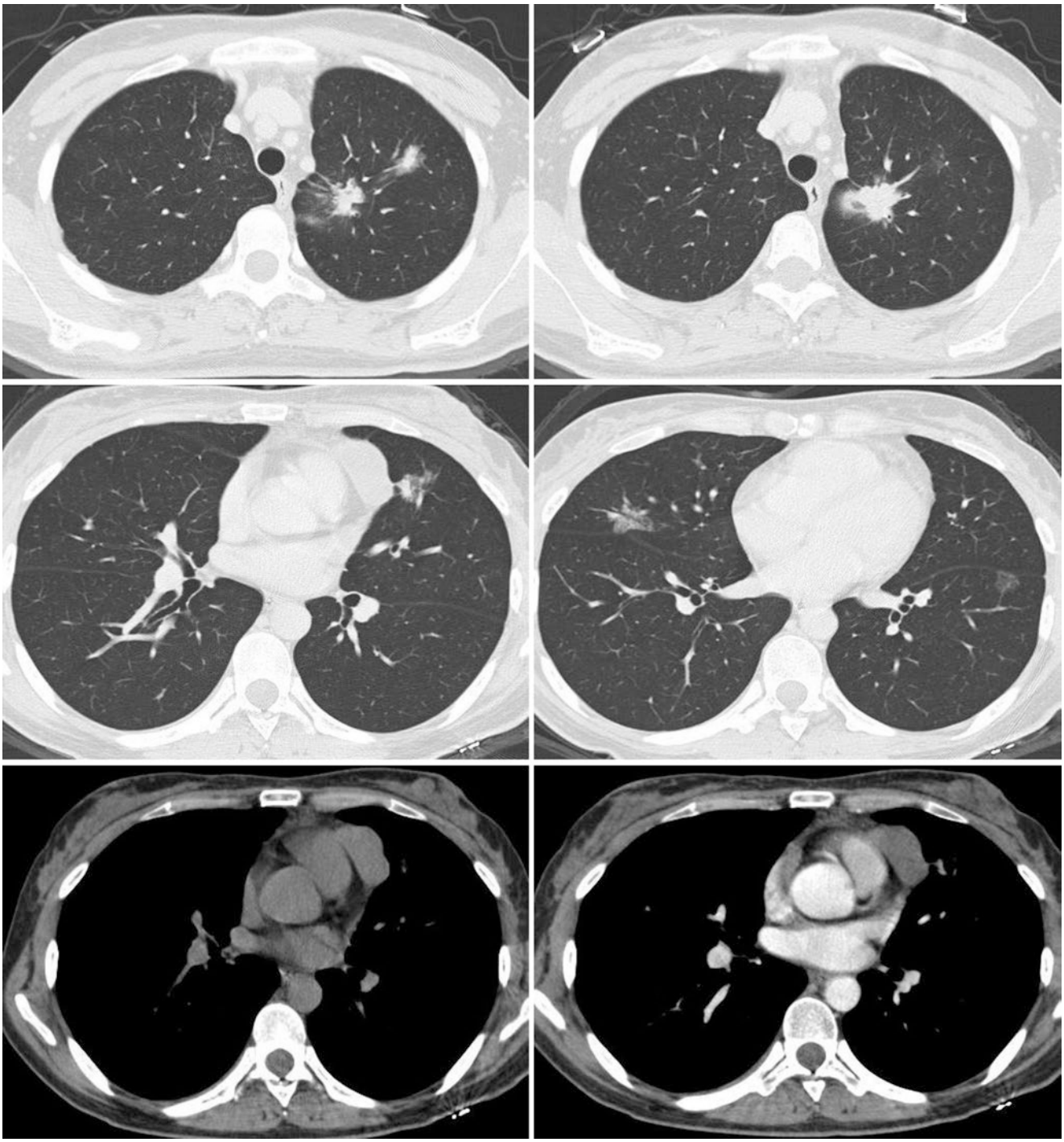

Fig. 3.52 Chest CT images of a 34-year-old woman complained of chest pain for more than 4 months

thymolipomas are also known to be associated with myasthenia gravis. However, thymolipomas are characterized by predominance of adipose tissue and lack fibrous tissue component. The sclerosing thymomas are differentiated from lipofibroadenomas by the presence of large islands of polygonal cells in a dense collagenous stroma without intermixed adipose tissue. Intraductal type fibroadenoma composed of interstitial and epithelial components. Epithelial cells are arranged as crack under the fibrous element, and the lack of fat cells and thymic components may be helpful in the distinguishing diagnosis.

Thymectomy is the treatment of choice. It rarely invades the pleura, pericardium, great vessels, or adjacent organs and has a recurrence rate of <10%. The 10-year survival rate is

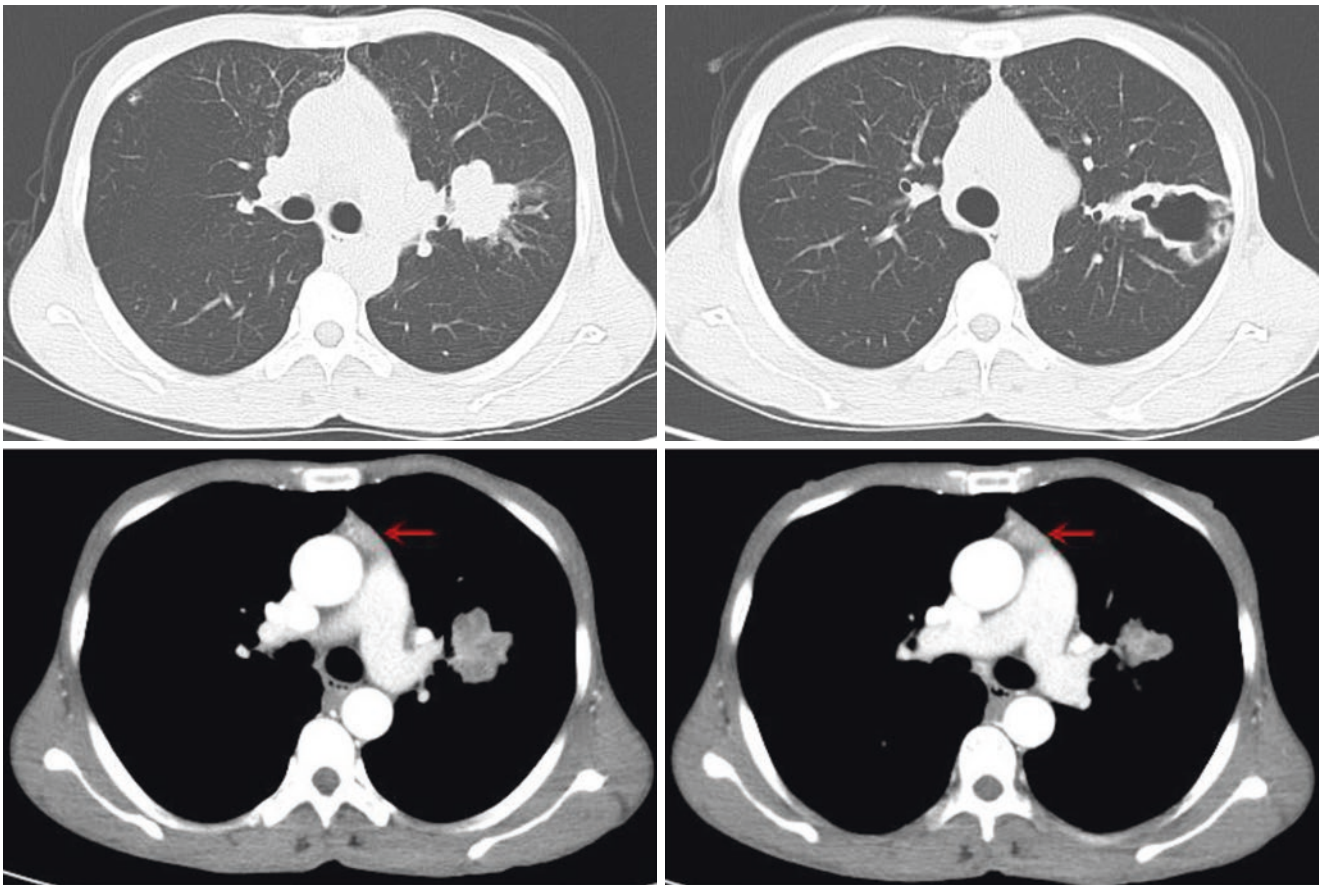

Fig. 3.53 Type B1 thymoma (red arrow) with poorly differentiated squamous cell carcinoma in a 52-year-old woman

higher than 90% for stage I or II. The striking morphology and immunohistochemical features of this entity have been highlighted in this article in view of its rarity and classic histomorphology.

3.8.14 Case 14

A 42-year-old man found a mediastinum mass for 20 days.

Chest CT: An anterior mediastinal mass with regular margin, mild enhancement, and cystic component (Fig. 3.55).

[Diagnosis] Metaplastic thymoma.

[Diagnosis basis] The patient underwent surgical treatment. Intraoperatively, the tumor was about 10 × 8 × 8 cm in size, the capsule is intact and adheres to the lungs, and the tumor wall has no boundary with the pericardium. Fine needle puncture, a part of the chocolate sac fluid was drawn. The pericardium was the tumor wall, and the tumor was completely removed. The cut surfaces of the mass revealed cystic change and hemorrhage of central parts surrounded by tan-gray, slightly elastic solid areas. The pathology showed that the capsule was intact, no tumor invasion was observed. The tumor had the characteristics of biphasic differentiation. The epithelial cell and the spindle cell are staggered. The epithelial cells are arranged in islands or in the shape of anastomosis. The spindle-shaped cells arranged in a bundle, with a small amount of collagen fibers interspersed, and small blood vessels dilated and congested. The pathology is consistent with metaplastic thymoma. Immunohistochemistry demonstrated positivity for CK (epithelial cells), Vimentin (spindle cells), CD3 (scattered lymphocytes), and CD5 (scattered lymphocytes), and negativity for CD117, Syn, CgA, CD1a, CD56, D2-40, and TdT-T. The staining index for Ki-67 was 1%.

[Analysis] Metaplastic thymoma is a rare biphasic tumor of the thymus typically found incidentally as a rounded anterior mediastinal mass in asymptomatic patients, or in association with thymic cysts.

Suster et al. [24] firstly reported a case of metaplastic thymoma, and they referred to it as a thymoma with pseudosarcomatous stroma. They concluded that the spindle cells were not neoplastic in nature but were actually reactive fibroblasts/myofibroblasts. However, 5 cases of low-grade metaplastic carcinoma were reported by Yoneda et al. [25] and they considered both the epithelial and the spindle-cell components to be neoplastic. It is speculated that these tumors repre-

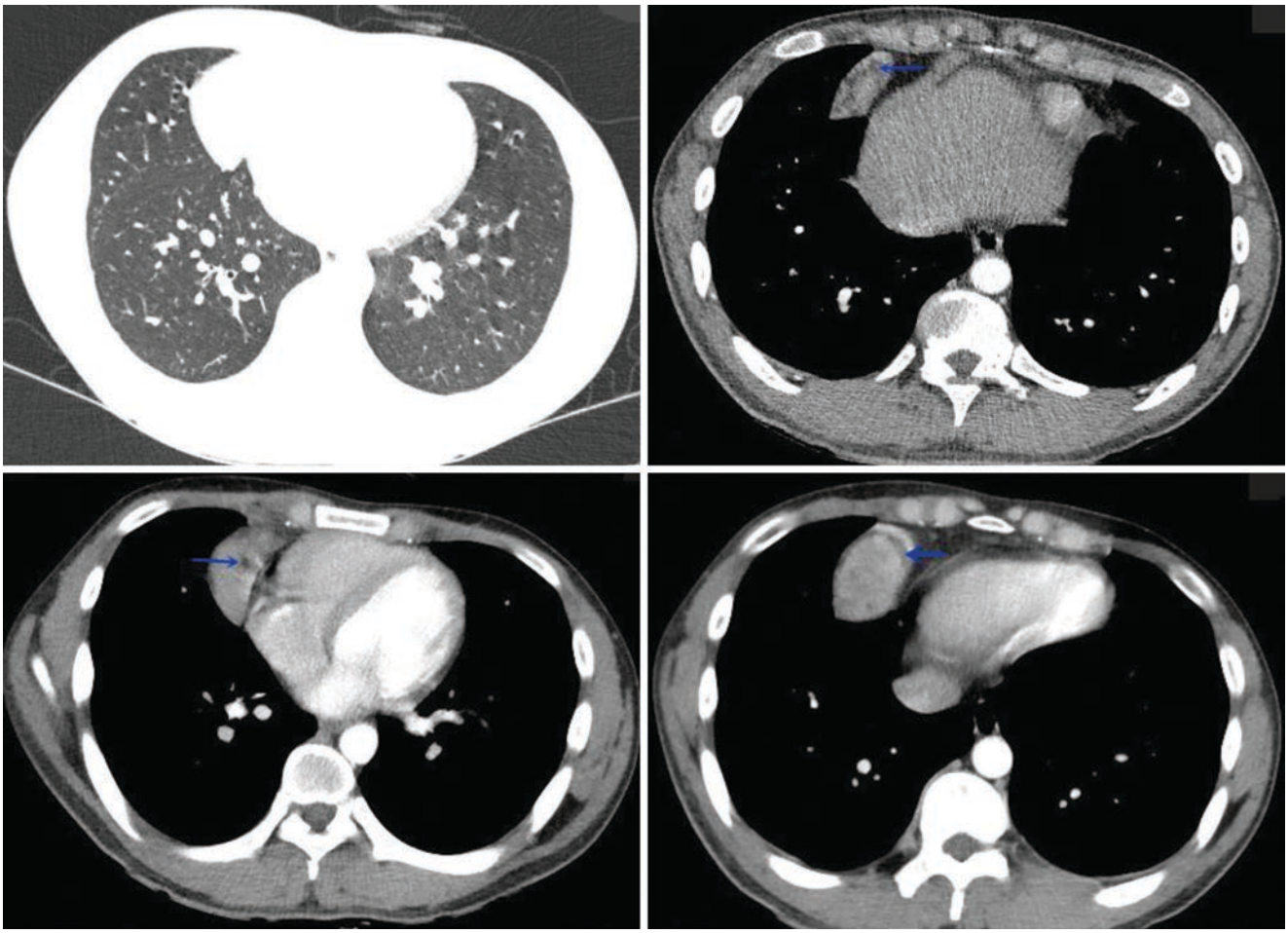

Fig. 3.54 Chest CT images of an 18-year-old man's physical examination revealed mediastinal mass

sented a low-grade malignancy that should be distinguished from more aggressive sarcomatoid carcinomas because the clinical course was indolent, and the spindle cells were bland compared with those of sarcomatoid carcinomas. The term metaplastic thymoma was adopted in the WHO classification of thymic tumors subsequent to 2004. This metaplastic phenomenon is also called as epithelial–mesenchymal transition (EMT). EMT is an essential lose epithelial characteristics and polarity and acquires mesenchymal (spindle) morphologic features with cytoskeletal reorganization. The transdifferentiated spindle components always show the loss of cytokeratin and E-cadherin expression and upregulate expression of mesenchymal markers (vimentin). Vivero et al. [26] reported metaplastic thymoma characterized by *YAP1-MAML2* fusion and lacking the *GTF2I* mutations found in Type A and AB thymomas.

Histologically, metaplastic thymoma is well-demarcated or encapsulated, lacking the lobulation and fibrous bands of conventional thymomas and displaying a distinctive dual population of keratin-positive epithelioid cells in an anastomosing nested pattern and a variably cellular keratin-negative spindle cell component. The ratio of epithelioid and spindle cells varies between tumors. Some authors proposed that the spindle cells represent a reactive stromal component based on their ultrastructural features, while others believed that both components are neoplastic based on their immunohistochemical and histologic features. Metaplastic thymoma pursues a benign clinical process and there are very few reports of recurrence or malignant transformation.

Despite typical morphologic features, metaplastic thymoma should be distinguished from highly malignant and typically benign spindle cell tumors of the thymus. Thymic carcinosarcoma or sarcomatoid carcinoma usually presents with high-grade spindle cell components, showing obvious atypia, readily identified mitotic figures and prominent coagulative necrosis, and aggressive clinical behavior. Owing to its low-grade appearance of spindle cell component, metaplastic thymoma can easily be distinguished from thymic carcinosarcoma and sarcomatoid carcinoma. The other differential diagnosis is type A and/or AB thymoma. If the spindle cell component is predominant in metaplastic thymoma, it is difficult to distinguish. However, some of the

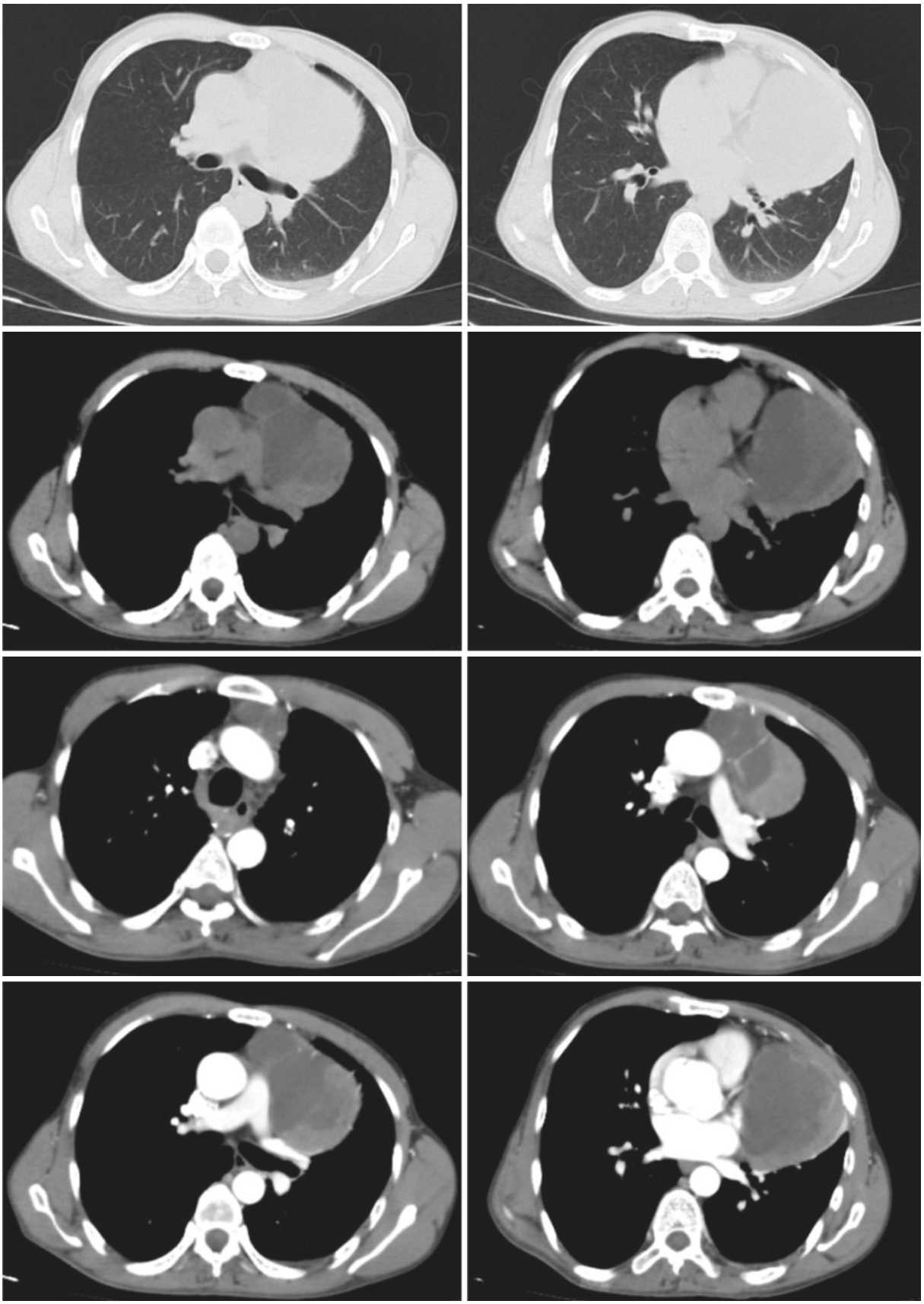

Fig. 3.55 Chest CT images of a 42-year-old man found a mediastinum mass for 20 days

features such as lack of connection with myasthenia gravis, tumor lobulation and perivascular spaces, inability to harbor immature lymphocytes, and loss of E-cadherin expression in spindle cell components could be helpful to diagnose metaplasia Thymoma. The majority of metaplastic thymomas previously reported showed a benign clinic course; however, a patient in whom local recurrence developed at 14 months and who died within 6 years was described by Yoneda et al. [25].

3.8.15 Case 15

A 68-year-old man complained of cough and depression for 4 months.

Chest CT: A heterogeneously enhancing mass occupied the left posterior mediastinum with irregular contours and necrosis (Fig. 3.56).

[Diagnosis] Thymic squamous cell carcinoma.

[Diagnosis basis] This case is mainly the identification of lymphoma and thymic epithelial tumor. The patient is older and the mass grows laterally, which is helpful for the diagnosis of thymic epithelial tumors. This case has an irregular or lobulated shape, and obvious necrosis within the lesion, supporting the diagnosis of thymic carcinoma. The patient underwent thymic tumor resection. Postoperative pathology showed poorly differentiated cancer, with obvious atypical tumor cells and polymorphic nuclei. Combined with immunohistochemistry, it is consistent with squamous cell carcinoma.

[Analysis] Thymic carcinoma accounts for less than 10% of thymic tumors, which is defined as a tumor exhibiting clear-cut cytologic atypia and a set of cytoarchitectural features no longer specific to the thymus and are similar to other organ carcinomas. Immature T lymphocytes were lacked; the lymphocytes present are usually mature T or B lymphocytes and are mixed with plasma cells. A variety of histologic types are recognized, most having their counterpart in identical tumors arising from other organs, including squamous cell carcinoma, basaloid carcinoma, mucoepidermoid carcinoma, lymphoepithelioma-like carcinoma, clear cell carcinoma, sarcomatoid carcinoma, adenocarcinoma, NUT carcinoma, and undifferentiated carcinoma. The most common subtype in Western countries is the poorly differentiated, non-keratinizing squamous cell carcinoma.

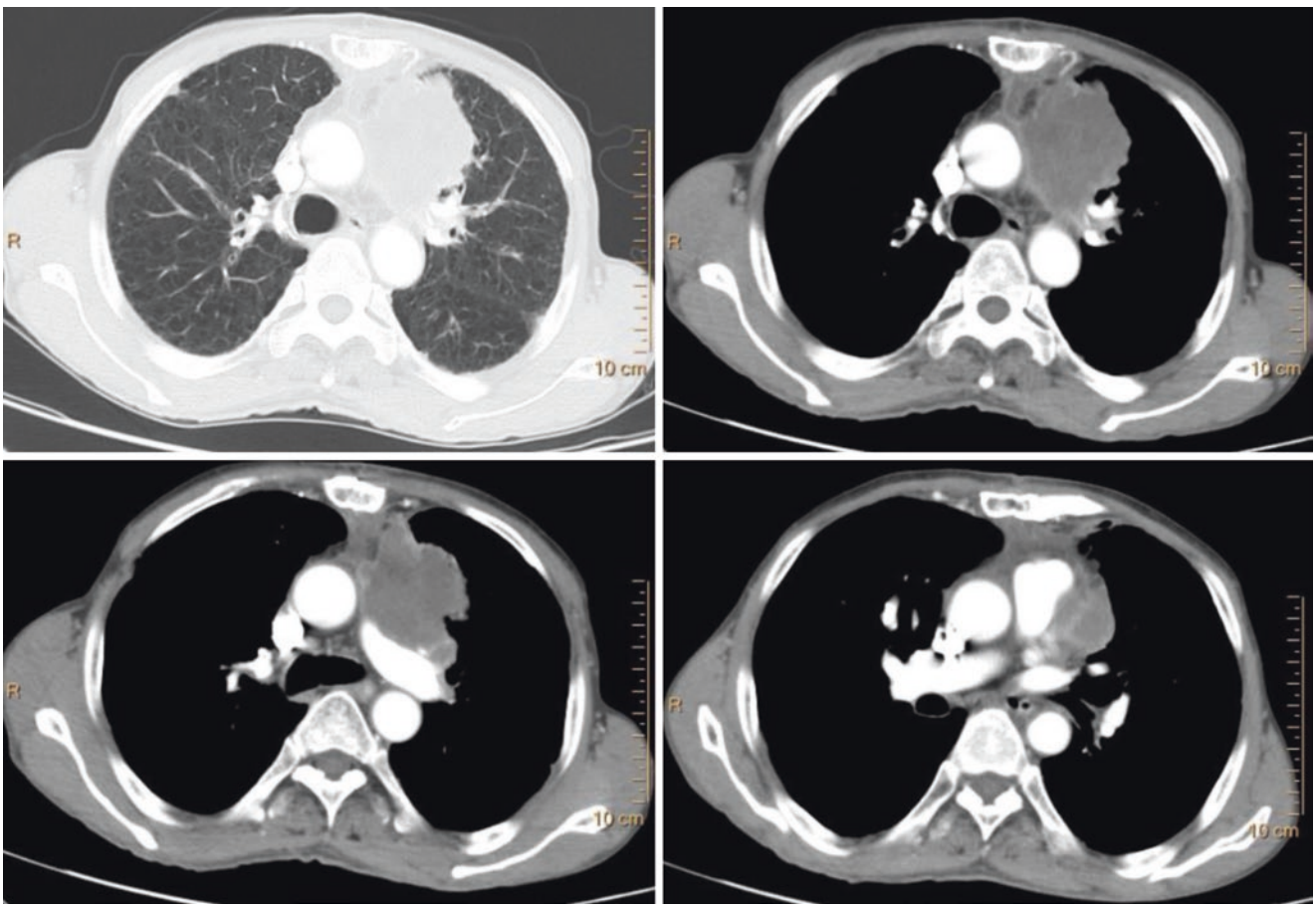

Fig. 3.56 Chest CT images of a 68-year-old man complained of cough and depression for 4 months

It has been proved that many immunohistochemical markers can be used for the diagnosis of thymic carcinoma. Detection of CD5 in the tumor cells suggests a squamous thymic carcinoma. Certain proteins of GLUT-1, CA-IX, c-KIT, MUC-1, CEA, and CK18 may stain positive for thymic carcinoma. Some thymic carcinomas overexpress CD117, which is the product of c-KIT. Of note, only a small proportion has c-KIT mutations. Interestingly, p53 protein accumulation is common in thymic carcinomas, whereas uncommon gene mutation is noticed. In multivariate analysis, IGF-1R expression was amplified in thymic carcinoma, which proved to be an independent factor of poor prognosis. Chromosomal abnormalities have also been observed in thymic carcinoma. In patients with thymic carcinoma, trisomy 8, del (16), t(1;16), loss of chromosome 16q, 6, 3p, 17p, gain of 1q, 17q, and 18,t(15;19) have been reported. In addition, it has been observed that p16INK4 promoter methylation prevents RB phosphorylation.

The symptoms caused by thymic carcinoma owe to pressure effect of the mass to surrounding mediastinal tissues. These symptoms include chest pain, cough, shortness of breath, dysphagia, hoarseness of voice, superior vena cava syndrome, and phrenic nerve palsy. Because of its anatomical location in the anterior mediastinum, thymic carcinoma may be locally invasive and cause pericardial and pleural effusion. Extrathoracic disease presents in only a minority of patients, such as lymph node invasion, liver, kidney, bone, or thyroid metastases. Interestingly, thymic carcinoma is not associated with paraneoplastic phenomena, such as myasthenia gravis, which is common in thymoma.

In general, thymic carcinomas show the same histological features as analogous extra-thymic carcinomas. However, it may be difficult to distinguish B3 thymoma from thymic squamous cell carcinoma in a small percentage of cases. B3 thymomas typically show lobular growth, obvious perivascular spaces, minor/moderate nuclear atypia, lack of intercellular bridges, the presence of TdT+ immature T cells, and lack of expression of CD5, CD117, GLUT1, and MUC1 in neoplastic epithelial cells. The identification of thymic carcinoma and lung squamous cell carcinoma also needs to be combined with immunolabeling. In addition to the commonly used keratin, thymoma is mostly p63 and PAX8 positive. The paired-domain transcription factor PAX8 is diffuse and moderately expressed in thymoma. FOXN1 and CD205 are almost all positive for thymoma, and 68–76% and 10–59% are positive for thymic carcinoma. Because these antibodies are almost negative in squamous cell carcinomas of non-thymic origin, they are of diagnostic value in identifying tumors of thymic origin.

3.8.16 Case 16

A 59-year-old man was found to have enlarged left cervical lymph nodes for 12 days.

Chest CT: A heterogeneously enhancing mass occupied the left posterior mediastinum; multiple enlarged lymph nodes were seen in mediastinum, bilateral hilum, and bilateral clavicle area; the left diaphragm was elevated (Fig. 3.57).

PET-CT: There was a large soft tissue mass in the thymus area, and the radioactive uptake was increased. The maximum SUV was about 8.8. Multiple enlarged lymph nodes increased radioactive uptake, the maximum SUV was about 9.2 (located on the left clavicle). The left diaphragm was elevated, and part of the lung tissue in the lower lobe of the left lung was compressed and consolidated (Fig. 3.58).

[Diagnosis] Thymic cancer with lymph nodes metastases.

[Diagnosis basis] A middle-aged male has lateral occupancy of the thymus, with hilar, mediastinum, bilateral supraclavicular areas, and neck lymph node enlargement and high PET-CT uptake, suggesting thymic epithelial tumor with lymph nodes metastases. The patient's left diaphragm is elevated, suggesting phrenic nerve paralysis, which is considered to be caused by tumor involvement. The normal phrenic nerve runs at the junction of the mediastinum and the lungs. Therefore, thymic tumors growing laterally can easily compress or invade the phrenic nerve, causing paralysis of the phrenic nerve. So this case first considers thymic carcinoma with lymph nodes metastases. The patient underwent a biopsy of the left supraclavicular lymph node. Pathology suggests squamous cell carcinoma.

[Analysis] Thymic carcinoma is the rarest malignancy accounting for only 5% of all thymic neoplasms and 15–20% of thymic epithelial tumors. Squamous cell carcinoma is the most common subtype of thymic carcinoma and accounts for 61.8%. Thymic carcinoma commonly appears in the fifth decade of life and has a very poor prognosis. Most patients with thymic carcinoma present with locally advanced or metastatic disease, which confers a median overall survival of 2 years.

In computed tomography, thymic carcinoma usually occurs as a large mass in the anterior mediastinum with irregular borders, lobular margins, and areas of low attenuation because of necrosis, cyst formation, and hemorrhage (Fig. 3.59). Thymic carcinoma can grow laterally, with common central or basic central growth (Fig. 3.60). Mediastinal fat and great vessel invasion (Fig. 3.61), mediastinal adenopathy, pleural and pericardial effusions may also be visualized (Fig. 3.62). Pleural implants are rare (Fig. 3.63). Elevated diaphragm muscles suggest phrenic nerve palsy, and highly suggest a diagnosis of thymic carcinoma (Fig. 3.64). PET-CT shows high metabolic uptake (Fig. 3.65). In patients who

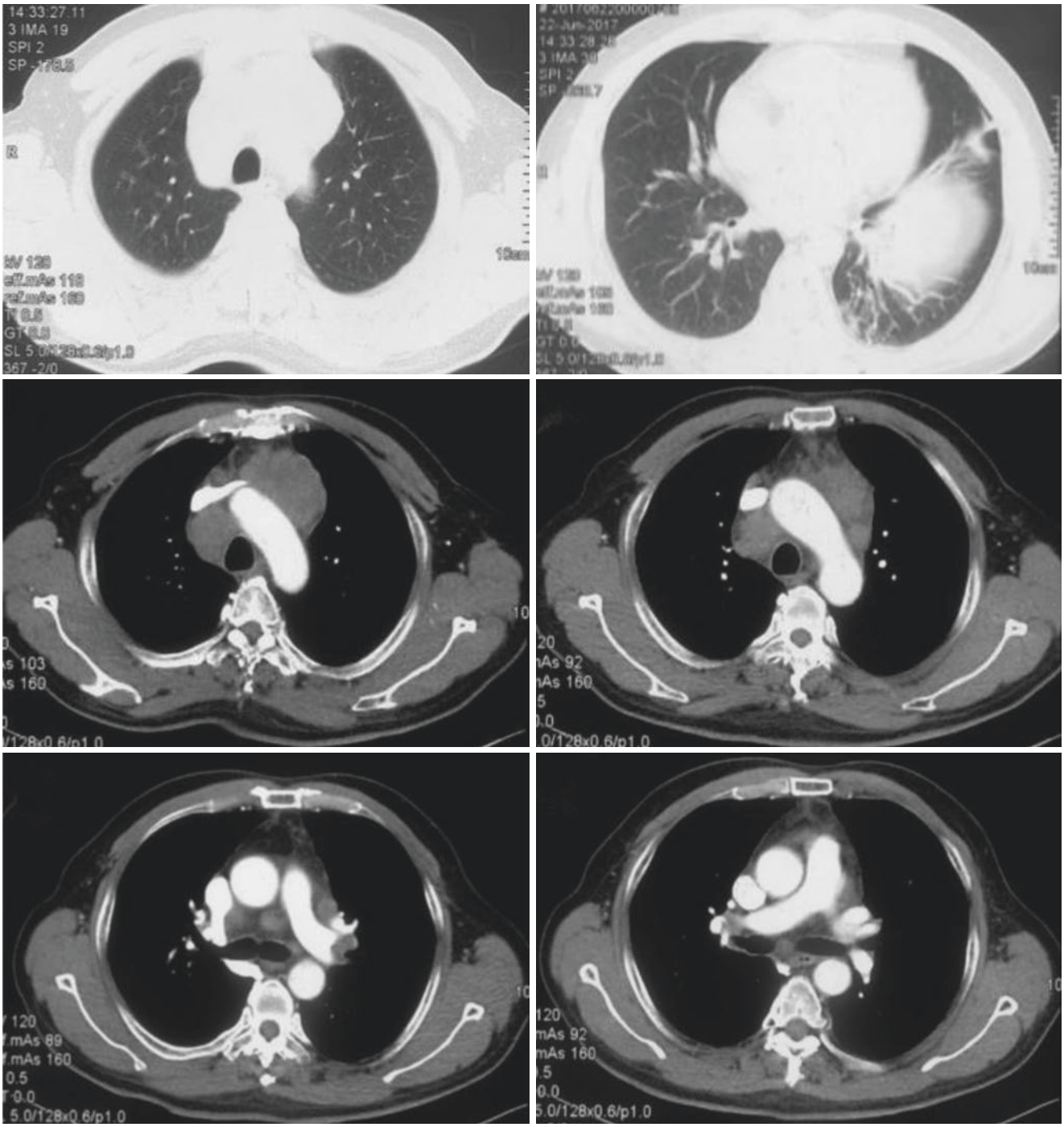

Fig. 3.57 Chest CT images of a 59-year-old man were found to have enlarged left cervical lymph nodes for 12 days

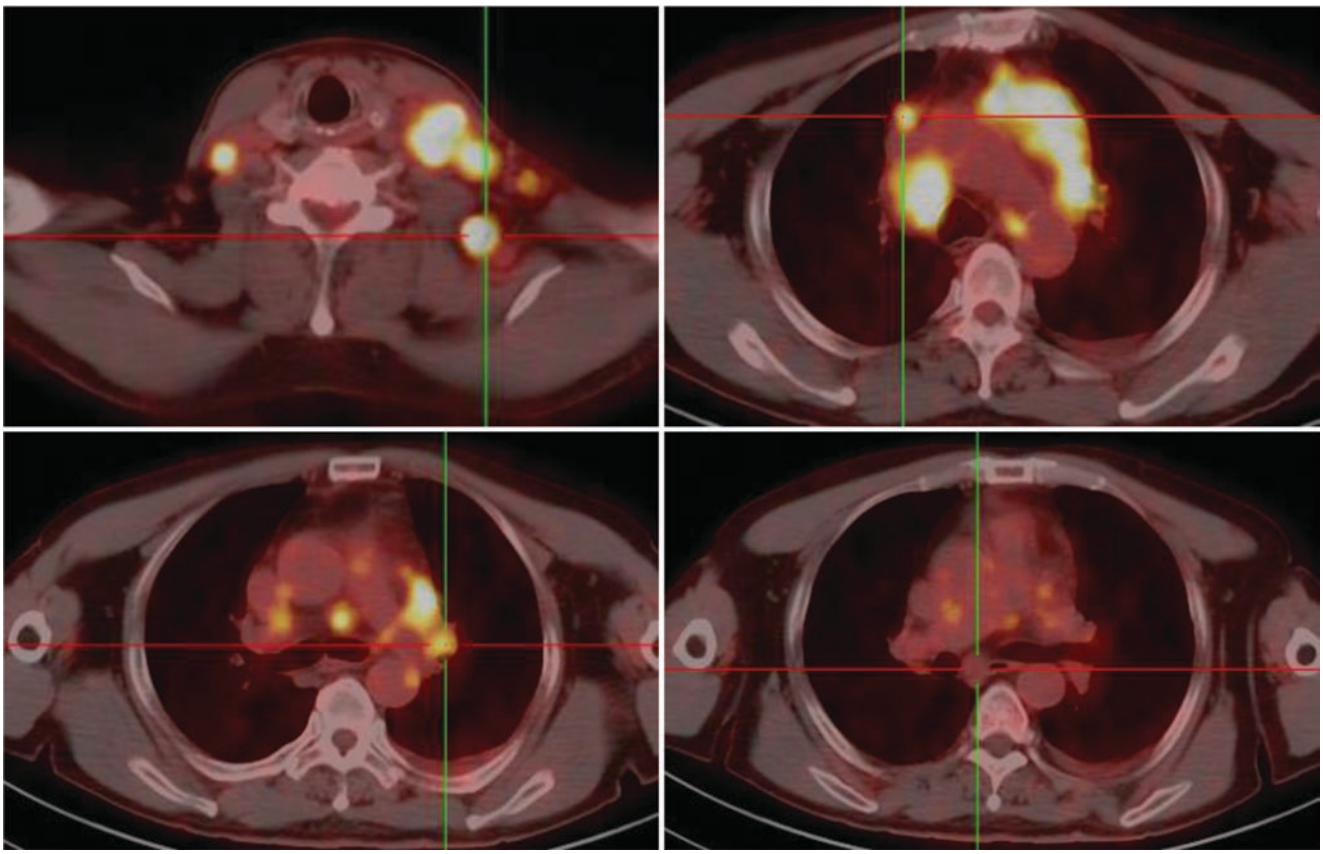

Fig. 3.58 PET-CT of a 59-year-old man was found to have enlarged left cervical lymph nodes for 12 days

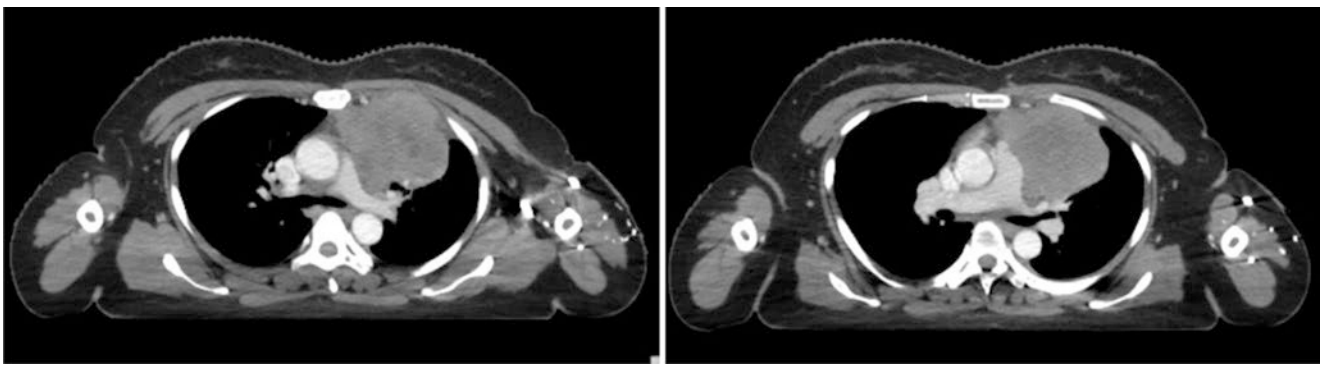

Fig. 3.59 A 32-year-old woman with a heterogeneously enhancing mass with necrosis

cannot tolerate iodine contrast, MRI can be a choice. The presence of low signal foci within the anterior mediastinal mass in MRI T2-weighted images is associated with thymic carcinoma.

3.8.17 Case 17

A 38-year-old man complained of paroxysmal chest pain and tightness for more than half a month.

Chest CT: An enhancing mass occupied the anterior mediastinum with multilocular cystic structures (Fig. 3.66).

[Diagnosis] Thymic mucoepidermoidcarcinoma.

[**Diagnosis basis**] Intraoperatively, the tumor was mainly cystic, measured 10 × 8 × 7 cm, and invaded the bilateral mediastinal pleura and pericardium. The pathology was thymic mucoepidermoid carcinoma.

[Analysis] Thymic mucoepidermoid carcinoma (MEC) is a relatively common neoplasm of the salivary glands, which rarely arises in other sites, including esophagus, anal canal,

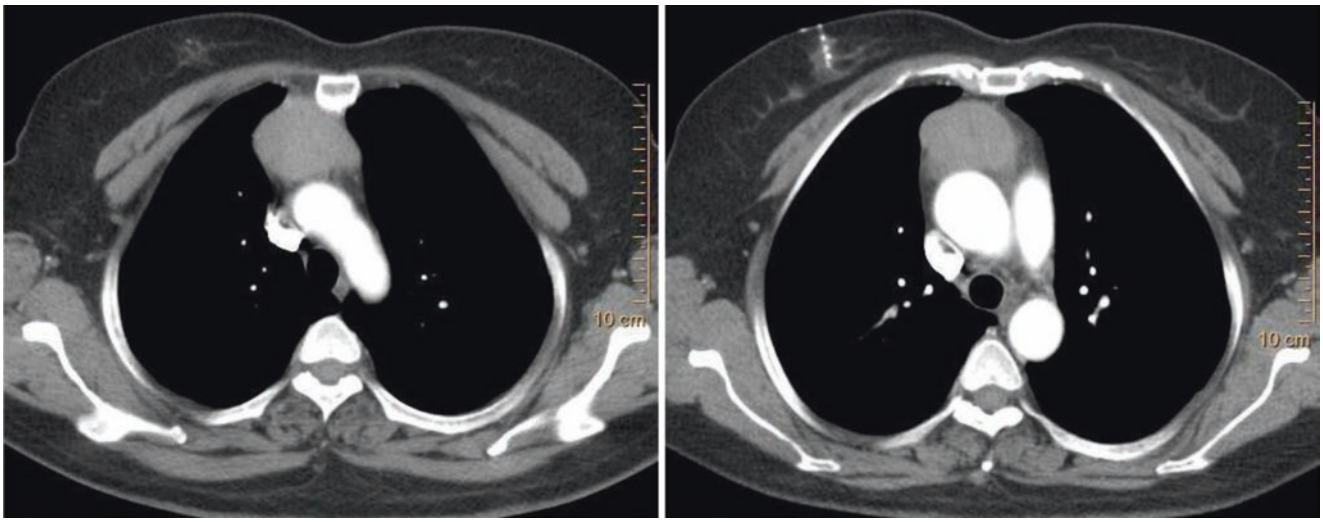

Fig. 3.60 A 55-year-old woman with a centrally growing mass of anterior mediastinum

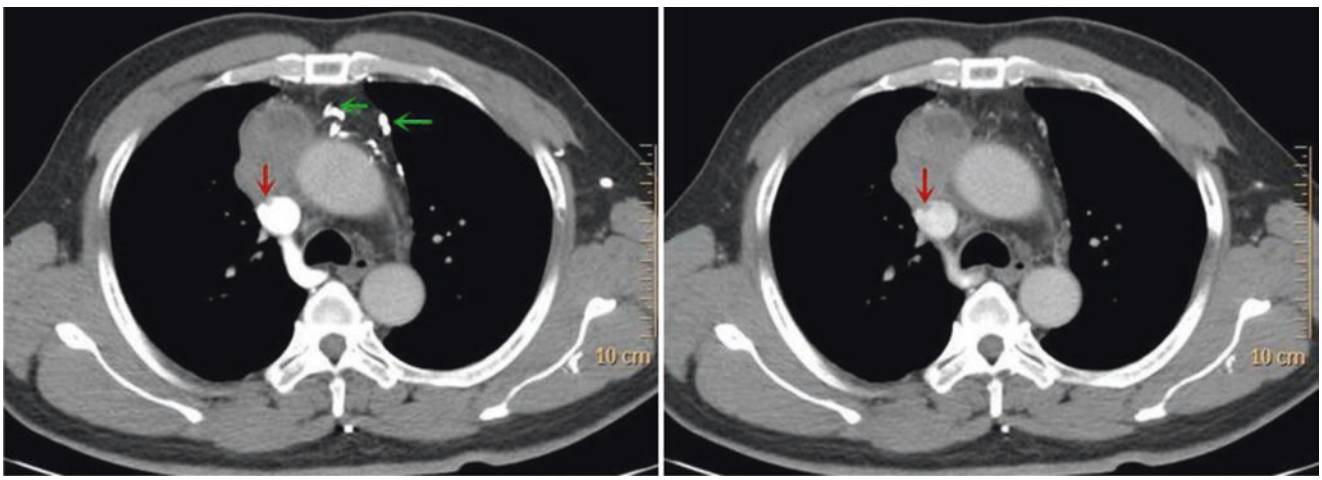

Fig. 3.61 A 55-year-old man with thymic squamous cell carcinoma, invading the superior vena cava (red arrow) with a compensatory collateral circulation (green arrow)

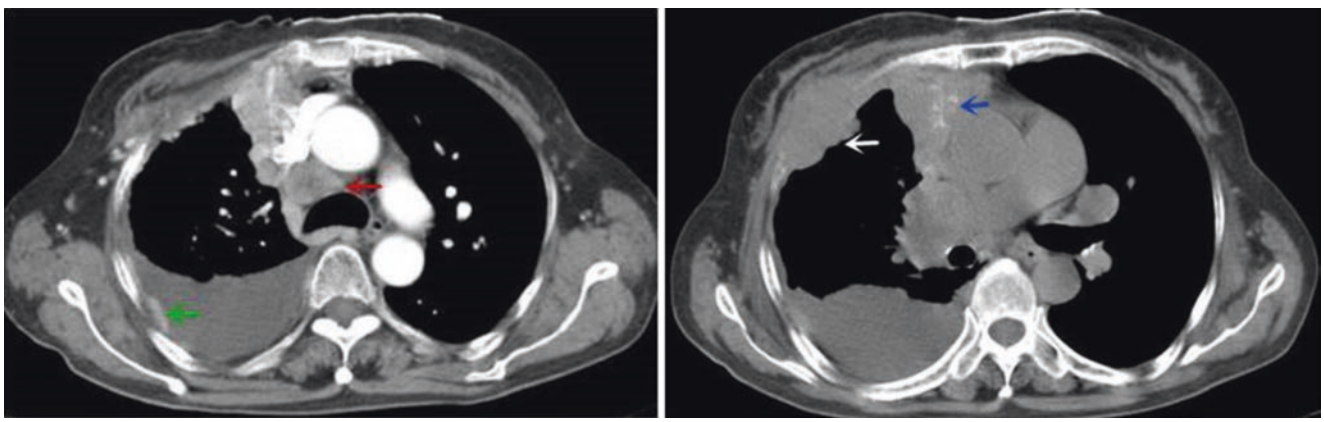

Fig. 3.62 A 59-year-old woman with thymic squamous cell carcinoma with sediment-like calcifications (blue arrow), involving lymph nodes (red arrow), ribs (white arrow), pleura (green arrow)

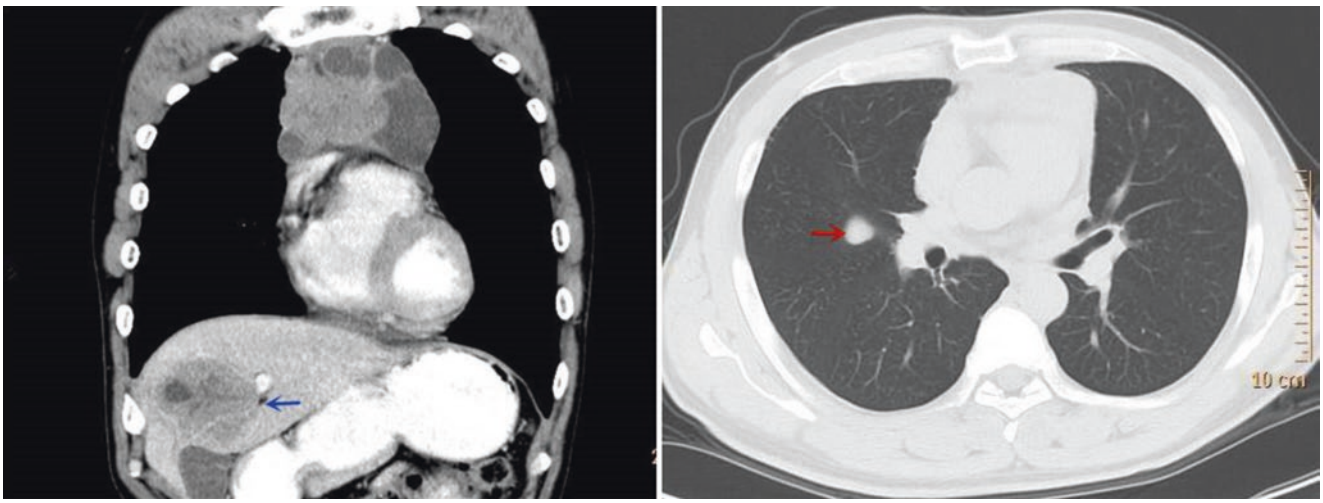

Fig. 3.63 A 38-year-old man with poorly differentiated squamous cell carcinoma, with interlobar pleura (red arrow) and liver metastasis (blue arrow)

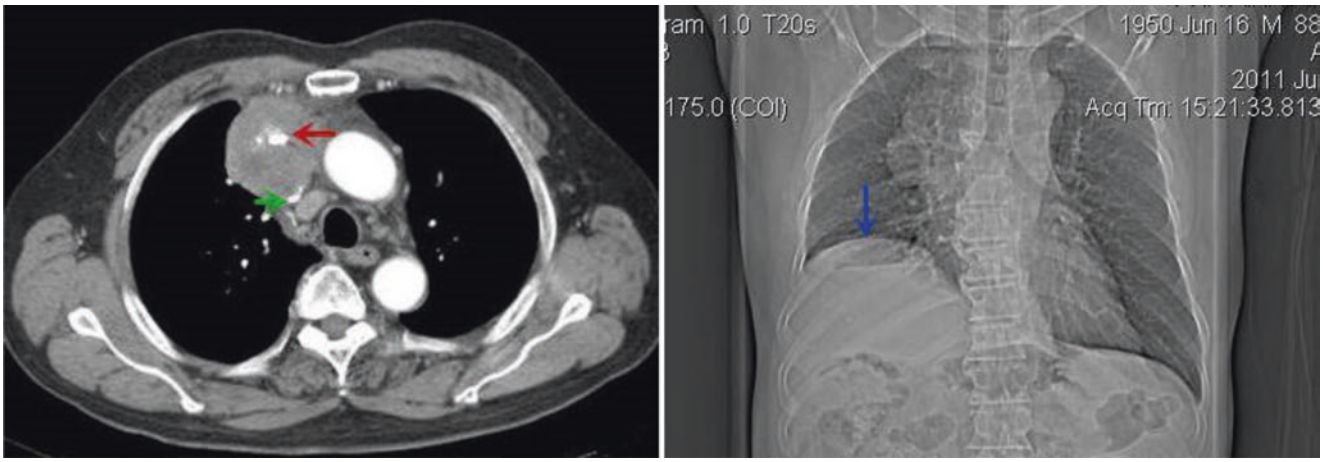

Fig. 3.64 A 61-year-old man has a heterogeneously enhancing mass in the anterior mediastinum, with coarse calcifications (red arrow), involvement of the superior vena cava (green arrow), and paralysis of the right phrenic nerve (blue arrow)

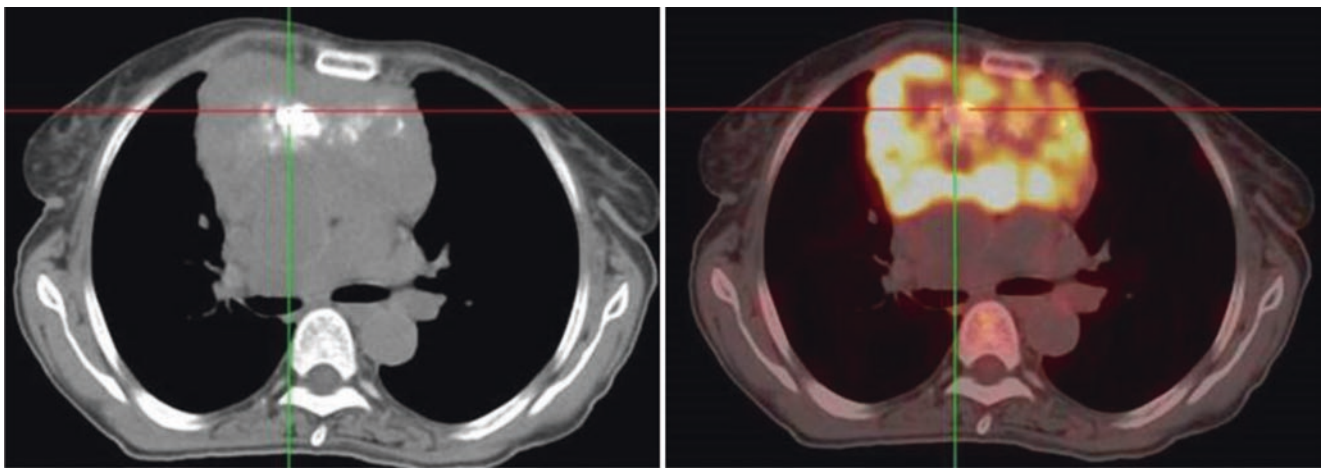

Fig. 3.65 A 64-year-old woman with thymic squamous cell carcinoma, the maximum SUV value was 9.9

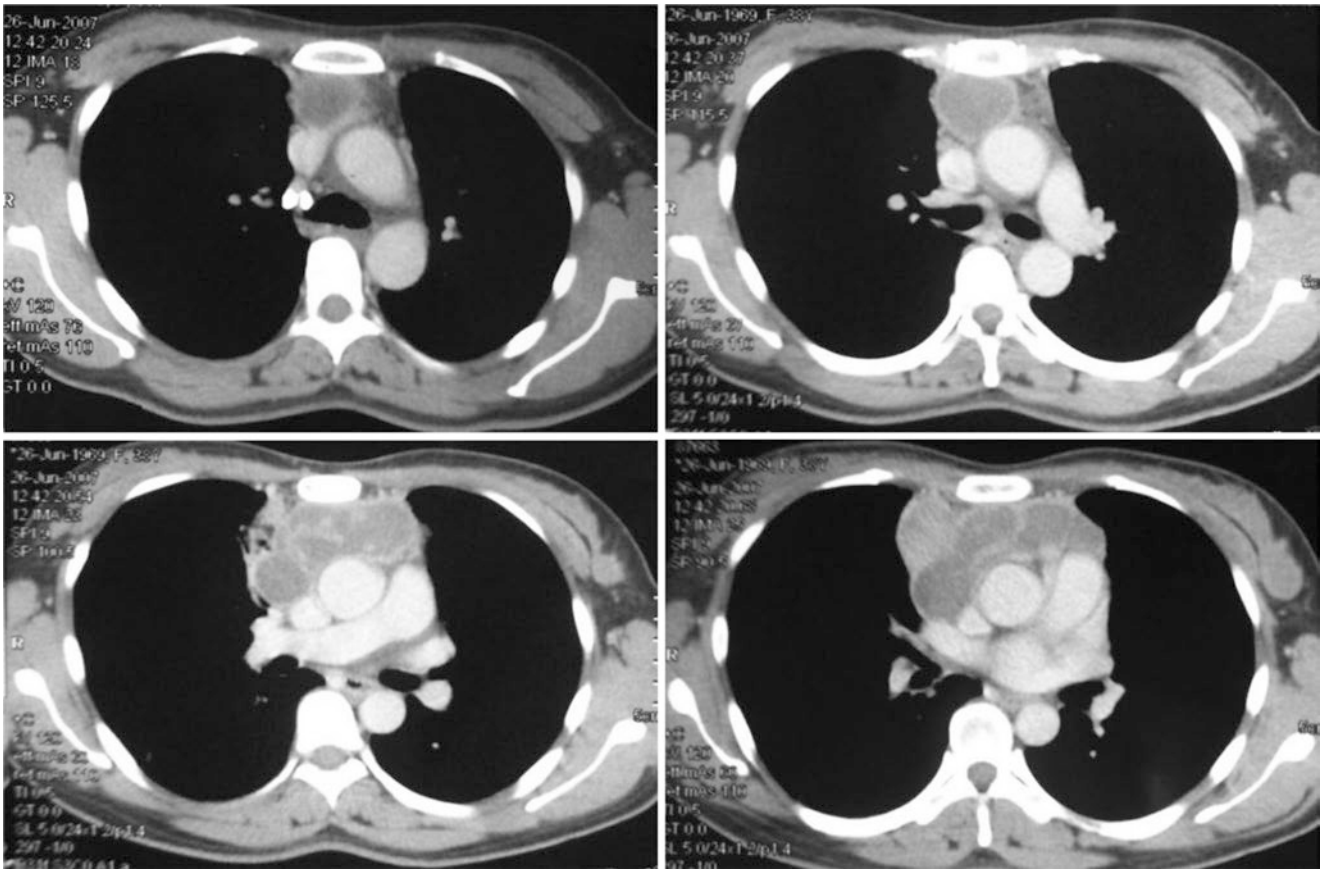

Fig. 3.66 Chest CT images of a 38-year-old man complained of paroxysmal chest pain and tightness for more than half a month

breast, lachrymal sac, thyroid gland, or uterine cervix. Thymic MEC is an extremely rare variant of thymic carcinoma that exhibits classic MEC histopathological features—namely, epidermoid, intermediate, and mucous cells. Primary thymic MEC is rare, and comprises approximately 2% of published thymic carcinoma. MEC was first described by Stewart et al. in 1945, whereas thymic MEC was first recognized by Snover et al. in 1982 [27].

The pathogenesis of thymic MEC is still unknown. It has been suggested that thymic MEC could be derived from thymic epithelium, because in some cases, there is a transition between tumor cells and benign cyst-lining epithelium, and residual nonneoplastic thymic parenchyma within the walls of the cysts has been reported. However, some authors also speculated that pluripotent epithelial stem cells of endodermal origin are the pathogenesis of thymic MEC. There was a strong association between MEC and t (11; 19) (q21; p13) in nonthymic anatomical sites. The MAML2 rearrangement is a member of the Master Mind Like gene family on chromosome 11q21, and is harbored specifically in thymic MEC similar to MEC in other anatomical sites, suggesting thymic MEC is not only histologically but also biologically related to non-thymic cases of MEC.

Patients with thymic MEC commonly present with respiratory symptoms including chest pain and exertional dyspnea. On CT scans, thymic MEC is often well-circumscribed, homogenous masses with multilocular cystic structures in the anterior mediastinum. This can vary depending on tumor grade. In some cases, local invasion to adjacent structures is observed. The histological characteristics of these tumors are squamoid mucin-producing cells with intermediate type cells. Histological analysis also showed that these tumors ranged from well- to poorly-differentiated. High-grade MECs are characterized by invasive growth pattern, solid nests with fewer cystic spaces, nuclear pleomorphism, increased mitotic activity, and necrosis, which make it difficult to distinguish high-grade MEC from poorly differentiated squamous cell carcinoma or adenosquamous carcinoma.

Surgical resection is the mainstay of treatment for low-grade tumors, and some require radiotherapy to prevent local recurrence or disease progression.

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