Neuroendocrine Tumors of the Thymus

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The endocrine system is the collection of glands that produce hormones which regulate metabolism, growth and development, sexual function, tissue function, reproduction, sleep, and mood, among other things. The endocrine system consists of the pituitary gland, thyroid gland, parathyroid glands, adrenal glands, pancreas, ovaries (in females), and testicles (in males). In addition to endocrine glands, there are a large number of scattered endocrine cells in many other organs, which secreted hormone-like substances playing an important role in regulating physiological activities. In 1969, Pearse [1] named these endocrine cells with amine precursor uptake and decarboxylation (APUD) cells because they can synthesize and secrete amines, which are produced by decarboxylation of amine precursors (amino acids). With the continuous expansion of APUD cell types and distribution, it is found that many neurons in the nervous system also synthesize and secrete the same amines and/or peptides as APUD cells. Therefore, these neurons with secretory function (secretory neurons) and APUD cells are collectively called the diffuse neuroendocrine system (DNES). DNES is an expansion on the basis of APUD and it combined the nervous system and endocrine system as a whole body, which regulate and control the dynamic balance of the body's physiological activities.

Neuroendocrine tumors of the thymus were first described by Rosai and Higain [2]. Although thymic tumors are the most common cause of an anterior mediastinal mass, thymic neuroendocrine tumors comprise only 4–7% of all anterior mediastinal tumors and represent only 0.4% of all neuroendocrine tumors. According to the definition of WHO for thymic tumor classification in 2004, thymic neuroendocrine tumor is an epithelial tumor mainly or completely composed of neuroendocrine cells. It emphasized that tumor tissue is mainly or completely composed of neuroendocrine cells, mainly reflecting that the diagnosis should be differentiated from thymic carcinoma containing scattered and clustered neuroendocrine cells.

4.1 Classification

Thymic neuroendocrine tumors were commonly referred to as thymic carcinoids in the past, but more and more studies have shown that thymic neuroendocrine tumors are a group of diseases with obvious differences in biological behavior, pathological characteristics, clinical manifestations, and prognosis. The WHO classified thymic neuroendocrine tumors into four types: typical carcinoid, atypical carcinoid, small-cell carcinoma (SCC), and large-cell neuroendocrine carcinoma (LCNEC) according to tumor necrosis, differentiation degree, and proliferation rate in 2004. The descriptive terms "well-differentiated neuroendocrine carcinoma" (referring to carcinoids) and "poorly differentiated neuroendocrine carcinoma" (referring to LCNEC and SCC) of the 2004 WHO Classification were abandoned in 2015, because LCNEC and even SCC may be highly differentiated in terms of neuroendocrine features. Following the strategy in the lung, the 2015 WHO Classification criteria distinguished typical and atypical carcinoids as low- and intermediate-grade neuroendocrine tumors, respectively, from high-grade neuroendocrine carcinomas including LCNEC and SCC. Unlike neuroendocrine tumors in the lung, which are mainly typical carcinoid, the majority of thymic neuroendocrine tumors are atypical carcinoid.

4.2 Pathology

The thymic carcinoid demonstrated typical neuroendocrine growth illustrated by a nested, organoid, trabecular, or rosette-like architecture. Typical carcinoids with minimal

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S. Zhang (ed.), *Diagnostic Imaging of Mediastinal Diseases*, https://doi.org/10.1007/978-981-15-9930-9_4

cytologic atypias, disposed in organoid patterns (nests, ribbons, or festoons) with fewer than 2 mitoses/2 mm^2 and no necrosis. Conversely, atypical carcinoids show the same morphologic features of typical carcinoid, but with a greater mitotic activity (2–10 mitoses/2 mm^2) and necrosis or no necrosis. The index may also fewer than 2 mitoses/2 mm^2 combined necrosis. SCC is composed of cells with scant cytoplasm, granular chromatin, inconspicuous nucleoli, and a high mitotic rate (>10 mitoses/2 mm^2). Combined SCC is SCC combined with any thymoma or thymic carcinoma. LCNEC consisting of large cells with cytologic neuroendocrine features and no small-cell features, arranged in nests or trabeculae. Diffuse and abundant necrosis and a high number of mitoses (>10 mitoses/2 mm^2) are common. Combined LCNEC is LCNEC combined with any thymoma or thymic carcinoma.

Immunohistochemistry may assist to formulate an appropriate differential diagnosis. The WHO has defined neuroendocrine tumors as those with strong and diffuse expression, usually more than one of the four neuroendocrine markers chromogranin A, synaptophysin, CD56, and NSE in more than 50% of tumor cells.

4.3 Clinical Features

Thymic neuroendocrine tumors usually occur in middle-aged and elderly people, which mostly at the age of 40–60 years, and mostly in men, with a male-to-female ratio of about 3:1. Most patients have mild symptoms, mainly as chest tightness, chest pain, cough, or superior vena cava syndrome. A few patients (30%) are found accidentally during physical examination. Some patients have systemic symptoms including anemia, weight loss, and fever. A few patients see the doctor because of the neck, supraclavicular lymph node metastasis, or distant metastasis.

Almost 50% of thymic neuroendocrine tumors are functional and are associated with endocrinopathies, the most common of which are Cushing's syndrome (adrenocorticotropic hormone–ACTH–ectopic production), hypertrophic osteoarthropathy, and acromegaly (growth hormone-releasing hormone-GH-RH-hypersecretion). Multiple endocrine neoplasia-1(MEN1) syndrome (Wermer syndrome) is seen in 19–25% of thymic neuroendocrine tumors; this tumor represents the major cause of death in MEN-1 patients.

4.4 Radiographic Features

The imaging findings of thymic neuroendocrine tumor have no characteristic changes, mainly in the anterior superior mediastinum, but also occasionally in the middle mediastinum or the posterior mediastinum. When the lesions are small, it is difficult to detect on X-ray. Most patients are not detected until clinical symptoms appear when the tumor size is generally larger. It is reported that the diameter of thymic neuroendocrine tumor is 2–20 cm, with an average of 8 cm. Moreover, patients with Cushing syndrome have smaller lesions, ranging from 3 to 5 cm. CT shows a heterogeneous or homogeneous mass, which can be round or oval. Unlike thymic squamous cell carcinoma, 50% of cases have a clear margin (Fig. 4.1). There are different forms of calcification in 30% of the tumors, which can be characterized as dotted, nodular, or linear (Fig. 4.2). Necrosis can be found on histological examination in 60–80% of tumors, which may be related to rapid growth and insufficient blood supply (Fig. 4.3). The contrast-enhanced scan shows mild to moderate enhancement (Fig. 4.4), some of which can be a high degree of enhancement (Fig. 4.5). Thymic neuroendocrine tumor usually shows invasive growth along the large blood vessel space, surrounding and invading the large blood vessel of mediastinum such as the superior vena cava, brachio-

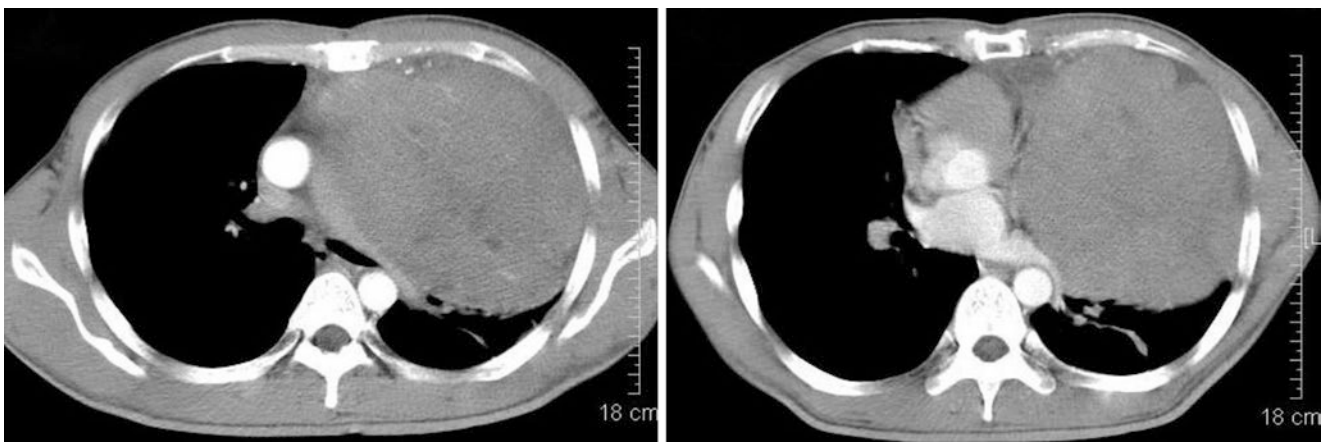

Fig. 4.1 A 32-year-old man with thymic carcinoid, contrast-enhanced CT scan revealed an anterior mediastinal huge tumor with clear margin

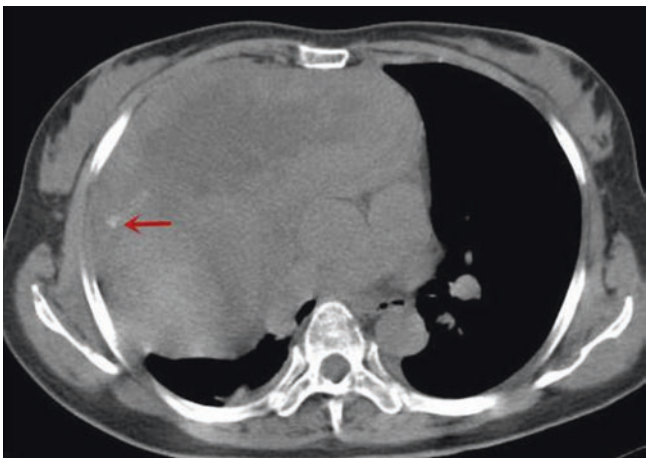

Fig. 4.2 A 42-year-old woman with thymic carcinoid, CT scan revealed an anterior mediastinal huge tumor with calcification (red arrow) and necrosis

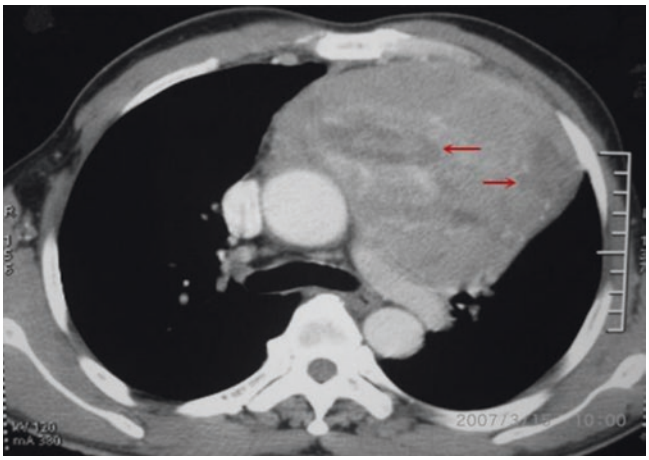

Fig. 4.3 A 47-year-old man with thymic carcinoid, CT scan revealed an anterior mediastinal huge tumor with necrosis (red arrow)

cephalic vein, pulmonary artery trunk, and ascending aorta. Cancer embolism can found in the superior vena cava (Fig. 4.6). Some tumors can directly invade the soft tissue and bone of the anterior chest wall. Most patients may have multiple lymph node metastases in mediastinum, hilum, and supraclavicular. About 30% of patients have distant metastasis including pelvic, liver, intrapulmonary, and extensive bone metastases when they went to see the doctor. Osteogenic or thoracic metastasis indicates this diagnosis (Fig. 4.7). Some LCNEC and SCC cannot differentiate from thymic carcinomas on imaging (Fig. 4.8).

4.5 Treatment

Surgery is the main curative-intent treatment, and the survival of patients with surgical resection is significantly better than that of nonsurgical patients. Complete resection represents the most significantly favorable prognostic factor on overall survival. Postoperative radiotherapy can lessen local recurrence, especially for patients who cannot be completely removed in the late stage of tumor, but it has no significant effect on long-term survival. There is no evidence on whether chemotherapy can be used after the operation, but the appropriate chemotherapy can be chosen according to the preoperative chemotherapy. Chemotherapy may then be an option for aggressive disease, but somatostatin analogues and everolimus are suitable as well.

The overall treatment effect of thymic neuroendocrine tumor is poor. The 3-, 5-, and 10-year survival rates reported in the literature are 50–66%, 33–53%, and 0–10%, respectively. In some centers, the 5-year and 10-year survival rates can reach about 80% and 60%. The main causes of treatment failure are local recurrence and/or distant metastasis. The incidence of local recurrence or distant metastasis can be as

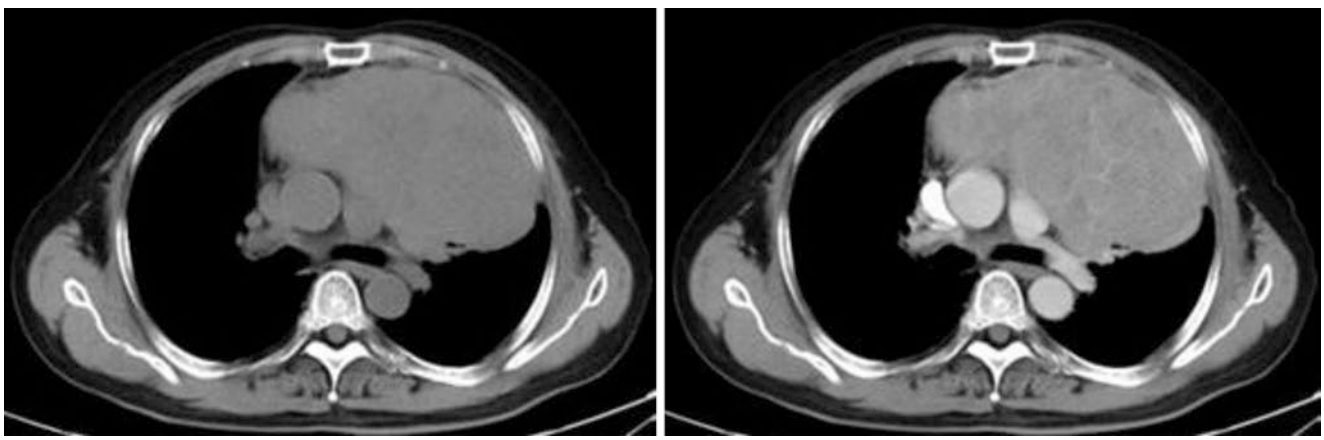

Fig. 4.4 A 62-year-old man with thymic carcinoid, the unenhanced and contrast-enhanced CT attention was 40 HU and 72 HU, respectively

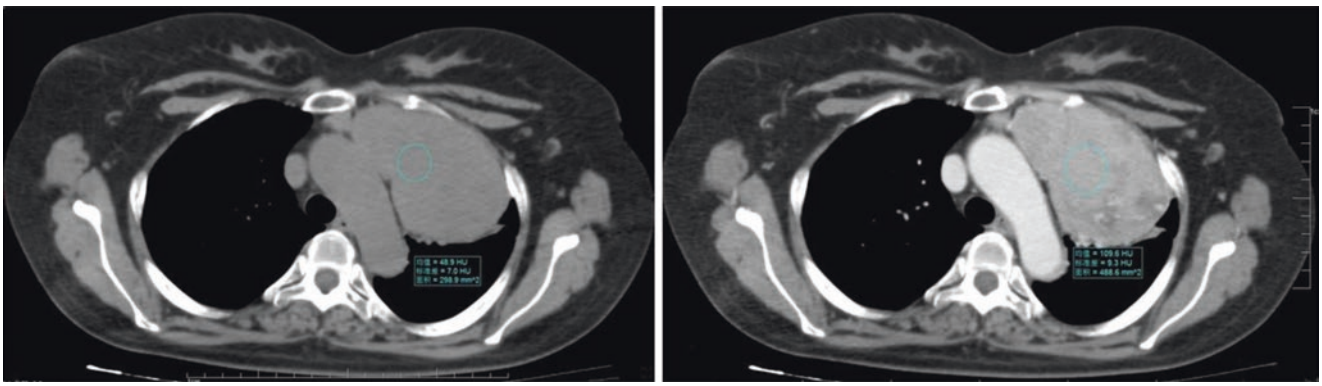

Fig. 4.5 A 33-year-old woman with atypical thymic carcinoid, the unenhanced and contrast-enhanced CT attention was 48.9 HU and 109.9 HU, respectively

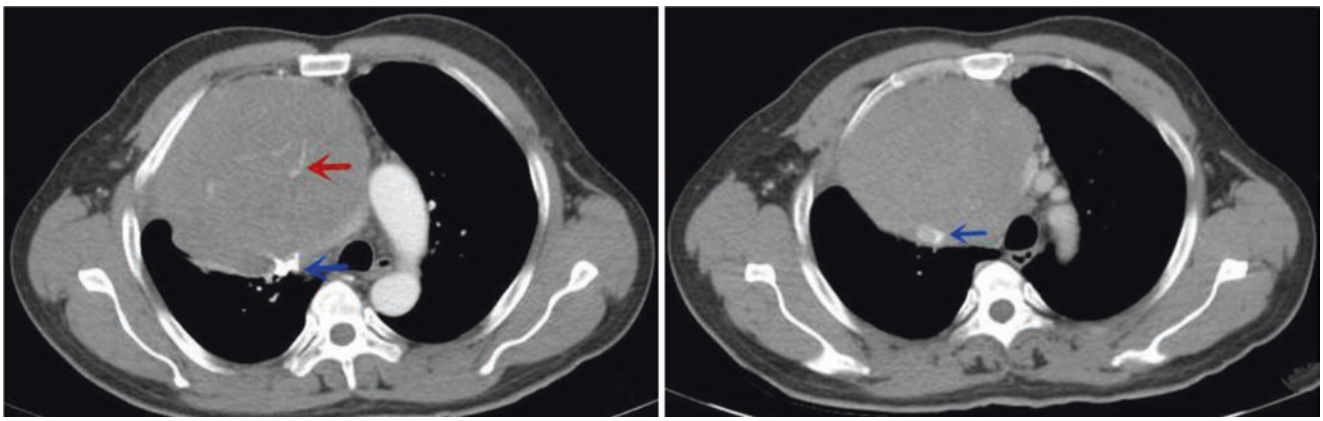

Fig. 4.6 A 54-year-old man with thymic carcinoid complained of facial swelling for 1 month. Tubular vascular shadow (red arrow) could be seen in the tumor, the superior vena cava was invaded, and tumor thrombus (blue arrow) could be seen in it

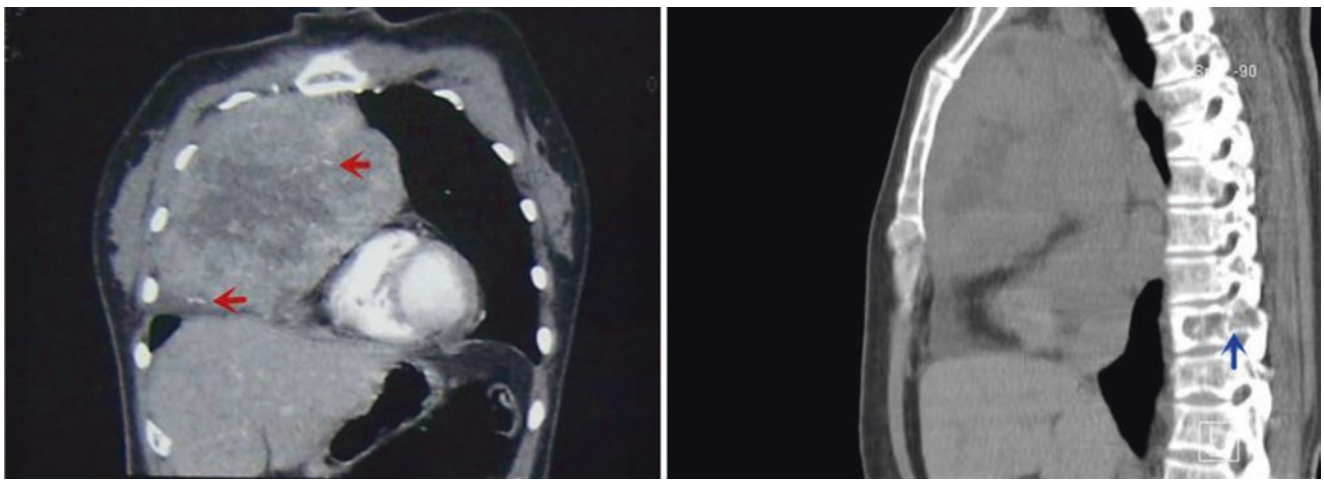

Fig. 4.7 A 42-year-old woman with thymic carcinoid with thoracic spine metastasis (blue arrow), the tumor showed clear margin, necrosis, and vascular shadow (red arrow)

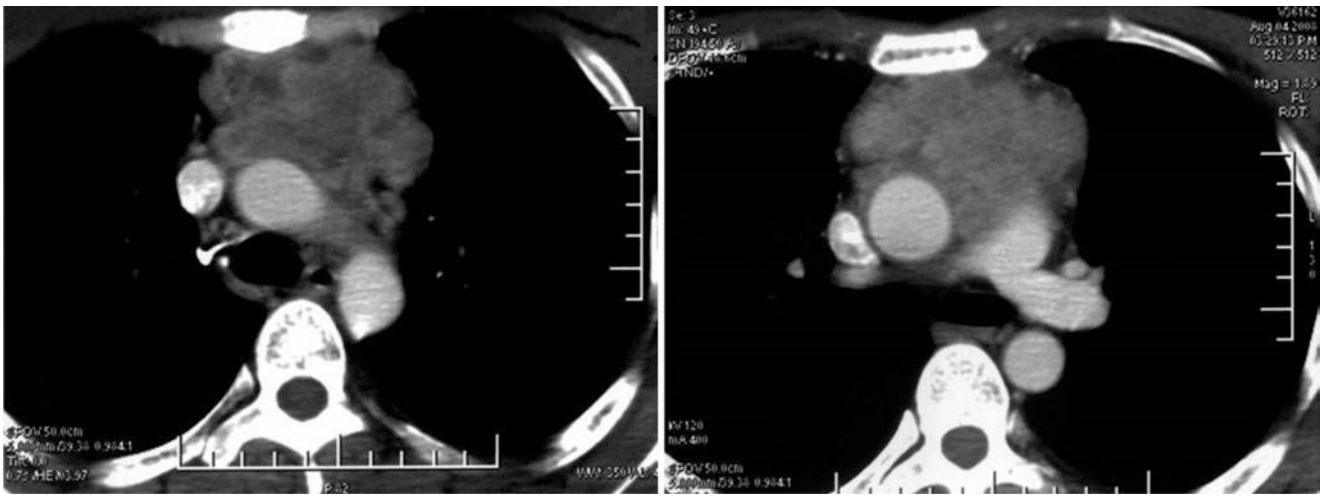

Fig. 4.8 A 39-year-old man with LCNEC. The tumor had irregular margin, uneven internal density, obvious necrosis, and invasion of the pericardium

high as 20–80%. The treatment of recurrence largely depends on its extent. Repeated resection may be considered for local or regional recurrence. For systemic recurrences, management relies on multiple treatments, including somatostatin analogues, chemotherapy regimens, everolimus, and peptide receptor radiotargeted therapy.

4.6 Prognosis

The prognosis of thymic neuroendocrine tumor is related to histological grade, clinical stage, endocrine abnormality, local recurrence, and metastasis. The prognosis of well-differentiated subtypes is better than that of poorly differentiated subtypes. Similar to thymoma, the later Masaoka staging suggested the more aggressive and the worse prognosis. The 5-year survival rate of patients with Cushing syndrome or MEN-1 is significantly lower than that of patients without endocrine syndrome. Patients with thymic neuroendocrine tumor have a higher rate of lymph node metastasis (62.3% vs. 33.5%) than patients with thymic carcinomas. Lymph node metastasis is an independent prognostic factor that significantly affecting survival time of patients.

4.7 Case Analysis

4.7.1 Case 1

A 64-year-old man complained chest tightness for 1 week.

Chest CT: There was a large soft tissue mass in the anterior mediastinum with a clear edge. The contrast-enhanced scan showed slight uneven enhancement and patches of enhanced vascular shadow in the lesion, and further enhancement in the venous stage (Fig. 4.9).

[**Diagnosis**] Atypical thymic carcinoid

[**Diagnosis basis**] In this case, the superior vena cava is invaded and moved outward (green arrow), suggesting that the lesion originated from the mediastinum. The patient is an elderly male, malignant germ cell tumor may be excluded. Calcifications (red arrow) and large patchy necrosis with unclear borders are seen in the lesion. Untreated lymphoma calcification is rare, and the borders of lymphoma necrosis areas are more clear, the above characteristics can exclude the diagnosis of lymphoma. The lesion is located in the anterior mediastinum, thymus-derived tumors need to be considered. Thymoma is rare in huge thymus soft tissue masses. This case also has no common complications of thymoma, such as myasthenia gravis, and does not support the diagnosis of thymoma. Thymic carcinoma is larger than thymoma, and generally has a uniform soft tissue density. It is more common than thymoma in low-density necrosis area, which is not proportional to the size of the mass. Vascular invasion in thymic carcinoma is common. Therefore, this diagnosis of thymic carcinoma cannot be completely ruled out in this case. In this case, the enhancement is obvious, the internal lamellar low-density necrosis and linear vascular-like enhancement (blue arrow) are characteristic of thymic carcinoid. Combining calcification is seen in 30% of thymic carcinoids, so the diagnosis is considered first. Postoperative pathology showed that the tumor cells were round/oval, abundant in cytoplasm, and easy to see mitotic division. Immunohistochemistry demonstrated positivity for CKpanSyn and CgA, and the staining index for Ki-67 was about 20–30%. It is consistent with the diagnosis of atypical thymic carcinoid (Fig. 4.10).

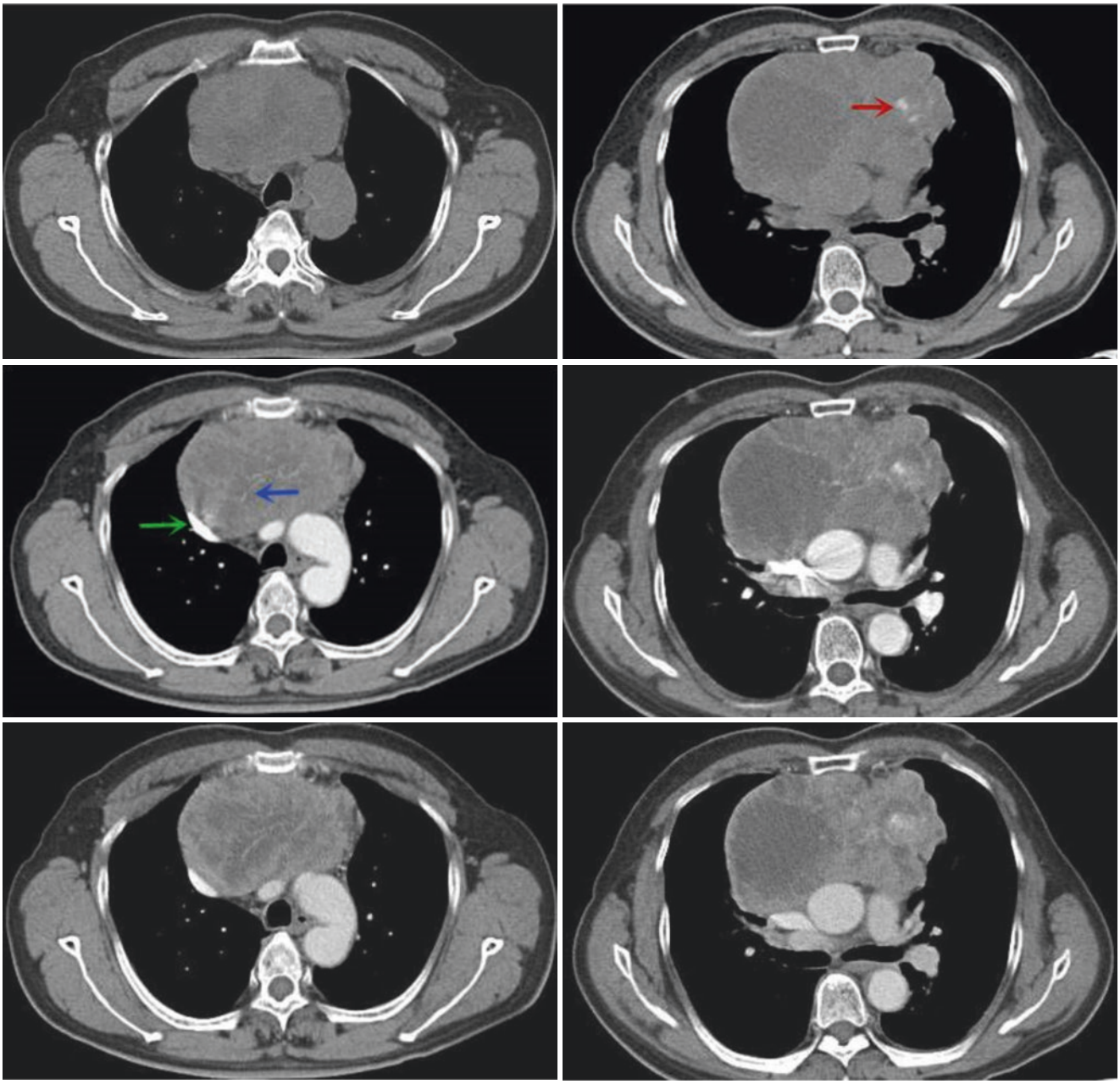

Fig. 4.9 Chest CT images of a 64-year-old man complained chest tightness for 1 week

[**Analysis**] Neuroendocrine tumors are uncommon types of cancers, also known as APUD tumors, which become increasingly prevalent. The majority of thymic neuroendocrine tumors are atypical thymic carcinoid accounting for approximately 40–50% of all thymic neuroendocrine tumors. Compared with typical carcinoid, atypical carcinoid usually exhibits high levels of nuclear isoforms, higher mitotic activity, and central necrosis of the tumors. Atypical thymic carcinoid tends to have an aggressive clinical course. These neoplasms show local recurrence or distant metastasis in 20–30% of patients and reported overall 5- and 10-year survival rates are 56–77% and 30%, respectively. Atypical thymic carcinoid has the following features: male predominance, patients older than 40 years, and rare patients with myasthenia gravis. The symptoms were atypical, such as cough, chest pain, phrenic nerve palsy, superior vein cava syndrome, or an incidental finding.

Images of thymic carcinoids usually demonstrate a large anterior mediastinal mass. Contrast-enhanced CT is the main and efficient method used to discover and diagnose mediastinal mass. Thymic carcinoid was seen as an irregular soft-tissue mediastinal mass with heterogeneous enhancement on

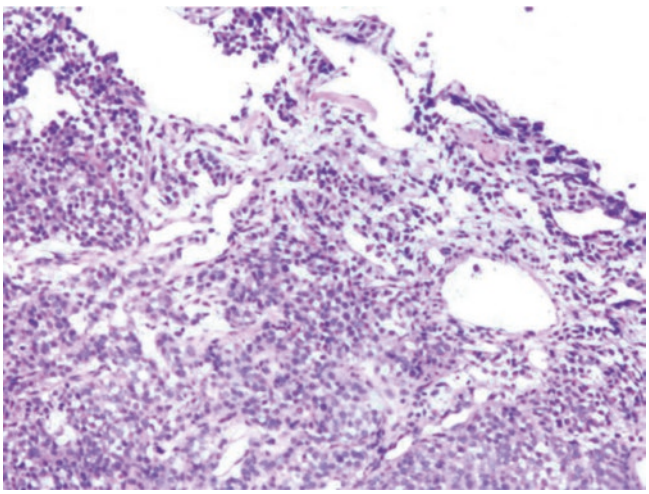

Fig. 4.10 The pathological feature of atypical carcinoid of the thymus

contrast-enhanced CT was reported by Restrepo et al. [3], which may present with calcifications or invade surrounding normal structures. A feature of thymic carcinoid was reported by Rosado de Christenson et al. [4], that is, presence of sharp margins, lobular contours, calcification, mediastinal invasion, and distant metastases on CT imaging. Kan et al. [5] reported that the marginal cystic/necrotic component and hypervascular signs should be included as a characterization for the diagnosis of atypical carcinoid tumors. Shimamoto et al. [6] reported that thymic carcinoids tended to have a high prevalence of large masses, irregular contours, heterogeneous intensity on T2 weighted images, heterogeneous enhancement, and local invasion on CT and/or MRI. Necrotic or cystic component is often seen in atypical carcinoid. Radiologic features of thymic carcinoid mimic those of high-risk thymomas and/or thymic carcinomas.

4.7.2 Case 2

A 75-year-old man complained chest tightness, cough, and expectoration for more than 1 year, aggravation with fever for 2 weeks.

Chest CT: A large mass in the left middle mediastinum with clear margin, compression, and displacement of the heart and large vessels, and the contrast-enhanced scan showed significant geographic pattern enhancement (Fig. 4.11).

[**Diagnosis**] Thymic carcinoid

[**Diagnosis basis**] As an elderly male with lateral mediastinal tumors, thymic tumor is the first consideration. The mass is so large that the possibility of thymus neuroendocrine tumor is high. The mass is oval, with a clear boundary. The contrasted-enhanced scan is a high degree of enhancement, and the necrosis and vascular shadow are obvious. Thus, the possibility of thymic carcinoid is considered first. The surgical specimen shows that the lesion originated from mediastinum and the pathology is thymic carcinoid. Immunohistochemistry demonstrated positivity for Syn, CgA, NSE, CD56 and CK, and the staining index for Ki-67 was about 2%.

[**Analysis**] Thymic carcinoids are rare tumors that are histologically closely related to neuroendocrine carcinomas of other organ systems. In immunohistochemistry, the characteristics of the tumors include consistent expression of pancytokeratin, CAM5.2, chromogranin A, synaptophysin, neuron-specific enolase, and CD56. CgA is considered to be the most reliable marker, while small- and large-cell carcinomas are usually weakly positive or negative. PAX8 was found to label not only thymomas and thymic carcinomas but also approximately one-third of thymic carcinoids, whereas TTF-1 is only rarely expressed. Although TTF-1 negative and PAX8 positive are more common in thymic carcinoids, immunohistochemical markers do not clearly differentiate between thymic and primary neuroendocrine tumors of lung. The survival rate for patients with thymic carcinoids is significantly worse than patients with pulmonary primaries.

Unlike thymoma, thymic carcinoid is not associated with myasthenia gravis and pure red cell aplastic anemia. However, compared with thymoma, it has more invasive behaviors and distant metastasis is easy to occur with invasion and metastasis in 20~50% of patients. The most common sites of metastasis are regional lymph nodes, lung, and bone. Bone metastases often present as osteogenic bone destruction, and bone scan shows multiple abnormal radioactive concentrations, which is helpful for the diagnosis of the disease.

The most effective treatment and an important prognostic factor is complete resection. Due to the high rate of recurrence and metastasis of these tumors, lymph node sampling should be performed during resection. Nodal staging may help to guide adjuvant treatment. Systemic nodal dissection or sampling is yet to be standardized. For patients with unresectable or metastatic tumors, the recommendation is chemotherapy with or without radiotherapy. However, its clinical use is limited due to its toxic and side effects. For those who have positive somatostatin receptor imaging, somatostatin analogues (SSAs) may be an option. Targeted therapeutic drugs, such as tyrosine kinase inhibitors (e.g., sunitinib) and mTOR inhibitors (everolimus), may be beneficial in the treatment of atypical thymic carcinoid, but neither has been shown to achieve significant tumor shrinkage. In this case, the edge of the tumor is clear and neat, and there is no adhesion between the tumor and the surrounding structures during the operation, so the tumor can be completely removed with a good prognosis.

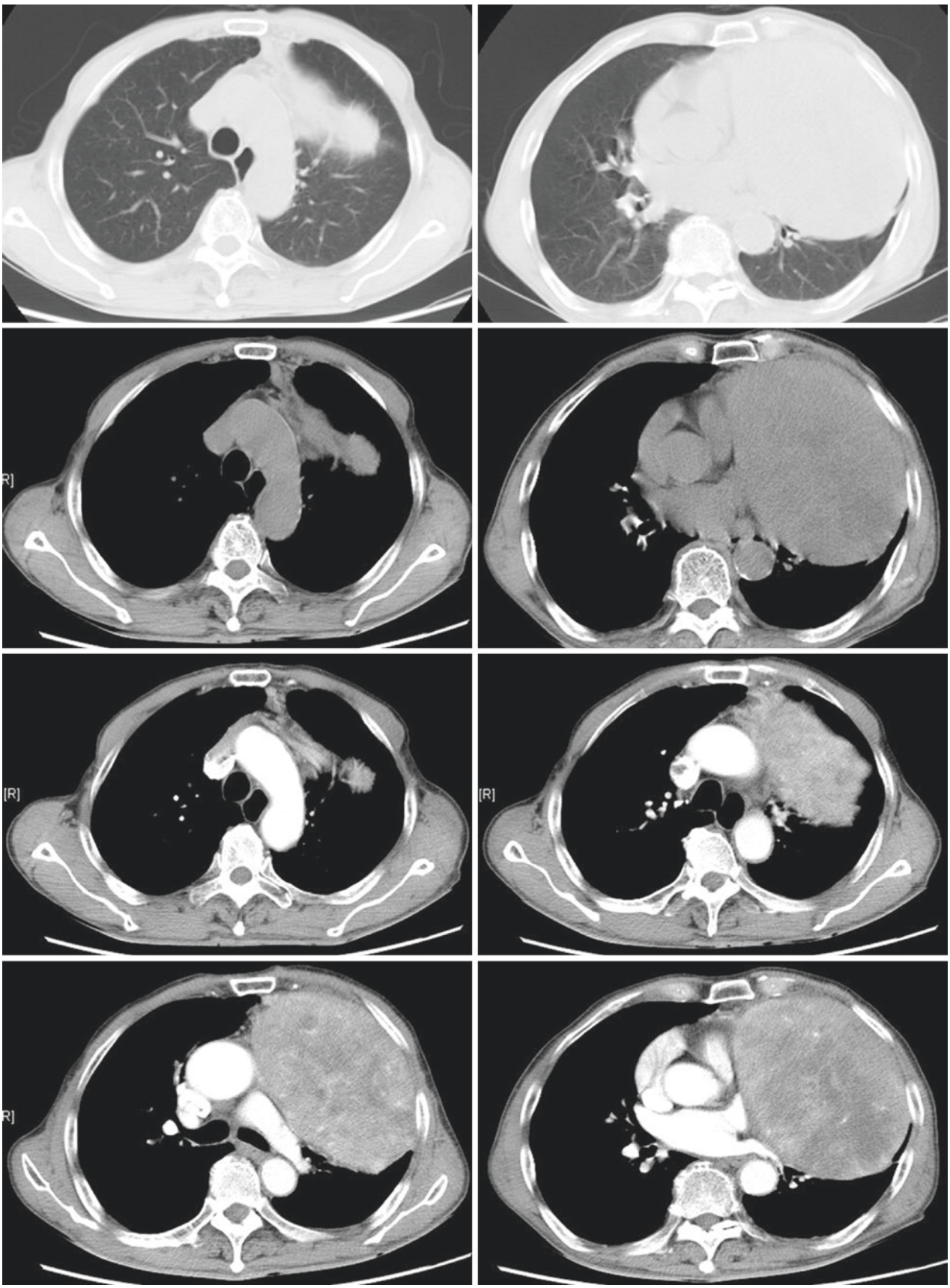

Fig. 4.11 Chest CT images of a 75-year-old man complained chest tightness, cough, and expectoration for more than 1 year, aggravation with fever for 2 weeks.

4.7.3 Case 3

A 46-year-old woman complained of obesity, darkening of the skin, hair growth for 7 years, and aggravation for 6 months. The patient's appetite increased 7 years ago consciously and the staple food was 1.2–1.5 kg a day. Her weight increased 30 kg within 2 months, accompanied with black and oily skin and increased beard. Five years ago, the patient was admitted to the hospital and found serum cortisol higher than normal (the result is unknown). Her blood pressure was 240/160 mmHg and the glucose tolerance test showed hyperglycemia, and no abnormality was found on the pituitary MRI. She took cyproheptadine two tablets at a time, three times a day; captopril one tablet at a time, one time a day; metformin two tablets at a time, three times a day. Her blood pressure was maintained at about 140/90 mmHg and do not follow the blood glucose. She stopped to take cyproheptadine after 2 years by herself. The pituitary MR imaging was performed 3 years ago and still found no abnormality. The patient's weight kept increasing, with gasping after activity, swollen legs, and streaming eyes for nearly half a year. Ten days ago, the patient's serum cortisol levels were found as 797 nmol/L and 679 nmol/L at 0800 and 1600, respectively. She was diagnosed as "Hypercortisolism and Diabetes mellitus" after the glucose tolerance test. Metformin was given two tablets at a time, three times a day; captopril was given one tablet at a time, one time a day, but the symptoms did not improve significantly. Her blood pressure was 160/113 mmHg and weighed 73 kg. Physical examination revealed typical Cushingoid features, such as moon face, central obesity, dark skin, multiple acne in face and back skin, low hairline, thickened hair, and visible beard. Serum adrenocorticotrophic hormone (ACTH) levels were found as 95.66 pg/ml, 157.9 pg/ml, and 231.0 pg/ml at 00 00, 0800, and 1600, respectively. Both low- and high-dose dexamethasone suppression tests were normal. B-ultrasound showed enlargement of external muscles of both eyes. Abdominal CT showed bilateral adrenal hyperplasia.

Chest CT: A soft tissue mass measured 5.8 cm × 3.0 cm located in the anterior mediastinum, with spot or strip calcifications. The unenhanced and contrast-enhanced CT attentions were 38 HU and 72 HU, respectively. The lesion showed invasive growth with unclear demarcation with surrounding tissues, and that bilaterally brachiocephalic veins and superior vena cava were involved (Fig. 4.12).

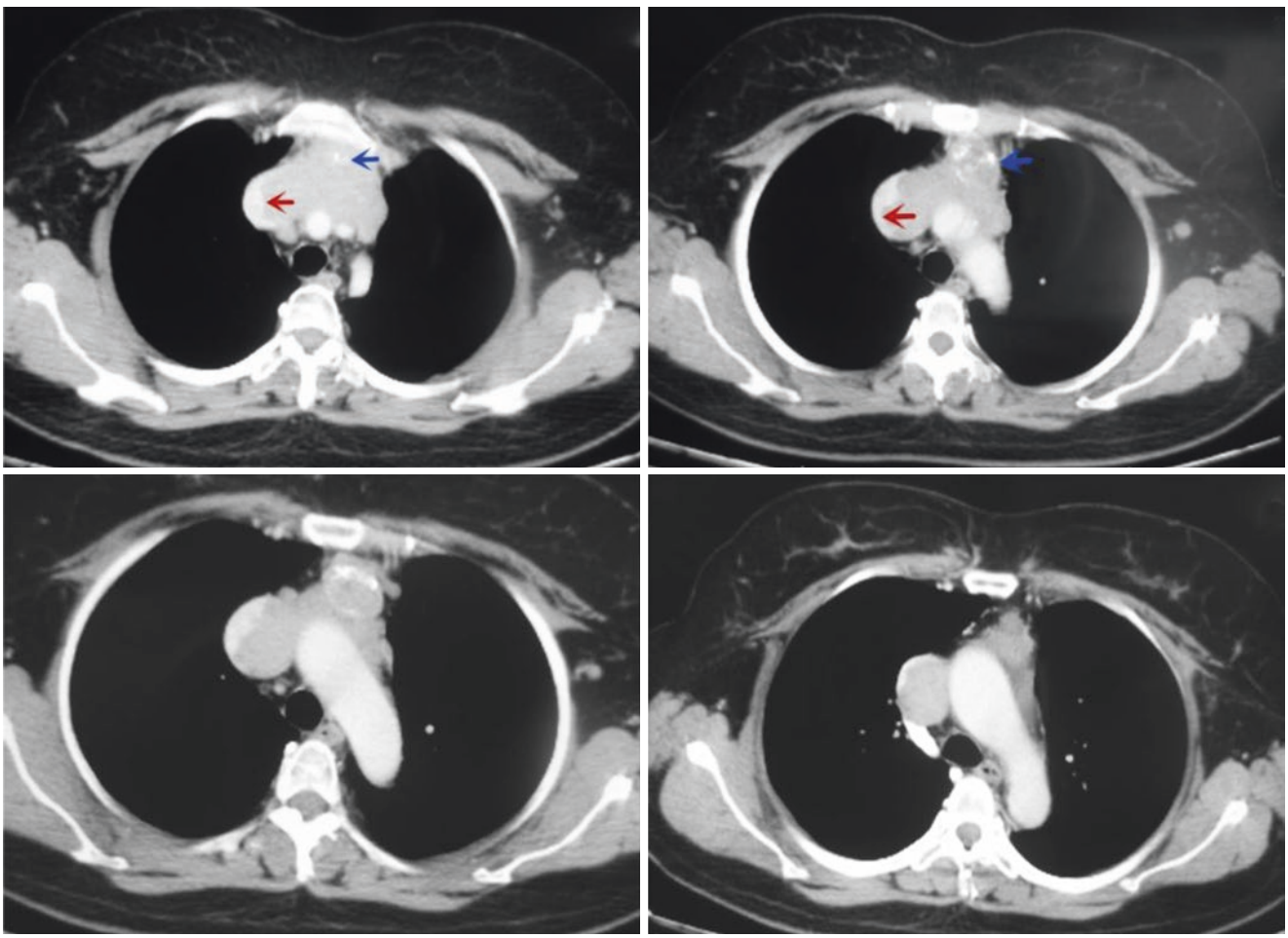

Fig. 4.12 Chest CT images of a 46-year-old woman

[**Diagnosis**] Atypical thymic carcinoid with ectopic ACTH syndrome

[**Diagnostic basis**] This patient has a history of hyperglycemia, hypertension, and obesity for 7 years. Both cortisol and ACTH increase and the circadian rhythm disappears. The low- and high-dosed examethasone suppression tests are both negative. Physical examination shows a typical Cushing syndrome. Pituitary and adrenal diseases are excluded and ectopic ACTH syndrome is considered first. The patient is a middle-aged woman with lateral mediastinal mass so that thymic tumor is considered firstly. Its internal density is not uniform and this is some spot or strip calcifications (blue arrow). The contrast-enhanced scan shows moderate enhancement and obvious vascular invasion (red arrow). The tumor thrombus in the superior vena cava is formed. So, the atypical thymic carcinoid is considered firstly. Transthoracic tri-cut biopsy was performed, and pathological examination revealed atypical thymic carcinoid.

[**Analysis**] Cushing's syndrome (CS) is a set of clinical symptoms that occur as a result of hypercortisolemia. An excessive concentration of cortisol in the body can have either exogenous or endogenous (adrenals, pituitary, ectopic) etiology. In most cases, its origin is iatrogenic. The incidence of endogenous CS varies from 0.2 to 5 cases in a million of the population in a year, with a median age of onset around 41.4 years and a female preponderance in a 3:1 ratio. There are two forms of endogenous CS: excessive secretion of ACTH causing ACTH-dependent, and ACTH-independent, caused by autonomous hyperactivity of the adrenal cortex. Compared with ectopic ACTH syndrome (EAS), Cushing disease (CD) caused by an ACTH-secreting pituitary adenoma is more common, while corticotropin-releasing hormone-producing tumors causing CS are exceedingly rare (<1%).

The first descriptions of CS concerning ACTH-secreting tumors not located in the pituitary gland come from 1928. The term of EAS was first proposed by Liddle in 1963 [7]. The most common cause of EAS is small cell lung cancer (45%), followed by thymic (15%), bronchial (15%), and pancreatic neuroendocrine tumors (10%). EAS from thymic neuroendocrine tumors is seen in 40–50% of hormonally active thymic neuroendocrine tumors. A meta-analyses of EAS cases reported in the literature have shown that males had a clear advantage and appeared earlier in the second and third decades of life. The intensity of symptoms in patients with ectopic ACTH-producing tumors depends on the serum cortisol levels and the growth rate of the tumor. EAS from thymic neuroendocrine tumors has a worse outcome than that of biochemically inactive thymic tumors, which may be due to its inherent aggressiveness coupled with the devastating metabolic derangements resulting from CS.

Due to the lack of specific CT manifestations of thymic carcinoid, it is necessary to closely combine the clinical data. When the anterior mediastinal lesions are complicated with endocrine symptoms, the diagnosis of thymic carcinoid ought to be considered first; when there is a definite clinical manifestation of Cushing syndrome without pituitary tumor or adrenal adenoma, or with pituitary tumor combined with adrenal hyperplasia, chest CT scan should be performed to find tumors less than 1 cm in diameter.

In a series of 74 cases studied by Wick et al. [8], the thymic neuroendocrine tumors associated with CS had a higher 10-year mortality rate (65%) than those without endocrinopathy (29%) or those with multiple endocrine neoplasia (50%). Neary et al. [9] studied 12 cases (eight males and four females) diagnosed between 1986 and 2010 with CS and thymic neuroendocrine tumors who underwent surgical resection. Eleven of Twelve patients presented have classic features of CS at a median age of 21 years (range, 7–51). All patients underwent thymectomy. Among them, 9 of 10 tumors exhibited positive ACTH immunochemistry. Median tumor diameter was 5 cm (range, 1–11.5). Six patients recurred 20–28 months after surgery with metastases to mediastinal lymph nodes ($n = 5$), bone ($n = 5$), liver ($n = 1$), parotid gland ($n = 1$), and breast ($n = 1$). Four of five patients treated with radiation therapy also received chemotherapy. All recurrent patients received ketoconazole; four later underwent bilateral adrenalectomy. Six recurrent patients died 22–90 months (median, 57) after thymectomy. At last review, six patients were alive 14–90 months (median, 49) after thymectomy. Thus, thymic ACTH-producing neuroendocrine tumor is an aggressive disease that should be considered in CS with ectopic ACTH secretion, particularly in younger patients.

Treatment options for thymic carcinoids are surgical excision, chemotherapy, somatostatin receptor analogs, and radiotherapy. Due to the aggressivity of atypical carcinoid, lesions are usually diffuse and multifocal; therefore, only a limited number of patients can achieve the surgical cure. Although different chemotherapy regimens are recommended, the success rate is <30%. Ose et al. [10] retrospectively examined 30 patients with thymic neuroendocrine tumor, 5- and 10-year survival was determined as 77% and 35%, whereas relapse-free survival was 48% and 29%, and cancer-specific survival was 90% and 48%, respectively. The overall survival rate of patients who received macroscopic complete resection was significantly higher. As for relapse-free survival patients, TNM Stage I or II and received adjuvant therapy patients showed good survival rates.

4.7.4 Case 4

A 47-year-old man complained of fatigue, dizziness, central obesity for more than 2 months. He went to the hospital half a month ago. Chest CT showed anterior mediastinal soft tis-

sue mass. Adrenal CT showed bilateral adrenal hyperplasia. Serum cortisol levels were found at 1306 nmol/L and 1524 nmol/L at 0800 and 1600. The level of aldosterone was 216 pg/ml, the level of angiotensin II was 157 pg/ml, and the level of renin was 0.5 ng/L. The high-dose dexamethasone suppression test was unable to suppress serum cortisol levels. He was hospitalized for further treatment. His blood pressure was 149/66 mmHg. Physical examination revealed typical Cushingoid features, such as full moon face, central obesity, and slight pitting edema of lower limbs. Serum glucose was 8.04 mmol/L, serum potassium was 2.8 mmol/L. Serum cortisol levels were found as 1388 nmol/L, 1930.8 nmol/L, and 1511 nmol/L at 1600, 00 00, and 0800, respectively. Serum aldosterone was 904.3 pg/ml. Serum corticotropin levels were found as 113.0 pg/ml, 63.80 pg/ml, and 209.3 pg/ml at 1600, 00 00, and 0800, respectively. No significant abnormality was found on MRI in the sellar region. Abdominal CT showed bilateral adrenal hyperplasia.

Chest CT: There is nearly circular soft tissue density nodular with a clear boundary in the left anterior mediastinum, without obviously enlarged lymph nodes in mediastinum (Fig. 4.13).

[**Diagnosis**] Thymic carcinoid with ectopic ACTH syndrome

[**Diagnostic basis**] Intraoperatively, obvious hyperplasia was observed in both the left and right thymus lobes, and a 2 cm × 1.5 cm × 2 cm tumor was found in the left upper lobe of the thymus gland. The thymus tumor was resected completely. Pathology was thymic carcinoid with incomplete capsule. Immunohistochemistry demonstrated positivity for CK (partial), Syn, CgA, NSE, and ACTH, and the staining index for Ki-67 was <1%. The blood cortisol and corticotropin were normal (454.80 nmol/L, 41.58 pg/ml) and potassium was also normal (4.6 mmol/L) at 10 days after surgery.

[**Analysis**] EAS is usually associated with typical carcinoids or small cell lung cancers, while it has been observed with other tumors including medullary thyroid carcinomas, pheochromocytomas, pancreatic islet cell tumors, and prostate carcinomas. In contrast to EAS caused by SCLC with its rapid onset and progression, slowly growing, small neuroendocrine tumors causing EAS is often difficult to distinguish from Cushing's disease (CD) based on their clinical, endocrine, and biochemical features. Thymic neuroendocrine tumors causing EAS occurs at any age (4–64 years, mostly between 20 and 40 years old). The most common manifestations include Cushingoid features indistinguishable from CD, but hypertension, severe hypokalemia, and edema are more frequent than CD.

Investigation of EAS begins with clinical suspicion confirmed with biochemical evidence of hypercortisolism and elevated ACTH, followed by localization of the source: pituitary or ectopic. Various case series have confirmed that an ACTH level >200 pg/mL suggests EAS over CD. Imaging studies are used to visualize the extent of tumor and assess metastatic disease.

Thymic carcinoid with Cushing syndrome has smaller lesions, which is consistent with this case. EAS is a clinical syndrome caused by tumor cells outside the pituitary secreting a large amount of ACTH, causing adrenal hyperplasia and releasing a large amount of cortisol. It is a kind of heterologous endocrine syndrome, which can appear in the early stage of the tumor even before the tumor symptoms and can also appear in the late stage of the tumor. In general, the hormone secretion of tumor is not regulated by internal factors, nor is it inhibited by exogenous hormones. Hormone levels can drop after effective treatment. The dexamethasone test fails to improve the symptoms and signs in patients of thymic carcinoid with EAS. Patients will have hypokalemia and metabolic diabetes. The imaging examination indicates that the adrenal glands are significantly enlarged and the symptoms

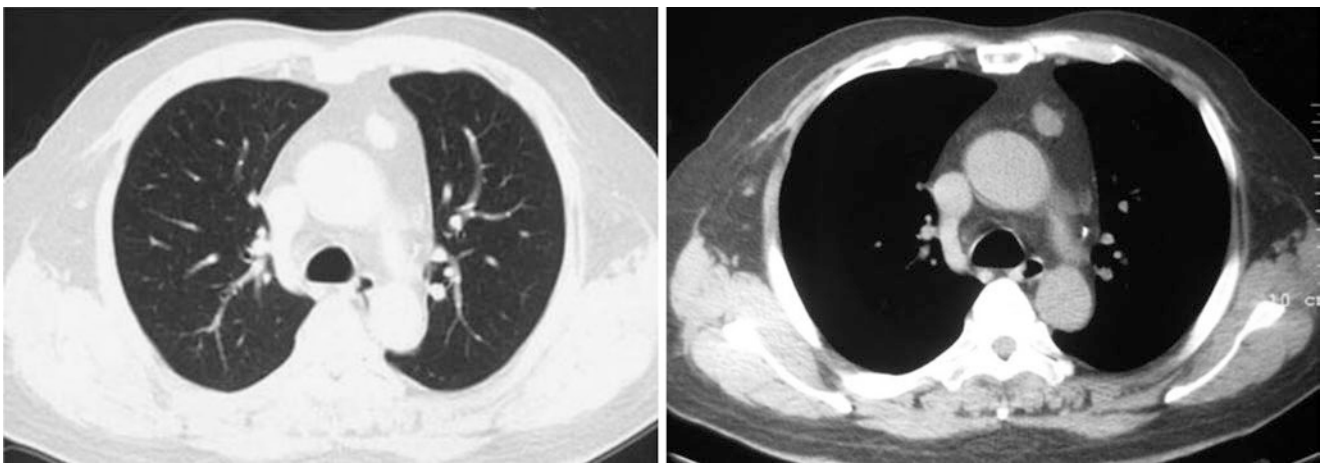

Fig. 4.13 Chest CT images of a 47-year-old man

cannot significantly be relieved even the adrenal gland is removed by surgery. Severe hypokalemia can lead to arrhythmia or even threat to life. Blood cortisol and ACTH levels decrease rapidly after the operation, and the short-term effect of the operation is obvious. Active potassium supplementation before surgery and hormone replacement after surgery can help patients to pass the perioperative period safely.

4.7.5 Case 5

A 46-year-old man complained of chest tightness for 2 months and eyelid edema for 1 week. Serum NSE was 99.89 ng/ml (normal 0~20.5).

Chest CT: A soft tissue mass of anterior mediastinum with mild enhancement (Fig. 4.14).

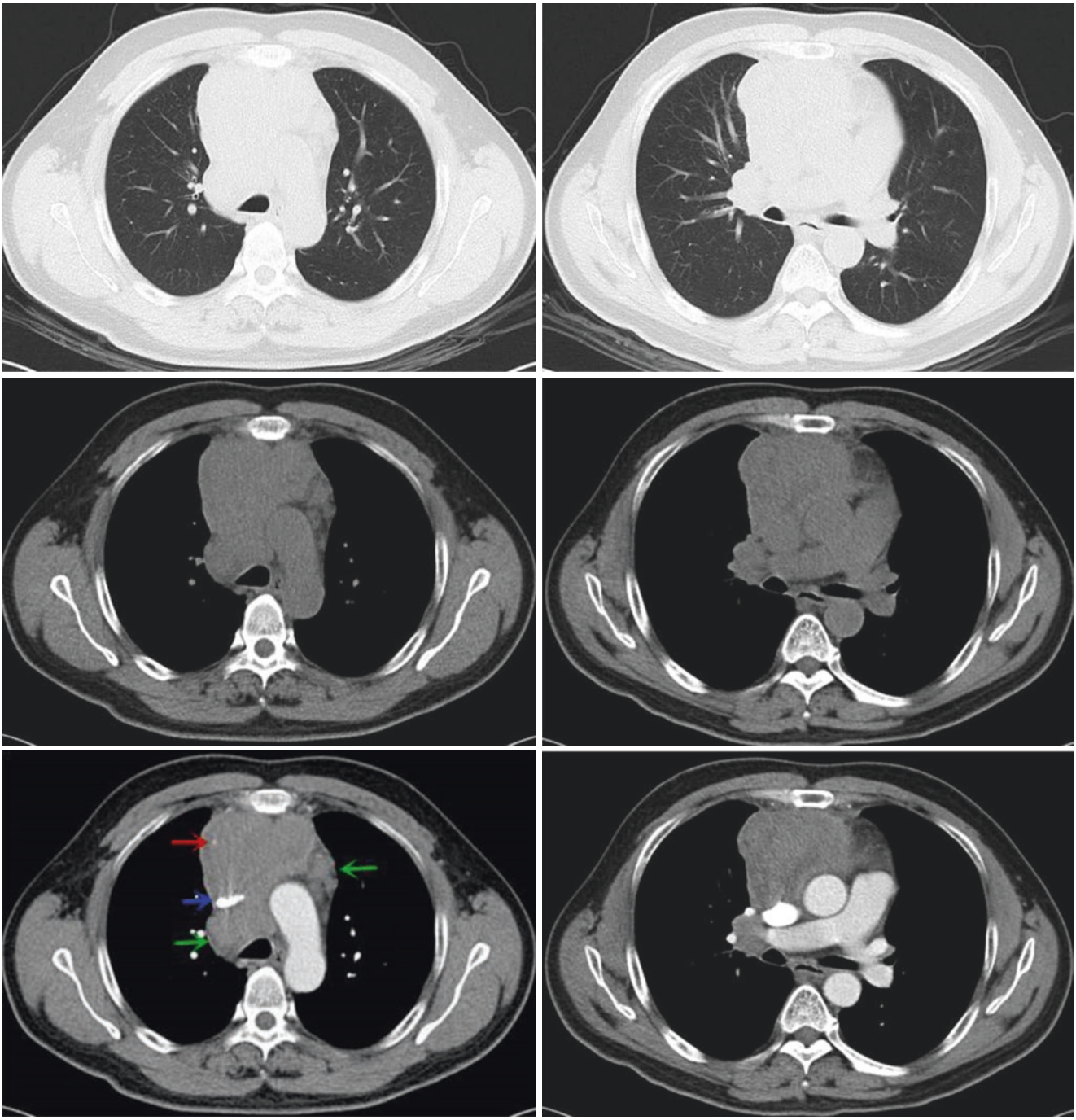

Fig. 4.14 Chest CT images of a 46-year-old man complained of chest tightness for 2 months and eyelid edema for 1 week

[**Diagnose**] Small-cell carcinoma of the thymus

[**Diagnose basis**] A middle-aged man with a soft tissue mass in the anterior mediastinum, a thymic tumor is first considered. The superior vena cava is involved and displaced (blue arrow), vascular shadow can be seen in the mass (red arrow), mediastinal lymph nodes show enlargement and fusion (green arrow). Combined with a significant increase in NSE, support the diagnosis of small-cell carcinoma of the thymus. Puncture pathology showed that the cancer cells were arranged in nests. Immunohistochemistry demonstrated positivity for CK, CK19, CD117, CgA, and Syn, and negativity for CK5/6, CD20, TdT, and CD5, and the staining index for Ki-67 was 60%. Pathology combined with immunohistochemistry, small-cell carcinoma of the thymus is considered.

[**Analysis**] Small-cell carcinoma (SCC) of the thymus is high-grade tumors with small cell morphology (scant cytoplasm, often fusiform tumor cells with ill-defined cell membranes, and nuclei with "pepper and salt-chromatin" without prominent nucleoli). Crush artifacts, high mitotic count, and extensive necrosis are characteristic findings. The majority of SCC originates in the lung, and those originating from extrapulmonary organs are rare, accounting for only 2.5–4% of SCC. SCC accounts for only about 10% of all thymic neuroendocrine tumors with an estimated incidence of 1 per 50 million inhabitants. Immunohistochemical markers are important for the diagnosis of SCC of the thymus. Most but not all tumors show keratin expression. Expression of neuroendocrine markers is common, but not required for the diagnosis. Similar to SCC in other (extrapulmonary) organs, the detection of TTF-1 cannot prove to be a primary tumor of the lung, but should always prompt close correlation with clinical findings. The genetic characteristics of thymic SCC and pulmonary SCC are not significantly different.

Nearly half of the patients have no symptoms before the surgery, most of which are discovered accidentally during chest examinations. A small number of patients only have anterior chest pain, cough, hemoptysis, shortness of breath, and other nonspecific symptoms. At the time of diagnosis, most tumors are in an advanced stage with infiltration of neighboring organs, such as pericardium or lungs, or with distant metastases to the lung, brain, liver, or bone. A few patients may be associated with abnormal endocrine symptoms, mainly Cushing syndrome, which is related to ectopic secretion of ACTH by tumor cells.

The imaging findings of SCC of the thymus have no specificity. CT can clearly show the soft tissue mass of the anterior mediastinum. Due to the invasive growth of the tumor, the majority of the boundary is unclear, and the low-density fat gap between the tumor and the surrounding structure disappears. There is an uneven enhancement and the superior vena cava and trachea are often compressed and deformed. The tumor may surround the large blood vessels in the late stage of disease. In addition, mediastinal lymph nodes enlargement often can be seen, which is most common in mediastinal tumors with small-cell carcinoma and lymphoma (Fig. 4.15). MRI can help determine whether a tumor has invaded surrounding tissue.

4.7.6 Case 6

A 55-year-old man with postoperative colon cancer for more than 3 years. Physical examination showed the mediastinum occupation for more than 2 years. The patient has undergone radical ileocecal tumor resection for "intussusception" 3 years ago and the postoperative pathology showed moder-

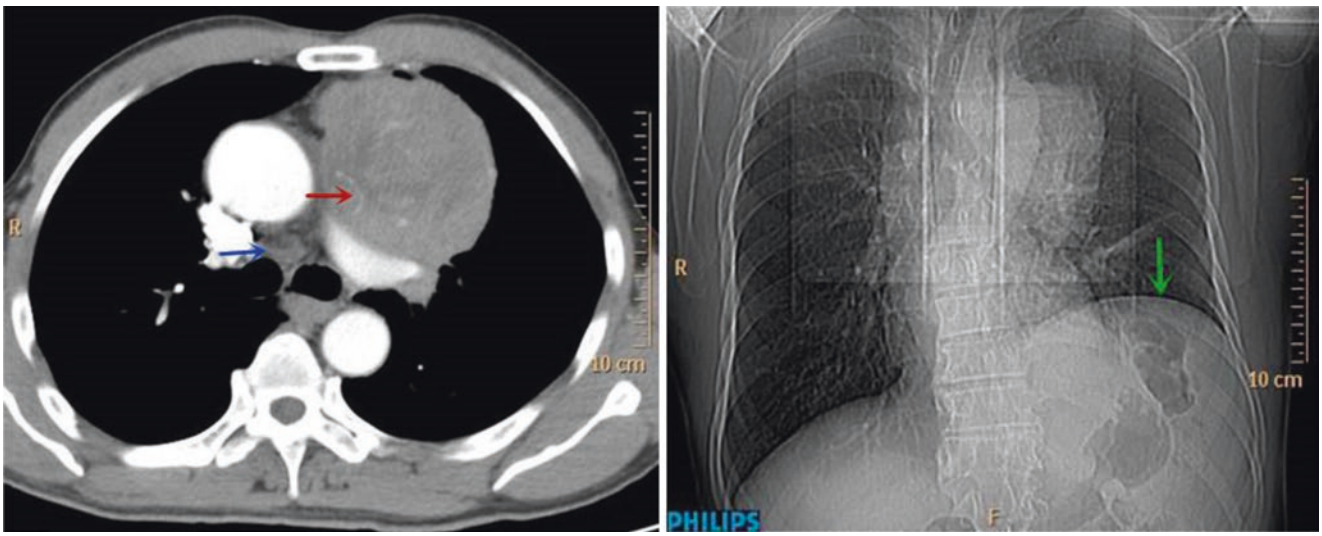

Fig. 4.15 A 57-year-old man with small-cell carcinoma of the thymus, showing intravascular tumor shadow (red arrow), mediastinal lymphadenopathy (blue arrow), and left phrenic nerve paralysis (green arrow)

ately differentiated adenocarcinoma, invading the whole layer. The patient undergoes adjuvant chemotherapy for 3 cycles and having good postoperative recovery. CT examination on April 17, 2013, showed a nodule with rich blood supply in the anterior mediastinum. No treatment is given. CT examination on October 21, 2015, showed that the volume of the anterior mediastinal tumor increased significantly compared with that of 2013. The patient had hypertension for 20 years and diabetic for 10 years. He had a 3-year history of abdominal lipoma resection and an 1-year history of lipoma resection in the buttock.

Chest and abdomen CT: A oval soft tissue mass with clear boundary in the left anterior mediastinum, the unenhanced and contrast-enhanced CT attention was 35HUand 66HU, respectively (Fig. 4.16).

[**Diagnosis**] Thymic carcinoid with MEN1

[**Diagnostic basis**] A middle-aged male with oval soft tissue mass in the left anterior mediastinum, contrast-enhanced

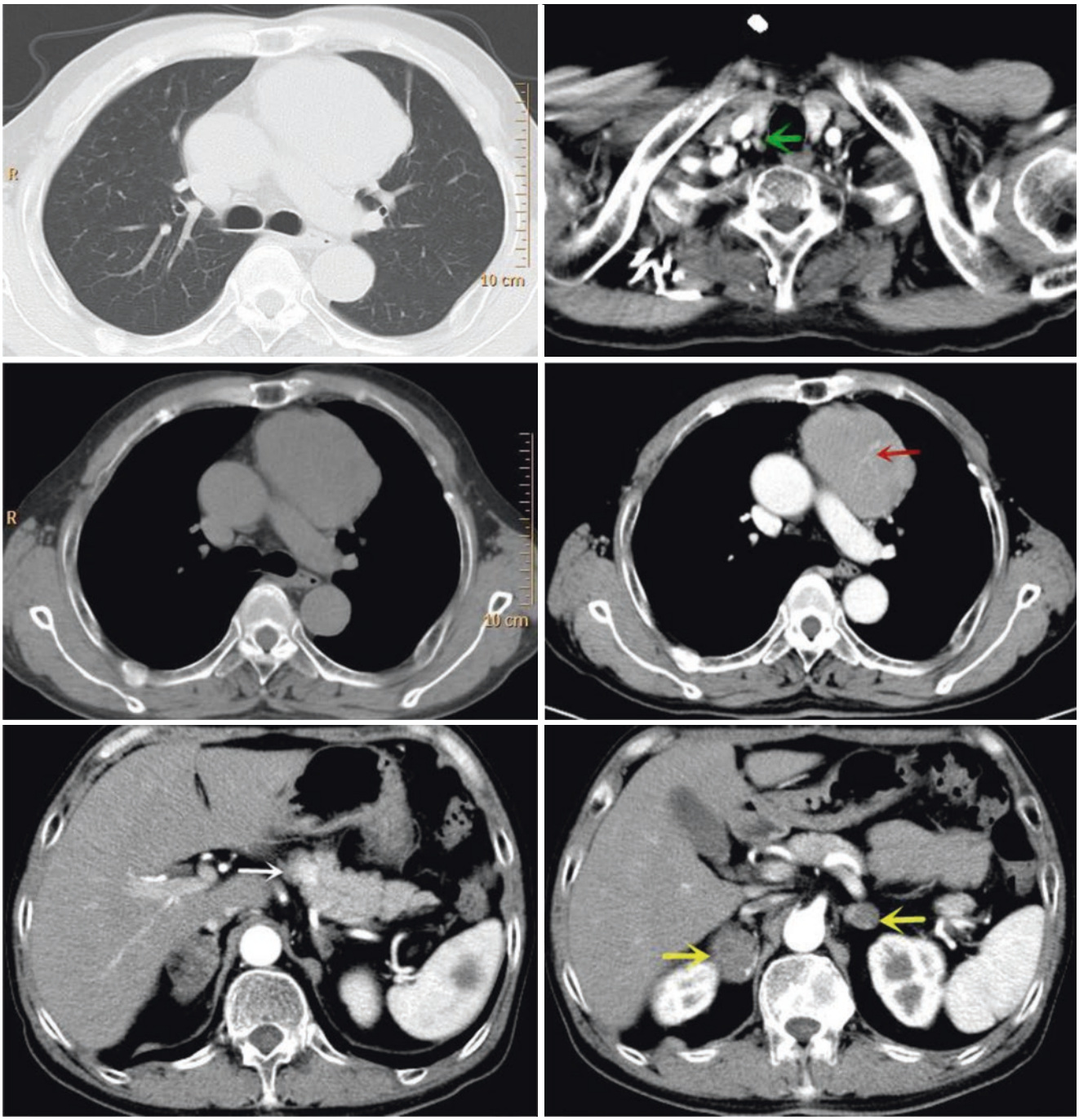

Fig. 4.16 Chest CT images of a 55-year-old man with postoperative colon cancer for more than 3 years

scan with moderate enhancement, the tumor vessels (red arrows) are clearly seen, thymic carcinoid is first considered. The patient has a history of lipoma resection in the abdominal wall and buttock. The neck CT shows parathyroid adenoma (green arrows), abdominal CT shows pancreatic neuroendocrine tumor (white arrows), and bilateral adrenal pheochromocytoma (yellow arrows), all of them support the diagnosis of thymic carcinoid with MEN-1. The mediastinal tumor was surgically removed, with a size of 8.5 cm×7 cm×5.5 cm and partial capsule attached to the surface. The cut surface was sallow and gray-red with coarse quality and bleeding. Pathology showed neuroendocrine carcinoma (atypical carcinoid), infiltrating the capsule and reaching the surrounding adipose tissue. Immunohistochemistry demonstrated positivity for CKpan, Syn and CD56, and negativity for CgA and CK5/6. The staining index for Ki-67 was 20–30%.

[**Analysis**] Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant tumor syndrome arising from an inactivating mutation on a tumor suppressor gene located on chromosome 11q13. If an individual has two or more primary MEN1-associated endocrine tumors (parathyroid adenoma/hyperplasia, gastroenteropancreatic tumor, and pituitary adenoma), MEN1 can be diagnosed. Hyperparathyroidism is most common and the incidence rate reaches 90%; pancreatic neuroendocrine tumor occurs in 60% and pituitary adenoma in 40% cases. In addition to these most common findings, the MEN1 patient may also develop other endocrine and nonendocrine tumors like carcinoid tumors of the thymus, bronchus, or stomach, cutaneous tumors, adrenocortical tumor, central nervous system tumors, lipoma, leiomyoma, collagenoma, and angiofibroma. The mutation site of the gene is not unique. Therefore, since the MEN-1 gene was first cloned in 1997, various patterns of mutation have been reported. Familial MEN-1 can be diagnosed if at least one first-degree relative also has one of the parathyroid adenoma, gastric, pancreatic and intestinal tumors, and pituitary tumors. Sporadic MEN-1 can be diagnosed if there is no family history. Carrying out the MEN1 gene test in an index case can confirm the diagnosis and allow early detection of asymptomatic mutation carriers, before MEN1-associated tumor can be detected. However, about 20% of MEN1 kindred have no mutation in the MEN1 gene. Unfortunately, there is no genotypic–phenotypic correlation in MEN1, which leads to different manifestations, even among family members, but nonsense and splicing mutations are associated with more aggressive neuroendocrine tumors. In this case, there are lipoma, parathyroid adenoma, pancreatic neuroendocrine tumor, and bilateral adrenal pheochromocytoma, in which gene sequencing shows a compound heterozygous mutation in exon 10 of the MEN1 gene. Therefore, it is diagnosed as MEN1.

There are 3–8% of MEN-1 patients involved with thymic neuroendocrine tumor. However, some studies found that thymic neuroendocrine tumors accounted for about 20% of the total deaths in patients with MEN1. Endocrine pancreatic tumor and thymic carcinoid are the two major causes of death in MEN1 patients. Chest screening by CT or MRI is strongly recommended for MEN1 patients because their thymic carcinoids are associated with a poor prognosis. The general principle of MEN1 treatment is surgical resection of the lesion, supplemented by medical treatment.

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