Thymic Hyperplasia

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Descriptions of the thymus date back to more than 2000 years ago, yet its functions were not known for centuries. The word thymus comes from the Latin derivation of the Greek word thymos, meaning warty excrescence due to its likeness to a bunch of thyme. Because thymos also means "soul" or "spirit," the thymus was misrepresented as the seat of the soul by the ancient Greeks. Galen of Pergamum (129–200 AD), an ancient Greek physician, who first noted that the thymus was proportionally largest during infancy, referred to the thymus as an "organ of mystery," a moniker that remained fairly accurate for almost two millennia.

1.1 Thymic Development and Anatomy

The thymus is a gland situated in the anterior mediastinum, embryologically derived from the third and fourth pairs of pharyngeal pouches. Over the next few weeks, this tissue migrates caudally and medially along the thymopharyngeal duct (deep to sternocleidomastoid muscle) to the anterior mediastinum. Subsequently, lymphoid cells from the liver and bone marrow migrate to the thymus, after that the thymus differentiates into a cortex and medulla. It overlies the pericardium, aortic arch, left innominate vein, and trachea. The thymus may extend superiorly to the lower pole of the thyroid and inferiorly to the diaphragm, which is attached to the thyroid by the thyrothymic ligament. Thymic lesions or ectopic thymic tissue can occur anywhere along the thymopharyngeal duct.

The thymus is a lymphatic organ that plays an important role in the development and maturation of the immune system during childhood, specifically T cells, which are vital in regulating cellular immunity, and B cells, which are vital in regulating humoral immunity. The size of the thymus varies with age. From a birth mean weight of 15 g, the size grows until puberty to a mean weight of 30–40 g, and then, it undergoes progressive atrophy, to no more than 5–15 g in the elderly. In early infancy, it reaches its largest relative size, because its rate of increase is less than the rest of the body in a growing child. After the age of 2 years, the thymus is less frequently visible. As children grow older and their immune systems mature, the thymus undergoes physiologic involution, eventually leading to scattered lymphocytes present within adipose tissue, yet it maintains its original configuration. The normal thymus attenuation is significantly higher and easier to show a fuller quadrilateral shape in 20–30-year-old women than in men of the same age.

On histologic examination, the thymus is organized into multiple lobules that are arranged into an outer cortex and an inner medulla. The cortex is composed of immature T-lymphocytes and thymic epithelial cells; the medulla is composed of maturing lymphocytes and whorls of spindle-shaped epithelial cells, which create Hassall corpuscles with keratinized cores.

1.2 Classification

Thymic hyperplasia consists of two subtypes, true hyperplasia and lymphoid hyperplasia (also known as follicular hyperplasia or lymphofollicular hyperplasia), which are clearly distinguished by pathologic analysis. These two entities are indistinguishable from one another at imaging.

True thymic hyperplasia shows an enlarged thymus gland with an increase in normal thymus tissue, determined by weight and volume, beyond the upper limit of normal for which particular age. Although a hyperplastic thymus may retain its normal shape, it more commonly loses its unique bilobed appearance and instead appears oval. Clinically, true thymic hyperplasia can be divided into three groups: those without a related preexisting condition; those recovering

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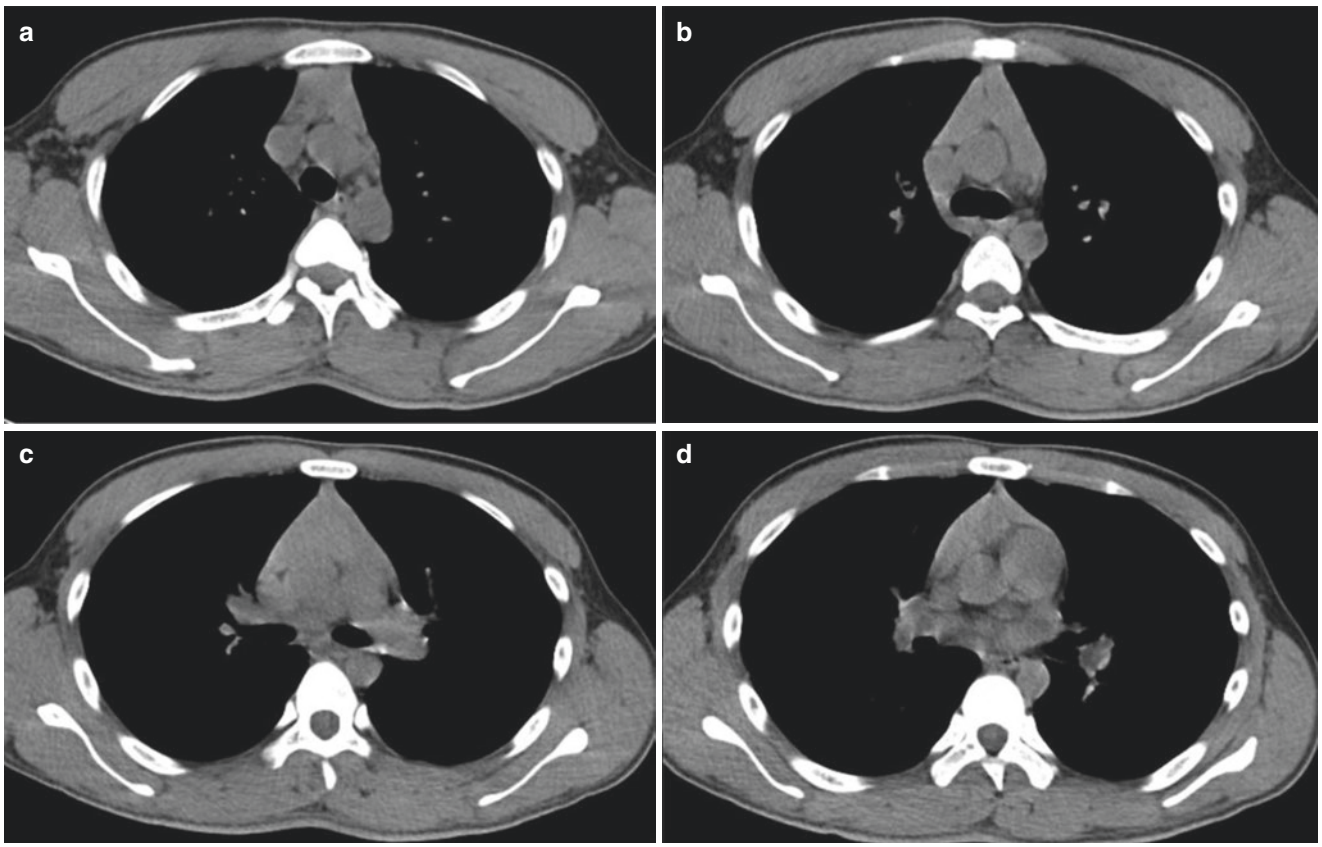

Fig. 1.1 A 20-year-old man had a history of hyperthyroidism and thymic hyperplasia, and complained of fear of heat and sweating for more than 2 months. Chest CT showed a triangular-shaped thymus with arrowhead morphology, homogeneous soft-tissue attenuation similar to that of muscle and unenhanced vessels, and slightly concave borders

from a recent stress event such as pneumonia, corticosteroid therapy, radiation therapy, chemotherapy, surgery, or burns; and those with other disorders such as hyperthyroidism (Fig. 1.1), sarcoidosis, or red blood cell aplasia. In response to these stressors, the thymus first shrinks and then grows back when the stress is eliminated; the thymus sometimes continues to grow and become larger than its original size, which is referred to as "rebound hyperplasia." Among patients with chemotherapy, approximately 10–25% may develop rebound hyperplasia, which usually occurs within 2 years of initiation of chemotherapy. However, there is a reported case of rebound hyperplasia that occurred 5 years after completion of chemotherapy. True thymic hyperplasia has been reported in a patient who received antitumor necrosis factor therapy for the treatment of rheumatic disease, in patients treated for human immunodeficiency virus infection, and in a patient following a severe infection. Additionally, Graves' disease has attracted attention as a cause of true thymic hyperplasia. The mechanism through which Graves' disease leads to true thymic hyperplasia has not yet been elucidated. So far, two possible mechanisms have been proposed. The first mechanism involves the expression of the TSH receptors in the thymus, which mediates thymic overgrowth through an autoimmune response. In some thymic hyperplasia cases accompanied by Graves' disease, the presence of TSH receptors in thymic tissues was revealed by a reverse transcription-polymerase chain reaction, northern blot analysis, and immunohistochemistry. Another mechanism involves the induction of hyperplasia in the thymus by the thyroid hormones. Nuclear T3 receptors are expressed in the murine thymic epithelium, and the thymus enlargement during T3 treatment. In addition, patients with Graves' disease who underwent radioiodine treatment showed a reduction in thymic volume in parallel with a decrease in serum T3 levels. In lymphoid hyperplasia, the thymus gland is not always enlarged, can be atrophic, or can be involved with a neoplasm.

Lymphoid hyperplasia, on the other hand, is characterized by the presence of an increased number of lymphoid follicles and germinal centers in the thymus. Unlike true hyperplasia, thymic lymphoid hyperplasia may occur with or without thymic enlargement. It is commonly associated with autoimmune diseases such as myasthenia gravis, thyrotoxicosis, systemic lupus erythematosus, rheumatoid arthritis, scleroderma, and other autoimmune conditions and has been reported to occur in the early stages of human

immunodeficiency virus infection. Thymectomy is often performed in patients with myasthenia gravis because of the improvement of myasthenic symptoms after thymectomy.

The pathogenesis of thymic hyperplasia remains unclear. In 1978, Levine et al. divided the thymic hyperplasia into two subtypes according to the characteristics of histomorphology [8]. The first is lymphoid follicular hyperplasia characterized by the presence of active lymphoid follicle primordial center. The pathophysiologic changes were as follows: thymic medulla expansion, cortex damage, and the presence as a chronic inflammatory reaction. The other is true thymic hyperplasia. The morphology and microstructure of true thymic hyperplasia were consistent with that of normal thymus in children's age, but its volume and weight were significantly larger than that of normal thymus (Fig. 1.2). But this type of hyperplasia has never been found in any other tissues and organs. Lymphoid follicular hyperplasia is also known as autoimmune thymitis, which is usually self-limited and without the increase of thymus volume. Studies have shown that myasthenia gravis was closely related to lymphoid follicular hyperplasia but not related to the true thymic hyperplasia.

1.3 Clinical Features

Thymic hyperplasia occurs in children or adolescents, which may be related to the active function of their thymus. Some patients may have congenital thymic hyperplasia, which were found in childhood due to symptoms or physical examinations. There was no significant difference between men and women.

Hyperplastic thymus may oppress the trachea, bronchus, lung tissue, and heart. The patients usually have symptoms of respiratory and circulatory systems, such as cough, dyspnea, fatigue after activity, or recurrent respiratory infection.

1.4 Radiographic Features

Typically, the thymus is visible on a computed tomography (CT) scan and fills the perivascular space throughout the first 20 years of life. It typically appears quadrilateral with convex borders in children younger than 5 years. As children grow, the thymus gradually becomes triangular with straight

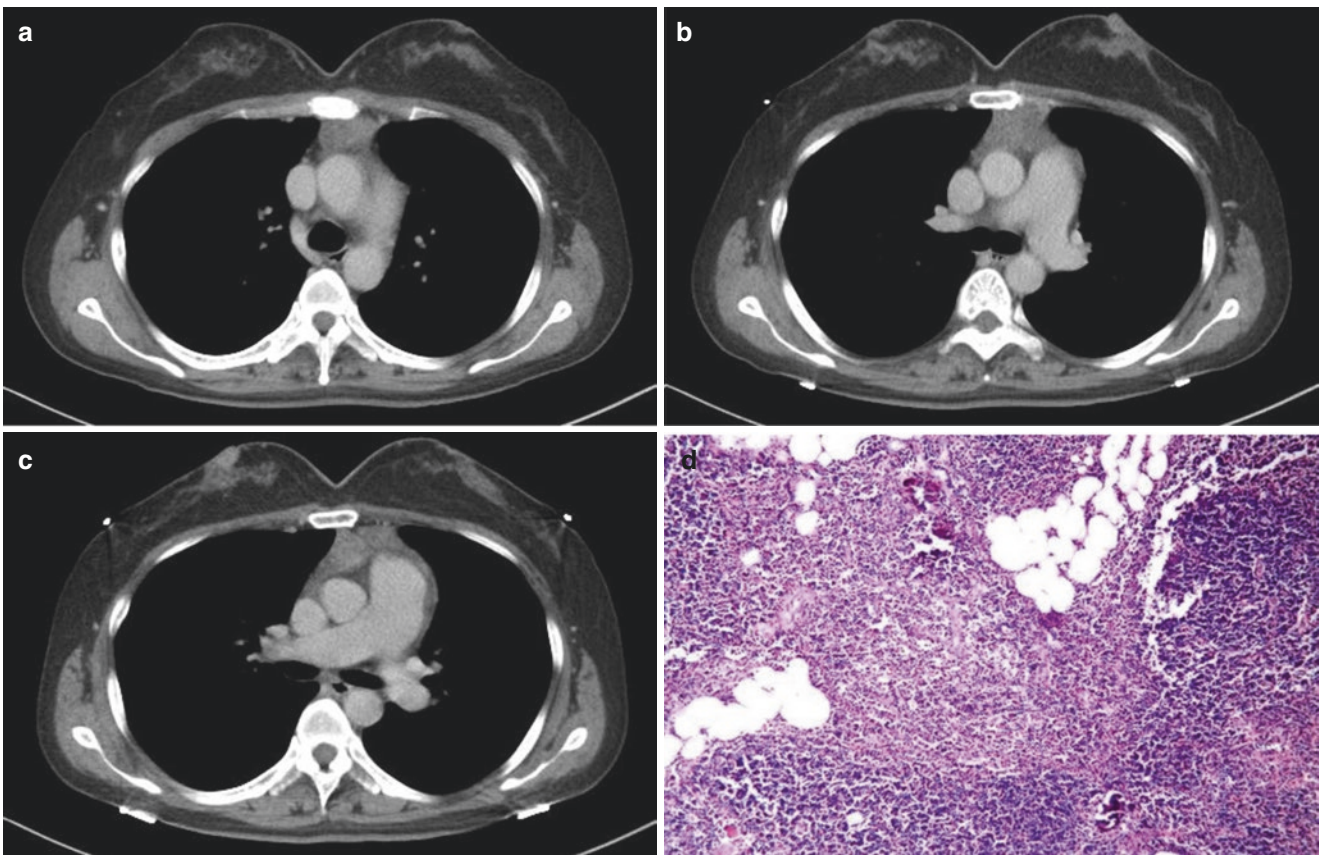

Fig. 1.2 A 33-year-old woman complained of limb weakness in the afternoon for more than 3 months. Pathology showed the thymus tissue, the lobular structure retained the skin and medulla differentiation, and the normal distribution of lymphocytes and epithelial cells

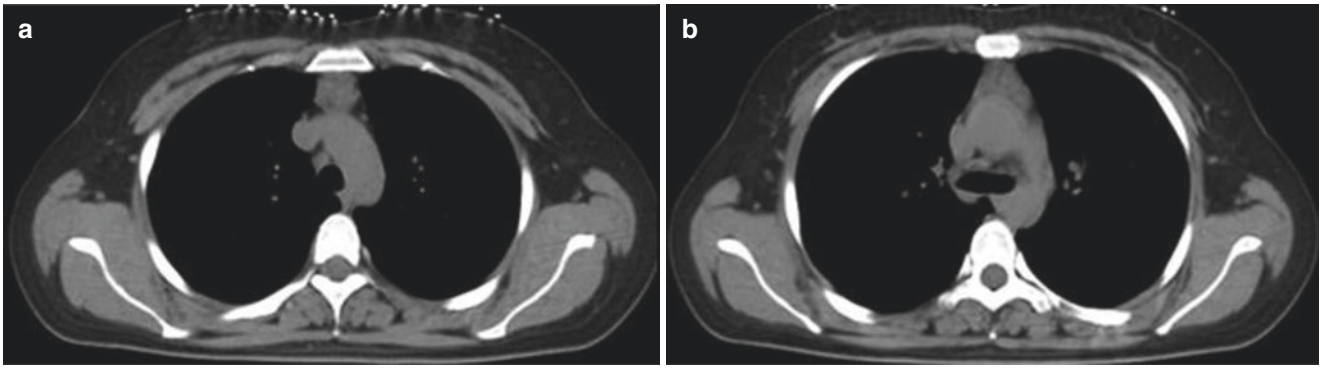

Fig. 1.3 Chest CT image in a 29-year-old woman showed a diffuse asymmetric enlarged thymus anterior to the aortic arch that exhibited lower attenuation compared to muscle and unenhanced vessels suggesting fatty infiltration

or concave borders. The left lobe is often slightly more prominent than the right, with concave or flat margins in the normal adult. On T1-weighted MR images (T1WI), adult thymic signal intensity is generally slightly greater than muscle but less than fat, and on T2-weighted images (T2WI) it is somewhat higher than muscle and equal to or slightly less than fat.

The CT scan of thymic hyperplasia can have the following typical features: (1) the thymus in the anterior mediastinum is enlarged, especially the thickness is increased, but it still maintains its normal shape, which is round, trapezoid, rectangle, or pear shape (Fig. 1.3), with smooth edge and lobulated shape; (2) about 30–50% of thymic hyperplasia has normal size and occasionally small calcification; (3) the thymus has muscular and uniform density, enhanced CT shows mild enhancement (Fig. 1.4). The density may be uneven, but there is no obvious nodular enhancement; (4) the interface between thymus and sternum, aortic arch, and leading edge of the heart is wide, but there is no erosion and wrapping of adjacent structures, and the boundary between thymus and surrounding normal structures is clear, no lymphadenopathy and pleura and pericardium are involved.

1.5 Differential Diagnosis

Thymic hyperplasia is easily confused with thymoma. Thymic hyperplasia is usually manifested by diffuse, symmetric enlargement of the thymus, a smooth contour, scattered fat and soft-tissue elements, normal vessels, and preserved adjacent fat planes. Thymoma occurs in adults. The mass is nodular or lobulated, with heterogeneity (i.e., hemorrhage or necrosis), or calcifications. It can be associated with pleural and pericardial involvement and lymph node metastasis. On CT enhanced scans, thymoma is homogeneous or heterogeneous mass, and the enhancement was obvious; thymic hyperplasia was slightly enhanced or not. Hormone therapy trials are also a method of identification. After hormonal treatment, the normal thymus and hyperplastic thymus often atrophy, and can increase again after stopping treatment, while thymoma does not respond to hormonal treatment.

All thymic hyperplasia are quadrilateral (with or without biconvex margins), triangular, or bilobed. Bipyramidal morphology and the presence of gross intercalated fat are each pathognomonic for thymic hyperplasia. Epithelial thymic tumors and other tumors involving the thymus do not demonstrate microscopic fat by histopathology. Therefore, the diagnosis of microscopic fat through MRI is extremely helpful to distinguish thymic hyperplasia from tumor. In 2007, Inaoka et al. demonstrated that chemical shift MRI may be used to detect the presence of microscopic or intravoxel fat within thymic lesions and thereby distinguish thymic hyperplasia from thymomas and lymphomas [9]. Forty-one patients whose thymic lesions were seen at chest computed tomography were assessed, and assigned to a hyperplasia group (n = 23, 18 with hyperplastic thymus associated with Graves' disease and 5 with rebound thymic hyperplasia) and a tumor group (n = 18, 7 with thymomas, 4 with invasive thymomas, 5 with thymic cancers, and 2 with malignant lymphomas). All patients in hyperplasia group had an apparent decrease in thymus gland signal intensity at chemical shift MR imaging, while no decrease in thymus gland signal intensity was shown in patients of tumor group. Therefore, mediastinal MRI is a reasonable choice if bipyramidal, bilobed, triangular, or quadrilateral morphology is found, in the absence of obvious intercalated fat throughout the lesion on CT, and the lesion appears mass-like. Mediastinal MRI including chemical shift MR imaging is to distinguish between thymic hyperplasia and thymic tumors, whether thymoma or lymphoma.

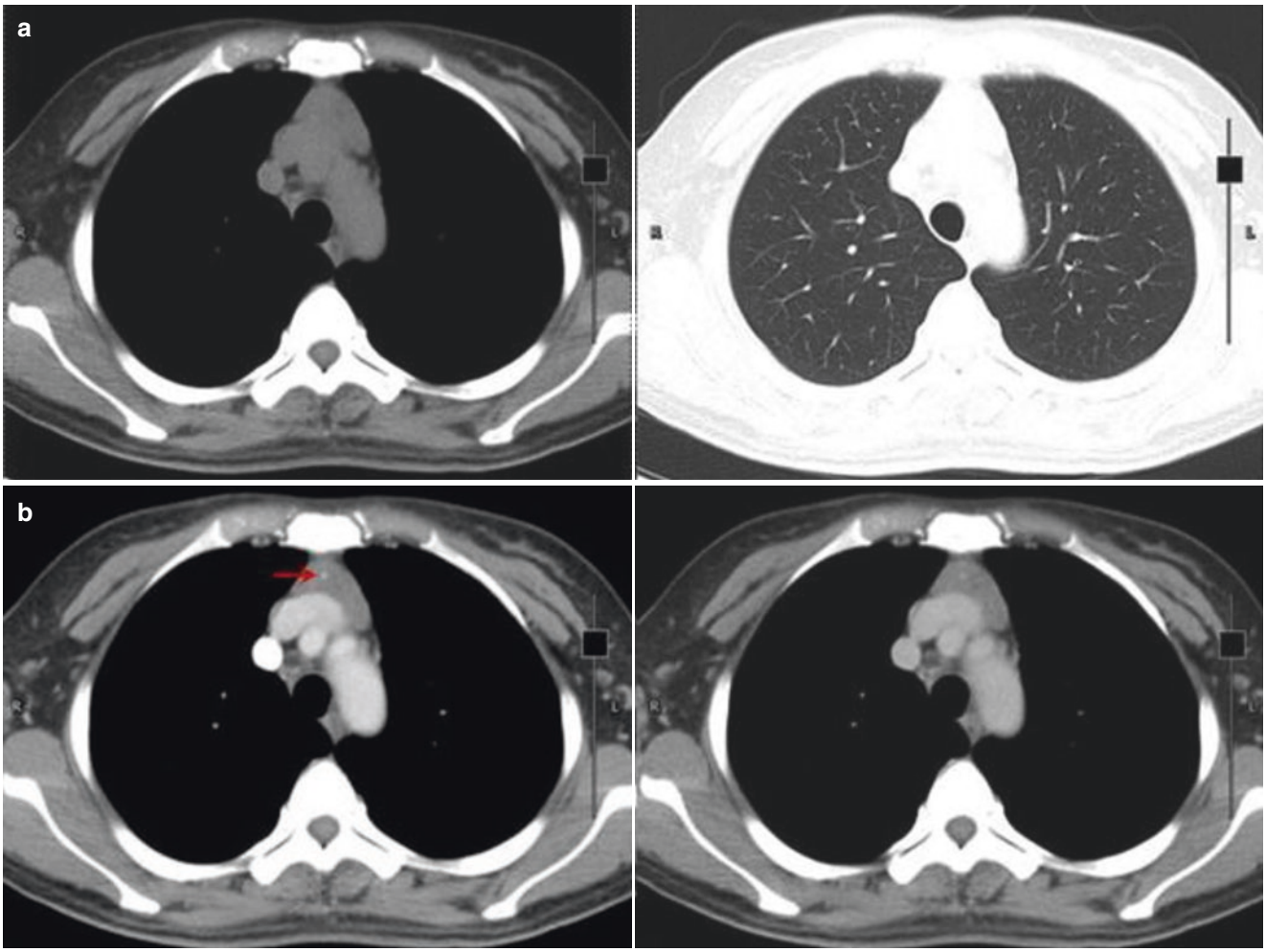

Fig. 1.4 Chest CT image in a 41-year-old woman showed a triangular or arrowhead-shaped thymus at the level of the aortic arch. Contrast-enhanced CT scan showed slightly enhanced and vascular shadow (red arrow)

1.6 Treatment

Pediatric patients with thymic hyperplasia can be treated with oral hormone as diagnostic therapy. Generally, thymus began to shrink after 1 week. However, the treatment of giant thymic hyperplasia remains controversial. The hormone therapy has no obvious effect, which may be related to the thymus being too large and insensitive to drugs. Studies have shown that thymectomy in children, especially infants less than 1-year-old, can cause a decrease in peripheral blood T lymphocytes. So thymectomy should be avoided as much as possible. Complete surgical resection is still an important method for the treatment of thymic hyperplasia, especially for patients with respiratory and circulatory system symptoms or other emergency conditions. Surgical treatment should be carried out as soon as possible to improve the symptoms of patients. Children who do not respond to hormonal therapy still need surgery after a little older.

1.7 Case Analysis

1.7.1 Case 1

A 30-year-old man complained of chest tightness for more than 3 months.

Chest CT: Multiple cystic low-density lesions were seen in the thymus area and around the superior vena cava, and the enhanced scan showed homogeneous enhancement (Fig. 1.5a–f).

[Diagnosis] Thymic hyperplasia.

[Diagnosis basis] Multiple cystic low-density lesions were seen around the thymus region and the superior vena cava. The lesions in the thymus region were pear shaped, conforming to the shape of the thymus. Enhanced scans showed homogeneous enhancement of lesions. The above features combined with patient age need to consider the possibility of thymic hyperplasia. The patient underwent medi-

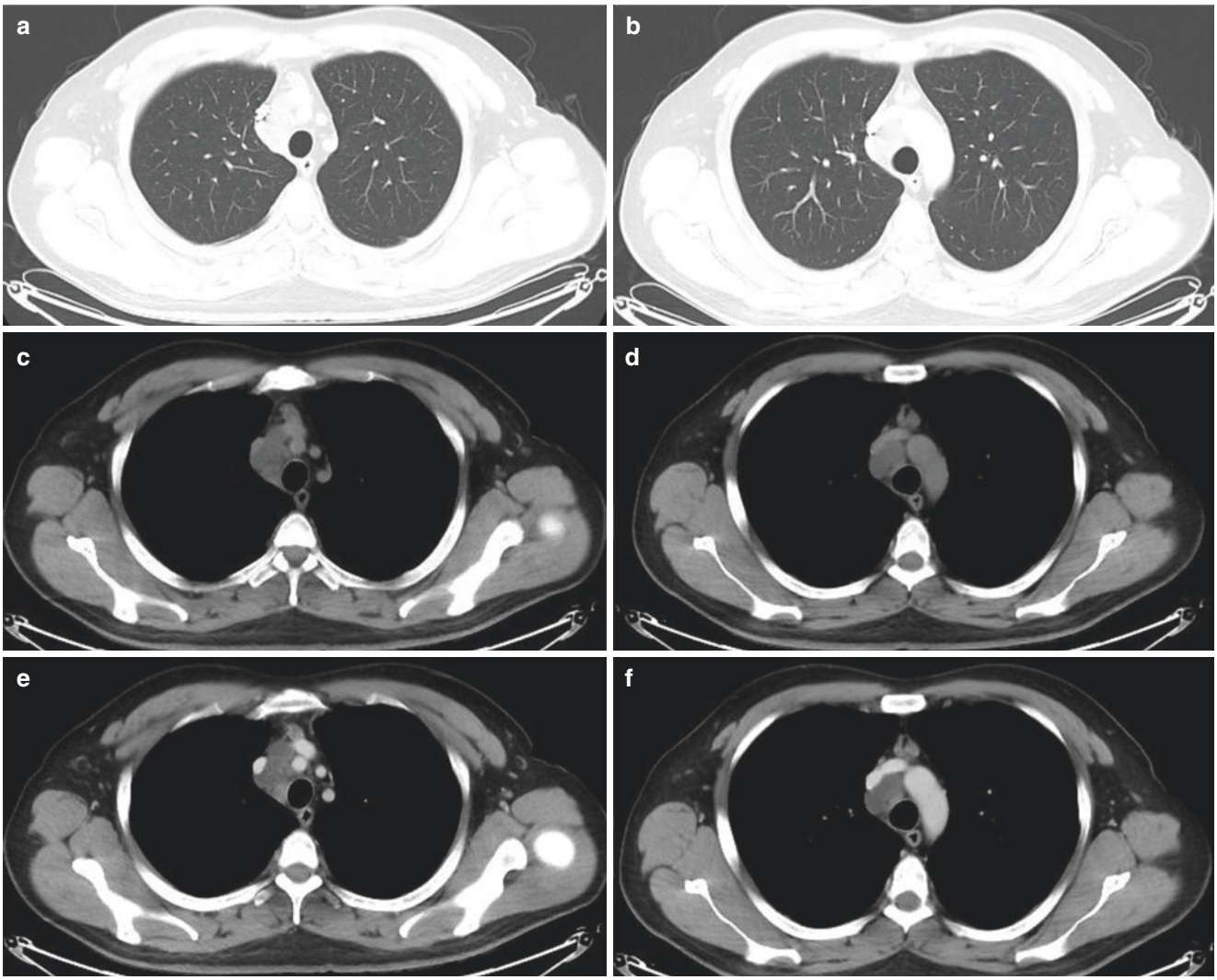

Fig. 1.5 (**a**–**f**) Chest CT image of a 30-year-old man complained of chest tightness for more than 3 months

astinoscopy. Intraoperatively, solid hyperplastic lymph node tissue was found in the posterior lower part of subclavian artery. Pathology showed that most of the tissues were fatty fibers and irregular blood vessels, in which small pieces of hyperplastic thymus tissue were seen (Fig. 1.6). Immunohistochemistry demonstrated positivity for CK, CD3 (Fig. 16b), CD20, CD21 (FDC), CD68, CD34 (vascular), and CD31 (vascular), and negativity for D2–40 and CK19. It is consistent with thymic follicular hyperplasia.

[Analysis] The thymus is sensitive to any kind of bodily stress, including systemic infection, tumors, surgery, and chemotherapy, and responds with rapid atrophy, regrows to its original size, or even larger. The thymus is disproportionately larger in infants but gradually replaced by fat and involutes throughout maturation. Nevertheless, the thymus maintains its ability to grow back at any time and age.

The most common morphologic feature of thymic hyperplasia was pyramidal shape, seen in 80% of the patients. Thymic lymphoid hyperplasia refers to the presence of thymic tissue with lymphoid germinal centers in the thymic medulla. It is observed in a number of autoimmune diseases, most commonly myasthenia gravis, being seen in up to 65% of myasthenia gravis patients.

To identify features that can differentiate true hyperplasia from lymphoid hyperplasia, the imaging characteristics of pathologically proven thymic hyperplasia were investigated by Araki et al. [10]. CT attenuation of lymphoid hyperplasia was found to be significantly higher than that of true hyperplasia, with the optimal threshold of greater than 41.2 HU for differentiating lymphoid hyperplasia from true hyperplasia. Other measurements, including length, thickness, diameters, and qualitative features, did not significantly differ between the two subtypes of thymic hyperplasia. The higher CT attenuation of lymphoid hyperplasia patients is not due to age differences, but likely reflects the histologic features of the entity composed of lymphoid follicles. The results were

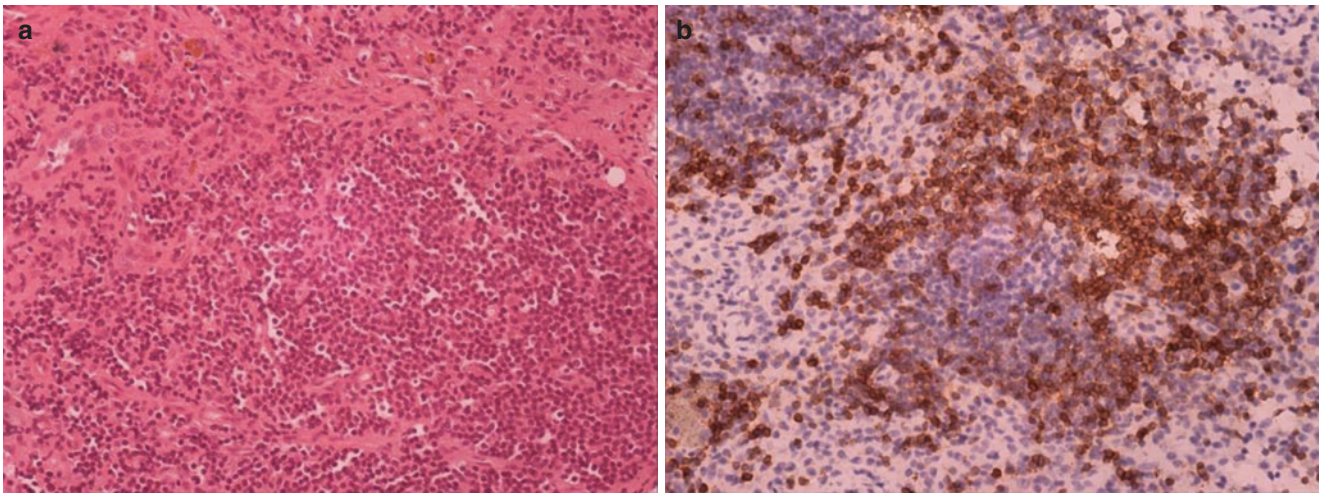

Fig. 1.6 H&E staining, 400×. Figure 1.8 Immunohistochemically, the CD3 was positive (400×)

somewhat counterintuitive, by pathologic definitions, true hyperplasia is defined as enlargement of the thymus gland, determined by weight and volume, beyond the upper limit of normal for that particular age, whereas lymphoid hyperplasia refers to the presence of an increased number of lymphoid follicles and may or may not be associated with enlargement of the thymus. Given the description, one might expect that the thymic gland with true hyperplasia is larger than the gland with lymphoid hyperplasia; however, their results showed no difference.

Thymic hyperplasia mainly depends on histological diagnosis. Thymic hyperplasia can be diagnosed once germinal center and/or lymphoid tissue hyperplasia and lymphoid follicle formation of medullary B cells are found in the medulla.

1.7.2 Case 2

A 26-year-old man was admitted to the local hospital half a year ago due to blepharoptosis (both sides), dysphagia, laborious breathing, and weakness of limbs. He was considered "myasthenia gravis, thymoma" and treated with double-filtration plasmapheresis, ventilator-assisted breathing, etc. He was discharged after the symptoms improved and treated with bromopyrimidine and dexamethasone. He was admitted half a month ago because of shortness of breath.

Chest CT: A soft tissue lesion was found in the anterior mediastinum and slightly enhancement under the enhanced CT scan (Fig. 1.7a–f).

[**Diagnosis**] Thymic hyperplasia

[**Diagnosis basis**] A young man had symptoms of myasthenia gravis. Chest CT scan showed soft tissue lesion containing fat density in the thymus region. The enhanced scan was slightly enhanced. The possible diagnosis is thymic hyperplasia. Intraoperatively, a piece of gray-red and gray-yellow tissue was sent for examination. The tissue was in an intact capsule. Histologically, it was confirmed that the tissue was thymus, which was consistent with thymus hyperplasia.

[**Analysis**] Myasthenia gravis is an autoimmune disorder of the neuromuscular junction characterized by muscle weakness, often initially involving the extrinsic ocular muscles and subsequently resulting in generalized myasthenia gravis in two-thirds of patients. Myasthenia gravis is often associated with thymic abnormalities. At onset, thymic lymphoid hyperplasia and thymoma can be found in up to 65% and 15% of patients, respectively. The association between lymphoid hyperplasia and myasthenia gravis has been well established and studied. Nicolaou et al. studied 45 patients with myasthenia gravis who underwent thymectomy and reviewed CT findings of 22 patients with lymphoid hyperplasia [11]. Among them, 10 had normal thymic tissue on CT, 7 had a diffusely enlarged thymus (defined as >1.3 cm thickness of the lobe for patients >20 years old), and 5 had a focal mass. In Araki et al. study [10], 7 of 10 patients with myasthenia gravis had lymphoid hyperplasia, whereas three had true hyperplasia. All three patients with myasthenia and true hyperplasia had a history of steroid use, which may explain the result.

Thymic lymphoid hyperplasia is seen in only 1–2% of normal individuals but is a common finding in patients with autoimmune diseases. In addition to myasthenia gravis, several other autoimmune diseases are associated with the development of thymic lymphoid hyperplasia. These include Graves' disease, progressive systemic sclerosis, rheumatoid arthritis, and systemic lupus erythematosus. In fact, the diagnosis of thymic lymphoid hyperplasia cannot be made outside the context of autoimmune disease. The presence of medullary lymphoid follicles is well documented in autoimmune diseases. This suggests an autoimmune-mediated basis for thymic lymphoid hyperplasia.

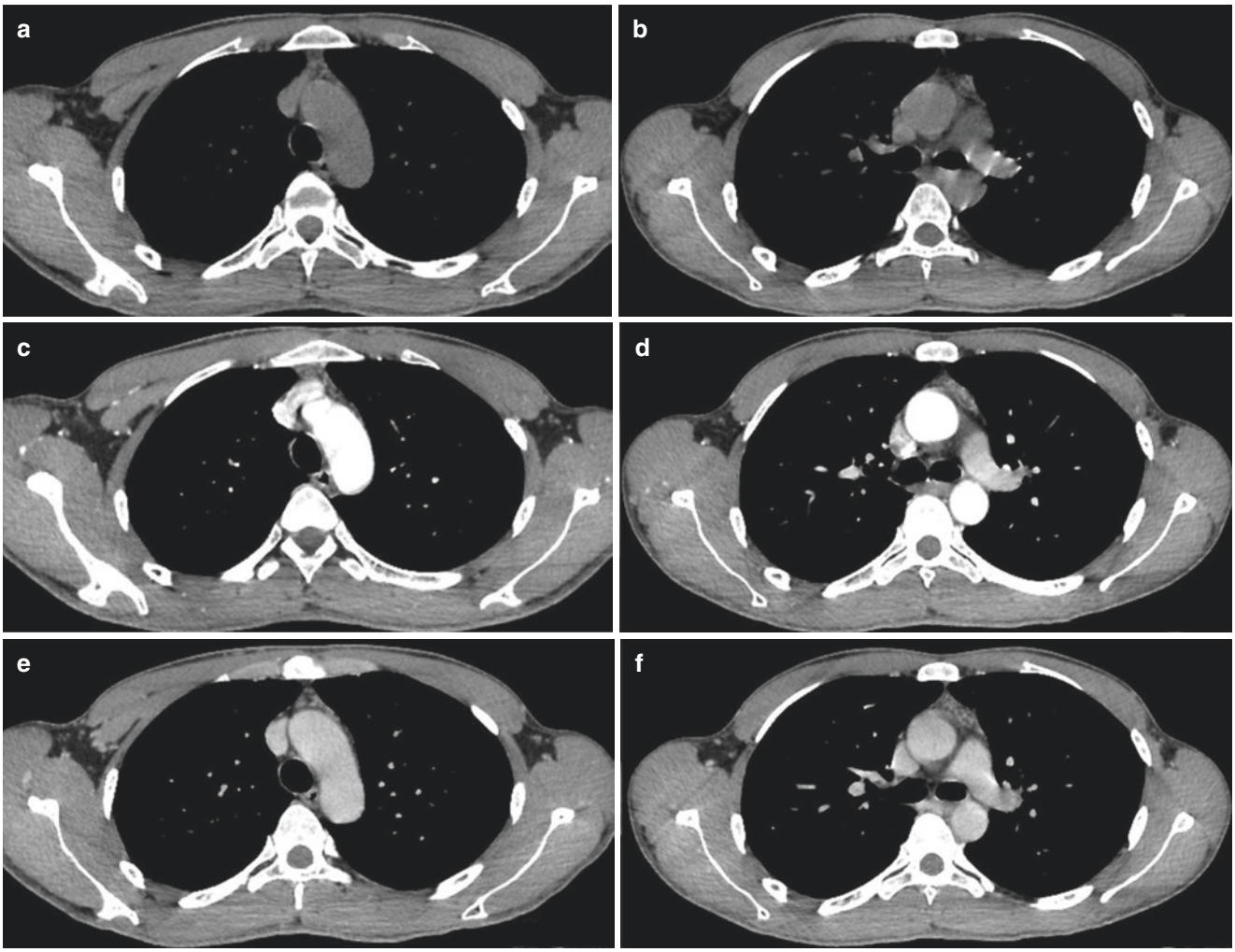

Fig. 1.7 (**a**–**f**) Chest CT image of a 26-year-old man

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