RadioGraphics

The Thymus: A Comprehensive Review[1]

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LEARNING OBJECTIVES

After reading this article and taking the test, the reader will be able to:

- Describe the embryologic and histologic features of the thymus.
- List the medical conditions associated with thymic disease.
- Discuss the spectrum of thymic diseases with radiologic-pathologic correlation.

TEACHING POINTS

See last page

Since first being described as such by Galen of Pergamum (130–200 AD), the thymus has remained an "organ of mystery" throughout the 2000-year history of medicine. The thymus reaches its maximum weight in puberty and subsequently undergoes involution, and thus is hardly an eye-catching structure on imaging studies performed in healthy adults. However, once there has been involvement of the thymus by a disease process, the gland demonstrates a variety of clinical and radiologic manifestations that require comprehensive understanding of each entity. Furthermore, it is important for radiologists to be familiar with the current World Health Organization histologic classification scheme for thymic epithelial tumors and to understand its clinical-pathologic, radiologic, and prognostic features.

Abbreviations: FDG = fluorodeoxyglucose, H-E = hematoxylin-eosin, SLE = systemic lupus erythematosus, SUV = standardized uptake value, WHO = World Health Organization

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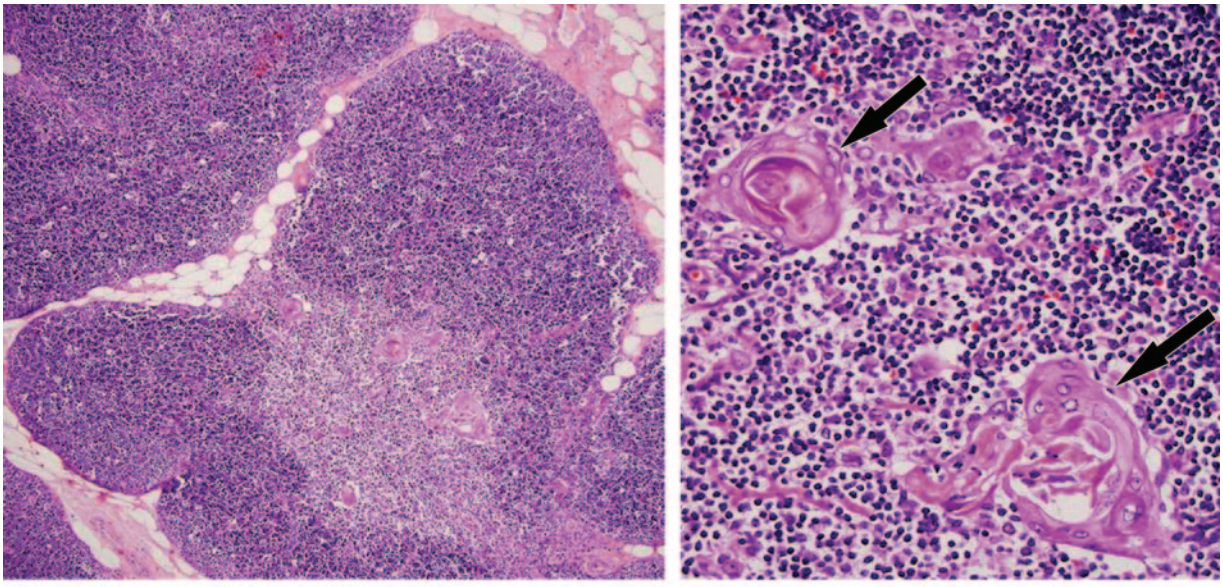


a. b.

Figure 1. **(a)** Photomicrograph (original magnification, ×10; hematoxylin-eosin [H-E] stain) of the thymus shows the cortex, mainly composed of lymphocytes (thymocytes), and the medulla, mainly composed of epithelial cells. **(b)** Photomicrograph (original magnification, ×40; H-E stain) of the medulla shows Hassall corpuscles (arrows) as round, keratinized formations with mature epithelial cells.

Introduction

The word *thymus* comes from the Latin derivation of the Greek word *thymos*, meaning "warty excrescence." Because *thymos* also means "soul" or "spirit," the thymus was misrepresented as the seat of the soul by the ancient Greeks (1–3). Galen of Pergamum (130–200 AD), who first noted that the thymus was proportionally largest during infancy (4), referred to the thymus as an "organ of mystery," a moniker that remained fairly accurate for almost two millennia.

In this article, we discuss and illustrate the embryologic and histologic features and the function of the thymus; medical conditions associated with thymic disease; and a wide spectrum of thymic diseases, with emphasis on the current World Health Organization (WHO) histologic classification scheme for thymic epithelial tumors. The aim of this article is to provide radiologists with a comprehensive understanding of the thymus and thymic diseases, and to enhance awareness of the current WHO classification scheme with radiologic-pathologic correlation.

Embryologic Features of the Thymus

Teaching Point

The thymus arises bilaterally from the third and fourth branchial pouches and contains elements derived from all three germinal layers (5–7). Development begins in the 6th gestational week. Migration of tissue occurs during the 8th week, leading to a fusion of the bilateral lobes, with the thymus occupying its final position in the anterosuperior mediastinum. In the course of its development, until the 9th gestational week, the thymus remains purely epithelial. By the 10th week, small lymphoid cells migrate from fetal liver and bone marrow, leading to lobulation of the gland. Further differentiation into cortex and medulla is completed by 14–16 weeks. Thereafter, the thymus grows rapidly and attains its greatest weight in relation to body weight before birth (average, 15 g) (5).

Because the thymus migrates from the third and fourth branchial pouches to the anterior mediastinum during its course of development, ectopic thymic tissue or ectopic thymoma can occur anywhere along this pathway. Often manifesting as a neck mass, these entities are sometimes examined with computed tomography (CT) or magnetic resonance (MR) imaging (8,9). Thus, knowledge of the embryologic features of the thymus is important in recognizing these entities.

Histologic Features of the Thymus

The cortex is composed primarily of lymphocytes (thymocytes), with a few epithelial and mesenchymal cells (Fig 1), whereas the medulla is composed of more epithelial cells but fewer lymphocytes. Epithelial cells compose the framework of the thymus; they are functionally essential for the maturation of T lymphocytes and thus are called "nurse cells" (5). Hassall corpuscles are the char-

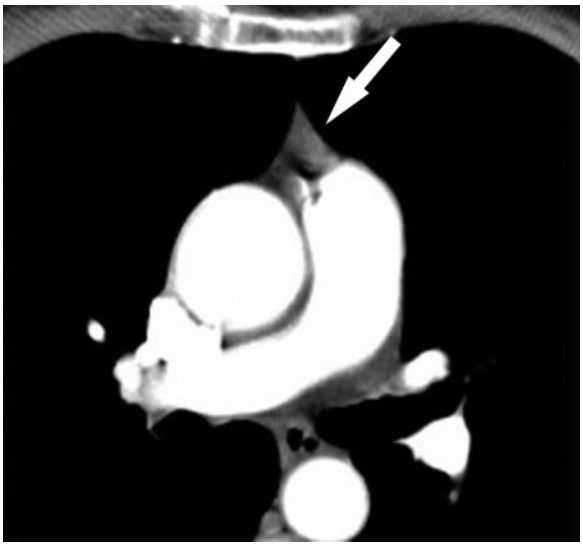


Figure 2. Contrast material–enhanced chest CT scan shows a normal thymus (arrow) as a triangular structure in the mediastinum anterior to the ascending aorta and the main pulmonary arterial trunk.

acteristic structures of the thymus and are found exclusively in the medulla (Fig 1). These entities are round, keratinized formations with mature epithelial cells and undergo marked cystic change into multilocular thymic cysts (5). In addition to epithelial cells and lymphocytes, the thymus contains a variety of other types of cells, including macrophages and myoid cells. Myoid cells are of great interest because of their potential role in the pathogenesis of myasthenia gravis (discussed later) (5). A basic knowledge of the histologic features of the thymus is essential for understanding the various pathologic conditions that affect this gland, including thymic epithelial tumors. Familiarity with the current WHO classification scheme, which is based on histologic features, is also essential (5).

Function of the Thymus

In ancient times, the thymus was believed to be the seat of the soul or the organ of purification of the nervous system (1–4). Later, the thymus was thought to be a protective thoracic cushion (10) or the regulator of fetal and neonatal pulmonary function (1,11). In 1832, Sir Astley Cooper suggested that this organ must perform some important function (12); however, the exact nature of this "important function" was not yet understood. What is currently known about thymic function is that the thymus is one of the central lymphoid organs and plays an important role in cellular immunity by generating circulating T lymphocytes. Although the need for the thymus to generate a continuous supply of T cells decreases with advancing age, the thymus continues to serve as the site of T-cell differentiation and maturation throughout life (5,13). One of the major functions of the thymus, the maturation of thymocytes, has been studied extensively with molecular and cellular biology. It is now known that various inductive, hormonal, and proliferative signals from epithelial cells contribute to the maturation of thymocytes (5). Of note, T-cell antigen receptors of thymocytes interact with epithelial major histocompatibility complex antigens in the process of thymocyte maturation (5).

Definition of "Normal Thymus" in Adults

What constitutes a normal thymus is another important issue. Because the thymus demonstrates unique changes over time, differentiation of a normal thymus from a thymic disorder can sometimes be problematic for radiologists.

As was mentioned earlier, Galen was the first to note that the thymus is proportionally largest during infancy (1,4). This observation was verified in 1777 by William Hewson, who studied the evolution of thymic size during fetal and infant life (1,11). After reaching its greatest weight in proportion to body weight before birth, the thymus continues to grow, reaching its maximum absolute weight at puberty. The thymus subsequently undergoes a process called involution, which is defined as a decrease in the size and weight of the gland with advancing age. This process starts at puberty, when the thymus is at its maximum absolute weight. During involution, the epithelial component atrophies, resulting in scattered small lymphocytes in abundant adipose tissue (5).

At CT, the thymus appears as a bilobed triangular structure located in the anterior mediastinum, most commonly anterior to the proximal ascending aorta, the pulmonary outflow tract, and the distal superior vena cava before it enters the right atrium (Fig 2) (14). Differentiation of the thymus from other mediastinal structures, such as lymph nodes or the superior sinus of the pericardium, may be difficult. Therefore, it is important to be familiar with the location, shape, and size of the normal thymus.

The size of a normal thymus has been extensively studied with CT and MR imaging (14–17). Baron et al (14) analyzed 154 mediastinal CT scans and reported that the mean thickness of a normal thymus decreased with advancing age from 1.1 cm (standard deviation, 0.4 cm) for the 6–19-year age group to 0.5 cm (standard deviation, 0.27 cm) for patients over age 50 years. The

maximum thickness was 1.8 cm in patients under age 20 years and 1.3 cm in patients over age 20 years. However, the thickness is greater at MR imaging (15–20 mm between ages 20 and 70 years), which may be due to better detection of *(a)* thymic tissue partially replaced by fat and *(b)* the margins of the thymus with this modality (17).

Medical Conditions Associated with Thymic Disease

A variety of pathologic conditions are known to be associated with thymic lesions, including thymoma and thymic hyperplasia.

Diseases Associated with Thymoma

Teaching Point

A variety of diseases are seen in association with thymoma (Table 1) (5,18,19). Among these diseases, myasthenia gravis is the most common and has the most well established association with thymoma. The other diseases, including pure red cell aplasia, hypogammaglobulinemia, SLE, rheumatoid arthritis, and nonthymic cancers, occur less frequently than myasthenia gravis but are relatively well recognized associated conditions (5,18). The causal relationship between thymoma and most of these diseases is not well understood.

Myasthenia gravis affects one-third to one-half of all thymoma patients, whereas 10%–20% of myasthenia gravis patients have thymoma (Fig 3) (20). In spite of the frequent association between thymoma and myasthenia gravis, the mechanism of the association is not fully understood. However, it is known that myasthenia gravis is an autoimmune disease affecting the nicotinic acetylcholine receptor at the neuromuscular junction, and production of autoantibodies against the acetylcholine receptor α subunit is assumed to cause myasthenia gravis (21). The source of acetylcholine receptors in the thymus is considered to be myoid cells, which are in very close contact with antigen-presenting interdigitating cells (5). Thymectomy improves myasthenia gravis in some patients regardless of whether thymoma is present (18).

Several hematologic disorders are known to be associated with thymoma; however, these disorders occur less frequently than myasthenia gravis and have been studied less. Pure red cell aplasia occurs in only 5% of thymoma patients, whereas thymomas are found in 50% of patients with pure red cell aplasia (22). The role of thymoma in the occurrence of pure red cell aplasia is not known at present. Suggested explanations include the following: *(a)* thymoma shares an antigen in common with cells of the erythroid series; *(b)* thymoma overproduces suppressor T cells, at times resulting in not only pure red cell aplasia but also hypogammaglobulinemia; and *(c)* both thymoma and pure red cell aplasia occur through the action of a common causative agent (23).

Table 1
Diseases Associated with Thymoma

Neuromuscular
Myasthenia gravis*
Lambert-Eaton syndrome
Limbic encephalopathy
Myotonic dystrophy
Sensorimotor radiculopathy
Hematologic
Pure red cell aplasia†
Hypogammaglobulinemia†
Hemolytic anemia
Acute leukemia
Multiple myeloma
Lymphoma
Pancytopenia
Gastrointestinal
Crohn disease
Nontropical sprue
Ulcerative colitis
Whipple disease
Endocrinologic
Addison disease
Cushing syndrome
Hyperthyroidism
Graves disease
Dermatologic
Pemphigus
Alopecia
Rheumatologic
Systemic lupus erythematosus (SLE)†
Rheumatoid arthritis†
Polymyositis
Scleroderma
Sjögren disease
Myocarditis
Miscellaneous
Nephrotic syndrome
Hypertrophy
Osteoarthropathy
Nonthymic cancers†

*Most common, with the most well established association with thymoma.
†Less common than myasthenia gravis, but with a well-known association with thymoma.

Medical Conditions Associated with Thymic Hyperplasia

There are two distinct histologic types of thymic hyperplasia: true thymic hyperplasia and lymphoid hyperplasia. These two types are associated with different groups of pathologic conditions

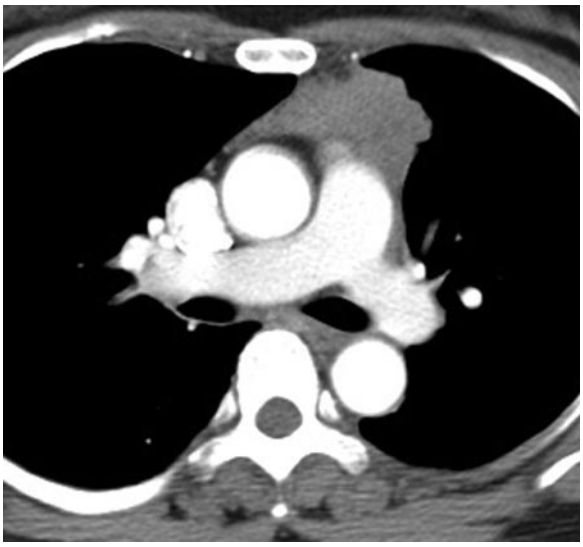


Figure 3. Thymoma in a 40-year-old woman with myasthenia gravis. Contrast-enhanced CT scan shows a partially lobulated, homogeneously enhancing anterior mediastinal mass. The mass was surgically removed, and pathologic analysis demonstrated an invasive type B2 thymoma.

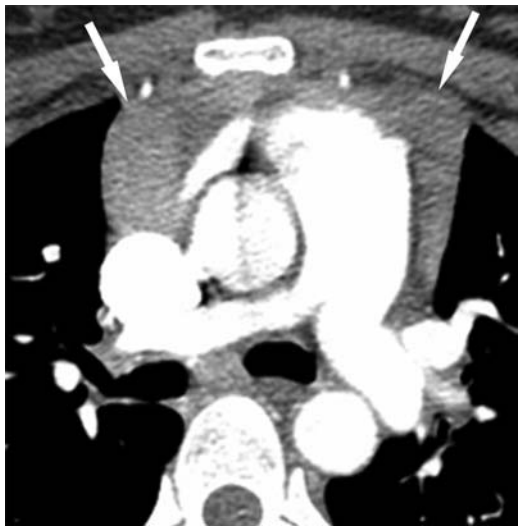


Figure 4. Thymic hyperplasia in a 25-year-old woman with Graves disease. Contrast-enhanced CT scan demonstrates a bilobed, homogeneous soft-tissue lesion (arrows) in the anterior mediastinum.

Table 2
Diseases Associated with Thymic Hyperplasia

True thymic hyperplasia
SLE
Rheumatoid arthritis
Scleroderma
Polyarthritis nodosa
Behçet disease
Hashimoto thyroiditis
Addison disease
Autoimmune hemolytic anemia
Thyrotoxicosis
Graves disease
Lymphoid hyperplasia
Rebound hyperplasia secondary to chemotherapy, radiation therapy, corticosteroid therapy, thermal burns, treatment for Cushing syndrome, or some other severe systemic stress

(Table 2) (5,24). Both true thymic hyperplasia and lymphoid hyperplasia manifest as diffuse symmetric enlargement of the thymus, so that it is difficult to distinguish between the two types on the basis of imaging findings alone (24).

True thymic hyperplasia is defined as enlargement of the thymus, which remains normally organized, beyond the upper limit of normal for a given patient age. This disease entity is seen when a patient is recovering from some recent stress, such as chemotherapy for neoplasm, corticosteroid therapy, irradiation, or thermal burns (5,18,24). Under such conditions, the thymus may respond by becoming atrophic; however, it grows back to its original size after cessation of the stress. The thymus sometimes grows to an even larger size after such stress, a phenomenon known as rebound hyperplasia (18). In a series of 29 patients, Choyke et al (25) demonstrated that rebound hyperplasia, defined as a greater than 50% increase in thymic volume over baseline, was noted in 25% of patients several months (range, 3–8 months; mean, 4.2 months) after cessation of chemotherapy.

Teaching Point

Lymphoid hyperplasia of the thymus refers to the presence of an increased number of lymphoid follicles (5). This condition is most commonly associated with myasthenia gravis, being seen in up to 65% of cases (24). Lymphoid hyperplasia of the thymus is observed in a number of immunologically mediated disorders, including SLE, rheumatoid arthritis, scleroderma, vasculitis, thyrotoxicosis, and Graves disease (Fig 4).

It is important that radiologists be able to distinguish thymic hyperplasia from neoplasm. Diffuse symmetric enlargement of the gland is the key morphologic feature of hyperplasia, whereas neoplasm tends to manifest as a focal mass, as in thymoma (24). However, differentiation may be difficult on the basis of morphologic features alone. Several new imaging approaches have been attempted, including chemical shift MR imaging and fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) (26,27).

Chemical shift imaging was recently used in an attempt to distinguish normal thymus from thymic hyperplasia, with the latter demonstrating

homogeneously decreased signal intensity on opposed-phase images. This finding suggests that chemical shift imaging may potentially be used to differentiate normal and hyperplastic thymus from neoplastic involvement of the thymus (26). However, further investigation with a larger study population will be needed.

FDG PET is often performed in patients with malignancy; however, differentiation between thymic hyperplasia and thymic involvement by malignancy is difficult because the thymus demonstrates normal physiologic uptake. In questionable cases, correlation with morphologic findings obtained at CT or MR imaging is appropriate (27).

Thymic Neoplasms with Radiologic-Pathologic Correlation

There are a variety of pathologic entities of the thymus. Of note, a variety of subtypes of thymic epithelial tumors with a broad spectrum of biologic and morphologic features exist, reflecting the unique histologic background of the thymus. Recently, several reports described specific CT, MR imaging, and FDG PET features of thymic epithelial tumors that reflect the WHO histologic subtypes (28–32). In this section, we discuss *(a)* thymic epithelial tumors and their classification, *(b)* imaging features of thymic epithelial tumors correlated with histologic subtypes, and *(c)* uncommon thymic neoplasms.

Thymic Epithelial Tumors and Their Classification

Thymic epithelial tumors, which include thymoma and thymic carcinoma, arise from thymic epithelium and demonstrate various histologic features and biologic behaviors (29). Thymoma is often divided into "noninvasive" and "invasive" types. Noninvasive thymoma manifests as a completely encapsulated tumor without microscopic evidence of growth outside the tumor capsule, whereas invasive thymoma demonstrates microscopic evidence of such growth, occasionally showing pleural implants and, rarely, hematogenous and lymphatic metastasis (5). It is impossible to differentiate between the two types solely on the basis of histologic features, and invasive thymoma may lack histologic features of malignancy. Therefore, the terms noninvasive and invasive are preferred over "benign" and "malignant" (5,18,33).

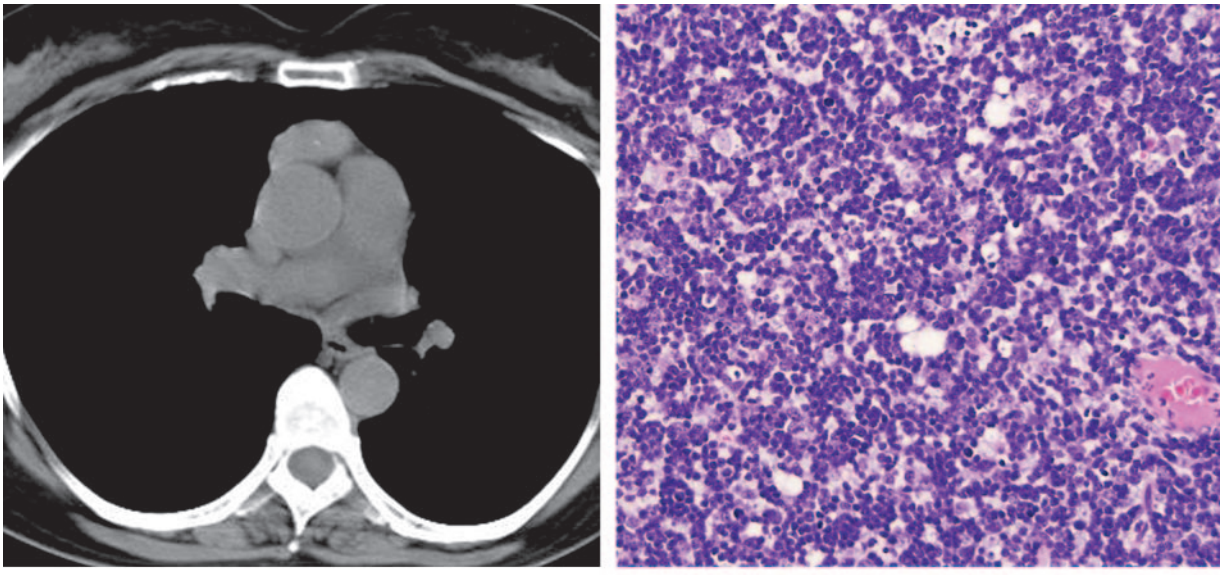
Several classification schemes and staging systems for thymic epithelial tumors have been proposed. Although there is some correlation between these various approaches and the invasiveness and clinical course of the tumor, most of them fail to provide consistent prognostic significance (30,34–47). The Masaoka clinical-pathologic staging system is based on surgical findings, including the presence of invasion or metastasis, and tumors are classified as follows: stage I, macroscopically encapsulated tumor with no microscopic evidence of capsular invasion; stage II, macroscopic invasion of the surrounding fatty tissue of the mediastinal pleura or microscopic evidence of capsular invasion; stage III, macroscopic invasion of a neighboring organ; stage IVa, pleural or pericardial dissemination; and stage IVb, lymphogenous or hematogenous metastasis (48). This staging system correlates with 5-year survival rates (48). The WHO proposed a consensus classification scheme for thymic epithelial tumors in 1999 that is based on histologic features (Table 3) (49). This histologic classification scheme reflects both the clinical and functional behaviors of thymic epithelial tumors and contributes to the clinical treatment of patients (50–52).

Table 3
WHO Classification Scheme for Thymic Epithelial Tumors

Tumor Type	Description
A	Medullary
AB	Mixed
B1	Lymphocyte rich, predominantly cortical
B2	Cortical
B3	Epithelial (well-differentiated thymic carcinoma)
C	Thymic carcinoma

Teaching Point

The WHO classification scheme correlates with invasiveness: Types A and AB are usually clinically benign and encapsulated (stage I), type B has a greater likelihood of invasiveness (especially type B3), and type C is almost always invasive. This scheme has been shown to reflect the clinical features of thymic epithelial tumors and to correlate with prognosis (52). Preoperative predictions based on WHO histologic subtypes of thymic epithelial tumors may help determine if tumors can be treated with surgical resection alone or if they require pre- or postoperative adjuvant treatment (30). However, most clinicians and radiologists are unfamiliar with this complicated classification scheme. In addition, poor interobserver reproducibility has been reported in the various WHO histologic subtypes (53).



a. b.

Figure 5. WHO type B1 thymoma (lymphocyte rich, predominantly cortical) in a 57-year-old woman. **(a)** Unenhanced CT scan shows a well-circumscribed, flattened soft-tissue lesion in the anterior mediastinum, with a maintained fat plane surrounding the lesion. **(b)** Photomicrograph (original magnification, ×40; H-E stain) shows cellular lobules consisting predominantly of lymphocytes, along with scattered small foci of medullary differentiation.

Several proposals to simplify the classification scheme according to similar prognostic appearance have been made to facilitate clinical-pathologic understanding of thymic epithelial tumors. Rieker et al (53) proposed a simplified classification scheme consisting of three subtypes: types A, AB, B1, and B2 as one group; type B3; and type C. However, the survival rates for patients with type B2 tumors are lower than those for patients with type A, AB, or B1 tumors (52,54). In addition, a large-scale report of thymic epithelial tumors stated that overall survival rates for patients with type A, AB, or B1 tumors were higher than those for patients with type B2 or B3 tumors (54). Jeong et al (30) simplified the WHO histologic classification scheme into three subgroups—low-risk thymomas (types A, AB, and B1), high-risk thymomas (types B2 and B3), and thymic carcinomas (type C)—and correlated CT findings in the three tumor subgroups with prognosis.

In summary, the Masaoka clinical-pathologic staging system is based on invasiveness of the tumor at surgery, and the system correlates with 5-year survival rates. The WHO classification scheme is relatively new and is based on histologic features. This scheme has been shown to correlate with the invasiveness and clinical behavior of tumors and with prognosis, has important preoperative implications for treatment strategy, and will be a standard classification scheme for thymic epithelial tumors.

Imaging Features of Thymic Epithelial Tumors Correlated with Histologic Subtypes

Computed Tomography.—Thymic epithelial tumors most frequently manifest as soft-tissue masses in the anterior mediastinum, vary in size, and can have smooth and lobulated borders. Because of their embryologic background and anatomic location, they can occur adjacent to the junction of the great vessels and the pericardium; less commonly, in the cardiophrenic angles or adjacent cardiac borders; and, rarely, in the neck or other mediastinal compartments (5,18). Conventional radiography may help detect relatively large lesions, especially on lateral projections as an opacity in the retrosternal area; however, this finding is often indeterminate, and smaller lesions may go undetected (18).

CT, of course, has a much higher sensitivity for detecting thymic epithelial tumors, and also allows evaluation of *(a)* invasion of the surrounding mediastinal fat, vascular structures, and adjacent lung; and *(b)* the presence of pleural and extrapleural seeding. On CT scans, thymic epithelial tumors usually appear as homogeneous, oval, rounded or lobulated soft-tissue masses in the anterior mediastinum (Fig 5) (18). In cases of

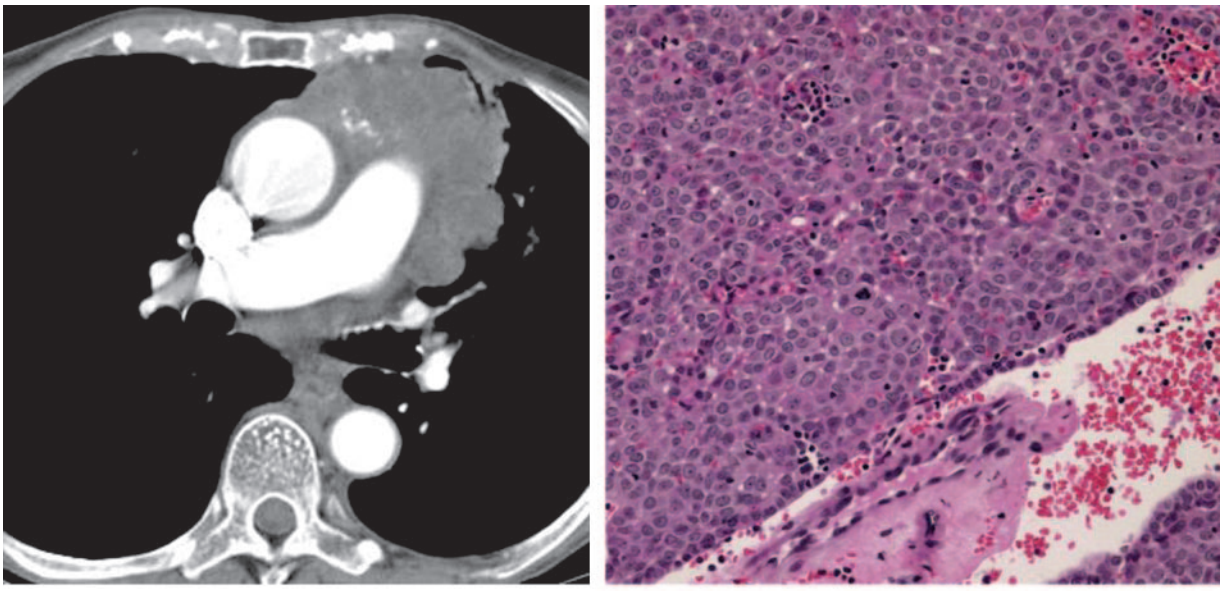


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Figure 6. WHO type B3 thymoma (epithelial, well-differentiated thymic carcinoma) in an 83-year-old woman. **(a)** Contrast-enhanced CT scan shows a lobulated anterior mediastinal mass with calcification, a finding that is commonly seen in type B tumors. Note the lobulated contour of the mass and the loss of the fat plane between the mass and the pleura-pericardium. **(b)** Photomicrograph (original magnification, ×40; H-E stain) shows a predominance of polygonal epithelial cells with nuclear atypia.

invasive thymoma or thymic carcinoma, invasion of the mediastinal fat or adjacent structures as well as pleural seeding may be seen.

With the increased prevalence of advanced CT technology, detailed characterization of thymic epithelial tumors at CT has become possible; therefore, the correlation of radiologic findings with WHO classifications, clinical behaviors, and prognosis has also been investigated (28–30). Because the current WHO classification scheme correlates with the oncologic behavior of thymic epithelial tumors and affects treatment strategy, familiarity with the imaging features that suggest specific histologic subtypes is important for radiologists, allowing them to contribute to the clinical treatment of affected patients.

Tomiyama et al (28) assessed the CT features of various subtypes of thymic epithelial tumors in 53 patients and reported that smooth contours and a round shape are most suggestive of type A tumors, irregular contours are most suggestive of type C tumors, and calcification is suggestive of type B tumors. Jeong et al (30) reviewed the CT findings in 91 patients who had undergone resection of thymic epithelial tumors and correlated these findings with their simplified classification scheme and with prognosis.

Table 4
CT Findings in Thymic Epithelial Tumors

Findings more common in high-risk thymomas and thymic carcinomas
Lobulated contour
Mediastinal fat invasion
Great vessel invasion
Findings associated with a significantly greater prevalence of recurrence and metastasis
Lobulated or irregular contour
Oval shape
Mediastinal fat invasion or great vessel invasion
Pleural seeding

Teaching Point

According to these investigators, CT findings that are more common in high-risk thymomas and thymic carcinomas include lobulated contour, mediastinal fat invasion, and great vessel invasion (Figs 6, 7; Table 4). Findings associated with significantly more frequent recurrence and metastasis include lobulated or irregular contour, oval shape, mediastinal fat invasion or great vessel invasion, and pleural seeding (Fig 8, Table 4). In the diagnosis of thymic tumors, radiologists should look carefully at the CT findings, which may serve as predictors of tumor invasiveness and of postoperative recurrence or metastasis.

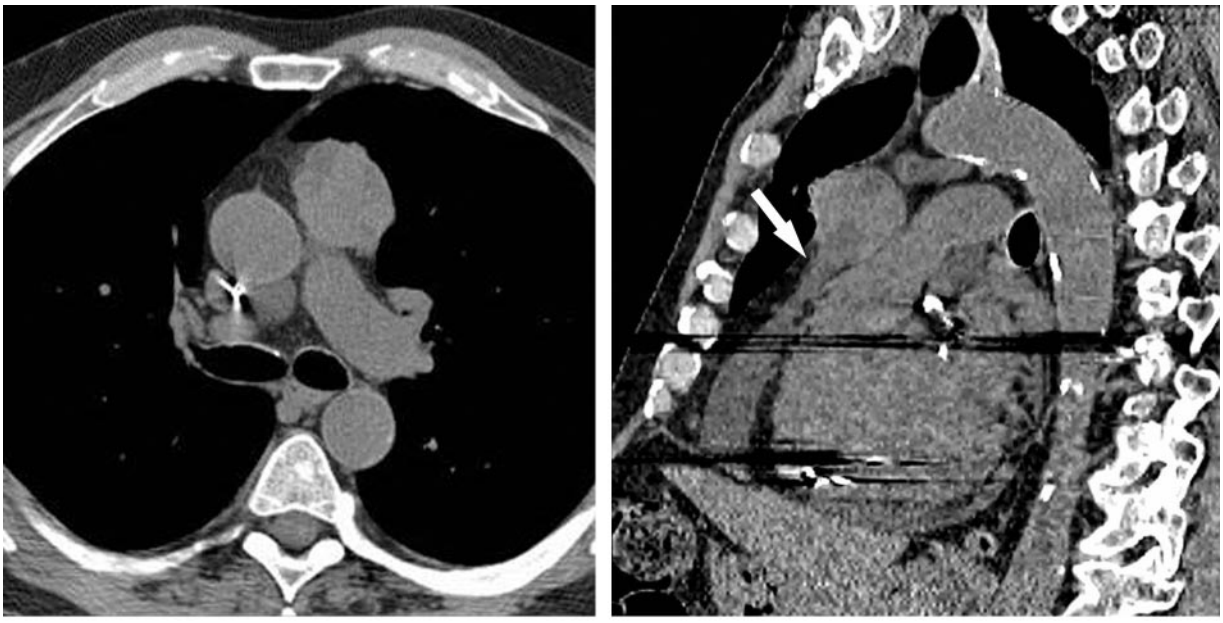

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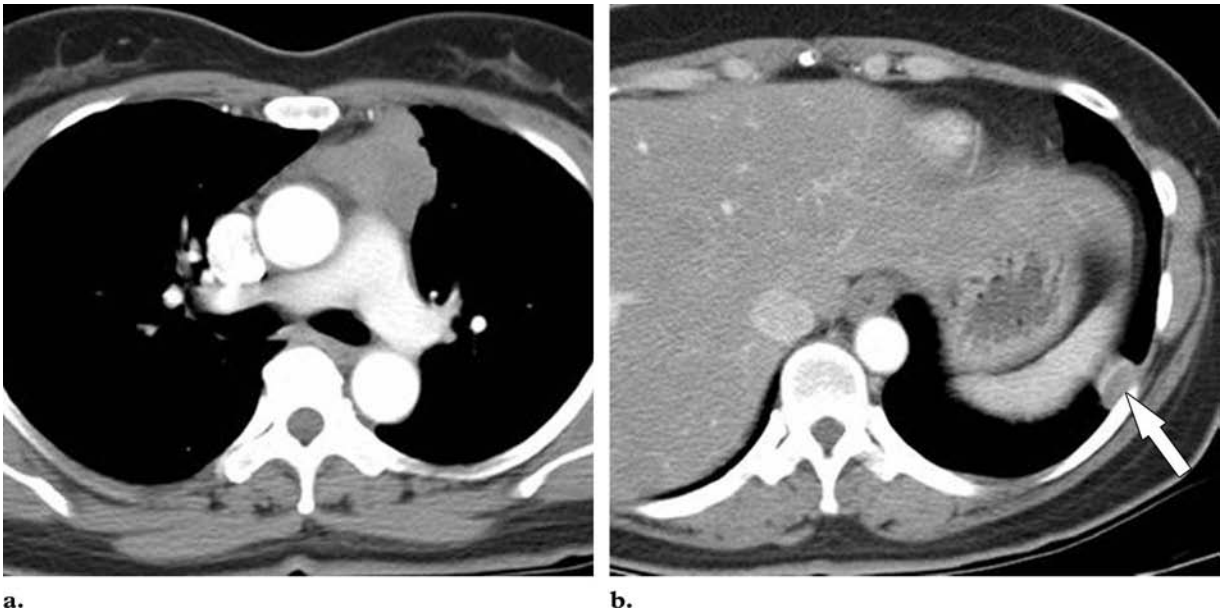
Figure 7. Incidentally noted thymic carcinoma in a 79-year-old man who presented with bronchiectasis and cough. **(a)** Unenhanced chest CT scan shows an anterior mediastinal mass with a somewhat lobulated contour. **(b)** On a sagittal reformatted image, the mass is closely attached to the pericardium with loss of the fat plane (arrow) between the two entities, findings that suggest pericardial involvement. Pericardial effusion is also noted. At surgery, pericardial invasion was noted, and pathologic analysis showed squamous cell thymic carcinoma.



a. b.

Figure 8. Pleural seeding from a WHO type B2 (cortical) thymoma in a 40-year-old woman who presented with myasthenia gravis. **(a)** Contrast-enhanced CT scan shows a lobulated anterior mediastinal mass. **(b)** Contrast-enhanced CT scan obtained at the level of the upper abdomen shows an enhancing pleura-based nodule (arrow), a finding that represents pleural seeding. Pathologic analysis showed a predominance of lymphoid cells (type B2 tumor).

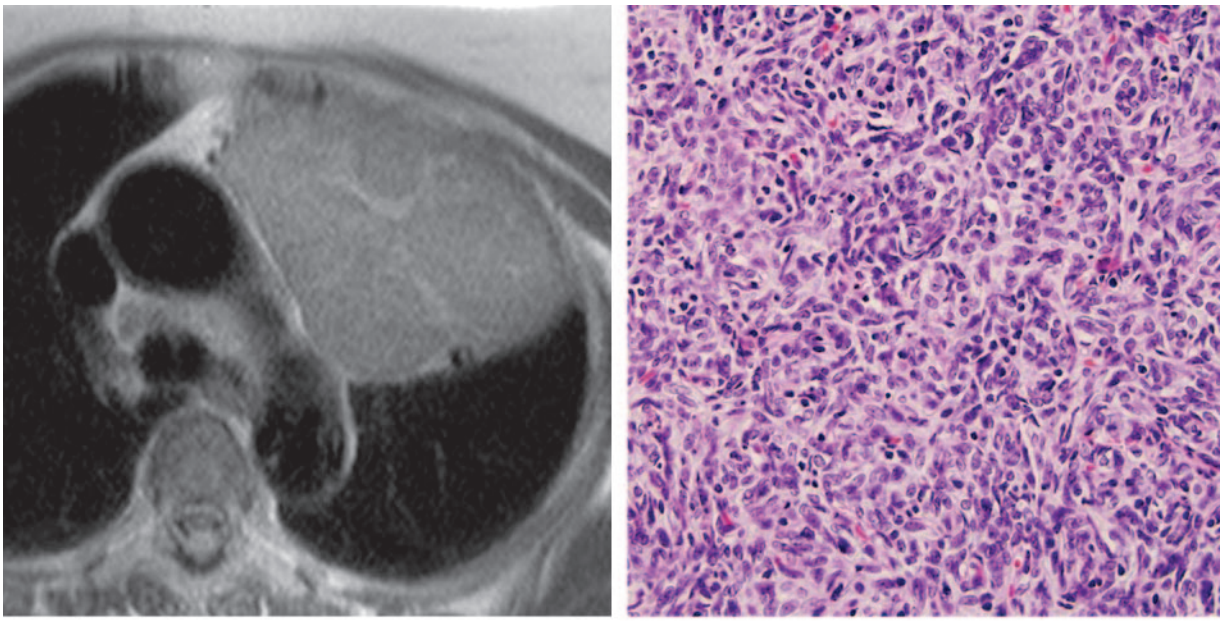


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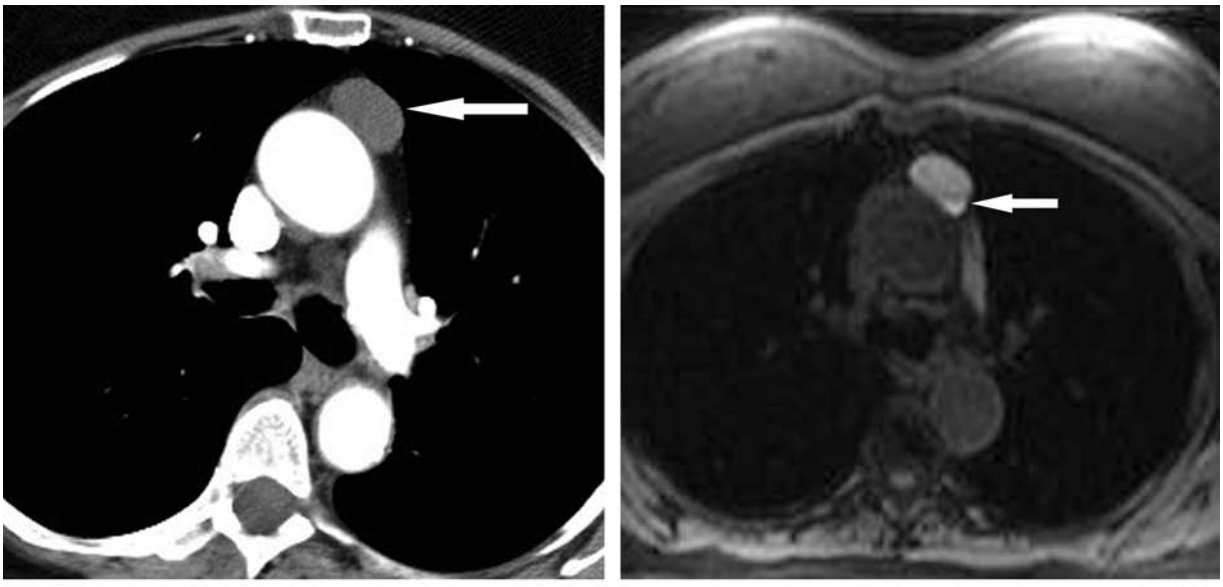
Figure 9. WHO type AB thymoma in a 68-year-old woman. **(a)** Axial half-Fourier acquisition single-shot turbo spin-echo MR image shows an anterior mediastinal mass that is slightly hyperintense relative to skeletal muscle. Although the fat plane between the mass and mediastinal structures appears to be maintained, the possibility of minimal chest wall invasion cannot be excluded with certainty. At surgery, the mass appeared well circumscribed and was excised entirely. No extracapsular invasion was noted. **(b)** Photomicrograph (original magnification, ×40; H-E stain) demonstrates mixed histologic features, with foci of medullary and spindle cells admixed with lymphocytes.

MR Imaging.—At MR imaging, thymoma has a signal intensity similar to that of muscle or normal thymic tissue on T1-weighted images and appears heterogeneous on T2-weighted images (Fig 9) (18,29,31). MR imaging may also be useful in differentiating between thymoma and thymic cysts that demonstrate increased CT attenuation due to hemorrhage or high mucinous content (Fig 10). T2-weighted and contrast-enhanced MR images also help detect solid components of cystic lesions, a finding that raises the possibility of cystic thymoma (Fig 11).

FDG PET.—FDG PET is another powerful diagnostic tool for the diagnosis, staging, and restaging of neoplasms in general. In thymic neoplasms, FDG PET may be useful in differentiating thymic carcinoma from other thymic neoplasms, thymic hyperplasia, and normal physiologic uptake (27). Sasaki et al (32) reported that the standardized uptake value (SUV) for thymic carcinoma was significantly greater than that for invasive or noninvasive thymoma. With an SUV cutoff point of 5.0, thymic carcinoma can be differentiated from thymoma with reasonably high sensitivity (84.6%), specificity (92.3%), and accuracy (88.5%). There was no statistically significant difference in SUV between invasive and noninvasive thymomas. It is speculated that FDG PET will prove to be effective in differentiating thymic carcinoma from other thymic diseases but far less so in differentiating between invasive and noninvasive thymoma (27).

Uncommon Thymic Neoplasms

Thymolipoma.—Thymolipoma is a rare, benign, slow-growing tumor that accounts for 2%–9% of all thymic neoplasms. It occurs most frequently in young adults and has no sex predilection. Thymolipoma is usually asymptomatic and manifests as a large anterior mediastinal mass. At histologic analysis, it is composed of mature fat and thymic tissue (5). Because of its soft and pliable nature, thymolipoma typically drapes itself around the heart and adjacent mediastinal structures, often becoming quite large before



a. b.

Figure 10. Thymic cyst in a 66-year-old woman. **(a)** Contrast-enhanced CT scan shows an incidentally noted anterior mediastinal lesion (arrow) with well-circumscribed borders and soft-tissue attenuation. The lesion is indistinguishable from a solid mass. **(b)** On a T2-weighted MR image, the lesion (arrow) is hyperintense and contains a fluid level, findings that indicate a hemorrhagic or mucin-containing cystic lesion. The lesion was surgically removed, and pathologic analysis demonstrated a thymic cyst.

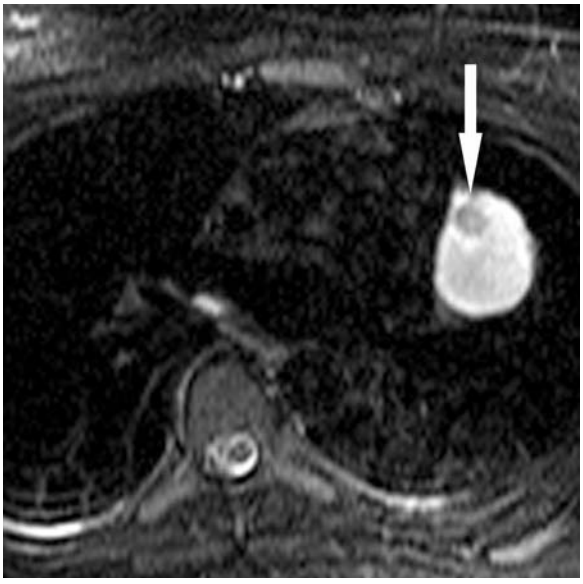
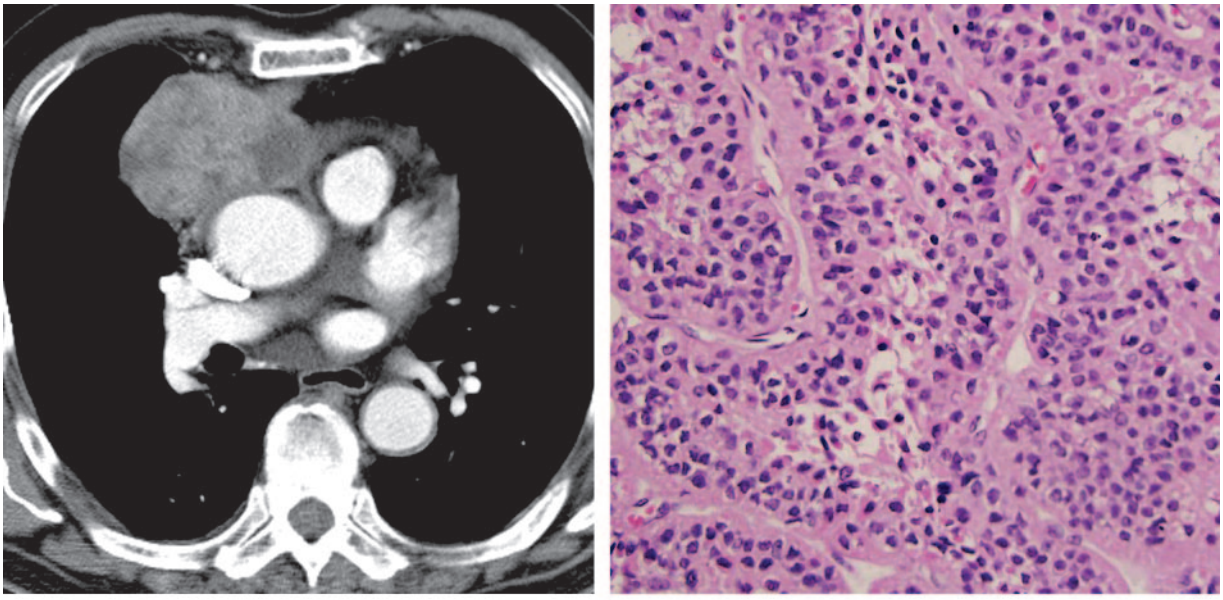


Figure 11. Cystic thymoma in a 48-year-old woman. Axial short inversion time inversion-recovery MR image shows hyperintense cystic lesions in the mediastinum abutting the pericardium. Note the hypointense nodular lesion (arrow), a finding that suggests the presence of a solid component. The nodule demonstrated enhancement after contrast material administration. Surgery was performed, and pathologic analysis helped confirm a cystic type AB thymoma.

coming to clinical attention. It is usually detected incidentally at routine chest radiography and may occasionally mimic cardiac enlargement or an elevated hemidiaphragm (55). At CT and MR imaging, thymolipoma manifests as a fatty mass with fibrous septa (18). Association with myasthenia gravis, Graves disease, aplastic anemia, and other hematologic disorders has been reported (56–58).

Thymic Carcinoid.—Thymic carcinoid is a rare primary malignant thymic neoplasm that occurs over a wide patient age range (median age, 43 years) and has a male predilection of 3:1. One-third of these tumors are functionally active, causing endocrinologic disorders such as Cushing syndrome (33%–40% of cases) or multiple endocrine neoplasia, specifically type 1 (19%–25%) (5,18,59–62). At imaging, a thymic carcinoid usually manifests as a large anterior mediastinal mass, often with invasion of adjacent structures and metastasis. Differentiation between thymic carcinoids and invasive thymic epithelial tumors may be difficult on the basis of imaging findings



a. b.

Figure 12. Thymic carcinoid in a 74-year-old man. **(a)** Contrast-enhanced CT scan demonstrates a lobulated, heterogeneously enhancing mass in the anterior mediastinum. Note the loss of the fat plane between the mass and the pericardium, a finding that suggests invasiveness. **(b)** Photomicrograph (original magnification, ×40; H-E stain) shows tumor cells in a trabecular growth pattern with oncocytic cytoplasm and oval to irregular nuclear contours.

alone (Fig 12) (18). Thymic carcinoid has a poor prognosis due to a high prevalence of recurrence and metastasis.

Lymphoma.—Lymphoma may involve the thymus as part of disseminated disease or sometimes as an isolated site. Hodgkin disease accounts for the majority of thymic lymphomas, with nodular sclerosis being the most common histologic finding identified in the thymus (18,24). The major imaging findings include thymic enlargement, sometimes with single or multiple masses. In general, it is difficult to distinguish lymphoma from other thymic masses, especially thymoma, on the basis of imaging findings alone. Distinguishing prominent but normal thymus in young patients and thymic hyperplasia from lymphomatous involvement of the thymus is also problematic (18,24). Use of chemical shift MR imaging and FDG PET in this setting have been described previously; however, further study will be needed to determine their utility (26,27).

Conclusions

Knowledge of the embryologic, histologic, and normal morphologic features of the thymus is essential for comprehensive understanding of the normal thymus and thymic diseases. Familiarity with the classification schemes for thymic epithelial tumors, especially the current WHO classification scheme, and awareness of the correlation between these classification schemes and radiologic findings are necessary if the radiologist is to contribute to the clinical treatment of affected patients.

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References

1. Jacobs MT, Frush DP, Donnelly LF. The right place at the wrong time: historical perspective of the relation of the thymus gland and pediatric radiology. Radiology 1999;210:11–16.
2. Haubrich WS. Medical meanings. Philadelphia, Pa: American College of Physicians, 1997; 225.
3. Skinner HA. Origin of medical terms. 2nd ed. Baltimore, Md: Williams & Wilkins, 1961; 404.
4. May MT. Galen on the usefulness of the parts of the body. Ithaca, NY: Cornell University Press, 1968; 30.
5. Shimosato Y, Mukai K. Tumors of the thymus and related lesions. In: Shimosato Y, Mukai K, eds. Atlas of tumor pathology: tumors of the mediastinum, fasc 21, ser 3. Washington, DC: Armed Forces Institute of Pathology, 1997; 158–168.
6. Lele SM, Lele MS, Anderson VM. The thymus in infancy and childhood: embryologic, anatomic, and pathologic considerations. Chest Surg Clin N Am 2001;11:233–253.
7. Suster S, Rosai J. Histology of the normal thymus. Am J Surg Pathol 1990;14:284–303.

8. Nagasawa K, Takahashi K, Hayashi T, Aburano T. Ectopic cervical thymoma: MRI findings. AJR Am J Roentgenol 2004;182:262–263.
9. Kakuno Y, Yamada T, Mori H, Matsuki M, Narabayashi I. Ectopic thymus presenting as neck mass. Nippon Igaku Hoshasen Gakkai Zasshi 2002;62:747–748.
10. Crotti A. The thymus gland. In: Crotti A, ed. Thyroid and thymus. Philadelphia, Pa: Lea & Febiger, 1922; 607–693.
11. Hewson W. Experimental enquires III. In: Cadell T, ed. Experimental enquiries into the properties of the blood. London, England, 1777; 1–223.
12. Cooper AP. The anatomy of the thymus gland. London, England: Longmand, Rees, Orme, Green, & Brown, 1833; 1–48.
13. Hong R. The thymus: finally getting some respect. Chest Surg Clin N Am 2001;11:295–310.
14. Baron RL, Lee JK, Sagel SS, Peterson RR. Computed tomography of the normal thymus. Radiology 1982;142:121–125.
15. Moore AV, Korobkin M, Olanow W, et al. Age-related changes in the thymus gland: CT-pathologic correlation. AJR Am J Roentgenol 1983;141: 241–246.
16. Francis IR, Glazer GM, Bookstein FL, Gross BH. The thymus: reexamination of age-related changes in size and shape. AJR Am J Roentgenol 1985; 145:249–254.
17. de Geer G, Webb WR, Gamsu G. Normal thymus: assessment with MR and CT. Radiology 1986;158:313–317.
18. Armstrong P. Mediastinal and hilar disorders. In: Armstrong P, Wilson AG, Dee P, Hansell DM, eds. Imaging of the diseases of the chest. 3rd ed. London, England: Mosby, 2000; 789–892.
19. Port JL, Ginsberg RJ. Surgery for thymoma. Chest Surg Clin N Am 2001;11:421–437.
20. Lewis JE, Wick MR, Scheithauer BW, Bernatz PE, Taylor WF. Thymoma: a clinicopathologic review. Cancer 1987;60:2727–2743.
21. Lennon VA, Lambert EH, Leiby KR, Okarma TB, Taib S. Recombinant human acetylcholine receptor alpha-subunit induces chronic experimental autoimmune myasthenia gravis. J Immunol 1991;146:2245–2248.
22. Rosenow EC 3rd, Hurley T. Disorders of the thymus: a review. Arch Intern Med 1984;144:763–770.
23. Masaoka A, Hashimoto T, Shibata K, Yamakawa Y, Nakamae K, Iizuka M. Thymomas associated with pure red cell aplasia: histologic and follow-up studies. Cancer 1989;64:1872–1878.
24. Mendelson DS. Imaging of the thymus. Chest Surg Clin N Am 2001;11:269–293.
25. Choyke PL, Zeman RK, Gootenberg JE, Greenberg JN, Hoffer F, Frank JA. Thymic atrophy and regrowth in response to chemotherapy: CT evaluation. AJR Am J Roentgenol 1987;149:269–272.
26. Takahashi K, Inaoka T, Murakami N, et al. Characterization of the normal and hyperplastic thymus on chemical-shift MR imaging. AJR Am J Roentgenol 2003;180:1265–1269.
27. Ferdinand B, Gupta P, Kramer EL. Spectrum of thymic uptake at ^{18}F-FDG PET. RadioGraphics 2004;24:1611–1616.
28. Tomiyama N, Johkoh T, Mihara N, et al. Using the World Health Organization classification of thymic epithelial neoplasms to describe CT findings. AJR Am J Roentgenol 2002;179:881–886.
29. Han J, Lee KS, Yi CA, et al. Thymic epithelial tumors classified according to a newly established WHO scheme: CT and MR findings. Korean J Radiol 2003;4:46–53.
30. Jeong YJ, Lee KS, Kim J, Shim YM, Han J, Kwon OJ. Does CT of thymic epithelial tumors enable us to differentiate histologic subtypes and predict prognosis? AJR Am J Roentgenol 2004;183:283–289.
31. Sakai F, Sone S, Kiyono K, et al. MR imaging of thymoma: radiologic-pathologic correlation. AJR Am J Roentgenol 1992;158:751–756.
32. Sasaki M, Kuwabara Y, Ichiya Y, et al. Differential diagnosis of thymic tumors using a combination of 11C-methionine PET and FDG PET. J Nucl Med 1999;40:1595–1601.
33. Rosado-de-Christenson ML, Galobardes J, Moran CA. Thymoma: radiologic-pathologic correlation. RadioGraphics 1992;12:151–168.
34. Suster S, Rosai J. Thymic carcinoma: a clinicopathologic study of 60 cases. Cancer 1991;67: 1025–1032.
35. Muller-Hermelink HK, Marino M, Palestro G, Schumacher U, Kirchner T. Immunohistological evidences of cortical and medullary differentiation in thymoma. Virchows Arch A Pathol Anat Histopathol 1985;408:143–161.
36. Kirchner T, Schalke B, Buchwald J, Ritter M, Marx A, Muller-Hermelink HK. Well-differentiated thymic carcinoma: an organotypical low-grade carcinoma with relationship to cortical thymoma. Am J Surg Pathol 1992;16:1153–1169.
37. Harris NL, Muller-Hermelink HK. Thymoma classification: a siren's song of simplicity. Am J Clin Pathol 1999;112:299–303.
38. Suster S, Moran CA. Thymoma, atypical thymoma, and thymic carcinoma: a novel conceptual approach to the classification of thymic epithelial neoplasms. Am J Clin Pathol 1999;111:826–833.
39. Kirchner T, Schalke B, Marx A, Muller-Hermelink HK. Evaluation of prognostic features in thymic epithelial tumors. Thymus 1989;14:195–203.
40. Quintanilla-Martinez L, Wilkins EW Jr, Choi N, Efird J, Hug E, Harris NL. Thymoma: histologic subclassification is an independent prognostic factor. Cancer 1994;74:606–617.
41. Quintanilla-Martinez L, Wilkins EW Jr, Ferry JA, Harris NL. Thymoma: morphologic subclassification correlates with invasiveness and immunohistologic features—a study of 122 cases. Hum Pathol 1993;24:958–969.
42. Blumberg D, Port JL, Weksler B, et al. Thymoma: a multivariate analysis of factors predicting survival. Ann Thorac Surg 1995;60:908–914.
43. Blumberg D, Burt ME, Bains MS, et al. Thymic carcinoma: current staging does not predict prognosis. J Thorac Cardiovasc Surg 1998;115:303–309.

44. Regnard JF, Magdeleinat P, Dromer C, et al. Prognostic factors and long-term results after thymoma resection: a series of 307 patients. J Thorac Cardiovasc Surg 1996;112:376–384.
45. Wilkins KB, Sheikh E, Green R, et al. Clinical and pathologic predictors of survival in patients with thymoma. Ann Surg 1999;230:562–574.
46. Lardinois D, Rechsteiner R, Lang RH, et al. Prognostic relevance of Masaoka and Muller-Hermelink classification in patients with thymic tumors. Ann Thorac Surg 2000;69:1550–1555.
47. Rios A, Torres J, Galindo PJ, et al. Prognostic factors in thymic epithelial neoplasms. Eur J Cardiothorac Surg 2002;21:307–313.
48. Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48: 2485–2492.
49. Rosai J, Sobin LH. Histological typing of tumours of the thymus. In: International histological classification of tumours. 2nd ed. New York, NY: Springer, 1999; 5–14.
50. Okumura M, Miyoshi S, Fujii Y, et al. Clinical and functional significance of WHO classification on human thymic epithelial neoplasms: a study of 146 consecutive tumors. Am J Surg Pathol 2001; 25:103–110.
51. Chalabreysse L, Roy P, Cordier JF, Loire R, Gamondes JP, Thivolet-Bejui F. Correlation of the WHO schema for the classification of thymic epithelial neoplasms with prognosis. Am J Surg Pathol 2002;26:1605–1611.
52. Okumura M, Ohta M, Tateyama H, et al. The World Health Organization histologic classification system reflects the oncologic behavior of thymoma: a clinical study of 273 patients. Cancer 2002;94:624–632.
53. Rieker RJ, Hoegel J, Morresi-Hauf A, et al. Histologic classification of thymic epithelial tumors: comparison of established classification schemes. Int J Cancer 2002;98:900–906.
54. Chen G, Marx A, Wen-Hu C, et al. New WHO histologic classification predicts prognosis of thymic epithelial tumors: a clinicopathologic study of 200 thymoma cases from China. Cancer 2002;95: 420–429.
55. Boiselle PM. Mediastinal masses. In: McLoud TC, ed. Thoracic radiology: the requisites. St Louis, Mo: Mosby, 1998; 431–462.
56. Rosado-de-Christenson ML, Pugatch RD, Moran CA, Galobardes J. Thymolipoma: analysis of 27 cases. Radiology 1994;193:121–126.
57. Matsudaira N, Hirano H, Itou S, Matsuura K, Kanou M, Ogawa T. MR imaging of thymolipoma. Magn Reson Imaging 1994;12:959–961.
58. Benton C, Gerard P. Thymolipoma in a patient with Graves' disease: case report and review of the literature. J Thorac Cardiovasc Surg 1966;51: 428–433.
59. Wick MR, Scott RE, Li CY, Carney JA. Carcinoid tumor of the thymus: a clinicopathologic report of seven cases with a review of the literature. Mayo Clin Proc 1980;55:246–254.
60. Economopoulos GC, Lewis JW Jr, Lee MW, Silverman NA. Carcinoid tumors of the thymus. Ann Thorac Surg 1990;50:58–61.
61. Lowenthal RM, Gumpel JM, Kreel L, McLaughlin JE, Skeggs DB. Carcinoid tumour of the thymus with systemic manifestations: a radiological and pathological study. Thorax 1974;29:553–558.
62. Rosai J, Higa E. Mediastinal endocrine neoplasm of probable thymic origin related to carcinoid tumor: clinicopathologic study of 8 cases. Cancer 1972;29:1061–1074.

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Teaching Points for The Thymus: A Comprehensive Review

Mizuki Nishino, MD, et al

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Page 336
The thymus arises bilaterally from the third and fourth branchial pouches and contains elements derived from all three germinal layers (5–7).

Page 338
A variety of diseases are seen in association with thymoma (Table 1) (5,18,19). Among these diseases, myasthenia gravis is the most common and has the most well established association with thymoma.

Page 339
The thymus sometimes grows to an even larger size after such stress, a phenomenon known as rebound hyperplasia (18).

Page 340
The WHO classification scheme correlates with invasiveness: Types A and AB are usually clinically benign and encapsulated (stage I), type B has a greater likelihood of invasiveness (especially type B3), and type C is almost always invasive.

Page 342
According to these investigators, CT findings that are more common in high-risk thymomas and thymic carcinomas include lobulated contour, mediastinal fat invasion, and great vessel invasion (Figs 6, 7; Table 4).