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REVIEW AND PERSPECTIVES

The spectrum of ectopic thymomas

Annikka Weissferdt[1] · **Cesar A Moran**[1]

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Abstract Thymomas are rare tumors that usually manifest in the anterosuperior mediastinum. Occasionally, thymomas may also originate from ectopically dispersed thymic tissue and can arise in locations such as the neck, lung, or pleura or other locations in the thoracic cavity. The occurrence of thymomas in these ectopic locations can cause substantial diagnostic difficulty as the entity is almost never included in the differential diagnosis and its biphasic morphology can cause further complications during the diagnostic process. In this review, we summarize the clinical and pathological spectrum of ectopic thymomas and discuss the histogenesis, treatment, and prognosis of these extraordinary tumors.

Keywords Thymus · Ectopic · Thymoma · Neck · Lung · Pleura · Thorax

Introduction

Thymomas are epithelial neoplasms of the thymic gland. These tumors are uncommon lesions that have a reported incidence of 0.13–0.15 cases per 100,000 in the USA [1, 2]. In 96 % of the cases, the tumors arise in the anterosuperior mediastinum while the remainder occurs in ectopic locations [3]. Ectopic thymomas are thought to originate from aberrant thymic tissue displaced during embryologic development of the thymic gland, and their distribution and frequency closely correlates with that of ectopic thymic tissue [4–7]. The highest incidence is therefore in the cervical region followed by the lungs and pleura. Other reported sites include the thyroid gland, pericardium, and middle/posterior mediastinum along with isolated cases in various other thoracic locations (Fig. 1). Altogether, less than 130 cases of ectopic thymomas have been reported in the medical literature to date; notably, this is after exclusion of tumors with a connection to the anterosuperior mediastinum or cases that had a concurrent or prior history of a mediastinal thymoma. In addition, we do not consider ectopic thymomas those tumors that have been designated as *ectopic hamartomatous thymoma*, *spindle epithelial tumor with thymus-like differentiation* (*SETTLE*), or *carcinoma showing thymus-like differentiation* (*CASTLE*) that can occur in the neck or thyroid gland [8, 9]. Although thymic differentiation has been proposed as a common denominator for the latter [8, 9], an unequivocal thymic component has not been demonstrated universally [10], and except for *CASTLE*, similar tumors have not been recognized in the thymic gland raising the possibility that they represent distinct clinicopathologic entities.

Due to their unexpected location, ectopic thymomas are frequently mistaken for more common lesions at these sites, especially since the initial diagnostic approach is often based on fine needle aspiration or core biopsy material. Questions also remain about the optimal medical management for such tumors as well as the parameters that best predict clinical outcome. As such, awareness of the phenomenon of thymomas arising in an ectopic location and their accurate diagnosis are crucial for patient management, therapeutic strategies, and prognostication.

✉ Annikka Weissferdt
aweissferdt@mdanderson.org

[1] Department of Pathology, MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA

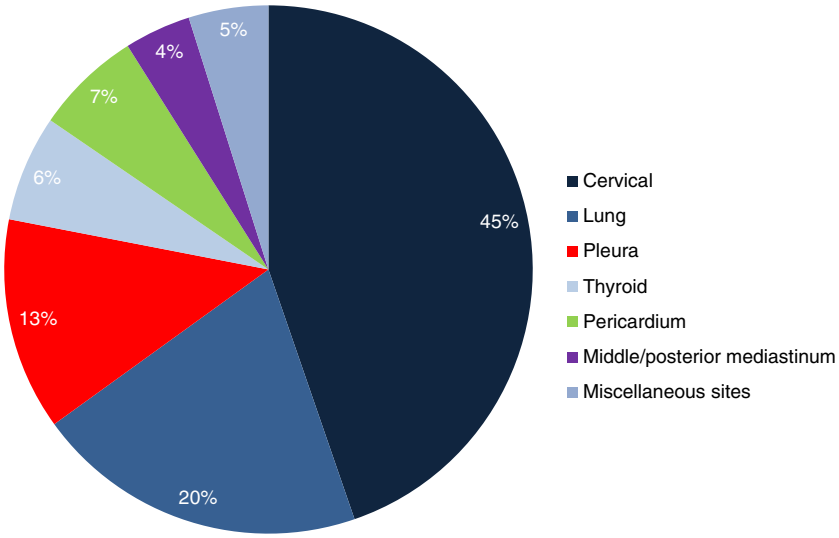

Fig. 1 Incidence of ectopic thymomas by site

Histogenesis

Although the histogenesis of ectopic thymomas largely remains a subject of speculation, the most popular theory to explain the existence of such tumors remains the displacement of thymic tissue during embryogenesis. The thymus is derived from the third and to a minor extent from the fourth pharyngeal pouches [4, 7]. During the sixth week of gestation, the thymic primordia develop from a sacculation of the ventral, endodermally lined portion of the third pharyngeal pouch. At the same time, the cervical sinus attaches to the primordia surrounding them with a layer of ectodermally derived tissue [4, 7]. After caudal and medial migration, during the eighth week, the thymic primordia enlarge toward their lower poles to form two epithelial bars that fuse in the midline and occupy their final position in the anterosuperior mediastinum [5]. During this final descent, the tail portion of the organ becomes thin and breaks up into small fragments that usually disappear. Sporadically, however, these thymic rests may persist and give rise to ectopic thymic tissue or even thymic neoplasia [5].

While this concept provides proficient explanation for the existence of thymic tissue in the submandibular area, lateral neck, thyroid, paratracheal region, and pericardial location, it fails to provide an explanation for the presence of thymic rests or neoplasms in the lung and pleural surfaces [11]. The pulmonary system develops much earlier than the thymus (during the third gestational week) and originates from the ventral groove of the larynx/pharynx caudal to the pharyngeal pouches [11]. It then descends caudally during the fourth week of fetal life which is prior to the development of the thymic primordia. Thus, it is difficult to explain how thymic tissue should become dispersed within the developing lung and how this could account particularly for the peripheral intrapulmonary thymomas [11, 12].

Another hypothesis suggests that ectopic thymomas can originate from stem cells, i.e., uncommitted germinative cells that have the capacity to develop along different cell lineages [13]. Such concept is supported by the existence of other primary intrapulmonary tumors corresponding to tissues that are not native to the lung such as meningiomas, glomus tumors, or melanoma [13–16]. Further deliberations include tumor origin from a monodermal teratoma or migration of a mediastinal thymoma into the lung although these theories have not met unanimous approval [17, 18]. To date, the displacement and stem cell theories remain the most widely accepted concepts.

Cervical ectopic thymomas

The neck region is the most frequent site of ectopic thymoma accounting for nearly 50 % of all cases [8, 19–35]. Most of these are located in the anterolateral neck close to the inferior poles of the thyroid gland, but further examples have been described around the submandibular and parotid regions and in the area of the suprasternal notch [8, 25–27]. Cervical thymomas occur much more frequently in females than in males with a ratio of 3:1 and at a mean age of 46 years [8, 19, 26–32]. Patients typically present with an enlarging neck mass that is often clinically confused with a thyroid lesion. Contrary to mediastinal thymomas that are associated with myasthenia gravis or other autoimmune diseases in up to 30–50 % of cases, ectopic cervical thymomas are only sporadically linked with such disorders [33, 34]. The diagnosis of these tumors can prove a diagnostic challenge particularly since the preliminary workup of neck masses is commonly based on fine needle aspiration (FNA). Due to the small sample size and biphasic nature of the thymoma, this may often

lead to an erroneous diagnosis suggestive of a lymphomatous process or undifferentiated carcinoma depending on which cell population predominates [21–24, 31, 32].

Ectopic pulmonary thymomas

Intrapulmonary thymomas, defined as primary thymomas beneath the visceral pleura or entirely surrounded by lung parenchyma, were first recognized by McBurney et al. in 1951 [36]. Since then, about 25 more cases have been reported, the majority as single case reports [12, 37–40]. The largest series on these unusual tumors consists of eight cases presented by Moran et al. in 1995 [11]. Intrapulmonary thymomas have only a slight predilection for the female gender (F/M ratio = 13:9), and in keeping with other ectopic thymomas, an association with autoimmune disease is rare [38]. The patient age ranged from 14 to 77 years with a median age of 50 years [12]. Primary pulmonary thymomas are more frequently located in the right than the left lung and predominantly affect the upper lobes [12]. Although most of the lesions are peripherally located, a hilar location with or without endobronchial component or multifocal distribution in the same lung may also occur [11, 12] (Fig. 2a, b). Cough, chest pain, pneumonia, or hemoptysis are common presenting symptoms, although the tumors are not infrequently discovered incidentally. Due to their unusual presentation as primary pulmonary masses, intrapulmonary thymomas are frequently misdiagnosed on core needle or bronchoscopic biopsies. Based on this limited sampling, the morphology and immunophenotype of the lymphocyte-rich variants (WHO type B1/B2) may easily be mistaken for lymphoma, while in instances in which the tumor is predominantly composed of epithelial cells (WHO types A and B3), diagnostic considerations may include primary non-small cell carcinoma or metastatic disease. In fact, in several of the reported cases, the tumors had originally been diagnosed as poorly differentiated squamous cell carcinoma, spindle cell carcinoma, metastatic carcinoma of unknown primary, or hemangiopericytoma [11, 37, 38].

Ectopic pleural thymomas

Moran et al. [41] described the first bona fide primary pleural thymomas in 1992. Although several authors had alluded to this phenomenon before [17, 42–44], critical review of the reported cases revealed tumor masses in the anterior superior mediastinum with diffuse involvement of the pleural surface thereby questioning the true ectopic nature of the lesions. Since the initial description of eight cases [41], a similar number has been reported as single case reports [45–51]. Similar to most ectopic thymomas, primary pleural thymomas show a female predominance (F/M ratio = 9:6) and only sporadic association with myasthenia gravis [49]. Presenting symptoms are often non-specific and can include respiratory difficulties, fever, and weight loss [41]. The mean age at diagnosis is 54.5 years [41]. Most of the cases present as diffuse pleural tumors encasing the lungs and clinically and radiologically mimicking malignant mesothelioma or metastatic pleural disease (Fig. 2c, d) [41, 48, 49]. Occasionally, however, the tumors may be well circumscribed and attached to the pleura by a pedicle thus raising the suspicion of a solitary fibrous tumor [45, 46].

Ectopic intrathyroidal thymomas

Primary intrathyroidal thymomas need to be separated from ectopic cervical thymomas that frequently occur in the general region of the thyroid and often adhere to the inferior poles of the gland. Similarly, as mentioned above, SETTLE and CASTLE are distinct clinicopathologic entities of the thyroid that need to be separated from these tumors. Thus, thymomas that arise completely within the thyroid parenchyma are exceptionally uncommon lesions with only eight cases reported in the medical literature (Fig. 2e, f) [8, 52–54]. A strong female predilection is typical for these tumors (F/M = 6:2), and patients characteristically present with neck pain, palpable neck nodule, or enlargement of the thyroid gland in the absence of thyroid dysfunction or other autoimmune disease. Fine needle aspiration is commonly performed as the initial diagnostic step and has the potential to be misinterpreted as lymphocytic thyroiditis, low-grade lymphoma, or even poorly differentiated carcinoma [54, 55]. Diagnostic difficulties often remain even after surgical resection. In fact, in the case reported by Asa et al. [52], the patient was initially diagnosed with and treated for an anaplastic thyroid carcinoma before the correct diagnosis of thymoma was established only at tumor recurrence.

Ectopic pericardial thymomas

The incidence of ectopic pericardial thymomas is very low with only eight reported cases to date, a female to male ratio of 5:3, and a mean age at presentation at 60 years [56–62]. Symptoms can range from asymptomatic to chest pain, weight loss, fever, and cardiac symptoms including cardiac enlargement, pericardial effusion, heart failure, and cardiac tamponade sometimes requiring emergency surgical intervention. Two of the reported cases showed an association with myasthenia gravis and hypogammoglobulinemia, respectively [56, 61]. The diagnosis is rarely established preoperatively, and metastatic carcinoma or lymphoma is more commonly suspected especially in cases with a pericardial mass lesion and associated pericardial effusion [58, 62].

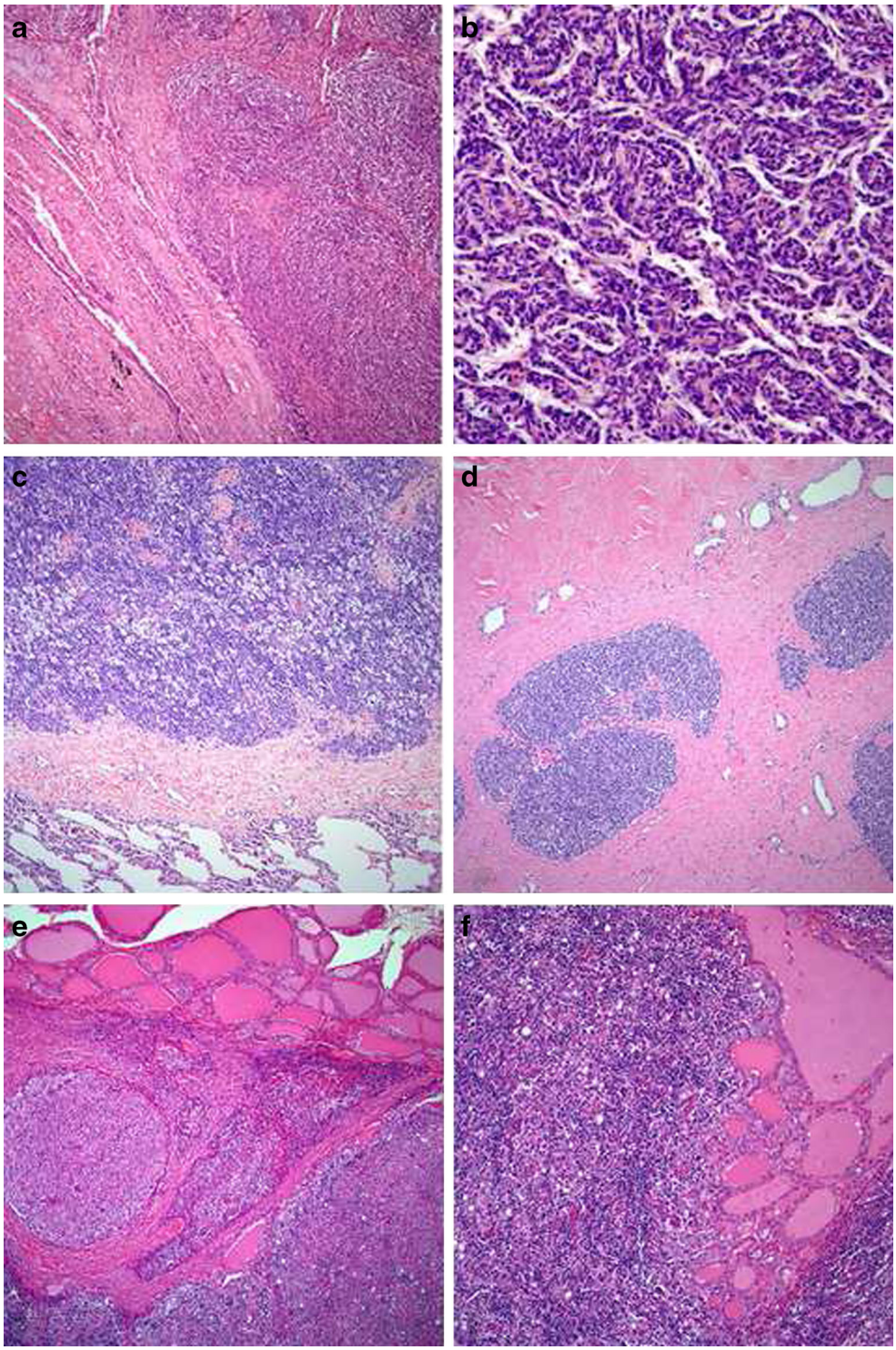

Fig. 2 **a** Ectopic thymoma arising in the lung parenchyma, **b** higher magnification of an ectopic pulmonary thymoma showing a spindle cell morphology with bland cytological features (WHO type A), **c** primary pleural ectopic thymoma, **d** the tumor is originating from the pleural surfaces without any connection to the mediastinum, **e** primary intrathyroidal thymoma, **f** note the entrapped thyroid follicles

Ectopic thymomas of the middle and posterior mediastinum

True ectopic thymomas may also rarely be identified in the middle or posterior mediastinum. Careful scrutiny of the published cases reveals that the majority of these either had a direct connection to the thymic gland or its surrounding adipose tissue and should therefore not be considered genuine ectopic thymomas in our opinion [63–67]. After exclusion of these cases, only five true ectopic thymomas remain, four of which affected females and one that was diagnosed in a male [68–72]. Myasthenia gravis or other autoimmune disease was not detected in any of these patients. In most cases, the tumors were discovered incidentally during routine medical checkup

although back pain, cough, or precordial discomfort have also been reported. Due to their position within the mediastinum, the preoperative differential diagnosis usually includes neurogenic tumors, teratomas, and lymphoid hyperplasia, but more frequently than in other ectopic sites, thymoma may already be suspected clinically.

Ectopic thymomas of other locations

In addition to the sites discussed above, sporadically ectopic thymomas have also been recognized in various other anatomic locations. Wadon in 1934 reported one of the first ectopic thymomas presenting as an intratracheal polyp [73]. In 1990, Jansen et al. described a 82-year-old female patient with an encapsulated thymoma arising from the dome of the right hemidiaphragm initially believed to be normal hepatic tissue with herniation through the diaphragmatic muscle [74]. Despite the presence of associated thymoma-induced immunologic dysfunction, the final diagnosis was only established at post-mortem examination in this patient. MacLean et al. [75] found an ectopic thymoma in the area of the skull base to be the cause of dysarthria, dysphagia, and repeated aspiration in a 54-year-old woman diagnosed and treated for myasthenia gravis 7 years earlier. In 2005, Ko et al. [76] diagnosed a retrotracheal ectopic thymoma that was initially believed to be a submucosal tumor of the esophagus. After surgery and adjuvant chemoradiotherapy, the patient has remained disease-free at 5-year follow-up. A very unusual presentation of ectopic thymoma was reported by Miller et al. [77] detailing two thymomas that were arising within atrial cardiac myxomas, speculating that neoplastic transformation of thymic rests within a myxoma was the likely origin for these tumors. Lastly, Marandino et al. [78] documented a spindle cell thymoma (WHO type A) originating within the vertebrae of the thoracic spine in a 59-year-old female who had presented with back pain. A CT-guided needle biopsy did not reveal a definitive diagnosis after hemangiopericytoma, paraganglioma, sarcoma and metastatic carcinoma were ruled out, and the final diagnosis was only established on a subsequent curettage specimen.

Pathology

The gross and microscopic features of ectopic thymomas are similar irrespective of primary site and closely parallel those of their anterior mediastinal counterparts. Moreover, the whole range of thymoma types and variants has been described in ectopic sites.

Gross pathologic examination will reveal round or oval-shaped masses with a smooth or bosselated surface. The cut surface is often pale tan in color and has a dense consistency. Thick fibrous septa separating the tumor into lobules are a characteristic feature of these tumors. Microscopically, thymomas are notorious for showing a great spectrum of cytoarchitectural features depending largely on the shape of the tumor cells as well as the proportions of neoplastic epithelial cells and lymphocytes. The *spindle cell type* (*WHO type A*) is characterized by a proliferation of bland fusiform cells with minimal or absent cytologic atypia and only scattered mitotic activity. The lymphocytic component is usually sparse. Cases in which zones of spindle cells alternate with areas of round or ovoid cells and a more conspicuous lymphocytic infiltrate correspond to the category of *mixed thymoma* (*WHO type AB*). The neoplastic epithelial cells in *conventional thymomas* (*WHO types B1 and B2*) are round or polygonal in shape and contain vesicular nuclei, small eosinophilic nucleoli, and abundant cytoplasm. These tumors characteristically are infiltrated by numerous immature T cells. Similar to spindle cell thymomas, these tumors lack any significant cytological atypia or increased mitotic activity. *Atypical thymomas* (*WHO type B3*) show a predominantly epithelial cell population which may show a higher degree of cytological atypia and occasional mitotic figures. Similar to spindle cell thymomas, this variant is characterized by a scarce infiltrate of immature lymphocytes. Fibrous septa and perivascular spaces may be seen to varying degrees in all subtypes [79]. Depending on the primary site, entrapment of native tissue or invasion of adjacent structures may be identified and are important to mention in the pathology report as adjuvant medical treatment may be considered depending on the degree of infiltration. As indicated above, the morphological spectrum of ectopic thymomas also includes some rarer variants such as rhabdomyomatous thymoma, micronodular thymoma, or thymoma with pseudosarcomatous stroma [27, 59, 69] requiring familiarity with the whole range of thymoma subtypes for correct diagnosis.

Immunohistochemical features

Immunohistochemically, ectopic thymomas show the same phenotype as anterior mediastinal thymomas. The difficulty with the diagnosis of these tumors not only lies in their wide morphologic spectrum but also in the fact that to date, no specific immunohistochemical marker for these neoplasms exists. Thymomas are epithelial tumors and react with a range of cytokeratins including pancytokeratin (AE1/AE3), low molecular weight cytokeratin (CAM5.2), high molecular weight cytokeratin (34ßE12), and CK5/6 [80–82]. These stains will typically highlight the lace-like pattern of the epithelial cells

between the non-neoplastic lymphocytes in the conventional thymomas (WHO type B1/B2) and a more cohesive or sheet-like appearance in spindle cell (WHO type A) and atypical thymomas (WHO type B3) [83–85]. Since ectopic thymomas are often confused with lymphomas, this characteristic staining pattern may be of great help in the separation of these two neoplasms. Further markers associated with thymomas include p63 or p40 and Pax8 (polyclonal). These markers are very useful given their diffuse and strong nuclear reactivity in up to 100 % of cases [81, 86–88]. The reactivity with Pax8 is very useful in the differential diagnosis with pleuropulmonary neoplasms such as mesothelioma or non-small cell lung carcinomas all of which are typically negative for this marker [89–91]. However, caution must be exercised when dealing with ectopic thymomas in the thyroid gland as Pax8 reactivity is a characteristic feature of various primary thyroid neoplasms and should therefore not be used to distinguish these tumors [92]. The non-neoplastic T lymphocytes are positive with CD1a+, CD3+, CD4+, and/or CD8+ as well as CD99 and TdT [93–95]. In those cases, in which the reactivity with TdT can potentially cause confusion with a T cell lymphoblastic lymphoma, which can be the case with the lymphocyte-rich variants of thymoma (WHO types B1 and B2), diligent search for a keratin-positive epithelial cell component is warranted and should confirm the diagnosis.

Treatment and prognosis

Due to the low incidence of ectopic thymomas, clinical studies about treatment and outcome are very limited and no standard therapy has been outlined. Moreover, recurrence rates and mortality are difficult to estimate due to the small number of cases and lack of long-term follow-up. For that reason, the treatment of ectopic thymomas is largely based on that of anterior mediastinal thymomas and complete surgical resection remains the standard of care [96]. Induction chemotherapy should be considered in patients with locally invasive disease followed by surgical resection, irradiation, and/or consolidation chemotherapy [97]. Thus, multimodality therapy is often indicated in patients with locally advanced, metastatic, or unresectable disease [96].

According to this treatment algorithm, complete surgical resection is also the treatment of choice also for ectopic thymomas and surgery should be attempted in all patients that are deemed operable irrespective of tumor site. Radiation and/or chemotherapy have been suggested in cases that are considered inoperable, show invasion of local structures, or are incompletely resected in order to prevent recurrence or metastasis [11, 12, 35, 41, 49, 55–62].

The natural course of ectopic thymomas is difficult to predict. Although most cases have proven to be indolent if completely resected, sporadic cases with tumor recurrence and even distant metastasis have been recognized [19, 20, 28]. It has to be noted though that the assessment of the degree of aggressiveness in ectopic thymomas remains a challenging task as for some locations, for instance the pleural surfaces, the usual criteria, such as capsular invasion, can hardly be applied and parameters to predict the biologic behavior remain to be defined [41]. Thus, close clinical follow-up seems prudent in any case of ectopic thymoma given its potential to metastasize [41].

Differential diagnosis

The differential diagnosis for ectopic thymomas not only depends on the primary site but also on the morphological characteristics of the tumor. The lymphocyte-rich variants (WHO type B1/B2) are often confused for lymphoma or in cases of intrathyroidal lesions for lymphocytic thyroiditis. In these cases, it is vital to think about the possibility of thymoma and to tailor the diagnostic workup accordingly. As mentioned above, a simple cytokeratin stain can confirm the presence of the—often subtle—epithelial component in such cases and should be included in any antibody panel. In combination with a TdT-positive lymphocytic component, a diagnosis of thymoma should be straightforward.

Cases in which the epithelial component predominates (WHO type B3) have the potential to be confused with poorly differentiated carcinoma, especially squamous cell carcinoma or in cases of lung, pleural, or pericardial primaries with metastatic disease. This is based not only on the morphological features but also on the immunophenotype of thymomas that can closely resemble that of squamous cell carcinoma. In this context, close attention to morphological detail, namely an absence of cytologic atypia and mitotic activity together with other organotypical features of thymoma such as perivascular spaces and a sprinkling of lymphocytes, is essential to arrive at the correct diagnosis. The diffuse growth pattern of some primary pleural thymomas can also be mistaken for malignant mesothelioma. Close clinical correlation with particular emphasis on asbestos exposure as well as application of a targeted immunohistochemical panel to include mesothelioma-associated markers (calretinin, thrombomodulin, WT-1) may aid in the differential diagnosis.

Finally, the fusiform appearance of spindle cell thymomas (WHO type A) can easily evoke the impression of dealing with a mesenchymal lesion, particularly in cases of lung and posterior mediastinal tumors in which hemangiopericytoma, synovial sarcoma, or neurogenic tumors can enter the differential diagnosis. In these cases, strong reactivity for cytokeratin and negative staining with mesenchymal markers such as CD34 or S100 would argue in favor of thymoma.

Comment

The occurrence of thymomas in ectopic locations is a highly unusual phenomenon. Due to a low index of suspicion and absence of any specific clinical features, these tumors are often mistaken for other more common pathologic processes and may only be diagnosed correctly after surgical resection. In keeping with the migration tract of the thymic gland during embryologic development, the distribution of ectopic thymomas appears to be limited to locations within the thoracic cavity as well as the head and neck region with the vast majority located in the anterolateral neck followed by the lung and pleura.

Ectopic thymomas do share certain similarities with their orthotopic mediastinal counterparts such as a similar age at presentation with a peak in the fifth and sixth decades, same histologic spectrum, and immunohistochemical phenotype (Table 1). On the other hand, ectopic thymomas more frequently occur in female patients with a female to male ratio of 2.2:1, while the sex distribution in orthotopic thymomas is approximately equal. An association with myasthenia gravis or other autoimmune disorder is only sporadically seen in ectopic thymomas, however, signs and symptoms of myasthenia gravis in the absence of an anterior mediastinal mass should always prompt clinicians to search for an ectopic primary before ruling out a thymic neoplasm.

The diagnosis of ectopic thymomas can be extremely challenging based on the non-specific clinical presentation as well as the abnormal location for thymoma. Fine needle aspiration and core needle biopsy are minimally invasive techniques commonly employed in the initial diagnostic workup of these lesions. Due to the small sample yield and morphologic heterogeneity of thymomas, these tumors are often erroneously interpreted to represent more common neoplastic or non-neoplastic processes and correct diagnosis may be delayed until surgical resection is performed. Awareness of the existence of ectopic thymomas coupled with familiarity of the histological spectrum of thymomas is essential in this situation. In addition, the results of anxillary techniques, such as immunohistochemical studies, must be interpreted in the context of the tumor site and the native tissues in that area.

Owing to the small number of cases, reliable data about the optimal treatment of patients with ectopic thymomas are still lacking. In many cases, the treatment is therefore modeled on that for mediastinal thymomas. In certain locations, however, such as the pleura, what constitutes invasion is difficult to define and the treatment may have to be based on individual circumstances. Likewise, it appears that the most important variable in terms of prognosis—as for mediastinal thymomas—is the presence or absence of tumor invasion into neighboring structures although close clinical follow-up is warranted even for encapsulated tumors as late local recurrence and distant metastasis have been described.

Ectopic thymoma should be included in the differential diagnosis of any tumor in the thoracic or cervical regions. Accurate diagnosis is critical as many of the entities that enter the differential diagnosis require alternative treatment modalities and are associated with different biologic behavior.

Table 1 Ectopic thymomas compared with orthotopic thymomas

Feature	Ectopic thymomas	Orthotopic thymomas
Incidence of all thymomas	4 %	96 %
Site	Neck, lung, pleura, thyroid gland, pericardium, middle/posterior mediastinum	Anterosuperior mediastinum
Clinical features	F > M; 5th to 6th decade; symptoms depend on primary site	F = M; 5th to 6th decade; chest pain, SOB, cough or asymptomatic
Association with autoimmune disorders	Rare	30–50 %
Histology	Spindle cell (WHO type A), conventional (WHO type B1/B2), atypical thymomas (WHO B3) including mixed types and rarer variants	Spindle cell (WHO type A), conventional (WHO type B1/B2), atypical thymomas (WHO type B3) including mixed types and rarer variants
IHC phenotype	CK, CK5/6, p63, p40, Pax8+ (epithelial cells); CD1a, CD99, TdT+ (lymphocytes)	CK, CK5/6, p63, p40, Pax8+ (epithelial cells); CD1a, CD99, TdT+ (lymphocytes)
Treatment	Complete surgical resection (additional radiotherapy/chemotherapy for invasive cases or residual disease)	Complete surgical resection (additional radiotherapy/ chemotherapy for invasive cases or residual disease)
Prognosis	Parameters to be determined; if capsule present based on absence or presence of capsular invasion; all potentially malignant	Based on absence or presence of capsular invasion; all potentially malignant

F female, *M* male, *CK* cytokeratin, *TdT* terminal deoxynucleotidyl transferase, *IHC* immunohistochemical

Compliance with ethical standards

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