

Review

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# Thymic carcinoma: review and update

Kirill Karlin, Phillip D. Michaels

Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA 02115, USA.

**Correspondence to:** Dr. Phillip D. Michaels, Department of Pathology, Beth Israel Deaconess Medical Center, 300 Brookline Avenue, Boston, MA 02215, USA. E-mail: pmichael@bidmc.harvard.edu

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## Abstract

Thymic carcinoma (TC) is a rare thymic epithelial neoplasm with an aggressive clinical course. There are many recognized histologic subtypes as described by the fifth edition of the World Health Organization (WHO) Classification of Thoracic Tumors; however, given the rarity of this tumor group, diagnosis remains a challenge, especially on limited tissue samples. Additionally, rare variants of TC are continuing to be established, particularly in the era of molecular diagnostics. Herein, histologic subtypes are described as the rare subtypes of TC in the context of their immunoprofile, cytogenetic or molecular features, clinical presentation, and ensuing challenges.

**Keywords:** Thymic carcinoma, NUT carcinoma, thymus, KIT, thymoma

## INTRODUCTION

Thymic carcinoma (TC) is a rare thymic epithelial neoplasm (TEN) with heterogeneous features. Compared to thymomas, TC displays a more aggressive clinical course with high rates of metastases and recurrences. The estimated median overall survival rate between all stages is 6.6 years<sup>[1]</sup>. From a pathology perspective, TC does not have a specific unifying morphologic picture and can present with different histologic features. In general, TC shows greater architectural distortion and cytologic atypia when compared to thymomas. Immunohistochemistry can be beneficial in differentiating primary TC and metastatic disease; however, the final diagnosis is based on a careful pathologic, clinical, and radiographic correlation.



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TC can present with locally invasive symptoms such as cough, chest pain, or superior vena cava syndrome. Red cell aplasia or dysglobulinemia occurs more commonly in thymoma, and is infrequent in TC<sup>[2]</sup>. Unlike thymomas, the presentation of paraneoplastic syndrome and myasthenia gravis has rarely been reported and if present, the diagnosis of TC is challenging as this is an active area of controversy<sup>[3,4]</sup>.

The majority of the TC cases present with local invasion into adjacent mediastinal structures. In retrospective studies, metastases were described in 50%-65% of TC cases<sup>[5,6]</sup>. Even after surgical resection, TC behaves aggressively and shows frequent recurrences.

A unifying etiology of TC is currently unknown with the oncogenesis differing from subtype to subtype. As an example, NUT carcinoma, a rare thoracic cancer that is clinically aggressive and contains undifferentiated tumor cells, is characterized by a nuclear protein in testis (*NUTM1*) gene fusion and thymic mucoepidermoid carcinoma by the classic mastermind-like transcriptional coactivator 2 (*MAML2*) fusion<sup>[7]</sup>. Additionally, the loss of chromosome 16q in thymic squamous cell carcinoma has been described<sup>[8,9]</sup>. In rare scenarios, TC occurs with a coinciding thymoma, raising the possibility that the carcinoma may harbor an existing clonal relationship with the thymoma.

Multiple staging systems have been developed for thymomas and TC with much controversy over utility. The emphasis on the capsule of the Masaoka-Koga system does not translate to TC as they often do not present with a capsule. Previously, thymomas have been classified as malignant if there was an invasion into the capsule or demonstrated metastatic disease. In general, it is preferred to use the terms “thymoma” or “thymic carcinoma”, as “malignant thymoma type II” and “WHO type C thymoma” are no longer accepted terminology.

### **Clinical features**

TC is an aggressive neoplasm that accounts for 14%-22% of all TEN<sup>[10]</sup>. It can occur in all age groups but is most frequent in adults with a mean age of 46 and a slight male predominance (1.5:1 male-to-female)<sup>[11]</sup>. Most patients present with symptoms related to the anterior mediastinal location of the mass, such as chest pain, shortness of breath, and superior vena cava syndrome. The tumors often present at advanced stages with an invasion of local anatomic structures and a significant proportion developing metastasis to lymph nodes and distant sites.

### **Diagnostic challenges**

Differentiating between a metastasis to the anterior mediastinum and TC can be a diagnostic challenge<sup>[12,13]</sup>. The diagnosis is especially challenging when pathologists are confronted with limited tissue, such as a core biopsy. This can be the case when complete resection is not feasible due to age or underlying comorbidities of the patient.

As the differential diagnosis of anterior mediastinal masses is broad, cytokeratin staining is useful in differentiating between lymphoid neoplasms and carcinomas. Expression of c-KIT (CD117) can be a helpful marker in diagnosing TC, as positive immunoreactivity for c-KIT is more commonly seen with TC<sup>[14,15]</sup>. Similarly, CD5 expression can be seen in TC and only positive in a small subset of thymomas<sup>[16]</sup>. **Table 1** provides a list of morphologic, immunohistochemical, and radiographic features that may assist in the differentiation between thymoma and TC.

### **Gross appearance**

On gross examination, TC appears large, firm, infiltrating, and can have cystic changes or necrosis. Up to 15% of TC can be encapsulated<sup>[17]</sup>. Some gross examination clues can suggest a particular histological

**Table 1. Comparison between thymoma and thymic carcinoma**

	<b>Thymoma</b>	<b>Thymic carcinoma</b>
Cytologic features	Mild to moderate atypia	Marked atypia
Mitotic figures	Lower	More frequent
Lymphocytes	Perivascular spaces, immature T-cell phenotype	Mature T- and B-cells
Growth and necrosis	Lobular, usually lacks vascular invasion and necrosis	Infiltrative, can show vascular invasion and necrosis
Immunohistochemistry	Epithelial cells negative for c-KIT (CD117). Immature TDT-positive T-cells present	Epithelial cells positive for c-KIT (CD117) in 60%-80% of cases. CD5 often expressed
Imaging	More regular, less necrotic, and cystic	Irregular borders, necrotic and cystic areas Lymphadenopathy and/or, pleural effusion

subtype, such as the appearance of a mucoid cut surface, which may hint toward a mucoepidermoid carcinoma<sup>[18]</sup>.

## RESULTS

### Histological subtypes

In 1982, Snover *et al.*<sup>[19]</sup> originally defined five distinct histologic variants of TC. The subtypes are similar to carcinomas seen in other organs and indicate that the thymic epithelium can differentiate in many ways.

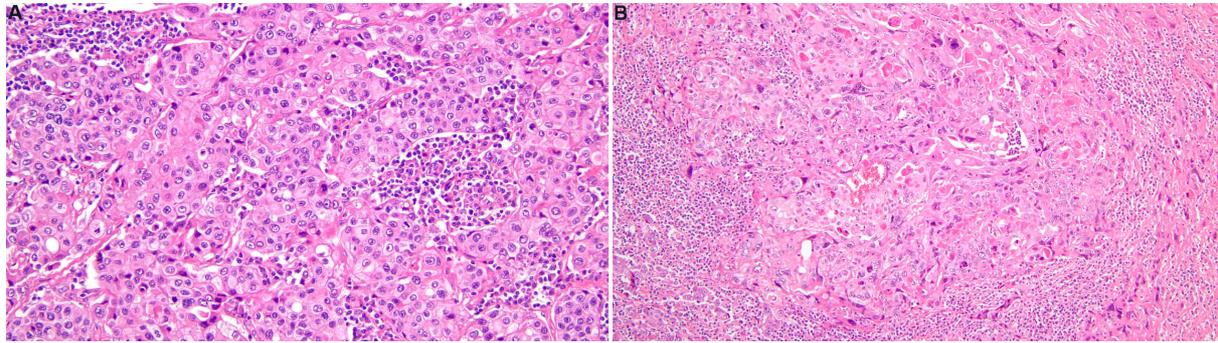
In 2021, the fifth edition of the World Health Organization (WHO) Classification of Thoracic Tumors was released with the recognized categories of TC largely remaining the same when compared to the fourth edition<sup>[20]</sup>. The primary changes in the WHO 2021 include the addition of a hyalinizing subtype characterized by an *EWSR1* translocation for clear cell carcinoma, which corresponds to the same hyalinizing subtype of clear cell carcinoma of the salivary gland. Another change is in the terminology of adenocarcinomas, where “mucinous adenocarcinoma” is changed to “enteric-type adenocarcinoma”, and “papillary adenocarcinoma” is changed to “low-grade papillary adenocarcinoma” due to its bland histologic features and rather indolent clinical course. Lastly, “micronodular thymic carcinoma with lymphoid hyperplasia” as a subtype of squamous cell carcinoma was added.

Combined TC with more than one histological type is not common, but is reported and can occur. If present, the features of the different components should be reported in 10% increments and termed “combined thymic carcinoma”, which is in line with the WHO 2021 recommendation.

### Squamous cell carcinoma of the thymus

Squamous cell carcinoma of the thymus is the most common morphological subtype accounting for approximately 70% of all thymic carcinomas<sup>[21,22]</sup>. Most commonly, it occurs in the sixth decade with a slight male predominance. Clinically, it often presents with symptoms associated with mass effect within the mediastinum. Up to a third of the patients are diagnosed incidentally on imaging<sup>[23]</sup>. On imaging, the lesions present as more irregular with necrotic and cystic components. The majority of patients present at advanced clinical stages. Histologically, this entity is comparable to squamous cell carcinomas arising in other locations, and it is important to exclude metastasis from other organs. Squamous cell carcinoma does not resemble normal thymic architecture, can present as keratinizing or non-keratinizing, lacks encapsulation, and can grow in nests with a round to oval nuclei [Figure 1A and B]. *EGFR* mutations are potentially associated with a worse prognosis<sup>[24]</sup>.

On immunostaining, the tumor cells are positive for pankeratin. CD5, c-KIT (CD117), GLUT1, and MUC1 can also be positive. p16 expression is found in approximately 65% of thymic squamous cell carcinomas<sup>[25]</sup>.



**Figure 1.** Thymic squamous cell carcinoma. Different varieties of thymic squamous cell carcinoma, including non-keratinizing (A, 20×) and keratinizing (B, 10×) forms.

In the recent WHO, micronodular thymic carcinoma with lymphoid hyperplasia was added as a subtype of squamous cell carcinoma, which is the malignant counterpart to micronodular thymoma with lymphoid hyperplasia<sup>[26]</sup>. This carcinoma shows lymphoid stroma with prominent germinal centers and nodules of spindle cells, which show marked atypia. Compared to micronodular thymoma, micronodular thymic carcinoma with lymphoid hyperplasia lacks TdT-positive T-cells around the tumor islands and the tumor cells often express c-KIT (CD117) and CD5.

#### Basaloid carcinoma of the thymus

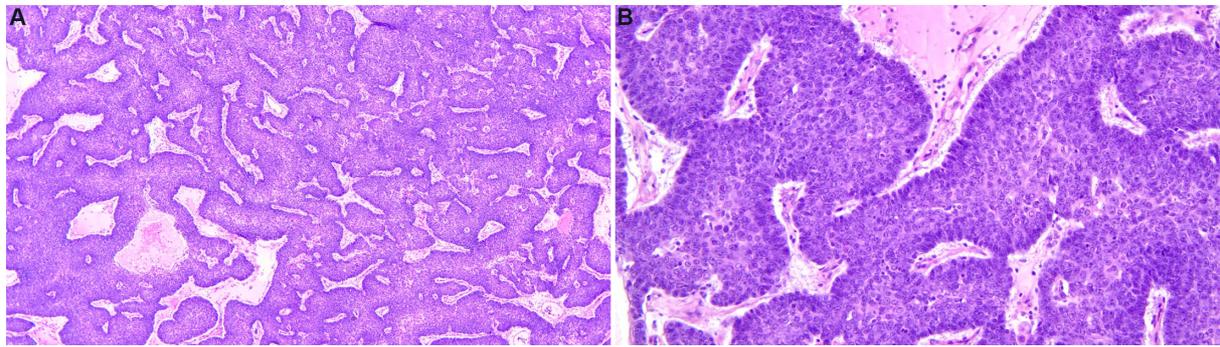
Basaloid carcinoma is a rare subtype of TC and represents less than 5% of all TC. It occurs most commonly between the fifth and sixth decade and has a slight male predominance. About 60% of the cases are diagnosed incidentally on imaging. Histologically, basaloid carcinoma of the thymus presents itself with small nests/cords of hyperchromatic round to oval tumor cells that show prominent peripheral palisading of nuclei with a subset demonstrating cystic changes [Figure 2A and B]. Basaloid carcinomas are typically associated with a less aggressive clinical course. On immunostaining, the tumor cells are positive for pankeratin. Approximately 75% of cases are positive for p40/p63 and c-KIT (CD117)<sup>[27]</sup>.

#### Mucoepidermoid carcinoma of the thymus

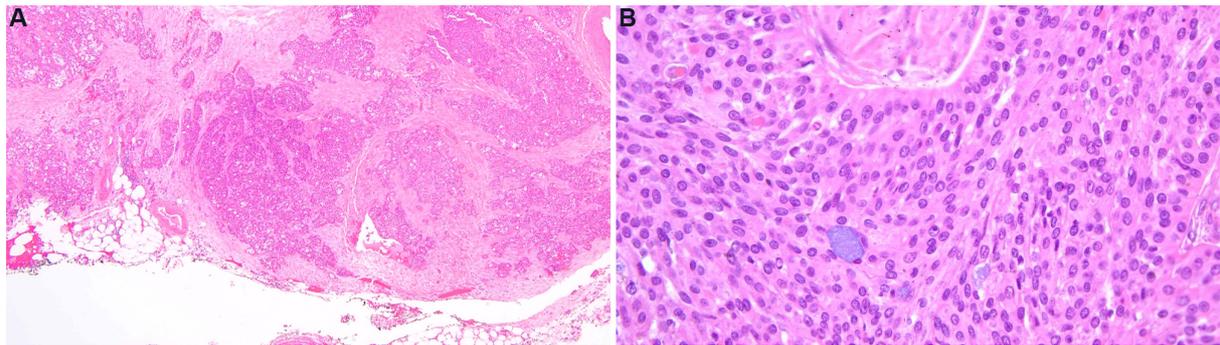
Mucoepidermoid carcinoma is a rare subtype of TC, accounting for less than 5% of all TC. Histologically, it presents as a mix of squamous and glandular components<sup>[28]</sup>. Intermediate cells with polygonal shapes and eosinophilic cytoplasm can be observed. The squamous epithelial aspect of this carcinoma usually presents as sheet-like growth with atypical cells that display keratinization and intercellular bridges [Figure 3A and B]. A characteristic *MAML2* rearrangement is disease-defining.

#### Lymphoepithelial carcinoma of the thymus

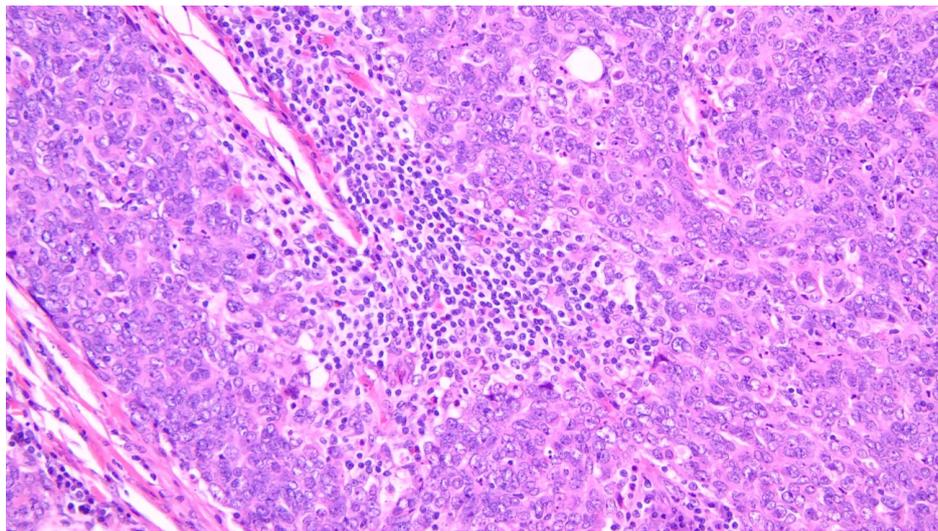
Lymphoepithelial carcinoma, formerly known as lymphoepithelioma-like carcinoma, is a rare TC accounting for about 1.3%-6% of all TC<sup>[29]</sup>. Although the term of lymphoepithelial carcinoma denotes a prominent lymphoid background, these tumors could be conceptualized as poorly-differentiated, non-keratinizing squamous cell carcinomas in their appearance. An association with Epstein-Barr virus (EBV) in the pathogenesis of this tumor has been reported<sup>[30-32]</sup>. Histologically, the tumor presents as a poorly differentiated, nonkeratinizing squamous cell carcinoma. The carcinoma has large, polygonal cells and shows a syncytial growth pattern. A prominent lymphoid background with scattered plasma cells is seen surrounding the tumor cells [Figure 4]. By immunohistochemistry, tumor cells show variable reactivity for CD5, are positive for c-KIT (CD117), and commonly express PD-L1<sup>[33]</sup>. If associated with EBV, the tumor cells show positive nuclear labeling for EBV-encoded small RNA on *in-situ* hybridization. The inflammatory component is highlighted by mature B- and T-cells with polyclonal plasma cells.



**Figure 2.** Basaloid carcinoma. Cords (A, 2×) of hyperchromatic cells with round to oval nuclei (B, 20×).



**Figure 3.** Mucoepidermoid carcinoma. A glandular growth pattern is observed (A, 2×) while a subset of cells display intracytoplasmic mucin (B, 20×).



**Figure 4.** Lymphoepithelial carcinoma of the thymus (20×). Islands of poorly differentiated, non-keratinizing tumor cells are embedded in a lymphoid-rich stroma.

### **Sarcomatoid carcinoma of the thymus**

Sarcomatoid carcinomas account for approximately 5% of all TC. Clinically, these carcinomas present with similar symptoms as other TC and show very aggressive behavior with the majority of patients presenting with advanced disease at diagnosis. A comprehensive case series by Suster and Moran<sup>[34]</sup> described the

microscopic features of this tumor as showing a spindle cell proliferation with a high mitotic count [Figure 5]. In a minority of instances, the tumor can appear similar to a spindle cell thymoma. Some areas can show a different growth pattern, such as rhabdomyoblastic or cartilaginous differentiation. Sarcomatoid carcinoma arising from metaplastic thymoma has been described<sup>[35,36]</sup>.

### Clear cell carcinoma of the thymus

Originally described by Snover *et al.*<sup>[19]</sup>, this TC shows a lobulated growth pattern with cellular morphology ranging from uniform clear cells with minimal nuclear pleomorphism to larger, more pleomorphic tumor cells with prominent nucleoli [Figure 6]. There is no glandular component, and lymphocytes can be admixed within the tumor. Cells show abundant cytoplasmic glycogen that is Periodic acid-Schiff (PAS) positive and is usually negative for mucicarmine. Clinically, these carcinomas have a poor prognosis. A large case series by Hasserjian *et al.*<sup>[37]</sup> described the clinical symptoms, which are similar to other TC with overall survival estimated at 4-24 months.

Cases of thymic carcinoma with clear cell morphology and substantial hyalinization carrying an *EWSR* translocation have been described<sup>[38]</sup>. In the most recent WHO classification, hyalinizing clear cell carcinoma with *EWSR1* translocation is recognized as a potential subtype of clear cell carcinoma.

### Low-grade papillary adenocarcinoma of the thymus

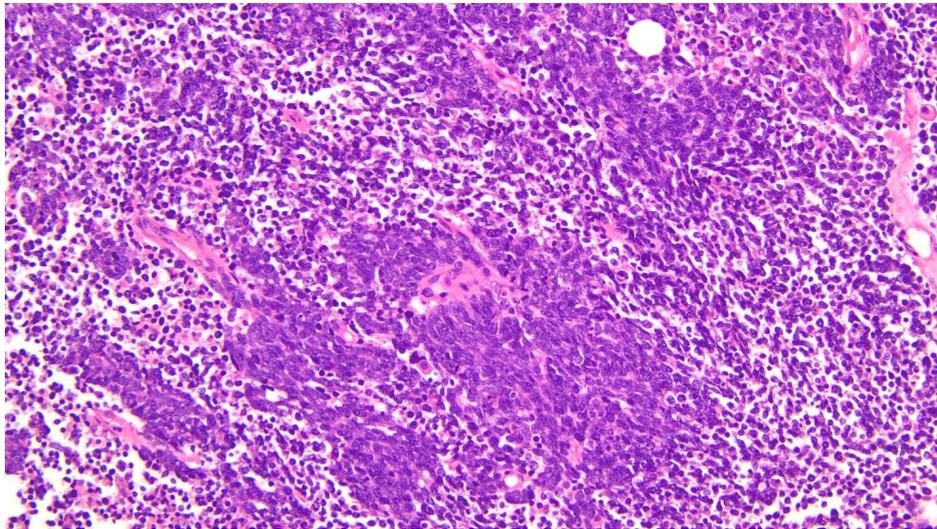
Low-grade papillary adenocarcinoma of the thymus is reported to occur in up to 3% of TC. An association between low-grade papillary adenocarcinomas of the thymus and type A thymoma, A/B thymoma, or multilocular thymic cysts have been made<sup>[39]</sup>. Clinically, an elevated carcinoembryonic antigen level has been reported<sup>[40]</sup>. Histologically, this tumor shows predominantly tubular and papillary structures with fibrovascular cores that are separated by fibroconnective tissue. Psammoma bodies can be present. No prominent nuclear atypia is seen. If high-grade atypia is present, a diagnosis of thymic adenocarcinoma, NOS should be considered. Immunohistochemistry can be helpful in excluding papillary neoplasms of thyroid, lung, and other extrathoracic sites, as the tumor cells are negative for thyroglobulin, TTF-1, calcitonin, CK20, CDX2, CD20, and PAX8<sup>[41]</sup>.

### Enteric-type adenocarcinoma of the thymus

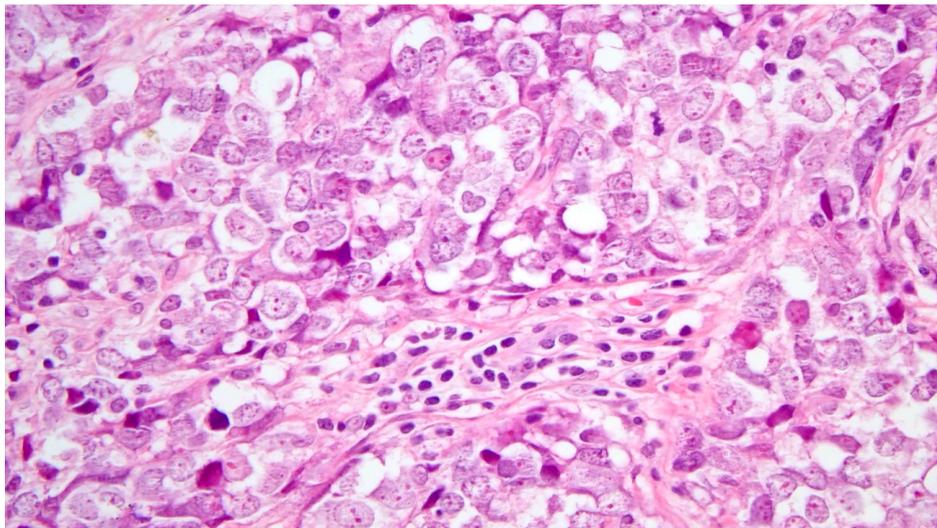
Enteric-type adenocarcinoma of the thymus accounts for less than 5% of all TC, and is more commonly seen in male patients. The term “mucinous (colloid) adenocarcinoma” is no longer recommended as the WHO preferred nomenclature is “enteric-type adenocarcinoma of the thymus”. Previously, mucinous adenocarcinoma has been divided into enteric, mucinous, and colloid types, which indicate the different types of mucin<sup>[42]</sup>. Histologically, enteric-type adenocarcinoma is composed of small cells present within extracellular mucin [Figure 7]. By immunohistochemistry, tumor cells are positive for at least one marker of the gastrointestinal tract (CK20, CDX2, and/or MUC2)<sup>[43]</sup>. Tumor cells are negative for TTF-1 and c-KIT (CD117)<sup>[44]</sup>. *KRAS*, *TP53*, *TGFB2* mutations commonly seen in adenocarcinomas of the gastrointestinal tract have been described in enteric-type adenocarcinoma of the thymus<sup>[45,46]</sup>.

### Adenocarcinoma, not otherwise specified

Adenocarcinoma, not otherwise specified (NOS) encompasses TC not meeting the diagnostic criteria for low-grade papillary or enteric-type adenocarcinoma<sup>[47]</sup>. The recent WHO classification includes the following provisional categories: tubular adenocarcinoma, non-mucinous adenocarcinoma, high-grade papillary adenocarcinoma, and signet-ring cell carcinoma with a gastric immunophenotype. By immunohistochemistry, the carcinomas of this category do not express gastrointestinal markers, are positive for epithelial markers, and show variable expression profiles for c-KIT (CD117) and CD5.



**Figure 5.** Sarcomatoid carcinoma (20×). Spindle cell morphology of tumor cells growing in a primarily diffuse pattern.



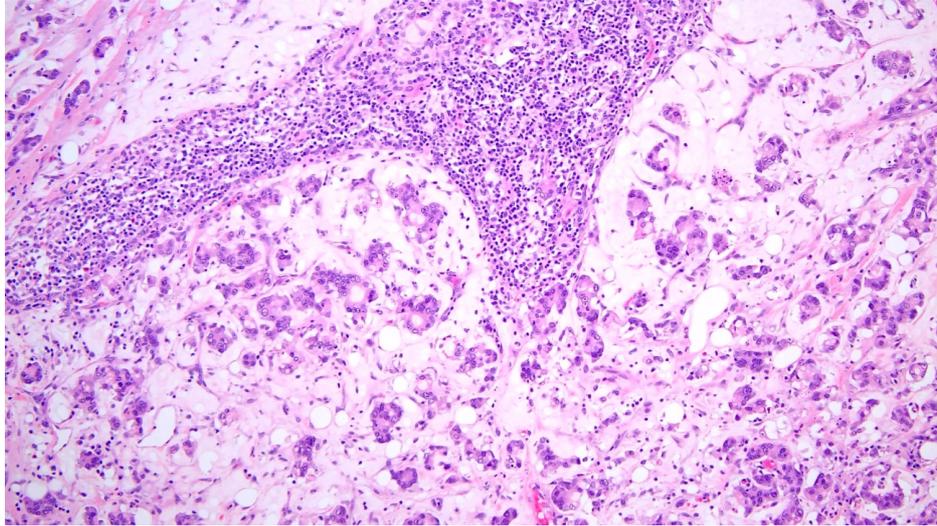
**Figure 6.** Clear cell carcinoma (40×). A dense infiltrate of large, pleomorphic cells with intracytoplasmic glycogen that is Periodic acid-Schiff (PAS) positive.

### Adenosquamous carcinoma

Adenosquamous carcinoma, similar to its pulmonary counterpart, is a primary TC that shows both glandular and squamous differentiation, where each component constitutes  $\geq 10\%$  of the tumor. If the glandular component is  $< 10\%$ , a diagnosis of squamous cell carcinoma is preferred. Only rare case reports are available describing adenosquamous carcinomas<sup>[48]</sup>. By immunohistochemistry, the tumor is positive for epithelial markers, and the squamous component is highlighted by CK5/6 and p63/p40.

### NUT carcinoma of the thorax

NUT carcinoma of the thorax is defined by the presence of the *NUTM1* gene rearrangement. These carcinomas behave aggressively and are most commonly diagnosed at an advanced disease stage with a reported median survival of 6.5 months<sup>[49]</sup>. Histologically, they present as tumors with sheets and nests of monotonous, small- to intermediate-sized, undifferentiated round to oval cells with prominent nucleoli.



**Figure 7.** Enteric-type adenocarcinoma of the thymus (10×). Small tumor cells arranged in a glandular pattern with extracellular mucin.

The cells are evenly spaced with a distinct separation between the cells. Foci of abrupt keratinization are estimated to be present in about one-third of the cases. A glandular component is not present. NUT immunostain reveals a speckled nuclear expression pattern in about 87% of the cases<sup>[50]</sup>. Tumor cells can stain positive for CD34, which could represent a potential diagnostic pitfall<sup>[51]</sup>. Together with the NUT immunostain, identifying *NUTM1* rearrangement by molecular methods plays a key role in diagnosing this TC subtype. The most common translocation is t(15;19)(q14;p13.1), resulting in a fusion of *NUTM1* and *BRD4*<sup>[52]</sup>. Less commonly, fusions of *NUTM1* to other genes encoding for proteins related to *BRD4* have been reported (*BRD3*, *NSD3*, *ZNF532*, *ZNF592*)<sup>[53-55]</sup>.

#### **Thymic carcinoma with adenoid cystic carcinoma-like features**

Thymic carcinoma with adenoid cystic carcinoma-like features is a rare TC subtype with only a few cases reported in the literature. Cases are described as having indolent behavior<sup>[56,57]</sup>. Histologically, the tumor shows features comparable to adenoid cystic carcinoma of the salivary glands and is made up of basaloid cells growing in a cribriform pattern. The tumor cells are small to intermediate in size with mild to moderate nuclear atypia. Cystic structures are seen with spaces filled with cellular debris and PAS-negative material. The material within the cysts is positive for basement membrane markers, such as laminin or collagen IV. Compared to adenoid cystic carcinoma, thymic carcinoma with adenoid cystic carcinoma-like features is negative for c-KIT (CD117), S-100, and smooth muscle markers<sup>[58]</sup>.

#### **Undifferentiated carcinoma of the thymus**

The category of undifferentiated carcinoma of the thymus represents a group of TC that are poorly differentiated and not assignable to other histologic subtypes identified by the recent WHO classification. Marked cellular pleomorphism and cellular atypia are present with high mitotic activity. Necrosis and hemorrhage are frequently present. Clinically, the tumors are highly aggressive and have poor outcomes.

#### **Thymic carcinoma, NOS**

Thymic carcinoma, NOS is a unique category of TC in which the carcinoma cannot be further categorized under WHO-defined entities. [Table 2](#) highlights exceedingly rare variants of TC and their features.

**Table 2. Thymic carcinoma, NOS subtypes**

Type	Features
Rhabdoid thymic carcinoma	TC showing a solid proliferation of large, pleomorphic cells with large nuclei, prominent nucleoli, and arranged in nests and sheets <sup>[59,60]</sup>
Hepatoid thymic carcinoma	Morphologic features resemble hepatocellular carcinoma, and by immunohistochemistry, are positive for hepatocyte paraffin 1 <sup>[61,62]</sup>
Undifferentiated large cell carcinoma associated with Castleman disease-like reaction	TC displaying solid nests of undifferentiated, large cells in a background of lymphoid stroma that resembles hyaline-vascular Castleman disease and often display a less aggressive clinical course <sup>[63]</sup>

TC: Thymic carcinoma.

## DISCUSSION

TC is a heterogeneous group of rare primary TEN that are clinically aggressive, often present at an advanced stage, and have characteristic molecular or cytogenetics findings in only a subset of cases. As TC is part of the differential of invasive anterior mediastinal masses that present with local symptoms, a core biopsy approach is often undertaken; however, this can provide a diagnostic challenge. Certain clues can help in the correct interpretation of core biopsies, such as marked atypia, frequent mitotic figures, infiltration, necrosis, and expression of c-KIT (CD117); however, interpretation may remain a challenge when metastatic tumors are within the differential diagnosis. If the initial core biopsy remains equivocal, thoracoscopic biopsies are useful in that adequate tissue is often obtained while also giving the advantage of visualizing the hemithorax for staging purposes and the ability to sample lymph nodes and pleura.

As a refinement of TC knowledge has changed over the years, there remains a fundamental conundrum when evaluating the histopathology of these tumors. Recent changes to the WHO have revealed only minor alterations in terminology, but now recognize the reporting of heterogeneous tumors. It is common for thymomas to harbor more than one histologic pattern; however, reporting this phenomenon in TC is relatively scarce. With this in mind, tumor heterogeneity may be misrepresented on core biopsies, thus limiting findings that are of diagnostic and prognostic significance. It is therefore important to correlate histologic and immunophenotypic findings with that of radiographic imaging; however, more studies are needed as to what degree of heterogeneity and morphologic components contribute to the outcome.

In the era of molecular diagnostics, future analyses of thymic carcinoma will prove to be a fruitful endeavor, given the rarity and aggressiveness of these tumors. It remains hopeful that the utilization or development of targeted therapies will change the clinical outcomes for patients, such as in the case of squamous cell carcinoma of the thymus harboring an activating *KIT* mutation and its responsiveness to imatinib<sup>[64]</sup>. Additionally, the utilization of next-generation sequencing has provided an insight into the molecular pathogenesis of thymic carcinoma, which can be further utilized to provide prognostic information for these tumors.

Lastly, the most appropriate staging schema for thymic carcinoma has long been fraught with controversy. It is recognized that certain staging methods lack definitive differentiation between thymoma and thymic carcinoma, particularly in regard to capsular invasion, which carries significantly different prognostic features depending on the final diagnosis. In the recent National Comprehensive Cancer Network Clinical Practical Guidelines in Oncology for thymomas and thymic carcinoma, encapsulated thymomas and stage I thymic carcinoma are effectively labeled as equal in staging, which would portend a similar clinical course<sup>[65]</sup>. This lack of uniformity in staging and applications in practice underscores the need for a systematic staging methodology founded on sound data and the understanding of disease biology.

The landscape of TC has changed considerably since the first description of TEN, particularly in regard to terminology, immunoprofile, and now with the advent of molecular diagnostic techniques, its underlying pathobiology. It will be of great interest to many pathologists, oncologists, surgeons, and radiologists to stay tuned for changes on the horizon as there still remains much to be discovered within the world of TC.

## DECLARATIONS

### Authors' contributions

Karlin Wrote the manuscript: Karlin K  
Reviewed and edited the manuscript: Michaels PD  
All authors approved the manuscript.

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Not applicable.

### Financial support and sponsorship

None.

### Conflicts of interest

Both authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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