

***Controversies in Cellular Pathology***

**Classification of thymic epithelial neoplasms:  
a controversial issue coming to an end?**

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**Abstract**

The classification of thymic epithelial neoplasms has been one of the most controversial issues in tumor pathology. There are two opposing schools of pathologists holding different views regarding the classification of thymic epithelial neoplasms. One school of pathologists believe that histological classification of thymomas is not possible or useful. Another school of pathologists believe that thymomas can be histologically subclassified despite their complex histomorphology and that these histological subtypes correlate with their aggressiveness and clinical behavior. A compromised histological classification has been established by World Health Organization (WHO) to designate thymic epithelial neoplasms with letters and numbers. This classification should be adopted internationally to facilitate the communication among concerned pathologists and oncologists. A simple histological classification of thymomas based on cytomorphology and supported by cytokeratin expressions is proposed and compared to the WHO and Müller-Hermelink's histogenetic classifications.

**Keywords:** thymic epithelial neoplasm • thymoma • thymic carcinoma •  
histological classification • cytokeratin

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## Introduction

Thymus is a complex lymphoepithelial organ composed of at least four different types of epithelial cells providing a microenvironment for the maturation and differentiation of T lymphocytes [1, 2]. Thymomas as tumors arising from thymic epithelial cells reflect this complexity by exhibiting a variety of histomorphologic types [3]. Consequently, histological classification of thymic epithelial tumors is a difficult task and has been one of the most controversial issues in tumor pathology. The evolution of a correct concept of the thymoma and various problems involved in the classification of thymic epithelial tumors will be reviewed. A recently proposed simple histopathological classification based on the cytomorphological features [2] is described for comparison with other classification systems currently in use [1, 4, 5].

## Historical aspects

The classification of thymic tumors was replete with misconceptions and misnomers for many years [6, 7]. It was not until 1976 that Rosai and Levine finally clarified the concept by proposing that designation of thymoma should be restricted to neoplasms of thymic epithelial cells [6]. Levine and Rosai emphasized the importance of the presence or absence of invasiveness and classified thymic epithelial tumors into benign encapsulated thymoma, type I malignant thymoma (invasive thymoma), and type II malignant thymoma (thymic carcinoma) [8]. No attempt was made to classify thymomas into histological types. Meanwhile, the traditional histological classification of Bernatz *et al.* [9] had been widely in use. It was based on the relative proportion of tumor epithelial cells and lymphocytes and classified thymomas into: predominantly lymphocytic, predominantly epithelial, predominantly mixed, and predominantly spindle cell types. This classification was relatively easy for pathologists to use. However, the histological subtypes so classified did not correlate consistently with their clinical behaviors [10]. Furthermore, including nonneoplastic lymphocyte as a major component in the classification scheme was misleading.

Therefore, this classification system has largely been abandoned.

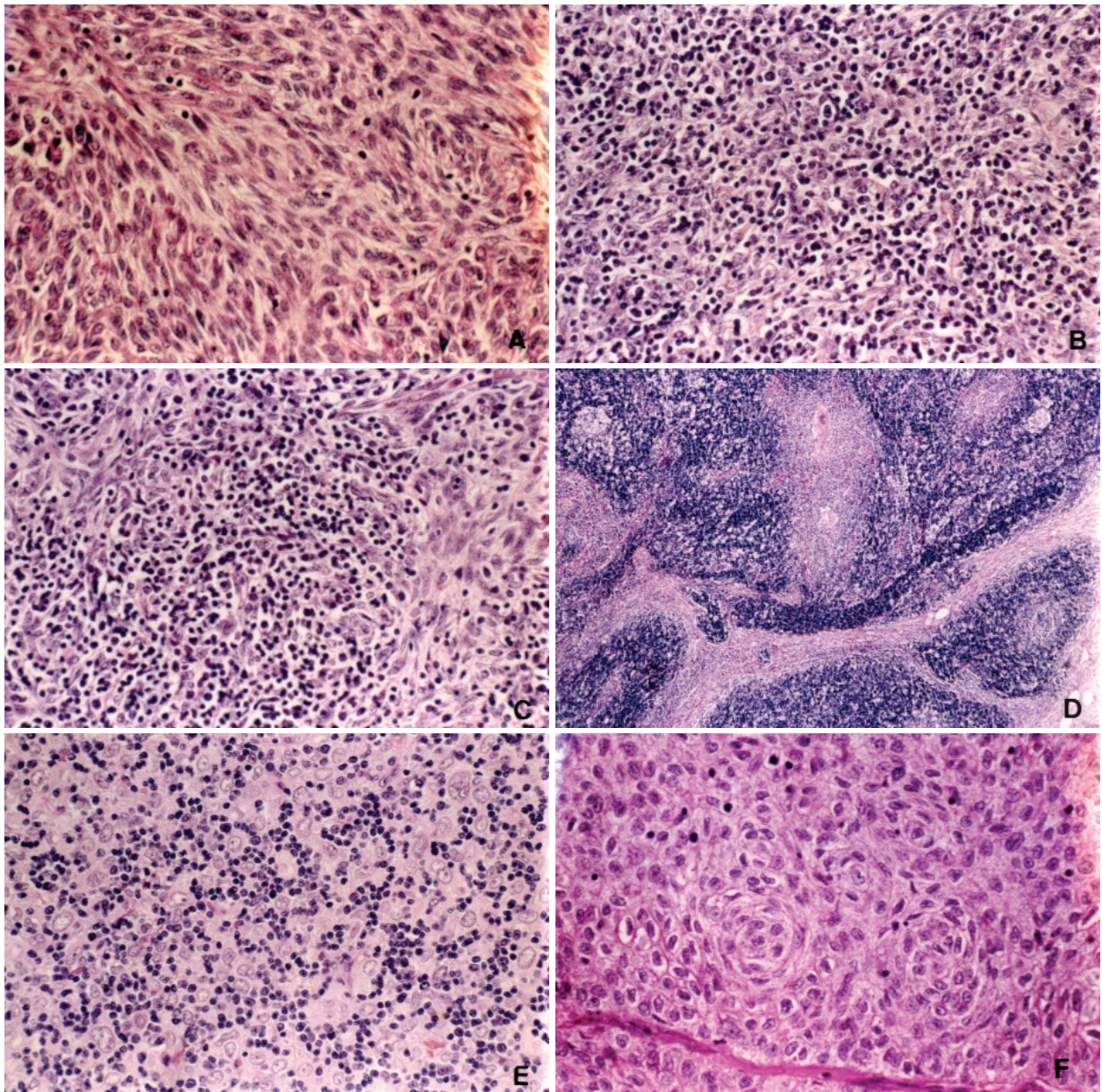
## Modern histological classification

The histological classification of thymomas was rekindled by the emergence of a histogenetic classification proposed by Müller-Hermelink and associates in 1980s [4, 11]. This classification was based on the assumption that thymomas could be regarded as tumors arising from different compartments of normal thymus. Thus, thymomas could be classified into five subtypes as derivatives of the medullary and cortical cells. The five subtypes were named as medullary, mixed, predominantly cortical, cortical, and well differentiated thymic carcinoma (WDTC) [5, 11]. Medullary and mixed thymomas were regarded as essentially benign nonaggressive tumors, whereas cortical, predominantly cortical, and WDTC were aggressive malignant tumors. This histogenetic classification was supported by several subsequent studies [10, 12-15]. The histogenetic concept was, however, not unanimously accepted because of lack of genuine histogenetic evidences. Meanwhile, a World Health Organization (WHO) committee for the histological classification of tumours of the thymus was organized by Dr. Juan Rosai including pathologists from eight countries in 1989. After more than a decade of debate among the committee members, a compromised histological classification system designated by letters and numbers was finally published in 1999 [3].

## The controversies and proposal of a simple histological classification

There are two schools of pathologists holding two different views regarding the classification of thymic epithelial tumors. One school of pathologists believe that histological classification of thymomas is not possible or useful [16-19] and support the concept of Levine and Rosai [8] to classify them into noninvasive and invasive thymomas. They even consider all thymomas to be potentially malignant. Another school of pathologists, on the other hand, believe that





**Fig. 1** A. Spindle cell thymoma (WHO type A), B. Small polygonal cell thymoma (WHO type AB), C. Mixed thymoma (WHO type AB), D. Organoid thymoma (WHO type B1), E. Large polygonal cell thymoma (WHO type B2), F. Squamoid thymoma (WHO type B3).

thymomas can be histologically subclassified despite their complex histomorphology and that the various histological types correlate with their aggressiveness and clinical behavior [2, 11-13, 20]. Müller-Hermelink's histogenetic classification [4, 5, 11] belongs to the second group. However, this classification system suffered from lack of direct histogenetic evidences to relate subtypes of thymoma so classified to different cell types seen in

normal thymus. Furthermore, medullary and mixed thymomas are not absolutely benign tumors as believed by Müller-Hermelink's group [20]. The most confusing misconception in the Müller-Hermelink's classification is to use the term "WDTC" for a subgroup of thymomas [5]. It is simply not logical to call a group of "thymomas" as "carcinomas" under the category of thymoma. This group of thymic tumors still maintain the lobular

**Table 1.** Histological features of subtypes of thymoma. Modified from [2].

Histologic Type	Microscopic Features
Spindle cell thymoma	Lobules of lymphocyte-poor spindle cells. May form cystic, glandular, or rosetting structures. Individual tumor cell is surrounded by reticulin fibers.
Small polygonal cell thymoma	Lobules of small polygonal cells with round or oval vesicular nuclei and indistinct nucleoli accompanied by abundant lymphocytes. May contain a minor number of spindle cells. Reticulin fibers surround lobules of tumor cells.
Mixed thymoma	Mixtures of lymphocyte-rich small polygonal cells and lymphocyte-poor spindle cells.
Organoid thymoma	Recapitulating the structure of normal thymus with lymphocyte-rich cortical areas and lymphocyte-poor medullary areas containing Hassall corpuscle-like structures.
Large polygonal cell thymoma	Lobules of large polygonal cells with large vesicular nuclei and prominent nucleoli and decreasing amount of lymphocytes.
Squamoid thymoma	Tumor cells assume squamoid appearance with increasing atypia. May show focal keratinization and whorling pattern and associated with CD99+ thymocytes. May show perivascular nuclear palisading.

growth pattern of a conventional thymoma and are accompanied by CD99+ thymocytes [21]. Therefore, it is more appropriate to call them a type of “thymoma” rather than “thymic carcinoma.” This view is further supported by their absence of CD5 expression and their frequent association with myasthenia gravis, two features usually seen in thymomas but not in thymic carcinomas [22-24].

Suster and Moran were the most vehement opponents of Müller-Hermelink’s histogenetic classification [16, 19] and instead proposed to

classify thymic epithelial tumors into well differentiated thymic epithelial neoplasm (thymoma), moderately differentiated thymic epithelial neoplasm (atypical thymoma), and poorly differentiated thymic epithelial neoplasm (thymic carcinoma) [16]. Their “atypical thymoma” actually corresponds to “WDTC” of Müller-Hermelink classification [5] and they lumped all the other variety of thymomas together without further subclassification. This simplified scheme serves no benefit for our efforts to understand further the

**Table 2.** Cytokeratin profiles of different histological types of thymoma.

Thymoma type	CK7	CK8	CK10	CK13	CK14	CK18	CK19	CK20
Spindle cell	+	+	–	–	+	+	+	–
Small polygonal cell	–	–	–	–	+	–	+	–
Mixed	+	+	–	–	+	+	+	–
Organoid	+	+	+	+	+	+	+	–
Large polygonal cell	+	–	–	–	–	–	+	–
Squamoid	+	–	+	–	–	–	+	–



**Table 3.** Comparison of different histological classifications of the thymic epithelial tumors.

<b>WHO Classification<sup>3</sup></b>	<b>Müller-Hermelink's Histogenetic Classification<sup>4,5</sup></b>	<b>Kuos Cytomorphologic Classification<sup>2</sup></b>
Type A Thymoma	Medullary Thymoma	Spindle Cell Thymoma
Type AB Thymoma	Mixed Thymoma	Small Polygonal Cell Thymoma
Type AB Thymoma	Mixed Thymoma	Mixed Thymoma
Type B1 Thymoma	Predominantly Cortical Thymoma	Organoid Thymoma
Type B2 Thymoma	Cortical Thymoma	Large Polygonal Cell Thymoma
Type B3 Thymoma	Well Differentiated Thymic Carcinoma	Squamoid Thymoma
Type C Thymoma	Thymic Carcinoma	Thymic Carcinoma

biological behavior of various histological types of thymoma.

We believe that thymomas can be further subclassified into various histological types without difficulty. The value of histological subclassification of thymomas is enhanced by their correlation with their invasive potential [2]. We proposed to classify thymomas (Table 1) simply based on their cytomorphologic features into spindle cell, small polygonal cell, mixed (spindle cell and small polygonal cell), organoid, large polygonal cell, and squamoid thymomas (Fig. 1) [2]. Our classification was supported by the cytokeratin immunohistochemical expression patterns [2] (Table 2). Different classifications are compared in Table 3. Our classification was purely

based on descriptive morphologic designations to circumvent the criticisms rising against Müller-Hermelink's histogenetic classification. In addition, we believe that there is a subgroup of lymphocyte-rich small polygonal cell thymoma characterized by cytokeratin 14 immunopositivity [2]. This group of thymoma has been grouped into the mixed thymoma group in the WHO and Müller-Hermelink's classifications [3, 4, 11]. Although they might have a small number of spindle cells, they are believed to be a separate distinctive subtype different from a mixed thymoma. By recognizing this subtype, mixed thymoma can then be appropriately defined as a thymoma with a mixture of lymphocyte-poor spindle cells and lymphocyte-rich small polygonal cells [2]. Spindle

**Table 4.** Histological Types of WHO Type C Thymoma (Thymic Carcinoma).

Epidermoid keratinizing (squamous cell) carcinoma
Epidermoid non-keratinizing carcinoma
Lymphoepithelioma-like carcinoma
Sarcomatoid carcinoma (carcinosarcoma)
Clear cell carcinoma
Basaloid carcinoma
Mucoepidermoid carcinoma
Papillary carcinoma
Undifferentiated carcinoma

cell thymomas can exhibit histological variants with cystic and glandular structures or rosetting pattern [3, 7]. The histologic features of different subtypes are summarized in Table 1.

Thymic carcinomas are histologically malignant neoplasms posing less problems. Diagnosis of a thymic carcinoma should be considered if a thymic tumor could not be readily classified into a known subtype of thymoma. We found that focal tumor necrosis is a useful indicator of a thymic carcinoma, especially during frozen section diagnosis [24]. In questionable cases, immunohistochemical demonstration of CD5 expression and the absence of tumor associated CD99+ thymocytes are helpful clues for the diagnosis of thymic carcinomas [21, 23]. Furthermore, thymic carcinomas are usually not associated with myasthenia gravis [24]. Similar to thymomas, thymic carcinomas exhibit a variety of histological types (Table 4)[3, 6, 7, 24, 25]. Further study is needed to refine the subtypes. In addition, neuroendocrine tumors can occur in the thymus. A variety of histological variants have been described for thymic carcinoid tumors [26, 27].

## Conclusions

The evolution of the classification of thymic epithelial tumors is reviewed with a discussion on the controversial issues encountered. Unfortunately, a unified classification system is still not available. For the time being, the compromised histological classification by WHO should be adopted internationally to facilitate communications among concerned pathologists and oncologists. With the aid of molecular studies [28], we might expect to see an universally acceptable classification system for this fascinating group of neoplasms in the near future.

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