



Problem areas and inconsistencies in the WHO classification of thymoma

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KEYWORDS

Thymoma;
 Atypical thymoma;
 Thymic carcinoma

The morphologic classification of thymoma has undergone numerous revisions in recent years and has been under continuous debate for the past several decades. With the introduction of the World Health Organization (WHO) schema for the classification of thymic epithelial neoplasms in 1999, a major step was taken toward achieving uniformity in the nomenclature of these tumors. A more recent iteration of the WHO morphologic classification of thymic epithelial neoplasms has now been published. Although these efforts have certainly contributed to clarifying many issues related to the pathology of thymoma, several problem areas and inconsistencies still remain surrounding this proposed schema. The purpose of this review is to address these problem areas, in particular as it relates to terminology, histopathologic criteria for diagnosis, and the prognostic significance for the various categories of the WHO schema. © 2005 Elsevier Inc. All rights reserved.

Thymoma classification has been a source of controversy for many years. Unlike most other tumor systems, no standard source for a widely agreed-upon system of histologic classification has been available for these tumors for many years. The two most respected and widely used references for the histopathologic classification of human tumors during the past four decades have been the atlases produced by the American Registry of Pathology in Washington DC (popularly known as the “AFIP fascicles”) and the series of monographs issued by the World Health Organization (WHO) on the histopathologic classification of tumors. When the first edition of the WHO monographs was introduced in the early 1960s, tumors of the thymus were not included as part of the series. For a period of nearly 30 years, the only widely accepted reference source available on thymic tumors was the AFIP fascicle on “Tumors of the

Thymus” by Rosai and Levine, published in 1976.¹ In this extensively quoted reference, the authors made the statement that “a review of 164 cases of thymoma in preparation for this fascicle strengthened our previous belief that once the term thymoma is restricted to the tumor of thymic epithelial cells, with or without a lymphocytic component, all further subdivisions are artificial. We have found that all the morphologic criteria that have been used for this purpose, such as the shape of the nucleus of the epithelial cell, the relative number of lymphocytes, and the number of rosettes, exhibit such a continuous range within thymomas as to prevent any rigid separation based on these criteria. Therefore, the authors of this new series can only repeat the statement made by Castleman in the first series that *‘no attempt is made in this fascicle to give a special name to any particular variant’*” (italics ours).¹ Thus, for a considerable period of time, thymic epithelial neoplasms were “orphaned” and pathologists had to choose among the various competing histologic classifications published by individual investigators over the years.²⁻⁹ The most widely used of these classifications was the one proposed by Bernatz and

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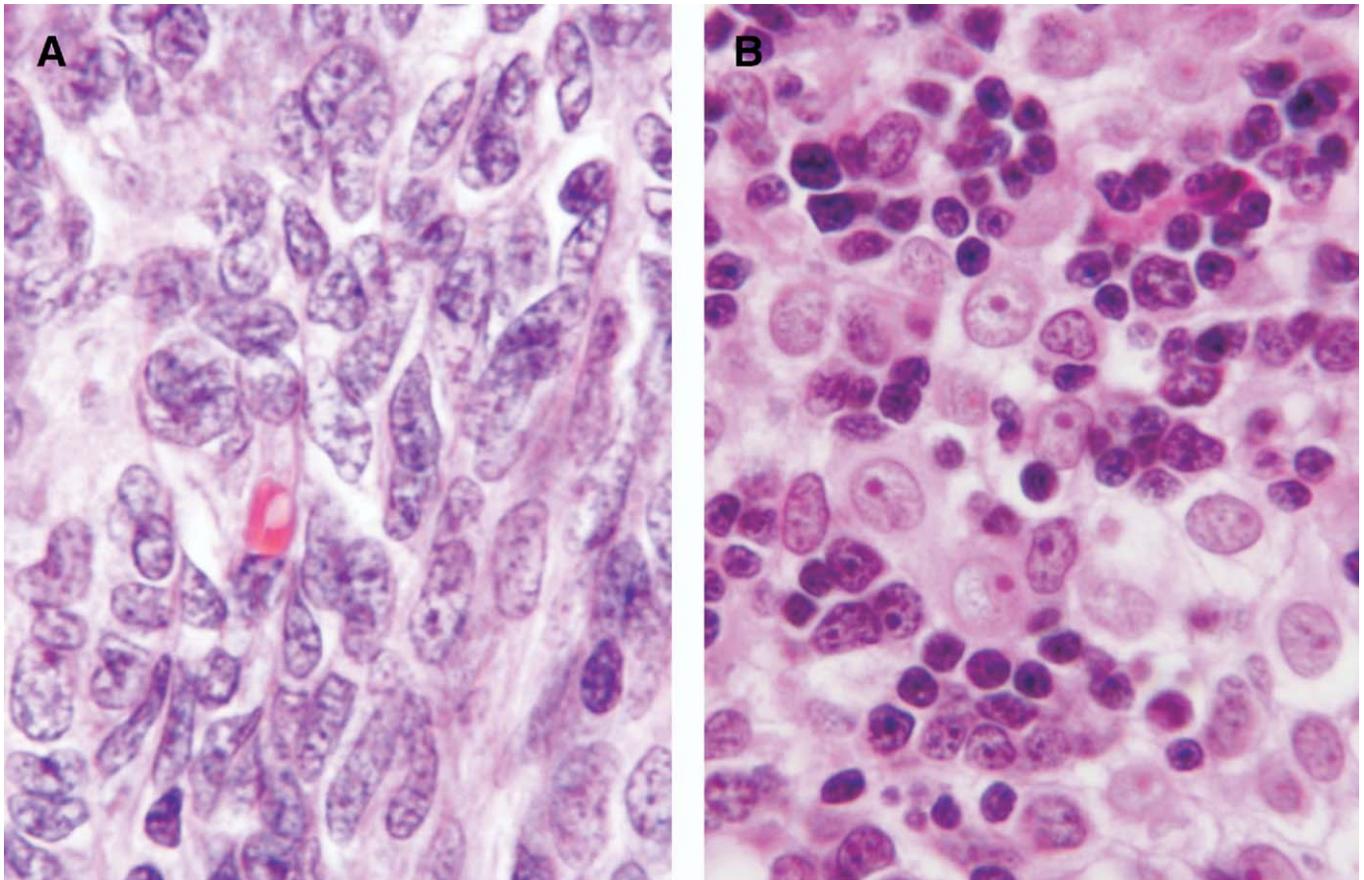


Figure 1 Two basic cell types of thymomas. (A) WHO type A thymoma composed of oval to spindle cells with dispersed chromatin and scant rim of amphophilic cytoplasm. (B) WHO type B thymoma composed of round epithelial cells with round vesicular nuclei with scant nuclear chromatin, small eosinophilic nucleoli, and ample amphophilic to lightly eosinophilic cytoplasm.

coworkers² from the Mayo Clinic in 1961, who divided these tumors based on the shape of the epithelial cells (round versus spindle) and the relative proportion of lymphocytes within the tumor (lymphocyte-predominant versus epithelial-predominant). This morphologic system of classification, which was later acknowledged by its authors to be of limited value for prognostication,¹⁰ was widely accepted in the USA and many other countries. This situation was not improved by the publication of the most recent AFIP fascicle on tumors of the mediastinum in 1997, in which the authors also elected to follow in the steps of their predecessors and did not adopt or sanction any of the available classifications in existence at the time.¹¹

A major step forward was achieved in 1999 with the publication of the first WHO book on the histological typing of tumors of the thymus.¹² This monograph was the result of lengthy deliberations over a period of many years by an international panel of experts headed by Dr. Juan Rosai to devise a unified, standard classification for these tumors from the available systems then in existence. Unfortunately, a consensus could not be achieved by the members of the panel, and after much deliberation, a compromise formula was adopted that assigned a combination of letters and numbers to the various existing histologic types of thymoma.

The fact that this was a compromise formula intended to satisfy the conflicting views of the various members of the panel was openly acknowledged by the authors of the monograph who stated that “the terminology chosen here is a noncommittal one based on a combination of letters and numbers. It is *not proposed as a new classification*, but mainly to facilitate comparison among the many terms and classification schemes that have been offered over the years” (italics ours).¹²

WHO schema for the classification of thymic epithelial neoplasms

Two major types of thymoma were identified in the WHO schema, depending on whether the neoplastic epithelial cells and their nuclei showed a spindle or oval shape (designated as type A), or a round epithelioid appearance (designated as type B)¹² (Figure 1A and B). Tumors with a combination of these two cell types were designated as type AB. Type B thymoma was further subdivided on the basis of the proportional increase and emergence of atypia of the neoplastic epithelial cells into three subtypes, respectively

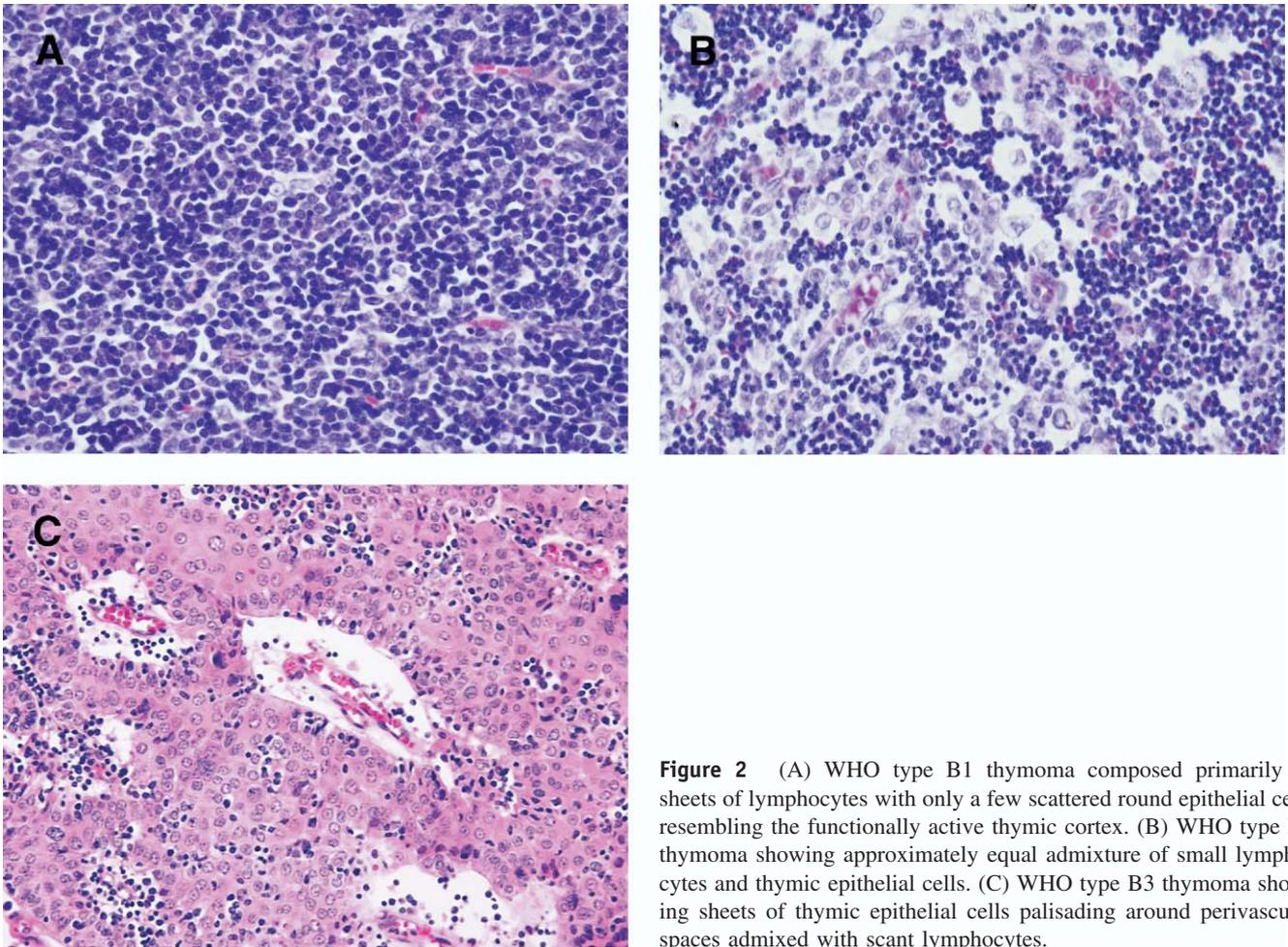


Figure 2 (A) WHO type B1 thymoma composed primarily of sheets of lymphocytes with only a few scattered round epithelial cells resembling the functionally active thymic cortex. (B) WHO type B2 thymoma showing approximately equal admixture of small lymphocytes and thymic epithelial cells. (C) WHO type B3 thymoma showing sheets of thymic epithelial cells palisading around perivascular spaces admixed with scant lymphocytes.

designated as B1, B2, and B3 (Figure 2A–C). Type C thymoma was regarded as a tumor showing overt cytologic features of malignancy (ie, equivalent to thymic carcinoma) (Figure 3). Thus, in essence, the morphologic premise for this classification was also based on the same principles as that of the traditional classification presented more than 40 years earlier by Bernatz and coworkers² (ie, the tumors are classified in both systems according to the shape of the neoplastic epithelial cells and to their relative proportion of lymphocytes).

Despite the apparent noncommittal nature of this compromise formula, the WHO classification represented a major step forward in the field for several reasons. First, it provided, for the first time, a unified schema supported by a reputable international organization for the histopathologic classification of these tumors, something that had been hitherto altogether lacking. It additionally acknowledged the existence of several “archetypal” morphologic expressions of these tumors, as well as the fact that they all constitute part of a single family of tumors representing a morphologic continuum that ranges from very low-grade tumors (thymoma type A) to high-grade tumors (thymoma type C). But the most important contribution of the WHO classification was to provide a framework that would allow

the comparison of the different terms used by the various existing classifications of thymoma. This latter feature has facilitated the successful comparison of results among various published clinical series of thymoma that utilized dif-

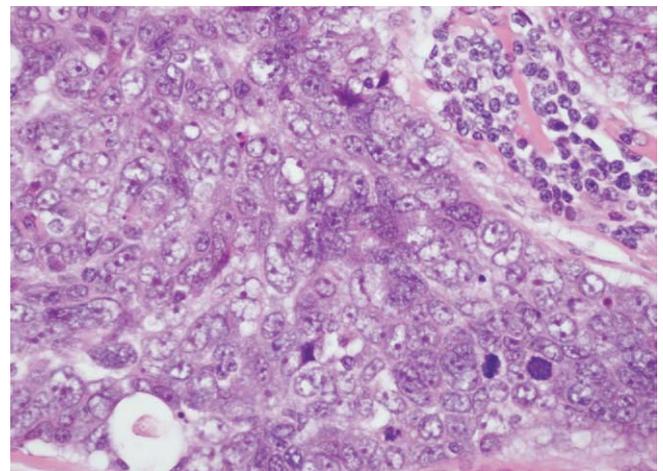


Figure 3 Thymic carcinoma, poorly differentiated, nonkeratinizing squamous cell type, characterized by overt cytologic atypia with large, vesicular nuclei with prominent eosinophilic nucleoli, scant cytoplasm, and frequent mitotic figures.

Table 1 Comparison of WHO schema for the classification of thymic epithelial neoplasms with other existing classification systems

WHO ¹²	"Traditional" Bernatz et al. ²	Kirchner and Muller-Hermelink ⁸
Type A	Spindle cell thymoma	Medullary thymoma
Type AB	(Combined thymoma)	Mixed thymoma
Type B1	Lymphocyte-rich	Predominantly cortical
Type B2	Mixed lymphoepithelial	Cortical
Type B3	Epithelial-rich	Well-differentiated thymic carcinoma
Type C (Thymic carcinoma)	-	Other types of carcinoma

ferent classification systems.¹³ It has also served to dispel the misconception that the competing terms employed by the various classifications made reference to quite different entities than those from the other classifications, whereas in reality all the different terms actually corresponded to identical tumor types, except under different designations (Table 1).

Several criticisms, however, were directed at the original schema proposed by the WHO. First, it was pointed out that the use of a combination of letters and numbers was not an optimal way for designating the various histologic types and that this usage is in general discouraged by clinicians who prefer more intuitive terms that will more readily reflect the biologic behavior of the tumors. This criticism, however, need not apply if we were to acknowledge the original intent of the authors of the WHO monograph, who explicitly stated in their monograph that the combination of letters and numbers used was *not* meant as a new classification system or as a replacement for any of the terms employed over the years, but simply as a means for *comparing* the various terms among the already existing classifications.¹² We, for example, utilize the WHO schema in our daily practice by adding it inside parenthesis after the diagnosis of our cases of thymoma. In this way, we hope to ensure that if the case is seen at another institution, the local pathologist or clinician there will be able to understand our interpretation by referring to the WHO schema and translating it into their preferred nomenclature.

Another criticism of the WHO schema is that it lacks a scientific basis and relies instead on an arbitrary assignment of letters and numbers that do not reflect any physiologic, histologic, immunologic, molecular, or histogenetic basis for the classification of these tumors. To the authors' credit, in their original monograph a mnemonic was offered to facilitate the use of the schema that equated type A thymoma with the word "atrophic" for those tumors composed of cells that resembled the "effete" spindle cells seen in the regressed, atrophic thymus of the adult; type B was associated with "bioactive" for the tumors showing active recruitment of T-lymphocytes; and type C was associated with "carcinoma" for the tumors showing overt cytologic features of malignancy. However, this still did not provide a unifying theme to the system, and the "functional" implications suggested by the terms "atrophic" and "bioactive" were not further elaborated on or explained in their writing.

The original WHO schema presented in 1999 has now been superseded by the more recent publication of the new WHO book on "Pathology and Genetics of Tumors of the Lung, Pleura, Thymus and Heart."¹⁴ The most recent version of the WHO classification of thymoma has essentially retained the same terminology as the one applied in the original proposal for types A, AB, and B1–3 tumors. The only significant changes were the elimination of the type C thymoma from the schema, with the latter tumors being segregated into a separate and distinct category designated as thymic carcinoma, and the introduction of various specific subtypes of unusual thymomas, including micronodular thymoma with lymphoid stroma, "metaplastic" thymoma and others, that could not be properly classified into the other categories. The group of individuals who devised the new version of the WHO classification of thymic tumors comprises a much more expanded cadre of experts than the original WHO panel, and its leadership has been switched from that of Dr. Rosai to Dr. Muller-Hermelink.¹⁴ In this new version of the WHO classification, the authors reiterated the statement made in the original version that "available data do not allow to unequivocally assign thymic tumors to defined functional and anatomical compartments of the normal thymus,"¹⁴ thus essentially reiterating the current lack of support for the histogenetic proposal underlying previous classification schemes such as ones that divided thymic tumors into those derived from the cortex and the medulla.^{7,8}

A number of studies have been published in recent years that purport to validate the clinical and biological relevance of the WHO classification.^{15–23} What most of these studies share is the fact that they have completely ignored the original message of the authors who introduced this classification in 1999,¹² namely, that the WHO schema based on a combination of letters and numbers was never intended as a "new" histologic classification for thymic tumors, but simply as a means for translating the other existing classifications into a common language. The WHO schema essentially identified and selected for inclusion several common morphologic appearances that these tumors can adopt and, because multiple conflicting terms were already available for the different tumor types, they were given new designations based on the combination of letters and numbers. It should then come as no surprise that studies utilizing this new nomenclature should parallel previous studies in

the literature and thus “validate” the new terminology, since the tumors under question are essentially the same as the ones that existed previously, except now under different names (A, AB, B1-3, etc). In either case, despite the apparent strong support for the adoption of this system for clinical practice, several problems and inconsistencies continue to surface with regards to the new WHO classification of thymic epithelial neoplasms. Herein we will address some of these problem areas.

Problem areas and inconsistencies in the WHO classification

Problem areas with the current WHO classification of thymic epithelial neoplasms center mainly around the following issues: (1) problems associated with the histopathologic criteria for diagnosis of the various subtypes; (2) the existence of rare and unusual morphologic types of thymoma that cannot be fit into any of the WHO categories; (3) problems associated with lack of interobserver reproducibility; and (4) conflicting claims regarding the clinical significance and prognostic value of the various WHO diagnostic categories.

Histopathologic criteria for the WHO classification of thymic epithelial neoplasms

Some of the difficulties involved in accurately reproducing the histopathologic criteria of the current WHO schema of thymic epithelial neoplasms have been addressed previously.^{16,24} A significant problem is posed by the degree of overlap and imprecision in the histologic criteria, particularly as it relates to the lesions predominantly composed of round or polygonal cells. Another problem is posed by the lack of correlation between the stated rationale for the different categories and their actual features. An example of this is the definition of type AB thymoma. In the original WHO monograph it is stated that “there are two major types of thymoma depending on whether the neoplastic epithelial cells and their nuclei have a spindle/oval shape (here designated as type A), or whether these cells have a dendritic or plump (“epithelioid”) appearance (here designated as type B). *Tumors combining these two morphologies are designated as type AB*” (italics ours).¹² However, the current WHO classification defines AB thymoma as “a mixture of lymphocyte-poor type-A thymoma component and a more lymphocyte-rich type-B component.”¹⁴ The lymphocyte-rich “type-B component” is further described as one in which the tumor cells are made up predominantly of “small polygonal epithelial cells with small round oval or spindle pale nuclei showing dispersed chromatin and inconspicuous nucleoli that are paler and smaller than those of B1 or B2 thymoma.” The description provided thus does *not* correspond to a true type B-thymoma (ie, one made up of round, epithelioid cells as per the original definition) but rather to

the morphology of a conventional type A thymoma that happens to contain an abundance of small lymphocytes. Furthermore, the description of “small *polygonal* epithelial cells with small round oval or spindle nuclei” is confusing since these cells are *not* polygonal but oval/spindled, as is the shape of their nuclei. The “type-B component” in AB thymoma thus, strictly speaking, does not conform to their own definition of a type B thymoma (ie, the cells are small, spindled and virtually indistinguishable from those seen in type A), and indeed, the illustrations provided in both the original monograph as well as the new WHO book clearly depict a tumor composed of small spindle cells in both the lymphocyte-rich and the lymphocyte-poor areas. In other words, type AB thymoma, defined by the WHO as a tumor that is supposed to combine type A (spindle cell) with type B (round, epithelioid cells) areas within the same lesion, is essentially composed only of spindle cells (type A), except that it contains areas with abundant lymphocytes admixed with areas showing paucity of lymphocytes. To our minds, what is being described here is essentially a lymphocyte-rich spindle cell thymoma (ie, a type A thymoma with abundant lymphocytes). It is no wonder then that the biologic behavior of these tumors should parallel closely that of conventional type A thymoma. To equate the lymphocyte-rich areas in these tumors with type B thymoma (or “cortical,” in accordance with the “histogenetic” classification) simply based on the presence of abundant lymphocytes is an oversimplification of the matter. “Cortical” tumors (ie, type B tumors composed of round/polygonal cells) may also have few lymphocytes (eg, type B2 and B3 thymoma or epithelial-rich thymoma), and conversely, thymomas made up of spindle cells may also contain an abundance of lymphocytes (eg, micronodular thymoma with lymphoid hyperplasia). The fact is that neither “cortical” nor “medullary” (or type A and type B for that matter) are defined in either classification by the number of lymphocytes, but by the shape and size of the epithelial cells. The rationale for the designation of this morphologic variant of thymoma as “type AB” is therefore flawed and confusing and does not conform to the stated criteria in the WHO proposal.

Somewhat conflicting and confusing criteria also exist for the type B tumors. Type B1 thymoma is defined as a tumor that resembles the normal functional thymus and combines large expanses indistinguishable from the normal thymic cortex with areas resembling the thymic medulla. The neoplastic epithelial cells are said to be scant and composed of oval cells with pale round nuclei and small nucleoli, although it is also stated that some cells may be large and occasionally have conspicuous nucleoli. Perivascular spaces are said to be scarce but pale areas of “medullary” differentiation are claimed to be always present. The tumor is regarded as the equivalent of the lymphocyte-rich thymoma in the Bernatz and coworkers classification² and to “organoid” or predominantly cortical thymoma in the Kirschner and Muller–Hermelink classification.⁸ Type B2 thymoma, on the other hand, is defined as a tumor in which

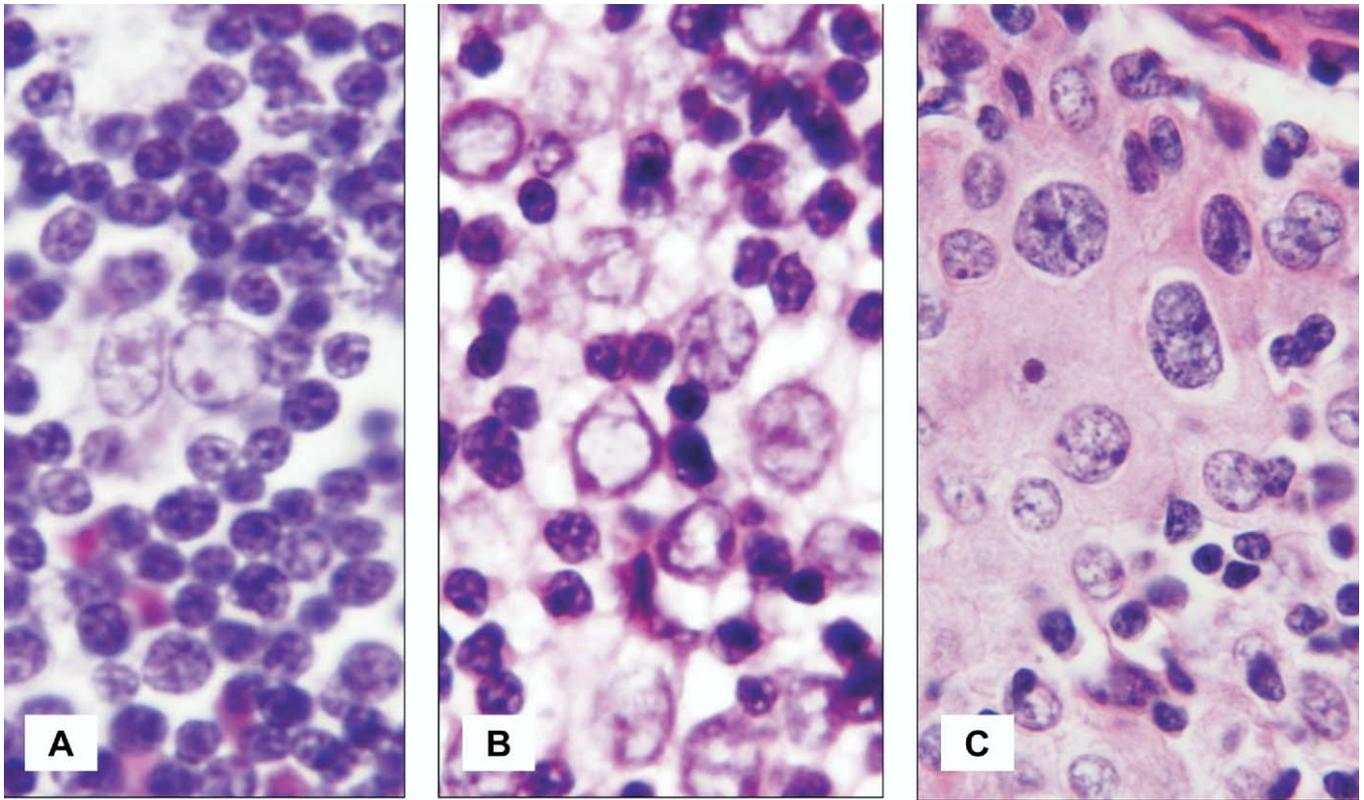


Figure 4 Example of thymoma showing a gradient of histologic findings within the same tumor. (A) Lymphocyte-rich area with abundant lymphocytes and a few normal-appearing thymic epithelial cells. (B) Area showing increase in the number of thymic epithelial cells, with prominent margination of chromatin and small nucleoli, resembling WHO type B2. (C) Areas showing sheeting of thymic epithelial cells, with enlarged nuclei, marked increase in nuclear chromatin, and sharply defined cell borders reminiscent of WHO type B3.

the neoplastic thymic epithelial cells are increased in number and appear as scattered plump cells among a heavy population of lymphocytes. The epithelial cells are described as large, polygonal, with large vesicular nuclei and large, centrally placed prominent nucleoli. The tumor cells can show a tendency to palisade around vessels and fibrous septa. Areas of “medullary” differentiation are claimed not to be a feature of these tumors; instead, prominent dilated perivascular spaces are said to be commonly found. These tumors are regarded as the equivalent of “cortical” thymoma in the Kirschner and Muller–Hermelink classification,⁸ and of mixed lymphoepithelial thymoma in the Bernatz and coworkers² classification. The main difference between types B1 and B2 appears to be in the size of the epithelial cells, these being “larger and more numerous,” and with no areas of “medullary” differentiation in type B2 as opposed to B1. The problem in real life is that thymomas are characterized by marked cellular heterogeneity, and the features of the tumor, including the relative size of its epithelial cells as well as their relative proportion of lymphocytes can vary considerably from field to field within the same lesion, thus making exact categorization based on the above criteria a difficult exercise.^{1,25–28} Assigning tumors to either of these two categories is only possible when dealing with the extreme ends of the spectrum or with “classical” examples of these categories. But, in real life, a wide spectrum of over-

lapping features can be observed in these tumors making rigid categorization of these two subtypes quite difficult to accomplish, particularly when numerous sections from a large resection specimen are available for review (Figure 4A–D). The “predominantly cortical” or “organoid” thymoma that constitutes the prototype of the WHO type B1 is an extremely rare neoplasm that probably accounts for less than 5% of all thymic epithelial neoplasms. The majority of “cortical” (type B) tumors show a broad range of features that include variable ratios of lymphoid to epithelial cells within the same lesion, and variable proportions of perivascular spaces and areas of “medullary differentiation,” etc. The rigid histologic criteria proposed by the WHO, therefore, may only be reproducible and easy to apply in small core biopsies or when only a limited number of histologic sections are available for review, but may prove bewildering and impractical when carefully examining a properly sampled resection specimen in which an appropriate number of sections has been obtained.^{28,29}

Another problem with the morphologic definitions of the WHO type B thymoma is that they do not actually follow the proposed rationale for their terminology. When the WHO terminology was introduced, it was stated that “type B thymomas are further subdivided on the basis of the proportional increase (in relation to the lymphocytes) and emergence of atypia of the neoplastic epithelial cells into

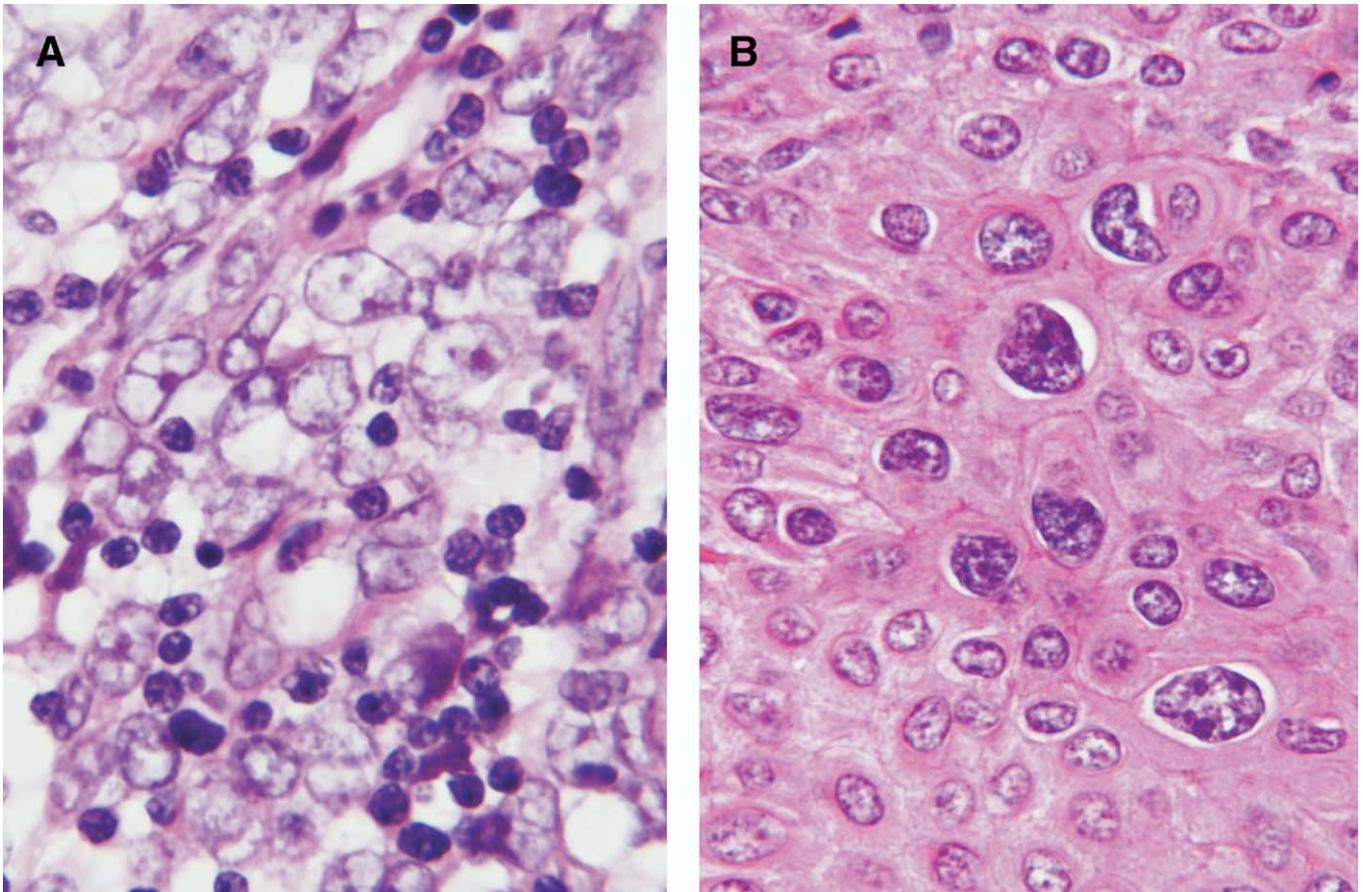


Figure 5 Comparison of nuclear features between thymoma type B2 and B3. (A) WHO type B2 thymoma showing increased number of epithelial cells admixed with few lymphocytes. The epithelial cells are round to oval, with vesicular nuclei, small nucleoli and peripheral margination of nuclear chromatin. The cytoplasm is amphophilic and the cell borders are not visible. (B) WHO type B3 thymoma composed of cohesive sheets of thymic epithelial cells. The epithelial cells show nuclear enlargement and nuclear irregularities, with marked increase in nuclear chromatin, small and sometimes multiple nucleoli, and abundant eosinophilic cytoplasm. Notice the sharply delimited cell borders that result in a polygonal configuration closely resemble paved epithelium.

three subtypes, respectively designated as B1, B2 and B3.”¹² Yet, the new WHO book clearly defines type B3 thymoma as a tumor composed of medium-sized, polygonal epithelial cells in which the nuclei are *smaller* than those in type B2, with less prominent nucleoli.¹⁴ This clearly represents a contradiction, not only in terms of their stated rationale, but also with the fact that if anything, the neoplastic epithelial cells in tumors of the thymus composed predominantly of round or polygonal cells with scant lymphocytes are characteristically much larger and atypical than in those tumors that contain a higher proportion of immature lymphocytes. The reason such tumors adopt a “squamoid” appearance is because of the emergence of very sharply defined and thickened cell membranes, which impart them with a pavement-like architecture. The epithelial cells are not only of similar or larger size than those in Type B2 thymoma, but their nuclei are much larger, irregular, hyperchromatic with clumped chromatin and often large, prominent nucleoli (Figure 5A and B). The nuclear-to-cytoplasmic ratio is greatly increased in type B3 as opposed to B2 thymoma. Bizarre nuclei and multilobated forms are

frequently seen, and mitoses can be often encountered, including atypical mitoses, in contrast with the bland-appearing vesicular nuclei with small, round, eosinophilic nucleoli seen in type B2 thymoma (Figure 6 A–C). Obviously, transitions and subtle gradations in the size and shape of the cells, as well as in their relative proportions are a common feature of these tumors creating the problem of where to draw the line in separating B2 from B3. In fact, the WHO book goes on to state that combined thymomas exhibiting B2 and B3 areas can occur in 17% to 29% of cases.¹⁴ This percentage is likely to be much higher if only properly sampled lesions are taken into account. In a previous study, we were able to demonstrate that the identification of morphologically heterogeneous areas is nearly doubled with increased sampling (ie, when more than 5 histologic sections were available for examination in any given tumor),²⁸ indicating that the larger the size of the tumor (and therefore, the greater the number of sections available for examination), the higher the likelihood that morphologically heterogeneous areas will be encountered. The extensive overlap and heterogeneity that these tumors

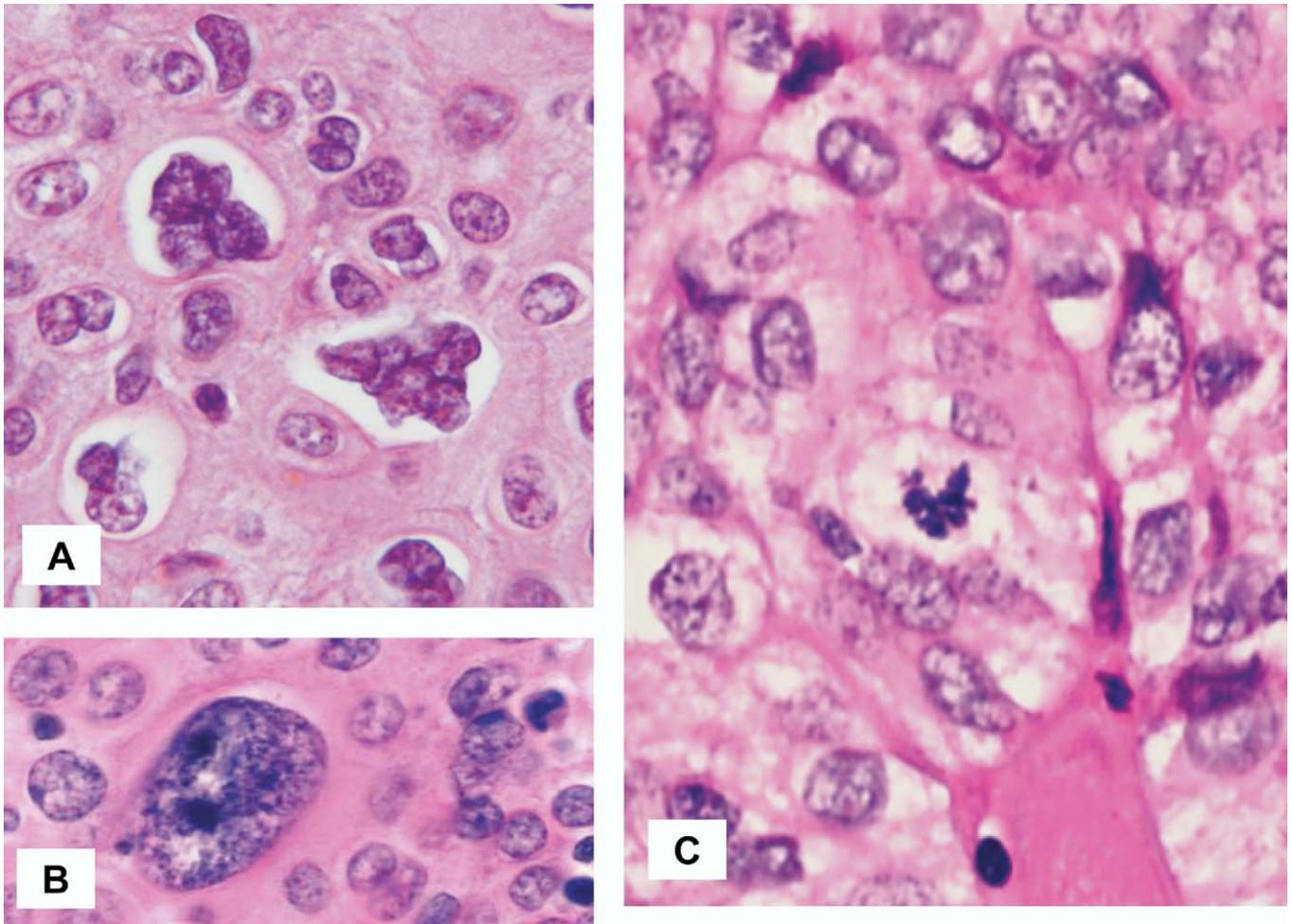


Figure 6 Spectrum of nuclear irregularities and atypia in WHO type B3 thymoma. (A) Bizarre multilobated and multinucleated cells. (B) Pronounced nuclear enlargement with prominent, often multiple nucleoli. (C) Occasional abnormal mitotic figures.

are able to display thus make it almost meaningless (and quite difficult) to reliably separate types B2 from B3 in clinical practice when adequately sampled specimens are being evaluated.

Unusual morphologic variants of thymoma that do not fit into the current WHO categories

The new WHO book on tumors of the thymus presents several “unusual” types of thymoma, which have been separated into distinctive categories in the updated classification, including micronodular thymoma with lymphoid stroma, “metaplastic” thymoma, and other rare thymomas such as microscopic thymoma and sclerosing thymoma.¹⁴ A rationale for why these tumors are regarded as examples of thymoma yet cannot be successfully assigned to any of the standard categories in the current WHO schema is not offered. In addition to the above, several other unusual variants of thymoma that escape the criteria of the WHO definitions for the standard types have been described.^{30–33} As more of these unusual variants of thymoma are recognized, how can they be reconciled with the current his-

topathologic classification for these tumors? Which criteria should be applied for their assessment and prognostication? The mere acknowledgment of these unusual morphologic variants already undermines the value and authority of the proposed classification by pointing out the existence of a number of exceptions to the general schema. Such variants expose one of the weaknesses of the WHO schema; the lack of a valid underlying or unifying principle of classification for these tumors.

Interobserver reproducibility of the WHO classification of thymoma

An important feature of any morphologic classifications of human neoplasia should be its ability to be easily reproduced among different observers. The WHO classification ran into difficulties in this area since its inception. In fact, problems with reproducibility were already being raised for the “histogenetic” classification of Kirchner and Muller–Hermelink, whose diagnostic categories served as “precursors” for the WHO schema.³⁴ Difficulties in the reproducibility of the WHO schema

have been recently voiced by Rieker and coworkers,²⁴ who showed in a large multicenter study that interobserver agreement for the subgroup of WHO type B (B1, B2, and B3) thymoma was only 0.49 using Kappa statistics (with a value over 0.8 indicating excellent agreement, and a value of 0.4 or less indicating poor agreement). The fact is that interobserver as well as intraobserver reproducibility can be quite poor for the WHO system, particularly among pathologists with limited exposure to these rare tumors. This results in a situation that mandates seeking a second opinion with an “expert” simply to accurately classify a given tumor. The majority of discrepancies arise within the group of type B thymomas, but difficulties also exist for types AB, as previously mentioned, and for distinguishing type B3 from well-differentiated squamous cell carcinoma of the thymus. Such difficulties are inherent to any system of classification that involves complex categories with extensive overlap among the different subtypes, particularly in tumors such as thymic epithelial neoplasms that are often characterized by morphologic heterogeneity and variations in morphology from field to field within the same tumor. The more complex the classification system, the less the likelihood that good reproducibility will be obtained. In fact, the study by Rieker and coworkers,²⁴ demonstrated excellent reproducibility (Kappa value of 0.97) when the various categories for the tumors in the study were merged into three groups only.

Conflicting results on clinical outcome for the various WHO categories

The latest version of the WHO classification of thymic epithelial neoplasms makes it a point of stressing the clinical validity of the various WHO subtypes based on their correlation with the outcome of the patients. In fact, the authors postulate a linear progression in terms of malignancy for these tumors, with thymoma of types A, AB, B1, B2, B3, and thymic carcinoma representing histologic subtypes showing an increasing order of malignancy. The authors reiterated their belief that type A and AB thymomas behave as benign tumors, type B1 as a low-grade malignant tumor, type B2 as a slightly more aggressive tumor, and type B3 (in advanced stages) as an aggressive malignant neoplasm similar to thymic carcinoma.¹⁴ This claim is based on a single study of 200 cases of thymoma from China by Muller-Hermelink and colleagues.¹⁵ Unfortunately, this information is at odds with other published studies in the literature. For example, in a study by Chalabreysse and coworkers,¹⁶ type A and AB thymomas showed a more aggressive behavior than all type B-tumors, and the differences in survival between type B1 to 3 were found to be minimal. In a study by Rieker and coworkers,²⁴ thymomas of type AB and B1 were the ones that followed the most favorable outcome, while types A and B2 behaved much worse and essentially showed overlapping survival

curves. These differences could be explained on the basis of inconsistencies in accurate histologic classification of the tumors among the different groups of investigators, sampling errors, or due to regional differences in treatment and behavior for the different patient populations. But the fact remains that there are still unaccountable differences in prognosis reported in the literature for the various WHO subtypes that cannot be easily ignored. We are, therefore, not yet at the point where generalized assumptions can be made or where we can accept without question the claims of the WHO panel.

A further point of contention is the insistence of the WHO panel and their supporters that type A and AB thymoma are benign neoplasms without the capability for aggressive behavior.^{14,15} This position is contradicted by years of published literature demonstrating that spindle cell thymoma, when matched for stage, can be as aggressive and as lethal as any other type of thymoma, with recurrences, distant metastases, and death due to tumor having been repeatedly and amply documented.^{2-5,9,10,16,24,35,36}

Conclusion

There is no question that the current WHO schema is a step forward from what existed previously in the field of thymoma histopathology, and that it has significantly advanced our understanding of these lesions. However, with continuous progress in our understanding of the biology of these tumors, and with an honest acknowledgment of the problems and limitations imposed by the current WHO schema, it is perhaps time to heed the words of the authors of the original WHO monograph who stated in their preface: “It will be appreciated, of course, that this classification reflects the present state of knowledge and that modifications are almost certain to be needed as experience accumulates.”¹² We trust that the next generation of thymoma classification will take into account these shortcomings and difficulties and move in the direction of a more reasonable, coherent, and logical system for the histopathologic classification of these fascinating and complex neoplasms.

References

1. Rosai J, Levine GD: Tumors of the thymus, fascicle 13, in Atlas of Tumor Pathology, Second Series. Washington DC, Armed Forces Institute of Pathology, 1976
2. Bernatz PE, Harrison EG, Claggett OT: Thymoma. A clinicopathologic study. *J Thorac Cardiovasc Surg* 42:424-444, 1961
3. Lattes R, Jonas S: Pathological and clinical features in 80 cases of thymoma. *Bull N Y Acad Med* 33:145-147, 1957
4. Masaoka A, Monden Y, Nakahara K, et al: Follow-up study of thymomas with special reference to their clinical stages. *Cancer* 48:2485-2492, 1981

5. Bergh NP, Gatzinsky P, Larson S, et al: Tumors of the thymus and thymic region. I. Clinicopathological studies on thymomas. *Ann Thorac Surg* 25:91-98, 1978
6. Levine GD, Rosai J: Thymic hyperplasia and neoplasia: a review of current concepts. *Hum Pathol* 9:495-515, 1978
7. Marino M, Muller-Hermelink HK: Thymoma and thymic carcinoma: relation of thymoma epithelial cells to the cortical and medullary differentiation of the thymus. *Virchows Arch* 407:119-149, 1985
8. Kirschner T, Muller-Hermelink HK: New approaches to the diagnosis of thymic epithelial tumors. *Prog Surg Pathol* 10:167-189, 1989
9. Verley JM, Hollmann KH: Thymoma. A comparative clinical study of clinical stages, histologic features, and survival in 200 cases. *Cancer* 55:1074-1096, 1985
10. Bernatz PE, Khonsari S, Harrison EG Jr, et al: Thymoma: factors influencing prognosis. *Surg Clin North Am* 53:885-892, 1973
11. Shimosato Y, Mukai K: Tumors of the mediastinum, fascicle 21, in *Atlas of Tumor Pathology*, 3rd series. Washington, DC, Armed Forces Institute of Pathology, 1997, pp 33-157
12. Rosai J: Histological typing of tumors of the thymus, in *World Health Organization International Histological Classification of Tumors* (ed 2). Berlin, Springer-Verlag, 1999
13. Suster S, Moran CA: The mediastinum, in Weidner N, Cote R, Suster S, Weiss LM (eds): *Modern Surgical Pathology*. Philadelphia, PA, WB Saunders Co, 2003, pp 439-504
14. Travis WD, Brambilla E, Muller-Hermelink HK, et al: Pathology and genetics of tumors of the lung, pleura, thymus and heart, in *World Health Organization Classification of Tumours*. Lyon, IARC Press, 2004
15. 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* 95:420-429, 2002
16. Chalabreysse L, Roy P, Cordier J-F, et al: Correlation of the WHO schema for the classification of thymic epithelial neoplasms with prognosis. A retrospective study of 90 tumors. *Am J Surg Pathol* 26:1605-1611, 2002
17. Penzel R, Hoegel J, Schmitz W, et al: Cluster of chromosomal imbalances in thymic epithelial tumors are associated with the WHO classification and the staging system according to Masaoka. *Int J Cancer* 105:494-498, 2003
18. Okumura M, Ohta M, Miyoshi S, et al: Oncological significance of WHO histological thymoma classification. A clinical study based on 286 patients. *Jpn J Thorac Cardiovasc Surg* 50:189-194, 2002
19. Kim DJ, Yang WI, Choi SS, et al: Prognostic and clinical relevance of the World Health Organization schema for the classification of thymic epithelial tumors: a clinicopathologic study of 108 patients and literature review. *Chest* 127:755-761, 2005
20. Park MS, Chung KY, Kim KD, et al: Prognosis of thymic tumors according to the new World Health Organization histologic classification. *Ann Thorac Surg* 78:992-997, 2004
21. Kondo K, Yoshizawa K, Tsuyuguchi M, et al: WHO histologic classification is a prognostic indicator in thymoma. *Ann Thorac Surg* 77:1183-1188, 2004
22. Inoue M, Starostik P, Zettl A, et al: Correlating genetic aberrations with World Health Organization-defined histology and stage across the spectrum of thymomas. *Cancer Res* 63:3708-3715, 2003
23. 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* 25:103-110, 2001
24. Rieker RJ, Hoegel J, Morresi-Hauf A, et al: Histologic classification of thymic epithelial tumors: comparison of established classification schemes. *Int J Cancer* 98:900-906, 2002
25. Lattes R: Thymoma and other tumors of the thymus. An analysis of 107 cases. *Cancer* 15:1224-1260, 1962
26. Salyer W, Eggleston JC: Thymoma. A clinical and pathological study of 65 cases. *Cancer* 37:229-249, 1976
27. Sellors TH, Thackaray AC, Thomson AD: Tumors of the thymus. *Thorax* 22:193-221, 1967
28. Moran CA, Suster S: On the histologic heterogeneity of thymic epithelial neoplasms: impact of sampling in subtyping and classification of thymomas. *Am J Clin Pathol* 114:760-766, 2000
29. Marchevsky AM, Hammond EA, Moran CA, et al: Protocol for the examination of specimens from patients with thymic epithelial tumors located in any area of the mediastinum. *Arch Pathol Lab Med* 127:1298-1303, 2003
30. Moran CA, Suster S, Koss MN: Plasma cell rich thymoma. *Am J Clin Pathol* 102:199-201, 1994
31. Suster S, Moran CA, Chan JKC: Thymoma with pseudosarcomatous stroma. Report of an unusual histologic variant of thymic epithelial neoplasm that may simulate carcinosarcoma. *Am J Surg Pathol* 21:1216-1223, 1997
32. Moran CA, Koss MN: Rhabdomyomatous thymoma. *Am J Surg Pathol* 17:633-636, 1993
33. Moran CA, Suster S: Thymomas with prominent adenomatoid features: a clinicopathological and immunohistochemical study of 12 cases. *Mod Pathol* 14:224A, 2001
34. Dawson A, Ibrahim NBN, Gibbs AR: Observer variation in the histopathological classification of thymoma: correlation with prognosis. *J Clin Pathol* 47:519-523, 1994
35. Pan C-C, Wu H-P, Yang C-F, et al: The clinicopathologic correlation of epithelial subtyping in thymoma: a study of 112 consecutive cases. *Hum Pathol* 25:893-899, 1994
36. Regnard J-F, Magdeleinat P, Dromer C, et al: Prognostic factors and long-term results after thymoma resection: a series of 307 patients. *J Thorac Cardiovasc Surg* 112:376-384, 1996