

ITMIG Consensus Statement on the Use of the WHO Histological Classification of Thymoma and Thymic Carcinoma: Refined Definitions, Histological Criteria, and Reporting

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Disclosure: Dr. Kurrer, Dr. Lauriola, Dr. Marino, Dr. Molina, Dr. Mukai, and Dr. Nicholson report to have received a travel grant by International Thymic Malignancy Interest Group for the meeting on which this report is based. Research on thymic tumors by Dr. Marx and Dr. Ströbel is supported by the BMBF (grant: 01DL12027). Dr. Molina reports to have received personal payments as board member of Merck and to have received travel grants by Mundipharma and Amgen. All other authors declare no conflict of interest.

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ISSN: 1556-0864/14/0905-0596

Introduction: The 2004 version of the World Health Organization classification subdivides thymic epithelial tumors into A, AB, B1, B2, and B3 (and rare other) thymomas and thymic carcinomas (TC). Due to a morphological continuum between some thymoma subtypes and some morphological overlap between thymomas and TC, a variable proportion of cases may pose problems in classification, contributing to the poor interobserver reproducibility in some studies.

Methods: To overcome this problem, hematoxylin-eosin-stained and immunohistochemically processed sections of prototypic, “borderland,” and “combined” thymomas and TC ($n = 72$) were studied by 18 pathologists at an international consensus slide workshop supported by the International Thymic Malignancy Interest Group.

Results: Consensus was achieved on refined criteria for decision making at the A/AB borderland, the distinction between B1, B2, and B3 thymomas and the separation of B3 thymomas from TCs. “Atypical type A thymoma” is tentatively proposed as a new type A thymoma variant. New reporting strategies for tumors with more than one histological pattern are proposed.

Conclusion: These guidelines can set the stage for reproducibility studies and the design of a clinically meaningful grading system for thymic epithelial tumors.

Key Words: Thymoma, Thymic carcinoma, Histological classification, Diagnostic criteria.

(*J Thorac Oncol.* 2014;9: 596–611)

The World Health Organization (WHO) classification^{1,2} is the most widely used histological classification of thymomas and thymic carcinomas (TCs). Like classification schemes in most other tumors, the WHO classification assigns tumors to “entities” that have fundamental morphological differences, distinguishing type A, AB, B1, B2, and B3 thymomas (and rare other thymomas) from TCs. This “primate” of histology distinguishes the WHO histological classification from other schemes that separated tumors mainly on the basis

of tumor stage³ or tumor grade, such as the thymoma-atypical thymoma-TC scheme proposed by Suster and Moran.⁴ Despite of its value for the comparability of pathologic and clinical studies^{5,6} and its biological and clinical relevance,⁷⁻⁹ the WHO classification has been criticized for poor interobserver reproducibility or inconsistencies in some studies.⁹⁻¹¹ To address these issues at an interdisciplinary conference organized by the International Thymic Malignancy Interest Group (ITMIG) in New York, in March 2011, the participants (Appendix 1) agreed that the WHO classification should be maintained but needs refinement of histological criteria for better management of the following problem areas that likely contribute to poor interobserver reproducibility:

1. Thymomas with features intermediate between prototypic subtypes (borderland cases)
2. Tumors with atypia, high mitotic activity, and necrosis
3. Tumors showing more than one histological pattern

To achieve refined diagnostic criteria, an interdisciplinary team of 18 pathologists (Appendix 2), two surgeons, and an oncologist reviewed prototypic and difficult-to-classify thymic epithelial tumors (TETs) during a consensus slide workshop in December 2011. The workshop was organized in Mannheim by ITMIG and with additional support by the European Society of Pathology. Descriptions given in the WHO classification of tumors of the thymus monograph (2004) were critically reviewed and revisions discussed by the panel. Two strategies were followed to better convey agreed-upon criteria. First, there was consensus to replace the “narrative style” of the WHO classification by tables that list major (indispensable) and minor (typical) findings in addition to findings that are considered compatible with the diagnosis. Second, illustrations of prototypic histological findings were complemented by “galleries of figures” that illustrate difficult-to-classify tumors at the “borderlands” between prototypic cases.

MATERIALS AND METHODS

Collection and Prescreening of Thymoma and TC Cases

Participants were requested to submit paraffin blocks or sections of resection specimens of instructive (prototypic, borderland [see end of this paragraph], or other difficult-to-classify) cases of thymomas and TCs to the Institute of Pathology, University Medical Centre Mannheim. Hundred five specimens were received. Selection was made by PS and AM to exclude cases of low-technical quality and to reduce the number of clear-cut prototypic thymoma cases among the frequent thymoma subtypes, to retain a reasonable number of the most informative examples likely to achieve the purpose of the workshop, that is, to refine diagnostic criteria based on hematoxylin-eosin (H&E)-stained sections and immunohistochemical results. By this strategy, cases with a broad morphological spectrum among the different thymic tumors were retained. Due to our interest in borderland cases with differential diagnostic value, the series was highly selected and, therefore, may not be representative of all morphological variants.

Of 72 cases that were selected for review at the consensus workshop, only 58 could finally be fully evaluated due to time restrictions. Usually, one block was chosen for each case, on which 11 immunohistochemical stains were performed at the Institute of Pathology, University Medical Centre Mannheim. Before the workshop, the 72 selected cases were assigned by PS and AM to three groups to address the spectrum of type A and AB thymoma ($n = 29$; finally evaluated: 16 type A and 5 AB thymomas); the spectrum of B1, B2, and B3 thymoma ($n = 27$; finally evaluated: 6 B1, 16 B2, and 5 B3 thymomas); and the borderland between thymoma and TC ($n = 16$; finally evaluated: 7 B3 thymomas and 3 TCs). The term “borderland,” referred to throughout this article, is not intended to be a category of thymoma in the proposed classification. The term refers to cases in which a decision between two diagnoses is difficult, usually because diagnostic criteria are quantitative rather than qualitative.

Histology and Immunohistochemistry

In addition to H&E staining, the following antibodies were applied on formalin-fixed, paraffin-embedded tissue using a routine immunoperoxidase technique:

1. “Conventional” antibodies: Pancytokeratin (AE1/3), CD5 (T cells, epithelial cells of many TCs), CD117 (epithelial cells of many TCs), TdT (immature T cells), desmin (myoid cells in the medulla).
2. Antibodies to cortical epithelial cells: Beta5t (thymus cortex-specific proteasome subunit), prss16, and cathepsin V (both cortex-restricted proteases).
3. Medullary thymic epithelial cell markers: CD40, claudin 4, and AIRE (autoimmune regulator). Details of the antibodies are given in Supplementary Table S1 (Supplemental Digital Content 1, <http://links.lww.com/JTO/A576>).

Workflow and Strategy to Achieve Consensus

A representative H&E-stained section of each case was presented by the submitting pathologist using a multihead microscope. Basic clinical data (age, sex, tumor size and stage, and myasthenia gravis status) but neither the original diagnosis nor the information whether a given case was considered prototypic or difficult-to-classify by the submitting panelist were provided. The 18 participating pathologists were asked (1) to allocate each case to one of the WHO thymoma types or to the TC category, (2) to identify difficult-to-classify cases, and (3) to roughly quantify histologically diverse components in cases with histological heterogeneity. Each participant entered his/her H&E-based “primary diagnosis” (WHO thymoma type or TC) on a personal data sheet. Subsequently, immunostaining results were presented using a digital projector, results were discussed, and then each participant entered his/her “final diagnosis” on his/her data sheet. The “consensus diagnosis,” that is, the final diagnosis made by the majority of the panelists (always >50%), was established by voting. “Consensus rate” represented the percentage of cases with a given consensus diagnosis (e.g., type B2 thymoma) to which 100% of the

panelists finally agreed. Such cases (with 100% final agreement among the panelist) were labeled as “prototypic” and all others as borderland cases. The concordance rate was the percentage of cases with an achieved consensus diagnosis in which the H&E-based primary diagnoses were in agreement with the consensus diagnoses (i.e., the fraction of cases of a given WHO type that was “correctly diagnosed” ab initio) (Supplementary Table S2, Supplemental Digital Content 2, <http://links.lww.com/JTO/A577>).

Consensus on Major and Minor Diagnostic Criteria and Their Proposed Application

Following the identification of prototypic cases with 100% consensus and related borderland cases (cases with incomplete consensus that underlined the necessity of refined diagnostic criteria), the panel members compared prototypic cases of different histological types at the multihead microscope to identify histological and (possible) immunohistochemical “major criteria” that were either consistently present or consistently absent in the prototypic cases of a given histological category. In terms of application, major criteria are features that are either an absolute requirement or an absolute contraindication for a given diagnosis. Minor criteria are features that may be typical, common, rare, or even exceptional for a given tumor entity and thus are supportive but not required for diagnosis. As an example, the diagnosis of type B1 thymoma requires the presence of “thymus-like architecture throughout,” including medullary islands and cortical cytology (implying a high density of thymocytes and a low density of epithelial cells), as well as the absence of clustered epithelial cells, while Hassall’s corpuscles and a “large lobular growth pattern” are typical (and often helpful) but dispensable minor criteria.

Gallery Approach

As morphological criteria are often not categorical variables but form a continuum,⁴ the description of major and minor diagnostic criteria may not be able to resolve all diagnostic problems in borderland cases. Therefore, we produced agreed upon but admittedly arbitrary galleries of images to visually depict the spectrum, for example, relatively epithelial-rich B1 thymoma compared with the relatively epithelial-poor B2 thymoma.

RESULTS

Ad hoc Reproducibility

In approximately 85% of cases, overall there was full agreement between the H&E-based primary diagnoses and the consensus diagnoses. Discrepancies concerned borderlands between type A and AB thymomas (16% disagreement), B1 and B2 thymomas (15% disagreement), and between B3s and TCs (39% disagreement, but with too low a number of cases to draw conclusions). Immunohistochemistry improved diagnosis mainly at the type A versus AB borderland. Details are given in Supplementary Table S2 (Supplemental Digital Content 2, <http://links.lww.com/JTO/A577>).

Spectrum of Type A and AB Thymoma

Type A thymoma.

Agreed-upon “major/indispensable” criteria and “minor/typical” criteria are given in Table 1 for “conventional” (non-atypical) type A thymomas that were tentatively separated from the rare “atypical type A thymomas” on the basis of mitotic activity and coagulative necrosis (see below). In contrast to the descriptions in the WHO classification,² it was found that lack of reticulin fibers (or collagen IV expression) did not reliably distinguish type A from B3 thymomas. Lack of cortex-specific immunohistochemical markers favors a diagnosis of type A thymoma (Table 1). The broad morphological spectrum of conventional type A thymoma is depicted in Figure 1 (Supplementary Fig. S1, Supplemental Digital Content 3, <http://links.lww.com/JTO/A578>).

The new concept of atypical type A thymoma.

This concept emerged during multidisciplinary discussions in New York and based on the case review in Mannheim. Although the term “benign” was used in the 2004 WHO classification in the discussion of type A thymoma,² it is well documented that even type A thymomas can present in advanced stages including metastasis indicating that all thymomas are malignant, although to a variable extent.^{12,13} Seven of the 16 type A thymomas studied were labeled as an “atypical” variant. Agreed criteria of “atypia” were increased mitotic activity (4 or more per 10 high power field) and “true” (coagulative) tumor necrosis (in contrast to ischemic or biopsy-induced necrosis) (Fig. 2). Other criteria (e.g., hypercellularity, enlarged hyperchromatic nuclei, large nucleoli, increased Ki67 index, and extent of atypical areas) were difficult to quantify or could not be agreed upon. Recent articles^{14,15} have addressed the issue of atypical type A thymoma, and the latter authors¹⁵ suggest that necrosis may predict aggressiveness. Although the concept was

TABLE 1. Major and Minor Criteria of “Conventional” Type A Thymomas

Major criteria

Spindled and/or oval-shaped tumor cells lacking nuclear atypia (see text)

Paucity^a or absence of immature, TdT(+) thymocytes throughout the tumor

Minor criteria

Occurrence of rosettes and/or subcapsular cysts (to be distinguished from PVS)

Presence of focal glandular formations

Pericytomatos vascular pattern

Paucity or absence of PVS contrasting with presence of abundant capillaries

Lack of Hassall’s corpuscles

Complete or major encapsulation

Expression of CD20 in epithelial cells; absence of cortex-specific markers^b

^aPaucity implies no (immature) lymphocyte-rich regions with dense, “impossible-to-count” TdT(+) lymphocytes; or at most 10% tumor regions with moderate (see text) immature lymphocyte counts (Fig. 2).

^bBeta5t, PRSS16, and cathepsin V by immunohistochemistry (IHC). PVS, perivascular space.

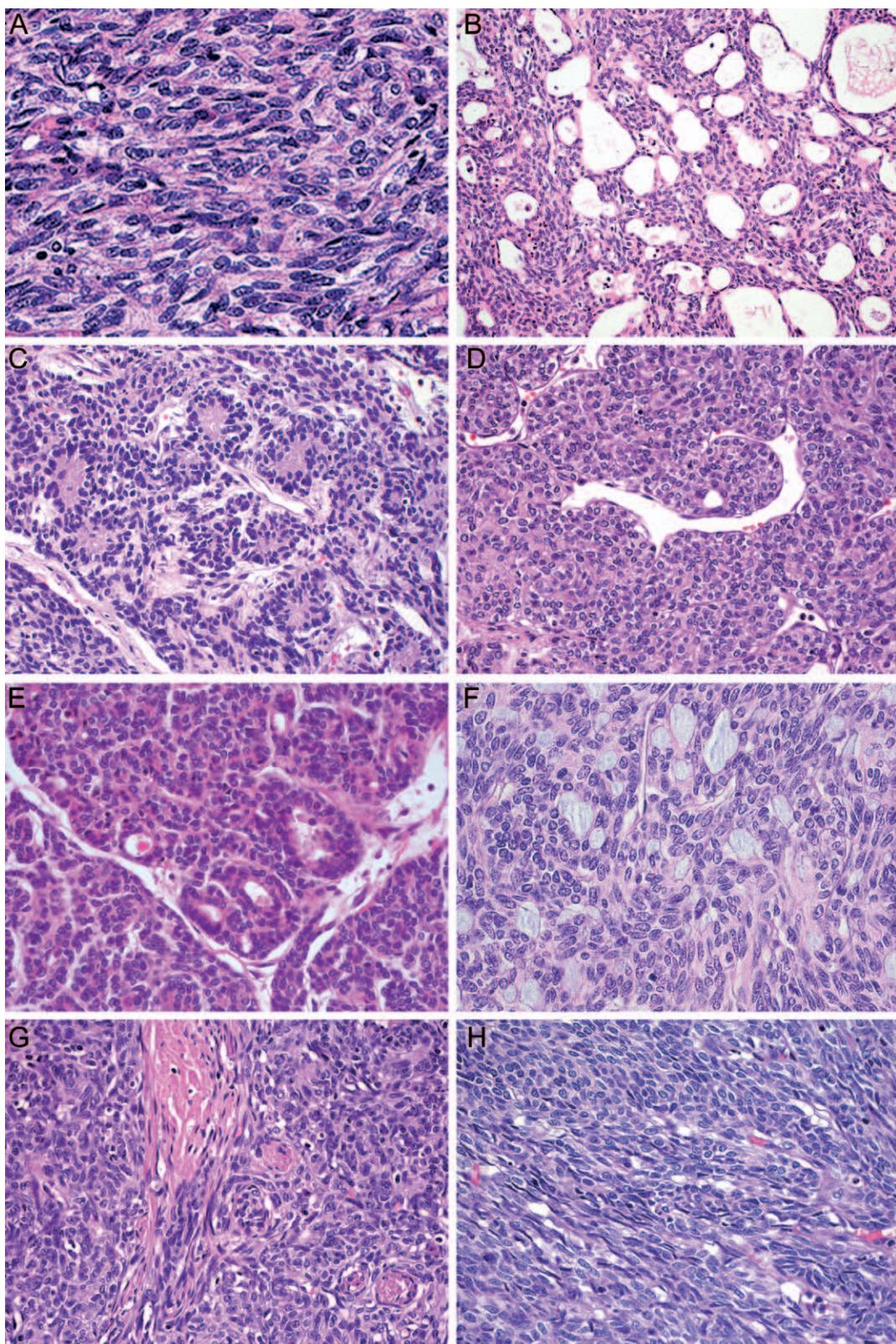


FIGURE 1. Spectrum of common histological patterns of conventional World Health Organization type A thymomas. Often, several patterns occur in the same tumor. Spindle cell pattern (A), microcystic (B), resetting (C), hemangiopericytoma like (D), glandular/adenoid (E), mucoid (F), whorls forming (G), and synovial sarcoma-like pattern (H). For rare other patterns of type A thymoma, see Supplementary Figure S1 (Supplemental Digital Content 3, <http://links.lww.com/JTO/A578>) (hematoxylin-eosin, $\times 100$ or $\times 200$).

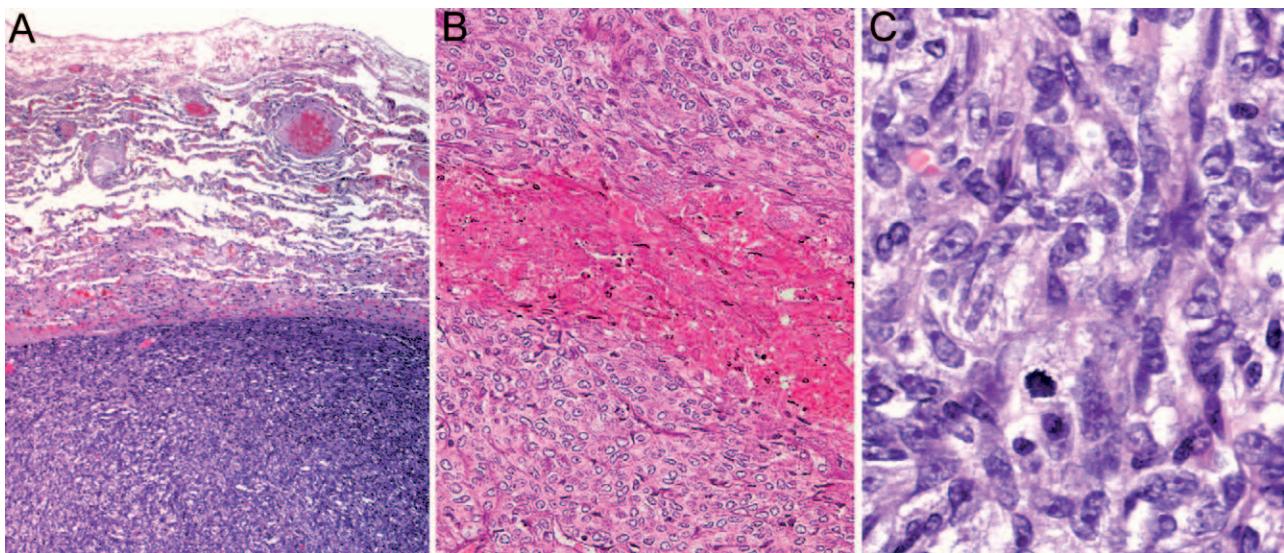


FIGURE 2. Atypical type A thymoma. *A*, Pulmonary metastasis of type A thymoma (hematoxylin-eosin [H&E], $\times 50$). *B*, Spindle cell type A thymoma with comedo-type necrosis (H&E, $\times 200$). *C*, Mitotic activity in a more epithelioid area (H&E, $\times 400$).

considered, a division of type A thymoma into new entities, that is, A1, A2, and A3 subtypes (analogous to the type B lineage), was rejected due to a lack of available convincing data.

Type A versus AB thymoma.

The imprecise WHO definition of AB thymomas as “organotypic thymic epithelial neoplasms composed of a mixture of lymphocyte-poor type A thymoma component and a more lymphocyte-rich type B-like component...” may explain the variable frequencies reported for type A (5–30%) thymomas in different series.¹⁶ Immunohistochemistry showed that epithelial cells of AB thymomas express both cortical and medullary markers in an intermingled pattern, whereas type A thymomas lack cortical markers.¹⁷ Independent of this difference between type A and AB thymomas, type A thymomas should harbor no or only few TdT+ T cells (easy to count) (grade 1) or a moderate amount of TdT+ T cells (I could count if I had to) (grade 2) in 10% or less of a given biopsy (Fig. 3). Moderate numbers of TdT+ T cells above the arbitrary 10% threshold in available biopsies or any area with abundant (impossible to count) TdT+ T cells (grade 3 by number of TdT+ T cells) would favor a diagnosis of AB thymoma over type A thymoma. Diagnostic criteria distinguishing type A and AB thymoma are compared in Table 2.

Type A versus spindle cell B3 thymoma.

Prominent and abundant perivascular spaces (PVSs) would strongly favor a diagnosis of type B3 thymoma, whereas uniform nuclei, abundance of capillary vessels, rosette formation, cystic spaces, and epithelial expression of CD20 would favor type A thymoma. Nevertheless, distinction between atypical type A thymoma and spindle cell B3 thymoma can be more difficult because nuclear atypia is present in both, and immunohistochemical studies may be required.

Type AB versus micronodular thymoma.

A minor component of micronodular thymoma (MNT) with lymphoid stroma^{18–20} is a frequent finding in type A and

AB thymoma. To distinguish AB thymoma from MNT, it is necessary to identify immature TdT+ T cells in a background of epithelial cells (which is the defining feature of AB thymomas) and the absence of an epithelial cell-free lymphoid stroma (which would qualify the case as MNT) (Fig. 4).

Type AB versus B1 thymoma.

This rare differential diagnostic challenge is discussed below.

Spectrum of Type B Thymomas

There was consensus that subdivision of B thymomas into B1, B2, and B3 subtypes should be maintained, considering (1) the unique “thymus-like” structure of B1 thymomas; (2) the distinct histology of type B3 thymomas; and (3) the more aggressive behavior of B2 compared with B1 thymomas.^{6,21–23} Nevertheless, type B thymomas apparently represent a continuum from B1 to B3 thymomas which show a spectrum of lymphocyte to epithelial predominance: the borderlands between them contribute to the suboptimal interobserver reproducibility of the WHO classification.^{10,11,16}

Distinguishing B1 thymomas from B2 thymomas.

B1 thymomas are consistently lymphocyte-rich, epithelial-poor tumors that closely mimic normal thymus at both low and high magnification. A “sine qua non feature” of B1 thymomas is presence of prominent “medullary islands” (Fig. 5) that contain epithelial cells with or without Hassall’s corpuscles; a majority of mature, TdT(−) T cells; and scattered CD20+ mature B cells. Desmin+ myoid cells and AIRE+ medullary epithelial cells are inconsistently present. Medullary islands can also occur in B2 thymoma (Fig. 6). PVS and abundant TdT+ T cells occur in both B1 and B2 thymomas, but PVSs are often inconspicuous in B1 thymomas. Therefore, the distinguishing features of B2 thymomas are (1) increased number of epithelial cells compared with normal thymus often visible at low magnification and (2) epithelial cell clusters (defined

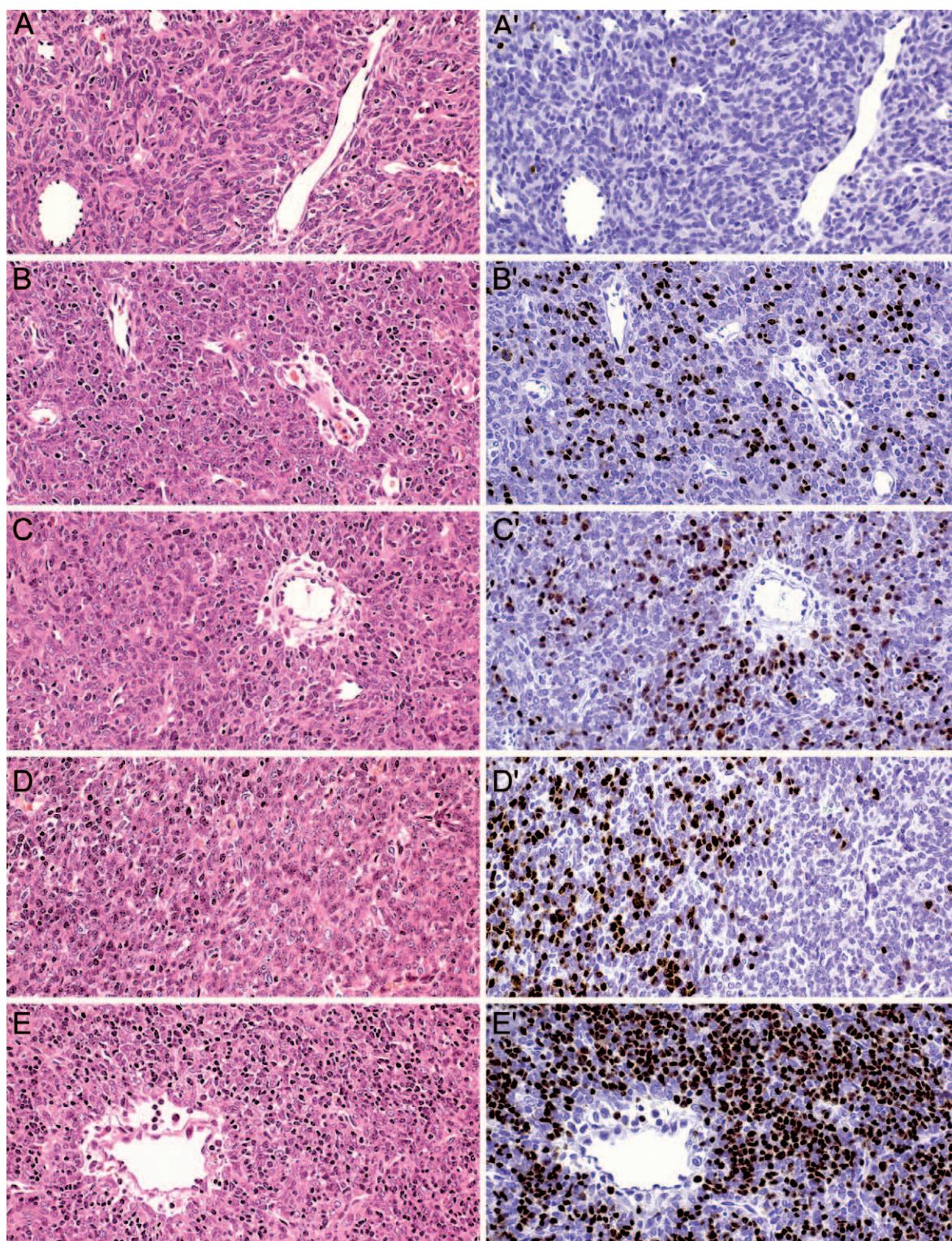


FIGURE 3. Type A thymoma and borderland to AB thymoma. *A*, Almost lymphocyte-free type A thymoma. *A'*, Serial section with only single TdT+ immature T cells. *B* and *C*, Type A thymomas with low (easy to count) numbers of lymphocytes. *B'* and *C'*, Serial sections showing TdT+ immature T cells. *D* and *D'*, Thymoma at the borderland between A and AB with focal, moderate (could count if I had to) number of TdT+ T cells. By definition, thymomas with moderate numbers of TdT+ T cells in >10% are counted among type AB thymomas. *E* and *E'*, Type AB thymoma with a high number of immature T cells (impossible to count). Any tumor area with such a high number of TdT+ T cells is incompatible with a diagnosis of type A thymoma (*A-E*, hematoxylin-eosin, $\times 200$; *A'-E'*, serial sections, TdT expression, immunoperoxidase, $\times 200$).

TABLE 2. Major and Minor Histological Features Encountered in Type A and AB Thymomas

	Type A Thymoma	Type AB Thymoma
Major criteria		
Biphasic pattern at low magnification due to variable lymphocyte content	No	Common ^a
High epithelial cell content	Yes	Yes
Spindled or oval epithelial cells ^b	Yes	Yes
Paucity ^c or absence of TdT+ T cells	Yes	No
Medullary islands ^d	No	Rarely present ^{a,e}
Minor criteria		
Small lobular growth pattern	No	Rare
Large lobular growth pattern	Common	Common
Perivascular spaces	Rarely present	Rarely present
CD20 expression in epithelial cells	Common	Common
Cortical marker expression ^f	No	Yes

^aThese features are minor criteria in type AB thymoma.

^bAtypia in type AB thymoma has not been addressed so far.

^cAs defined in Table 1.

^dDetection of medullary islands is usually clear-cut on hematoxylin-eosin staining but may require immunohistochemistry (IHC), particularly when Hassall's corpuscles are missing.

^eIn lymphocyte-rich areas, usually with lack of Hassall's corpuscles.

^fBeta5t, PRSS16, and cathepsin V (detectable by IHC in epithelial cells within lymphocyte-rich areas).

as at least three contiguous epithelial cells) (Supplementary Fig. S2, Supplemental Digital Content 4, <http://links.lww.com/JTO/A579>). Nuclear size of epithelial cells is not a helpful distinguishing feature. On immunostaining, the keratin+ epithelial cell network in B1 thymomas resembles that of normal thymus, whereas the network of epithelial cells in B2 thymomas is significantly denser (Fig. 7). The differential diagnosis between type B1 and B2 thymoma is highlighted in Table 3.

Distinguishing B1 thymomas from AB thymomas.

Like B1 thymomas, AB thymomas can be lymphocyte rich and can show medullary islands. Nevertheless, Hassall's corpuscles are almost always absent, while they occur in 50% of B1 thymomas. Epithelial cells inside lymphocyte-rich areas of AB thymomas have a spindled or oval morphology. Rarely, the lymphocyte-rich areas in AB thymomas may mimic B1 thymomas. In such cases, distinguishing features are bland, spindled tumor cells, even in less than 10% of a TdT+ T cell-rich tumor, and CD20 expression in epithelial tumor cells that is found in 50% of AB thymomas but not B1 thymomas.

Distinguishing B2 thymoma from B3 thymoma.

As a “rule of thumb” H&E-stained B2 and B3 thymomas give a “blue” versus “pink” impression, respectively, due to the prominent T cells in B2 versus B3 thymomas. Nevertheless, there are borderland cases that defy classification by description and are depicted here in an agreed-upon gallery as either B2 or B3 cases (Fig. 8) (Supplementary Fig. S3, Supplemental Digital Content 5, <http://links.lww.com/JTO/A580>). Previously described distinguishing criteria such as PVS and nuclear size are not helpful for this distinction.

Distinguishing Thymoma from TC

In general, TCs show the same histological features as analogous extra-thymic carcinomas (Table 4).^{1,2,24–27} Nevertheless, distinction of B3 thymoma and thymic squamous cell carcinoma (TSCC) may be difficult in a small percentage of cases. B3 thymomas typically show lobular growth, conspicuous PVS, minor/moderate nuclear atypia, lack of intercellular bridges, presence of TdT+ immature T cells, and lack of expression of CD5, CD117, GLUT1, and MUC1 in neoplastic epithelial cells.^{28–31} However, the following equivocal situations were felt to need clarification.

Histologically typical B3 thymomas with epithelial expression of CD5, CD117, MUC1, or GLUT1.

Based on the consensus about the overriding importance of “conventional histology” and despite the expression of CD5, CD117, MUC1, or GLUT1, expression of these markers in an otherwise typical B3 thymoma should not change the diagnosis to TC.

Histologically typical B3 thymomas but with absence of TdT+ T cells.

Focal absence of TdT+ T cells can occur in conventional B3 thymoma as illustrated in the 2004 WHO classification (p. 165).² Therefore, tumors that lack TdT+ T cells in the available histological material but otherwise show features of typical B3 thymomas and CD5/CD117 negativity should be called B3 thymomas.

“B3 thymoma-like tumors” with expression of CD5 and/or CD117 and lack of TdT+ T cells.

Two such previously undescribed tumors were reviewed. They showed no major atypia and no intercellular bridges, and the patients did not have myasthenia gravis. In the absence of two features of TSCC (clear-cut nuclear atypia and intercellular bridges) and lack of an important feature of B3 thymomas (TdT+ T cells), these tumors were tentatively labeled as “B3/TSCC borderline TETs” (Fig. 9). If a comparable case would show relevant atypia, a diagnosis of “TSCC with organoid features” was considered the more appropriate designation (Fig. 10).

Borderland between “thymoma with anaplasia” and TC.

Anaplasia occurs in rare B2 and B3 thymomas. It is usually a focal phenomenon and the tumors show maintained “organotypic” features, such as TdT+ T cells, PVSs, lobular growth pattern, and absence of CD5/CD117 expression. Such tumors should be labeled as “B2 (or B3 or other) thymoma with anaplasia” according to the WHO classification² (p. 165). The clinical significance of this finding is not known.

Borderland between atypical type A thymoma and (spindle cell) TC.

As to this borderland, analysis of TdT is not helpful, as absence of TdT+ thymocytes does not exclude a diagnosis of atypical type A thymoma. Epithelial expression of CD20 is a potential marker of type A thymomas, but this is infrequently present in atypical type A thymomas. The usefulness of CD5, CD117, MUC1, and GLUT1 in this differential has not

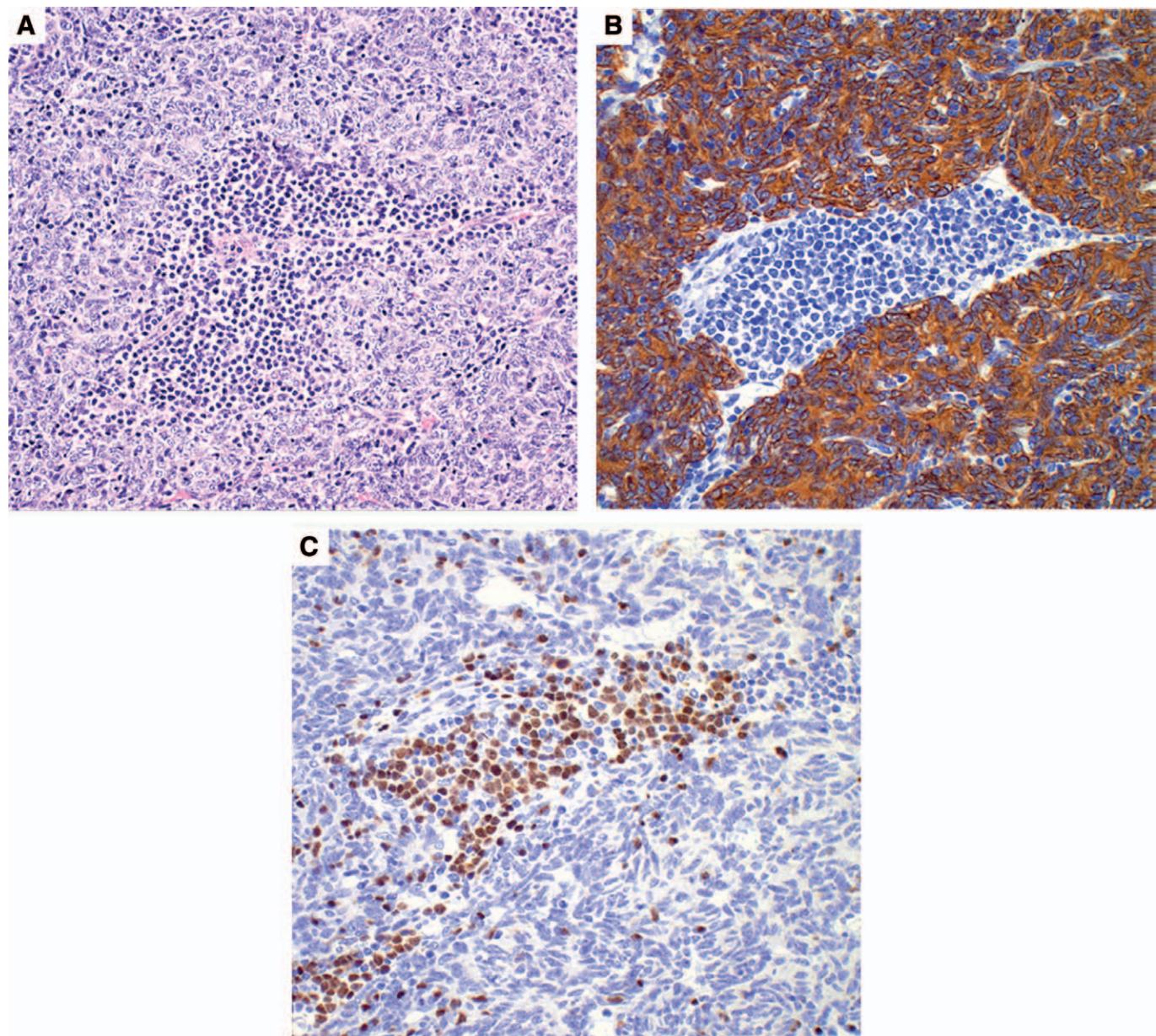


FIGURE 4. Micronodular thymoma (MNT). *A*, MNT with central lymphocyte-rich area surrounded by lymphocyte-poor epithelial cells. *B*, Absence of epithelial cells in the lymphocyte-rich area as shown by cytokeratin (AE1/3) immunostaining. *C*, TdT expression in the lymphocytes in the epithelial-free area of an MNT (the proportion of TdT+ cells in MNTs is highly variable, in the case shown here it is quite high); in type AB thymomas, TdT+ T cells are always intermingled with cytokeratin+ epithelial cells (*A*, hematoxylin-eosin; *B* and *C*, immunoperoxidase, $\times 100$).

been well tested either. Nevertheless, similar to B3 thymomas, morphologically classical type A thymomas should not be reclassified as TC only on the basis of CD117 and CD5 expression. New “subtype-specific” markers are needed to study this unresolved borderland.

“Combined TETs”—abolishment of the term and new rules for reporting.

Taking into account that thymomas with heterogeneous histological features including B1, B2, and B3 components

are very common, there was consensus that the term “combined thymoma” should be abandoned (whether heterogeneity is identified by H&E structure alone or immunohistological studies is not relevant in this context). Instead, the diagnosis in such tumors should follow an approach analogous to Gleason scoring, listing all subtypes starting with the predominant component; minor components should be reported with 10% increments. Of note, AB thymoma is a distinct entity for which the 10% rule does not apply (see above). For scientific

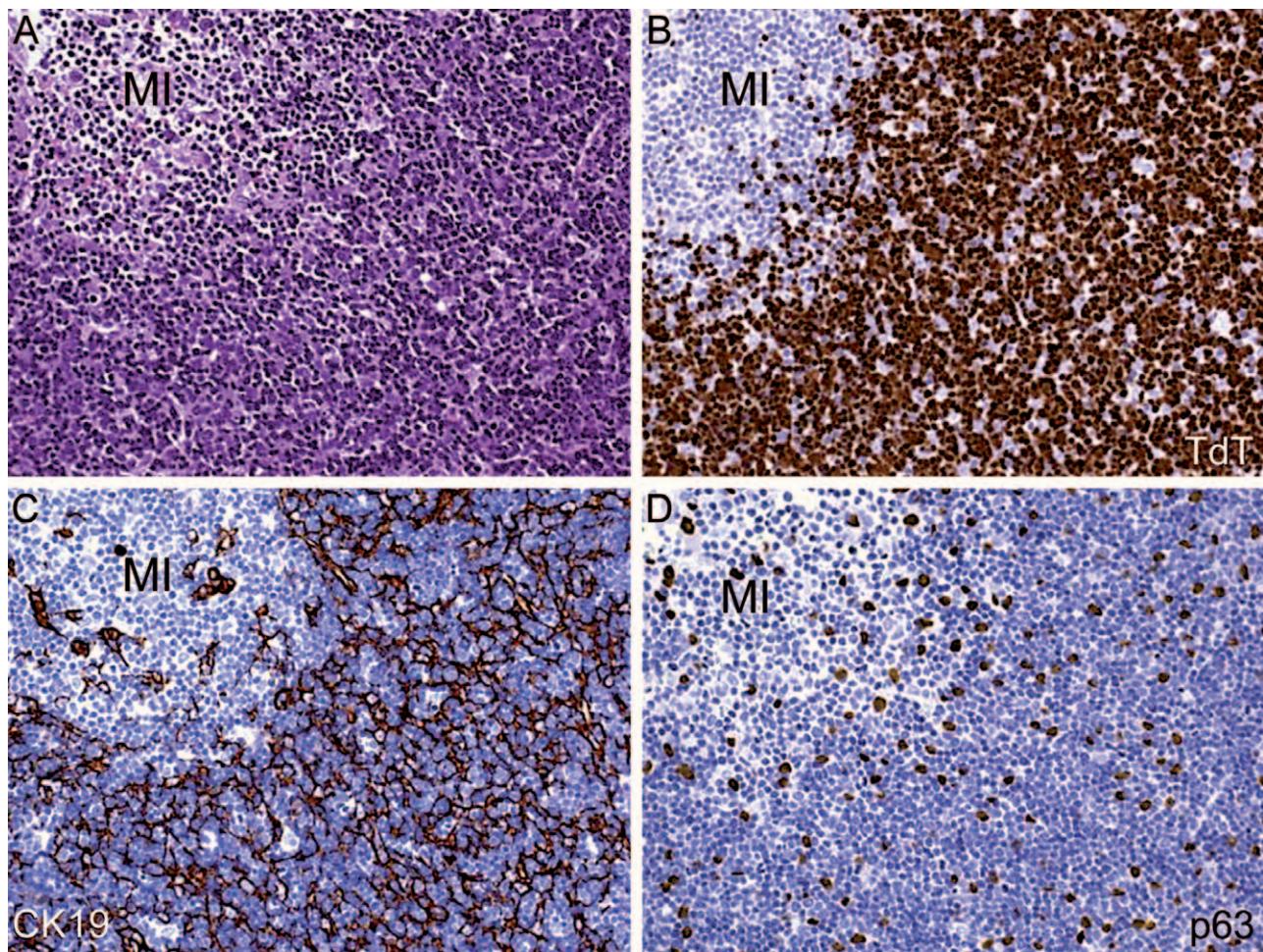


FIGURE 5. Prototypic type B1 thymoma. *A*, Organoid architecture with medullary island (MI; here without Hassall's corpuscle) and preponderance of darker staining cortical area. *B*, TdT expression by immature T cells occurs almost exclusively in the cortical area. *C*, Cytokeratin expression (antibody AE1/3) shows a loose network of epithelial cells in the cortical and medullary areas; by contrast, perivascular spaces are distinctly epithelial free (Fig. 8). *D*, Low number of evenly spaced neoplastic thymic epithelial cells as highlighted by p63 staining of tumor cell nuclei (*A*, hematoxylin-eosin; *B–D*, immunoperoxidase, $\times 100$; serial sections).

and statistical purposes, thymoma components of 0% to 10% can be neglected, and the respective tumor counted among the “pure” thymoma subtypes according to the dominant component.

By contrast, heterogeneous tumors that comprise a TC component of whatever size/percentage in addition to a thymoma component should be labeled as TC (specifying the percentage and histological type) followed by listing of the accompanying thymoma components (with quantitation as detailed above).

DISCUSSION

The consensus achieved on the revised histological criteria for thymomas and TCs was based on microscopic review of a large collection of highly informative, often difficult-to-classify cases. There was agreement to maintain the widely accepted WHO framework but to improve historic definitions² and introduce new terms, when appropriate, with the aim to improve

interobserver reproducibility (to be tested). The term borderland is not intended to represent a proposal for a new type of thymoma. It should not be used for pathologic diagnosis; in this article, this term refers to problem cases for the panel to review with the intent of refining the 2004 classification. Another caveat concerns the selection of only one paraffin block per case for our analysis. This restriction was dictated by the limited time of the meeting but compatible with our aim to refine histological criteria rather than checking the contributors’ original diagnoses. In face of the common histological heterogeneity of thymomas, we explicitly recommend extensive sampling of all thymic tumors.³²

General Reproducibility

Previous reproducibility studies^{10,11} and meta-analyses^{16,22} revealed poor agreement on the distinction between A and AB thymomas, between B1, B2, and B3 thymomas, and between B3 thymomas and TSCTC. This was not the case in the slide workshop: agreement between the individual panelists’

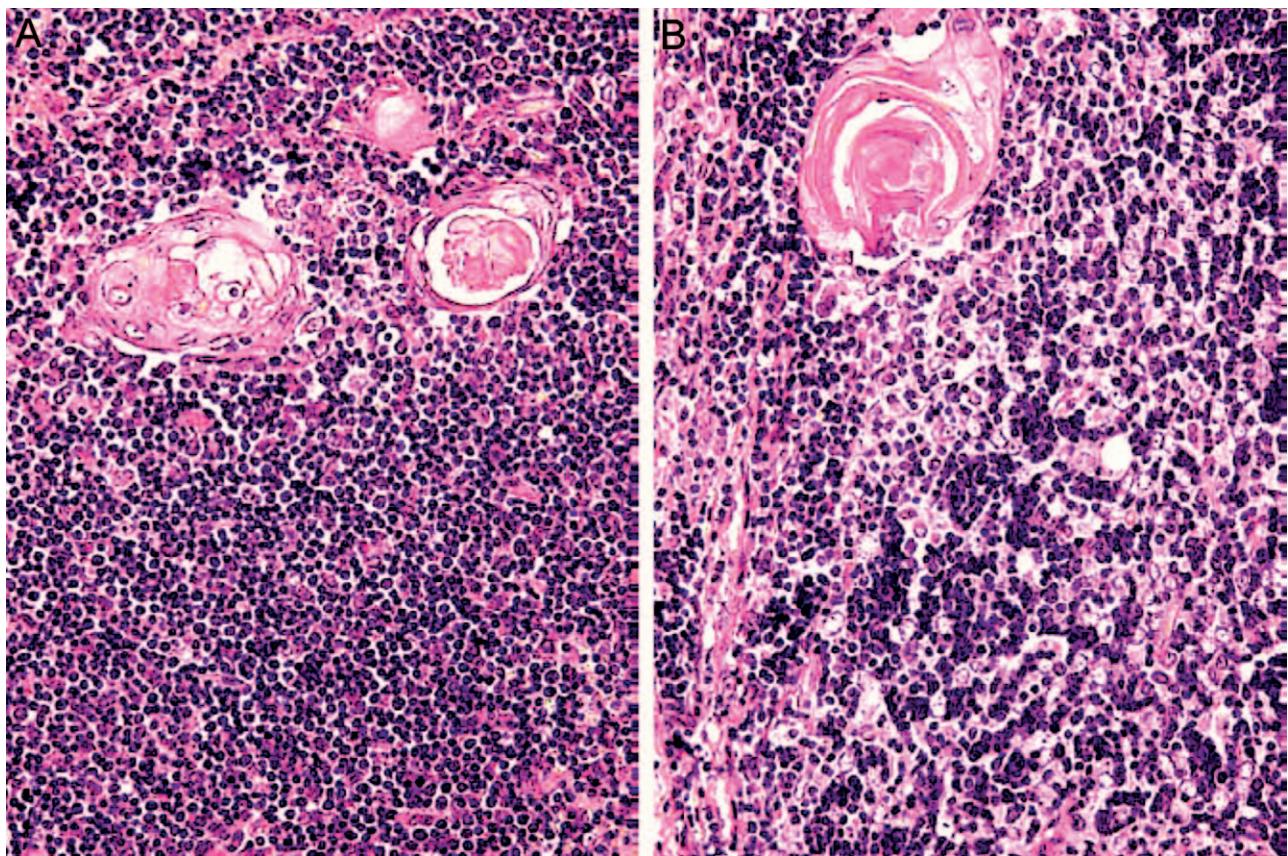


FIGURE 6. Hassall's corpuscles as optional feature in type B1 and B2 thymoma. *A*, Hassall's corpuscle in a lymphocyte-rich type B1 thymoma with almost no discernible epithelial cells. *B*, Hassall's corpuscle in a more epithelial-rich type B2 thymoma with easily discernible neoplastic epithelial cells (hematoxylin-eosin, $\times 200$).

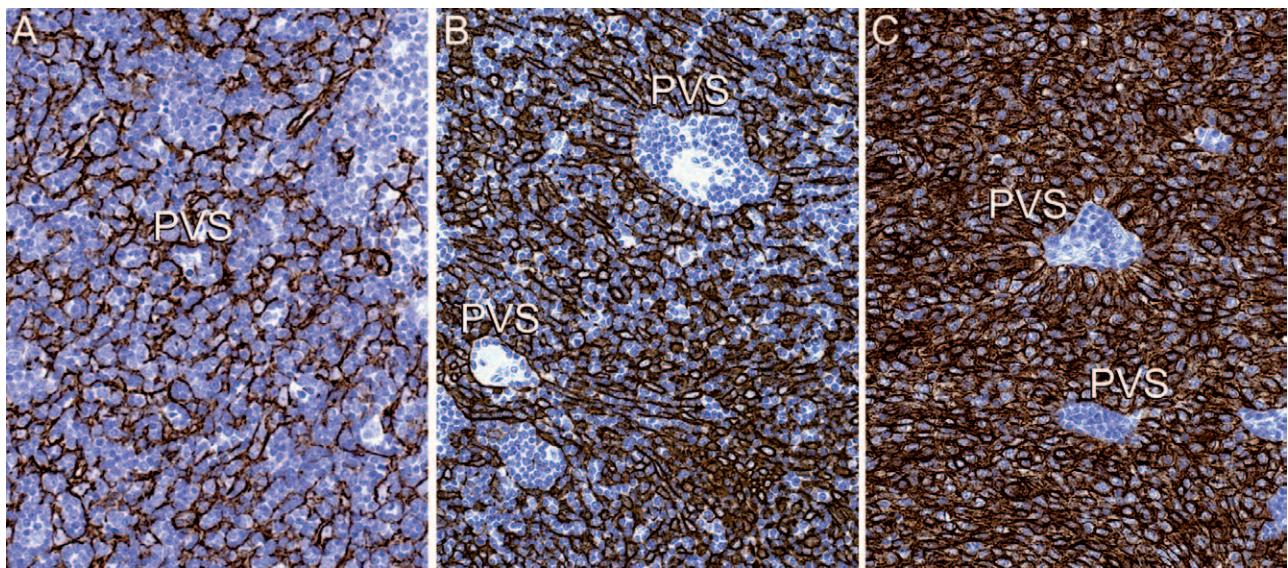


FIGURE 7. Density of epithelial cell networks and delineation of perivascular spaces (PVS) are helpful features to distinguish B1, B2, and B3 thymomas. *A*, Loose epithelial cell network and inconspicuous PVSs in B1 thymoma. *B*, Distinctly denser epithelial cell network and conspicuous PVSs in type B2 thymoma. *C*, Even denser epithelial cell staining in B3 thymoma (pancytokeratin antibody AE1/3, immunoperoxidase, $\times 200$).

TABLE 3. Major and Minor Histological Features of Type B1 Versus B2 Thymomas

	Type B1 Thymoma	Type B2 Thymoma
Major criteria		
Thymus-like pattern throughout	Consistently present	Rarely present ^a
Medullary islands (+/- Hassall's corpuscles)	Consistently present	Occasionally present ^a
Confluence of epithelial cells in cortical areas ^b	No (like in the NT)	Yes
Absence of type A areas (even if <10%)	Yes	Yes
Minor criteria		
Small lobular growth pattern	Rare	Common
Large lobular growth pattern	Common	Rare
Perivascular spaces	Commonly present	Commonly present
Keratin ^{+c} network like in NT	Yes	Denser than in NT

^aThese features are, therefore, minor criteria of type B2 thymomas.

^bDefined as at least three contiguous epithelial cells.

^cOn immunostaining.

NT, normal thymus.

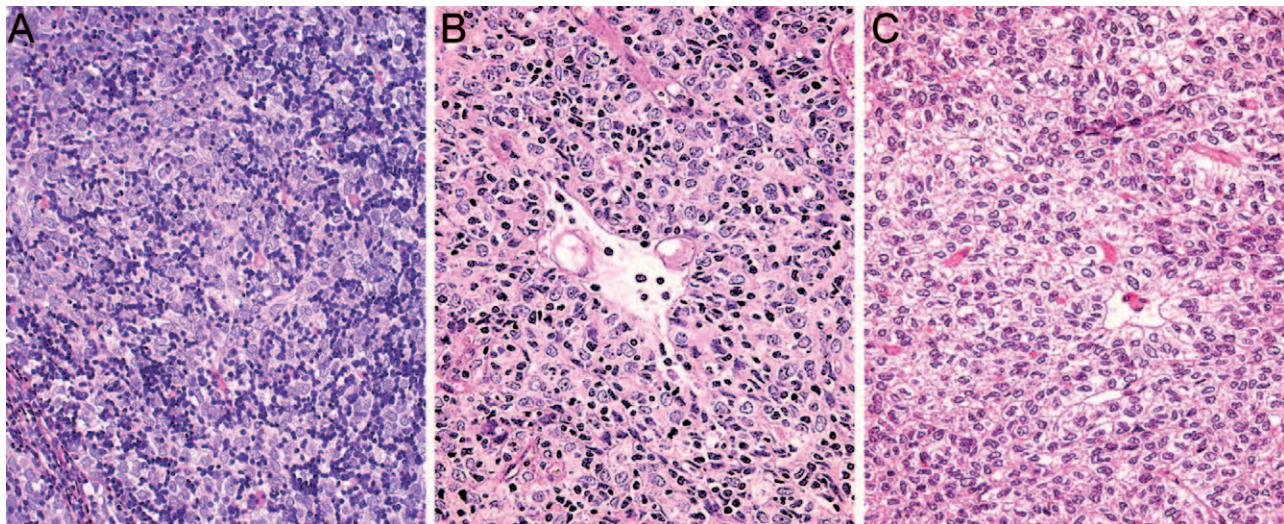


FIGURE 8. Distinction between type B2 and B3 thymomas. *A*, B2 thymoma: typically impression of a blue staining tumor on hematoxylin-eosin (H&E) staining due to the high content of lymphocytes. *B* and *C*, B3 thymoma: impression of a pink staining tumor due to the (variable) paucity of lymphocytes and abundance of lightly eosinophilic or clear epithelial cells (H&E, $\times 200$).

H&E-based thymoma diagnoses and the consensus diagnoses was more than 80% (Supplementary Table S2, Supplemental Digital Content 2, <http://links.lww.com/JTO/A577>). The high degree of ad hoc consensus suggests that poor interobserver reproducibility in some previous studies might have been due to imprecisely formulated diagnostic criteria.

New Criteria in Prototypic A and AB Thymoma

The WHO classification has been criticized^{9,12,13,33} for imprecise descriptions of A and AB thymoma and for calling them benign. First, there was agreement that A and AB thymomas are tumors of low malignant potential. Second, the description of A thymomas was refined by introducing immunohistochemical criteria: (1) the neoplastic epithelial cells of A thymomas lack cortical markers (e.g., the beta5t proteasome subunit) throughout the tumor; (2) the new criterion

of “paucity of immature T cells” was explicitly specified in terms of quantity of TdT+ cells: thymomas at the A/AB borderland with a more than 10% grade 2 component of TdT+ T cells are now classified as type AB thymomas. The proposed TdT grading and the 10% threshold were arbitrarily set and clearly need validation by clinicopathological correlation²³ in sufficiently sampled³² cases. Third, the potentially confusing term “B-like area” is now replaced by “lymphocyte-rich” component in AB thymomas,² although the presence of cortical markers in AB thymomas¹⁷ reveals some truth in the original term. Fourth, the criticized⁹ statement given in the WHO classification that lymphocyte-rich areas in AB thymomas harbor polygonal tumor cells is replaced: tumor cells in such areas are, indeed, typically spindly or oval. These new definitions and clarifications will likely make type A thymoma an even rarer entity.¹⁶

TABLE 4. Criteria for the Histological Diagnosis of TC

Major (indispensable)
Clear-cut atypia of tumor epithelial cells with the severity typical of carcinoma
Exclusion of “thymoma with atypia and/or anaplasia” and of typical or atypical carcinoids
Exclusion of metastasis to the thymus and germ cell and mesenchymal tumors with epithelial features
Minor (typical)
Infiltrative growth pattern
Small tumor cell nests within desmoplastic stroma
Absence of immature, TdT+ T cells (with rare exceptions)
Immunohistochemistry: epithelial expression of CD5, CD117; extensive expression of GLUT1, MUC1 ^a
Features compatible ^b with the diagnosis of TC
Invasion with pushing borders
Occurrence of perivascular spaces
Occurrence of “Hassall-like” epidermoid whorls and/or of myoid cells
Occurrence of (usually rare) immature, TdT+ T cells

^aCD5, CD117, GLUT1, and MUC1 are expressed by many nonthymic cancers.

^bAlthough most of these features are “organotypic,” that is, characteristic of thymoma, their presence does not exclude a diagnosis of TC if major diagnostic criteria of TC are fulfilled.

TC, thymic carcinoma.

The New Tentative Concept of Atypical A Thymoma

The long-held view that A thymomas are benign has prevented the general acceptance of aggressive type A thymoma variants.^{12–14} Based on the current series of type A thymomas many of which showed overt invasiveness and metastasis, there was agreement that the type A thymoma family includes a small subset of aggressive tumors. Nevertheless, a large unbiased cohort of randomly collected, clinically well-annotated type A thymomas needs to be studied to define the frequency of atypia and to define which one or which profile (if any) of the candidate atypia markers will predict aggressiveness in this variant of type A thymoma. Before such data are available, further subdivision of type A thymoma into different entities in analogy to the B1, B2, and B3 paradigm appears premature.¹⁴

Refined Criteria for the Distinction Between B Thymoma Subtypes

Classification of B thymomas has shown poor reproducibility: reported percentages of B1 thymomas have ranged widely from 5% to 35%,¹⁶ and series with low percentages^{6,34–36} often reported a more favorable outcome than series with high percentages of B1 thymomas (the latter series may, in fact, have been “contaminated” by the more aggressive B2 thymomas).^{10,37} The current study found that several previously suggested distinguishing criteria² are in fact shared by B1 and B2 thymomas and are only quantitatively different (Table 2). Nuclear size and atypia also did not reliably distinguish between B thymomas.^{9,38} Only two important criteria of B1 thymomas remained: absence of confluent epithelial cell clusters

outside the “palisades” of PVSS and low “thymus-like” epithelial cell content on H&E and keratin staining (Fig. 7; Supplementary Fig. S2, Supplemental Digital Content 4, <http://links.lww.com/JTO/A579>).

Most B2 and B3 thymomas are easily distinguished by their lymphocyte-rich (blue) and lymphocyte-poor (pink) microscopic appearance, respectively; however, they do form a continuum. Due to lack of “objective” (qualitative) markers, setting a threshold between them is somewhat arbitrary, and respective descriptions are prone to poor reproducibility. Therefore, borderland cases that were “eminently” attributed by consensus to either the B2 or B3 subtype are depicted in the B2 versus B3 gallery (Supplementary Fig. S3, Supplemental Digital Content 5, <http://links.lww.com/JTO/A580>).

Clarifying Borderlands Between Thymomas and TCs

Most TCs are easily distinguished from thymomas by their typical differentiation, degree of atypia, and loss of organotypic features. Nevertheless, distinction of B3 thymomas and thymomas with anaplasia from TC can be challenging. Following the principle that H&E structure “trumps” ancillary criteria, it was agreed that rare tumors that look like B3 thymomas on H&E but either express CD5/CD117 or lack TdT+ T cells as single “TC-associated” feature should be called B3 thymomas. Such tumors have indeed been described.³⁹ For tumors that looked like B3 thymomas on H&E but showed two features of TC, namely CD5/CD117 expression and lack of TdT+ T cells, we propose calling them “B3/TC borderline tumors”—in analogy to rare “grey zone lymphomas.”⁴⁰ In case of anaplasia, we kept the WHO concept: anaplasia occurring against a thymoma background should be mentioned in the diagnosis but should not entail a diagnosis of TC.

As to intratumorous TdT+ T cells in TC, the WHO classification states that TC lacks TdT+ T cells. Nevertheless, myasthenia gravis, which appears to depend on intratumorous thymopoiesis,^{41,42} has been described even in association with rare sarcomas that contained TdT+ T cells^{43,44} showing that intratumorous thymopoiesis is not necessarily restricted to thymomas. Therefore, the rare occurrence of TdT+ T cells in an otherwise typical TC is not sufficient to reassign the tumor to the category of thymoma. Analysis of a large number of cases of TC for TdT+ T cells is needed to determine the frequency of such cells in TC.

Thymic tumors with more than one tumor component are so common^{6,45} that we recommend modification of the rules for their reporting. First, we agreed that thymomas which are composed of different thymoma subtypes should no longer be called “combined thymomas.” Instead, in analogy to Gleason scoring, different components should be listed (and quantified with 10% increments) beginning with the predominant histology. Second, for statistical and study purposes, thymoma components of 10% or less in a thymoma can be disregarded and the given tumor classified according to the predominant component. The 10% threshold was found to be of prognostic relevance in one previous

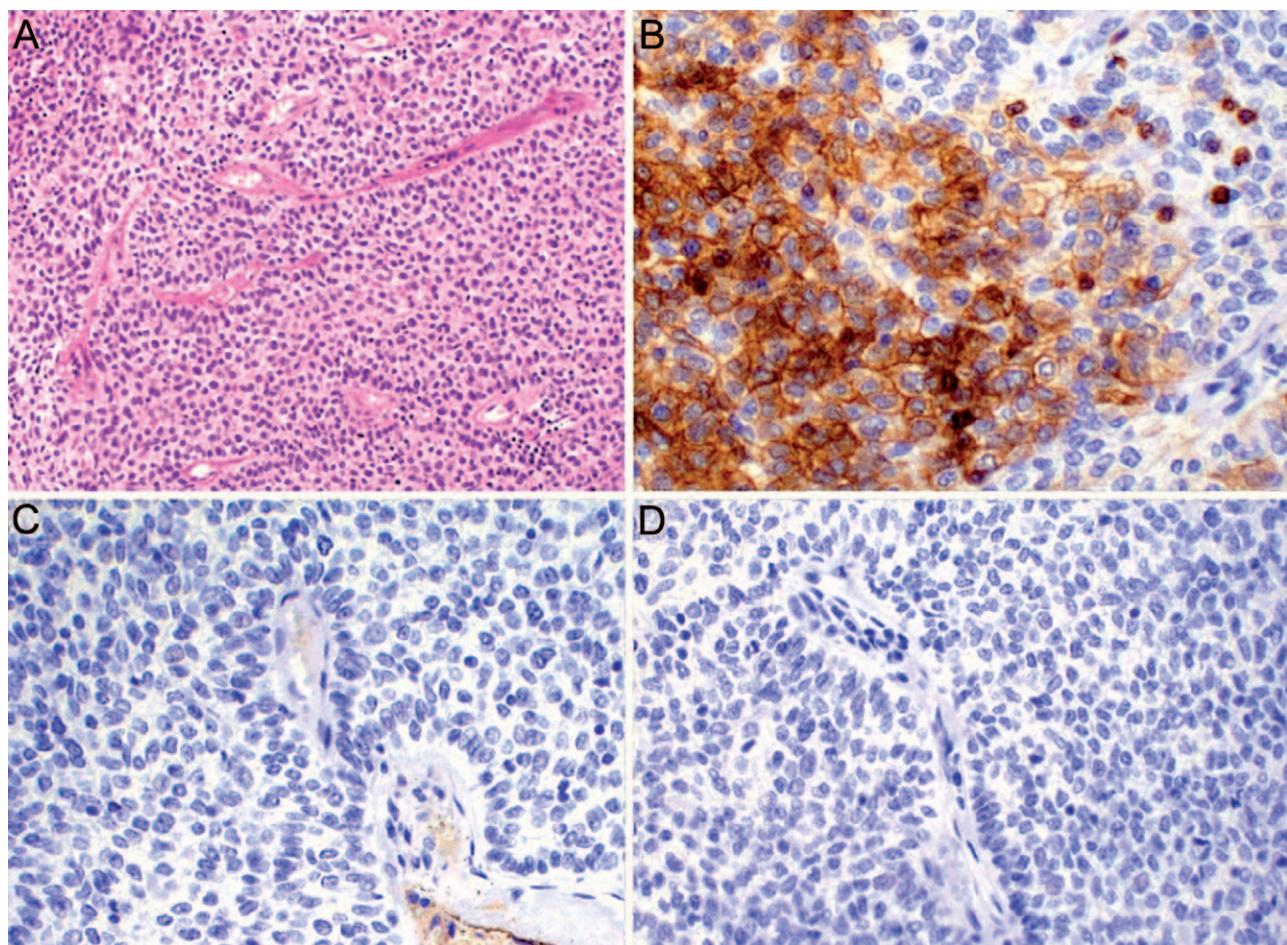


FIGURE 9. B3 thymoma/thymic squamous cell carcinoma borderline thymic epithelial tumor. *A*, Tumor with a B3 thymoma-like histology on hematoxylin-eosin (H&E) with perivascular spaces and minimal atypia but without lymphoid cells. *B* and *C*, Expression of CD5 (*B*) but not of CD117, chromogranin, and CD56 (*C*) in neoplastic epithelial cells. *D*, Absence of TdT+ T cells (*A*, H&E, $\times 100$; *B–D*, immunoperoxidase, $\times 100$).

study⁶ but needs independent reevaluation in biopsies and resection specimens. Third, there was consensus that the reporting of histologically heterogeneous thymic tumors comprising a carcinoma component should be different from the reporting of thymomas: such tumors should in the first place be labeled as carcinomas with listing of the proportion, differentiation, and grade, followed by the list of the thymoma component(s) as listed above.

Open Questions and Perspectives

First, the current proposals including the “gallery approach” to delineate thymoma subtypes from each other need to be tested for interobserver reproducibility. Second, to define the sensitivity and specificity of the proposed new criteria, they need to be tested by the current panelists in an independent, large series of randomly selected thymomas and TC. Third, multivariate analysis will be important to validate or adjust thresholds (e.g., the “10% rule”) or “re-refine” other criteria that so far are largely arbitrary, borrowed from the realm of lung cancer or mesothelioma pathology⁴⁶ or based on rare historic studies.⁶ A more

reproducible histological classification of thymomas and TCs may provide the foundation for developing a grading system for TETs that helps stratify tumors into clinically relevant, prognostic groups.² Currently, it is an open question whether the rare B1 and the common B2 thymomas as defined here are best counted among the low and intermediate grade TETs, respectively,^{6,23,34} or whether they should be considered members of the same grade.⁴ As reliable histological subtyping that reflects morphological diversity might mirror biological diversity including the expression of different therapeutic targets, future studies will have to investigate whether the refinements proposed here improve prognostic stratification and the predictive power of the WHO classification.

ACKNOWLEDGMENTS

The International Thymic Malignancy Interest Group was the main sponsor of the meeting; additional funding was provided by the European Society of Pathology.

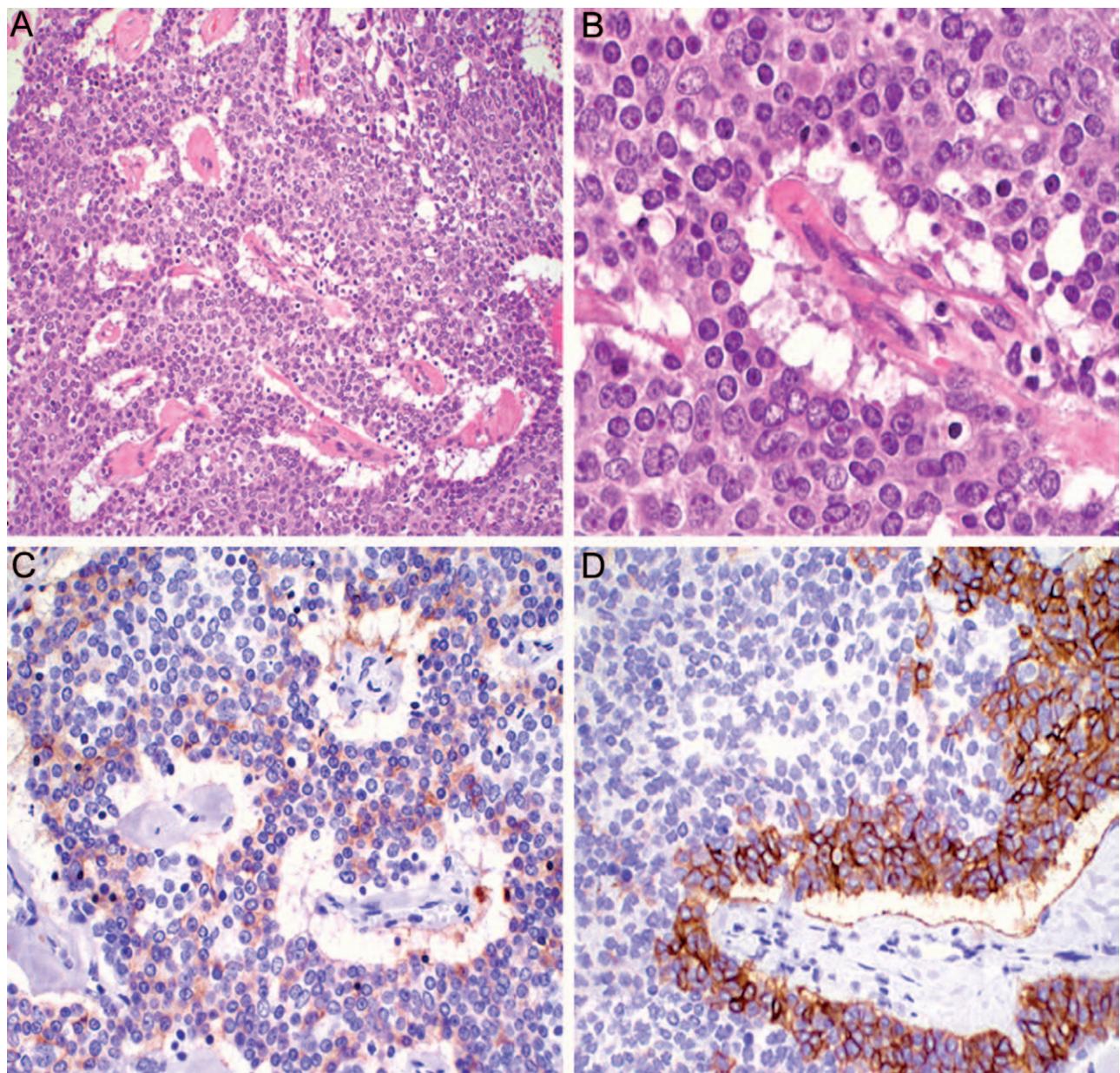


FIGURE 10. Thymic squamous cell carcinoma with organoid features (contributed by Prof. K. Mukai). *A* and *B*, Tumor with B3 thymoma-like architecture, including perivascular spaces, however with lack of lymphoid cells (absence of TdT expression, not shown) and with more nuclear atypia than the tumor shown in Figure 9. *C* and *D*, Moderate expression of CD5 and focal, strong expression of CD117 (*A* and *B* hematoxylin-eosin; *C* and *D* immunoperoxidase, $\times 100$).

APPENDIX 1. PARTICIPANTS OF THE INTERNATIONAL THYMIC MALIGNANCY INTEREST GROUP WORKSHOP AT THE MEMORIAL SLOAN-KETTERING CANCER CENTER, NEW YORK, MARCH 2011

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Maureen Zakowski (New York, NY), and Jie Zhang (Shanghai, China).

APPENDIX 2. PARTICIPANTS OF THE INTERNATIONAL THYMIC MALIGNANCY INTEREST GROUP SLIDE WORKSHOP AT THE INSTITUTE OF PATHOLOGY, UNIVERSITY MEDICAL CENTRE MANNHEIM, UNIVERSITY OF HEIDELBERG, MANNHEIM, GERMANY, DECEMBER 2011

Sunil Badve (Indianapolis, IN), Lara Chalabreysse (Lyon, France), John Chan (Hongkong, China), Gang Chen (Shanghai, China), Laurence de Leval (Lausanne, Switzerland), Frank Detterbeck (Thoracic Surgery, New Haven, CT), Nicolas Girard (Oncology, Lyon, France), Michael Kurrer (Zurich, Switzerland), Jim Huang (Surgery, New York, NY), Libero Lauriola and Mirella Marino (Rome, Italy), Alexander Marx (Mannheim, Germany), Yoshihiro Matsuno (Sendai, Japan), Thierry Molina (Paris, France), Kiyoshi Mukai (Tokyo, Japan), Andrew Nicholson (London, United Kingdom), Daisuke Nonaka (Manchester, United Kingdom), Ralf Rieker (Erlangen, Germany), Juan Rosai (Milano, Italy), Philipp Ströbel (Mannheim, Germany), and William Travis (New York, NY).

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