On the Histologic Heterogeneity of Thymic Epithelial Neoplasms: Impact of Sampling in Subtyping and Classification of Thymomas

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Abstract and Introduction

Abstract

Six hundred thirty cases of thymomas were evaluated to determine morphologic heterogeneity. The thymomas were grouped in 4 categories using previous terminology. Stratification according to the number of sections available for examination revealed a marked difference in distribution by histopathologic type. A cutoff number of 5 sections appears to provide a difference in subgrouping these tumors. In addition, the proportion of invasive tumors increases with the number of sections examined. Final classification may be affected by the extent of sampling. Histopathologic classification of thymoma, although of academic interest, may have limited practical relevance for assessment of prognosis in limited biopsy tissue. Proper evaluation of histology and aggressive potential in thymoma should be based on ample sampling and assessment of capsular integrity, which is best accomplished on thoroughly sampled resection specimens rather than incomplete or limited biopsy samples.

Introduction

Thymic epithelial neoplasms have been the subject of much controversy over the years owing to difficulties in predicting prognosis and behavior. Because of the complexity of these tumors, several attempts at classification have been presented in the literature.[1-5] Nevertheless, major drawbacks and reluctance to accept many of these classifications have been acknowledged, with the majority of studies suggesting that histopathologic features in these tumors in general correlate poorly with prognosis.[6-11] Currently, the controversy has been exacerbated by the fact that some investigators believe that histologic subtyping of thymomas is a predictor of progno-sis,[2,3,12-14] while others believe that staging of the tumor at the time of diagnosis remains the single most important parameter for the assessment of these tumors. Whether subtyping or staging are independent prognostic factors remains unsettled.

The present study emphasizes the importance of sampling in the evaluation of thymic epithelial neoplasms and highlights the histologic heterogeneity of these tumors. Our results indicate that histologic categorization of these tumors may not be reliable when based on insufficient or limited sampling, such as biopsy material. Furthermore, it underscores the importance of extensive sampling for the assessment of capsular invasion, a reliable prognostic factor for the assessment of clinical behavior in these tumors.

Materials and Methods

A total of 1,428 cases accessioned under the diagnosis of thymoma were retrieved from the files of the Department of Pulmonary and Mediastinal Pathology, Armed Forces Institute of Pathology, Washington, DC; the Department of Pathology, Mount Sinai Medical Center, Miami, FL, and from the personal consultation files of both authors between January 1954 and January 1997. Of the cases retrieved, 798 cases were excluded because of lack of adequate histologic material, incomplete clinical information, or reclassification into a different diagnostic category because the slides corresponded to biopsy material only. The 630 cases that form the basis of this study represent cases in which a surgical resection of the tumor was performed and for which clinical information and histologic material were available for evaluation. The number of sections available for review in all cases ranged from 1 to more than 10 per case. Most of the material studied was received in consultation. Therefore, a bias may exist in the material analyzed.

Cases were divided into 4 major groups depending on specific histologic features, in accordance with previously published classifications.[1-3,5] The groups are as follows:

- Group 1: Cortical, predominantly cortical, organoid, lymphocyte-rich, mixed lymphocytic-epithelial thymomas

- Group 2: Spindle cell and medullary thymomas
- Group 3: Predominantly epithelial thymoma, atypical thymoma, and polygonal cell thymoma and well-differentiated thymic carcinoma
- Group 4: Mixed (Marino and Muller-Hermelink[3]), medullary and cortical, lymphocyte-rich and spindle cell, epithelial-rich and spindle cell, and epithelial-rich and lymphocyte-rich thymomas, well-differentiated thymic carcinoma and spindle cell thymoma or cortical thymoma or lymphocyte-rich thymoma

Each group of tumors was matched with the number of sections studied per case.

Results

The results of the present study comparing the number of sections studied with the final classification of the tumors are given in Table 1.

Group 1 Image 1 consisted of 229 cases and accounted for the largest percentage of cases in the study (36.3%). In this group, 25 cases (10.9%) were invasive. In group 1, fewer than 5 sections were available for review in 129 (56.3%) of 229 cases. The 157 tumors in group 2 Image 2 accounted for 24.9% of the total cases studied, with 32 cases (20.4%) representing invasive thymomas. Approximately 75% of the cases in this group had fewer than 5 sections available for review (117/157). Group 3 Image 3 comprised 55 tumors and accounted for 8.7% of all cases studied; 14 cases in this group (25%) were invasive. Approximately two thirds of the cases in group 3 (36/55) had fewer than 5 sections available for review. Group 4 Image 4 included 189 tumors and accounted for 30% of the cases studied. In this group, 23 cases (12.2%) were invasive. Fewer than 50% of the cases in this group (84/189) had fewer than 5 sections available for review.

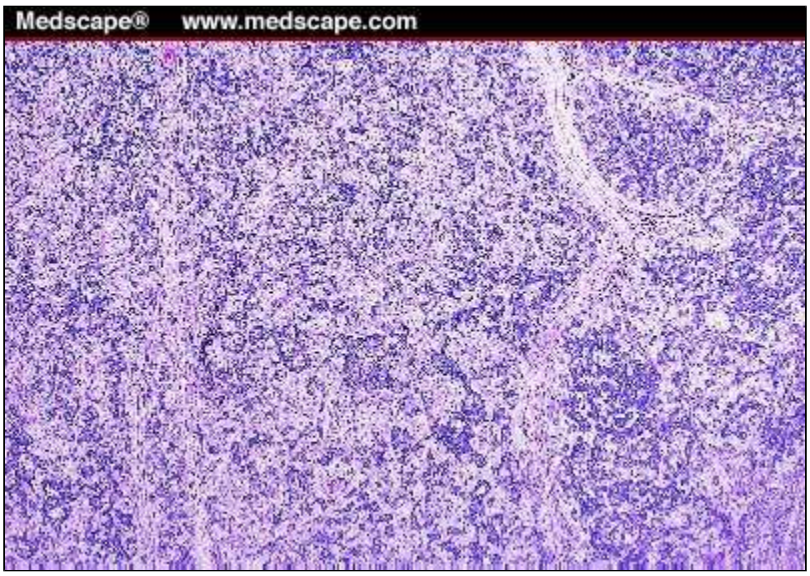

Image 1. Thymoma group 1, mixed epithelial/lymphocytic-cortical thymoma (H&E, x50).

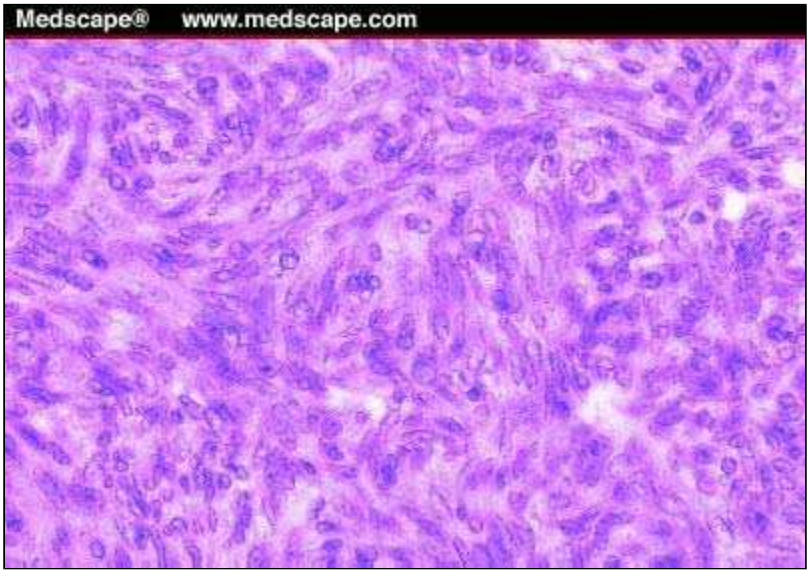

Image 2. Thymoma group 2, spindle cell thymoma-medullary thymoma (H&E, x75).

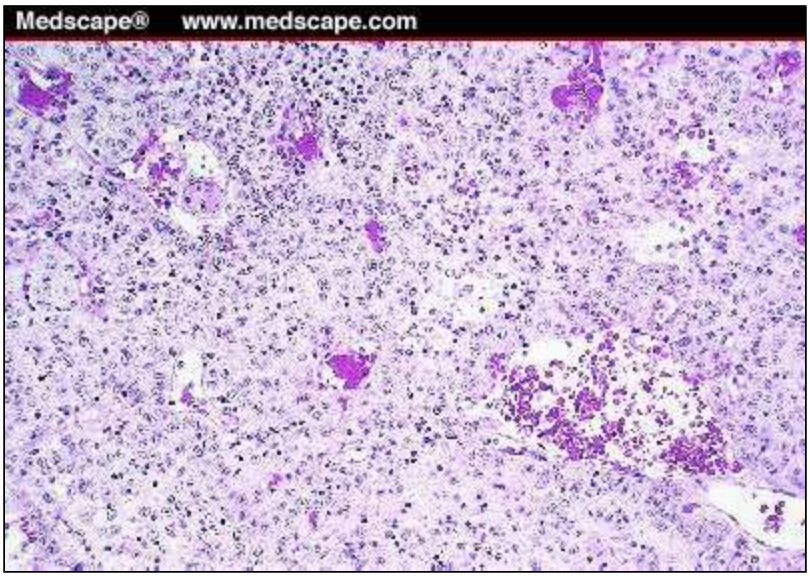

Image 3. Thymoma group 3, atypical thymoma-well-differentiated thymic carcinoma (H&E,x60).

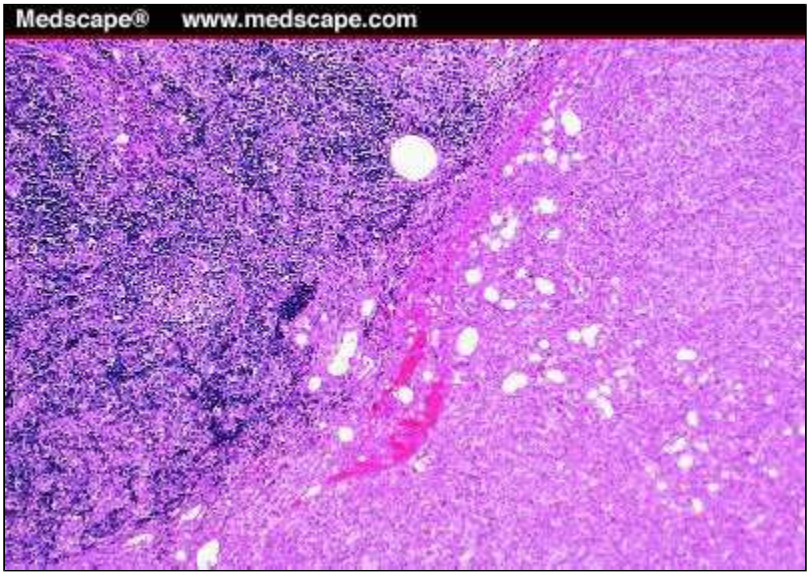

Image 4. Thymoma group 4, mixed histologic features (H&E, x60).

When the tumors were separated based on the number of sections studied, important differences were observed in the distribution of the histopathologic diagnostic categories, depending on whether fewer than 5 sections or 5 or more sections were available for review. The number of cases that could be categorized in group 1 remained approximately the same irrespective of the number of sections available for review (36.3% for the entire group overall, 35.2% for cases with fewer than 5 sections available for examination, and 37.9% for cases with 5 or more sections available for examination), but the proportions varied substantially for the other groups Table 2.

In group 2, 117 cases had fewer than 5 sections available for examination compared with 40 cases for which 5 or more sections were available. Group 2 thymomas thus corresponded to 32.0% of the total number of cases with fewer than 5 sections compared with only 15.2% of those with 5 or more sections available for review, indicating that when more sections are available for review, chances are lower that any given case will be categorized as a pure spindle or "medullary" thymoma. In the present study, when 5 or more sections were available for review, the number of cases that could be categorized as pure spindle or medullary thymoma was reduced to half of that of the group with fewer than 5 sections.

In group 3, 36 cases had fewer than 5 sections available for examination compared with 19 cases for which 5 or more sections were available. Group 3 thymomas thus accounted for 9.8% of the total cases with fewer than 5 sections compared with 7.2% of those with 5 or more sections available for review.

In group 4, 84 cases had fewer than 5 sections, and 105 had 5 or more sections available for review. Group 4 thymomas thus accounted for 23.0% of the total cases with fewer than 5 sections compared with 39.8% of those with 5 or more sections, thus confirming the observation that when a larger number of sections is available for review, the likelihood is increased that a tumor will be classified as mixed. In the present study, the number of tumors displaying mixed histologic features increased when 5 or more histologic sections were available for examination compared with cases in which mixed features could be identified with fewer than 5 sections.

The sampling factor also seems to influence the incidence of invasiveness, although to a lesser extent. In the present study, 94 cases showed gross and/or histologic evidence of invasion accounting for 14.9% of the total cases in the study. Invasiveness was observed in all histologic groups (Table 1). There were 25 invasive tumors in group 1 (10.9% of this group), 32 in group 2 (20.4% of group 2), 14 in group 3 (25% of group 3), and 23 in group 4 (12.2% of group 4). When tumors were analyzed by number of sections, there was a mild increase in the number of invasive tumors for those in which 5 or more sections were available for review (52 cases) compared with those with fewer than 5 sections (42 cases). Interestingly, the most striking differences were observed for group 4, in which the number of invasive cases more than doubled when 5 or more sections were available for review.

Discussion

Over the years, there has been great controversy about the best manner to correlate histologic features of thymoma with clinical behavior and prognosis. In 1955, Castleman[15] stated that it was not only difficult but also hazardous to try to classify thymomas based on the embryonic development of the thymus gland and added that, owing to the many variations within a given tumor, there were no foolproof criteria based on histologic features that would allow separation of those tumors limited to the thymus from those that infiltrated adjacent structures. In 1961, Bernatz et al[1] described 138 cases of thymoma and presented a histologic classification

based on the relative proportion of lymphocytes to epithelial cells and on the shape of the epithelial cells. This histologic classification, which had been applied previously in a somewhat modified form by Castleman[15] and by Lattes and Jonas,[16] essentially divided these tumors into 4 groups: lymphocyte-rich, epithelial-rich, mixed, and spindle cell type. The authors noted the existence of invasive thymomas across all of their histologic types and concluded that when these tumors are invasive, the outcome is similar regardless of the histologic subtype.

Salyer and Eggleston[17] observed that invasive growth of thymoma could not be predicted by the histologic type and that invasion or implants occurred with all histologic variants. In 1976, Rosai and Levine[18] reiterated Castleman's view expressed more than 20 years earlier and concluded that histologic subclassification of thymoma was of limited prognostic value and that the status of capsular invasion was a more reliable feature for the assessment of clinical behavior in these tumors. The concept thus emerged that assessment of capsular integrity (ie, staging) was far more important for prognostication of clinical behavior than histologic subclassification, a contention that has been supported by many other published studies.[19-30]

The topic of histologic heterogeneity in thymoma also has been cited frequently in the literature. Lattes and Jonas,[16] in a study of thymoma, pointed out the need for examining multiple sections for proper histologic categorization owing to the great variation in histologic composition. Salyer and Eggleston,[17] in their study of thymoma, acknowledged that assigning these tumors to various histologic types was a subjective exercise, considering the variation of pattern and cell predominance within a given tumor, and regarded histologic subcategorization of thymoma as "somewhat arbitrary." They pointed out, for example, that an area that is predominantly epithelial may be present in an otherwise predominantly lymphocytic tumor. They also highlighted the fact that although tumors classified as mixed in the scheme by Bernatz et al[1] are represented by tumors with an approximately equal amount of lymphocytes and epithelial cells, the size and shape of the epithelial cells can vary widely. They further speculated that some of the apparent variances observed between the reported series may have been the reflection of subjective differences in histologic categorization by the respective investigators.

Lewis et al,[31] in a large clinicopathologic review of thymoma from the Mayo Clinic, Rochester, MN, acknowledged that histologic classification of the tumors was made difficult because the ratio of epithelial cells to lymphocytes seems to comprise a continuous spectrum, and many variations may be found within a given tumor. The concept of heterogeneity in thymomas has been supported further by immunohistochemical studies. Studies have demonstrated that the proliferating epithelial cells in thymoma show a range of expression and frequently coexpress antigens presumed to be specific for cortical and medullary epithelial cells of the thymus.[32,33]

The belief that histologic subtyping of thymoma is inferior to evaluation of invasiveness for the prognostication of these tumors has been challenged in recent years. In 1985, Marino and Muller-Hermelink[3] presented a new histologic classification of thymoma that divided these tumors into cortical, medullary, and mixed based on the putative similarities of the tumor cells to 2 of the normal compartments of the thymus gland. The authors stated that these 3 categories reliably correlated with invasiveness. It should be pointed out that the mixed category in the Marino and Muller-Hermelink classification differs from that of the classification of Bernatz et al[1] in that in the former, mixed thymoma refers to tumors displaying clearly identifiable areas of cortical and medullary thymoma existing side by side within the same tumor mass, whereas in the latter, mixed refers to an equal admixture of thymic epithelial cells with lymphocytes. The introduction of this new concept of mixed thymoma was very important, since it acknowledged a much neglected fact in many of the previous classifications, ie, that many of these tumors can and indeed often do contain areas in which the neoplastic epithelial cells can adopt a round, polygonal, and spindled appearance within the same tumor mass, resulting in tumors that harbor an admixture of growth patterns that span the gamut of histologic subtypes described for various classifications.

A few years later, Kirchner and Muller-Hermelink[34] revised this classification and introduced 2 new categories, predominantly cortical (also designated as organoid) thymoma and well-differentiated thymic carcinoma. A number of studies in support of the classification by Marino and Muller-Hermelink3 have been presented in the literature.[13,14,35,36] The majority of these studies seem to support the contention that the various histologic types in the "histogenetic" classification of Marino and Muller-Hermelink[3] closely correlate with invasiveness and, therefore, can reliably serve to predict clinical behavior for these tumors. Moreover, the majority of these studies seem to indicate that the medullary and mixed categories represent entities that are biologically distinct from cortical and well-differentiated thymic carcinoma, the latter following a more aggressive clinical behavior, while the former essentially represents benign, noninvasive, nonmetastasizing neoplasms. However, in the majority of these studies, there has been a lack of information about the number of sections studied per case. In addition, in many of these studies, the information has been based largely on tumors that were studied by biopsy samples alone. The effect of tumor sampling and histologic heterogeneity in the final histologic classification for the studies supporting the Muller-Hermelink classification has thus not been adequately documented.

In the present study, we compared the effect of tumor sampling on histologic classification in a large cohort of patients with thymoma who underwent complete surgical excision as their primary treatment. Our study demonstrated that final histopathologic classification into any of the currently available classification schemes could vary considerably depending on the number of sections examined. The greatest variations were observed for histologic groups 2 and 4. When fewer than 5 histologic sections were available for review, 32.0% of the tumors were classified into group 2; when 5 or more sections were available for review, fewer than half the number of cases (15.2%) could be classified into this group. The inverse phenomenon was observed for group 4 lesions; when fewer than 5 sections were available for review, only 23.0% of cases could be classified in this group, whereas when 5 or more sections were examined, the proportionate number of tumors classified as mixed was substantially higher (39.8%). These findings seem to indicate that when more tissue sections are examined per case in thymomas, there will be a lesser likelihood that a tumor will be classified as

the pure type, at the expense of an increase in the number of mixed cases.

These findings not only have some bearing on the significance of histologic categorization for prognostication in thymoma but they also raise the issue of the validity of previous studies addressing histogenetic and other classification schemes based on the study of limited histologic material. It is of interest that in the present study, invasive tumors could be identified in all of the histologic groups. Most notably, the largest percentage of invasive tumors corresponded to group 2, a type of tumor deemed to be benign and rarely invasive by the proponents of the Muller-Hermelink classification.[13,14,37-40]Moreover, the number of invasive tumors increased slightly when 5 or more histologic sections were available for review, indicating that the extent of sampling also may influence the probability of finding invasion in a given neoplasm.

Furthermore, it is noteworthy to mention that approximately 15% of thymomas in our series were invasive lesions regardless of their histologic subtype. This reinforces our opinion that thymomas should be regarded as potentially malignant neoplasms regardless of the histologic subtype, with a clear-cut potential for recurrence and metastasis if untreated.[41-48]

One important question that is drawn from this study pertains to the issue of proper sampling of these tumors. We consider that these tumors should be handled in a manner similar to uterine smooth muscle tumors for the purpose of adequate tissue sampling. We recommend that at least 1 section be taken per centimeter of tumor diameter, or a minimum of 10 sections for tumors of considerable size. In addition, it is important to ink the outer surface of the gross specimen to determine the extent of infiltration beyond the capsule by tumor and the adequacy of the surgical resection margins.

The present study underscores the histologic heterogeneity of thymoma and indicates that final classification may be affected by the extent of sampling, with more cases falling into the mixed category when more sections are examined. These findings suggest that histologic subclassification of thymoma, although of academic interest, may be of limited practical relevance for assessment of prognosis, particularly with limited biopsy material or in incompletely sampled cases.

Tables

Table 1. Comparative Analysis Between Number of Sections and Subtype of Thymomas for 630 Cases*

	Group 1		Group 2		Group 3		Group 4		Total	
No. of Sections	No. (%)	Invasive	No. (%)	Invasive	No. (%)	Invasive	No. (%)	Invasive	No.	Invasive
1	33 (36)	1	33 (36)	2	11 (12)	0	15 (16)	1	92	4
2	38 (37.6)	4	38 (37.6)	4	3 (3.0)	0	22 (21.8)	3	101	11
3	26 (27)	3	29 (30)	6	13 (13)	4	29 (30)	2	97	15
4	32 (42)	4	17 (22)	6	9 (12)	1	18 (24)	1	76	12
5	25 (33)	1	18 (24)	4	4 (5)	2	29 (38)	4	76	11
6	17 (39)	3	5 (11)	2	2 (5)	0	20 (45)	1	44	6
7	20 (57)	4	2 (6)	2	4 (11)	3	9 (26)	1	35	10
8	12 (39)	1	5 (16)	3	2 (6)	1	12 (39)	2	31	7
9	6 (40)	1	3 (20)	0	0 (0)	0	6 (40)	1	15	2
10	20 (32)	3	7 (11)	3	7 (11)	3	29 (46)	7	63	16
Total	229 (36.3)	25 (10.9)	157 (24.9)	32 (20.4)	55 (8.7)	14 (25)	189 (30.0)	23 (12.2)	630	94 (14.9)

* The percentages for invasive tumors (given in parentheses) are based on the group total. Group 1 includes cortical, predominantly cortical, organoid, lymphocyte-rich, and mixed epithelial-lymphocytic thymomas; group 2, medullary and spindle cell thymomas; group 3, predominantly epithelial, polygonal cell, and atypical thymomas and well-differentiated thymic carcinoma; and group 4, mixed thymomas: medullary and cortical, lymphocyte-rich and spindle cell, epithelial-rich and spindle cell, and epithelial-rich and lymphocyte-rich thymomas.

Table 2. Comparison of Histologic Groups of Thymoma for 630 Cases With Fewer Than 5 Sections vs 5 or More Sections*

Histologic Group	<5 Sections (n = 366)	>/=5 Sections (n = 264)
1	129 (35.2); invasive, 12	100 (37.9); invasive, 13
2	117 (32.0); invasive, 18	40 (15.2); invasive,14
3	36 (9.8); invasive, 5	19 (7.2); invasive, 9
4	84 (23.0); invasive, 7	105 (39.8); invasive, 16

* Data are given as number (percentage). Group 1 includes cortical, predominantly cortical, organoid, lymphocyte-rich, and mixed epithelial-lymphocytic thymomas; group 2, medullary and spindle cell thymomas; group 3, predominantly epithelial, polygonal cell, and atypical thymomas and well-differentiated thymic carcinoma; and group 4, mixed thymomas: medullary and cortical, lymphocyte-rich and spindle cell, epithelial-rich and spindle cell, and epithelial-rich and lymphocyte-rich thymomas.

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