Original Article

Thymoma diagnosis and categorization in the current scenario: Morphological analysis based on interobserver variability

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Abstract:

BACKGROUND: Thymomas are not so common tumors that are encountered in day-to-day pathology reporting. The WHO system was proposed in 2015. Although, through its detailed reporting, the WHO elaborates all subtypes and morphological clinches to diagnosis, it was important to ascertain its reproducibility in our day-to-day reporting.

AIMS: The aims of the study were (1) to study the interobserver agreement, concordance rates, and variability in the classification of a large number of thymomas received in our department as per the WHO 2015, (2) to correlate the WHO subtype with Masaoka–Koga stage, and (3) to study the variations in demography of thymomas in Indian patients as compared to those reported in the literature.

SETTING AND DESIGN: This retrospective study was done at a tertiary care teaching hospital with huge surgical oncology patient load, also pertaining to the cardiothoracic surgeries. It is predominantly an interobserver agreement design to study the reproducibility of the WHO 2015 classification on thymic epithelial tumors.

METHODS: Four pathologists have independently reviewed histopathology slides of 65 cases of thymomas and classified them into predefined categories. Kappa statistics was applied to the observations.

RESULTS: There was a substantial interobserver agreement in overall classification of thymomas with a Cohen's kappa score of 0.66. A better score was achieved for the classification of Group B thymomas. The WHO subtypes correlate well with the Masaoka–Koga staging system, and this finding is statistically significant. This article also presents the clinical details of a large number of thymoma cases.

CONCLUSION: The new WHO classification has good reproducibility among pathologists in thymoma reporting.

Keywords:

Classification, thymoma, thymus

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Thymomas are uncommon neoplasms arising from the thymic epithelium. The diagnosis is challenging, and the experience of individual pathologists is limited. Like many other rare cancers, the diagnosis and prognostication of thymomas require standard guidelines. Tumor size, histological subtype, and extent as defined by the Masaoka–Koga staging system are relevant prognostic factors.[1,2] Various classification systems for histological subtyping[3-6] have existed in the past – the WHO system was proposed in 1999,[7] modified in 2004,[8] and

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revised in 2015[9] with an intention to provide a universal formula to facilitate consensus and comparison among the existing classifications.

The WHO system divides thymic epithelial tumors into six clinically relevant categories – A, AB, B1, B2, B3, and thymic carcinoma. Although many authors have shown the clinical and prognostic relevance of the system, there have been arguments and controversies regarding the use of simpler classification systems for increasing interobserver concordance rates. Still, it continues to be the most widely used system; few studies have actually tested the reproducibility of the WHO system and the ease of its application in day-to-day reporting; further, there is less Indian literature in this regard.

The present study aims (1) to study the interobserver agreement, concordance rates, and variability in classification of a large number of thymomas received in our department as per the WHO 2015, (2) to correlate the WHO subtype with Masaoka–Koga stage, and (3) to study the variations in demography of thymomas in Indian patients as compared to those reported in the literature.

Methods

Surgically resected thymomas for various indications were retrieved from our records over 8 years (2010–2017). Presenting features and surgical and operative details were noted from the patient files. Masaoka–Koga and tumor node metastasis staging as Stage I, II, III, and IV had been done wherever relevant.[2] All cases were analyzed for the presence or absence of capsular invasion, mitosis, nuclear pleomorphism, and changes in the adjacent thymic tissue.

Instructions to classify thymomas into six WHO categories were circulated to four participating histopathologists. Each of them had access to classification criteria and detailed illustrations from the WHO blue book. An average of 4–6 sections including tumor with capsule was analyzed for each case. Briefly, the salient criteria are summarized in Figures 1-5, with the legends highlighting morphological description of the same. All the participants were blinded to others' results, i.e., the clinical, gross, and operative details of the cases. Diagnosis of a case was considered concordant if all four authors agreed on the same. Discordant cases were reanalyzed for arriving at a consensus diagnosis.

For statistical analysis, Chi-square test and Cohen's kappa for multiobserver agreement were used. Briefly, Cohen's kappa is a statistical parameter that helps evaluate the interobserver agreement and reliability. It takes into consideration, agreement occurring due to chance. Value of kappa was interpreted according to the existing standards.[10] "P" < 0.05 was considered statistically significant.

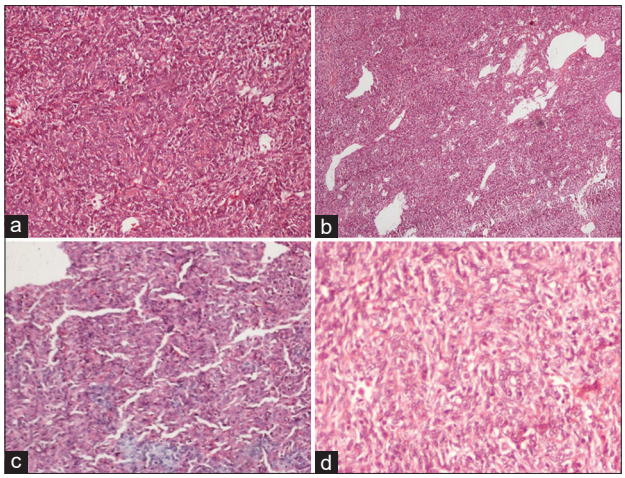

Figure 1: (a) The presence of fascicles and/or storiform arrangement which is (b) often intercepted by the presence of microcysts or (c) a prominent hemangiopericytomatous pattern (H and E, ×100). (d) The individual cells have oval nuclei with scant cytoplasm; lymphocytes are not discernible (H and E, ×200). These features characterize Type A thymomas

Results

Of a total of 140 thymectomies (for various indications) during the study period, there were 65 cases of thymomas. Presenting features for thymomas were myasthenia gravis in 27, pressure symptoms in 21, pain in 5, and incidental detection in 7 cases. As per the WHO categories, Type A, AB, B1, B2, B3, and C accounted for 12, 12, 13, 18, 4, and 2 cases, respectively. The remaining four cases were assigned to the combination B2–B3 category and two of these were agreed on by consensus. The mean age at presentation was comparable among all categories. Type B1 was the most common thymoma presenting with myasthenia gravis in nine cases. Incidental detection was most common with B2 thymoma. These results are summarized in Table 1.

The value of kappa with consideration of all six WHO categories was 0.66, which amounted to substantial agreement. Within the "bioactive" B category, the value of kappa improved to 0.73 (substantial agreement). Overall concordance (agreement among all four panelists) was seen in 50/65 (76.9% cases). Four cases were discordant between all four authors. Of these, two were initially assigned as either B2 or B3 to assign a definite WHO category. The remainder two cases were AB with predominantly B1 type areas and restriction of spindle cell component to a single small focus. All the cases were finally agreed on by a detailed morphological analysis with the help of the WHO blue book.

The correlation of the individual WHO categories with Masaoka–Koga stage is showed in Table 2. Tumor

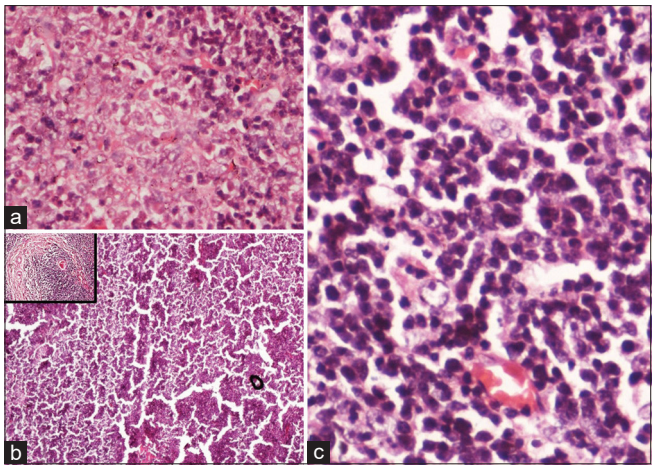

Figure 2: (a) Type AB thymoma has discreet Type A areas with spindle-shaped cells and Type B areas, which in this study were mostly lymphocyte rich Type B1 or B2 areas (H and E, ×400). (b) Type B1 thymomas show the presence of abundant lymphocytes and epithelial cells that are found with difficulty, sometimes requiring immunohistochemistry. Most of the epithelial cells are singly scattered; no large groups or clusters are found (H and E, ×40). Inset shows occasional Hassall's corpuscles. (c) High-power field of polygonal epithelial cells with vesicular nucleus and prominent nucleoli

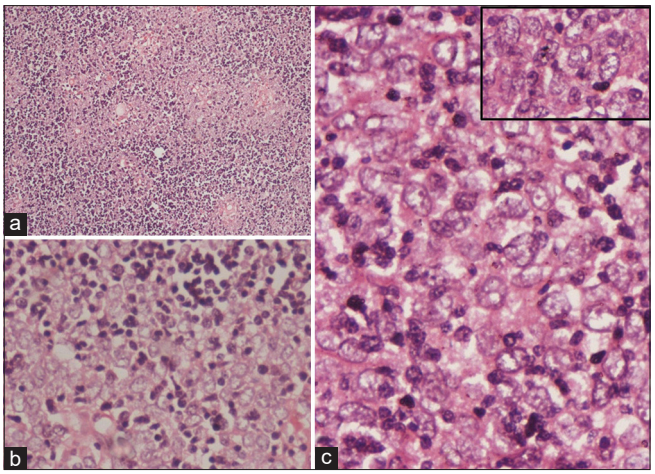

Figure 3: Type B2 thymomas characterized by (a) variable admixture of lymphocytes and epithelial cells (H and E, ×100). (b) When compared to B1 thymomas, the epithelial cells are much easily found (H and E, ×200). The epithelial cells may be in sheets or in groups (c) However, lymphocytes even if few are present (H and E, ×400). The cells have clear chromatin with prominent nucleoli. Mild anisonucleosis may be present (inset). However, overt pleomorphism or nuclear atypia is absent

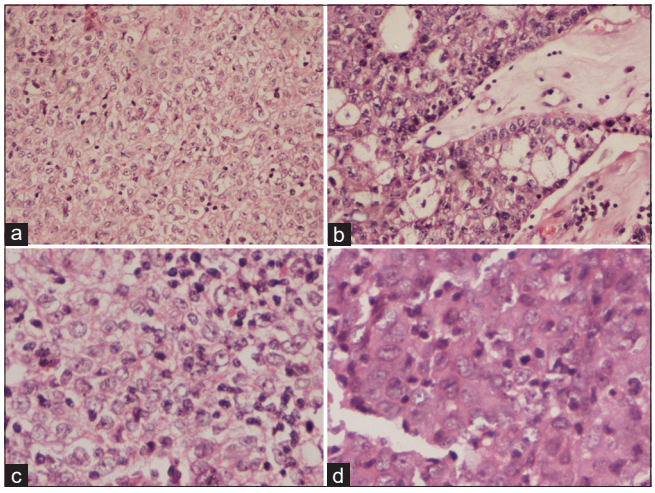

Figure 4: (a-d) Type B3 thymomas are characterized by sheets of polygonal epithelial cells with mild to moderate anisonucleosis with sparse or no discernible lymphocytes. Prominent epithelial formations, e.g., perivascular palisading may be seen (H and E, ×200)

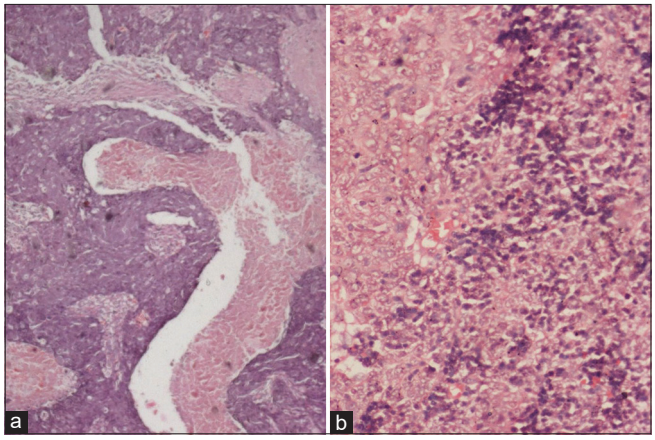

Figure 5: (a) Grossly invasive tumor with large areas of necrosis (H and E, ×100). (b) Combination of B2–B3 with distinct areas in both. In this category, percentage of each component decides prognosis

entirely confined by the capsule (Masaoka–Koga Stage I) was seen in 83%, 75%, and 92% of Type A, B1, and AB, respectively. Extension into and beyond the capsule (Masaoka–Koga Stages II–IV) was increasingly seen among Type B2 (33.3%), B3 (75%), B2–B3 (50%), and C (100%). For statistical analysis, the categories A, AB, and B1 were clubbed together in one broad group, as were B2, B3, B2–B3, and C. Tumors confined by the capsule (Masaoka–Koga I) are known to have a survival advantage when compared to those showing microinvasion into or invasion beyond capsule (Masaoka–Koga II–IV). In this context, application of Chi-square test to the results obtained showed that advanced WHO subtype is associated with higher Masaoka–Koga stage; the difference being statistically significant ($P = 0.017$) [Table 2-Part 2].

Discussion

In this study, 65 thymomas were classified according to the WHO scheme and substantial interobserver agreement was obtained. Type B2 was the most common subtype of thymomas and B1 was the type most frequently associated with myasthenia gravis. Combination B2–B3 thymomas were as common as B3 thymomas.

Comparisons between the various classification systems have been long debated.[3-8] Although the previous classifications were morphologically accurate, they lacked clinical accuracy. More debatable was the categorization of tumors of this functionally dynamic

Table 1: Presentation details of various categories of thymomas

WHO subtype	Number (percentage of total)#	Mean age (years)	Male: female ratio	Myasthenia gravis present	Other pressure symptoms	Adjacent thymus changes*
Type A	12 (18.5)	44.9	5:1	7	Pain, pressure s/s, incidental in 1 case	Follicular hyperplasia-1. Rest*
Type AB	12 (18.5)	52.5	1.4:1	4	Pain, pressure s/s, incidental in 2 cases	Morphology within normal limits*
Type B1	13 (20)	43.5	3.3:1	9	Pain, pressure s/s, palpitations, SOB, incidental in 4 cases	Follicular hyperplasia-1, thymic cyst-1. Rest*
Type B2	18 (28)	40.5	1.6:1	7	Pain, pressure s/s	Follicular hyperplasia-1, multilocular thymic cyst-1. Rest*
Type B3	4 (6)	52.6	3:1	0	Pain, pressure s/s	Not included in the specimen
Type B2-B3	4 (6)	50	4:1	0	Pain, pressure s/s	Not included in the specimen
Type C	2 (3)	45	1:1	0	Weight loss	Invasive carcinomas, so complete removal not possible

*Morphology within normal limits, #Percentages have been rounded off to the nearest decimal point. SOB=Shortness of breath

Table 2: Association of the WHO category with Masaoka-Koga stage [Table 2-Part 1] and its statistical significance [Table 2-Part 2]

Part 1: Association of the WHO category with Masaoka-Koga stage

Category of thymoma	Number of cases	Number of cases in stage M-I/percentage of cases in the category	Number of cases in stage M-II/percentage of cases in the category	Number of cases in stage M-III/percentage of cases in the category	Number of cases in stage M-IV/percentage of cases in the category
A	12	10 (83)	2 (16)	-	-
AB	12	9 (75)	3 (25)	-	-
B1	13	12 (92)	1 (8)	-	-
B2	18	12 (66.6)	5 (41.6)	1	-
B3	4	1 (25)	1 (25)	2 (50)	-
B2-B3	4	2 (50)	1 (25)	1	-
C	2	-	--	-	2 (100)

Part 2: Statistical significance of association between the WHO subtypes and Masaoka-Koga stage

WHO subtype	Stage restricted to M-I	Stage beyond M-I
A-B1 (*n*=37)	30	7
B2-C (*n*=28)	15	13

An advanced WHO subtype is associated with higher Masaoka–Koga stage (*P*=0.017)

organ as either cortical or medullary or mixed. The WHO system fulfills the criteria of reproducibility and clinical relevance, also proved in this study.

It was seen that there was substantial overall agreement while classifying thymomas into six WHO categories. The previous studies have shown variable kappa values, depending on the number of participating observers.[11-14] Until now, the existing literature shows that agreement within the B subgroup was much less.[15] In our study, kappa value was higher when only the B group was included in the study. Verghese *et al*. have shown an agreement of 0.45 with the WHO categories.[14] However, their study was a multicenter study with 17 pathologists. Similar studies by Chen *et al*. and Park *et al*. showed variable interobserver agreements and showed that kappa value increases when categories were clubbed.[11,12] Similar results were seen in the present study.

It was seen that it is relatively easy to assign tumors to categories A, B1, and C. Almost 100% concordance was seen in reporting B1 thymomas. However, an organoid B1 thymoma poses difficulty when we try to distinguish it from B2 thymoma. In these cases, vigilance for a clear vesicular nucleus, usually with a prominent nucleolus and occasional mitosis, should prompt one to classify it as a B2 thymoma. Differentiating pure B2 or B3 thymomas from combination tumors requires compulsory evaluation of multiple sections to decide the proportion of each component. At present, combination tumor is seen by the WHO as a subset of B2 thymomas; however, in this study, it was as common as B3 thymomas.

Previous authors have observed this overlap category of B2–B3.[11] However, a particular tumor with >30% B3 areas was assigned as B3, whereas in this study, we have assigned all tumors with both morphologies as B2–B3, irrespective of proportion. Whether the B2–B3 combination is more aggressive than pure B2 needs to be proven by more studies. In this study, one of the four patients with combination B2–B3 showed gross

infiltration of mediastinal structures at recurrence and died. Predominantly, this tumor showed B2 morphology with small focus of B3.

Previously, few studies on thymomas have been reported from the Indian subcontinent,[15-17] including one by the present authors. One of these[17] has compared invasiveness with the WHO subtype, and according to them, the classification was not difficult to apply. However, as thymomas are overall rare, it is crucial to create networks to coordinate the work among centers involved in the treatment of these tumors to offer the best diagnostic and therapeutic tools.[18]

Conclusion

Tumor stage as defined by Masaoka–Koga stage is the most important determinant of behavior of tumor. Although morphological overlaps are seen between the WHO categories, the classification system is nevertheless reproducible and produces uniformity in day-to-day reporting. Increasing familiarity with the criteria and strictly abiding by the same helps better classification.

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Conflicts of interest
There are no conflicts of interest.

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