# Thymic tumors

*all are not created equal*

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## Thymus tumors

**Organotypic neoplasms**

Spindle cells
- Type A
- Type AB

Polygonal cells
- type B1: thymus like architecture; richest in lymphocytes
- type B2:
- type B3: richest in epithelial cell

Special types
- Micronodular thymoma
- Metaplastic thymoma
- Other Rare thymomas

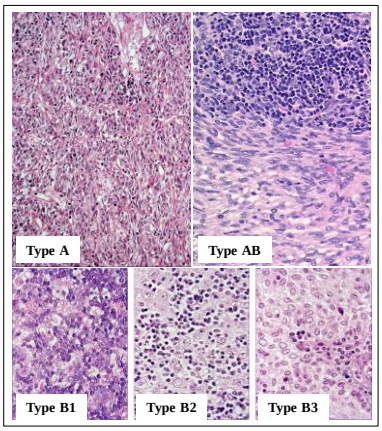
Indolent tumors

Aggressive tumors

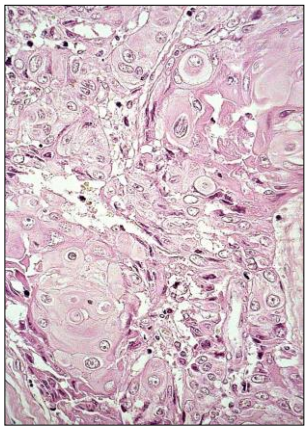
**Non-organotypic neoplasms**

Thymic carcinoma (Type C)

**Thymomas and Thymic Carcinomas (formerly Type C Thymomas)**




**WHO-defined Thymoma Subtypes**



**Squamous Cell Carcinoma, TSCC**

Courtesy of Alex Marx

# Thymomas

Organotypic (thymus like) features.

lobulation

medullary differentiation

perivascular spaces

Immature T lymphocytes (TdT+/Cd1a/,Cd99+)

# Thymomas

Epidemiology:

Rare tumors (annual incidence 1-5/million population)

Peak incidence 55-65 y/o

No sex predilection

Increased incidence of Myasthenia Gravis

Increased incidence of a second cancer

SPECIAL ARTICLE

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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**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

# Type A Thymoma

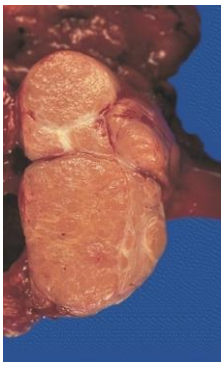
Rare tumor

Clinical features:

Myasthenia gravis in 25%

Tumor spread and staging
- 80% type A occurs in Masaoka stage I
- 17% type A occurs in Masaoka stage II
- 3% type A occurs in Masaoka stage III
- One single exceptional case of stage IV (2004 data)

Gross
- A well encapsulated tumor
- Thin white fibrous bands

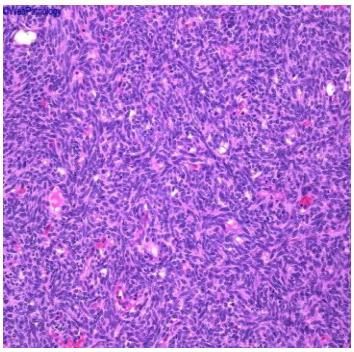


# Type A thymoma

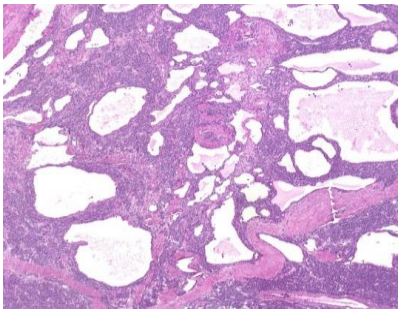
**TABLE 1.** Major and Minor Criteria of "Conventional" Type A Thymomas

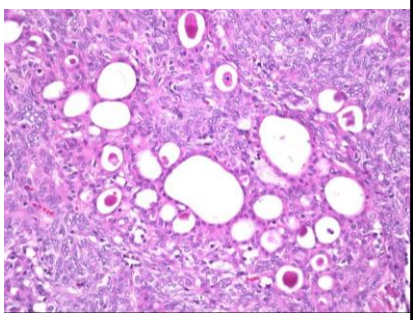
| |
|---|
| Major criteria |
| Spindled and/or oval-shaped tumor cells lacking nuclear atypia (see text) |
| Paucity[a] or absence of immature, TdT(+) thymocytes throughout the tumor |
| Minor criteria |
| Occurrence of rosettes and/or subcapsular cysts (to be distinguished from PVS) |
| Presence of focal glandular formations |
| Pericytomatous 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] |

[a]Paucity 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).
[b]Beta5t, PRSS16, and cathepsin V by immunohistochemistry (IHC).
PVS, perivascular space.

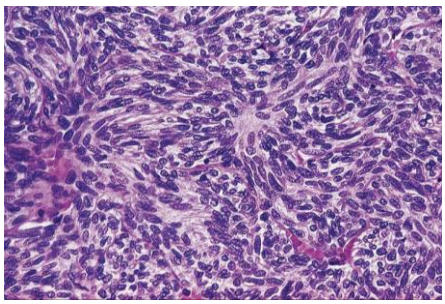


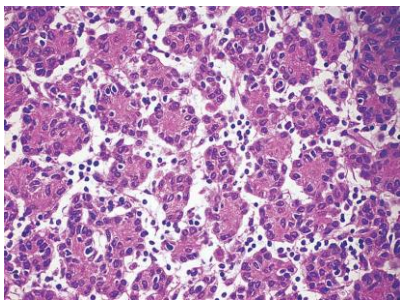
# Type A thymoma





Cystic spaces of various size





# Type A thymoma

Tumor cells

Individually surrounded by reticulin fibers,

Tumor cells Immunophenotype :

Acidic cytokeratins, (Ck 10, 12, 13, 14, 16, 17, 18, 19.)
- except Ck 20 which is focally positive
- Negative for basic cytokeratins (Ck 1, 2,3,4,5,6,7,8,9)
- EMA ,BCL-2, CD 57 variable to focally positive

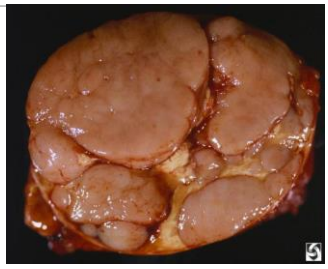
TP53 protein and Ki-67->no expression

**EGFR+/ C-kit and CD5 negative**

Lymphocytes
- Most mature T phenotype
- Few with immature T phenotype (+CD1a +CD3,,+CD4 +CD99, +TdT)
- Few B cells (CD 20 +)

Metallothionein and PE-35 ->positive (antigens present in normal thymus medulla)

# Type AB thymoma



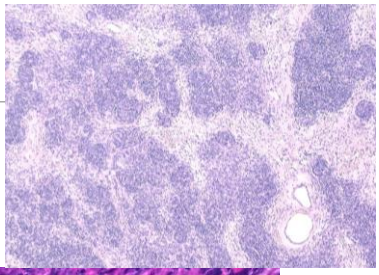
Organotypic

Most/second most common type of thymoma
- 15-45% of all thymomas

Clinical presentation similar to type A thymoma
- 14% associated with Myastenia Gravis

Tumor spread and staging (similar with Type A thymoma)
- 70% occur in Masaoka stage I
- 22% occur in Masaoka stage II
- 5.6% occur in Masaoka stage III
- Rare cases of stage IV have been reported.

# Type AB Thymoma



**Type AB thymoma is not simply a mixture of Type A and Type B patterns!!!!!!!**

It is better considered as a Type A thymoma with lymphocyte rich areas

Type A component:

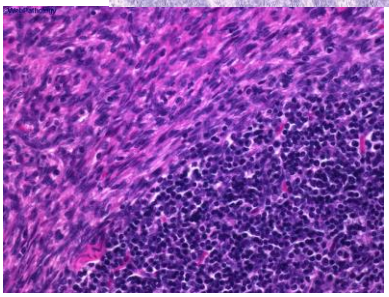
**All features of Type A thymoma**

- Can be extremely scanty to almost absent

Type B-like Component (unfortunate term)

**Differ from types B1, B2 and B3**

- Epithelial cells are the same as those of Type A



# Type AB thymoma

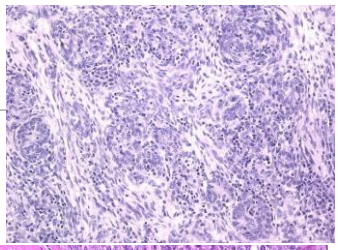
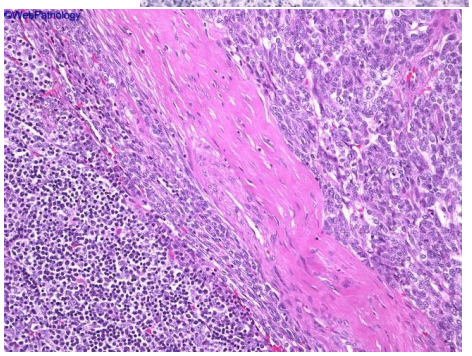


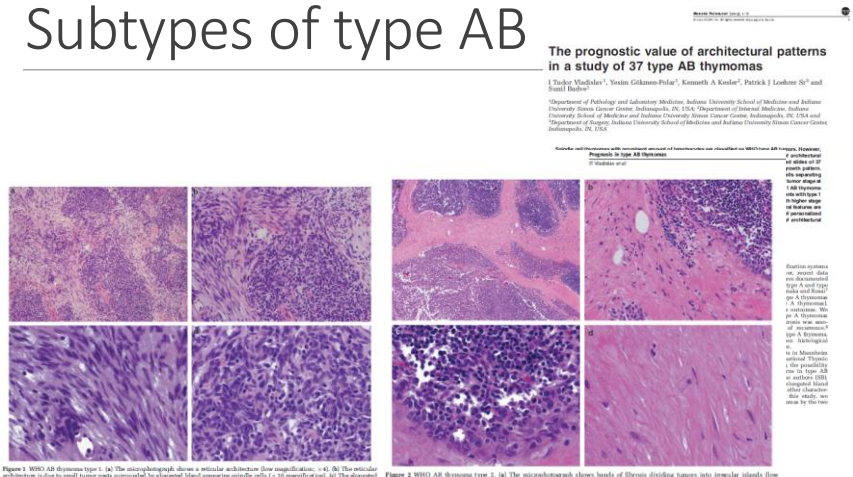
**TABLE 2.** Major and Minor Histological Features Encountered in Type A and AB Thymomas

| | 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 |

[a]These features are minor criteria in type AB thymoma.
[b]Atypia in type AB thymoma has not been addressed so far.
[c]As defined in Table 1.
[d]Detection of medullary islands is usually clear-cut on hematoxylin-eosin staining but may require immunohistochemistry (IHC), particularly when Hassall's corpuscles are missing.
[e]In lymphocyte-rich areas, usually with lack of Hassall's corpuscles.
[f]Beta5t, PRSS16, and cathepsin V (detectable by IHC in epithelial cells within lymphocyte-rich areas).



# Subtypes of type AB



The prognostic value of architectural patterns in a study of 37 type AB thymomas

I Tudor Vladislav[1], Yesim Gökmen-Polar[2], Kenneth A Kesler[2], Patrick J Loehrer Sr[2] and Sunil Badve[1]

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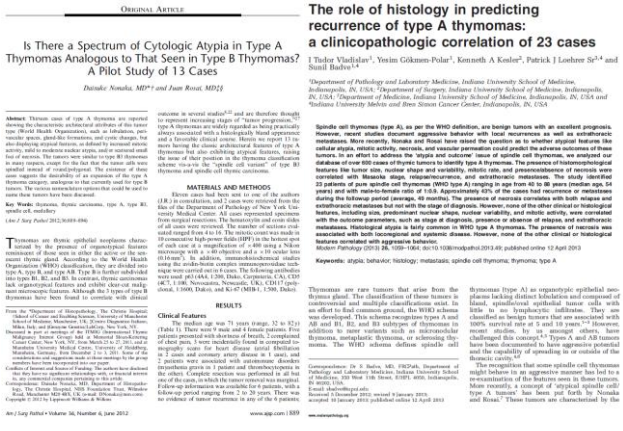
Figure 1 WHO AB thymoma type 1. (a) The microphotograph shows a reticular architecture (low magnification; × 4). (b) The reticular architecture is due to small tumor nests surrounded by elongated blood appearing spindle cells (× 10 magnification). (c) The elongated spindle cells have indistinct nucleoli and lack mitotic activity (high magnification; × 40). (d) Tumor nests composed of spindle cells admixed with lymphocytes (high magnification; × 40).

Figure 2 WHO AB thymoma type 2. (a) The microphotograph shows bands of fibrosis dividing tumors into irregular islands (low magnification; × 4). (b) The tumor is composed of admixture of plump spindle cells and lymphocytes; the amounts of lymphocytes can be variable (low magnification; × 10). (c) The tumor islands are composed of plump spindle cells admixed with lymphocytes. The cells may show variable degree of cytological atypia (high magnification; × 40). (d) The stroma is composed of fibroblastic cells and does not contain tumor cells but may contain a few lymphocytes (high magnification; × 40).

# Atypical type A – new entity

Type A tumors with necrosis or increased mitotic activity



ORIGINAL ARTICLE

Is There a Spectrum of Cytologic Atypia in Type A Thymomas Analogous to That Seen in Type B Thymomas? A Pilot Study of 13 Cases

Daisuke Nonaka, MD*† and Juan Rosai, MD‡§

The role of histology in predicting recurrence of type A thymomas: a clinicopathologic correlation of 23 cases

I Tudor Vladislav[1], Yesim Gökmen-Polar[2], Kenneth A Kesler[2], Patrick J Loehrer Sr[2,3] and Sunil Badve[1,3]

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**Spindle cell thymomas (type A), as per the WHO definition, are benign tumors with an excellent prognosis. However, recent studies document aggressive behavior with local recurrences as well as extrathoracic metastases. More recently, Nonaka and Rosai have raised the question as to whether atypical features like cellular atypia, mitotic activity, necrosis, and vascular permeation could predict the adverse outcomes of these tumors. In an effort to address the 'atypia and outcome' issue of spindle cell thymomas, we analyzed our database of over 600 cases of thymic tumors to identify type A thymomas. The presence of histomorphological features like tumor size, nuclear shape and variability, mitotic rate, and presence/absence of necrosis were correlated with Masaoka stage, relapse/recurrence, and extrathoracic metastases. The study identified 23 patients of pure spindle cell thymomas (WHO type A) ranging in age from 40 to 86 years (median age, 54 years) and with male-to-female ratio of 1:0.9. Approximately 43% of the cases had recurrence or metastases during the follow-up period (average, 49 months). The presence of necrosis correlates with both relapse and extrathoracic metastases but not with the stage of diagnosis. However, none of the other clinical or histological features, including size, predominant nuclear shape, nuclear variability, and mitotic activity, were correlated with the outcome parameters, such as stage at diagnosis, presence or absence of relapse, and extrathoracic metastases. Histological atypia is fairly common in WHO type A thymomas. The presence of necrosis was associated with both locoregional and systemic disease. However, none of the other clinical or histological features correlated with aggressive behavior.**

Modern Pathology (2013) 26, 1099–1104; doi:10.1038/modpathol.2013.49; published online 12 April 2013

Keywords: atypia; behavior; histology; metastasis; spindle cell thymoma; thymoma; type A

## Micronodular Thymoma with lymphoid stroma

Multiple, discrete nodules separated by an abundant lymphocytic stroma that usually contain prominent germinal centers.

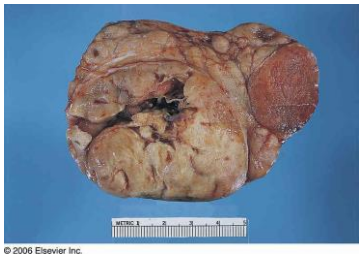
Up to 5% of all thymomas

Affect elderly patients (60-70 y/o)

Not associated with Myasthenia gravis (???)

Rarely occur together with typical type A and AB or B2 thymoma

None of our cases have recurred





## Micronodular Thymoma with lymphoid stroma

**Focally confluent epithelial nodules resembling Type A thymoma, separated by abundant lymphocytic stroma.**

May form micro and macroscopic cysts.

No Hassall corpuscles or perivascular spaces

May contain follicles with prominent germinal centers

**Epithelial nodules:**

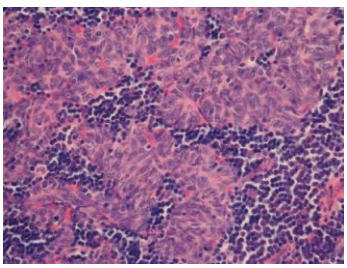
Slender or plump spindle cells with:

Bland oval nuclei

Nucleoli inconspicuous or absent

rare mitotic figures

Few lymphocytes within epithelial nodules



**Lymphocytic stroma**

Germinal centers

Small numbers of immature T cells may be scattered in and narrowly surrounding the nodules

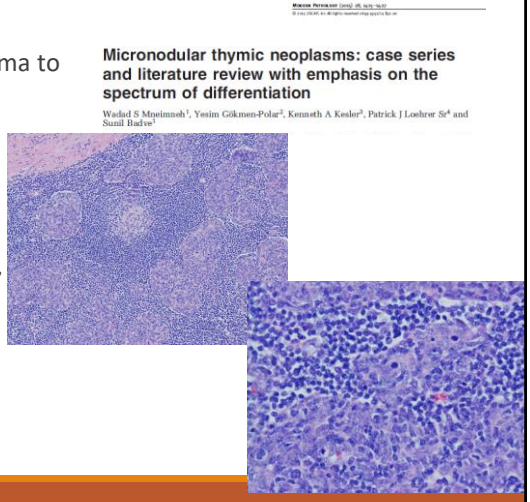
**No epithelial cells within lymphoid areas!!!!!**

# Micro-nodular neoplasms

Spectrum of disease from thymoma to thymic carcinoma

Describe cases with Myasthenia

None of thymomas in this “large” series recurred.



Micronodular thymic neoplasms: case series and literature review with emphasis on the spectrum of differentiation

Wadad S Mneimneh[1], Yesim Gökmen-Polar[2], Kenneth A Kesler[3], Patrick J Loehrer Sr[4] and Sunil Badve[1]

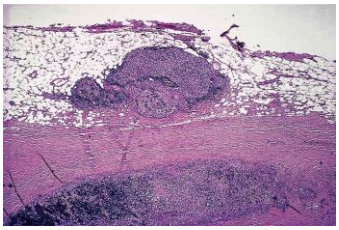
# Type B thymomas

ROUND /EPITHELIOID CELLS THYMOMA

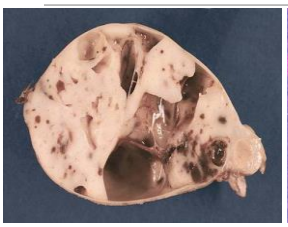
# Type B1 thymoma

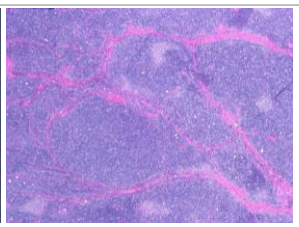
Organotypic
- Histological appearance very similar with normal thymus.
- Rare tumor (6-20%)
- 15-60% associated with myastenia gravis

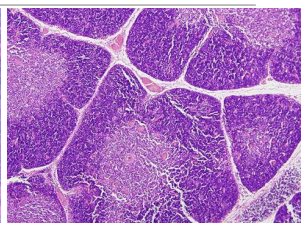
Tumor spread and staging
- 60% completely encapsulated ( stage I)
- 30% invades only mediastinal fat (stage II)
- 10% invades pleura , pericardum, great vessels (stage III)
- Rare cases stage IV



# Type B1 thymoma vs Normal thymus







Type B1 thymoma:
- Gross:
- Thick fibrous capsule and septae
- Cystic spaces or small hemorrhagic and necrotic area

Large excess of cortical area

Pale areas resembling thymic medulla

Fewer Hassall corpuscle

Thick fibrous capsule

Irregular fibrous septae

Normal Pediatric Thymus

# Thymoma type B1

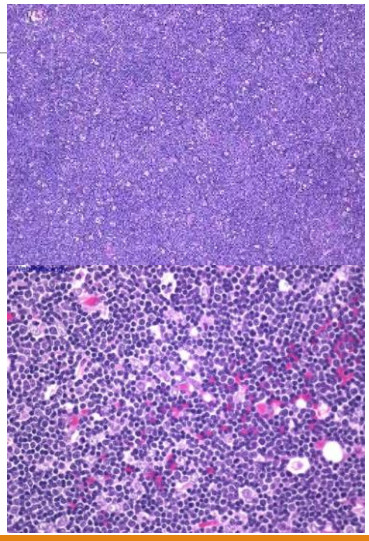
Cortical areas closely resemble normal cortex
- Lymphocytes with inconspicuous epithelial cells

Lymphocytes
- Densely packed, Nonneoplastic, Small, Immature T phenotype lymphocytes neoplastic

Epithelial cells
- Oval cell with pale round nuclei and small nucleoli
- Some cells may be large and occasionally may have well defined nucleoli
- Long dendritic processes, may be visible only on keratin stains.
- Do not form epithelial clusters

Medullary foci stand out as indistinctly circumscribed round pale zones
- Pale appearance due to loose packing of lymphocytes, largely mature T phenotype
- They do not resemble normal medulla Epithelial cells range from infrequent to occasional
- Hassall corpuscles range from absent to occasional

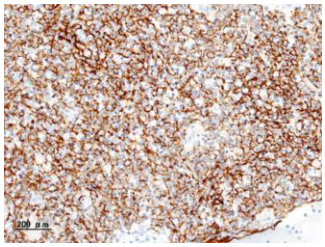
Starry sky appearance



# Thymoma type B1

Keratins
- Ck19 diffusely positive CK 7, Ck14, Ck18-focal positive
- Ck 20 negative
- CD5, CD20 , CD 70 negative
- EMA negative
- CD5 negative

Lymphocytes
- Cortical areas: immature T phenotype
  - +CD1a, +CD99, +TdT, +CD 4,+CD5)
- Medullary foci: usually mature T phenotype
  - -CD1a,-CD99, -TdT), +CD4 ,+CD5
- Few B cells



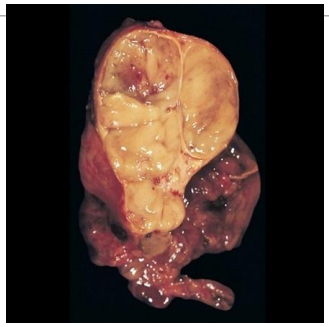
# Type B2 Thymoma

20-40% of all thymomas

Strong correlation with Myasthenia gravis !!!

Tumor spread and staging

- Stage I :10-40%
- Stage II: 15-53%
- Stage III: 20-50%
- Stage IVA: 9%
- Stage IVB: 3%



Encapsulated or vaguely circumscribed, Tan colored nodules separated by white fibrous septae, Cystic changes , hemorrhage and fibrosis

# Type B2 Thymoma

**Prominent large epithelial cells with numerous admixed lymphocytes**

- Lacks extensive areas of virtually pure epithelial cells
- Lacks extensive areas of virtually pure lymphocytes

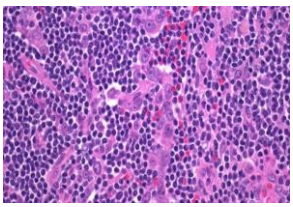
**Prominent polygonal epithelial cell population**

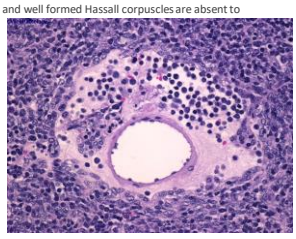
- Lack long thin processes
- Nuclei vesicular with prominent nucleoli
- May palisade

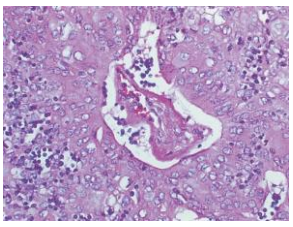
**Prominent lymphoid infiltrate**

- Lymphocytes may outnumber epithelial cells but do not obscure them

Medullary foci and well formed Hassall corpuscles are absent to infrequent







# B1 versus B2

**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[+/-] network like in NT | Yes | Denser than in NT |

[a]These features are, therefore, minor criteria of type B2 thymomas.
[b]Defined as at least three contiguous epithelial cells.
[c]On immunostaining.
NT, normal thymus.

# Type B3 Thymoma

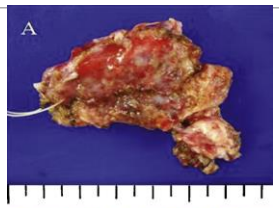
Thymic epithelial cells tumor capable of differentiating towards a less differentiated cortical-type epithelial cell than in B2 thymoma

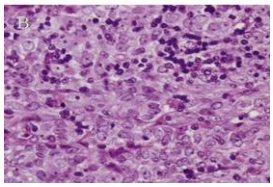
Up to 25% of all thymomas

Frequent associated with Myastenia gravis

# Type B3 Thymoma

Usually not encapsulated with infiltrative border

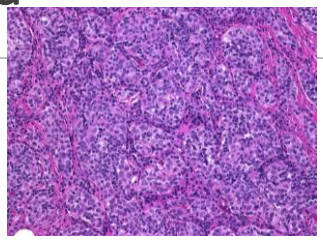


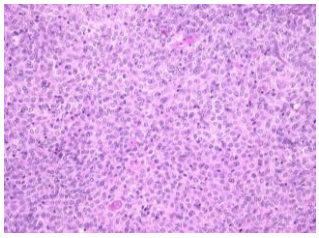




- Organotypic
- Up to 25% of all thymomas
- Frequent associated with Myasthenia gravis

- Tumor spread and staging
  - 15-60% (the majority) occurs in stage II and III Masaoka
  - 6-26% occurs in stage IV Masaoka
  - 5% stage I Masaoka
  - 7% -Distant metastases (lung , liver bone and soft tissue)

# Type B3 Thymoma





**Sheets of epithelial cells**

- Tumor cell form lobules separated by thick fibrous and hyalinized septa
- Mild to moderate atypia at most
  - Round to oval irregular nuclei
    - Frequently smaller than in B2
  - Nucleoli variable, frequently smaller than in B2
- Usually pale to clear cytoplasm
  - May suggest epidermoid/squamoid appearance
  - focally keratinized
- Prominent palisading around perivascular spaces and along septa
- Medullary islands absent
- Mitotic figures usually <2/hpf
- Tumor cell necrosis focal and rare
- Rare cases of true thymic carcinoma may arise in or adjacent to B3 thymoma

**Very few lymphocytes**

- Most are immature T cells

# B2 Versus B3

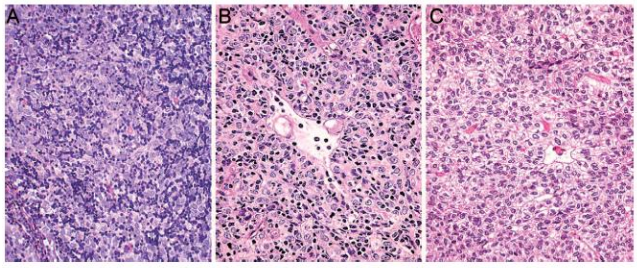



FIGURE 8. Distinction between type B2 and B3 thymomas. *A*, B2 thymoma: typically impression of a blue staining tumor on hematoxylin-eosin (H&E) staining due to the high content of lymphocytes. *B* and *C*, B3 thymoma: impression of a pink staining tumor due to the (variable) paucity of lymphocytes and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

# Type B3 Thymoma

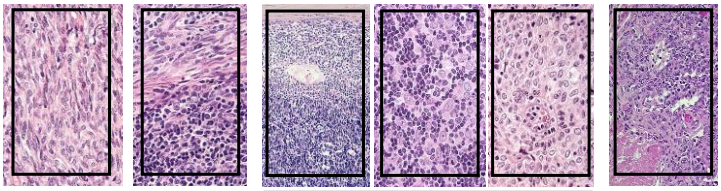
Variants:

- Combined thymoma (B2 and B3)
- Clear cell
- Large cell
- Focal or extensive Spindle cell formation
- B3 Thymoma with anaplasia
- Combined thymoma-thymic carcinoma (rare-3%)

## High Degree of Consensus (~80%) in Prototypic Cases

**WHO-Classification (1999, 2004, 2014)**

A AB B1 B2 B3 „C“



**~BUT 20% unclear:**
**"borderland cases" or unrecognized new entities**

Courtesy of Alex Marx

PATHOLOGISCHES INSTITUT Universitätsklinikum Mannheim

## Thymoma and recurrences

Old WHO states that

Type A/AB are benign
- Changed in the NEW WHO

Documented recurrences in all types
- ?better way of classification

**WHO types A and AB thymomas: not always benign**

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**The 2004 WHO classification of thymic tumors recognizes five major subtypes of thymomas and thymic carcinoma. Subtypes A and AB thymomas are purported to be benign neoplasms, although prior studies have suggested a potential for malignant behavior. The purpose of this study was to assess the clinical behavior of A and AB thymomas identified from a large institutional pathologic database. A retrospective slide review of 500 thymic epithelial tumors identified 71 (~14%) cases of types A and AB thymomas. Clinical history and follow-up information were obtained through retrospective chart review. There were 38 and 33 cases of types A and AB thymomas, respectively. Complete follow-up data were available in 37 (52%) cases. Eighteen (49%) patients (type A, n = 9 and type AB, n = 9) had evidence of recurrent/metastatic disease at an average of 62 months (range from 6 to 244 months) after initial diagnosis. Survival curves for patients with types A and AB thymomas, with and without recurrences, show a statistically significant difference (P = 0.001 and 0.005, respectively). Analysis of this large cohort confirms the potential for subtypes A and AB thymomas to show malignant behavior. Long-term clinical monitoring, therefore, appears to be justified in these cases. This study also shows the poor correlation between the WHO classification and tumor behavior**

*Modern Pathology* advance online publication, 10 September 2010; doi:10.1038/modpathol.2010.172

**Keywords:** type A; type AB; thymoma; WHO

Thymomas are rare tumors that arise from the epithelium of the thymic gland.[1] The rarity, histologic diversity, variable clinical behavior, and outcome have significantly limited our understanding of these tumors. Considerable and significant controversy continues to exist concerning the classification and clinical behavior of these tumors.

Characteristically admixed with a variable amount of lymphocytes (including no lymphocytes), thymomas are capable of rather diverse histopathology. This has resulted in a confusing array of classification schemas. Early work by Lattes[2] divided these lesions based on the predominant cell type into *lymphocytic, epithelial, mixed,* and *spindle* types.

In 1978, Levine and Rosai[3] postulated that encapsulated thymomas are essentially benign. This was based on the observation that most thymomas tend to be circumscribed and curable when amenable to complete surgical extirpation. Moreover, this held true irrespective of the histological features.[1] Thymomas were deemed malignant when invasive growth was present or sufficient cellular anaplasia was present to reflect the presence of carcinoma.

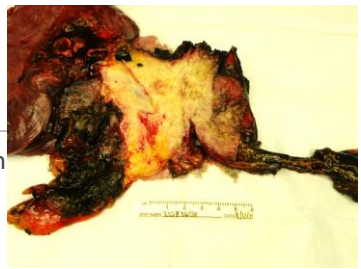
On the basis of the purported morphologic similarity with thymic cortical or medullary epithelium, the Muller-Hermelink classification recognized five subtypes: *medullary, mixed, predominantly cortical,* and *cortical,* as well as *well-differentiated thymic carcinoma.*[3,4] In 1999, the

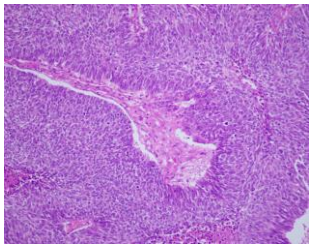
# Thymic Carcinomas

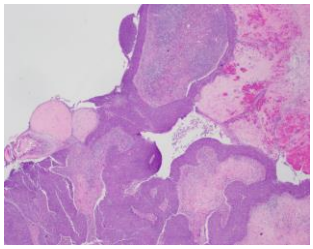
TUMORS WITH CYTOLOGIC ATYPIA

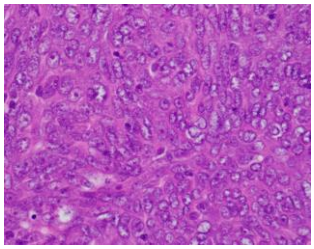
## Thymic carcinomas

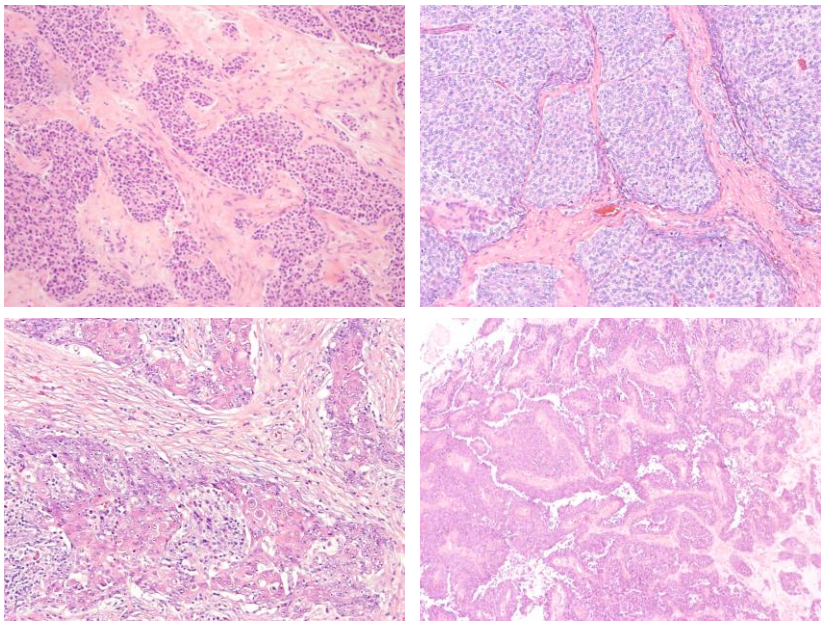
- Vary in histology but squamous most common
- Differential diagnosis
  - Lung carcinomas
  - NUT tumors





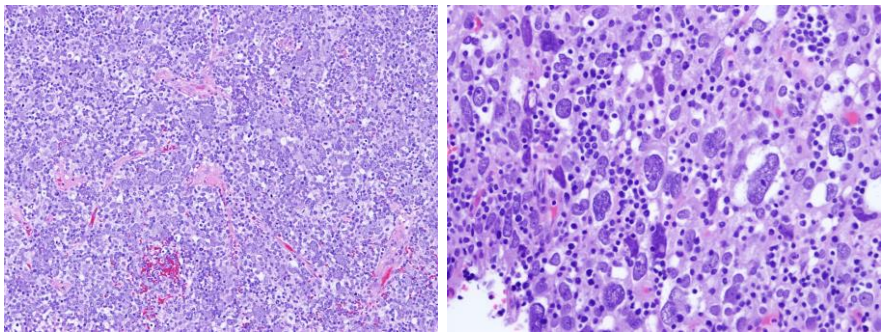






# Thymoma with anaplasia

Single cell anaplasia in a background of typical thymoma



# Conclusions

Thymic tumors -varied histology and behavior

Thymomas

- Spindle cell (Types A & AB) do recur
- Classification of type B thymomas is based on stromal characteristics
  - Needs to change?

Thymic carcinomas

- Mixed bag of lesions
- Better treatments are necessary

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