TUMORS OF THE MEDIASTINUM (II) THYMOMA AND THYMIC CARCINOMA

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Thymoma and Thymic Carcinoma

- **General Features:**
- **Thymoma** *is a term that should be restricted to neoplasms of thymic epithelial cells, independent on the presence/ or number of lymphocytes.*
- Seminoma, carcinoid tumor, Hodgkin's and non-Hodgkin lymphoma can all involve the thymus primarily.

- *They are considered as thymic tumors but should not be regarded as variants of thymoma.*
- *Nearly all thymomas present in adult life.*
- Thymomas in children are exceptional; most of the cases so *diagnosed in the past,* represent *lymphoblastic lymphomas of the thymus.*
- However, most of the cases occur near the age of puberty with an appearance and behavior equivalent to that of their adult counterpart, including an *occasional association with myasthenia gravis.*

- *The usual location of thymoma is the antero-superior mediastinum;* however, this tumor can also occur in *other mediastinal compartments* although a *posterior location is very rare.*
- It may occur in the neck, within the thyroid, pericardial cavity, cardiac myxoma, pulmonary hilum, lung parenchyma, or in the pleura itself, sometimes coating it in a *mesothelioma-like fashion.*

- **Radiographically,** thymoma usually presents as a *lobulated opacity that may be calcified.*
- CT scan and MRI are the methods of choice for diagnosis and evaluation of extent.
- **Fine-needle aspiration** was used for diagnosis of thymoma *based on the finding of dual population of epithelial cells and lymphocytes with the appropriate cytological features.*

- *Some younger children had highly malignant thymic neoplasms with unusual morphologic features,* the nature of which has not yet been thoroughly elucidated.
- It is possible that *some cases may represent the so-called* **NUT midline carcinoma.**
- Familial incidence of thymoma has been recorded only exceptionally.

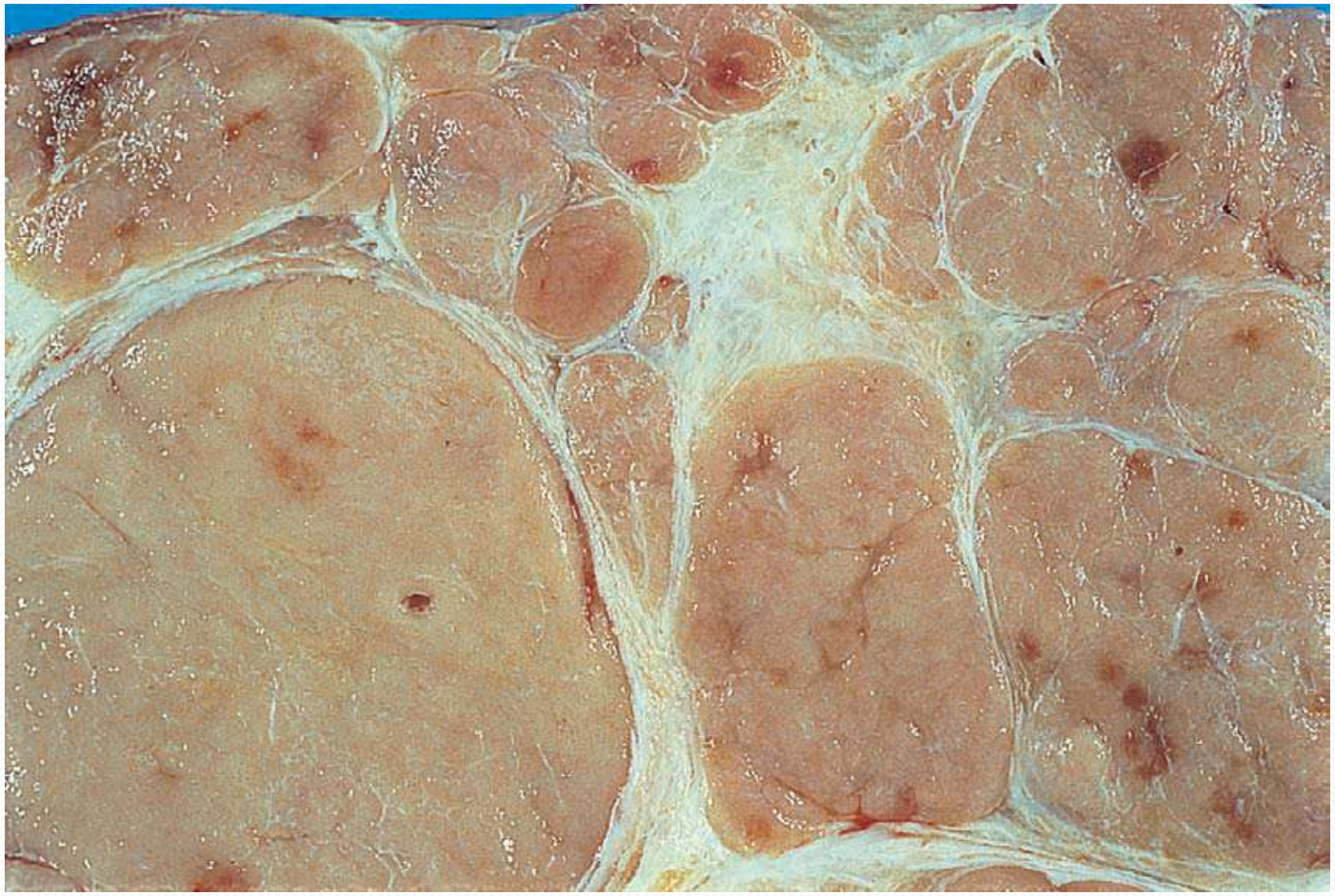
Pathologic Features of Thymoma

- **Grossly:**
- The typical thymoma is largely *solid, yellowish gray, and separated into lobules by connective tissue septa.*
- In approximately 80% of cases, *the tumor is well encapsulated and can be removed with ease.*
- *In the remainder, infiltration of surrounding structures is noted at surgery.*

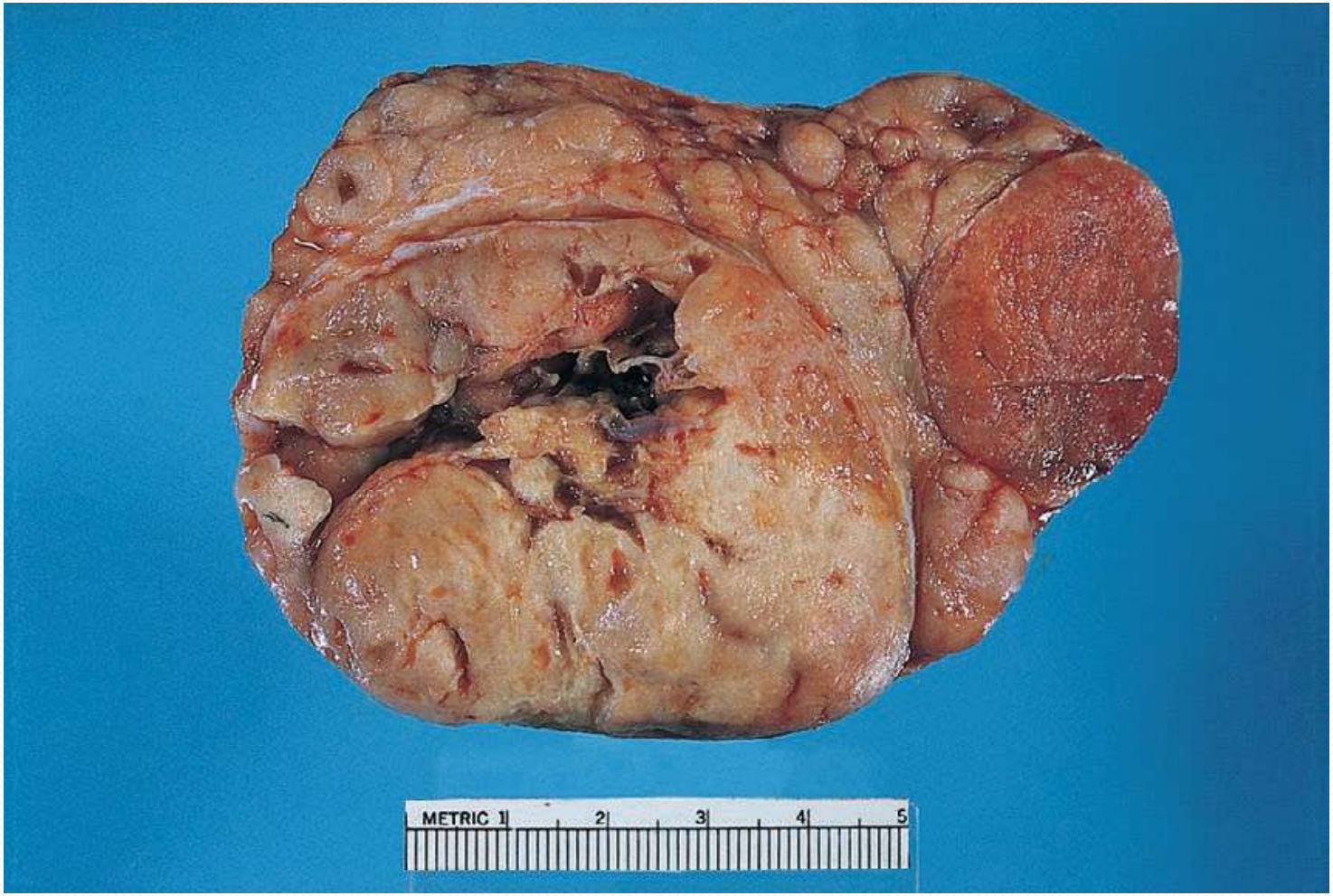
- Most clinically evident tumors are large, but very small thymomas *"microthymomas"* may be discovered incidentally in the course of cardiac surgeries or in thymectomy specimens from cases of myasthenia gravis or red cell aplasia.
- Foci of *necrosis and cystic degeneration are common,* particularly among larger tumors.

- Sometimes the entire tumor undergoes prominent cystic, necrotic, and hemorrhagic changes, *many sections being needed to identify the residual diagnostic areas.*
- Infarct-like necrosis and hemorrhagic degeneration does not convey poor prognosis in well encapsulated thymoma.
- *Predominantly cystic thymomas should be distinguished from multilocular thymic cysts* which can coexist with thymoma and other thymic neoplasms undergoing cystic changes.

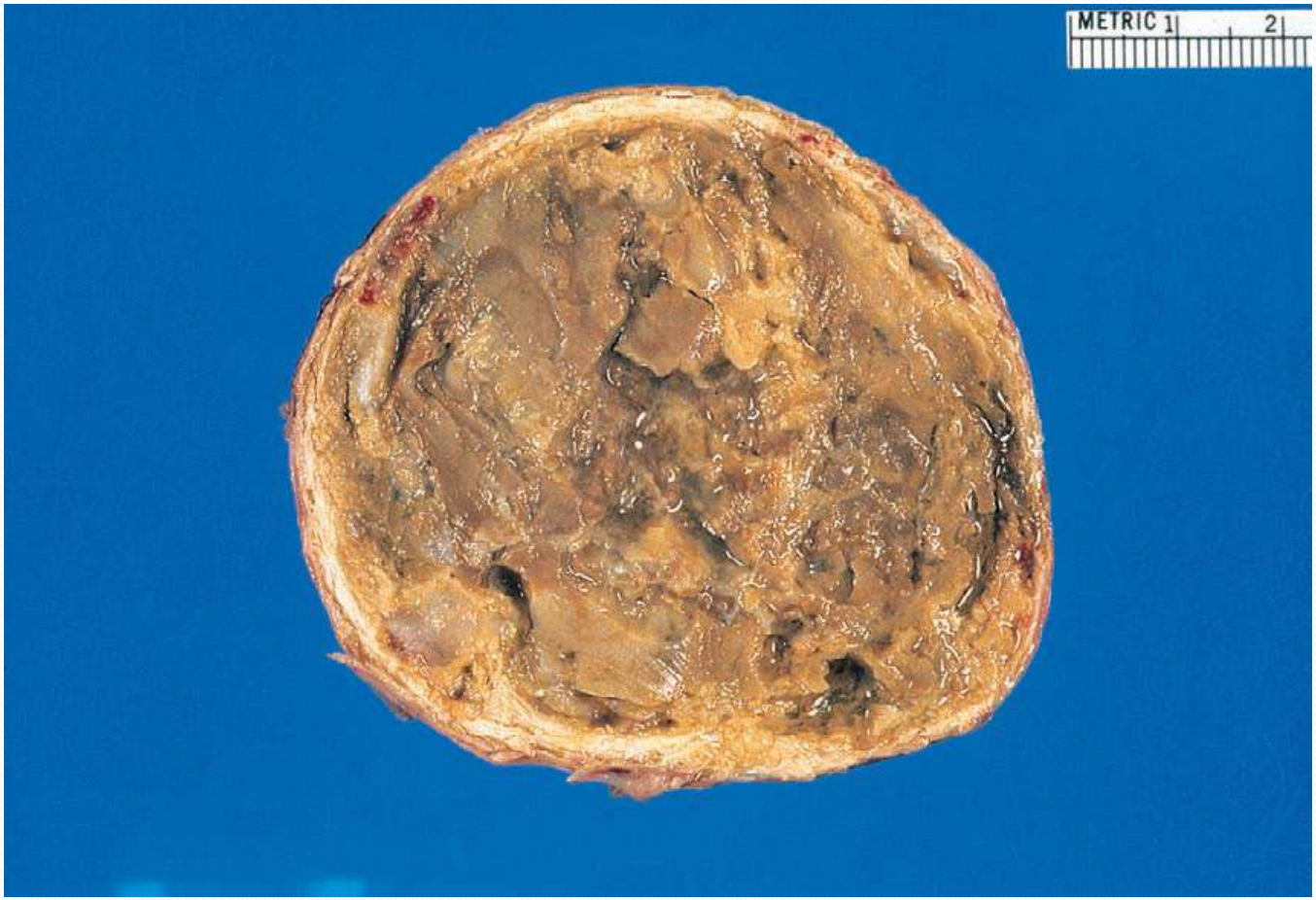
Gross Features of Thymoma



Gross Picture of Thymoma



Gross Picture of Thymoma



- **Microscopically:**
- The majority of thymomas are composed of *mixture of neoplastic epithelial cells and non-neoplastic lymphocytes, the proportion among them vary widely from case to case and in different lobules of the same tumor.*
- *The epithelial cells may have round-polygonal "plump", stellate, or spindle/oval shape.*

- *The nuclei are vesicular and of smooth contour; the nucleolus may be conspicuous, particularly when the nuclei are round or polygonal.*
- *The lymphocytes may appear mature "**inactive**" or show varying degrees of "**activation**"* manifested by *larger nuclear size, open chromatin pattern, visible nucleolus, identifiable cytoplasmic rim, and mitotic activity; however, they should not appear convoluted or cleaved.*

- *Thymomas with sizable component of epithelial cells often show one or more features suggestive of organoid differentiation, which correlate with the various subtypes.*
- *These include perivascular spaces containing lymphocytes, proteinaceous fluid, red blood cells, foamy macrophages, or fibrous tissue; rosettes without central lumens; gland-like formations within the tumor or, more often, in the tumor capsule; true glandular structures (an exceptional event); and whorls suggestive of abortive Hassall corpuscle formation.*

- *Well-formed Hassall corpuscles are occasionally found within thymomas.*
- *Their presence in large numbers is usually an indication of tumor presence and is more common in malignant lymphoma of the thymus than in thymoma.*
- *Presence of rosette-like structures with well-defined lumens should suggest a diagnosis of thymic carcinoid rather than thymoma.*

- *In lymphocyte-rich (type B1) thymomas, it is common to find round, lighter foci of medullary differentiation, an important clue to the diagnosis.*
- *Other helpful diagnostic features of thymoma are the thick, often calcified fibrous capsule, the lobular arrangement induced by these fibrous bands, the sharp interphase between tumor lobules and fibrous tracts, and the angular shape of some of the lobules, resembling arrowheads.*

- *Vascularization may be prominent and result in a mistaken diagnosis of hemangiopericytoma.*
- *Microcystic and pseudopapillary formations may be focally present.*
- *Sclerosis may be very extensive, possibly as a manifestation of tumor regression, and may obscure the neoplastic component.*
- *Exceptionally, there is a massive plasma cell infiltrate.*

- **By electron microscopy,** *neoplastic epithelial cells exhibit branching tonofilaments, complex desmosomes, elongated cell processes, and basal lamina.*
- *These characteristics have proven historically useful in segregation of thymoma from other anterior mediastinal tumors, such as thymic carcinoid, malignant lymphoma, seminoma, and solitary fibrous tumor.*

- **Immunohistochemistry:**
- *Epithelial cells of thymoma are immunoreactive for keratins; cytokeratin 7, high-molecular weight cytokeratins (CK5/6, 34βE12), p63 and p40 (ΔN-p63α), and PAX8.*
- *Staining for EMA is usually restricted either to the gland-like formations of spindle thymomas or to tumors predominantly composed of round or polygonal cells.*

- Thymomas express the tissue blood group (O) and peanut agglutinin receptor antigens, MHC class II molecules, epidermal and nerve growth factor receptors, growth hormone, and metallothionein.
- Two novel thymic epithelial markers-CD205 and Foxn1-are positive in nearly all thymomas and a subset of thymic carcinomas.
- Unfortunately, they are also sometimes expressed in carcinomas of other sites.

- *Stains for basement membrane material; as **laminin or type IV collagen,** show abundant deposition around individual tumor cells in spindle-shaped tumors and paucity of this material in those tumors made up of stellate, round, or polygonal cells.*

Classification of Thymoma and Thymic Carcinoma

- ***The subtypes of thymomas included in the WHO classification:***
- *Type A Thymoma (Spindle cell; medullary)*
- *Type AB Thymoma (Mixed)*
- *Type B1 Thymoma (Lymphocyte-rich; lymphocytic; predominantly cortical; organoid)*
- *Type B2 Thymoma (Cortical)*
- *Type B3 Thymoma (Epithelial; atypical; squamoid; well-differentiated thymic carcinoma)*

Type A Thymoma (Spindle Cell; Medullary)

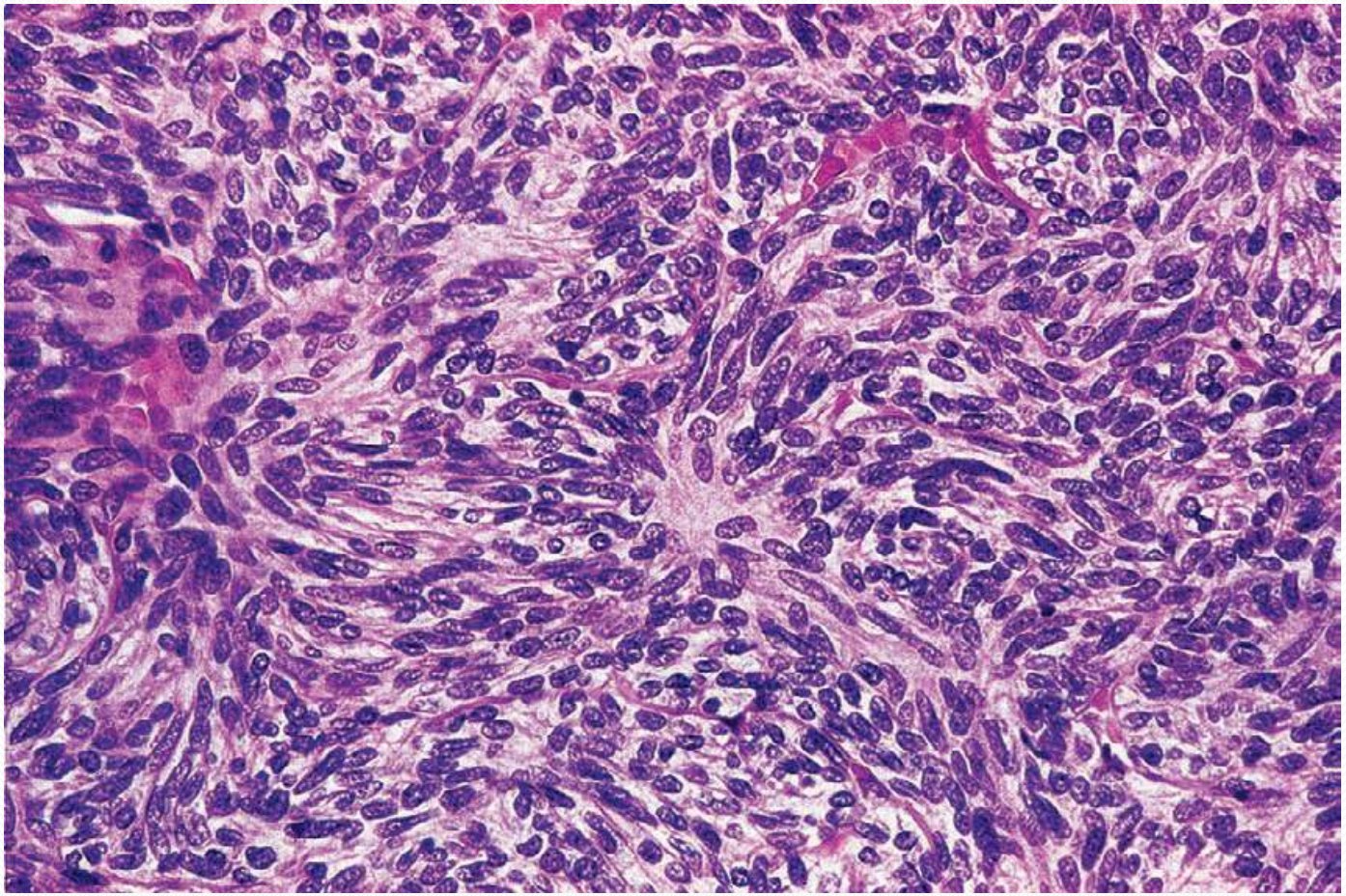
- The tumor is composed of neoplastic thymic epithelial cells having *spindle/oval shape,* and *lacking nuclear atypia,* and accompanied by *few or no non-neoplastic lymphocytes.*
- *The tumor may simulate that of mesenchymal tumor,* but IHC and ultrastructural features are those of epithelial tissue.
- *A peculiar feature of the neoplastic epithelial cells in type A thymomas* is *expression of* **CD20** *in about half of them.*

- *Rosette-like formations* (without central lumen), *foci with storiform pattern of growth,* and *gland-like formations* may be present, the latter often located within or immediately beneath the tumor capsule.
- Many features of cells of this tumor are *reminiscent of the cells seen in the atrophic thymus of adult,* some of which happen to be *located in the subcapsular (rather than medullary) region.*

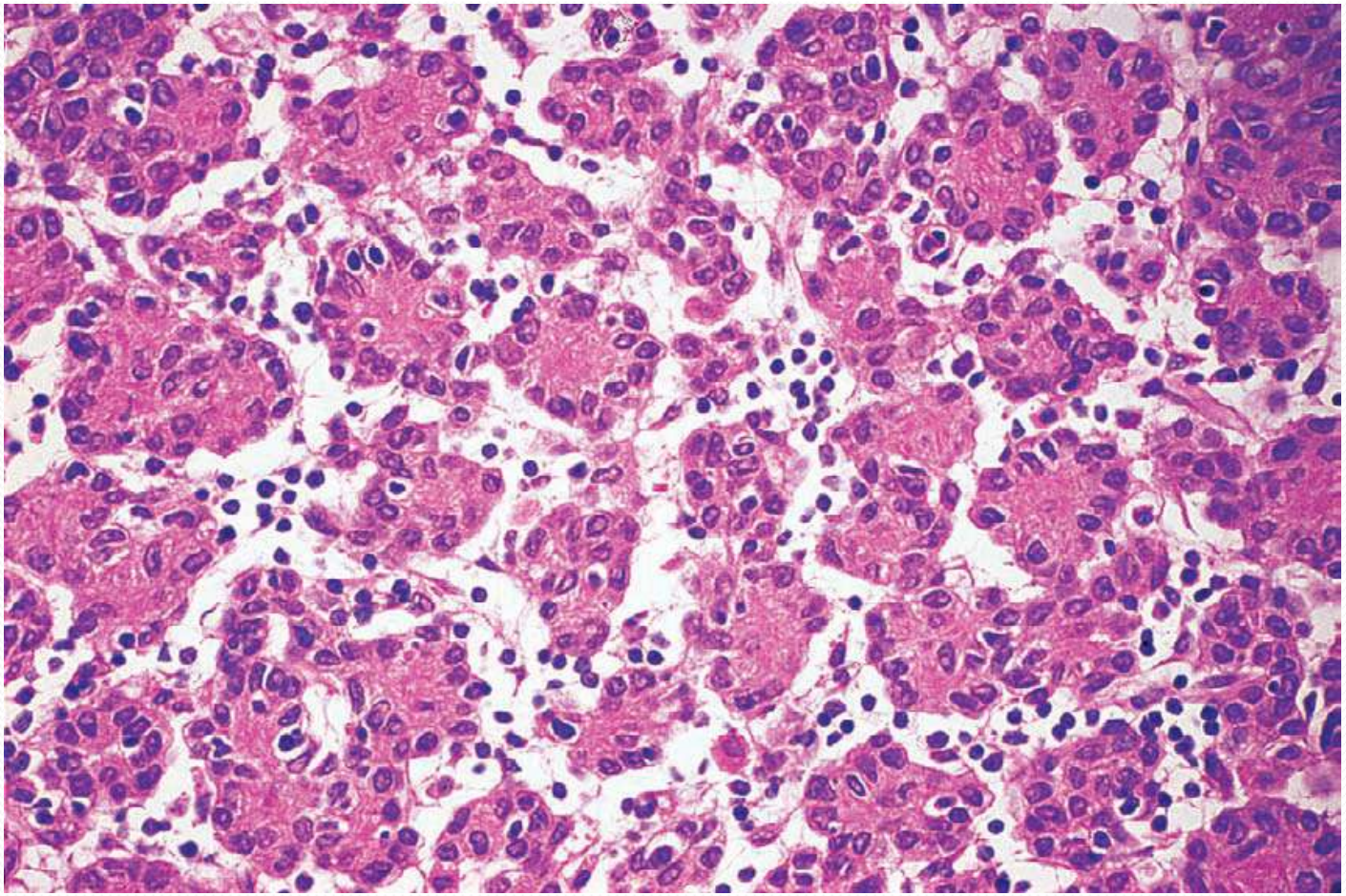
- *There are rare thymomas composed of spindle cells but exhibiting combination of hypercellularity, nuclear hyperchromasia, pleomorphism, mitotic activity, and/or necrosis.*
- *Mitotic activity (≥4/10 HPF) and necrosis* are proposed as the most reproducible features for identifying the rare variant; ***atypical type A thymoma.***
- ***Necrosis*** is the only feature that *predict higher tumor stage in type A and AB thymomas.*

- *Distinguishing atypical type A thymomas from spindle cell type B3 thymomas may be challenging given the potential presence of nuclear atypia in both.*
- *Positive staining for CD20 in type A thymomas* may be helpful.
- *In the absence of CD20 staining separating atypical type A from spindle type B3 thymomas hinges on other histological findings including rosette-like, glandular, and storiform growth in type A thymoma and perivascular spaces in type B thymomas.*

Type A (Spindle, Medullary) Thymoma



Type A Thymoma (Rosette Formation)

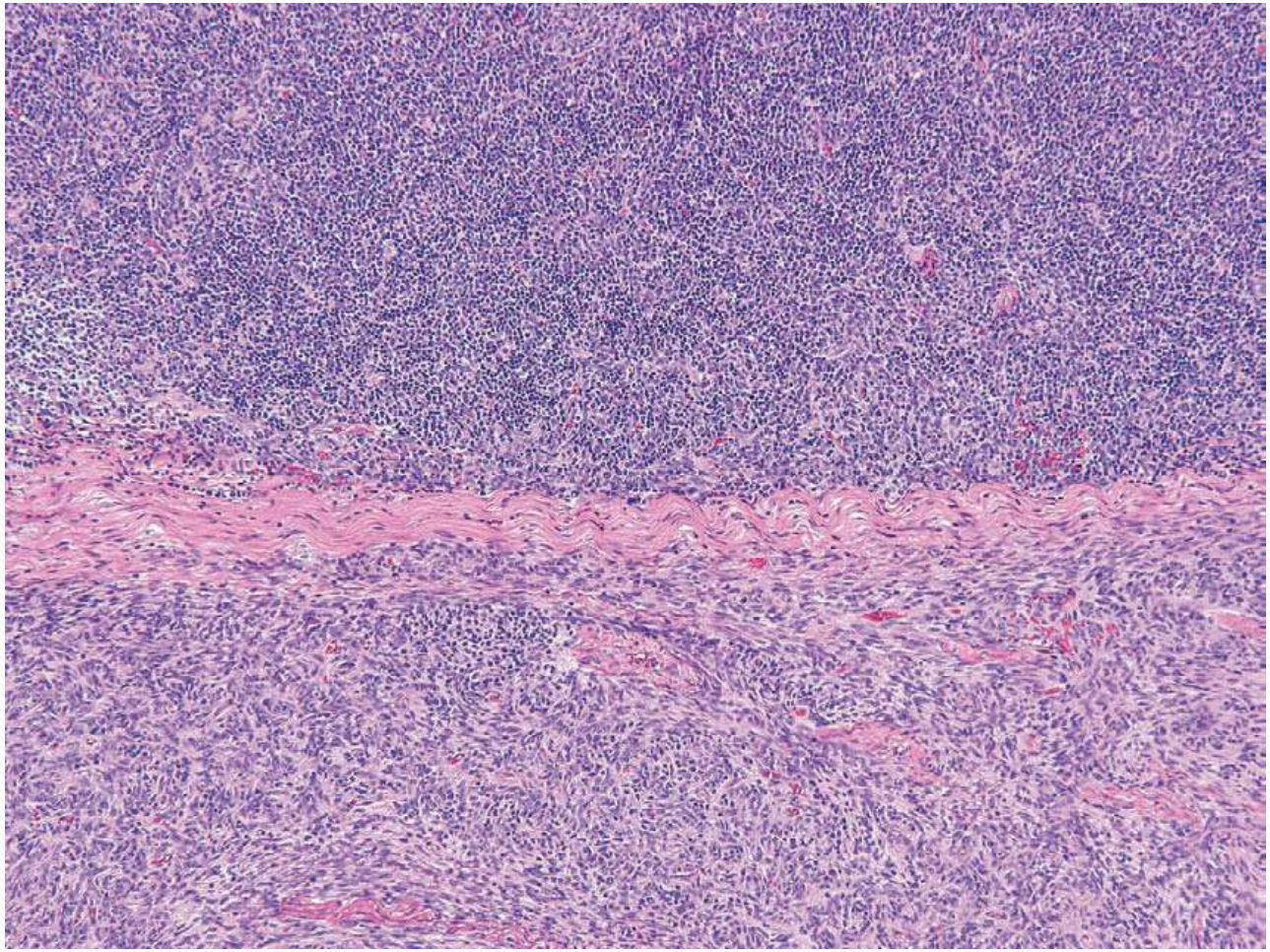


Type AB Thymoma (Mixed)

- *A tumor in which foci having the features of type A thymoma are admixed with foci rich in lymphocytes including significant proportion of immature T cells.*
- This is particularly *common type of thymoma.*
- *The segregation of the two patterns can be sharp or indistinct, and there is a wide range in the relative amount of the two components.*

- *Type A areas can be extremely scant, and therefore thorough sampling may be necessary to separate from type B1 thymomas.*
- *The presence of Hassall corpuscles strongly favors B1 thymomas.*
- *Spindled or oval morphology and/or immunoreactivity for CD20 in epithelial tumor cells within lymphocyte-rich areas strongly favor the diagnosis of AB thymoma over a type B thymoma.*

Type AB Thymoma

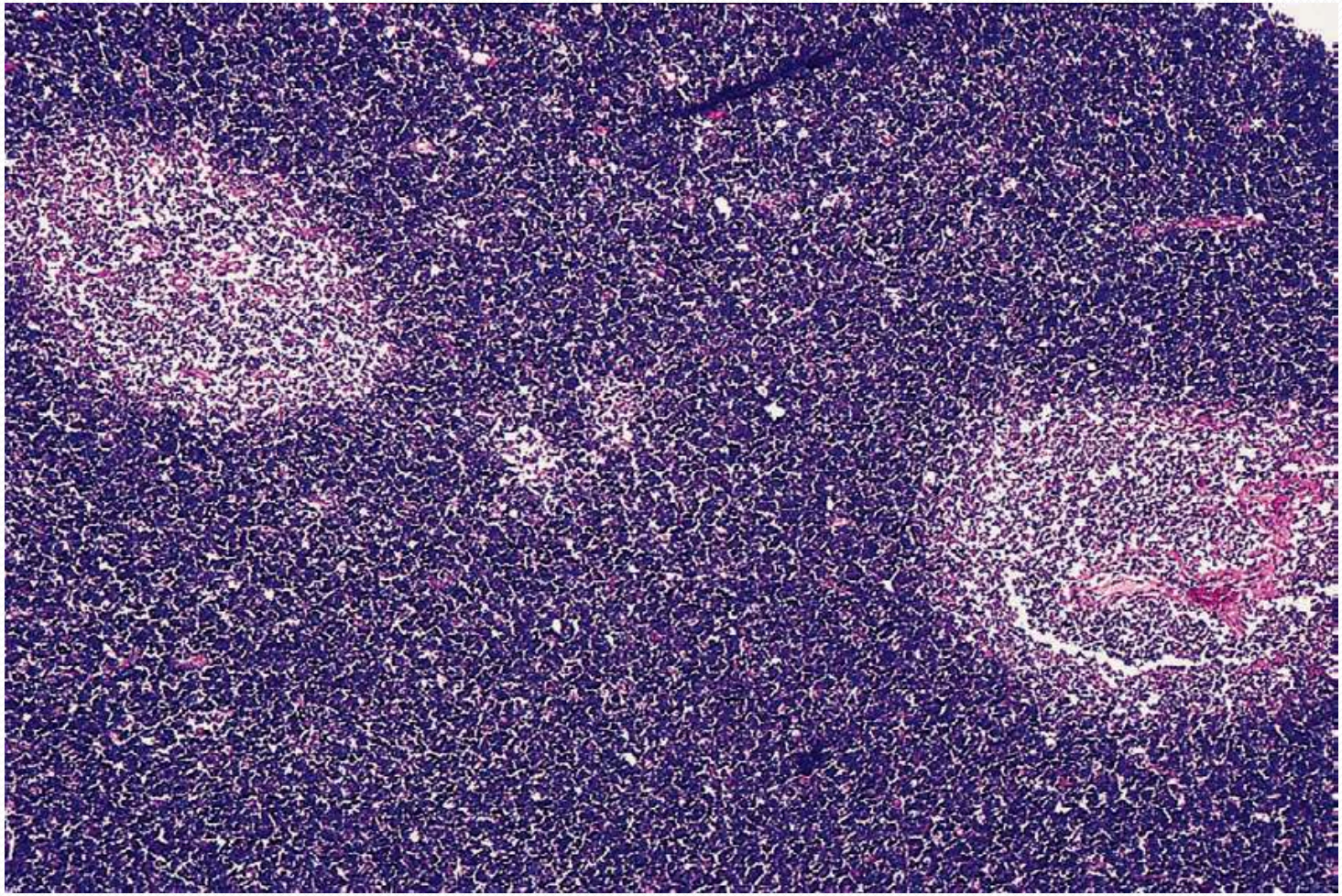


Type B1 Thymoma (Lymphocyte-Rich; Lymphocytic; Predominantly Cortical; Organoid)

- *A tumor that resembles the normal functional thymus in that it has an appearance indistinguishable from normal thymic cortex in which cytologically bland thymic epithelial cells are evenly dispersed within a background of immature T cells and accompanied by areas resembling thymic medulla.*

- *The resemblance between this tumor type and the normal active thymus is such that the distinction between the two may be impossible on high-power examination.*
- *Absence of epithelial cell clusters and presence of medullary islands are especially helpful in separating B1 from B2 thymoma.*

Type B1 Thymoma



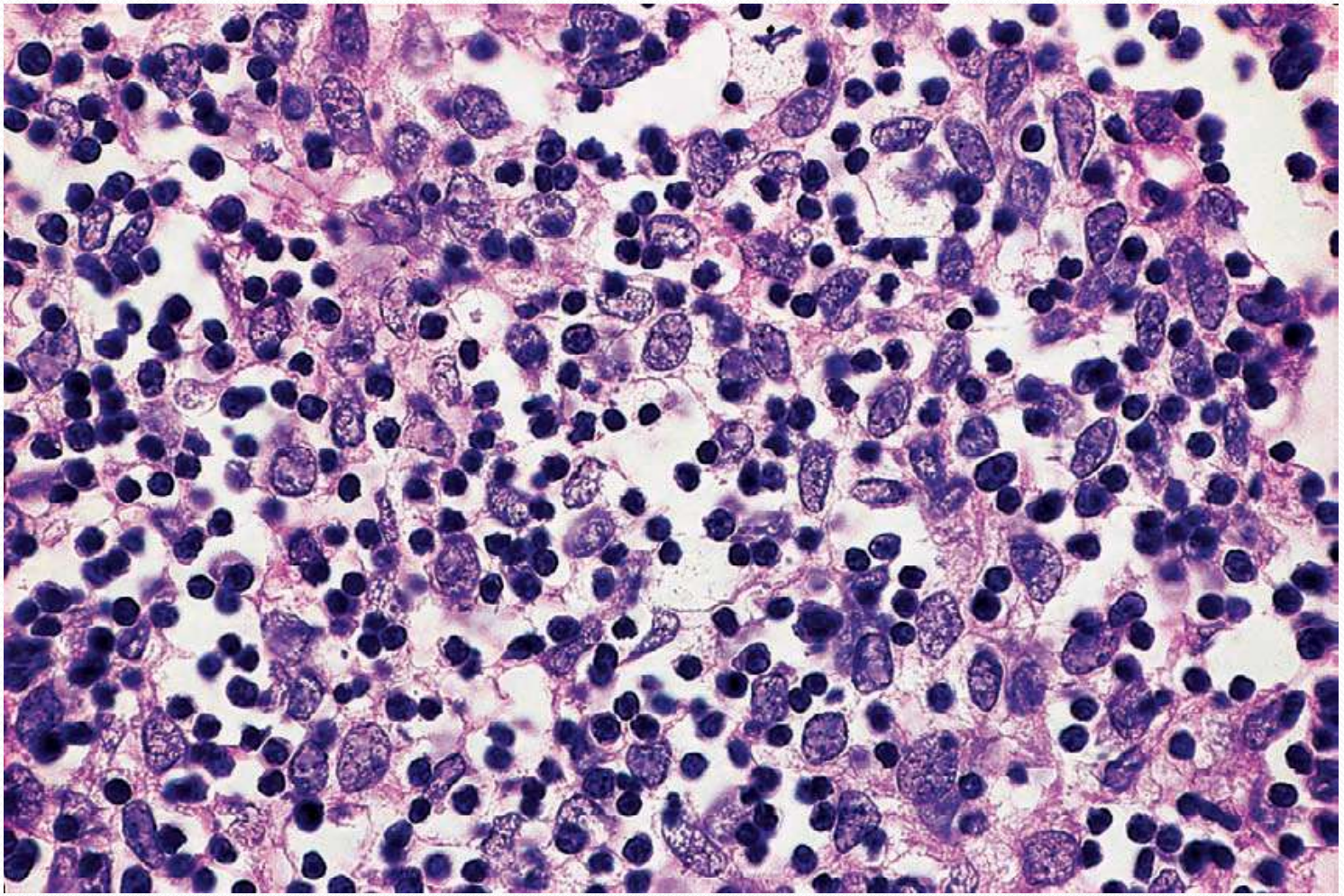
Type B2 Thymoma (Cortical)

- *A tumor in which the neoplastic epithelial component appears as scattered plump cell, often including small (≥3 contiguous epithelial cells) clusters, with vesicular nuclei and distinct nucleoli among a heavy population of immature T cells.*
- *Perivascular spaces are common and sometimes very prominent.*

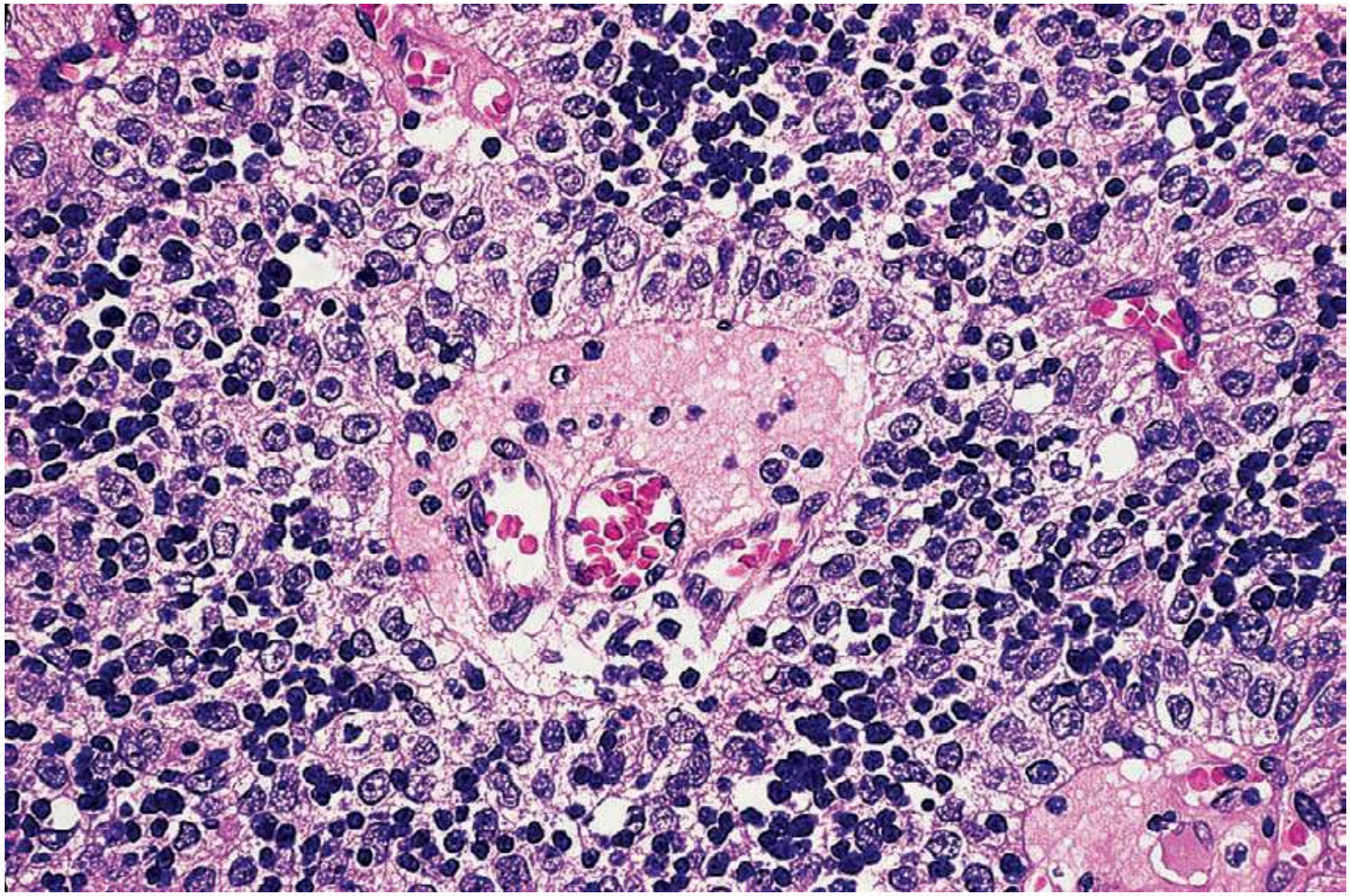
- *A perivascular arrangement of tumor cells resulting in a palisading effect may be seen.*
- *Medullary differentiation and rare Hassall corpuscles may be present but less conspicuous than in B1 thymoma.*
- *The cytoplasm of tumor cells tends to be abundant and the shape of cells are rounded or polygonal, this feature led to the alternative designation* ***(large) polygonal cell thymoma.***

- *Like B1 thymoma, type B2 thymoma is lymphocyte rich albeit to less degree, resulting in a mixed lymphocyte–epithelial pattern.*

Type B2 Thymoma



Type B2 Thymoma (Perivascular Space)



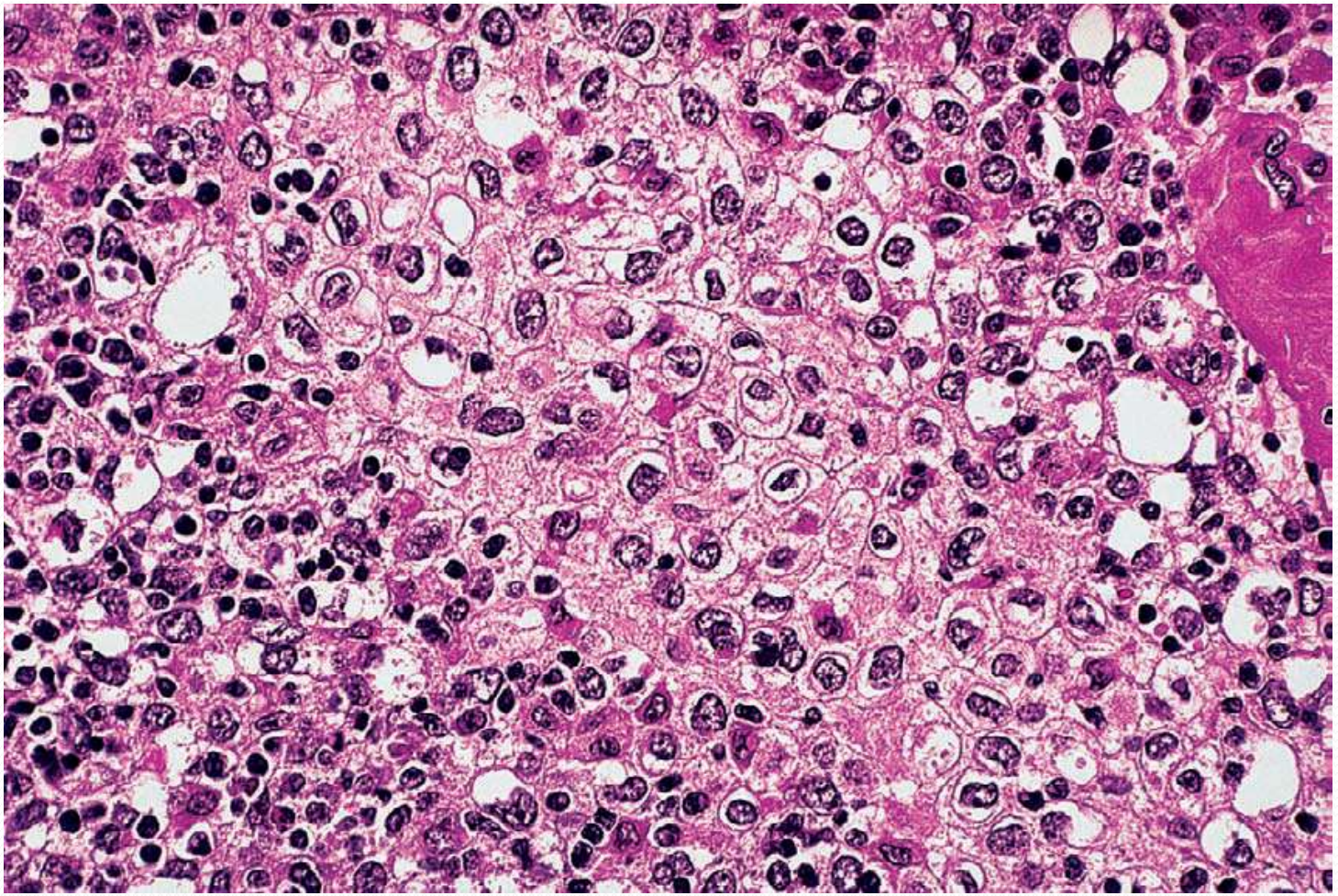
Type B3 Thymoma (Epithelial; Atypical; Squamoid; Well-Differentiated Thymic Carcinoma)

- *A type of thymoma predominantly composed of mildly atypical epithelial cells having round or polygonal shape admixed with minor component of immature T cells, resulting in a sheet-like growth of the neoplastic epithelial cells.*

- *This thymoma type was traditionally known as* ***epithelial,*** a term that is somewhat misleading since it implies that the other types of thymoma are not.
- *Another term that has been suggested for it is* ***atypical,*** but this is also somewhat inaccurate because the degree of atypia present in it may not be greater than that seen in type B2 thymoma, from which it is *distinguished on the basis of the proportionally larger number of epithelial cells compared to non-neoplastic lymphocytes.*

- *Another previously proposed term that was discarded is* ***well-differentiated thymic carcinoma,*** which is potentially confusing because in most classification schemes this tumor is included with the thymomas rather than with the thymic carcinomas.
- Another proposal is ***squamoid thymoma*** because of *the common presence of squamoid or squamous features in the tumor cells.*
- *However, this is neither a constant nor an exclusive feature of this tumor type.*

Type B3 Thymoma

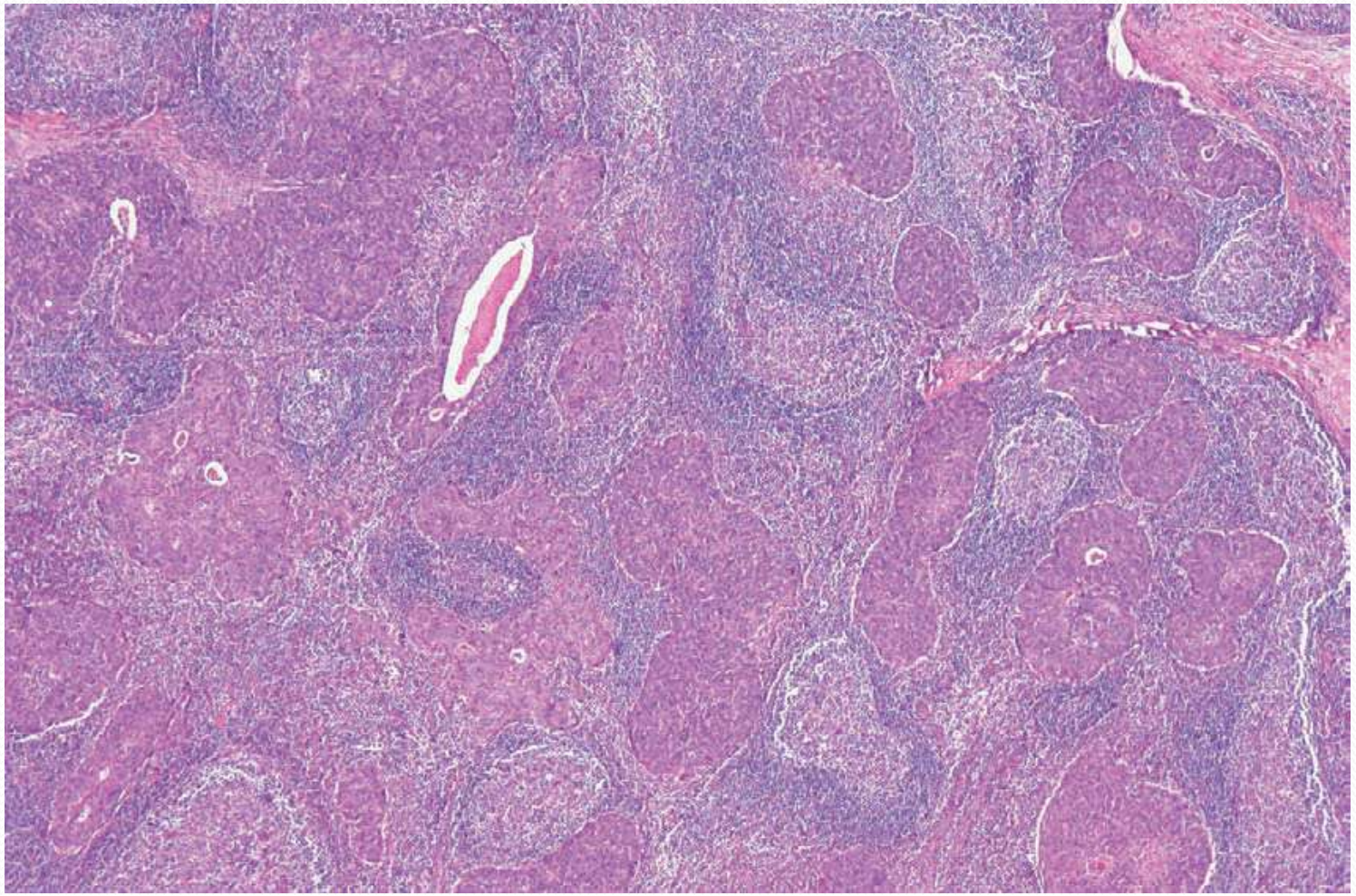


- ***Rare subtypes of thymoma that do not easily fit into the A-B nomenclature include:***
- ***Micronodular thymoma*** characterized by a *micronodular growth pattern in which epithelial islands are separated by lymphoid stroma that may include florid follicular hyperplasia.*
- *The lymphocytes are composed of B cells and mature T cells, and the epithelial cells are generally negative for CD20,* two findings that may be helpful in *distinguishing micronodular thymoma from type AB thymoma.*

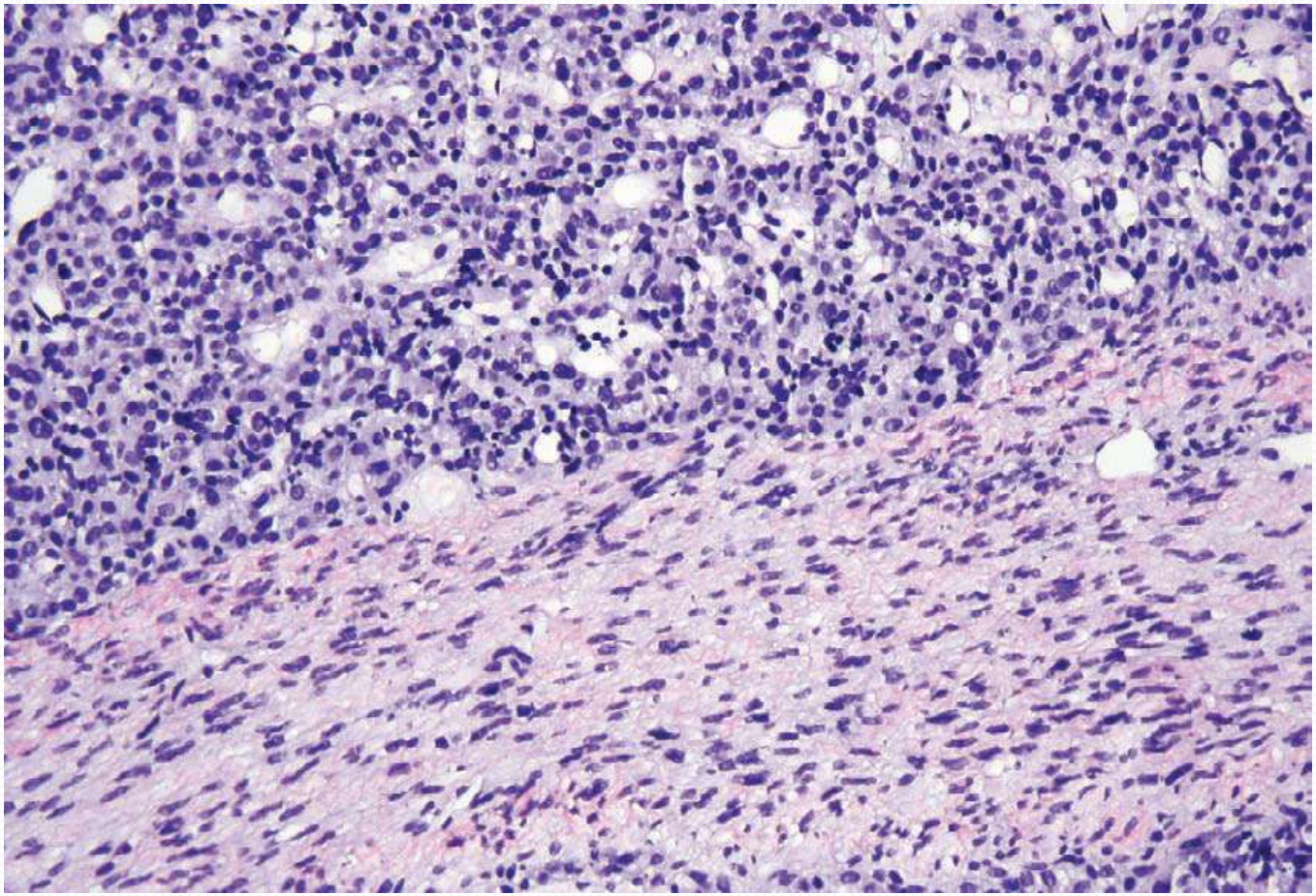
- ***Metaplastic thymoma*** is another rare subtype that, is a *biphasic tumor in which solid areas of epithelial cells are well demarcated from cytologically bland, fibroblast-like spindle cells.*
- ***Microscopic thymoma*** refers to *thymomas measuring less than 0.1 cm in greatest dimension and are usually discovered as multifocal incidental findings in thymectomies from patients with myasthenia gravis.*

- This lesion was referred to as ***nodular hyperplasia of thymic epithelium,*** which may be *a more accurate term.*
- ***Microscopic thymomas (nodular hyperplasia)*** are frequently found *in autopsies* as they are in patients with *myasthenia gravis*.

Micronodular Thymoma



Metaplastic Thymoma



Cytology

- *The most important criterion for cytological recognition of **thymoma** is the identification of distinct population of epithelial cells admixed with lymphocytes, confirmed by positive IHC for keratin.*
- ***Limitations of the procedure*** include *difficulty in separating various subtypes of type B thymoma* (not very important clinically) and *inability to detect invasion* (a critical prognostic factor).

Thank you