TUMORS OF THE MEDIASTINUM (III) THYMOMA AND THYMIC CARCINOMA

EMAN MS MUHAMMAD

Thymic Carcinoma

- ***Thymic tumor*** *exhibiting clear-cut cytological atypia and a set of cyto-architectural features no longer specific to the thymus (as for types A, AB, and B thymomas) but rather analogous to those seen in carcinomas of other organs as discussed before.*

Thymic Carcinoma

- *Thymic carcinoma is defined as thymic epithelial tumor exhibiting clear-cut cytological features of malignancy.*
- Despite its rarity, it displays a relatively large variety of microscopic patterns.
- ***As a group, they differ from other conventional types of thymoma in the following respects:***

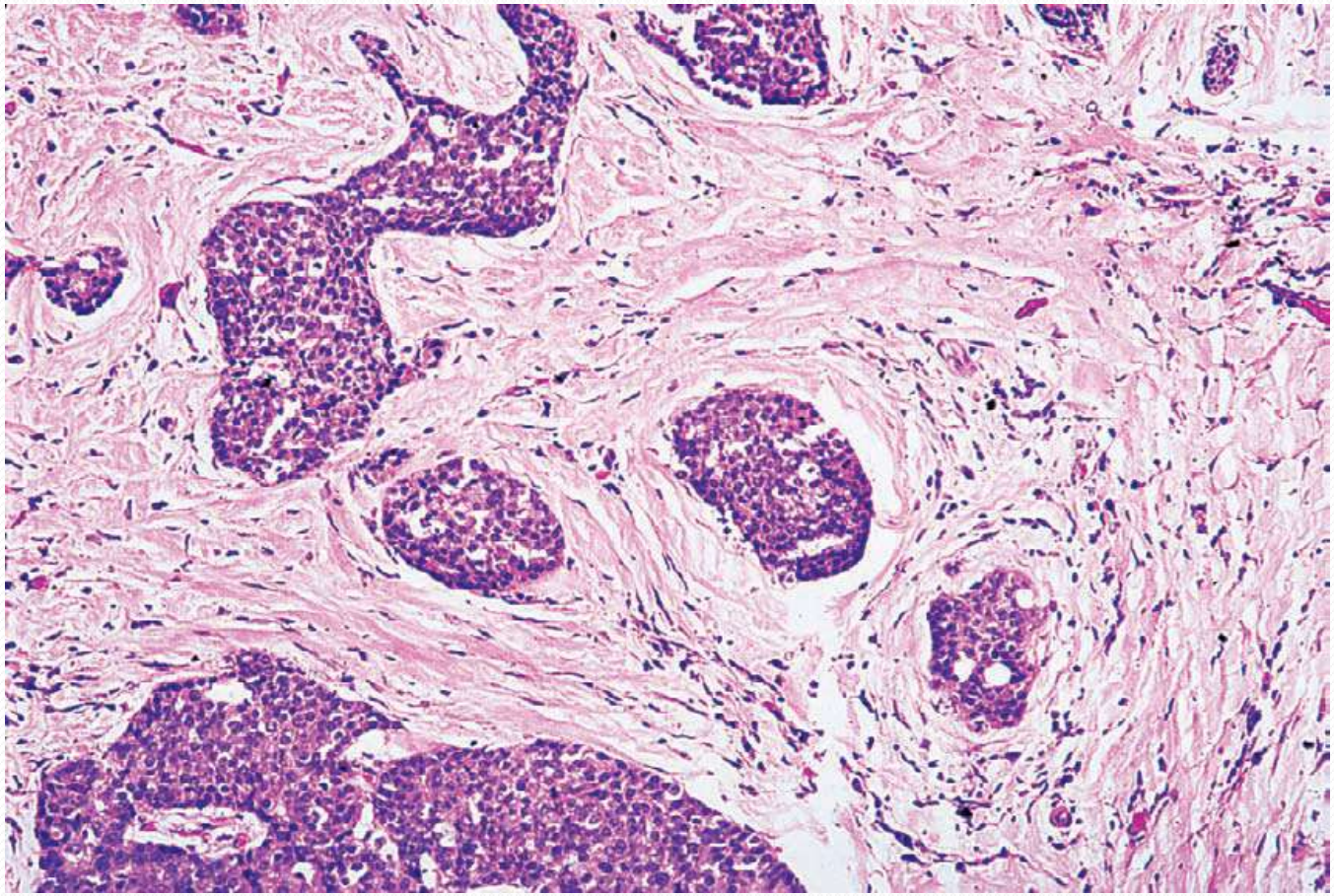
1. *They are very rarely associated with myasthenia gravis or any listed immune-mediated systemic diseases;*
2. *They generally lack all of the ancillary features of thymoma, such as perivascular spaces, foci of medullary differentiation, abortive Hassall corpuscles, rosettes, or gland-like spaces; and*
3. *They lack immature T lymphocytes.*

- *Lymphocytes may be present and even numerous, but they exhibit the phenotype of mature T or (rarely) B cells.*

- *Thymic carcinomas lack all of the morphologic and functional attributes of other thymoma types, allowing for the rare occurrence of intermediate or hybrid forms.*
- *Their appearance is similar to and sometimes indistinguishable from that of corresponding carcinoma types in other organs, and their specific identification as thymic neoplasms can therefore be difficult or impossible.*

- **Diagnosis** *is often one of the exclusion,* in the presence of a malignant epithelial tumor located in the thymic region in the absence of disease in the lung or any other organ.

Thymic Carcinoma



- ***Immunostains helpful in identification of the two major subtypes of thymic carcinoma are:***
- ***CD5*** *is present in the majority of thymic carcinomas but absent in other types of thymoma and in carcinomas of non-thymic origin;*
- ***CD117 (c-kit),*** *is positive in 80% or more of thymic carcinomas, almost always negative in thymomas, and occasionally positive in non-thymic carcinomas;*

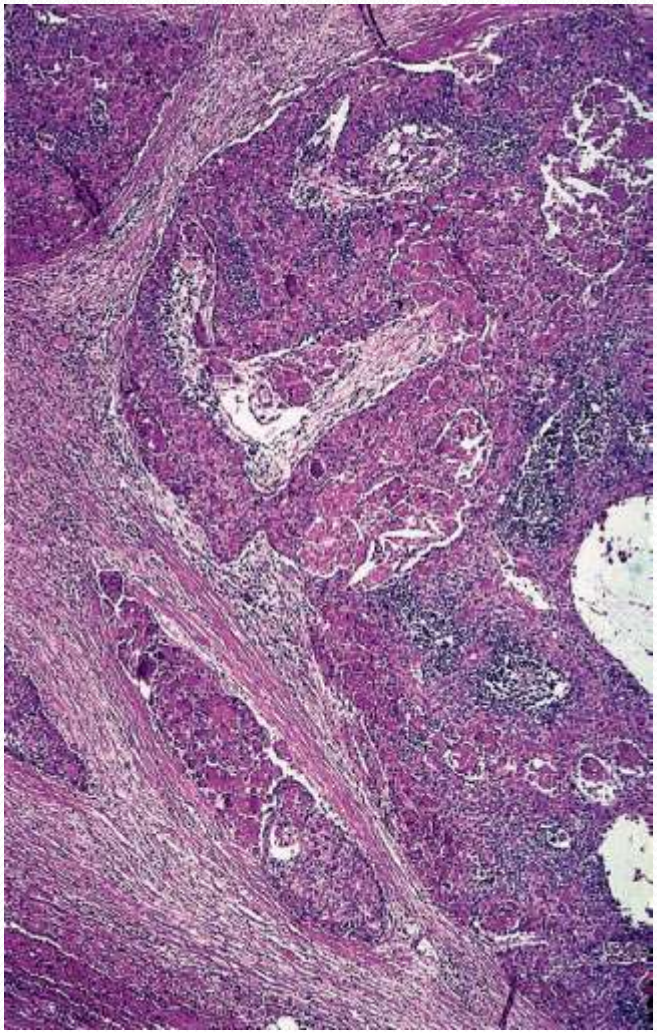
- ***CD70,*** TNF family that mediates the interaction between B and T lymphocytes which *is present in most thymic carcinomas but not in conventional thymomas;*
- ***CEA, MUC-1, and glucose transporter 1 (GLUT-1)*** are usually *positive in thymic carcinoma and are less commonly positive in B3 thymomas,*
- ***TTF-1,*** *stains high percentage of lung carcinomas but not thymic carcinomas.*

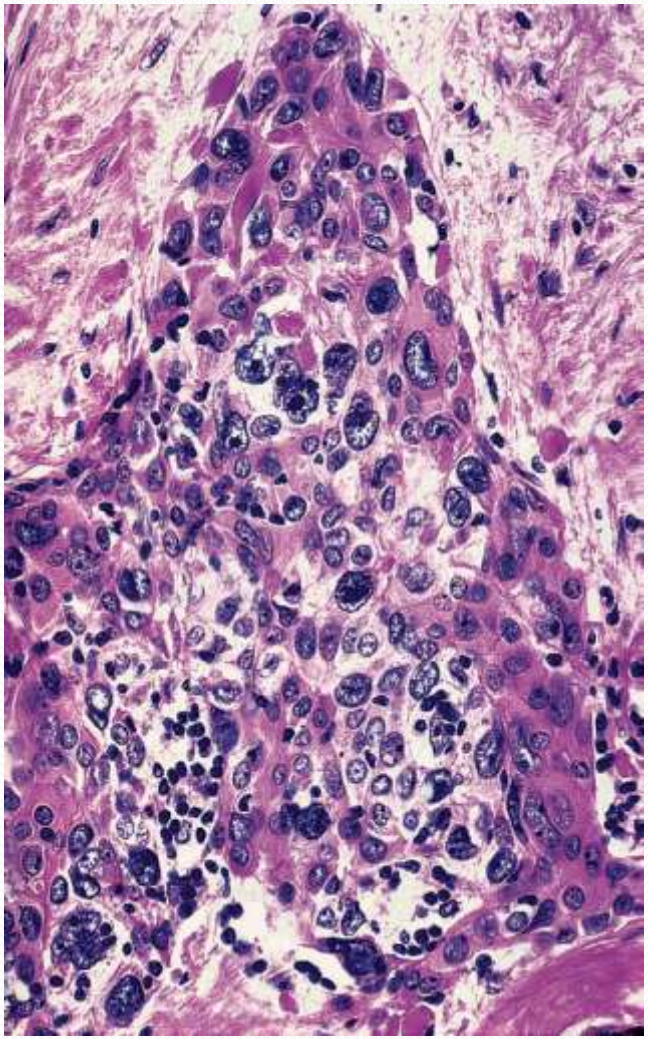
Squamous Cell Carcinoma (SCC)

- Like SCC in other sites, this form is composed of atypical polygonal epithelial cells arranged in characteristic epidermoid growth patterns often with associated *intercellular bridges.*
- The range of appearances is similar to SCC arising in other locations, including *well, moderately and poorly differentiated forms* that *may or may not demonstrate keratinization.*

- However, *a lobular pattern of growth* is generally maintained, and the tumor lobules are even more widely *separated from each other by fibrous bands* than in more conventional thymoma types.
- Before a diagnosis of primary SCC of the thymus is made, the *alternative possibility of metastatic carcinoma* (particularly from the lung) should always be considered.

Thymic Squamous Cell Carcinoma



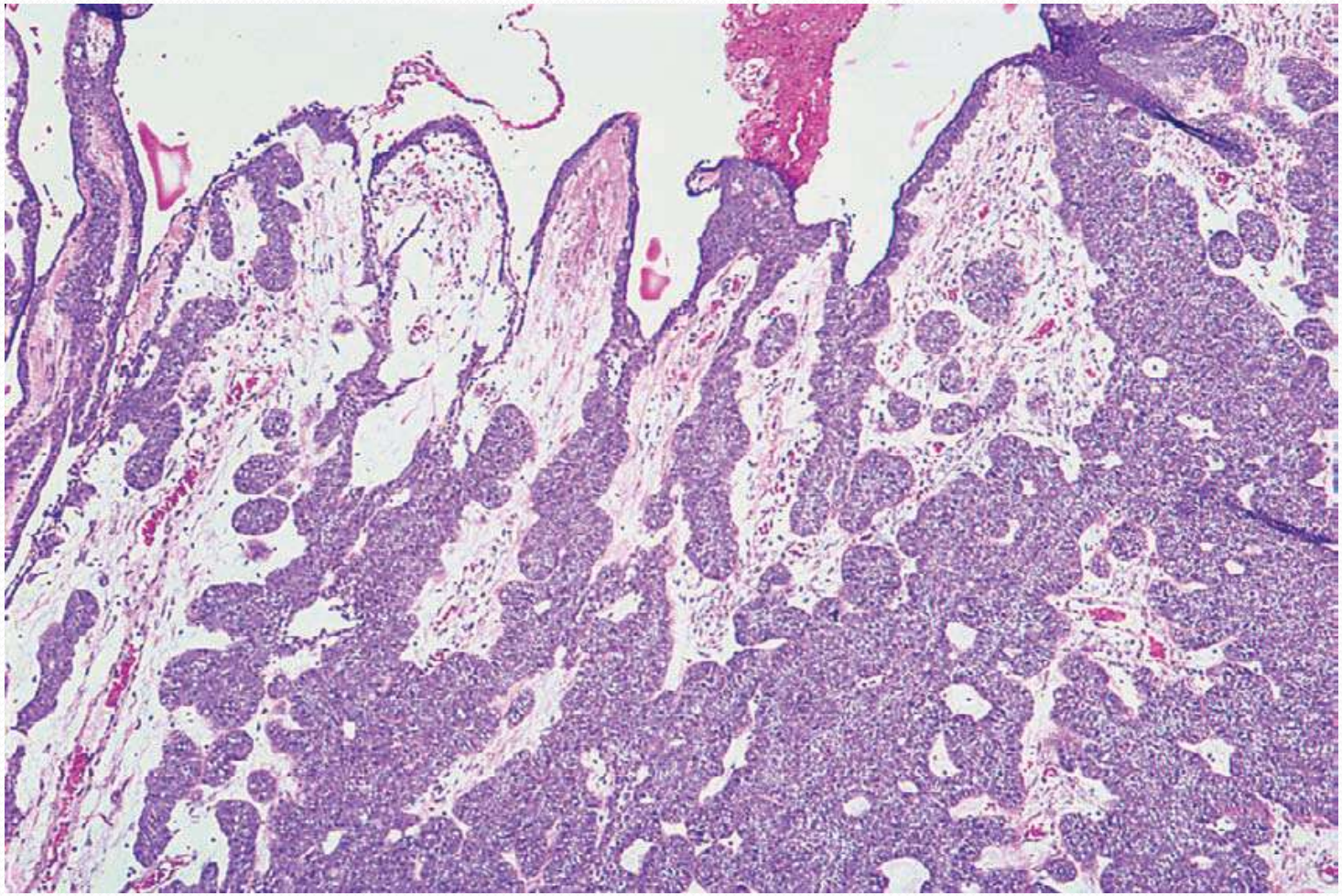


Basaloid Carcinoma

- This tumor is formed of *well-defined epithelial islands with prominent peripheral palisading, a combination of features typical of basaloid carcinomas arising in other sites including the lung.*
- *Focal squamous differentiation* is seen in a minority of cases.

- It may present as a *mural nodule in squamous-lined thymic cyst.*
- **The main differential diagnosis** is with *thymic carcinomas with adenoid cystic carcinoma-like features.*

Thymic Carcinoma of Basaloid Type

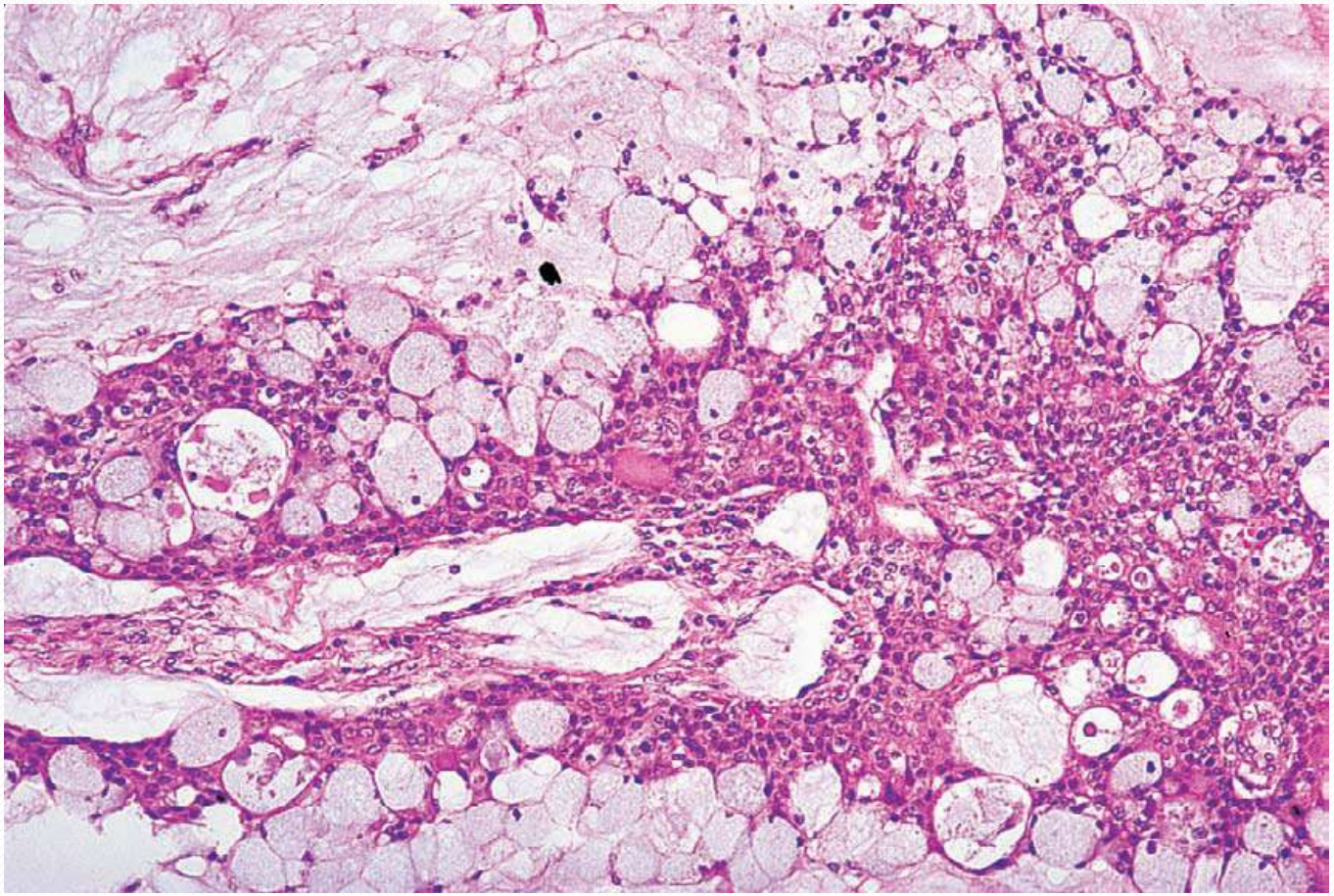


Mucoepidermoid Carcinoma

- *Alternate areas of squamous and mucin-producing glandular differentiation.*
- The histological features are *identical to mucoepidermoid carcinomas arising in major salivary glands and lung.*
- *Rearrangements of the **MAML2** gene characteristic of these tumors in other sites also occur in primary thymic mucoepidermoid carcinomas.*

- Most cases are *low-grade tumors and associated with good prognosis.*
- *High-grade and high-stage cases* are uncommon and portend a more aggressive and usually fatal course.

Thymic Carcinoma of Mucoepidermoid Type



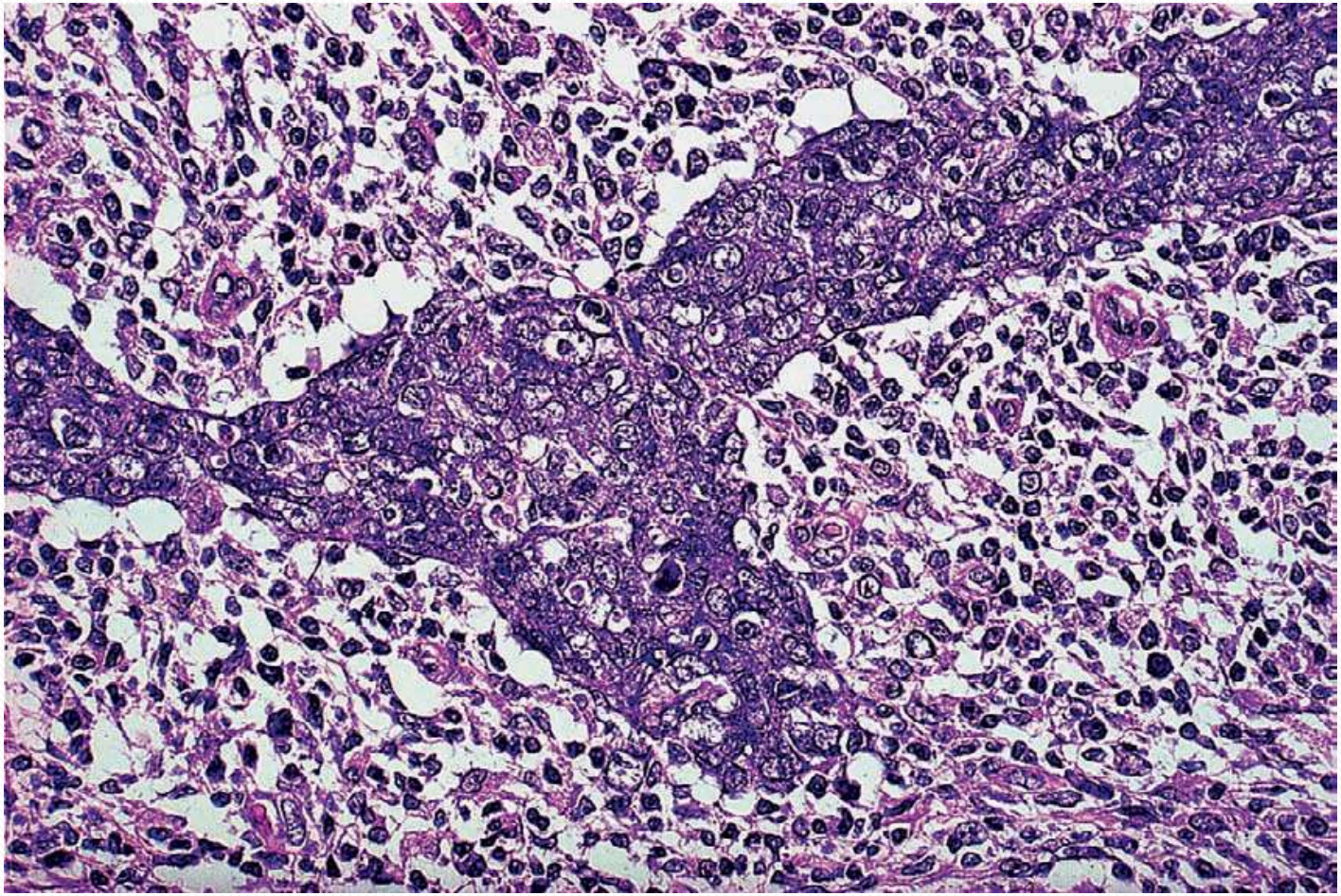
Lymphoepithelioma-Like Carcinoma

- The appearance is indistinguishable from of lymphoepithelial carcinoma (so-called lymphoepithelioma) of the tonsil and nasopharynx.
- *Large, deeply acidophilic nucleoli* that are *sharply outlined and perfectly round* are one of the hallmarks of this neoplasm, which is also characterized by a ***"syncytial"*** appearance.

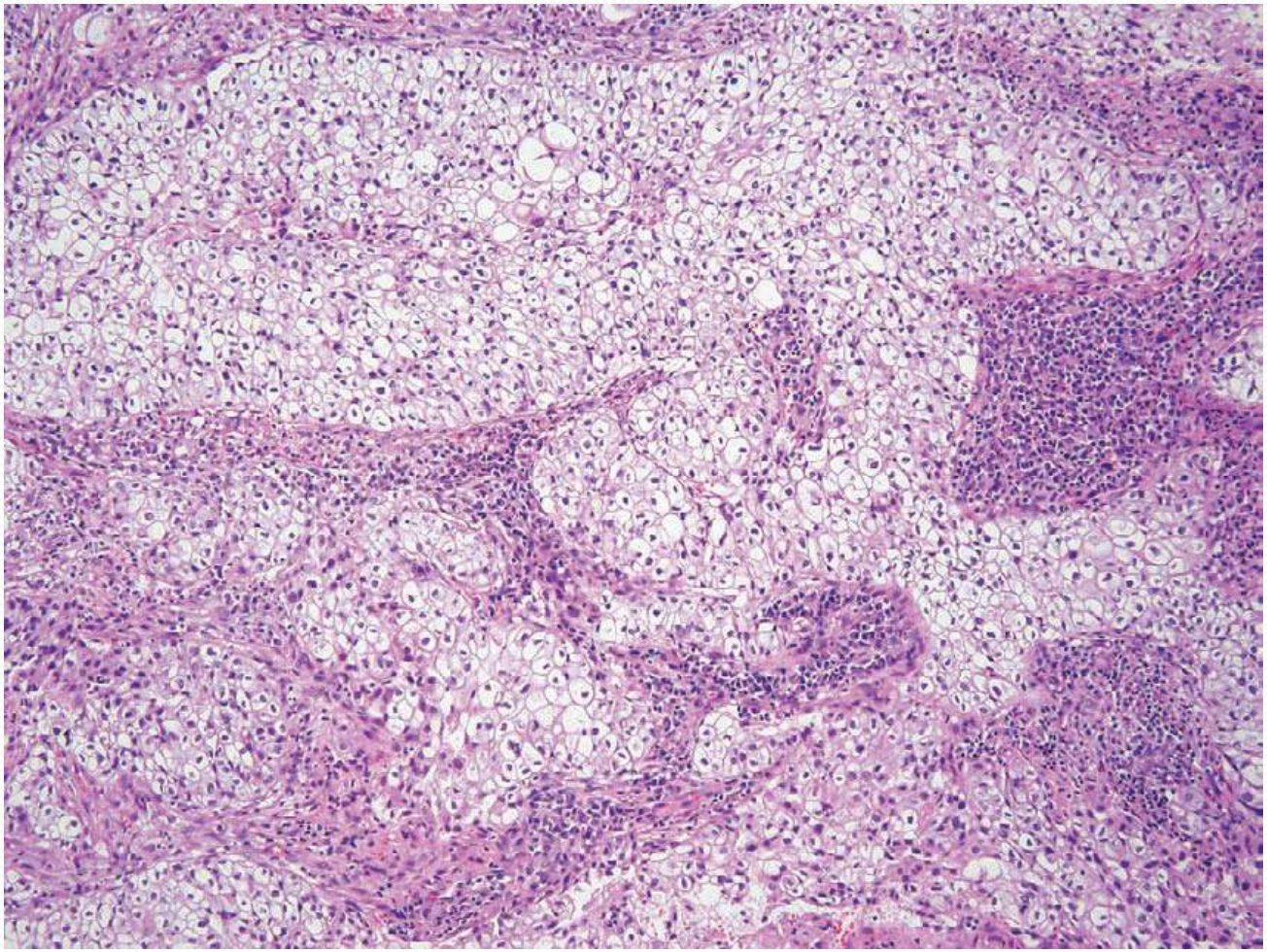
- *Keratinization and intercellular bridges are absent;* however, tumor cells are consistently *immunoreactive for keratin, including high-molecular-weight cytokeratins such as CK5/6, as well as p63 and p40.*
- **The lymphocytes** of this tumor, which can be very numerous, have the *phenotype of mature peripheral T cells rather than the immature thymocytes seen in ordinary thymoma.*

- Finding of ***EBV genome*** in some cases suggests *similarity with nasopharyngeal carcinoma*.
- *EBV is consistently absent from other thymic epithelial tumors.*
- **Clear cell carcinoma** is a rare variant *characterized by large amounts of glycogen-rich, clear cytoplasm in the tumor cells,* results in a resemblance to renal cell carcinoma.

Lymphoepithelioma-Like Variant of Thymic Carcinoma



Thymic Carcinoma of Clear Cell Type



Sarcomatoid Carcinoma (Carcinosarcoma)

- This malignant tumor simulates mesenchymal neoplasm by its *diffuse pattern of growth and the prominent spindling of tumor cells.*
- *Diagnosis is made by finding foci with epithelial appearance* or *evidence of epithelial phenotype in neoplastic spindle cells.*

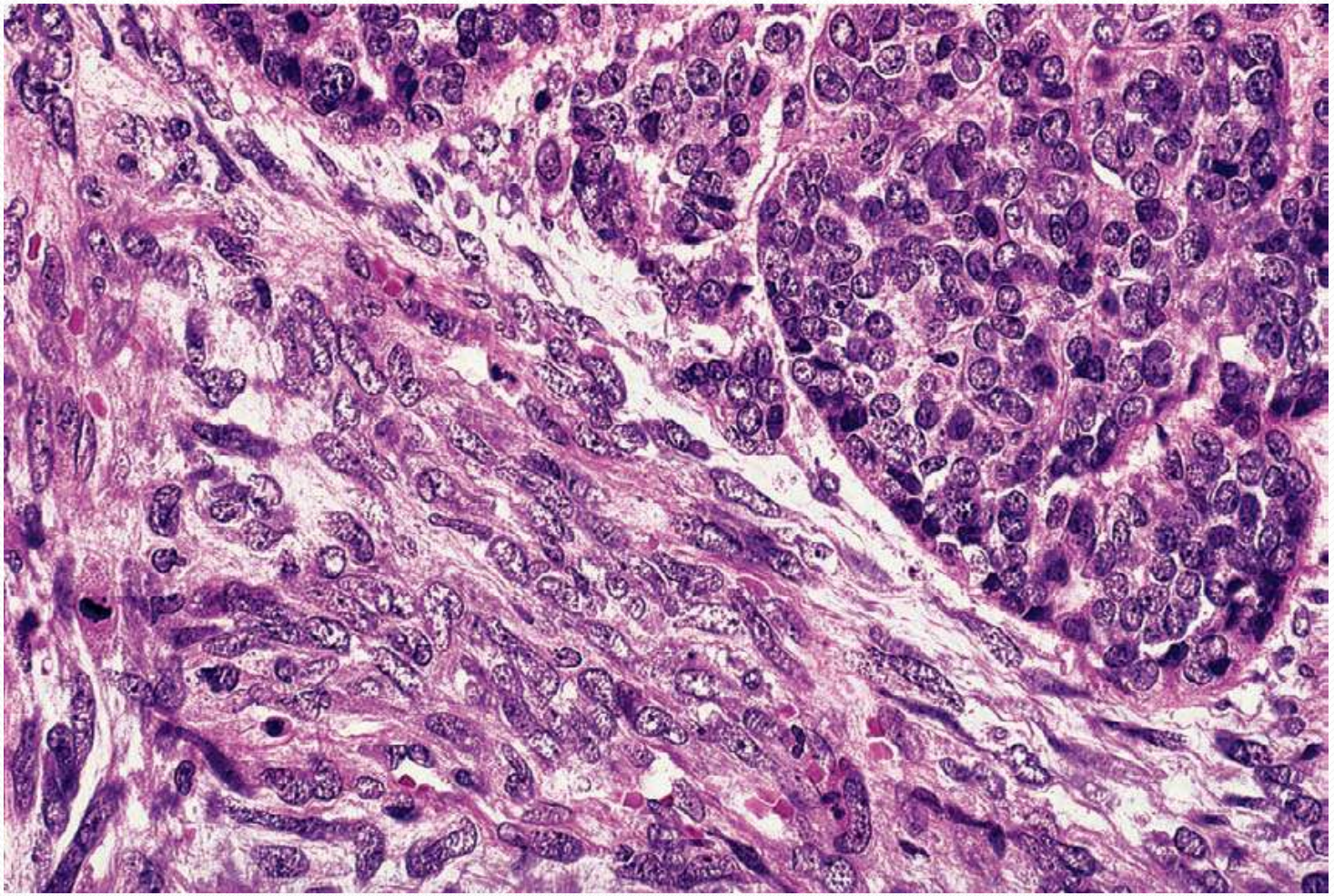
- *Distinction between sarcomatoid or spindle cell carcinoma and carcinosarcoma, both types represent carcinomas in which a component of the tumor undergoes* ***"phenotypic switch"*** **.**
- Sarcoma-like areas may include foci of cartilaginous and skeletal muscle differentiation, the latter is described as *rhabdomyosarcomatous thymic carcinoma.*
- *Skeletal muscle differentiation in cytologically bland* ***myoid cells*** is also described in thymomas and *is not by itself diagnostic of carcinoma.*

- *The differential diagnosis of sarcomatoid carcinoma includes germ cell tumors and malignant schwannoma* ***"triton tumor".***
- It also includes low-grade thymic tumor designated as ***metaplastic thymoma*** *in the current WHO classification and previously reported as thymoma with pseudo-sarcomatous stroma and low-grade metaplastic thymic carcinoma.*

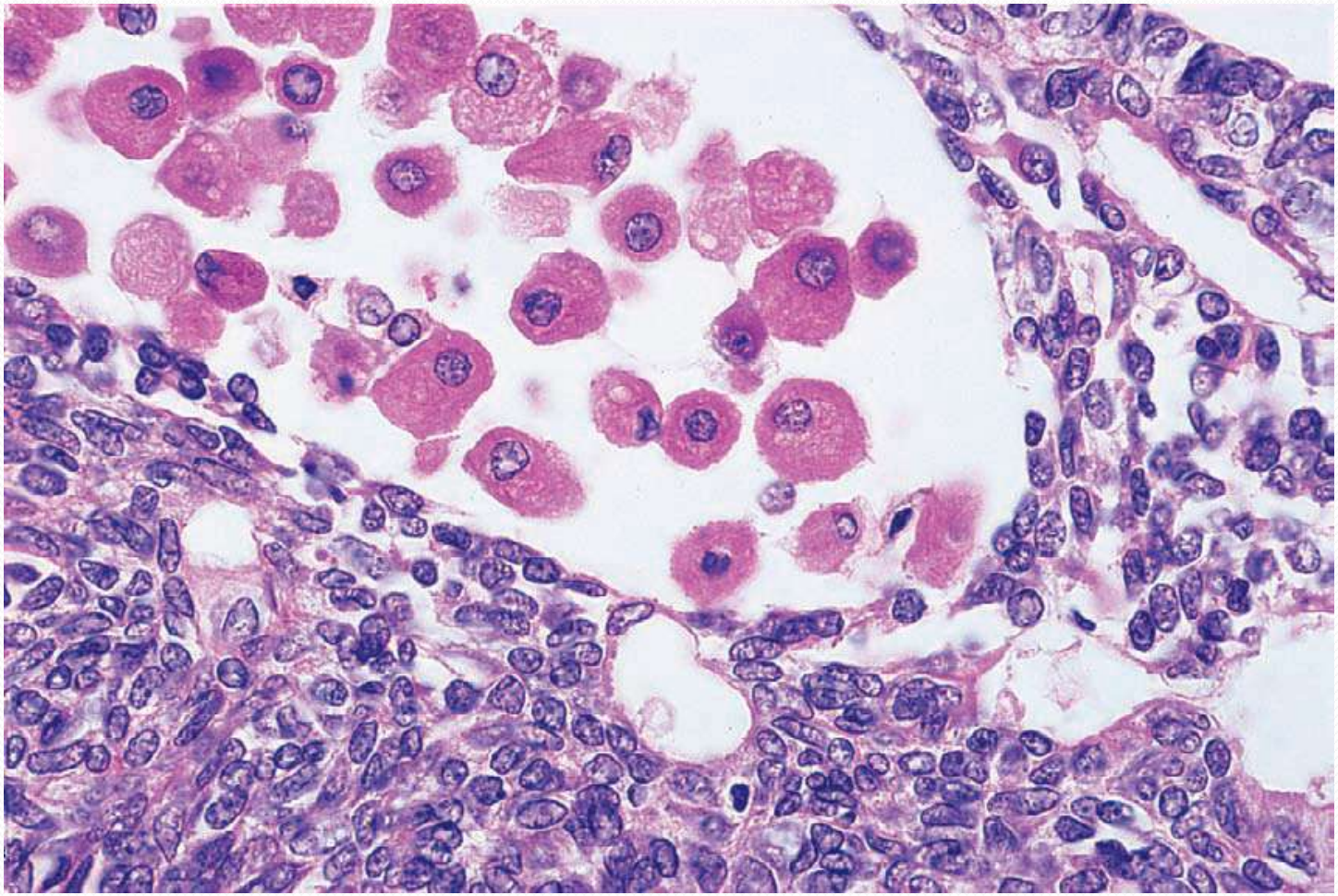
- It is characterized by *biphasic epithelial and spindle cell morphology, with absence of significant atypia and low proliferation rates in both components.*
- *WHO terminology places these tumors among thymomas "**metaplastic thymoma**" rather than thymic carcinomas while acknowledging the probable epithelial nature of the spindle cell component.*

- The appearance of the two components is very reminiscent of that seen in ectopic hamartomatous thymoma, suggesting that this lesion may represent its ***"orthotopic"*** counterpart.

Sarcomatoid Carcinoma of Thymus



Thymoma With Myoid Cells



Adenocarcinomas

- **Adenocarcinomas** are *extremely uncommon histologically heterogeneous group.*
- *Papillary adenocarcinoma resembles papillary thyroid carcinoma by virtue of the complex arborizing structure and the presence of psammoma bodies.*
- However, *it lacks optically clear nuclei, it is positive for CD5, and it shows no reactivity for thyroglobulin or TTF-1.*

- *Most cases have arisen from type A (spindle cell, medullary) thymomas.*
- *Mucinous and tubular adenocarcinomas are a rare variant including mucinous adenocarcinoma with enteric differentiation characterized by expression of cytokeratin 20 and CDX2.*

NUT (midline) carcinoma

- **NUT (midline) carcinoma** is highly aggressive and frequently lethal form of carcinoma.
- It affects younger individuals and accounts for fewer than 5% of poorly differentiated thymic carcinomas and undifferentiated thymic neoplasms.
- *It is high-grade carcinoma demonstrating squamous differentiation that affect midline structures, most commonly the mediastinum.*

- *Although **not pathognomonic,** the most common histological appearance is a highly undifferentiated carcinoma with variably conspicuous foci of abrupt squamous differentiation.*

- *Diagnosis depends on identifying the characteristic rearrangement of the NUT gene on chromosome 15q14 which results in fusion with a member of the bromodomain (BRD)-containing protein family, most commonly BRD4on chromosome 19.*
- *The disease-defining genotype can be identified using IHC for the fusion product, fluorescence in situ hybridization (FISH), or a reverse transcriptase-polymerase chain reaction (RT-PCR) technique.*

Undifferentiated (Anaplastic) Carcinoma

- *This tumor shows no detectable differentiation in any specific direction and tends to exhibit considerable pleomorphism.*
- *The more undifferentiated the neoplasm, the more seriously one should consider alternative possibilities, especially large cell or anaplastic lymphoma and germ cell tumors.*

- Upper mediastinal tumors in young adults have interpreted as undifferentiated thymic carcinoma with germ cell–like features, analogous to reported in the lung.
- Some cases of undifferentiated large cell carcinomas of the thymus *accompanied by a Castleman disease-like reaction* which featured an unexpectedly indolent behavior.

Rare variants of thymic carcinomas

1. *Carcinomas with adenoid cystic carcinoma–like features* resembles that in the salivary glands.

- These are among the rarest of thymic carcinomas; they tend to *present as multicystic lesions.*

2. The single example of *hepatoid carcinoma* on record so far *presented as a large solid mass* closely resembled HCC in nearly all respects except *that it was positive for cytokeratin 7 with co-expression of Hep Par-1 and negative staining for α-fetoprotein.*

Cervical Tumors of Thymic or Branchial Pouch Derivation

- *Ectopic thymic tissue and unilocular thymic cysts* can be found in the *lateral aspects of the neck* as a result of a malformation related to the third or possibly fourth branchial pouch.
- The following neoplasms can develop in a similar location and on have similar histogenetic basis.

1. **Ectopic (cervical) thymoma:**

- *The microscopic appearance of this tumor is not different from that of its mediastinal counterpart.*
- *A striking and unexplained predilection for the female gender is present.*
- *All reported cases behaved in a benign fashion.*

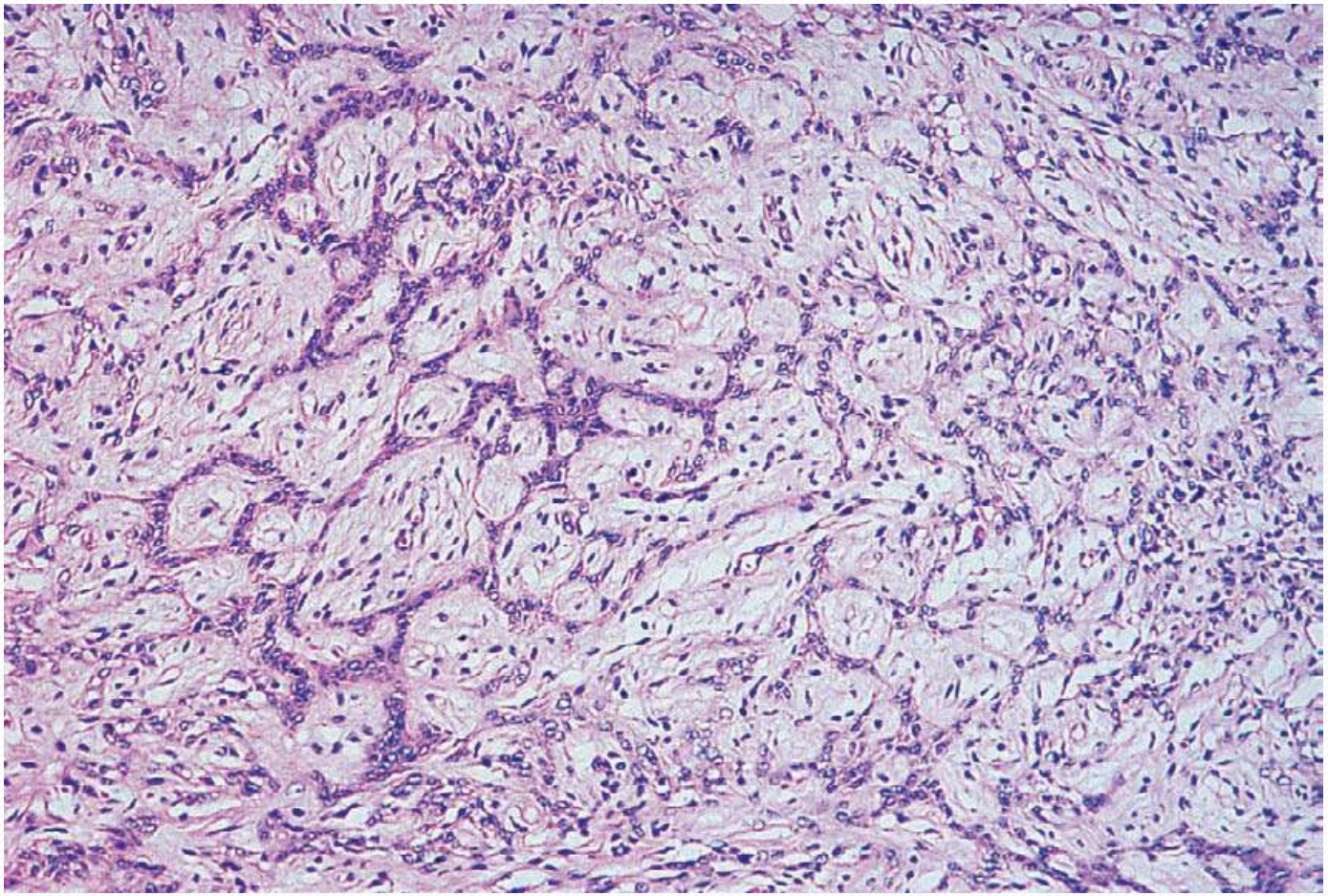
2. Ectopic hamartomatous thymoma:

- Location is the supraclavicular–suprasternal area.
- *It shares features of hamartomatous and neoplastic process.*
- *Nearly all patients are males, in contrast with the previous entity.*
- The bulk of the mass is *composed of epithelial cells that are extremely spindle shaped and mesenchymal-like.*
- *This finding often results in a misdiagnosis of Schwannian or fibroblastic neoplasm.*

- *However, ultrastructural examination or keratin immunostaining reveals their epithelial nature.*
- *Atypia, necrosis, and mitotic figures are absent.*
- *The other component (which can be very focal) is solid squamous nests, thin anastomosing cords (sometimes composed of clear cells), and epithelial-lined cysts.*
- *Islands of mature fat and clusters of small lymphocytes may also be present.*
- *This tumor, which may reach a huge size, does not seem to have a mediastinal counterpart.*

- *The behavior is benign, with occasional local recurrence, but exceptional cases with superimposed carcinoma are recorded.*
- *Although originally hypothesized to be derived from **third branchial arch**, others suggested origin from **branchial cleft remnants** that lack an embryological link to the thymus.*
- Ectopic hamartomatous thymoma is a rare clinically and histopathologically distinct entity that *should not be confused with other potentially more aggressive lesions.*

Ectopic Hamartomatous Thymoma



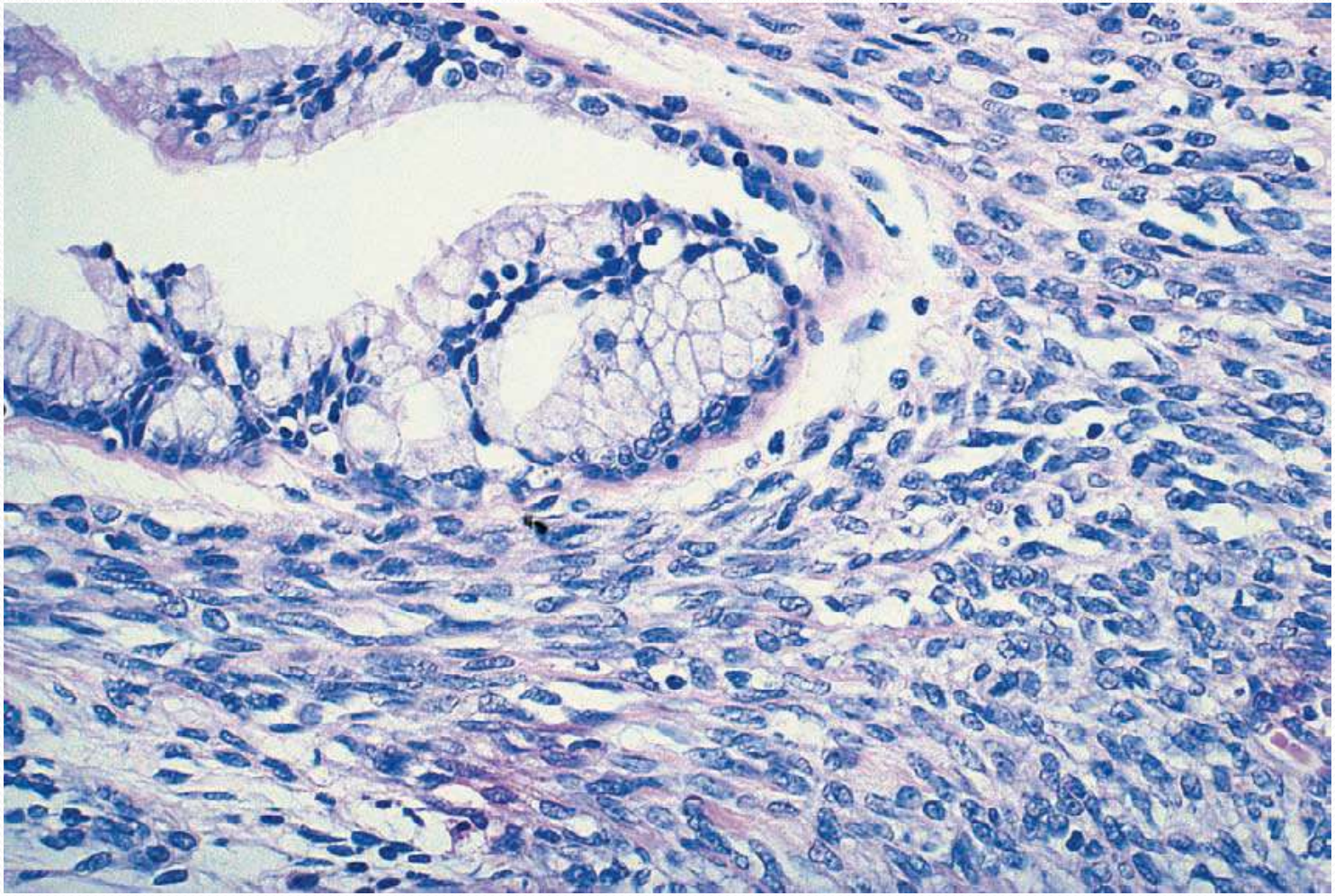
3. **Spindle epithelial tumor with thymus-like elements (SETTLE):**

- Most cases of this rare neoplasm was found in *adolescents or young adults* and was located *in or around the thyroid.*
- **Microscopically,** *biphasic pattern resulting from predominant spindle cell component (more cellular than in the previous type and mitotically active)* and *mucin-secreting, occasionally cystic glandular component is present.*

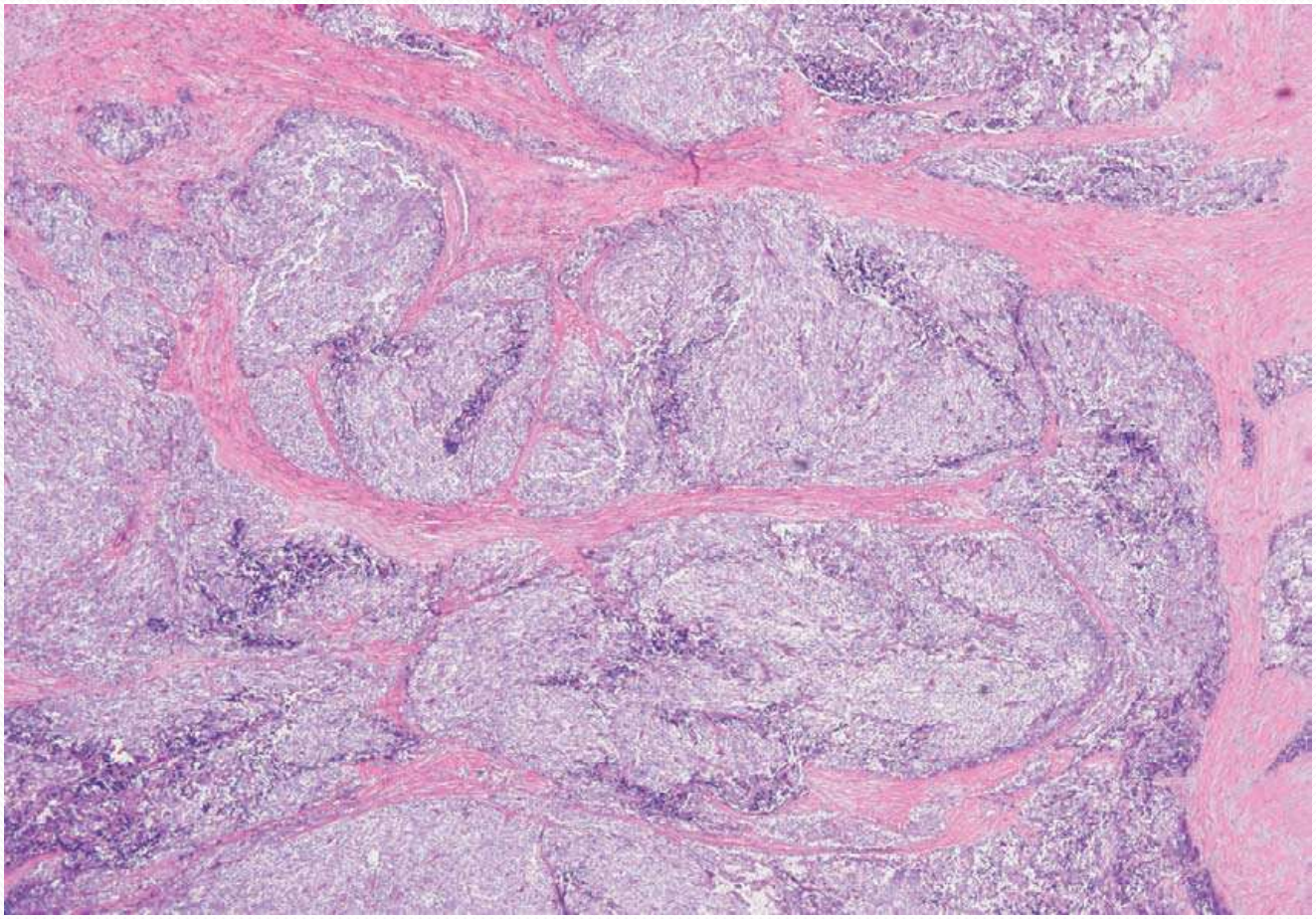
- *IHC and ultrastructurally, both tumor components have an epithelial phenotype.*
- *Prominent mitotic activity and focal necrosis was reported in some cases.*
- *K-RAS gene mutation was detected in a single example of this entity.*
- *SETTLE lacks the fusion genes characteristic of synovial sarcoma.*
- *Natural history is characterized by tendency for late (measured in years or decades) distant metastases.*

- The main differential diagnosis is ***synovial sarcoma,*** particularly when the spindle cell component predominates *"predominantly monophasic" to near exclusion of glandular element.*
- SETTLE should be favored in *the presence of stromal hyalinization, lower overall grade, presence of glomeruloid glandular structures, absence of intraglandular necrotic debris, and diffuse expression of high-molecular-weight keratin.*
- *If doubts persist, molecular studies for synovial sarcoma fusion genes can be helpful.*

Spindle Epithelial Tumor With Thymus-Like Elements (SETTLE)



“Monophasic” SETTLE

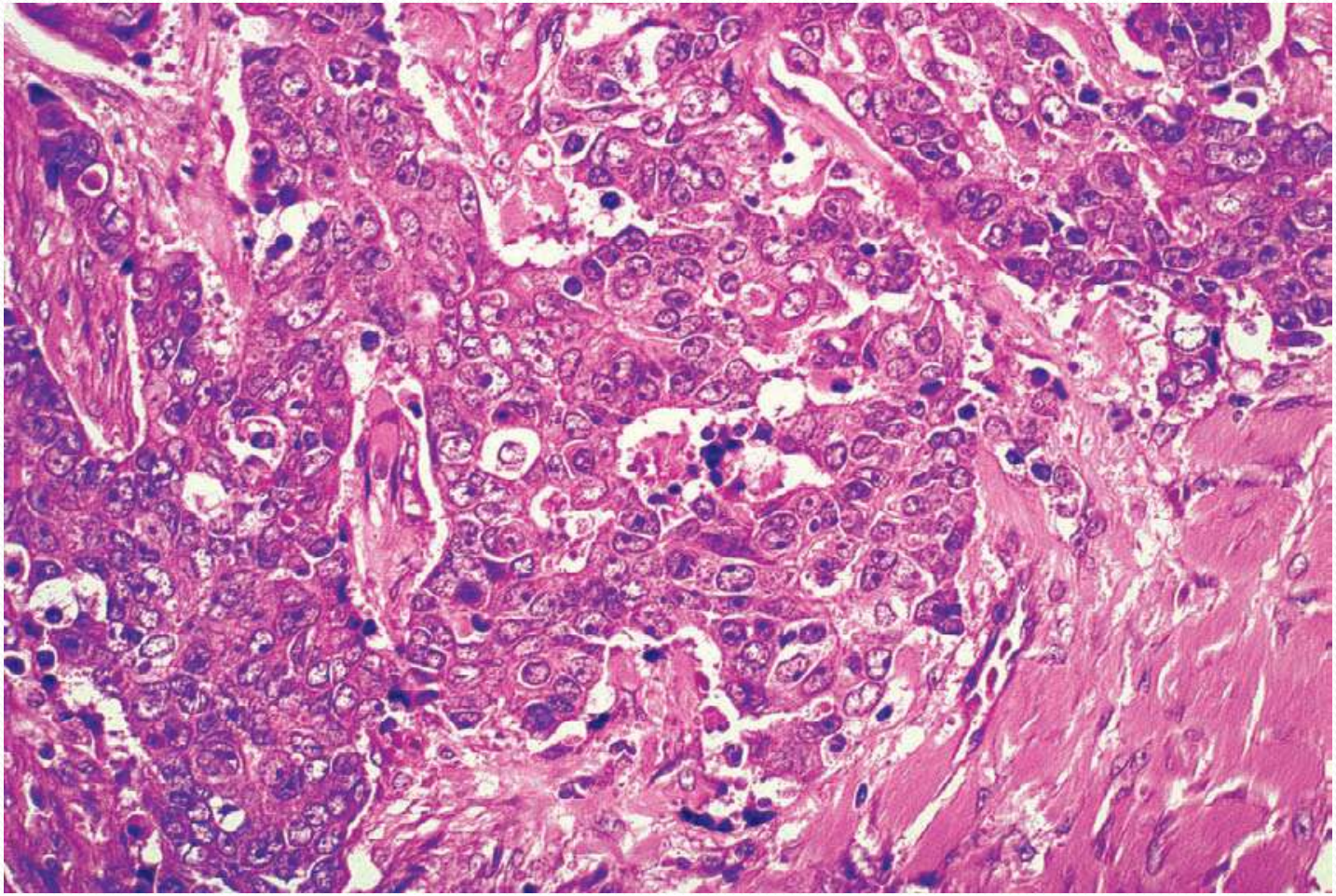


4. **Carcinoma with thymus-like elements (CASTLE):**

- *This tumor also tends to be located within or around the thyroid, to the point that most of the earliest reported cases were thought to represent squamous cell or undifferentiated carcinomas of this organ.*
- *Their microscopic appearance* is *indistinguishable from thymic carcinoma*, of which it can be *regarded as its ectopic (cervical) equivalent.*

- Support for the thymic rather than thyroidal origin of CASTLE is provided by its *immunoreactivity for CD5, CD117, high-molecular-weight keratin, Bcl-2, p63, and mcl-1 (all these markers are usually positive in thymic carcinoma) and negativity for thyroglobulin and TTF-1.*
- The tumor has ***tendency for late local recurrences,*** but its *behavior is indolent, more than undifferentiated thyroid carcinoma.*

Carcinoma With Thymus-Like Elements (CASTLE)



Thank you