23 Thymus and Mediastinum

The thymus is a lymphoepithelial organ in the anterior mediastinum and is the site of maturation for T cells, serving a similar function as lymph nodes for B cells. Unlike lymph nodes, however, the thymus has a prominent epithelial component. It is these epithelial cells that give rise to the tumors called thymomas and thymic carcinomas. Lymphomas can also arise within the thymus, as can tumors of other cell types that are found in smaller numbers in the thymus, such as nerves, fat, smooth muscle, and even germ cells. While lymphomas, germ cell tumors, and soft tissue tumors are familiar to us from other sites, the thymomas are unique to the thymus, are rarely seen, and suffer from a particularly opaque classification system, making them a pretty inaccessible subject. But thymomas, as it turns out, are not so bad once you get to know them.

Normal Histology

The thymus is a lobulated organ, as you will see best in examples of fetal autopsy thymus. Each lobule is made up of an outer cortex (the darker, more densely lymphocytic area) and an inner medulla (pale due to lower cellularity). Embedded invisibly within these areas is an extensive epithelial network, which is only noticeable on H&E as the squamous nests within the medulla called Hassall's corpuscles (Figure 23.1) but can be nicely highlighted by staining for cytokeratins. The epithelial cells within the cortex and medulla differ in their antigen profile and are presumed to give rise to different varieties of thymoma.

The lymphocytes within the thymus are a mix of B and T cells. The T cells begin life as lymphoblasts at the subcapsular perimeter of the thymus (Figure 23.2); like other lymphoblasts they are positive for the blast marker TdT by immunostain. As they mature and become exposed to antigens, they migrate inward through the cortex and to the medulla, finally leaving the thymus from the medullary vessels as mature T cells. Before maturity these immature T cells are called *thymocytes*. The B cells are not undergoing maturation but may organize into germinal centers as they do everywhere else in the body. The presence of lymphoid follicles and germinal centers is not, by itself, pathologic, but the autoimmune disease *myasthenia gravis* is associated with follicular hyperplasia within the thymus.

The thymus gradually involutes throughout life, which is to say the lymphoepithelial structure is gradually replaced by fat. In an adult, all that may remain is a mass of fat in the mediastinum with microscopically visible nests of lymphocytes and Hassall's corpuscles. It is the recognition of these corpuscles that enables you to definitively identify the tissue as the thymus. Most thymomas occur in adults, so evidently the involution is not protective against neoplastic transformation. The thymus may also be found anywhere along the anterior mediastinum, as far up as the thyroid, so always think of it when you see tiny squamous whorls within lymphoid tissue—interpreting ectopic thymus as metastatic carcinoma would be particularly egregious.

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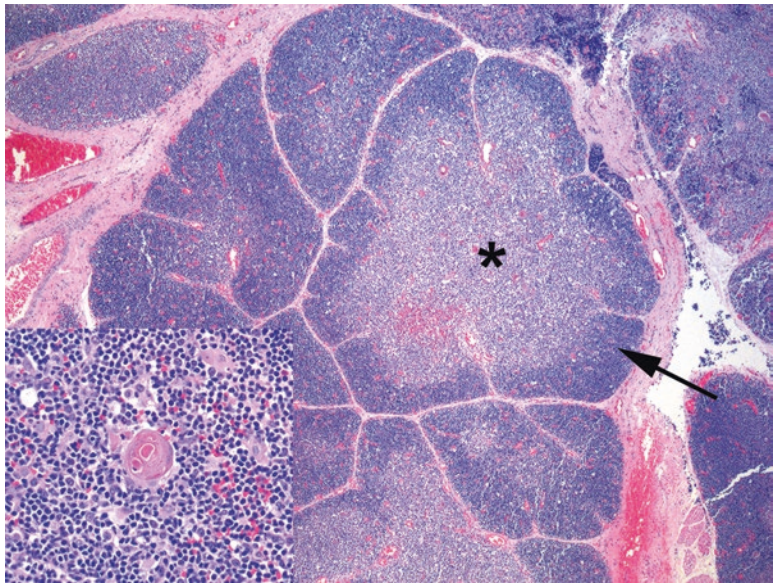

Figure 23.1. Normal fetal thymus. The lobular organization of the thymus is visible here, with darker outer cortical areas (*arrow*) and pale inner medulla (*asterisk*). Delicate fibrous bands separate the lobules. *Inset*: Hassall's corpuscles are small pink squamoid nests.

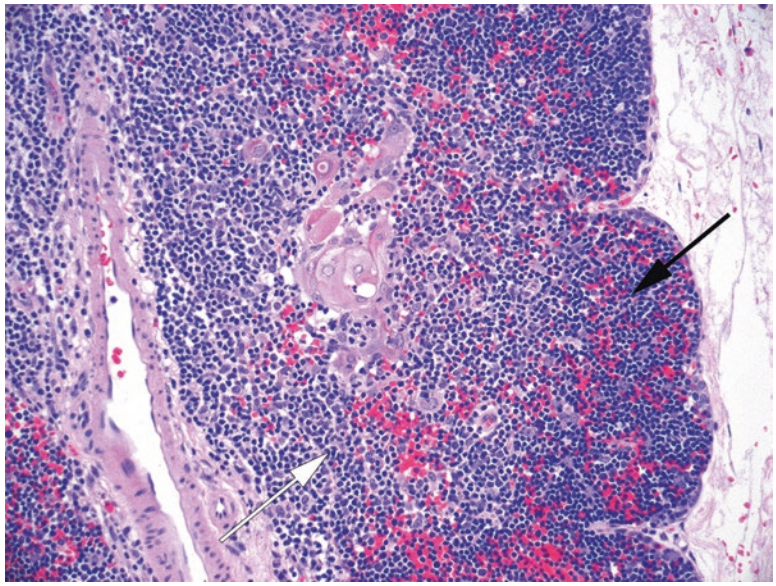

Figure 23.2. Normal thymic T cells. T cells begin as immature T cells with a high N/C ratio at the periphery of the outer cortex (*black arrow*) and migrate inward toward the medulla (*white arrow*) where they mature and exit the thymus.

Thymic hyperplasia is more of a clinical diagnosis than a pathologic one, as the thymus appears histologically normal, but simply weighs more than it should for age. True thymic hyperplasia is not associated with prominent lymphoid follicles and may be unrelated to autoimmune disease. *Thymic lymphoid hyperplasia* (also called thymic follicular hyperplasia or thymic germinal center hyperplasia), on the other hand, is characterized by prominent germinal centers and is often associated with myasthenia gravis. The weight or size of the thymus may be normal.

Neoplasms

The term *thymoma* refers to tumors of thymic epithelium. Many types of thymoma also have a lymphocytic component, but the lymphocytes are polyclonal bystanders; thymomas are not lymphomas. Lymphomas do occur in the thymus but most are the familiar varieties covered in other chapters (Hodgkin disease, T cell lymphoblastic lymphoma, anaplastic large cell lymphoma, etc.) and will not be discussed here. Of the thymomas, there are three basic categories (Table 23.1): thymomas presumably arising from medullary epithelium (called type A, usually indolent), thymomas presumably arising from cortical epithelium (type B), and a mixed type called Type AB. What used to be called a "Type C" thymoma is now designated thymic carcinoma. The carcinomas are often squamous but may take the morphology of almost any other carcinomas found elsewhere in the body. The thymomas, however, are unique to the thymus.

Type A thymomas are easily recognizable as tumors. They are encapsulated solid masses, often with thick fibrous bands, comprised of pure populations of spindled to epithelioid cells that clearly do not belong in normal thymus (Figure 23.3). The cells are bland, however, with

Table 23.1. Thymomas.

	Type B thymoma			
Type A thymoma	B1	B2	B3	Thymic carcinoma
Type AB				
Good prognosis	→ Increasingly worse prognosis →			Poor prognosis
Medullary (spindle/ ovoid) epithelium	Cortical epithelium			Many subtypes
EMA +, CK5/6 –	EMA – , CK5/6 +, some CD5 +			CD5 + or –
No atypia	→ Increasing epithelial atypia →			Atypical cells
Mature T cells	Immature T cells which are TdT +			N/A
Minimal lymphoid component	Dense lymphocytic component	Intermediate lymphoid component	Minimal lymphoid component	Minimal or no lymphoid component
Often spindled but many possible morphologies	Resembles normal thymus	Increasing epithelial cells	Sheets of epithelial cells	Sheets of malignant cells
Encapsulated (usually)	Encapsulated → to → infiltrative			Infiltrative

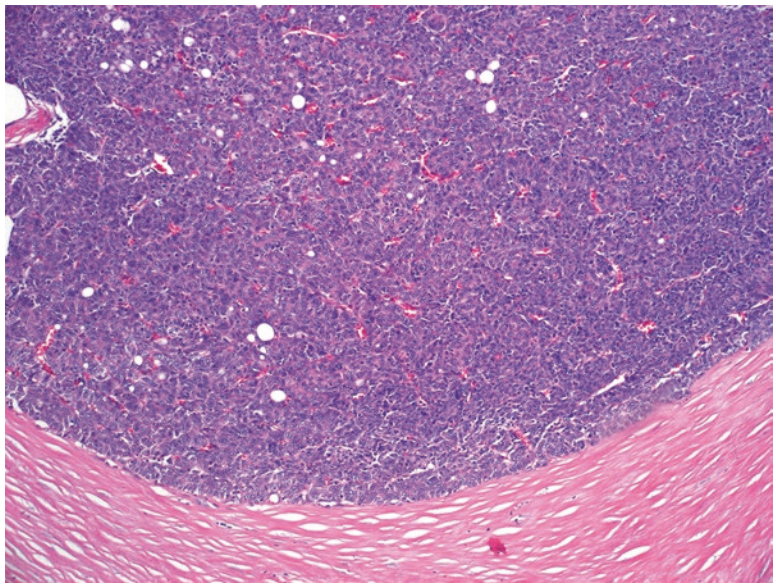

Figure 23.3. Type A thymoma. The cells are spindled and jumbled, with pale nuclei and overlapping cells. The dense fibrous capsule is typical. Lymphocytes are scarce. The architectural patterns in Type A thymoma can vary widely, however.

pale chromatin and no significant atypia or mitotic activity. Adjacent compressed thymus may be visible around the tumor; advanced stage or extension beyond the thymus is not common in this subtype. What makes the Type As tricky is that they may take on many different architectural patterns, including storiform, fascicular, hemangiopericytoma-like, rosetting, or cribriform. However, immunostains and their location in the thymus are usually enough to establish the diagnosis.

The *Type B thymomas* are lymphoepithelial tumors. Unlike the relatively pure epithelial populations of Type A thymomas and carcinomas, the Type B group recruits immature T cells to the tumor, which can mask the underlying neoplastic epithelium. The Type B thymomas are subdivided based on the relative proportion of lymphocytes and tumor cells, from B1 (lymphocyte-rich, so they look blue) to B3 (predominantly epithelium, so they look pink). The B1 thymomas are, in fact, so lymphocyte-rich that they may be mistaken for normal thymus or lymphoma (Figure 23.4). Like normal thymus, they may have pale areas of medulla with Hassall's corpuscles. Ideally they have a distorted architecture and thickened fibrous capsule that sets them apart from normal thymus. The B2 thymomas are not divided from B1 by strict criteria, but instead show increasing proportions of epithelial cells, now distinctly visible as nests and aggregates (Figure 23.5). Unlike in the Type A thymomas, the tumor cells in the Type B thymomas are somewhat atypical, with large vesicular nuclei and nucleoli. The background T cells, also unlike the Type A tumors, are immature and will stain for the blast marker TdT.

The B3 thymomas are the most aggressive of the Type B group. As above, there is not a strict cutoff between a cellular B2 and a B3, but the B3 thymomas are predominantly made up of atypical epithelial cells, with a sparse background of immature T cells (Figure 23.6). They frequently invade through the capsule and are more likely to present at high stage, with invasion into mediastinal structures. Unlike carcinoma, there should not be a desmoplastic stromal response.

The *Type AB thymoma* represents a collision or hybrid between a spindle-cell Type A and a lymphocyte-rich Type B (usually B1 or B2) tumor. The areas of each tumor type appear as discrete nodules (Figure 23.7) or intimately intermixed, and the cells within each component stain as would be expected in a pure tumor of that type (e.g., immature T cells in the Type B component). Remember that a Type A thymoma should not have a significant lymphocytic population, so the presence of lymphoid foci within a Type A may be enough to classify it as a Type AB. This is differentiated from the rare *micronodular thymoma*, in which small islands of spindled epithelioid cells are suspended in a background of predominantly mature B cells and germinal centers.

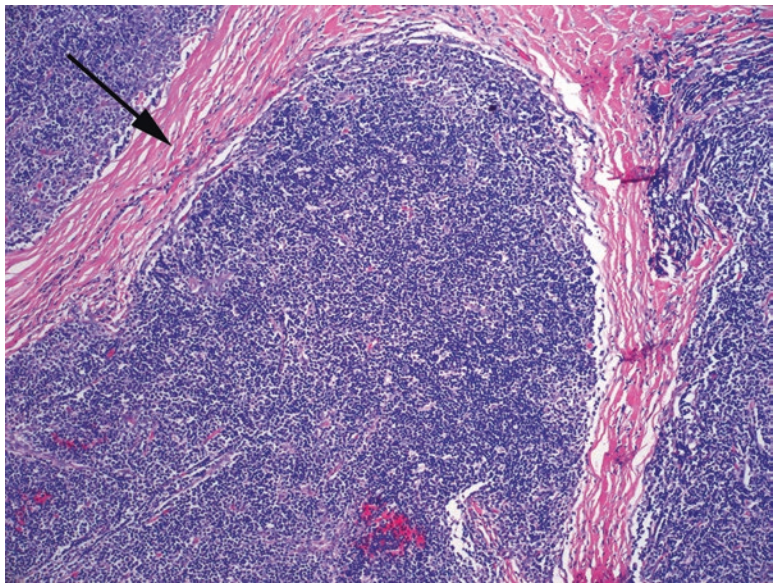

Figure 23.4. Type B1 thymoma. The tumoral epithelial cells are not even visible here due to the dense sheet of T cells, resembling normal thymus. The presence of thick sclerotic bands (*arrow*) helps to identify it as a tumor.

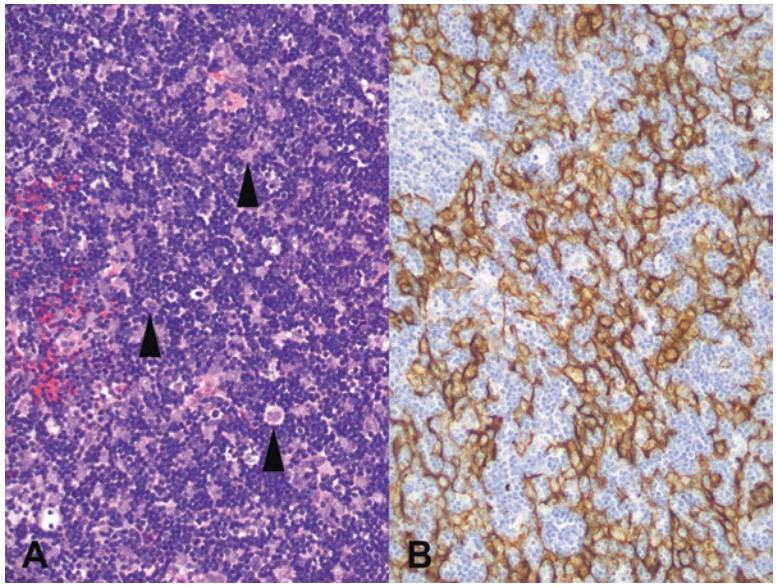

Figure 23.5. Type B2 thymoma. (**a**) In this example, there are identifiable epithelial tumor cells (*arrowheads*) in a background of lymphocytes. (**b**) A cytokeratin stain highlights the epithelial cells.

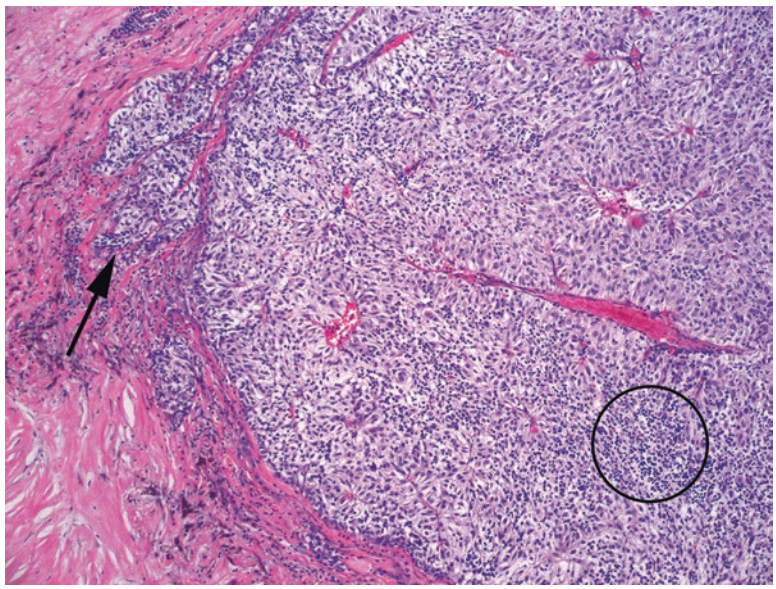

Figure 23.6. Type B3 thymoma. There is a population of spindled or epithelial cells with scattered lymphocytes (*circle*) and an infiltrative border (*arrow*). Unlike the spindled Type A thymoma, these cells show atypia and would stain for CK5/6, not for EMA.

Thymic carcinoma is a heterogeneous group of carcinomas that, while they arise in the thymus, are classified according to the conventional morphologic classifications found elsewhere in the body. A squamous cell carcinoma, therefore, may be keratinizing or nonkeratinizing and will stain for the usual markers of squamous differentiation. The two markers that are unique to thymic squamous carcinomas are CD5 and CD117 (c-kit), although neither is completely sensitive or specific. Other varieties of thymic carcinoma include lymphoepithelioma-like, mucoepidermoid (like the salivary tumor), basaloid, and carcinomas with NUT rearrangement (see next section). Adenocarcinomas do exist but are rare. Primary neuroendocrine tumors of the thymus are named as per the convention in the lung: carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma, and small cell carcinoma, of which atypical carcinoid is by far the most common.

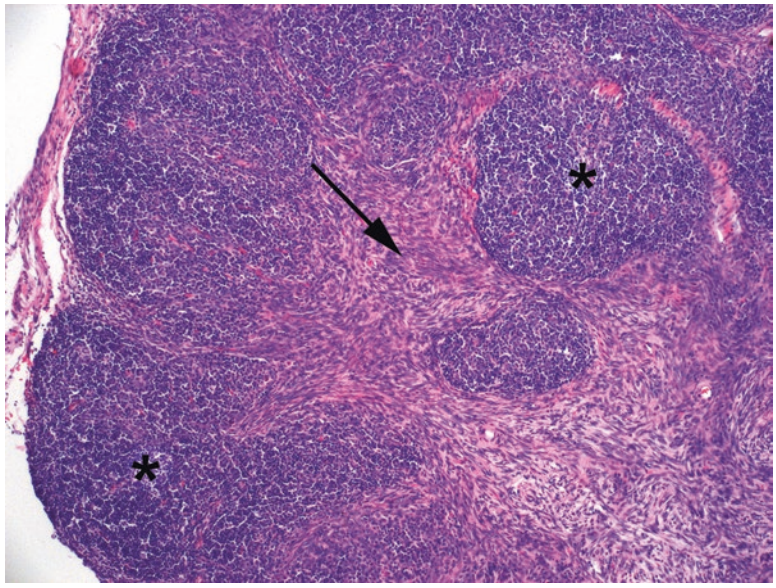

Figure 23.7. Type AB thymoma. This tumor has admixed features of the Type A (bland spindle cells, *arrow*) and Type B1 (lymphocytic areas, *asterisks*) thymomas.

Cysts

Thymic and mediastinal cysts include:

- Thymic cyst—an inclusion cyst within thymic tissue, lined by cuboidal, non-ciliated epithelium. May be uni- or multilocular and may have acute and chronic inflammation.
- Bronchogenic cyst—occurs anywhere in the anterior mediastinum. Lined with ciliated epithelium and resembling bronchus; may contain smooth muscle and cartilage.
- Enteric cyst—developmental anomaly from the gut, may occur in anterior or posterior mediastinum. Lined with squamous, columnar, or glandular mucosa.
- Esophageal duplication cyst—a pouch adjacent to but not connecting with the esophagus; lined with squamous mucosa and smooth muscle.
- Dermoid cyst—a type of teratoma, lined by keratinizing squamous epithelium and adnexal structures.

Other Tumors of the Mediastinum

The differential diagnosis for tumors of the anterior mediastinum includes thymic tumors, teratomas/germ cell tumors (arising from the germ cells embedded in the thymus), and lymphomas, as covered above, but also ectopic thyroid tissue (goiter or tumors). In the posterior mediastinum, a tumor is most likely to be of neural origin, such as a peripheral nerve sheath tumor or a paraganglioma. Chordomas, which are tumors of notochordal remnants, can also arise in the posterior mediastinum. A relatively new entity called *NUT midline carcinoma* arises in midline locations such as the head, neck, or mediastinum and is named after rearrangements in the *NUT* gene. This tumor is an extremely aggressive, poorly differentiated malignancy with somewhat paradoxically homogeneous tumor cells (Figure 23.8, a feature of many translocation-related tumors) and often shows areas of well-differentiated squamous carcinoma. The appearance of a poorly differentiated carcinoma in a young person would provoke an extensive workup, but in an older person, it might be mistaken for another more common entity such as poorly differentiated squamous carcinoma; the only way to identify it is through FISH or IHC for the NUT protein.

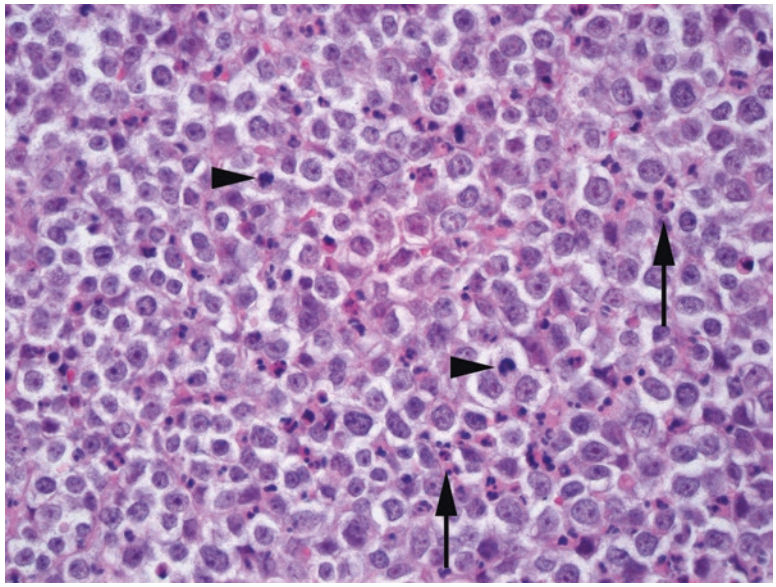

Figure 23.8. NUT midline carcinoma. This relatively uniform cell population shows medium-sized cells with clumpy chromatin and nucleoli and pale cytoplasm. Background neutrophils are common (*arrows*), as are mitotic figures (*arrowheads*).