The Thymus: Practical Anatomy and Histology

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Introduction

We have known about a structure in the mediastinal region that has been named the *thymus* for the last 2000 years, and yet we are still learning about it [1–4]. Interestingly, the issue of the name of this anatomical structure is still somewhat unsettled. Possible theories to account for its name include that it is derived from a plant with a similar name or from the Greek word *soul.* Several great scholars of antiquity including Ephesus and Galen de Pergamum were aware of this particular anatomical structure. Da Capri and Vesalio in the fourteenth century contributed to our understanding of the thymus by their work in anatomy, while other scholars during this period also contributed, predominantly to our understanding of the gross anatomy of the thymus. Even though great observations were made – such as the observation that the thymus is larger in the young than in the adult – for the most part, however, the thymus remained a mystery. An important development that allowed progress in our understanding of the thymus was the use of the optical microscope. Although for some time the progress seemed to have been negligible, toward the seventeenth century the concept was presented that the thymus was part of the lymphatic system. Regarding this issue, it was Hassall who in the middle of the eighteenth century presented his work on the microscopic anatomy of the thymus and described the differences between the thymus and lymphatic structures. Unfortunately, also in the eighteenth century and to some extent in early nineteenth century, some previous theories regarding the role of the thymus in certain pathological states were also revived. Concepts such as *thymic asthma* and *status thymolymphaticus* and its association with thymic death regained some acceptance, which unfortunately led to some controversial forms of therapy such as radiation exposure. Such concepts were taken for valid until approximately the mid part of the nineteenth century, when the use of radiation was completely refuted. In more recent decades, with the advent of thoracic surgery, diagnostic imaging, light microscopy, immunohistochemistry, and molecular biology, we have gained a wealth of knowledge regarding the thymus. However, we consider that there is still more to learn and to correlate with different tumoral conditions that have been described affecting the thymus.

Indeed, we have had 2000 years of knowledge regarding a structure that is more prominent in childhood than in adulthood, but yet, some of the most common tumors related to the gland occur in the adult patient population. It is very likely that the last word has not yet been written on the thymus, and as we progress in our knowledge of the thymus, much more is likely to be discovered. The attempt in this chapter is not to rewrite the abundant embryologic, anatomic, physiologic, and histologic characteristics of the thymus. On the contrary, our goal is to provide the diagnostic surgical pathologist with a practical guide to the most important aspects regarding this mysterious gland, so that such knowledge can be used in the diagnosis of the many conditions that may affect the thymus. More in-depth information regarding embryology, anatomy, physiology, and histology of the thymus can be easily encountered in dedicated textbooks on those disciplines.

Embryology and Anatomy

Current views regarding the embryology of the thymus have changed previous concepts about the thymus. Traditionally, it has been believed that the thymus derives from the endoderm of the third pharyngeal pouch on both sides. More recently, it has been stated that it is possible that the thymic epithelium derives from both endoderm and ectoderm of the third and fourth pharyngeal pouches. Even though the thymus seems to be differentiated by the 17th week, the differentiation of cortex and medulla of the thymus occurs in embryos of about 40 mm in length, while by the 10th week approximately 95% of the cells present are T-lymphocytes.

The anatomy of the gland is probably best observed in childhood when the thymus is larger. Normally, the thymus lies in the anterior mediastinum (Fig. 1.1). It has two upper horns (right and left) and extends into the neck area where

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the upper horns of the thymus may make contact with the lower poles of the thyroid gland. Downward, the thymus extends to the fourth or fifth costal cartilage. The anterior portion of the thymus is related to the sternum, while the posterior aspect is related to the upper pericardium, aortic arch, left brachiocephalic vein, and the front and sides of the trachea. The lateral aspects of the thymus are related to the mediastinal pleura, lungs, and phrenic nerve. The thymus receives its blood supply from the internal thoracic artery and the superior thyroid artery, while its drainage is conducted by the inferior thyroid, internal thoracic, and left brachiocephalic veins. The weight of the thymus changes with age. In normal conditions in newborns, the thymus weighs approximately 10–15 grs. (Fig. 1.2a, b); at puberty, it weighs in at 30–40 grs. at its peak; in adults after involutions, it weighs approximately 10 grs., and the gross appearance of the gland may be that of adipose tissue (Fig. 1.3). At the functional level, the thymus is known for producing some hormones and peptides, most notably thymic humoral factor (THF), thymulin, thymopoietin, and thymosins, which have immune properties [5, 6].

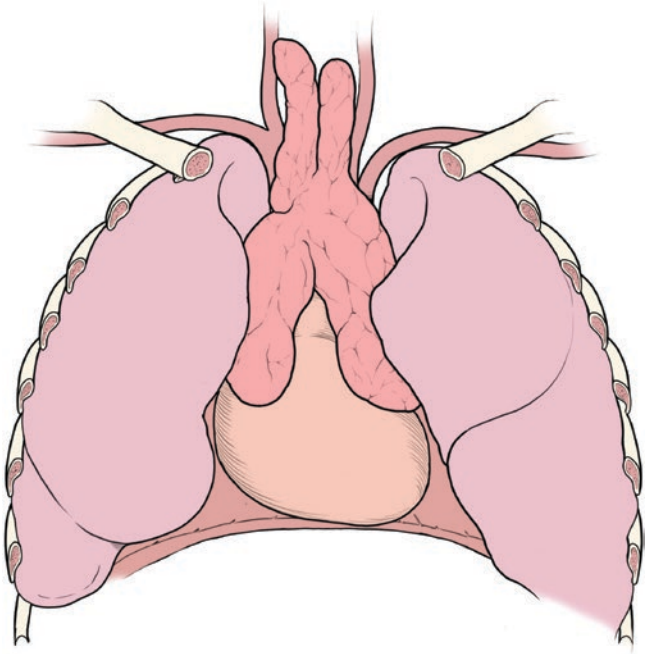

Fig. 1.1 Schematic view of the normal structures within the thoracic cavity. The thymus has two horns, the heart is behind, and the lungs are at the sides. (Copyright © 2016 with permission from Dr. Kalhor and Moran)

Histological Aspects

The schematic view of the normal thymus is depicted in Fig. 1.4. By light microscopy, the thymus appears as a lobulated structure in which each lobule has two basic components: the cortex and the medulla. Each one of these components of the thymic lobule is composed of lymphocytes (thymocytes), which are more prominent in the cortex than in the medulla, and epithelial cells (epitheliocytes), which are more prominent in the medulla than in the cortex [5, 7–10] (Figs. 1.5, 1.6, 1.7, 1.8, 1.9, and 1.10).

Thymic Lymphocytes (Thymocytes)

Thymic lymphocytes (thymocytes) represent approximately 90% of the total weight of the thymus, and, during their mat-

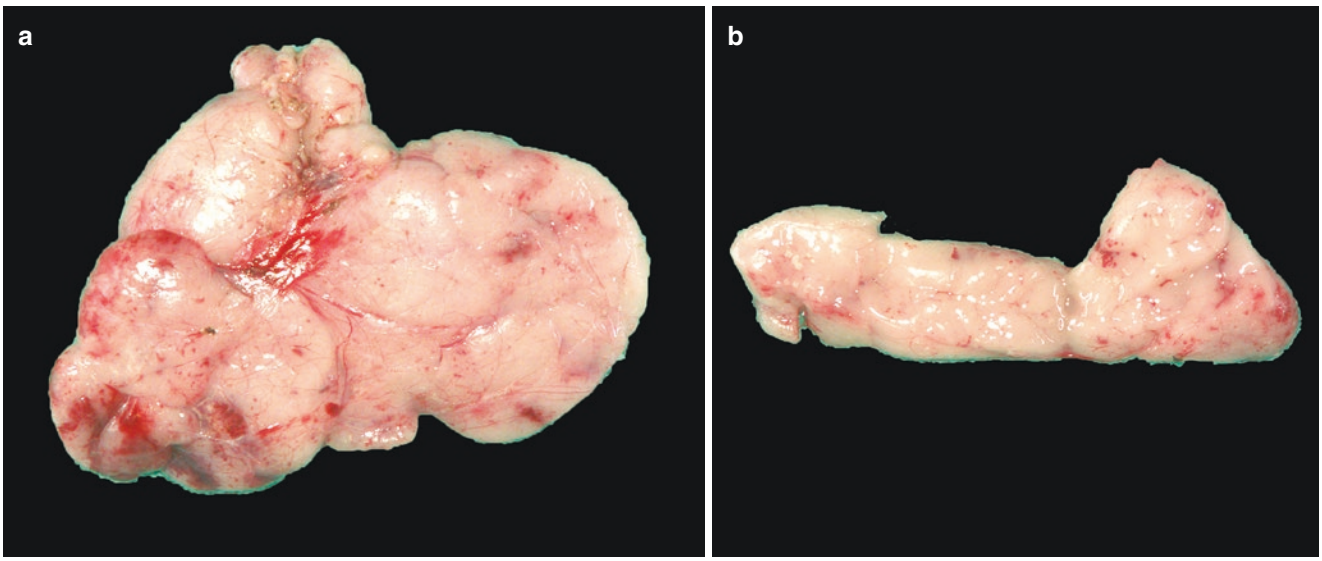

Fig. 1.2 (**a**) Normal thymus of a 2-month-old child with a more solid appearance. (**b**) Cut section the same thymus showing a more "fleshy" appearance. (**a**, **b**: Courtesy of Norma Quintanilla, MD – Texas Childrens Hospital, Houston)

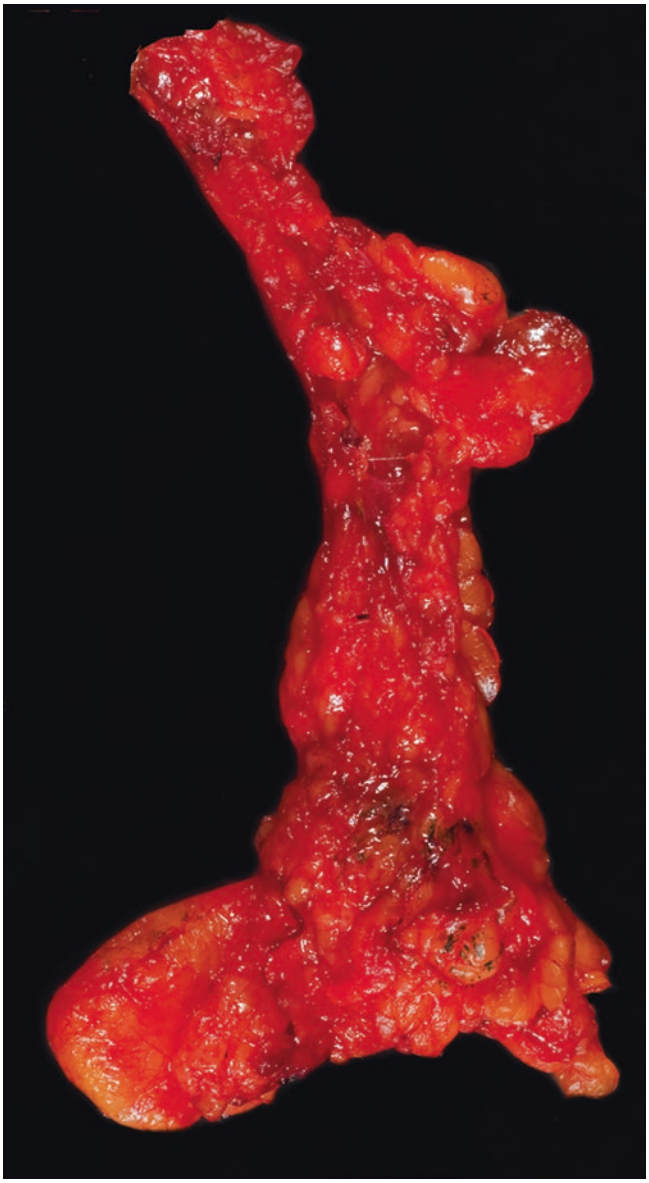

Fig. 1.3 Thymus of an adult individual showing more adipose tissue

uration, the thymocytes move from the deep cortex in the direction of the medulla. Figure 1.4 depicts the maturation process that the thymocytes undergo in the thymus. During this process of maturation and depending upon how strict one can be with this process, thymocytes could be divided into either three or four different types:

1. *Subcapsular thymocytes*: these are large blast cells, and they are double-negative CD4 and CD8. Also, these thymic blasts are CD3 negative. These large thymic blasts represent approximately 5% of the thymocytes.
2. *Cortical thymocytes*: these are smaller cells that may represent approximately 80–90% of the thymocytes. These cortical thymocytes are double-positive cells CD4 and CD8 positive and also CD3 positive.
3. *Medullary thymocytes*: these medullary thymocytes represent approximately 10–15% of the thymocytes and can be subdivided into two types of cells:
   (a) Single-positive medullary thymocytes, which can be positive for either CD4 or CD8
   (b) Immunocompetent single-positive medullary thymocytes, which are activated T-cells

Thymic Epithelial Cells (Epitheliocytes)

These cells are distributed in the thymus in different proportions. Epitheliocytes can be divided either into four or five different categories:

1. Subcapsular cortical (type 1).
2. Inner cortical (types 2–3): these cells are also known as thymic nursing cells (TNC).
3. Medullary (types 4–5).
4. Cells of Hassall's corpuscles: the Hassall's corpuscles are characterized by a concentric pattern of keratinization, and they are restricted to the medullary portion of the thymus. Hassall's corpuscles show a wide variety of changes depending not only on the age of the thymus but also on the different conditions that may affect the thymus pathologically (Figs. 1.11, 1.12, 1.13, 1.14, and 1.15).

Other Cellular Components of the Thymus

Even though most of the cellular component of the thymus is composed of thymocytes of T-cell lineage and epithelial cells, there are other cells in the thymus that are important and should be recognized:

1. *B-lymphocytes*: usually they present in the thymus in the form of germinal centers. However, they may appear singly admixed with T-cells and epithelial cells. Germinal centers may be seen normally in the thymuses of children and adolescents. It is possible that the origin of these germinal centers in a structure that is predominantly formed by T-cells is from preexisting perivascular B-cells. Needless to say, the presence of germinal centers is more commonly seen in pathological conditions such as myasthenia gravis and thymic hyperplasia, among others. However, it is important to mention that B-lymphocytes may also be seen clustering around Hassall's corpuscles, which have been suggested to be the cells that may give rise to thymic MALT lymphomas.

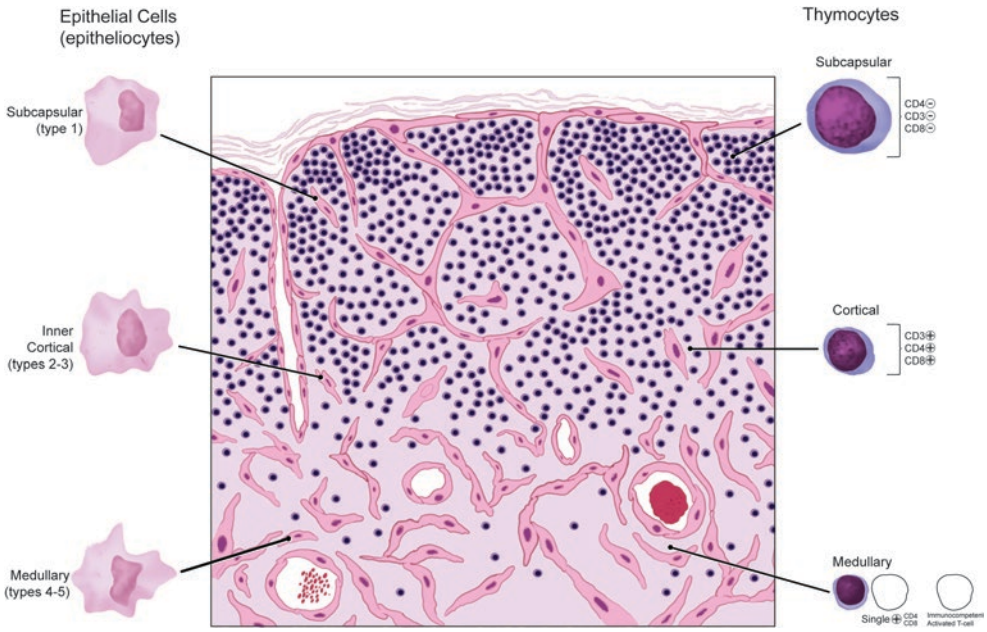

Fig. 1.4 Schematic view of a normal thymus showing the two main cells: thymocytes and epitheliocytes. (Copyright © 2016 with permission from Dr. Kalhor and Moran)

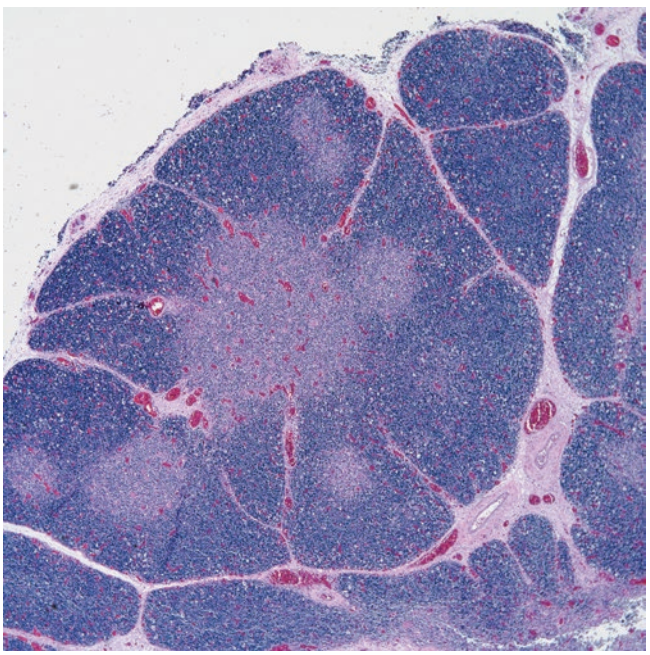

Fig. 1.5 Low power histological section of a normal thymus in a child under 1 year of age, showing a well-demarcated cortex and medulla

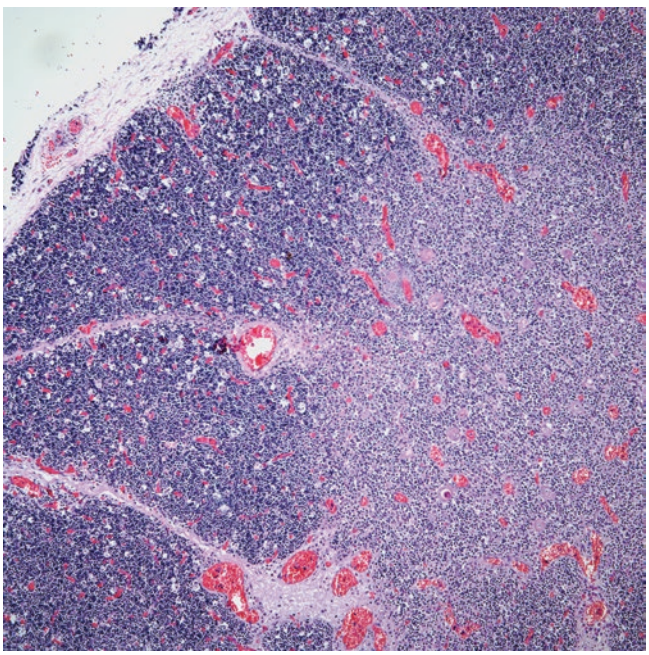

Fig. 1.6 Intermediate power view of a normal thymus showing well-defined cortex and medulla. Note the presence of Hassall's corpuscles

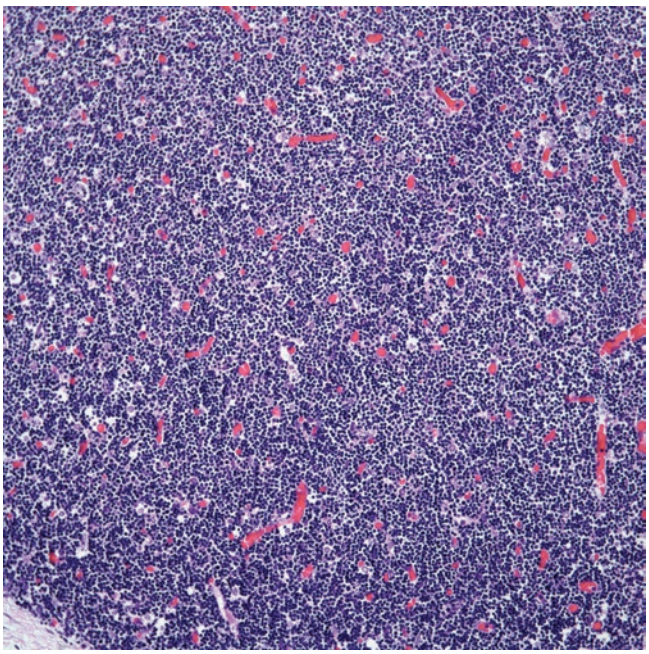

Fig. 1.7 High power view of the normal cortex of the thymus showing predominance of lymphocytes

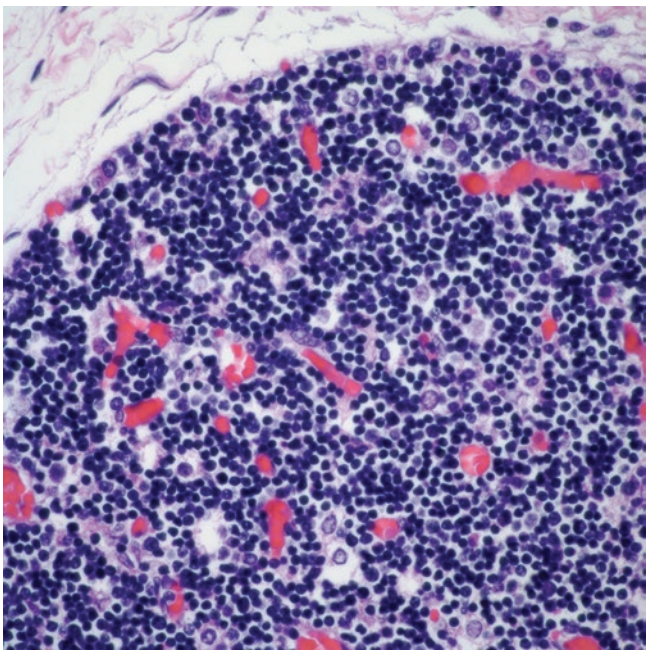

Fig. 1.9 High power view of the subcapsular cortex showing more atypical lymphoid cells

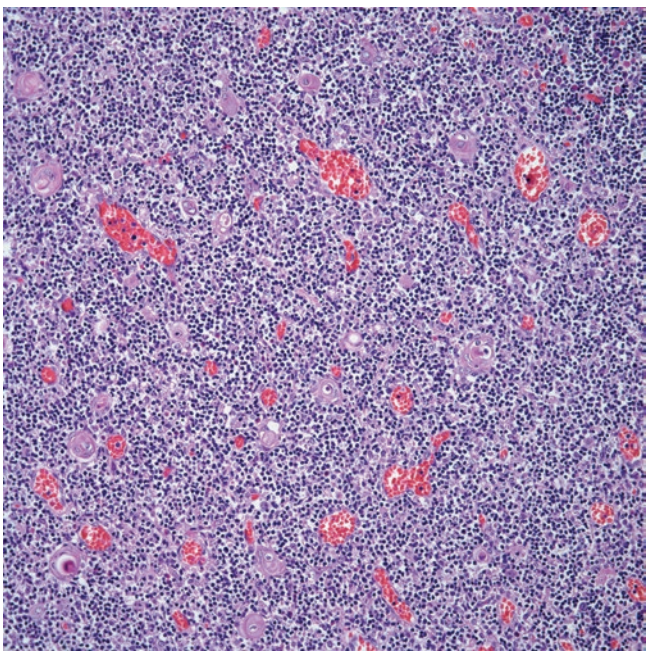

Fig. 1.8 High power view of the thymic medulla showing lymphocytes. However, epithelial cells are easily identified

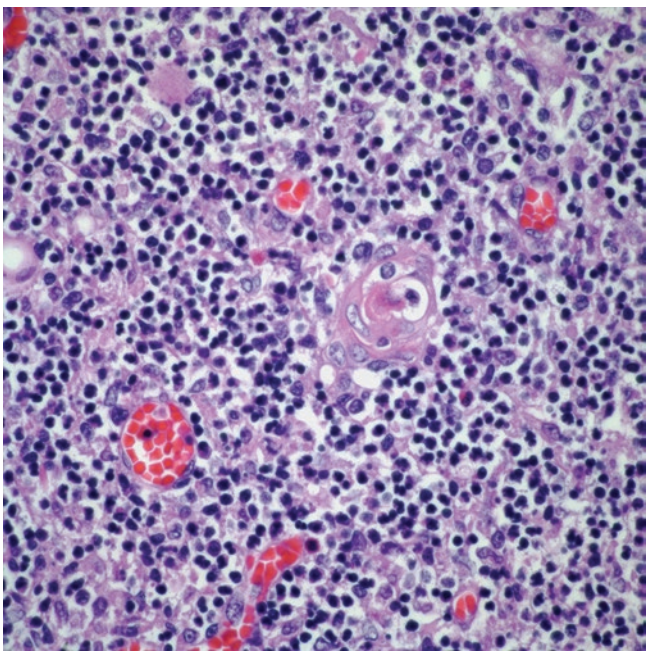

Fig. 1.10 High power view of the thymic medulla showing a Hassall's corpuscle surrounded by lymphocytes and epithelial cells

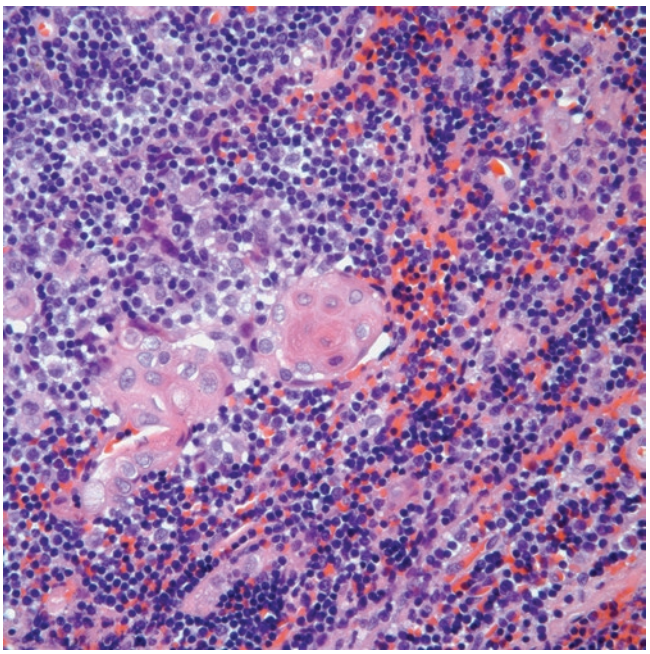

Fig. 1.11 Small Hassall's corpuscle with early keratinization and surrounded by lymphocytes

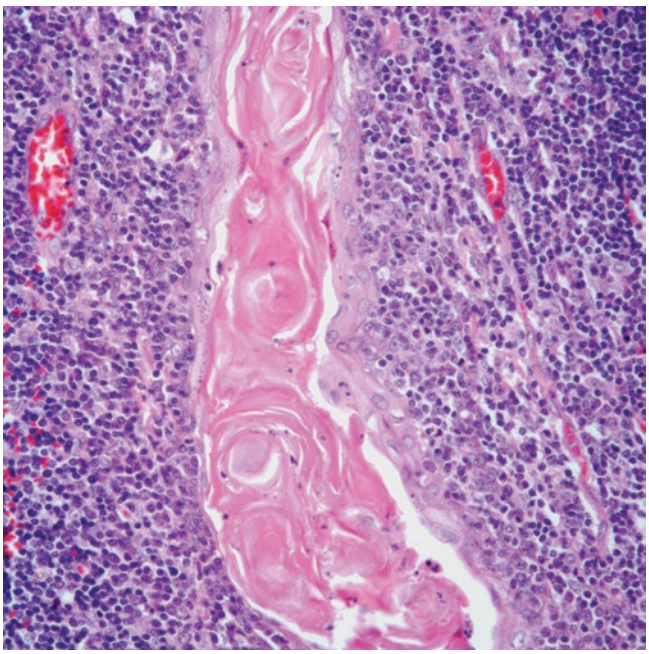

Fig. 1.13 Elongated Hassall's corpuscle with extensive keratinization

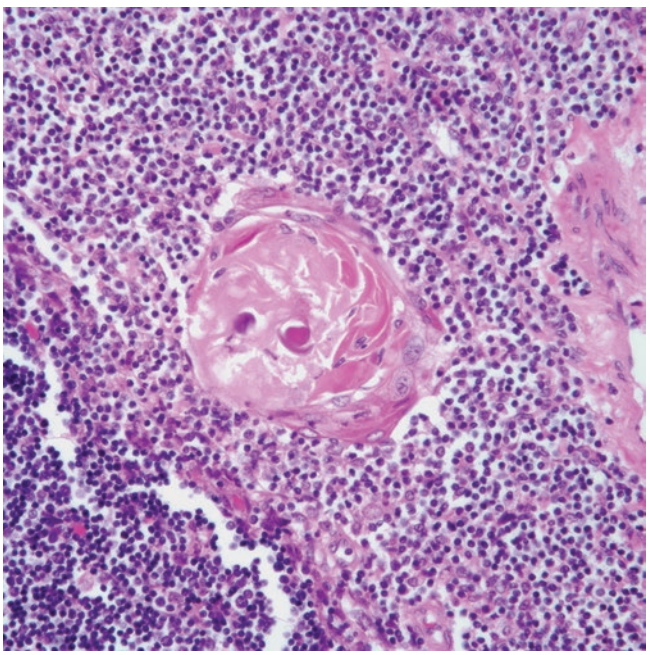

Fig. 1.12 Hassall's corpuscle with keratinization surrounded by epithelial cells and lymphocytes

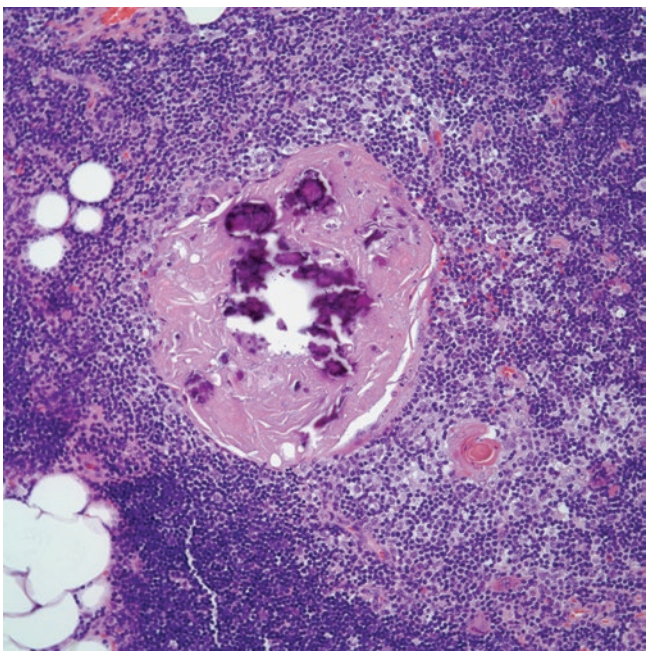

Fig. 1.14 Hassall's corpuscle with calcification

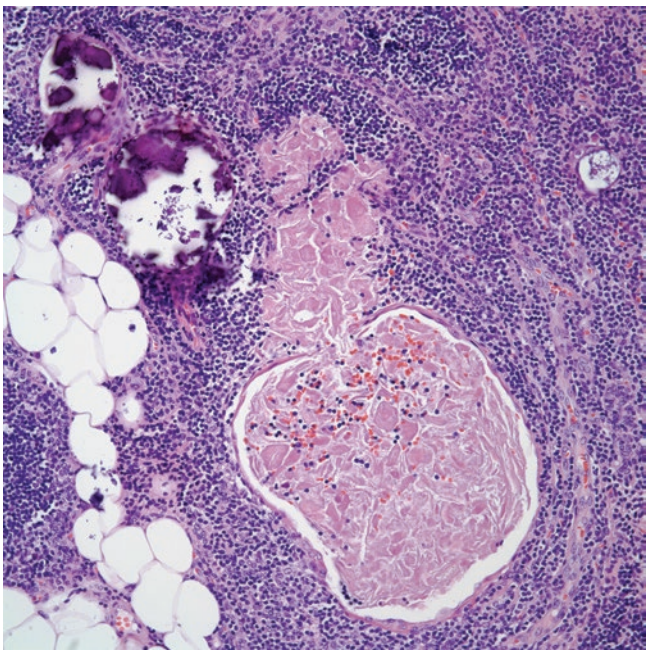

Fig. 1.15 Hassall's corpuscles showing calcification and keratinization

2. *Thymic macrophages*: these mononuclear cells are predominantly in the corticomedullary junction, where they phagocytize differentiating thymocytes.
3. *Interdigitating reticulum cells*: these cells are mainly located in the medulla.
4. *Langerhans cells*: these cells are also present in the medulla.
5. *Eosinophils*: these cells are more common in the connective tissue septa, and they are more commonly seen in thymuses of children.
6. *Mast cells*: these are also found in the connective tissue septa around vessels.
7. *Plasma cells*: they are not common in the thymus, and, when present, they are usually found in connective tissue septa and rarely in the medulla.
8. *Neuroendocrine cells*: these cells may represent a small component of the cellularity of the thymus.
9. *Myoid cells*: they may be located in the thymic medulla. These cells appear to be more conspicuous in pathological conditions such as myasthenia gravis and thymic hyperplasia. However, neoplasms showing extensive myoid component have been described.
10. *Germ cells*: these cells may also form a small component of the cellularity of the thymus.
11. *Sebaceous glands*: these glands rarely can be seen in the normal thymus, and it has been suggested that their occurrence may be related to the ectodermal distribution of the developing thymus.

Connective Tissue

The connective tissue present in the normal thymus contains vessels, fibrous tissue, nerves, and adipose tissue.

Thymic Involution

This process takes place as the individual becomes older, and possibly starts at puberty. Morphologically, one can identify such changes in the thymocyte population and the separation between the corticomedullary junction. Although this process is closely linked to age, in early involution, one may see the presence of decrease number of cortical thymocytes while in more advance stages, the thymic gland is virtually replaced by adipose tissue with only scattered islands of thymic epithelium or clusters of epithelial cells with or without scattered Hassall's corpuscles. The clusters of epithelial cells may be formed almost exclusively of spindle cells without lymphocytes. In some cases, the extensive areas of adipose tissue may be intermixed with connective tissue and strands of remnants of thymic epithelium. On the other hand, some thymic remnants are formed almost exclusively of lymphocytes, mimicking lymph nodes. However, in the periphery of these lymphoid remnants it is possible to identify some epithelial cells (Figs. 1.16, 1.17, and 1.18).

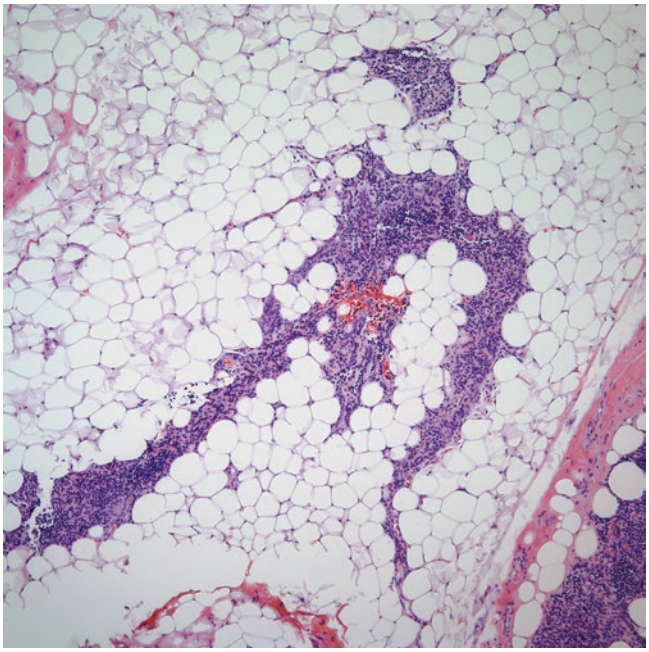

Fig. 1.16 Thymus with involution changes. Note the presence of abundant adipose tissue

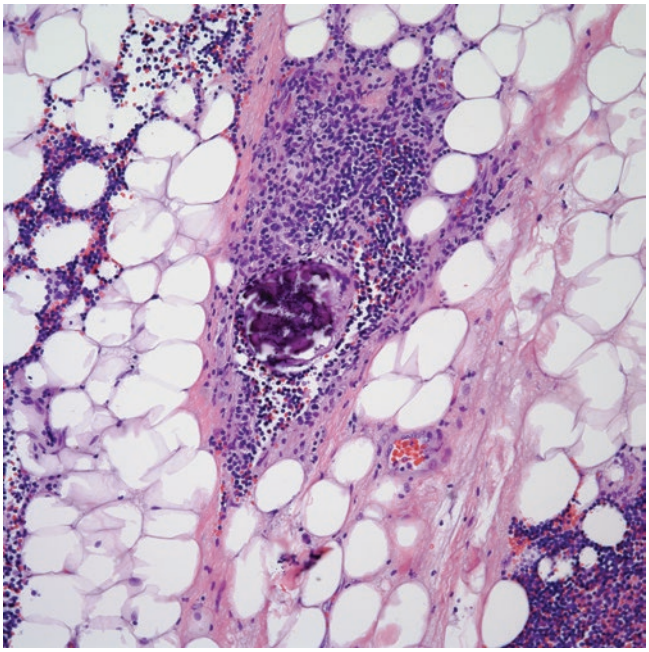

Fig. 1.18 Thymus with involution changes showing a calcified Hassall's corpuscle

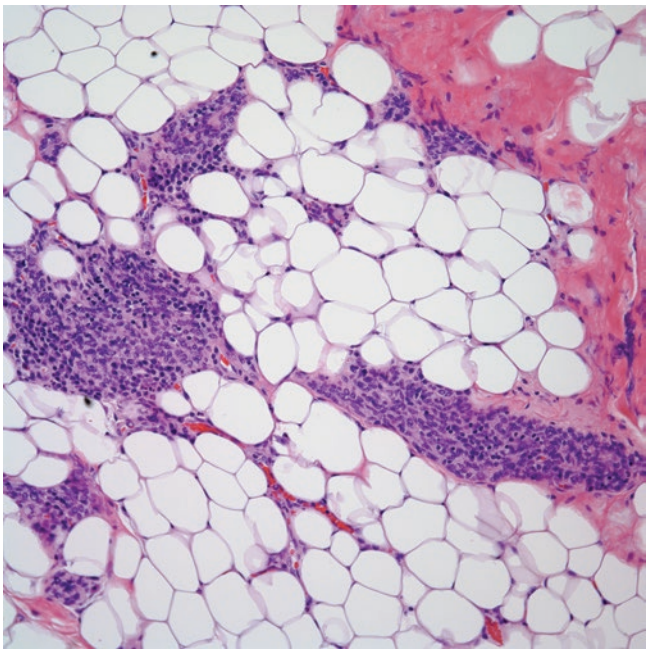

Fig. 1.17 Thymus with involution changes showing focal areas of residual thymic epithelium

Immunohistochemical Aspects

Although there are no large series on the immunohistochemical profile of the normal thymus, there are reports in which those studies have been performed by comparing the normal thymus to other thymic tumors, namely, thymomas and thymic carcinomas. Besides the conventional keratins and B- and T-cell markers, for instance, Cimpean [11] reported the expression of thymic epithelial cells for SOX2. According to the authors, the epithelial cells of the cortex and corticomedullary junction expressed SOX2. Wu and colleagues [12] evaluated the presence of p63 and X-linked inhibitor of apoptosis protein (XIAP) in thymic hyperplasia and thymoma, finding that p63 is consistently positive in nonneoplastic thymic epithelium, while XIAP expression was essentially negative in nonneoplastic thymus. Dotto and colleagues [13] also reported that p63 is positive in normal thymus. Chan and colleagues [14] evaluated the expression of MIC2 (O13) in normal thymus and showed that almost all lymphocytes in the cortex and fewer lymphocytes in the medulla express MIC2. Pescarmona and coworkers [15] evaluated the expression of nerve growth factor (NGF) and epidermal growth factor (EGF) in normal thymuses and identified that EGF is expressed in the subcapsular, cortical, and medullary epithelial cells, while the NFG was expressed only in the subcapsular and medullary epithelial cells. In our experience, we have observed normal thymus staining for pan-keratin, keratin 5/6, p40 (scattered cells), CD10 (scattered cells), common leukocyte antigen (CD45), CD20, S-100 protein, CD1a, CD8, CD4, Tdt, and CD23 in different proportion and intensity and in different components of the thymus, either cortex, medulla, or both (Figs. 1.19, 1.20, 1.21, 1.22, 1.23, 1.24, 1.25, 1.26, 1.27, 1.28, 1.29, and 1.30).

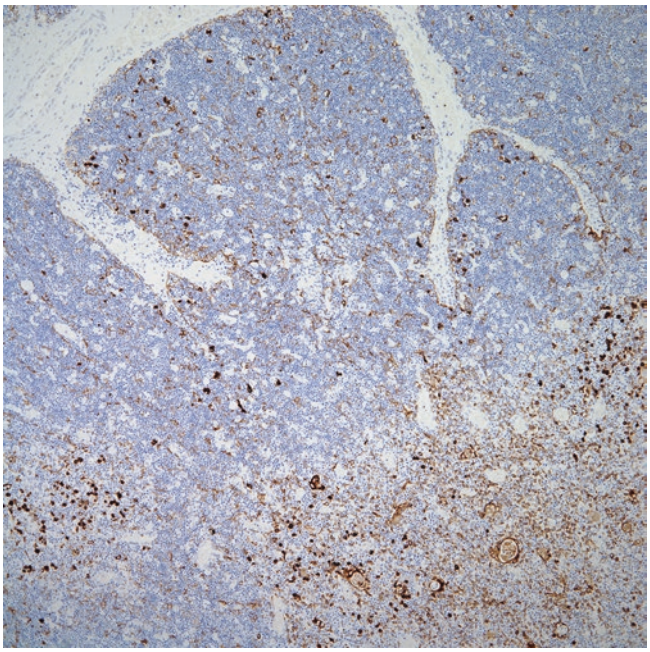

Fig. 1.19 Immunohistochemical stain for pan-keratin shows positive staining in the cortical and medullary epithelial cells. However, there is more in the medullary component

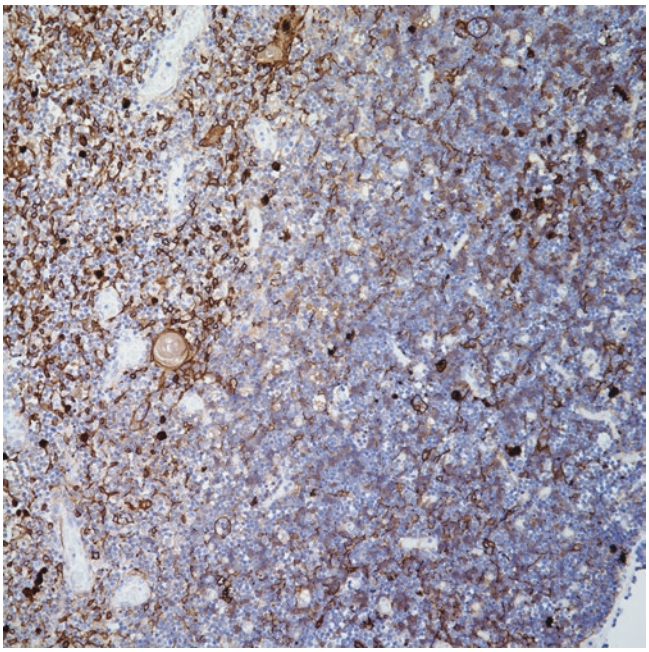

Fig. 1.20 Immunohistochemical stain for keratin 5/6 shows similar pattern as pan-keratin with staining of the epithelial cells of the cortex and medulla

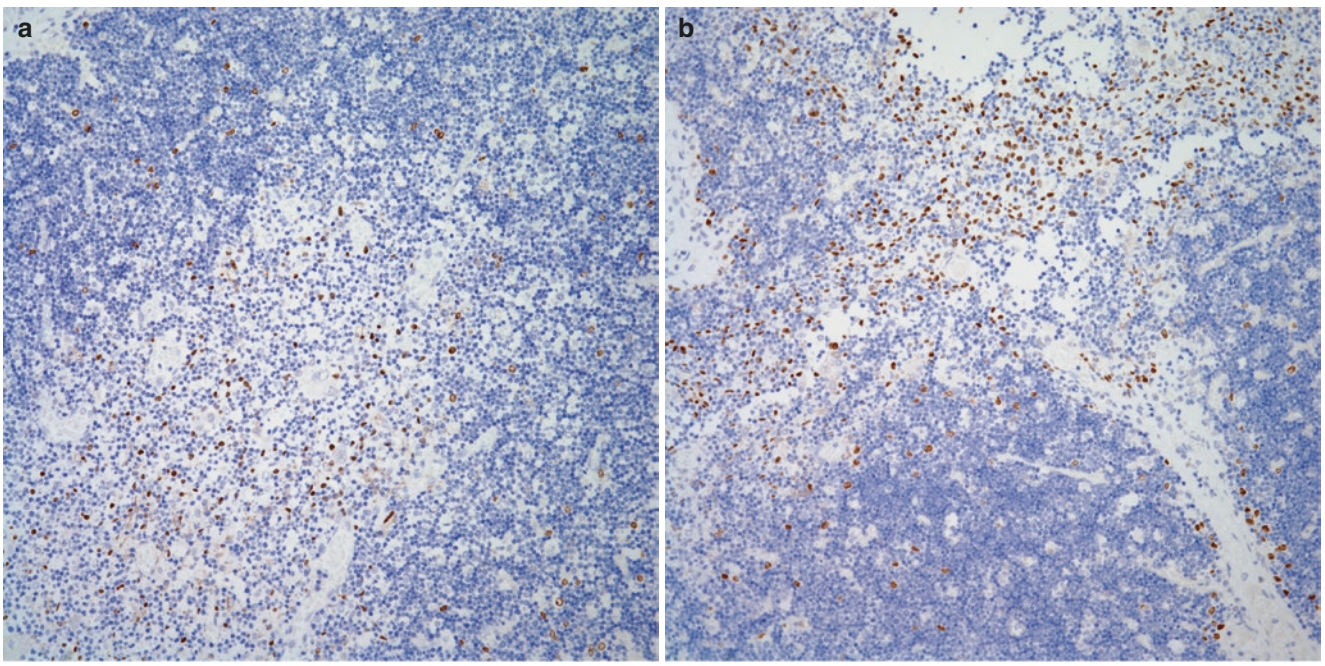

Fig. 1.21 (**a**) Immunohistochemical stain for p40 shows scattered positive epithelial cells in the cortex. More positive epithelial cells are in the medulla. (**b**) Higher magnification showing p40 staining more epithelial cells in the medulla

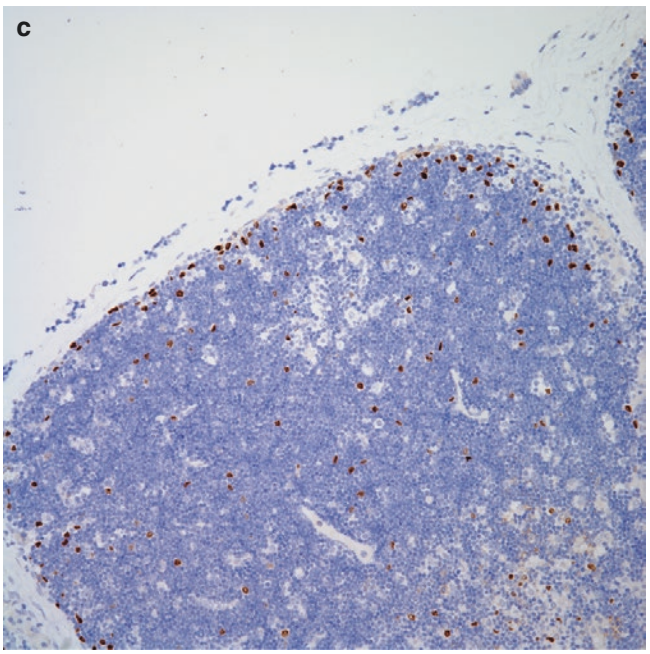

Fig. 1.21 (continued) (**c**) p40 stains only scattered epithelial cells in the cortex. However, many epithelial cells are in the subcapsular area

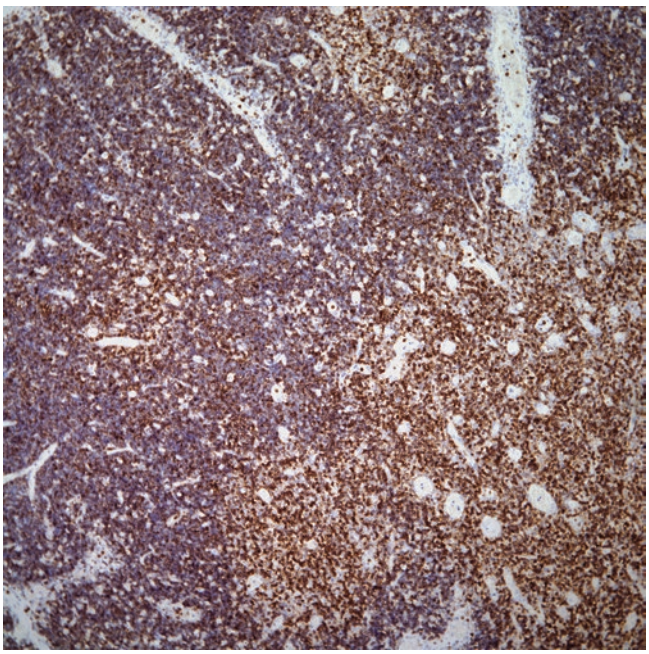

Fig. 1.23 Leukocyte common antigen shows positive staining in both cortical and medullary thymocytes

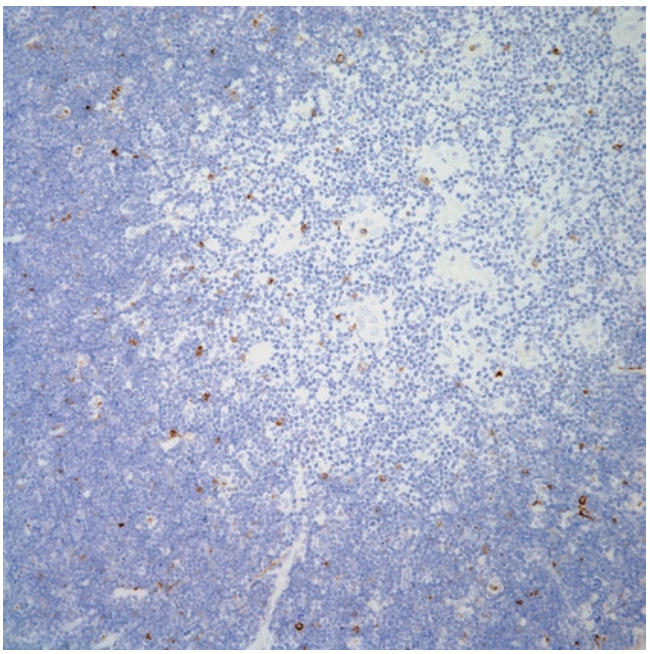

Fig. 1.22 CD10 immunostain shows scattered positive epithelial cells in the cortex and medulla

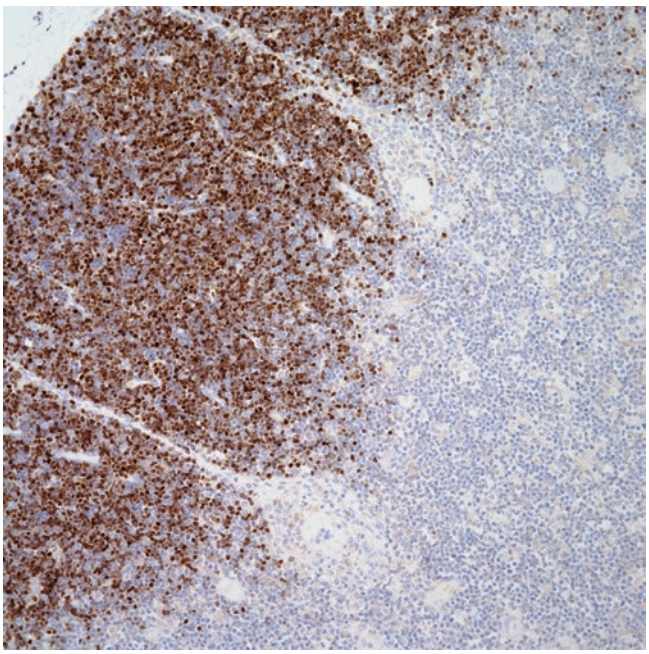

Fig. 1.24 Tdt immunostain shows positive staining in the cortical thymocytes

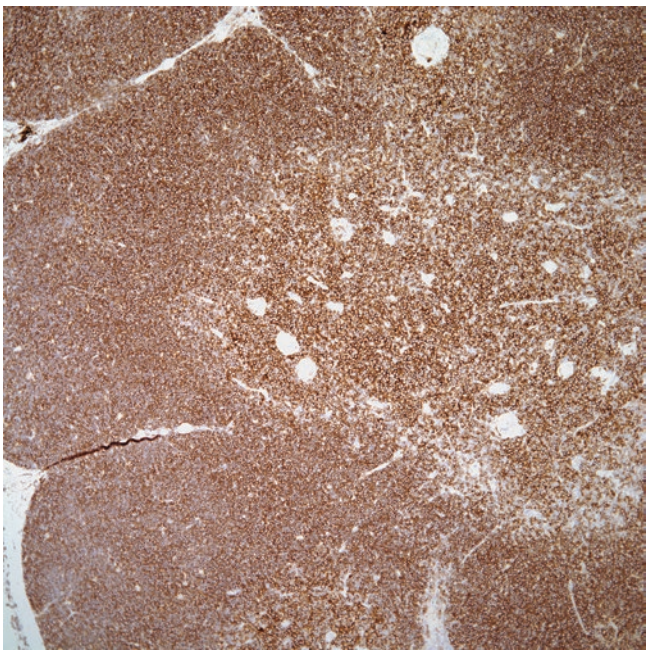

Fig. 1.25 CD4 immunostain shows positive staining of thymocytes in the cortex and medulla

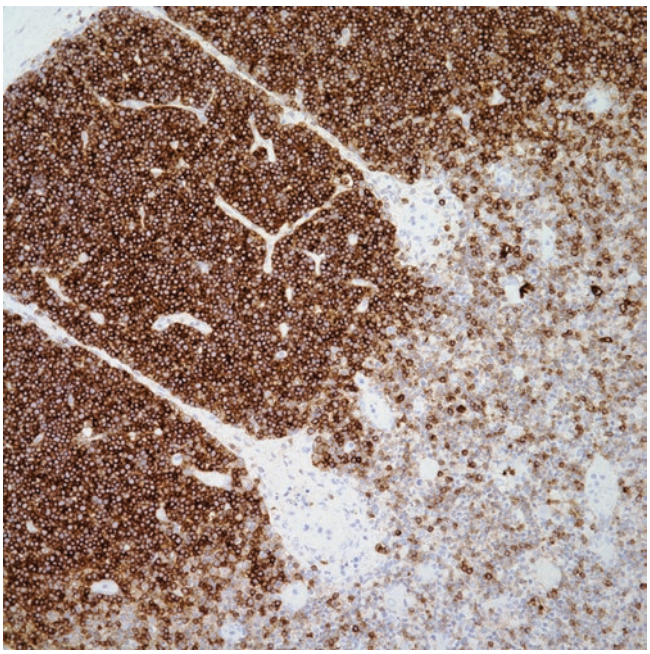

Fig. 1.27 CD1a shows predominantly positive staining of cortical thymocytes

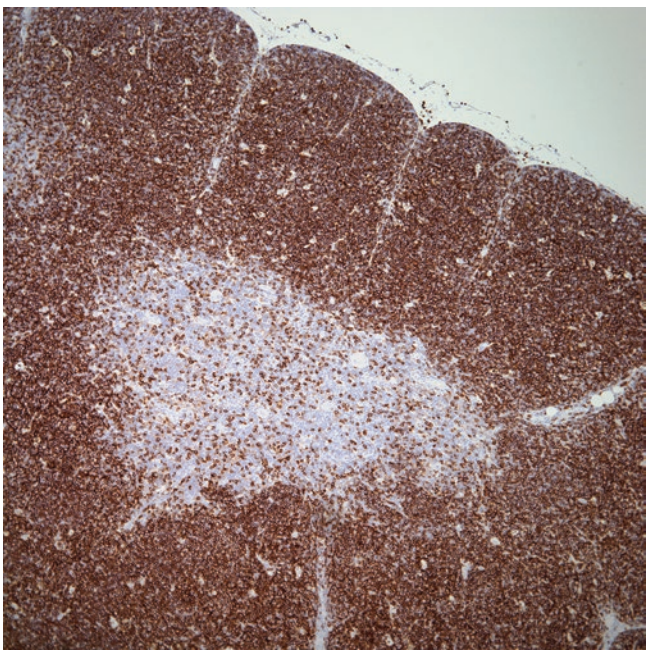

Fig. 1.26 CD8 shows predominantly positive staining of cortical thymocytes

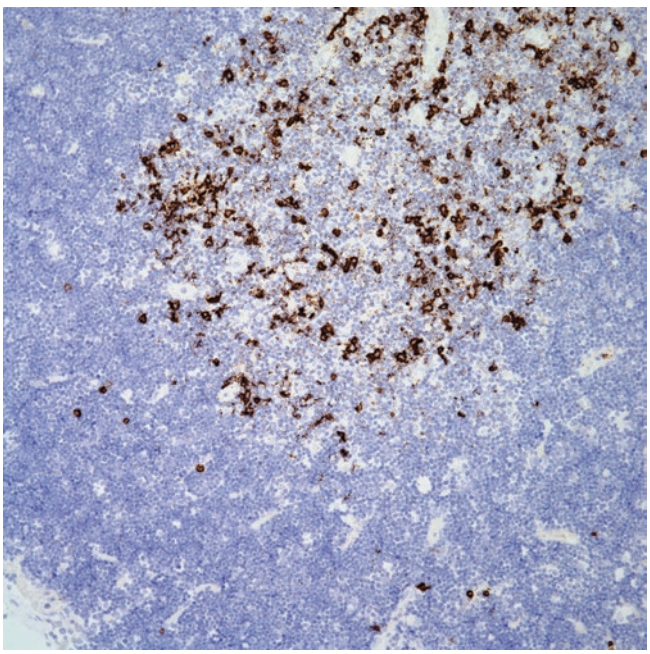

Fig. 1.28 CD20 shows scattered positive medullary thymocytes

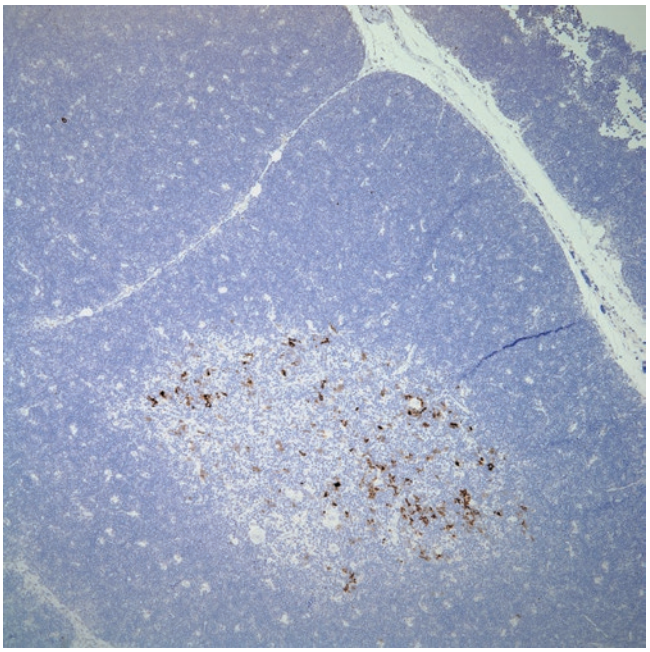

Fig. 1.29 CD23 shows scattered positive staining cells in the thymic medulla

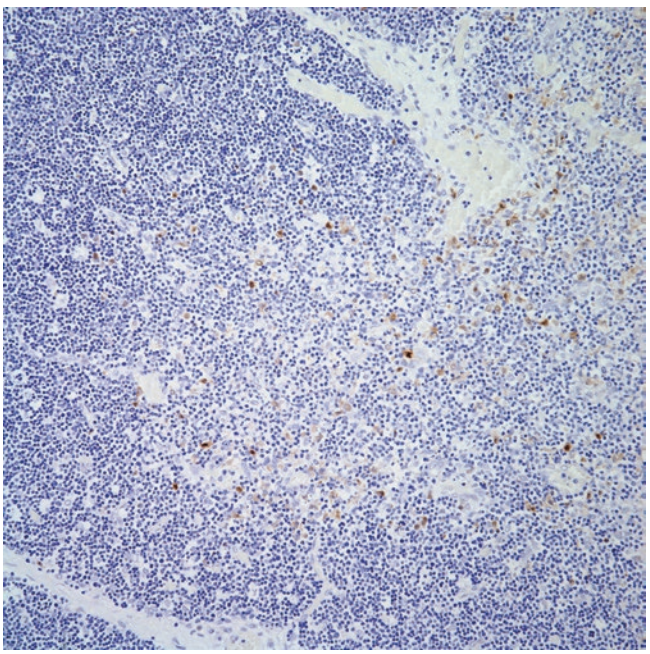

Fig. 1.30 S-100 protein shows positive scattered cells in the thymic medulla

References

1. Kirschner PA. The history of surgery of the thymus gland. Chest Surg Clin N Am. 2000;10:153–65.
2. Jacobs MT, Frush DP, Donnelly LF. The right place and the wrong time: historical perspective of the relation of the thymus gland and pediatric radiology. Radiology. 1999;210:11–6.
3. Miller J. the discovery of thymus function and thymus-derived lymphocytes. Immunol Rev. 2002;185:7–14.
4. Lavini C. Chapter 1: The thymus from Antiquity to the present day: the history of a mysterious gland. In: Lavini C, Moran CA, Morandi U, Schoenhuber R, editors. Thymus Gland Pathology. Milan: Springer; 2008.
5. Palumbo C. Chapter 2: Embryology and Anatomy of the thymus gland. In: Lavini C, Moran CA, Morandi U, Schoenhuber R, editors. Thymus Gland Pathology. Milan: Springer; 2008.
6. Kendal MD, Johnson HR, Singh J. The weight of the human thymus gland at necropsy. J Anat. 1980;131:483–97.
7. Suster S, Rosai J. Histology of the normal thymus. Am J Surg Pathol. 1990;14:284–303.
8. Henry K. Mucin secretion and striated muscle in the human thymus. Lancet. 1966;1:183–5.
9. Wolf M, Rosai J, Wright DH. Sebaceous glands within the thymus: report of three cases. Hum Pathol. 1984;15:341–3.
10. Isaacson PG, Norton AJ, Addis BJ. The human thymus contains a novel population of B-lymphocytes. Lancet. 1987;2:1488–92.
11. Cimpean A, Encina S, Raica M, Ribatti D. SOX2 gene expression in normal human thymus and thymoma. Clin Exp Med. 2011;11:251–4.
12. Wu M, Sun K, Gil J, Gan L, Burstein DE. Immunohistochemical detection of p63 and XIAP in thymic hyperplasia and thymomas. Am J Clin Pathol. 2009;131:689–93.
13. Dotto J, Pelosi G, Rosai J. Expression of p63 in thymomas and normal thymus. Am J Clin Pathol. 2007;127:415–20.
14. Chan JKC, Tsang WYW, Seneviratne S, Pau MY. The MIC2 antibody O13. Practical application for the study of thymic epithelial tumors. Am J Surg Pathol. 1995;19:1115–23.
15. Pescarmona E, Pisacane A, Pignatelli E, Baroni CD. Expression of epidermal and nerve growth factor receptors in human thymus and thymomas. Histopathology. 1993;23:39–44.