

Neda Kalhor
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Mediastinal Pathology

 Springer

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Preface

The mediastinum offers a wealth of pathology that is not limited to specific conditions. In the past, the mediastinum has been referred to as *Pandora's Box*, due to the different tumoral conditions that may appear in this thoracic area. It is of interest to highlight that the normal thymus itself has been a very mysterious gland in past decades, and we are still learning about it. Controversy has also existed in the past regarding the biologic behavior of the most common tumors seen in this area.

This textbook offers the collective experience of the authors and provides a practical approach to the diagnosis of the diverse tumors that can be seen in the mediastinum. Over the years during which we have practiced thoracic pathology, not only have we accrued the knowledge to approach this type of pathology but we also have looked into new ways to provide the best possible information so that patients afflicted with mediastinal tumors can be properly treated by their respective physicians. It is also important to highlight that, over the years, there have been different points of view regarding nomenclature and best way to predict clinical behavior in some of these tumors. In those particular areas, we are providing not only a historical perspective of what has been done in the past but also our own assessment of those changes. Nevertheless, we have tried to maintain a balance in the discussion, but inevitably we have stated our own personal approach. For the most part, the approach in this textbook is on daily practice, as pathologists are confronted with this type of pathology daily. In some areas, it is inevitable that current practice calls for ancillary tests, including immunohistochemistry and molecular techniques.

We are fortunate and indebted to Brett W. Carter, MD, and Edith M. Marom, MD, for their chapter on diagnostic imaging of mediastinal tumors. This subject is highly important in the assessment of any mediastinal tumor. In addition, we are also fortunate to have Larry R. Kaiser, MD, providing his views and sharing his wealth of experience as a thoracic surgeon in his chapter on the surgical approach to mediastinal tumors.

We consider that this textbook should be useful not only to general surgical pathologists or thoracic surgical pathologists but also to thoracic surgeons, radiologists, and oncologist, who are called upon to care of patients with mediastinal tumors. Finally, we hope that, by providing our experience with mediastinal pathology, all of us involved in the treatment and assessment of patients with mediastinal tumors can improve our daily communication in the interest of advancing patient care.

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Contents

1 The Thymus: Practical Anatomy and Histology	1
Introduction	1
Embryology and Anatomy	1
Histological Aspects	2
Thymic Lymphocytes (Thymocytes)	2
Thymic Epithelial Cells (Epitheliocytes)	3
Other Cellular Components of the Thymus	3
Connective Tissue	7
Thymic Involution	7
Immunohistochemical Aspects	8
References	12
2 Imaging of Mediastinal Tumors	13
Introduction	13
Classification of Mediastinal Compartments	13
General Considerations	15
Role of Imaging	15
Imaging Approach to Mediastinal Lesions	16
Fat-Containing Lesions	16
Teratoma	16
Thymolipoma	16
Lipoma and Liposarcoma	16
Cystic Lesions	16
Thymic Cyst	16
Teratoma	17
Pericardial Cyst	17
Bronchogenic Cyst	17
Esophageal Duplication Cyst	18
Meningocele	19
Soft Tissue Lesions	19
Thyroid Goiter	19
Thymic Epithelial Neoplasms	19
Lymphoma	20
Non-teratomatous Germ Cell Tumors	21
Thymic Hyperplasia	22
Esophageal Neoplasms	22
Neurogenic Neoplasms	22
Miscellaneous Lesions	24
Paraspinal Abscess	24
Extramedullary Hematopoiesis	24
Conclusions	26
References	26

3	Surgical Approaches to the Mediastinum	29
	Introduction	29
	Surgical Approaches to the Anterior Mediastinum	29
	Thymoma	30
	Germ Cell Tumors	33
	Parathyroid Adenomas	33
	Surgical Approaches to the Posterior Mediastinum	34
	References	37
4	Benign Tumors and Tumor-Like Conditions	41
	Introduction	41
	Cystic Tumors	41
	Foregut Cysts	41
	Mesothelial Cysts	47
	Thymic Cysts	48
	Solid Tumors and Tumor-Like Conditions	50
	Sclerosing/Fibrosing Mediastinitis	50
	Thymic Hyperplasia	59
	Adenomatoid Tumor	60
	Glomus Tumor	61
	Cholesteroloma	64
	Mediastinal Pecoma	65
	Sclerosing Hemangioma (Extrapulmonary Pneumocytoma)	65
	Histiocytic Tumors	67
	Langerhans Cell Histiocytosis (LCH)	67
	Rosai-Dorfman Disease (RDD)	69
	References	72
5	Salivary Gland-Type Tumors	75
	Introduction	75
	Benign Tumors	75
	Thymic Hyperplasia with Lymphoepithelial Sialadenitis (LESA)-Like Features	75
	Sebaceous Lymphadenoma	79
	Mixed Tumor (Pleomorphic Adenoma)	81
	Malignant Tumors	83
	Mucoepidermoid Carcinoma (MEC)	83
	Epithelial-Myoepithelial Carcinoma	88
	Adenoid Cystic Carcinoma	90
	Basaloid Carcinoma	90
	References	97
6	Staging for Thymoma and Thymic Carcinoma	99
	Introduction	99
	Staging of Thymoma	99
	Staging of Thymic Carcinoma	109
	Summary	113
	References	113
7	Thymoma	115
	Introduction	115
	Epidemiological Aspects	116
	Etiological Aspects	116
	Clinical Features	119
	Common Clinical Associations	119
	Histological Classifications and Clinical Studies	119

Pathological Aspects	133
Anatomical Orientation and Sampling	133
Gross Features	135
Histopathological Features	139
Conventional Thymomas	146
Atypical Thymoma	169
Thymomas with Mixed Histologies	172
Other Unusual Variants of Thymoma	215
Thymomas Without a Well-Formed Capsule or Incomplete Capsule	218
Invasive and Metastatic Potential of Thymomas	224
Immunohistochemical and Molecular Features	227
References	231
8 Thymic Carcinoma	237
Introduction	237
Clinical Features	238
Pathological Features	241
Macroscopic Features	241
Histopathological Features	241
Immunohistochemical and Molecular Features	277
NUT Carcinoma	283
References	284
9 Neuroendocrine Neoplasms	287
Introduction	287
Neuroendocrine Carcinomas	287
Clinical Features	288
Classification	291
Staging	294
Pathological Features	296
Immunohistochemical Features	312
Other Ancillary Studies	315
Differential Diagnosis	315
Paraganglioma	316
Clinical Features	316
Pathological Features	317
Immunohistochemical Features	320
Other Ancillary Studies	320
Differential Diagnosis	323
Parathyroid Tumors	325
Clinical Features	325
Pathological Features	326
Ancillary Studies	331
Differential Diagnosis	331
Thyroid Tumors	334
Clinical Features	335
Histopathological Features	335
Immunohistochemical Features and Other Ancillary Studies	335
References	337
10 Germ Cell Tumors	341
Introduction	341
Classification	342
Staging	342

Teratomas	345
Mature Teratoma	345
Clinical Features	345
Gross Features	346
Histological Features	347
Immunohistochemical Features	347
Differential Diagnosis	347
Immature Teratoma	347
Clinical Features	349
Gross Features	349
Histological Features	349
Immunohistochemical Features	349
Differential Diagnosis	350
Teratoma With Malignant Component	350
Clinical Features	351
Gross Features	352
Histopathological Features	352
Histochemical, Immunohistochemical, and Ultrastructural Features	352
Differential Diagnosis	352
Seminoma	353
Clinical Features	355
Gross Features	358
Histologic Features	358
Immunohistochemical Features	365
Ultrastructural Features	370
Differential Diagnosis	370
Non-seminomatous Germ Cell Tumor	370
Yolk Sac Tumor	370
Clinical Features	371
Gross Features	372
Histologic Features	372
Immunohistochemical Features	377
Ultrastructural Features	381
Differential Diagnosis	381
Embryonal Carcinoma	383
Clinical Features	383
Gross Features	383
Histologic Features	383
Immunohistochemical Features	385
Ultrastructural Features	388
Differential Diagnosis	388
Choriocarcinoma	389
Clinical Features	389
Gross Features	389
Histologic Features	390
Immunohistochemical Features	390
Ultrastructural Features	390
Differential Diagnosis	390
Combined Germ Cell Tumors	390
Clinical Features	390
Gross Features	392
Histologic Features	392
Summary	394
References	394

11 Neurogenic Tumors	399
Introduction	399
Benign Tumors	402
Ganglioneuroma	402
Neurofibromas	404
Schwannoma	409
Granular Cell Tumor	414
Malignant Tumors	415
Neuroblastoma/Ganglioneuroblastoma	415
Malignant Peripheral Nerve Sheath Tumor (MPNST)	427
Peripheral Neuroectodermal Tumor (PNET)/Extraskeletal Ewing Sarcoma	436
Pigmented Neuroectodermal Tumor of Infancy (Melanotic Progonoma, Retinal Anlage Tumor)	440
Ependymoma	442
Meningioma	445
Malignant Granular Tumor	446
References	450
12 Mesenchymal Tumors	455
Introduction	455
Adipose Tissue Tumors	456
Benign Lipomatous Tumors	456
Angiomyolipoma	460
Liposarcomas	463
Vascular Neoplasms	472
Mediastinal Hemangiomas	473
Epithelioid Hemangioendothelioma	476
Angiosarcoma	478
Muscle Tumors	481
Pathological Features	483
Immunohistochemical and Molecular Features	484
Differential Diagnosis	487
Rhabdomyosarcoma	487
Pathological Features	489
Immunohistochemical and Molecular Features	489
Differential Diagnosis	489
Fibroblastic, Myofibroblastic, and Fibrohistiocytic Tumors	489
Solitary Fibrous Tumor	489
Inflammatory Myofibroblastic Tumor	492
Angiomatoid Fibrous Histiocytoma	496
Giant Cell Tumor	498
Malignant Fibrous Histiocytoma	501
Biphasic Neoplasms	501
Synovial Sarcoma	502
Carcinosarcoma	508
Cartilaginous Tumors	509
Pathological Features	510
Immunohistochemical Features	513
Differential Diagnosis	513
Miscellaneous Tumors	513
Alveolar Soft Part Sarcoma	513
Chordoma	515
References	517

13 Lymphoproliferative Disorders	521
Introduction	521
Non-Hodgkin's Lymphoma	521
General Considerations	521
Demographics	522
Clinical Features	523
Pathological Features	525
Immunohistochemical Features	530
Molecular Features	530
Mediastinal Gray Zone Lymphoma	535
Anaplastic Large Cell Lymphoma (ALCL)	539
Mucosa-Associated Lymphoid Tissue (MALT)-Lymphoma	541
Pathological Features	541
Lymphoblastic Lymphoma	542
Clinical Features	545
Pathological Features	546
Hodgkin's Lymphoma	552
Clinical Features	552
Pathological Features	553
Immunohistochemical Features	557
Molecular Features	557
Follicular Dendritic Cell Sarcoma (FDCS)	557
Pathological Features	561
Mediastinal Plasmacytoma	561
Pathological Features	561
Castleman's Disease (CD)	561
Pathological Features	567
Extramedullary Hematopoiesis (EMH)	567
References	573
Index	579

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The Thymus: Practical Anatomy and Histology

1

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 knowl-

edge 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

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

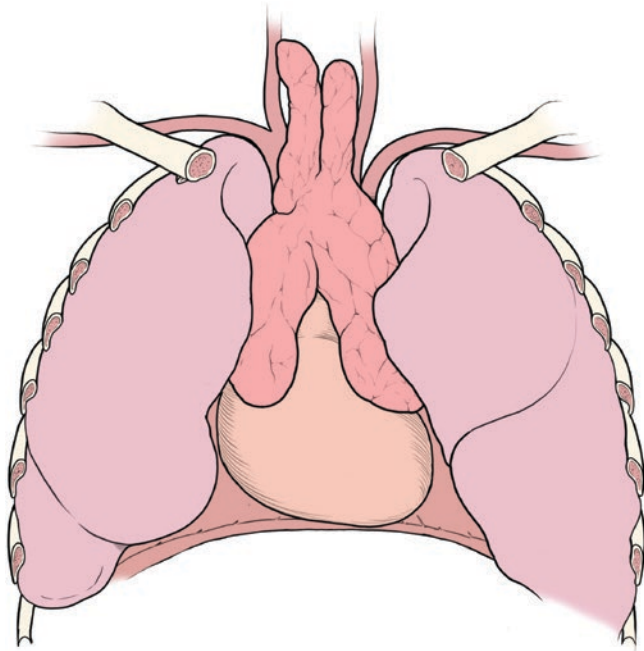


Fig. 1.1 Schematic view of the normal structures within the thoracic cavity. The thymus has two horns, the heart is behind, and the lungs are at the sides. (Copyright © 2016 with permission from Dr. Kalhor and Moran)

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].

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-

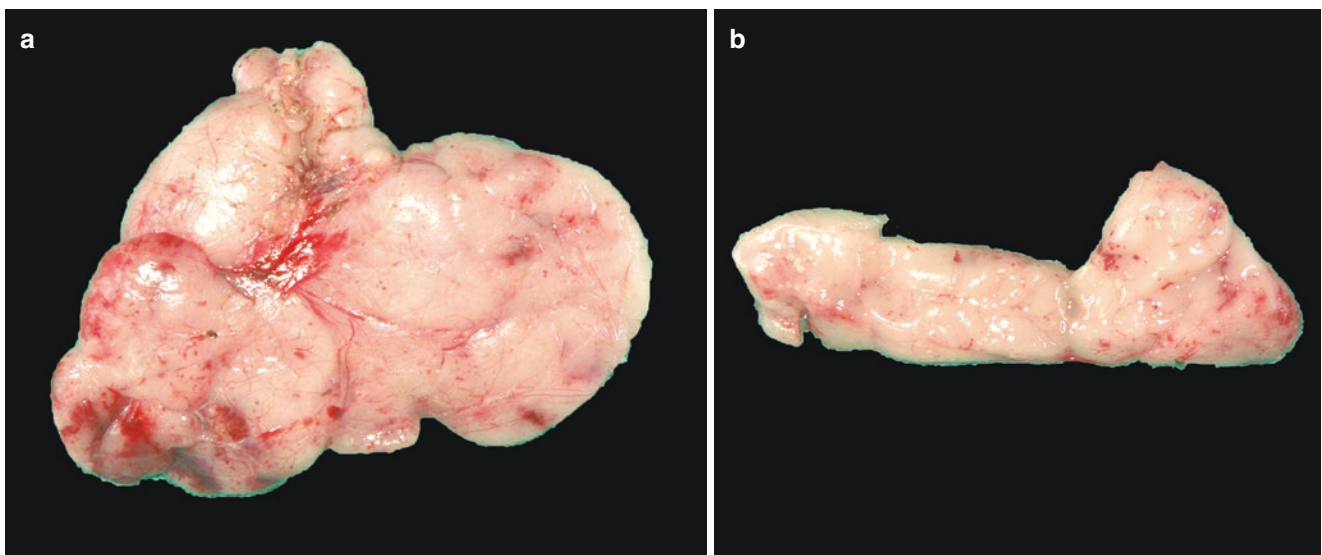


Fig. 1.2 (a) Normal thymus of a 2-month-old child with a more solid appearance. (b) Cut section the same thymus showing a more “fleshy” appearance. (a, b: Courtesy of Norma Quintanilla, MD – Texas Childrens Hospital, Houston)

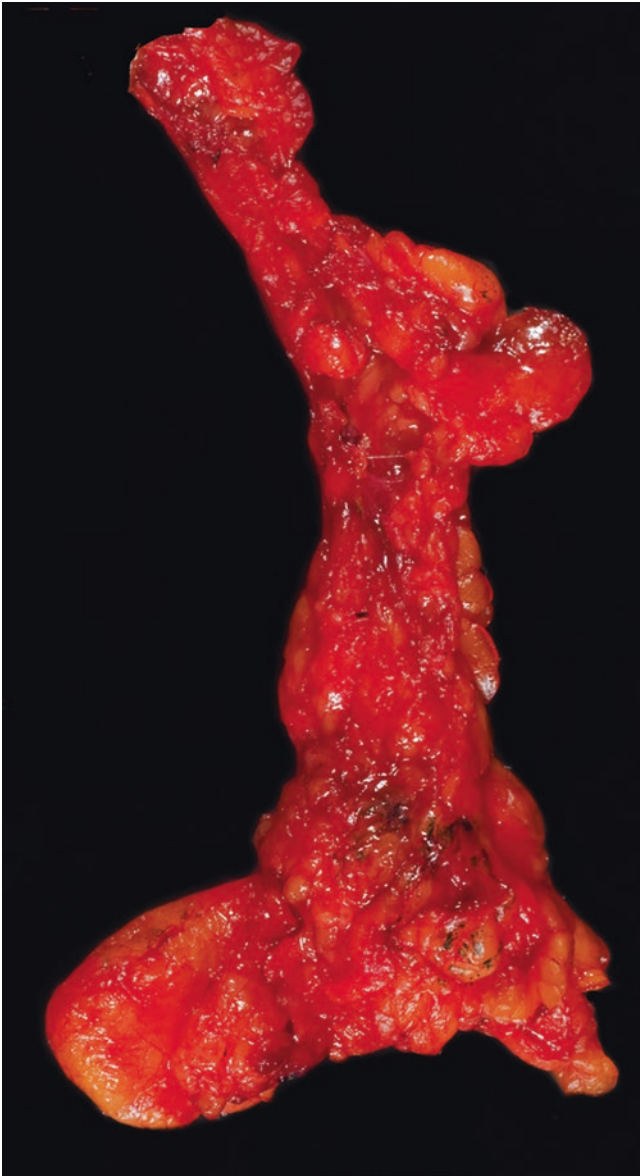


Fig. 1.3 Thymus of an adult individual showing more adipose tissue

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)

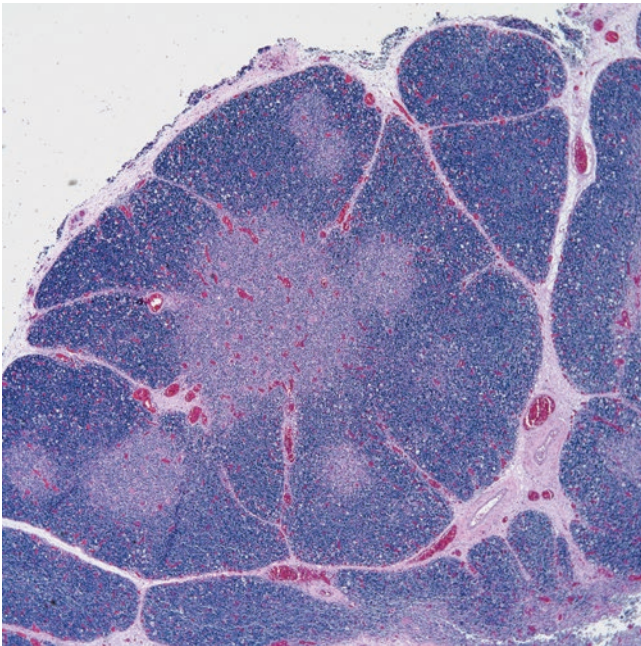
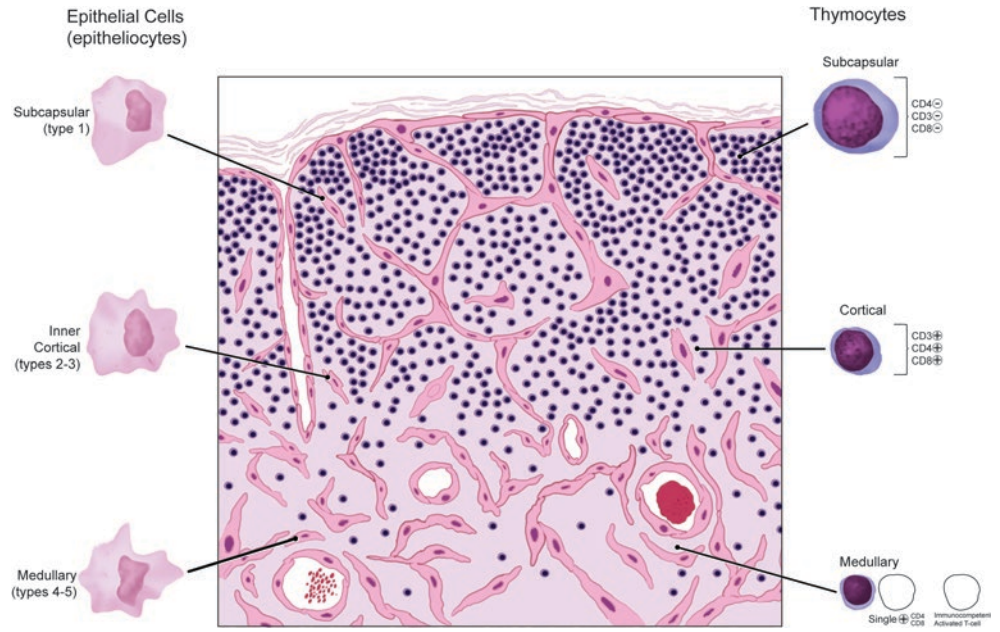


Fig. 1.5 Low power histological section of a normal thymus in a child under 1 year of age, showing a well-demarcated cortex and medulla

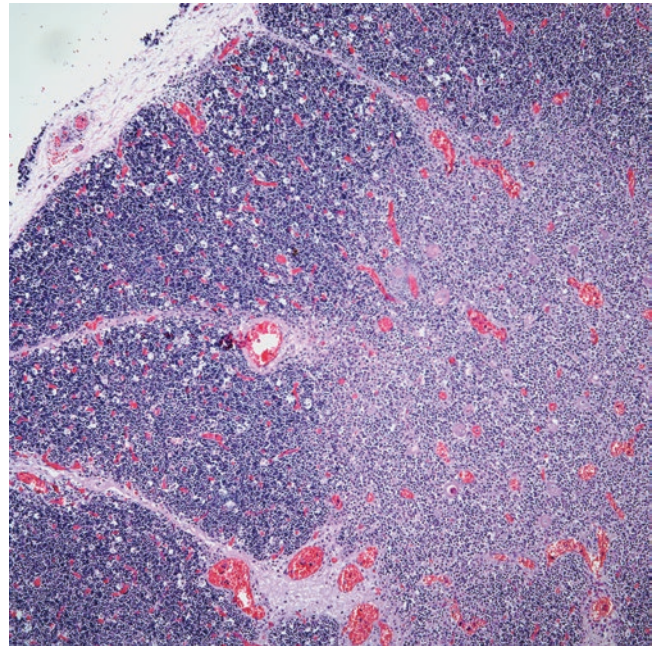


Fig. 1.6 Intermediate power view of a normal thymus showing well-defined cortex and medulla. Note the presence of Hassall's corpuscles

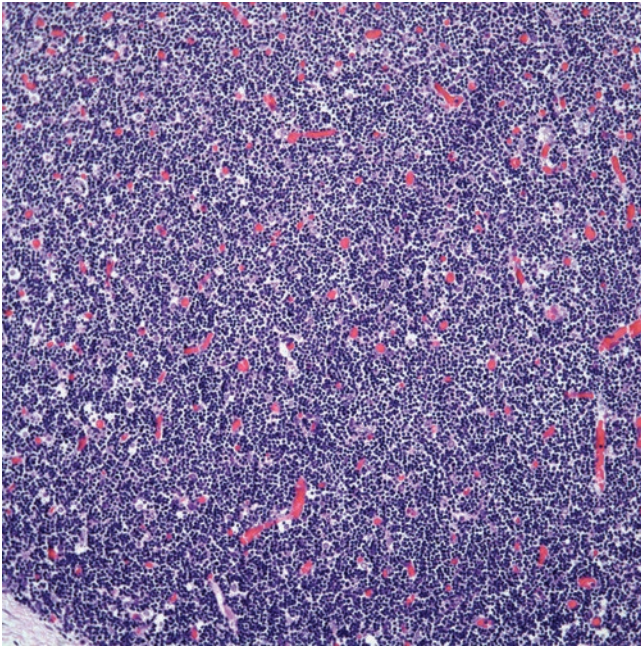


Fig. 1.7 High power view of the normal cortex of the thymus showing predominance of lymphocytes

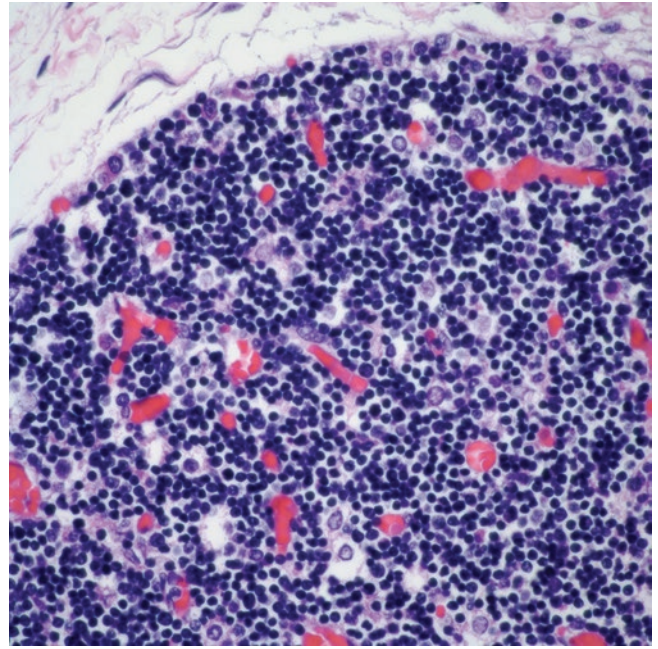


Fig. 1.9 High power view of the subcapsular cortex showing more atypical lymphoid cells

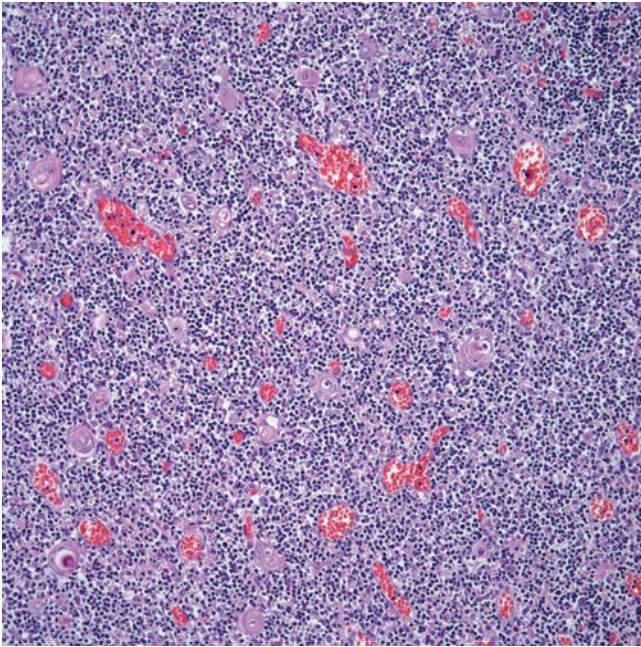


Fig. 1.8 High power view of the thymic medulla showing lymphocytes. However, epithelial cells are easily identified

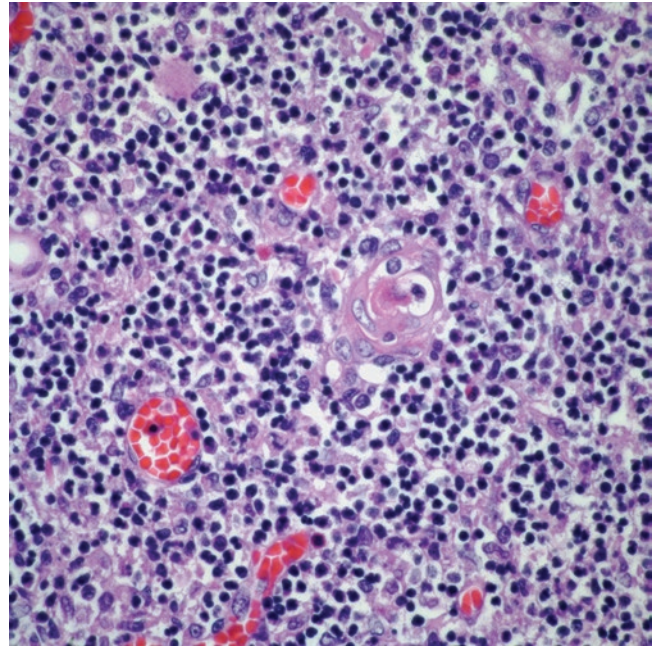


Fig. 1.10 High power view of the thymic medulla showing a Hassall's corpuscle surrounded by lymphocytes and epithelial cells

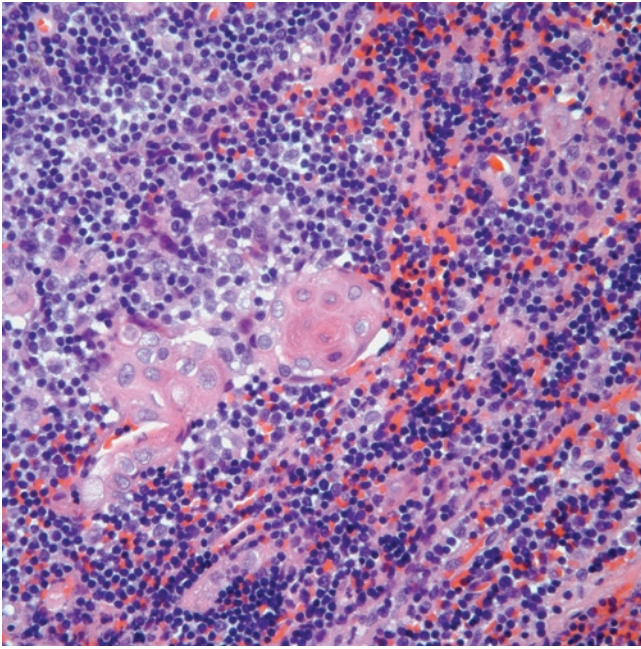


Fig. 1.11 Small Hassall's corpuscle with early keratinization and surrounded by lymphocytes

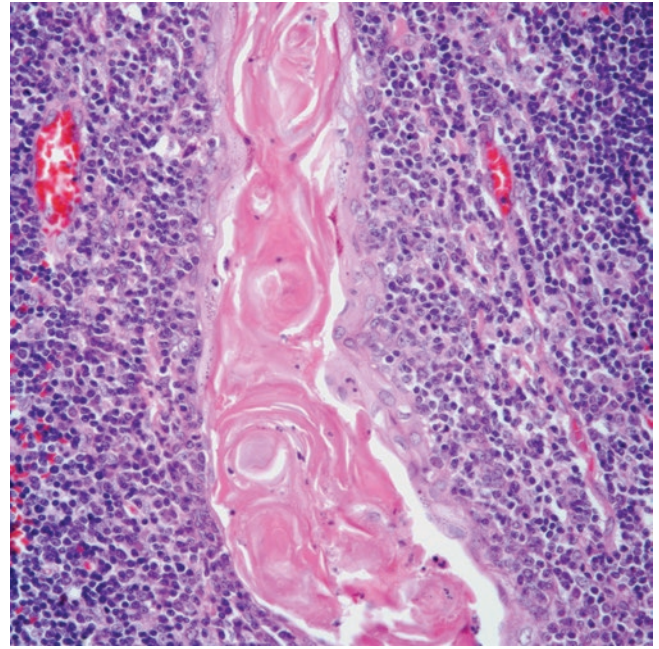


Fig. 1.13 Elongated Hassall's corpuscle with extensive keratinization

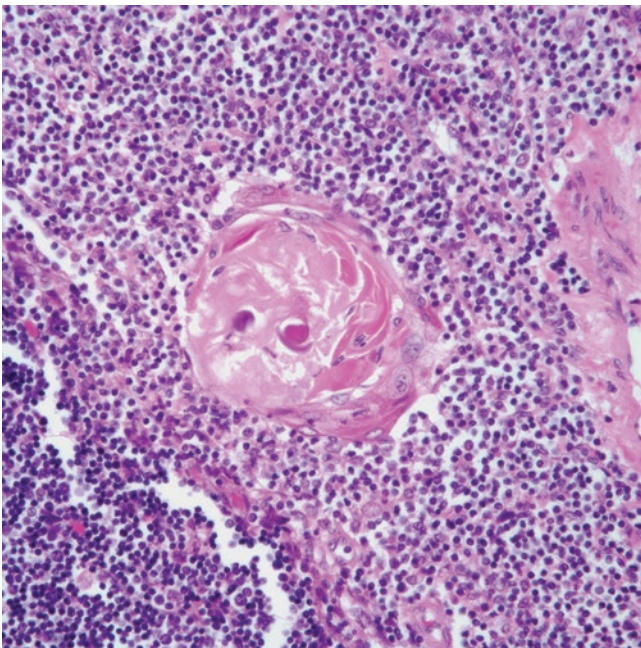


Fig. 1.12 Hassall's corpuscle with keratinization surrounded by epithelial cells and lymphocytes

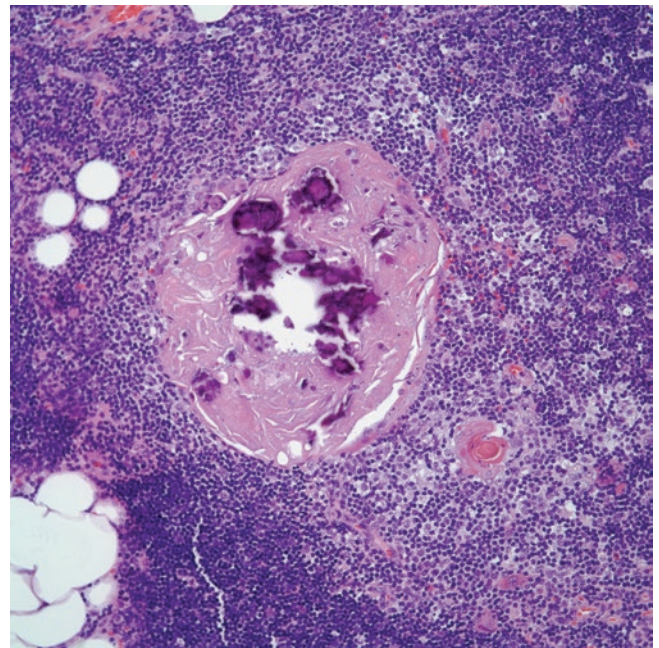


Fig. 1.14 Hassall's corpuscle with calcification

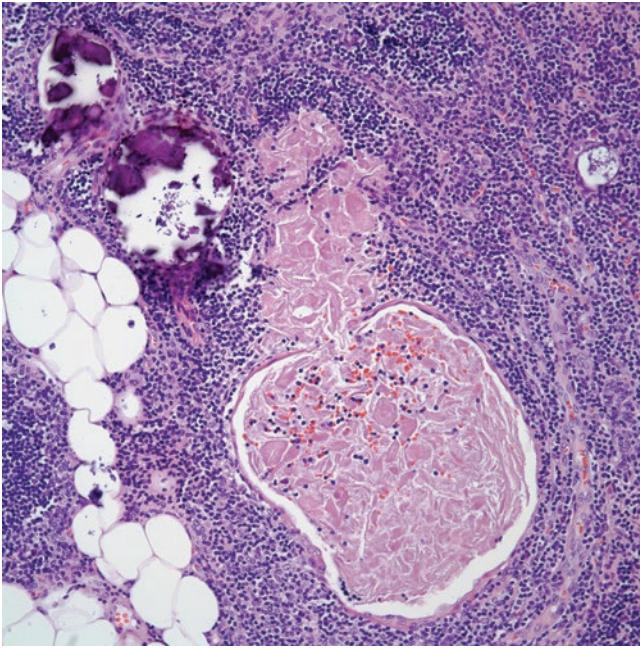


Fig. 1.15 Hassall's corpuscles showing calcification and keratinization

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).

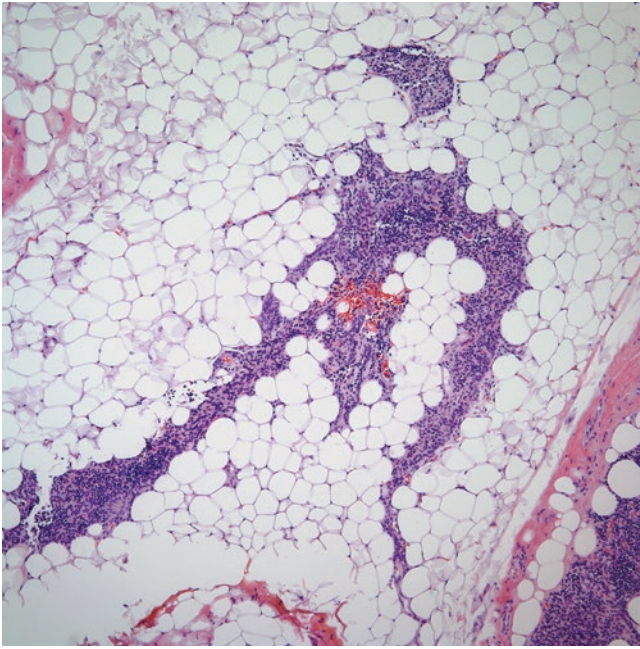


Fig. 1.16 Thymus with involution changes. Note the presence of abundant adipose tissue

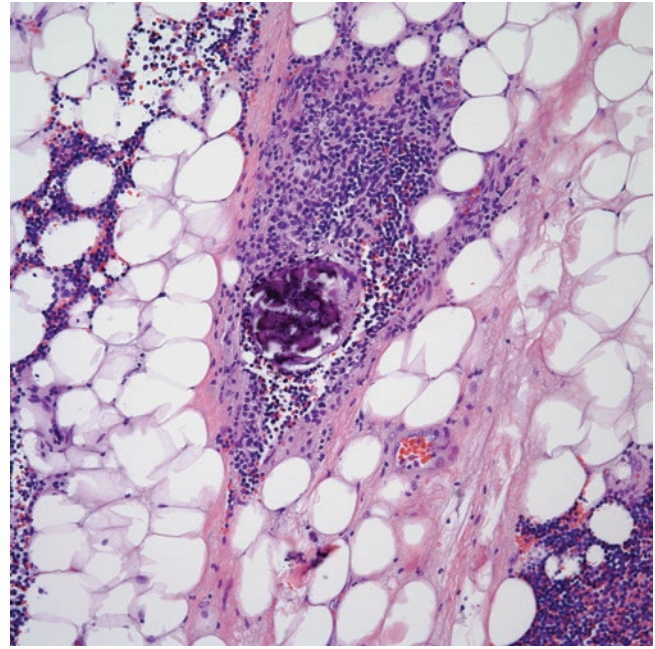


Fig. 1.18 Thymus with involution changes showing a calcified Hassall's corpuscle

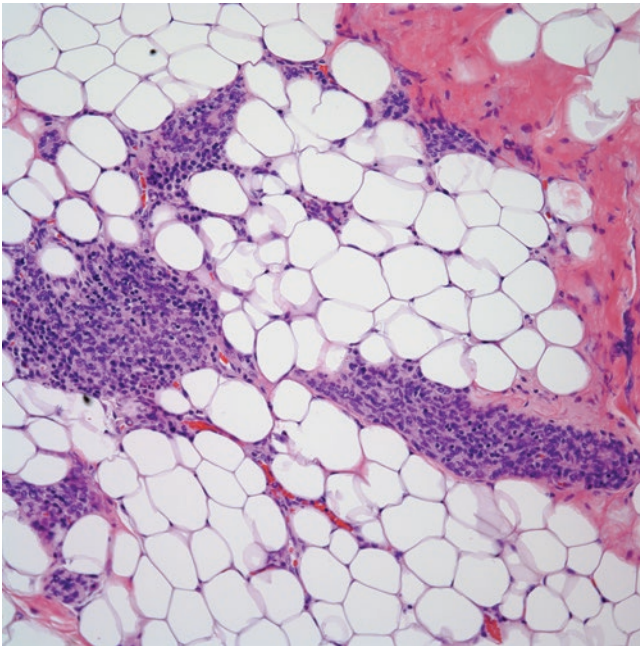


Fig. 1.17 Thymus with involution changes showing focal areas of residual thymic epithelium

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).