Histomorphology of Thymomas

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7.1 Introduction

Thymomas are rare but the most common anterior mediastinal masses with an incidence of 1.3–2.5/million per year. They show a wide age range, however uncommon in children and young adults, and do not have major sex predilection [1]. Over the years, different systems have been proposed for the histologic classification of thymomas. Due to a lack of consensus and the difficulties thereby faced by pathologists to subtype these tumors, in 1999 the World Health Organization (WHO) formed a panel of experts from different regions of the world to formulate a classification system of thymic epithelial tumors (TETs) [2].This classification system has been revised and the latest refinement of this classification was brought about in the 2015 edition of the WHO classification of tumors of lung, pleura, thymus, and heart [3].

7.2 WHO Classification of Thymomas

The 2015 WHO classification used an interdisciplinary approach to the diagnosis of TET with contributions from radiologists, oncologists, and thoracic surgeons [4]. The histomorphological and immunohistochemical features included in this classification were refined to increase reproducibility of thymoma subtypes as well as to simplify distinction between thymomas and thymic carcinomas. In this system, the existing subtypes of type A, AB, B1, B2, and B3 thymomas were retained with addition of certain obligatory and optional features for diagnosis [5]. These five main subtypes are broadly divided based on the neoplastic epithelial cells being spindled (A, AB) or epithelioid (B1–3) [6–8]. They are further subdivided depending on the content of neoplastic epithelial cells and the nonneoplastic immature T-cells. One addition was the recognition of mixed patterns and a proposal was made to record these subtypes in 10% increments. Also, all thymomas were recognized to have malignant potential and were excluded from benign category except for micronodular thymoma with lymphoid stroma which has uncertain behavior. This new classification system also incorporated the molecular basis of thymomas including the genetic, epigenetic, and transcriptomic changes [4].

7.3 Masaoka-Koga Staging for Pathologists

The importance of staging TETs lies in the fact that it is the most important prognostic factor surpassing the histologic classification [9]. The staging of TET is based on invasion, implants, lymph node involvement, and/or distant metastases. Fourteen different staging systems have been proposed in literature, of which the Masaoka-Koga and the TNM staging systems are more commonly followed worldwide. The Masaoka staging system [10] was developed in 1981 keeping in mind that all thymomas may be potentially malignant and that their prognosis may be determined by their stage.

Later on, Koga in 1994 [10] recommended a modification to this classification wherein a tumor invading into the capsule but not breaking through it was categorized as stage I whereas that infiltrating into normal thymic tissue as a result of transcapsular invasion was classified as stage II. Also, tumors invading into the pleura or pericardium were categorized as stage III based on the fact that only a thin layer of fibrous tissue exists between the thymus and the mediastinal pleura or pericardium, making it difficult to discriminate invasion into the adjacent organs from fibrous adhesion to the pleura or pericardium. The modified Masaoka-Koga staging is represented in Table 7.1.

In 2009, the International Thymic Malignancy Interest Group (ITMIG) and the International Association for the

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Table 7.1 Modified Masaoka-Koga staging of thymic epithelial tumors [10]

Stage I	Grossly and microscopically completely encapsulated
Stage II	
IIa	Microscopic transcapsular invasion
IIb	Macroscopic invasion into thymic or surrounding fatty tissue or grossly adherent to (but not breaking through) mediastinal pleura or pericardium
Stage III	Macroscopic invasion into neighboring organ, i.e., pericardium, great vessels, or lung
Stage IV	
IVa	Pleural or pericardial metastasis
IVb	Lymphatic or hematogenous metastasis

Table 7.2 TNM staging [12]

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor encapsulated or extending into the mediastinal fat, may involve the mediastinal pleura
T1a	• Tumor with no mediastinal pleura involvement
T1b	• Tumor with direct invasion of mediastinal pleura
T2	Tumor with direct invasion of the pericardium (either partial or full thickness)
T3	Tumor with direct invasion into any of the following: lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, or extrapericardial pulmonary artery or veins
T4	Tumor with invasion into any of the following: aorta (ascending, arch, or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus
Regional lymph node (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis
N1	Metastasis in anterior (perithymic) lymph nodes
N2	Metastasis in deep intrathoracic or cervical lymph nodes
Distant metastasis (M)	
M0	No pleural, pericardial, or distant metastasis
M1	Pleural, pericardial, or distant metastasis
M1a	Separate pleural or pericardial nodule(s)
M1b	Pulmonary intraparenchymal nodule or distant organ metastasis

Study of Lung Cancer (IASLC) formulated a consistent staging system for thymic tumors which would be easily followed worldwide. The classification system proposed by them was eventually accepted by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC)—the bodies responsible for defining stage classifications throughout the world [11, 12]. The TNM (tumor, node, metastasis) staging as proposed is described in Table 7.2.

The AJCC prognostic stage grouping for the above TNM classification is given in Table 7.3.

Table 7.3 AJCC prognostic stage grouping [12]

Stage I	T1a, T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IVA	Any T	N1	M0
	Any T	N0, N1	M1a
Stage IVB	Any T	N2	M0, M1a
	Any T	Any N	M1b

7.4 Type A Thymoma

7.4.1 Epidemiology and Clinical Features

Type A thymoma is a thymic epithelial tumor comprising of bland spindled/oval cells with few admixed immature lymphocytes. It is an uncommon subtype of thymomas. It has a slight female predominance and has a wide age range from 8–88 years. Type A thymomas are proposed to have originated from a thymic epithelial precursor with a potential for cortico-medullary differentiation. Paraneoplastic syndromes are less frequent with this subtype with approximately 20% which have associated myasthenia gravis [13]. On imaging, these are smaller with smooth distinct borders and show low FDG uptake on FDG PET-CT [14]. They are commonly low stage (modified Masaoka-Koga stage I–II) tumors with good prognosis [15].

7.4.2 Pathological Features

Grossly, type A thymomas are well circumscribed or encapsulated. They have a homogenous, light tan to white cut surface with some lobulations (Fig. 7.1).

Microscopically, these tumors have an incomplete or complete capsule with thick fibrous bands separating the parenchyma into lobulations. The tumor cells are arranged in a variety of patterns including glandular, fascicular, storiform, and hemangiopericytoma like (Figs. 7.2, 7.3, 7.4, and 7.5). Rosettes, whorls, microcystic change, and occasionally papillary arrangement are also seen (Figs. 7.6, 7.7, 7.8, and 7.9) [14]. Due to variety of patterns seen in type A thymoma, the differential diagnosis may range from adenocarcinoma to carcinoid/neuroendocrine tumor to sarcomas if a clinical history and site of the biopsy is not provided. Hassall corpuscles are absent. The tumor cells are spindled to oval with bland nuclei, fine chromatin, and inconspicuous nucleoli (Fig. 7.10). Mitotic activity is low that is <4 mitoses per 2 mm^2. These thymomas have almost no or very few immature (TdT+) lymphocytes, which are easily countable, and are present in less than 10% of tumor area [14]. Some type A

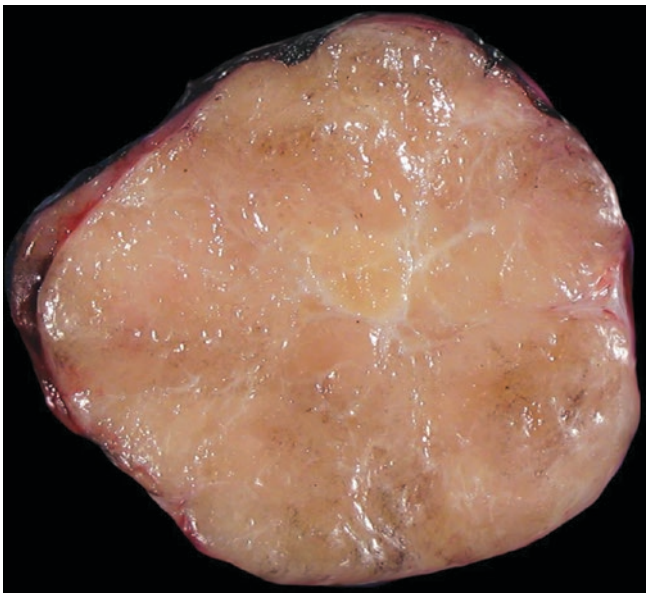


Fig. 7.1 Type A thymoma with homogenous light tan to white cut surface with some lobulations. Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

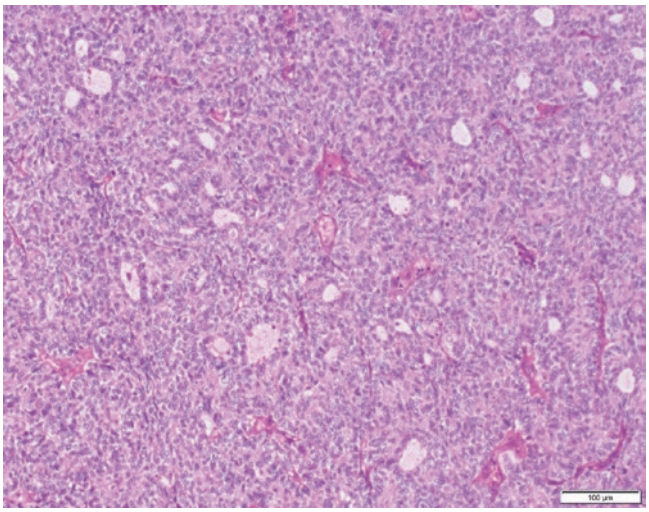


Fig. 7.2 Type A thymoma with a prominent glandular pattern of arrangement of cells (H&E ×100)

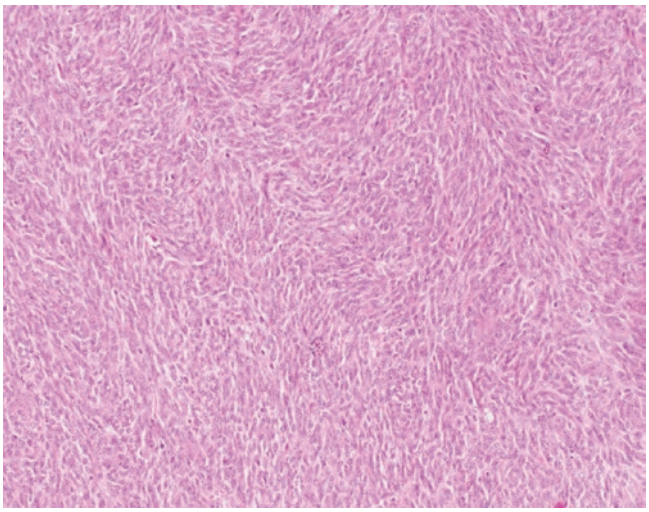


Fig. 7.3 Section from type A thymoma shows spindled epithelial cells predominantly in short intersecting fascicles with paucity of lymphoid cells (H&E ×40)

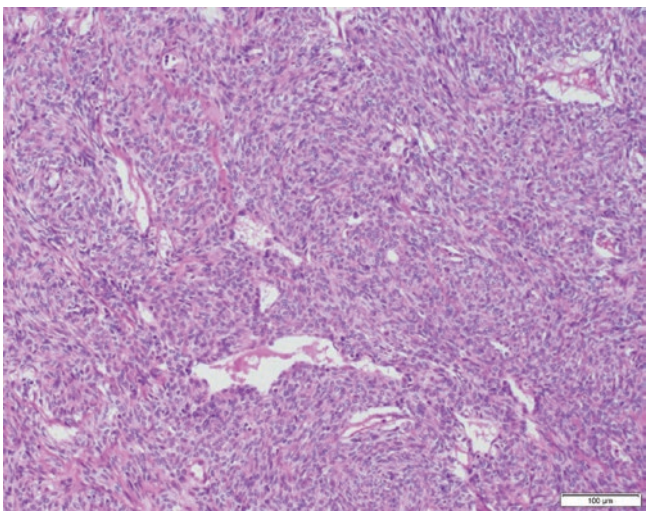


Fig. 7.4 Photomicrograph of type A thymoma shows predominantly spindled epithelial cells present in diffuse sheets and short fascicles with barely visible immature lymphocytes (H&E ×40)

thymomas may contain foci of micronodular thymoma with lymphoid stroma (Figs. 7.11 and 7.12) [16].

Immunohistochemically, the type A epithelial cells are positive for p63, PAX8, and FOXN1 and negative for CD5 and CD117. They frequently express CD20 focally.

7.4.3 Atypical Type A Thymoma

In addition to the above described features, the atypical features present in atypical type A thymoma are hypercellularity, increased mitotic counts (> = 4/10 high power fields), and focal areas of coagulative necrosis (Figs. 7.13, 7.14, 7.15, 7.16, 7.17, 7.18, and 7.19) [5, 14].

7.5 Type AB Thymoma

7.5.1 Epidemiology and Clinical Features

Type AB thymoma is a thymic epithelial tumor composed of a dual population of spindled epithelial cells and immature T lym-

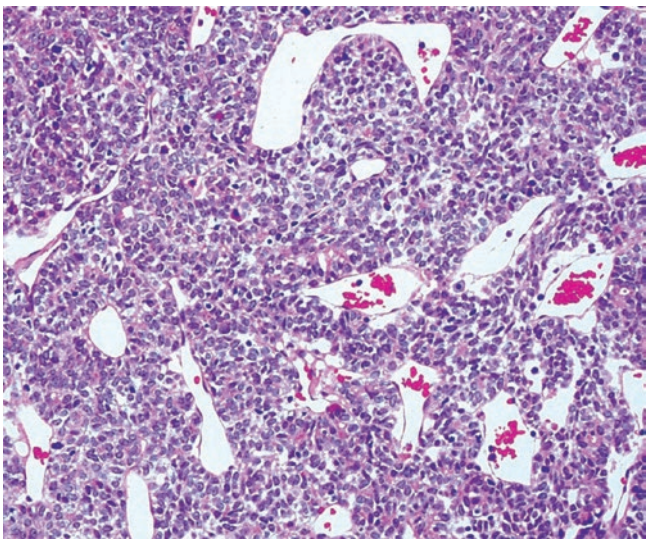


Fig. 7.5 Photomicrograph of type A thymoma with a hemangiopericytoma-like pattern of arrangement of epithelial cells (H&E ×200). Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

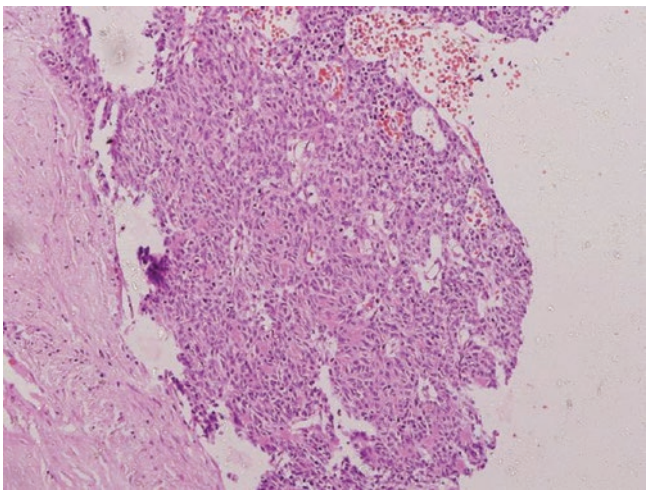


Fig. 7.6 Type A thymoma with pseudorosettes (H&E ×100)

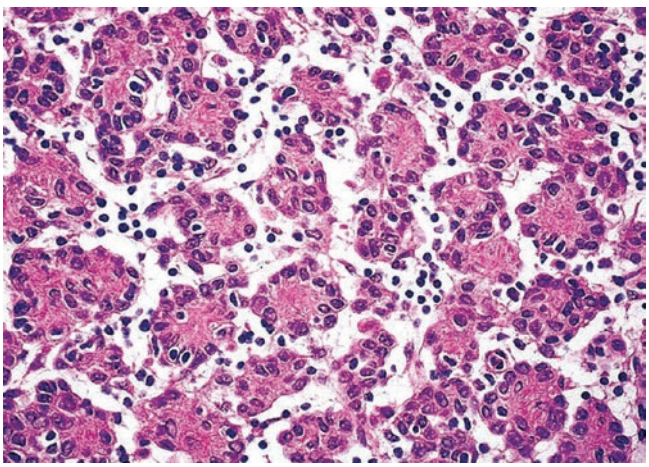


Fig. 7.7 Thymoma with formation of pseudorosettes. (H&E ×200). Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

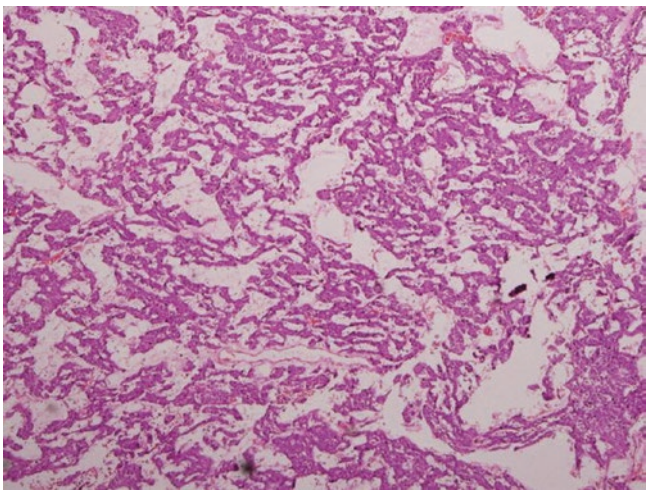


Fig. 7.8 Type A thymoma with a prominent reticular pattern of arrangement of epithelial cells (H&E ×40)

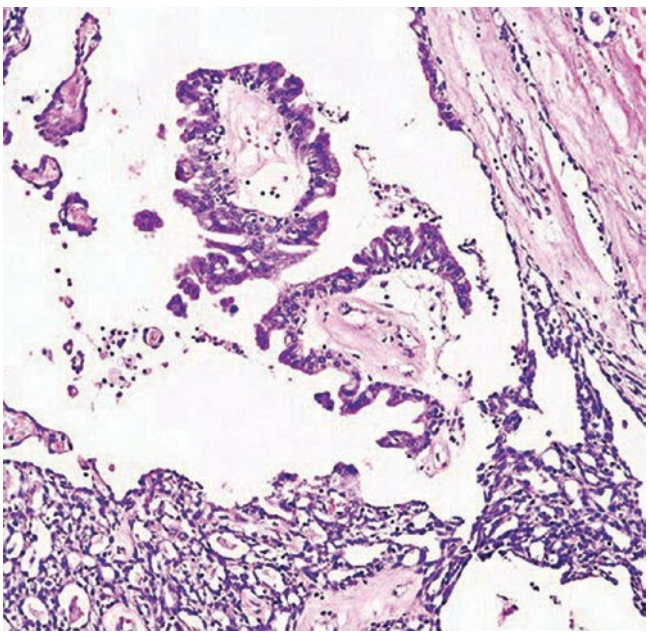


Fig. 7.9 Type A thymoma with areas of pseudopapillary formations (H&E ×40). Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

phocytes in variable proportions. Its incidence worldwide ranges from 15 to 43%. The patients are younger than that of type A thymoma. Of these patients 18–20% present with myasthenia gravis [13]. Most type AB thymomas are lower-stage tumors (stages I and II) [17].

7.5.2 Pathological Features

Grossly, these are commonly encapsulated tumors with a nodular cut surface having tan-colored nodules of varying sizes (Fig. 7.20).

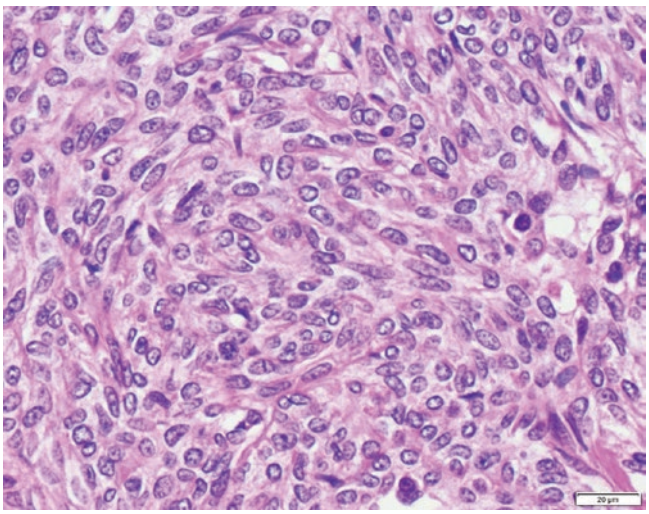


Fig. 7.10 High power view of type A thymoma shows spindled epithelial cells with elongated oval nuclei, bland chromatin, and inconspicuous nucleoli (H&E ×400)

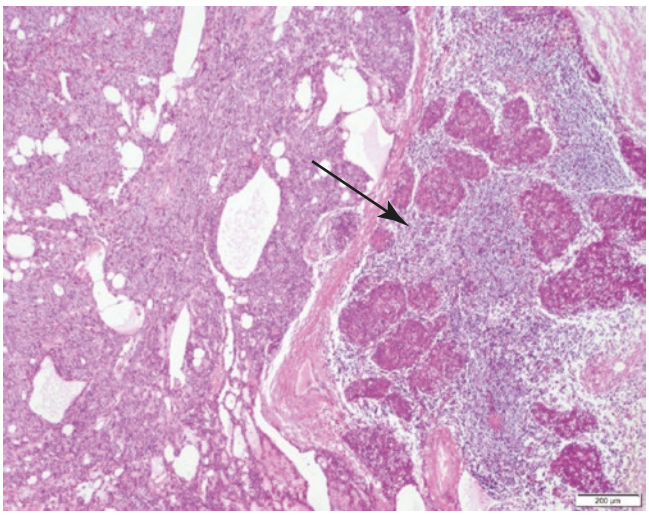


Fig. 7.12 Type A thymoma with adjacent focus of micronodular thymoma with lymphoid stroma (arrow) (H&E ×40)

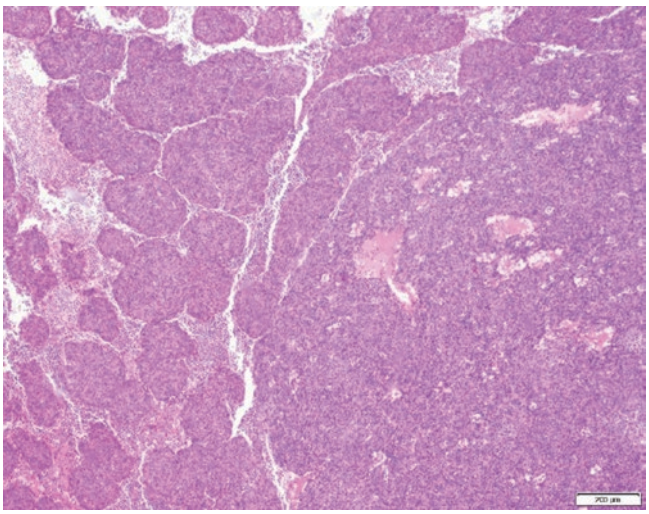


Fig. 7.11 A type A thymoma with spindled epithelial cells in sheets at the right half of the figure along with presence of micronodular thymoma with lymphoid stroma at the left half comprising of tumor cells in small nodules separated by lymphocyte rich stroma (H&E ×40)

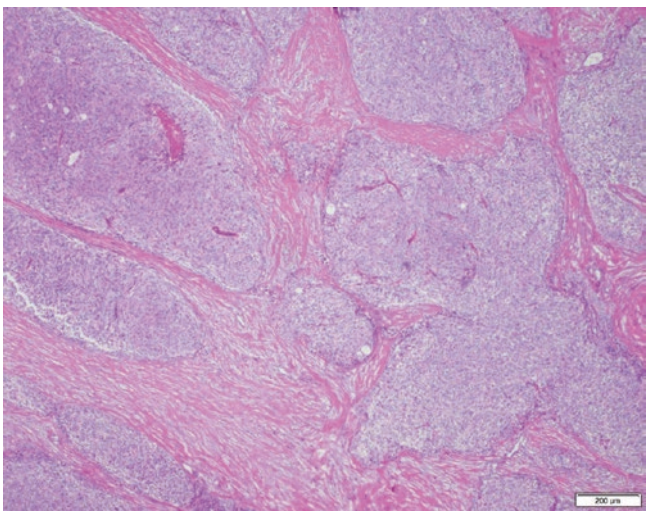


Fig. 7.13 Atypical type A thymoma shows a nodular arrangement of spindled epithelial cells separated by dense sclerotic stroma (H&E ×40)

Microscopically, type AB thymomas show a lobulated growth comprising of a variable mixture of lymphocyte-poor epithelial cells (type A-like) and a lymphocyte-rich type B-like area which may form separate nodules or may be intermingled (Fig. 7.21). The type A-like areas are composed of spindled epithelial cells in fascicles coursing around type B-like areas. The tumor cells of type B areas are small, oval to polygonal and have bland chromatin and inconspicuous nucleoli (Figs. 7.22, 7.23, 7.24, 7.25, 7.26, 7.27, 7.28, and 7.29). The lymphocytes are immature T-cells which are TdT + and are either difficult to count or countable in >10% of tumor area [18]. Hassall corpuscles are absent.

Immunohistochemically, the type A cells are positive for p63, PAX8, and FOXN1 and negative for CD5 and CD117. They frequently express CD20 focally. The epithelial cells present in the type B areas are CK14+. Ki-67 proliferation index is low.

7.6 Type B1 Thymoma (Blue on Low Magnification)

7.6.1 Epidemiological and Clinical Features

Type B1 thymomas form approximately 17–20% of all thymomas and have a female predominance [19]. It is most commonly seen in the fifth to sixth decades. Clinically, about a third of the patients are asymptomatic. Others develop local symptoms such as chest pain, cough, and dyspnea. The incidence of myasthenia gravis is more than that in type A

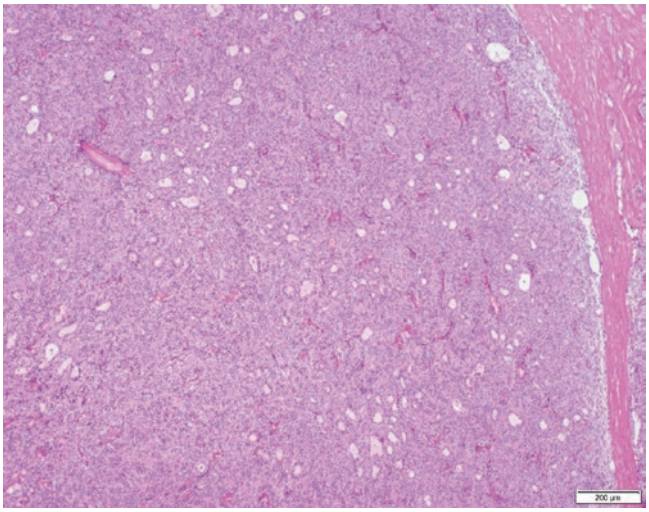


Fig. 7.14 Atypical type A thymoma with predominantly glandular pattern (H&E ×40)

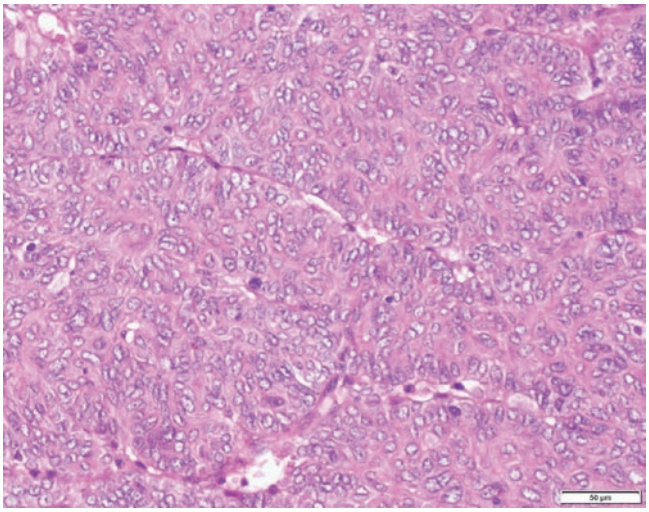


Fig. 7.16 Atypical A thymoma showing nuclear atypia in the form of nuclear enlargement, vesicular chromatin, and mitotic activity (H&E ×200)

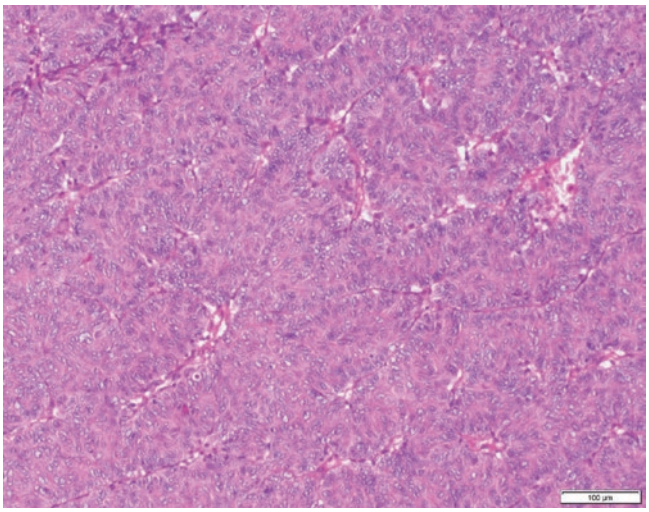


Fig. 7.15 Atypical type A thymoma with epithelial cells arranged in a trabecular pattern (H&E ×100)

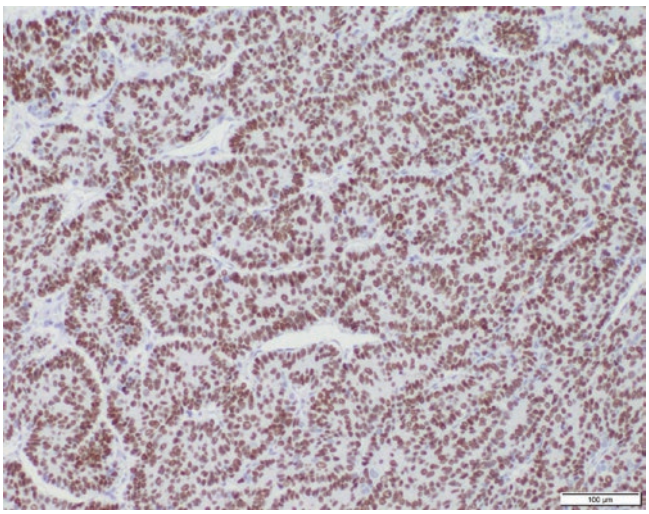


Fig. 7.17 Atypical A thymoma stained diffusely with p40 immunostain (strong nuclear positivity) (p40 ×40)

thymomas and occurs in about 44% patients [20]. About 50% of the tumors are in stage I. They are generally encapsulated and extension to adjacent structures and pleural dissemination are rare.

7.6.2 Pathological Features

Grossly, the type B1 thymomas are usually encapsulated and have a nodular external surface. The cut surface is soft, smooth, and tan-pink in color (Fig. 7.30).

Microscopically, type B1 thymomas have a thymus-like architecture where the cortical areas are the predominant population. The lobules, if present, are larger than normal thymus and are separated by fibrous septae. The neoplastic epithelial cells are barely visible and are embedded in a non-neoplastic immature lymphoid population (Figs. 7.31, 7.32, and 7.33). The epithelial cell clusters, if seen, should be less than three contiguous epithelial cells to designate the lesion as type B1 thymoma. The epithelial cells have oval to rounded nuclei with pale chromatin and small conspicuous nucleoli. Pale nodular areas commensurate with medullary foci are always present (Figs. 7.34 and 7.35). These areas have increased B-cells and mature T-cells (Fig. 7.36). Hassall corpuscles are also seen in these areas. Perivascular spaces may also be found in this subtype of thymoma [21].

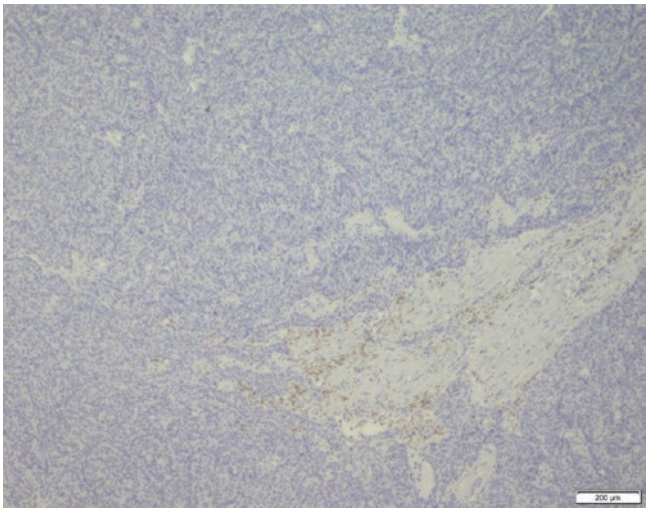


Fig. 7.18 Atypical A thymoma shows paucity of TdT-positive (comprising of less than 10% of tumor area) lymphocytes (TdT x40)

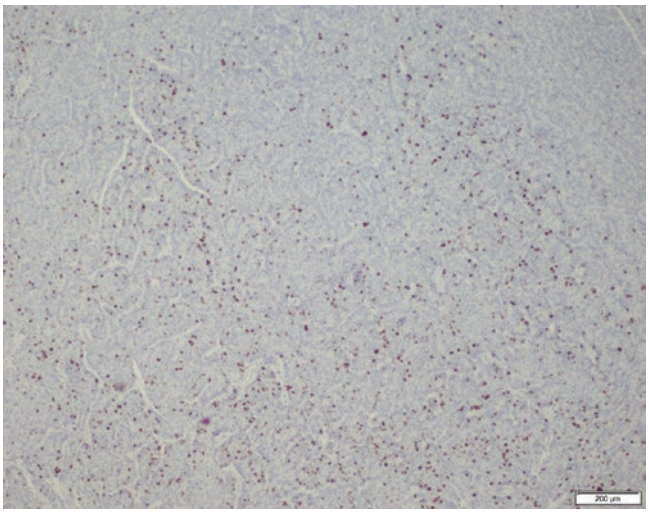


Fig. 7.19 Ki-67 (MIB1 labeling index) staining of atypical A thymoma which shows increased proliferation with 10–20% labeling (Ki-67 ×40)

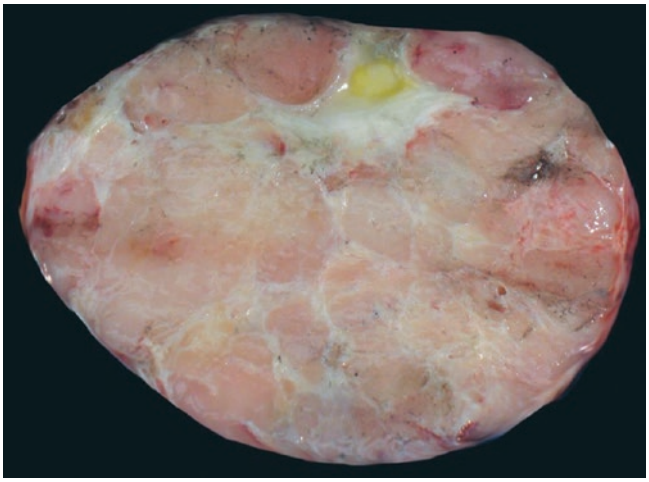


Fig. 7.20 Gross image of type AB thymoma showing a nodular cut surface having tan-colored nodules of varying sizes. Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

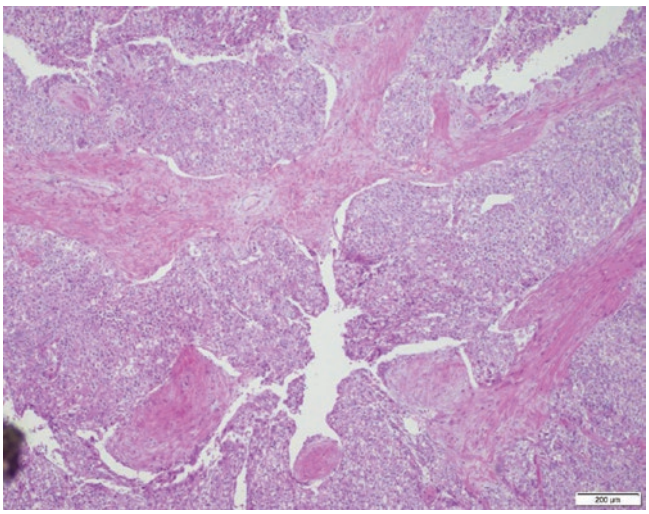


Fig. 7.21 Low power view of type AB thymoma with sheets of epithelial cells and admixed lymphocytes separated by thick fibrovascular septae (H&E ×40)

Distinctive features of type B1 thymoma are as follows:

1. Close resemblance to normal thymus
2. Non-involuted thymic cortex
3. Presence of medullary islands

Type B2 and B3 thymomas may be admixed with type B1 thymomas.

Immunohistochemically, the epithelial cells are diffusely positive for CK19 in a delicate network pattern in both the medullary islands and cortical areas (Fig. 7.37). CK20 is negative. All cases express p63 and PAX8. Lymphocytes are mostly immature T-cells expressing TdT, CD3, CD1a, CD4, and CD8. The lymphocytes in the medullary islands are CD3+, either CD4 or CD8 positive, and CD1a-; admixed with B-cells which are CD20+ and CD79a+.

7.7 Type B2 Thymoma

7.7.1 Epidemiology and Clinical Features

Type B2 thymomas are lymphocyte-rich tumors composed of polygonal neoplastic cells, which form small clusters, the density of which is higher than type B1 thymomas, in a background of immature T-cells. These form approximately a

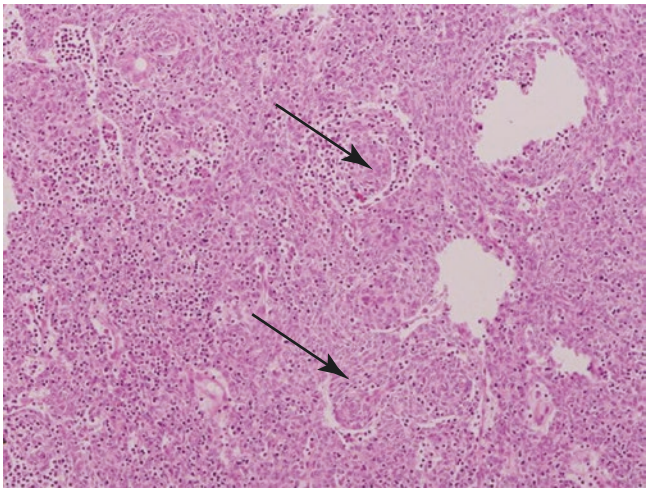


Fig. 7.22 Type AB thymoma with the epithelial cells exhibiting a whorling pattern (arrows) (H&E ×40)

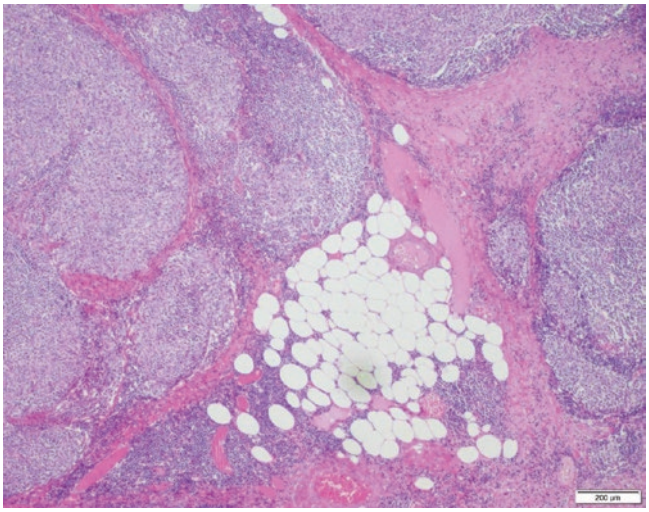


Fig. 7.24 Type AB thymoma with an area of entrapped adipocytes (H&E ×40)

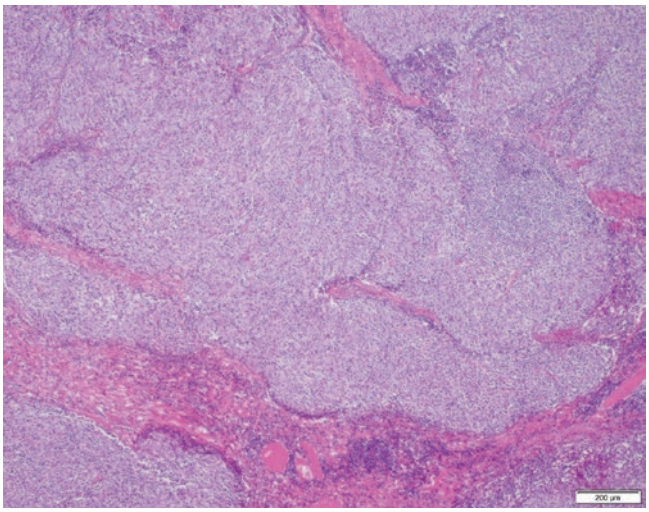


Fig. 7.23 Another case of type AB thymoma shows admixture of epithelial cells and lymphocytes (H&E ×40)

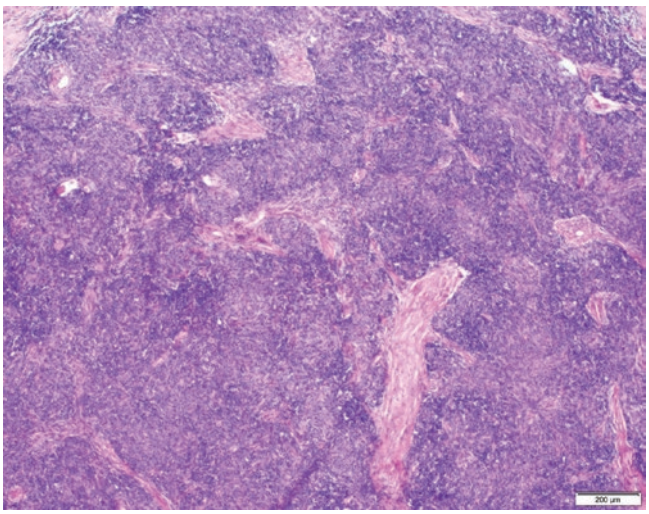


Fig. 7.25 Type AB thymoma with sheets of spindled thymic epithelial cells and thymocytes (thymic lymphocytes) separated by short thick bundles of fibrous septae (H&E ×40)

third of all thymomas [22]. They are found in adults. Clinical features vary from being asymptomatic to having local symptoms. Myasthenia gravis is a little more frequent in these thymomas (up to 54%) [20]. The type B2 thymomas are commonly seen infiltrating the surrounding fat as well as pleural space.

7.7.2 Pathological Features

Grossly, these tumors may be encapsulated or may invade the adjacent structures. The cut surface is lobulated, soft to firm, and gray-white with areas of necrosis, cystic change, and/or hemorrhage (Fig. 7.38).

Microscopically, the type B2 thymomas have lobular architecture with abundance of lymphoid cells surrounded by a fibrous tumor capsule (Figs. 7.39, 7.40, 7.41, 7.42, 7.43, and 7.44). Interspersed among the lymphoid cells are epithelial cells arranged singly or in clusters of > = 3 cells (Figs. 7.45, 7.46, and 7.47) [22]. The epithelial cells have round to oval nuclei with vesicular chromatin and small prominent nucleoli. Another typical feature of type B2 thymoma is the presence of perivascular spaces comprising of a central venule surrounded by a clear space containing proteinaceous fluid (Fig. 7.48). Hassall corpuscles are seen (Fig. 7.49). The medullary islands are not found. Associated areas of type B1 and B3 thymomas may be found.

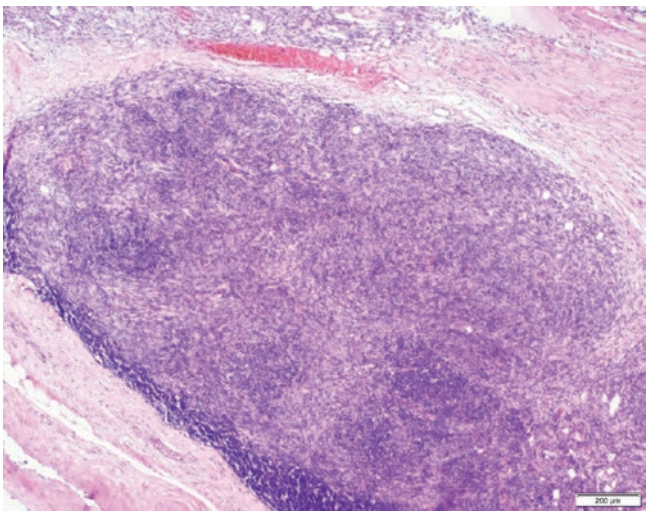


Fig. 7.26 A case of type AB thymoma with spindled thymic epithelial cells enmeshed within a fair number of lymphocytes (H&E ×40)

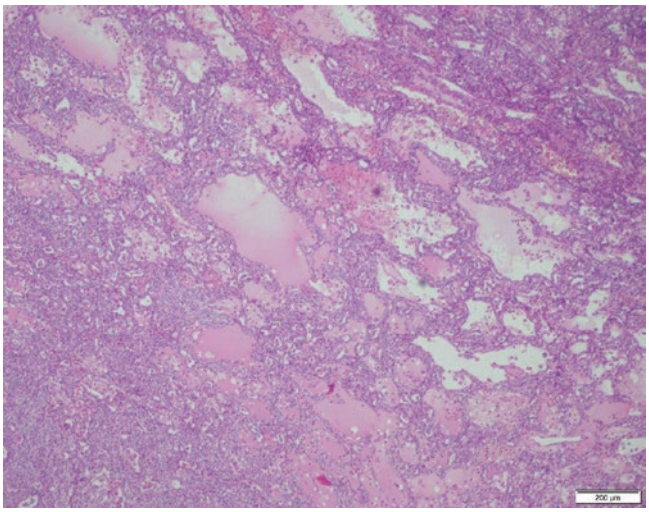


Fig. 7.27 Type AB thymoma with areas of fluid-containing pseudoglandular spaces (H&E ×40)

Immunohistochemically, the cytokeratin-positive network of epithelial cells is denser than type B1 (Fig. 7.50) surrounded by TdT+ immature T-cells.

7.8 Type B3 Thymoma (Pink on Low Magnification)

7.8.1 Epidemiology and Clinical Features

Type B3 thymomas are thymic epithelial tumors composed predominantly of polygonal epithelial cells in solid sheets displaying mild to moderate atypia along with intermixed nonneoplastic immature T-cells. The incidence of these

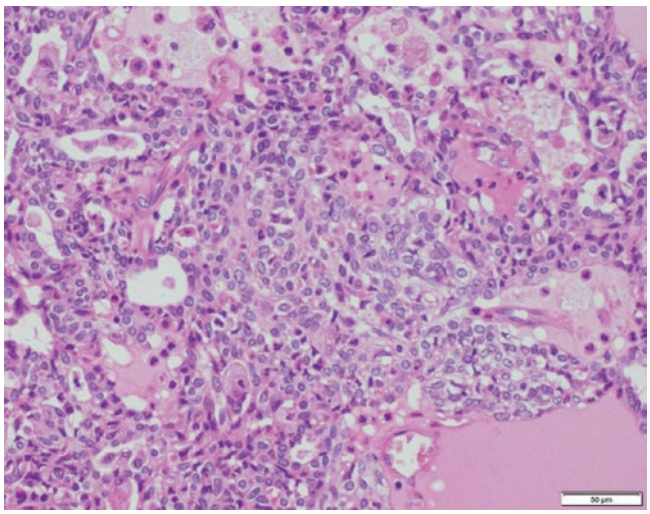


Fig. 7.28 Closer view of thymic epithelial cells in a case of type AB thymoma. Cyst macrophages are also seen within the fluid-containing spaces. Lymphocytes were seen in some other areas of the tumor (H&E ×200)

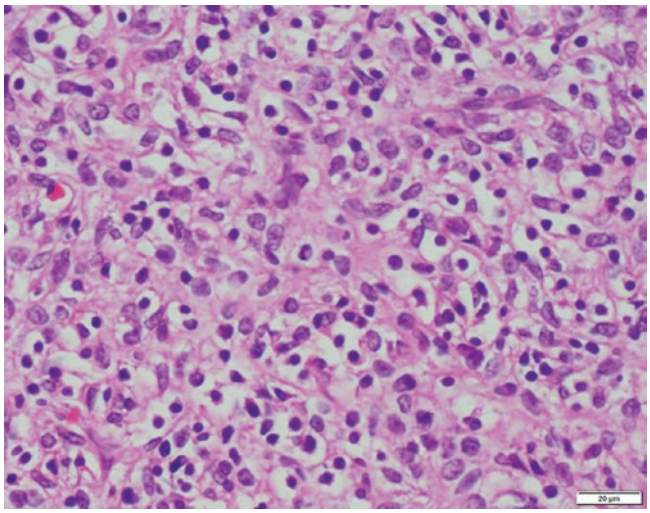


Fig. 7.29 High power view of type AB thymoma showing thymic epithelial cells with clear cytoplasm and well-defined cell borders admixed with fair number of lymphocytes (H&E ×200)

tumors varies with geographical location, being more common in Asian countries (30%) as compared to the West (15–17%) [19]. They have a mean age of presentation of 55 years and show a slight male predominance. Most patients have local symptoms or superior vena cava syndrome. Myasthenia gravis is seen in around 50% of the cases [20].

7.8.2 Pathological Features

Grossly, these tumors are poorly circumscribed with extensions into the surrounding mediastinal fat and adjacent struc-

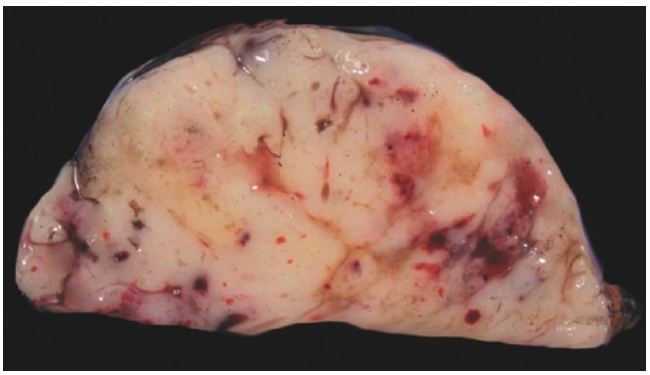


Fig. 7.30 Type B1 thymoma with a lobulated cut surface which appears soft smooth and tan pink in color along with areas of hemorrhage. Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

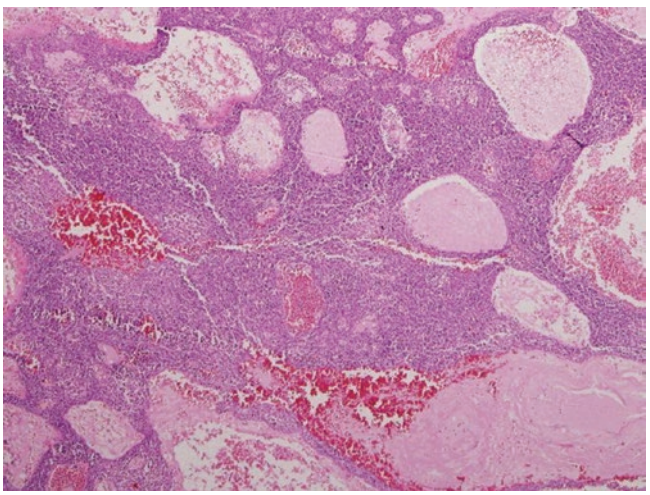


Fig. 7.31 Type B1 thymoma showing intermixed perivascular lakes containing lymph as well as areas of hemorrhage (H&E ×40)

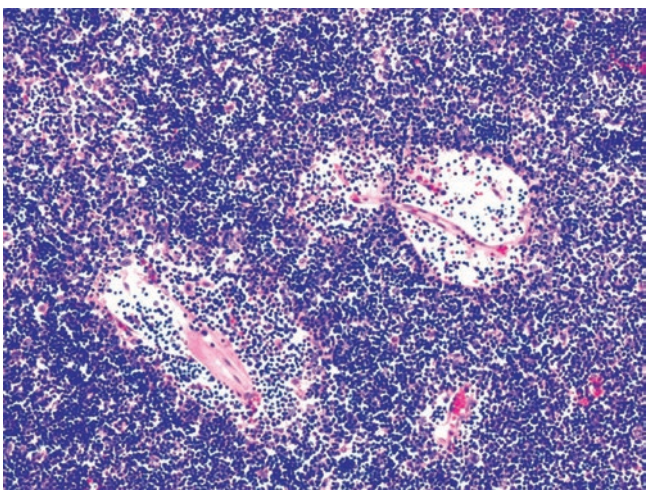


Fig. 7.32 Type B1 thymoma with perivascular spaces (empty spaces around blood vessels) (H&E ×100). Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

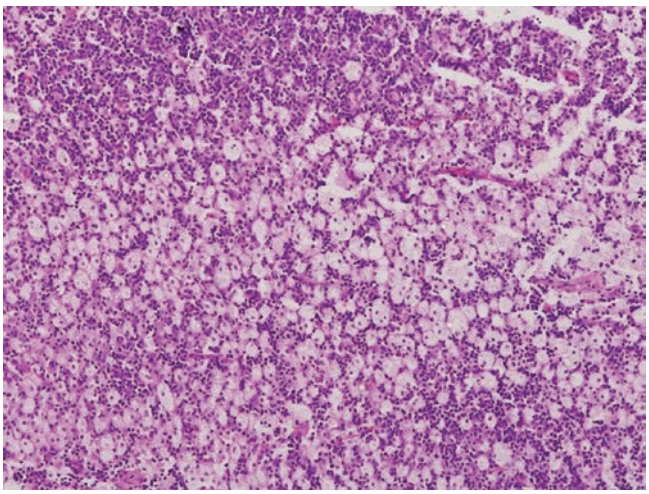


Fig. 7.33 Type B1 thymoma showing immature lymphocytes admixed with foamy histiocytes indicating xanthomatous change (H&E ×100)

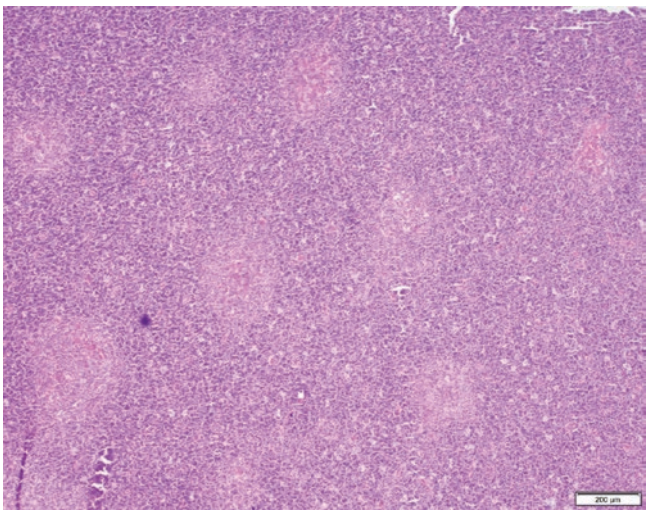


Fig. 7.34 Low power view of type B1 thymoma showing pale staining medullary islands surrounded by dark staining cortical regions (H&E ×40)

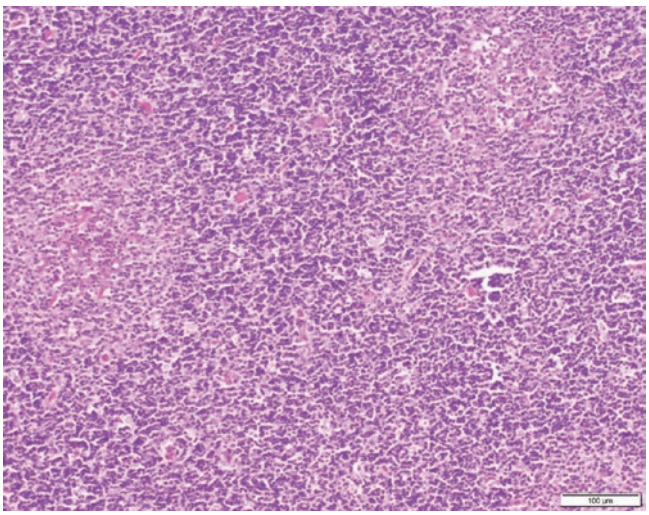


Fig. 7.35 Medium power view of type B1 thymoma showing pale medullary islands surrounded by dark cortical regions (H&E ×100)

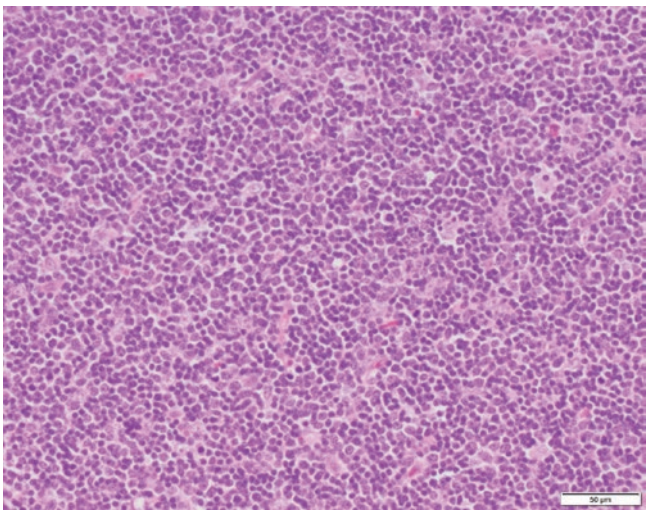


Fig. 7.36 High power view of type B1 thymoma shows predominantly lymphoid component and no easily identifiable epithelial cell clusters (H&E ×400)

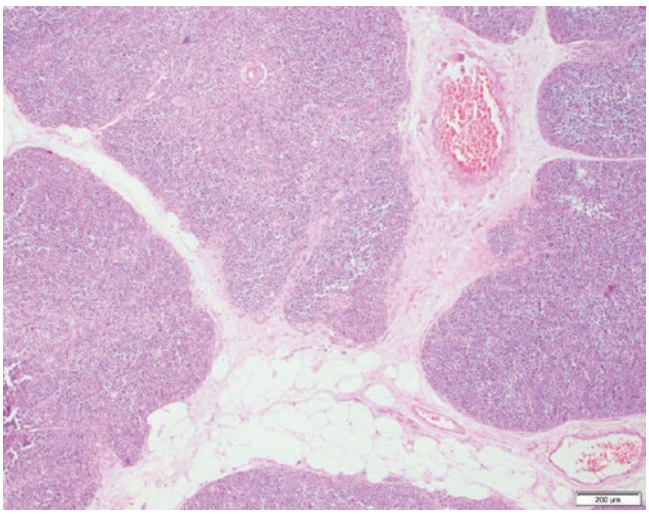


Fig. 7.39 Type B2 thymoma shows tumor present in lobules separated by fibroadipose tissue (H&E ×40)

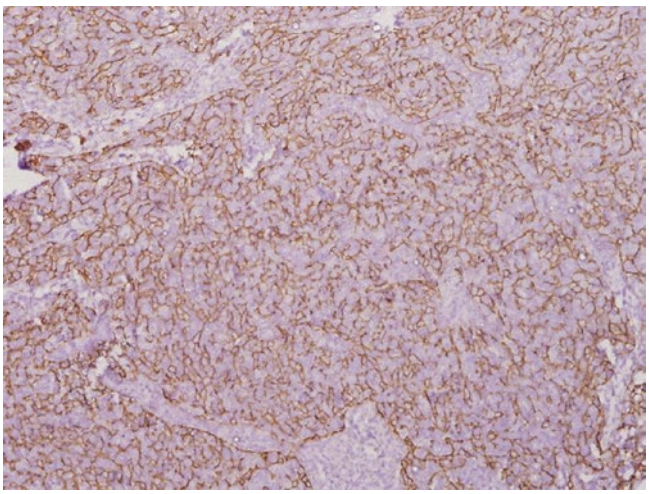


Fig. 7.37 Immunohistochemical stain of pan-cytokeratin in a case of type B1 thymoma highlighting a delicate network of epithelial cells intermixed with lymphoid cells (Pan-CK ×100)

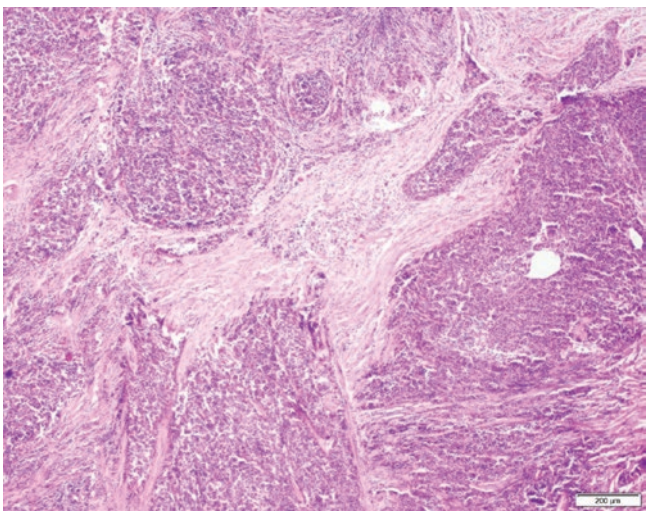


Fig. 7.40 Section from type B2 thymoma shows nodules of epithelial and lymphoid cells separated by fibrous stroma (H&E ×40)

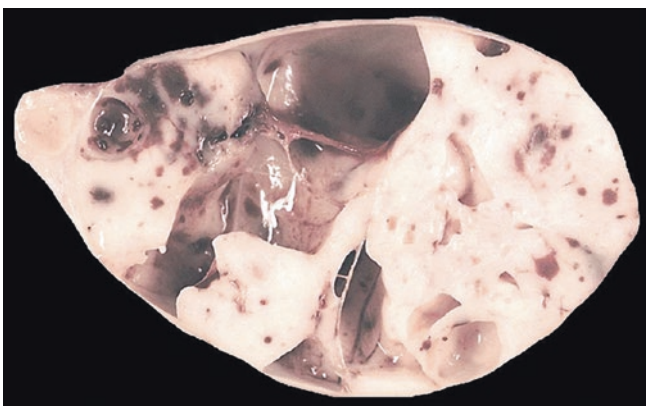


Fig. 7.38 Type B2 thymoma with a lobulated cut surface which is soft to firm and appear gray-white with areas of necrosis, cystic change, and/or hemorrhage. Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

tures (Fig. 7.51). Rare encapsulated and cystic forms are recognized [23]. The cut surface appears firm, gray to yellow in color with nodular appearance. There may be associated necrosis and hemorrhage.

Microscopically, the tumor shows a lobular architecture separated by fibrous septae and has pushing borders (Fig. 7.52). The tumor cells are present in solid sheets and are polygonal with eosinophilic to clear cytoplasm, round to oval nuclei with atypia and sometimes prominent nucleoli (Figs. 7.53, 7.54, 7.55, 7.56, 7.57, 7.58, 7.59, 7.60, and 7.61). There is paucity of intermixed immature lymphocytes. In addition, there are prominent perivascular spaces with epithelial palisading. Hassall corpuscles are rarely found. There may be coexisting areas of type B2 thymomas or thymic carcinomas [24].

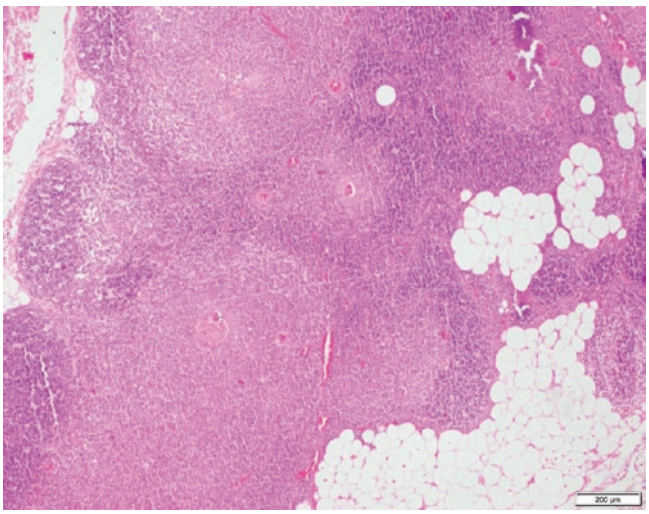


Fig. 7.41 Type B2 thymoma displays nodules of epithelial cells with surrounding lymphoid stroma infiltrating into the surrounding adipose tissue (H&E ×40)

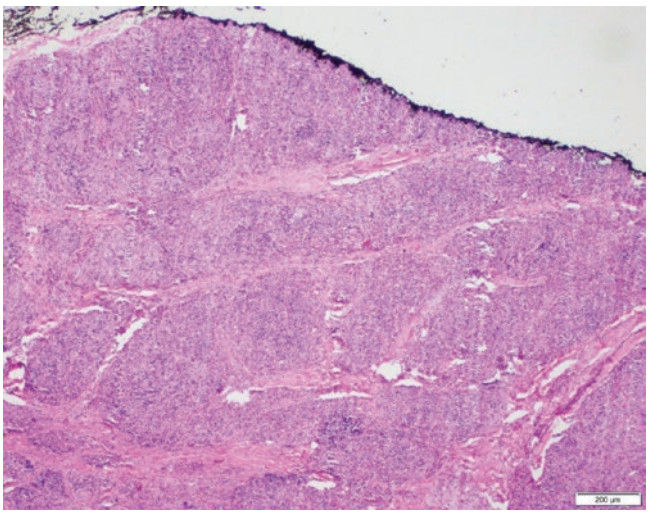


Fig. 7.43 Type B2 thymoma with capsular involvement (inked surface) (H&E ×40)

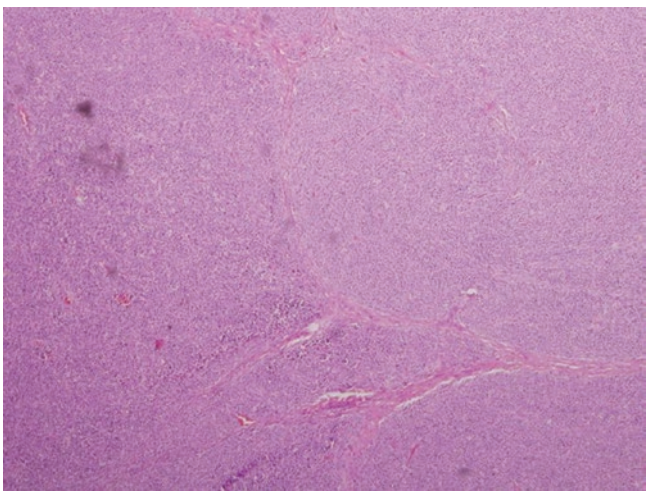


Fig. 7.42 Type B2 thymoma comprising of admixture of sheets of epithelial cells along with lymphocytes in lobular architecture separated by fibrous septae (H&E ×40)

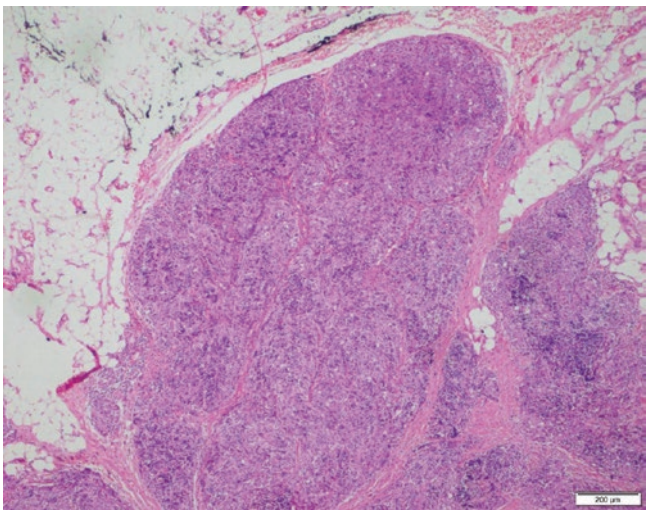


Fig. 7.44 Type B2 thymoma with lobular arrangement of tumor cells comprising of epithelial and lymphoid cells admixed together and infiltrating into the peritumoral adipose tissue (H&E ×40)

Immunohistochemically, the tumor cells are positive for pancytokeratin (Fig. 7.62), CK19, CK5/6, and CK7 and negative for CK20. They are also positive for p63, for PAX8, and focally for EMA. They are consistently negative for CD20, CD5, and CD117. Immature T-cells, if present, are positive for TdT.

7.9 Heterogeneous Thymomas

Thymomas with more than one histological pattern were earlier labeled as combined thymomas, a term which is no longer recommended to be used [5]. The diagnosis should include all the histologic subtypes mentioning the predominant pattern followed by minor components in 10% increments. Most common combination is B3 and B2. The rule does not apply to type AB thymomas. In case thymomas accompany a thymic carcinoma, then the entity is labeled thymic carcinoma irrespective of percentage of carcinoma component. Though, it is advisable to write percentage of each histologic type in the pathology report. The existence of this heterogeneity emphasizes the need for extensive sampling of the tumors. Some cases of such combinations of different thymoma subtypes have been shown in Figs. 7.63, 7.64, 7.65, 7.66, and 7.67.

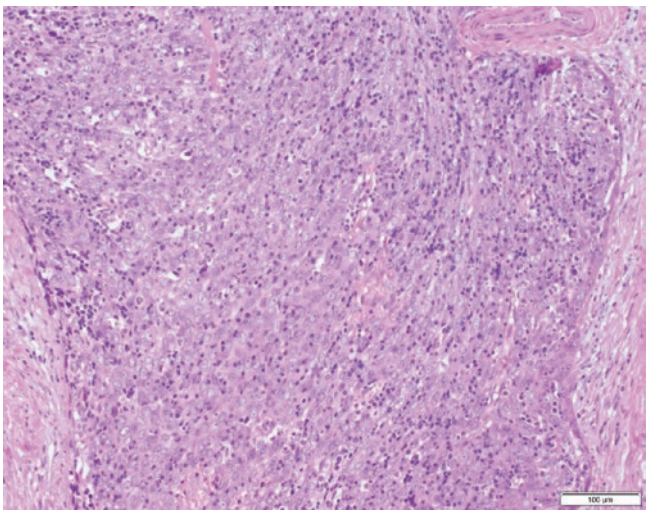


Fig. 7.45 Type B2 thymoma shows intricate admixture of epithelial cells and lymphocytes. The epithelial cells are polygonal with round to oval nuclei, pale chromatin, and prominent nucleoli (H&E ×100)

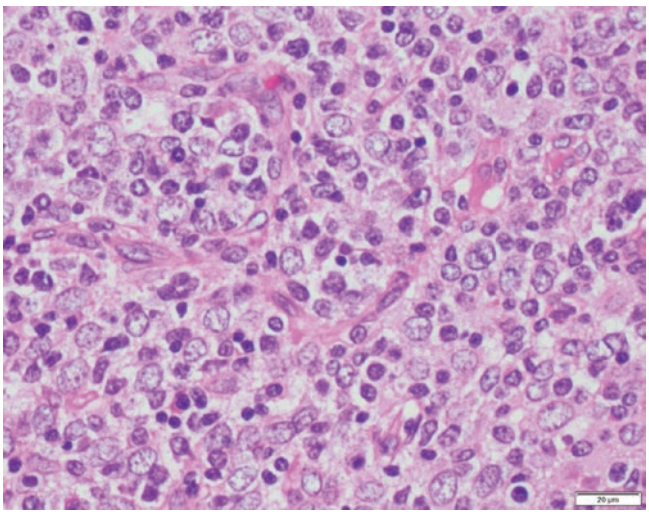


Fig. 7.47 Type B2 thymoma with epithelial cells having round to slightly oval nuclei, distinct nuclear membrane, pale chromatin, and conspicuous nucleoli (H&E ×400)

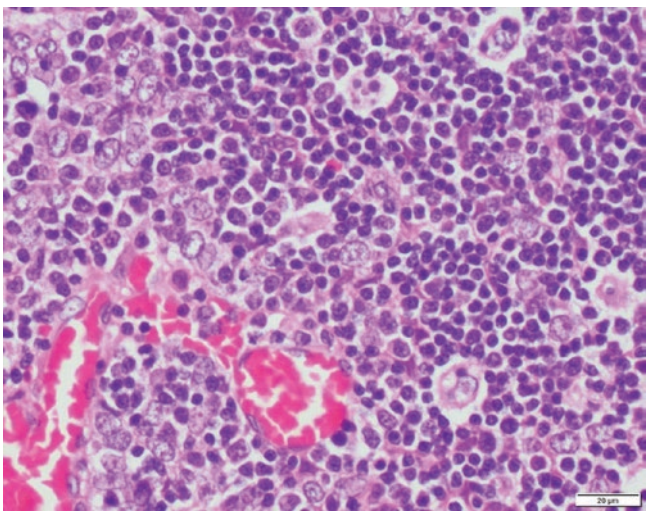


Fig. 7.46 Type B2 thymoma demonstrates polygonal epithelial cells having round to oval nuclei with pale chromatin, distinct nuclear membrane, and conspicuous nucleoli (H&E ×400)

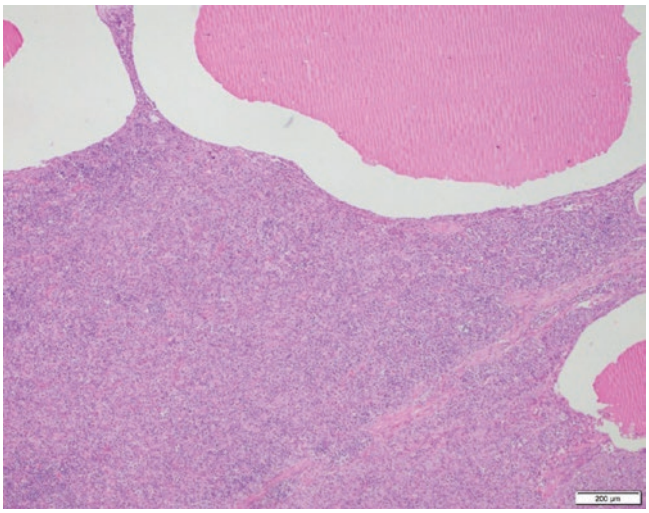


Fig. 7.48 Type B2 thymoma with presence of large perivascular spaces containing lymph-like proteinaceous material (H&E ×40)

7.10 Rare Types of Thymoma

7.10.1 Micronodular Thymoma

7.10.1.1 Epidemiology and Clinical Features

Micronodular thymoma with lymphoid stroma is a rare thymic epithelial tumor composed of multiple small tumor islands of spindled or oval epithelial cells surrounded by a lymphocyte-rich stroma. It accounts for only about 1% of all thymic epithelial tumors [6]. They have a slightly male predominance. The patients are usually asymptomatic and the tumor is generally detected incidentally. Most of them are localized and encapsulated.

7.10.1.2 Pathological Features

Grossly, the tumors are well circumscribed and encapsulated. The cut surface is soft and friable, homogenous, and light tan in color.

Microscopically, these tumors are characterized by multiple discrete small nests or solid islands of epithelial cells separated by a lymphocyte-rich stroma (Figs. 7.68, 7.69, 7.70, and 7.71). The lymphoid areas may even contain lymphoid follicles with or without germinal centers and plasma

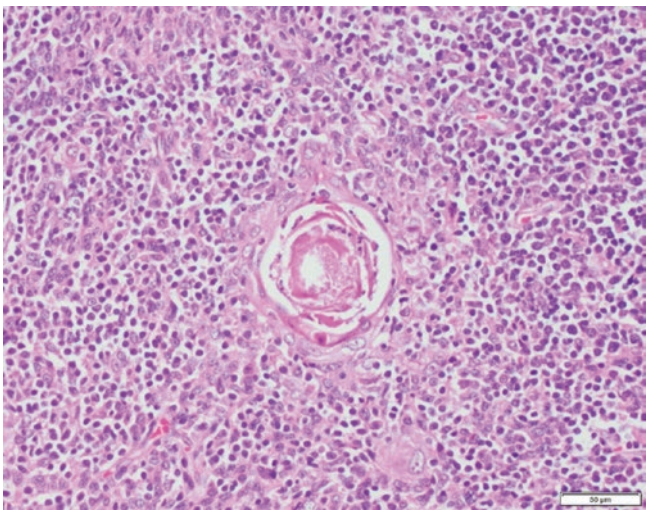


Fig. 7.49 Type B2 thymoma with admixture of epithelial and lymphoid cells along with a Hassall corpuscle in the center (H&E ×200)

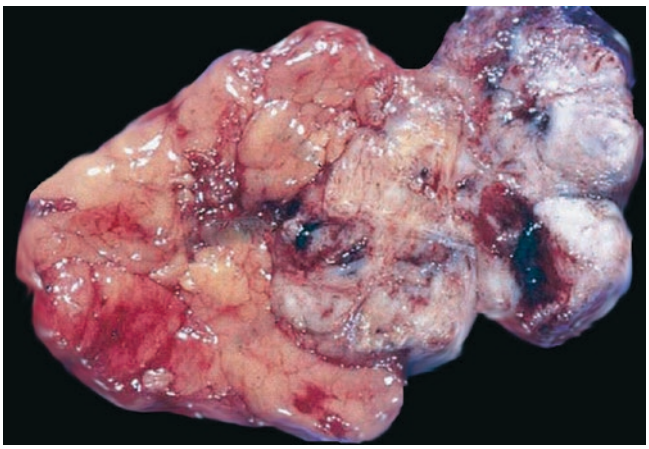


Fig. 7.51 Gross photograph of type B3 thymoma having a variegated cut surface with nodules, areas of hemorrhage, and extension into the surrounding soft tissues. Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

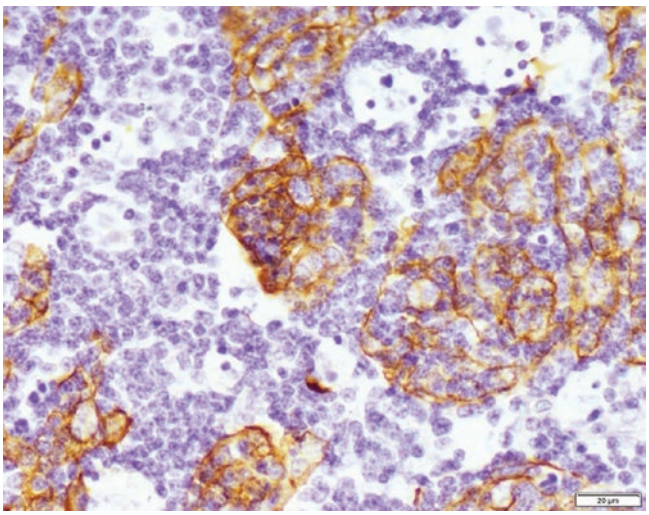


Fig. 7.50 Type B2 thymoma with immunohistochemical stain of pan-cytokeratin depicting epithelial cell clusters amidst a background of lymphoid cells (Pan-CK ×400)

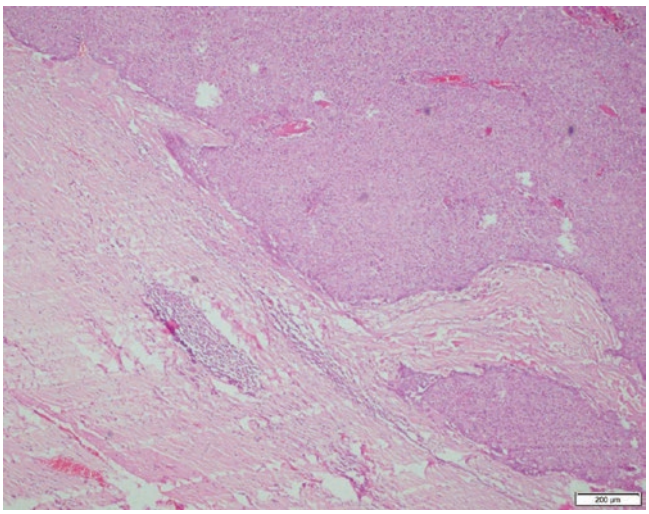


Fig. 7.52 Type B3 thymoma shows predominantly epithelial sheets with surrounding fibrous stroma (H&E ×40)

cells. The epithelial cells within the nodules are short spindled or oval with scant cytoplasm, elongated nuclei with dispersed chromatin, and inconspicuous nucleoli. Other associated findings may be micro- or macrocystic change, rosette-like structures, or glandular formation. However, a lobular architecture, Hassall corpuscles, or perivascular spaces are generally absent. There may be associated type A thymoma in about 30% cases [25]. Association with type AB and B2 thymomas is rare.

Immunohistochemically, the epithelial nodules stain for pan-cytokeratin, CK5/6, and CK19 and lack CK20. The lymphoid cells are an admixture of mature B-cells (CD20 and CD79a positive), mature T-cells (CD3+, TdT−), and immature T-cells (CD3+, CD1a+, TdT+, CD99+). The TdT-positive cells are scarce within the epithelial nodules which helps in distinguishing from type AB thymomas in which they are intermixed with the epithelial cells [5].

7.10.2 Sclerosing Thymoma

Sclerosing thymoma does not seem to be a distinct subtype of thymoma. It represents extensive sclerosis and hyalinization in any type of above described thymomas [26].

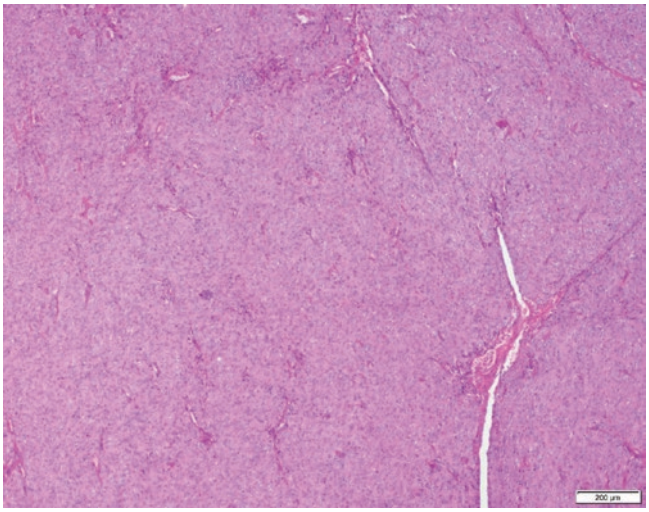


Fig. 7.53 Type B3 thymoma, a pink tumor, shows epithelial cells (H&E ×40)

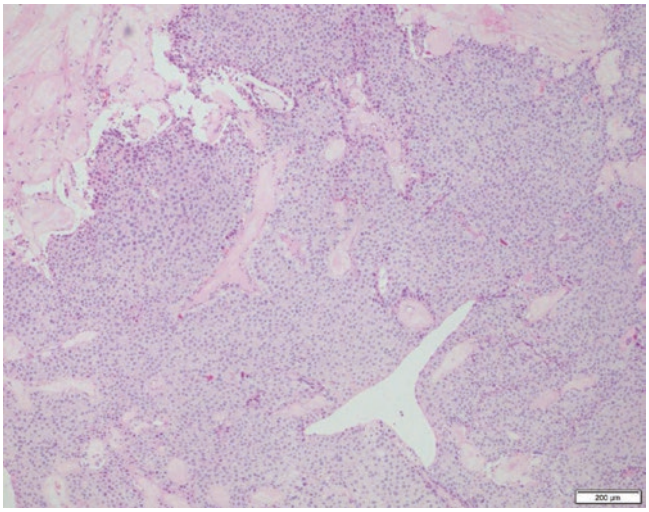


Fig. 7.55 Type B3 thymoma shows sheets of polygonal epithelial cells with hyalinized blood vessels (H&E ×40)

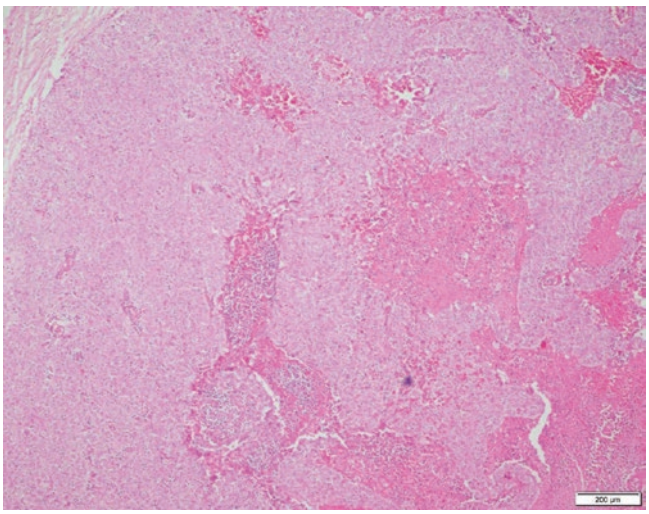


Fig. 7.54 Another case of type B3 thymoma with sheets of polygonal epithelial cells and a paucity of lymphoid cells (H&E ×40)

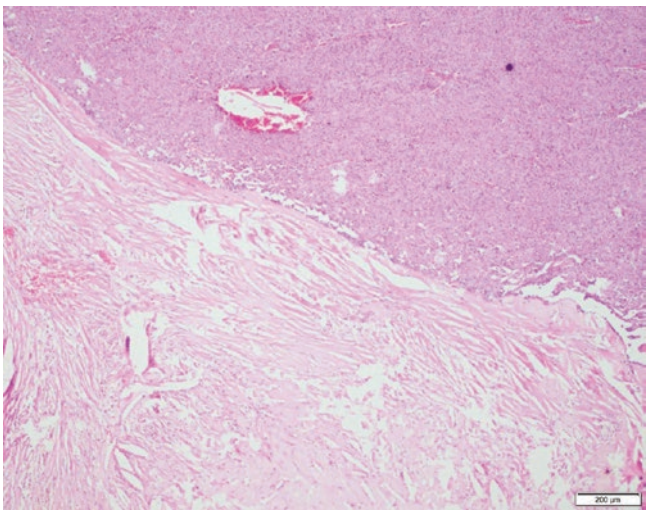


Fig. 7.56 Type B3 thymoma with adjacent areas of fibrosis and cholesterol clefts (H&E ×40)

7.10.2.1 Pathological Features

Grossly, the tumors are well circumscribed, with a light tan cut surface which is firm to hard in consistency (Fig. 7.72).

Microscopically, the tumor is composed of a predominantly hyalinized, fibrosclerotic stroma. The neoplastic thymic epithelial cells may not be detected on H&E staining and there may be a paucity of immature T-cells. Occasionally, areas of conventional thymomas are seen (Figs. 7.73, 7.74, 7.75, 7.76, 7.77, 7.78, and 7.79) [27]. These tumors are associated with degenerative changes in the form of dystrophic calcification, cholesterol granulomas, and cystic change.

Immunohistochemically, the epithelial cells are pancytokeratin+ and the immature T-cells, if present, are TdT+.

7.10.3 Metaplastic Thymoma

7.10.3.1 Epidemiology and Clinical Features

Metaplastic thymomas are extremely rare thymoma subtypes [28] which have a biphasic pattern comprising of solid epithelial areas in a background of spindle cell proliferation which appear bland. They are common in adults. These tumors are generally incidentally detected or the patients

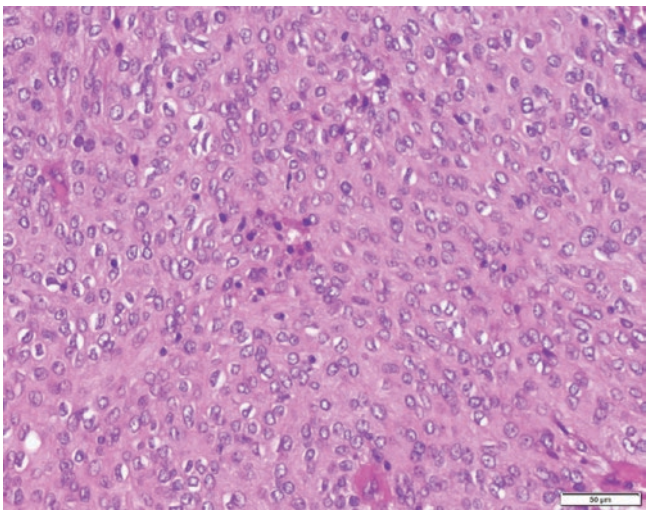


Fig. 7.57 Type B3 thymoma showing epithelial cells in sheets with sparsely distributed lymphocytes (H&E ×200)

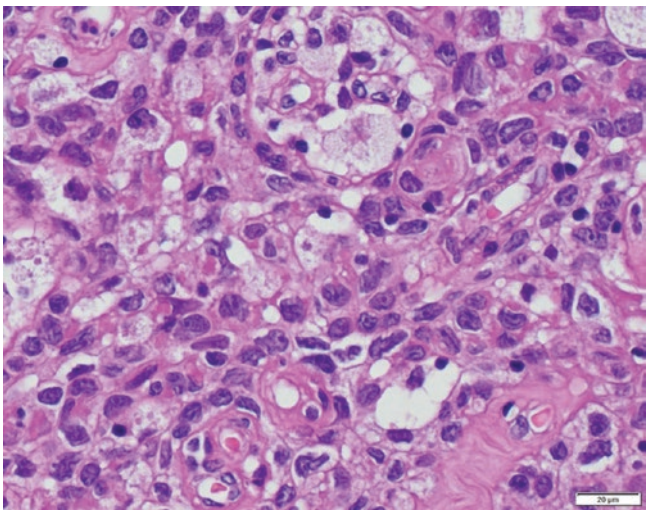


Fig. 7.59 Type B3 thymoma shows epithelial cells with nuclear atypia in the form of nuclear enlargement and hyperchromasia (H&E ×400)

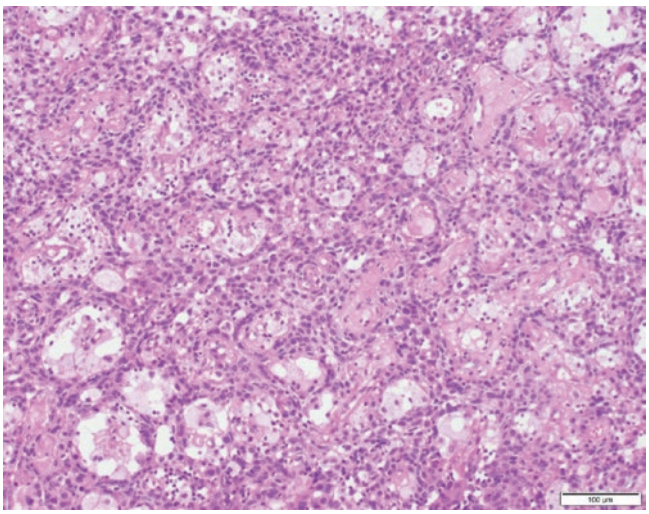


Fig. 7.58 Type B3 thymoma showing perivascular spaces filled with foamy histiocytes (H&E ×100)

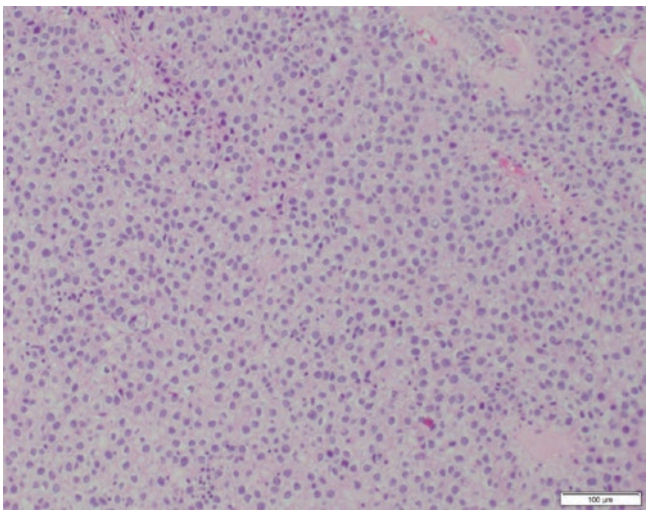


Fig. 7.60 Type B3 thymoma shows focal clearing of cytoplasm in epithelial cells (H&E ×100)

may have localized symptoms. They are commonly lower-stage tumors.

7.10.3.2 Pathological Features

Grossly, these tumors may be encapsulated or well circumscribed. They have a homogenous cut surface which appears yellow to gray-white in color.

Microscopically, the tumor shows a biphasic pattern comprising of epithelial and stromal components. The epithelial component may be present in solid sheets, trabeculae, or anastomosing islands. The epithelial cells may appear squamoid and have moderate eosinophilic cytoplasm with oval to rounded nuclei which may sometime exhibit pleomorphism. The spindle cell stroma is intermixed with the epithelial islands and is seen in short intersecting fascicles (Figs. 7.80, 7.81, 7.82, 7.83, 7.84, 7.85, and 7.86). There is an absence or paucity of lymphoid cells in the tumor [28, 29].

Immunohistochemically, the epithelial cells are positive for epithelial membrane antigen (EMA), cytokeratin, and p63 and the spindled cells show positivity for vimentin. The spindle cells may show focal EMA or cytokeratin positivity (Figs. 7.87, 7.88, 7.89, and 7.90).

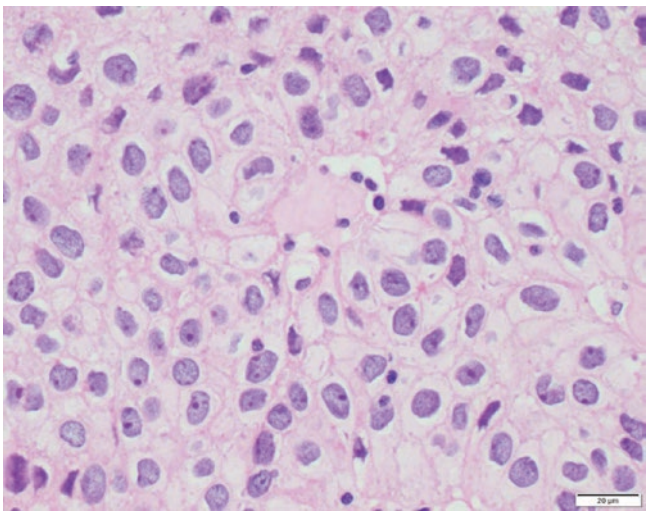


Fig. 7.61 Type B3 thymoma possesses epithelial cells with distinct cytoplasmic borders, clear cytoplasm, oval nuclei, vesicular chromatin, and prominent nucleoli (H&E ×400)

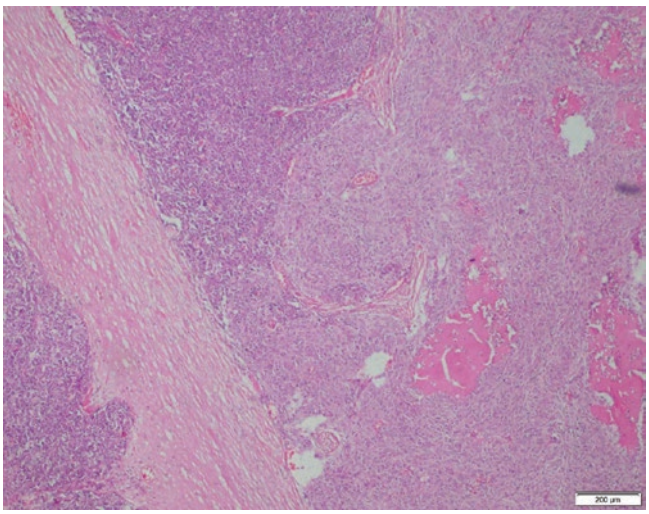


Fig. 7.63 A case of thymoma with type A areas (right half) and type B2 areas (left half) (H&E ×40)

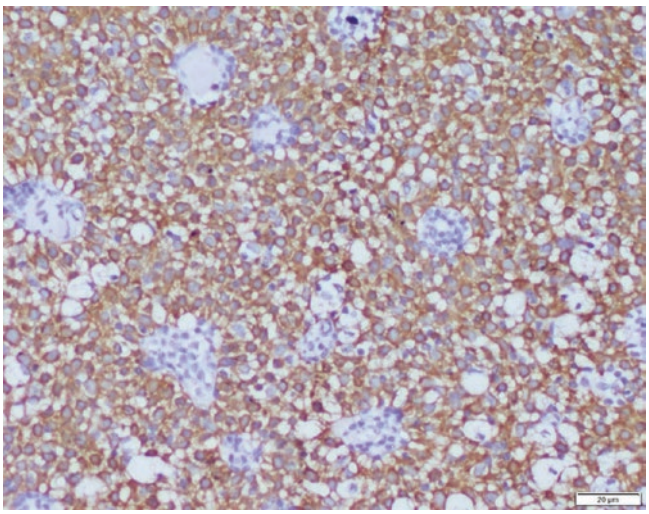


Fig. 7.62 Immunohistochemical stain of pan-cytokeratin outlining the thymic epithelial cells in a case of type B3 thymoma (pan-cytokeratin ×200)

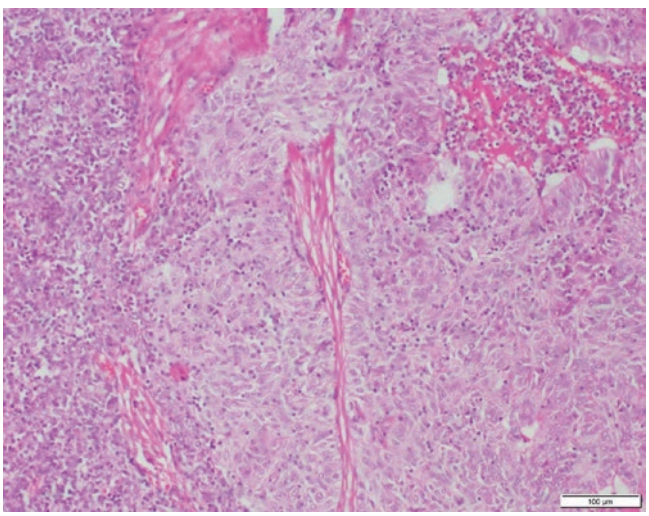


Fig. 7.64 High power view of thymoma showing spindled epithelial cells of type A area with adjacent focus of type B2 area (H&E ×100)

7.10.4 So-called Microscopic Thymoma or Nodular Hyperplasia of Thymic Epithelium

These are multifocal unencapsulated non-neoplastic thymic epithelial proliferations of <1 mm in diameter (Fig. 7.91). They are incidentally discovered on microscopy in thymectomy specimens of patients with myasthenia gravis. These are neither precursors of thymomas nor transformed to thymomas even after long clinical follow up [30]. On the other hand Microthymoma is a neoplastic lesion which is a conventional thymoma morphologically, but with a size of <1 cm. They have no prognostic relevance and are not staged [27].

7.11 Clinical Practice Points

7.11.1 Resection Specimens

- Difference between normal thymus and type B1 thymoma
- Type B1 thymoma shows lobulation and a similar lymphocyte phenotype as that of normal thymus and thymic hyperplasia; however, presence of interlobular fibrous septae, thick fibrous capsule, predominance of cortical areas over medullary foci, relative rarity of adipocytes and Hassall corpuscles, and lack of the regular arrangement of superficial cortical and deeper medullary areas point toward type B1 thymoma.

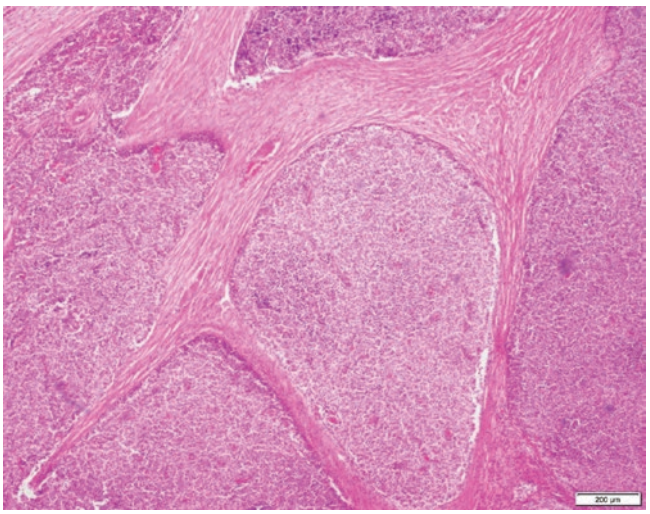


Fig. 7.65 A case of thymoma with equal type B2 and B3 components (H&E ×40)

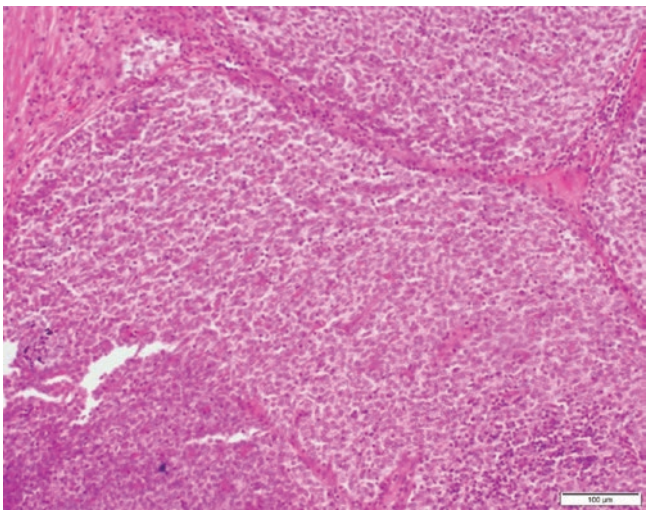


Fig. 7.66 Higher power view of same case showing B3 areas (H&E ×100)

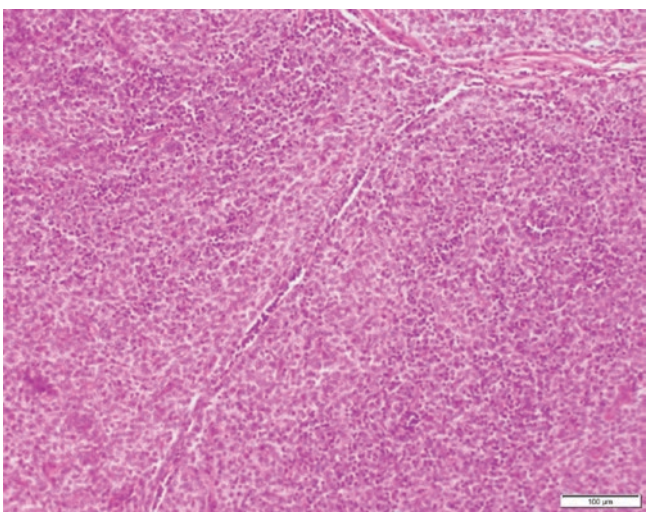


Fig. 7.67 Higher power view of same case showing a focus of type B2 areas (H&E ×100)

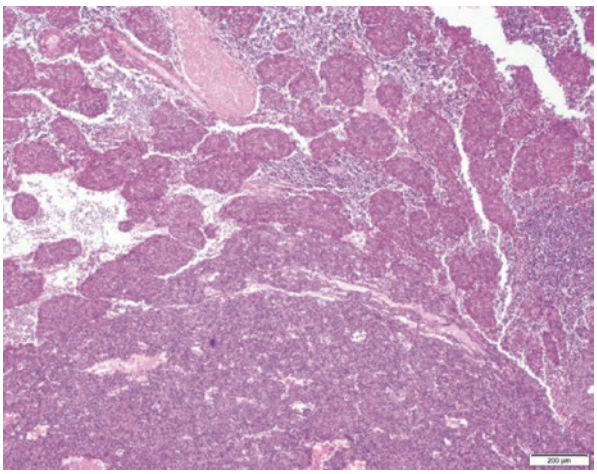


Fig. 7.68 Low power view of micronodular thymoma with lymphoid stroma shows nodules of epithelial cells lying dispersed in a lymphocyte predominant stroma (H&E ×40)

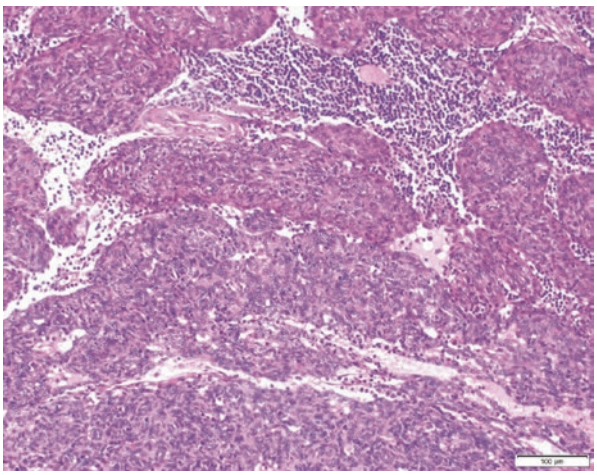


Fig. 7.69 Medium power view of micronodular thymoma with lymphoid stroma showing nodules of epithelial cell clusters in a lymphoid stroma (H&E ×100)

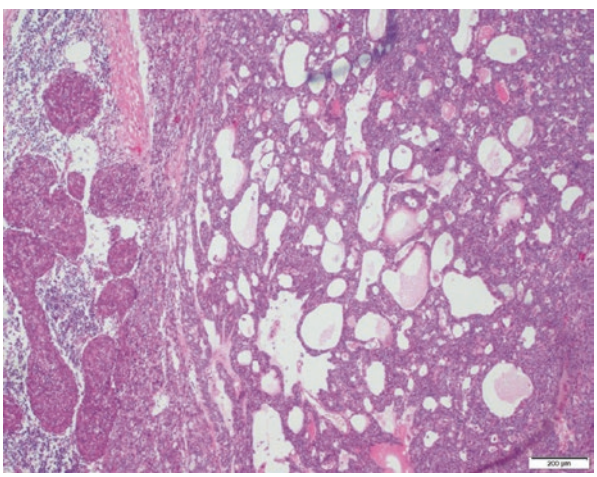


Fig. 7.70 Section from a case of combined type A thymoma and micronodular thymoma with lymphoid stroma showing a predominance of microcystic spaces giving a reticular pattern within the type A areas (H&E ×100)

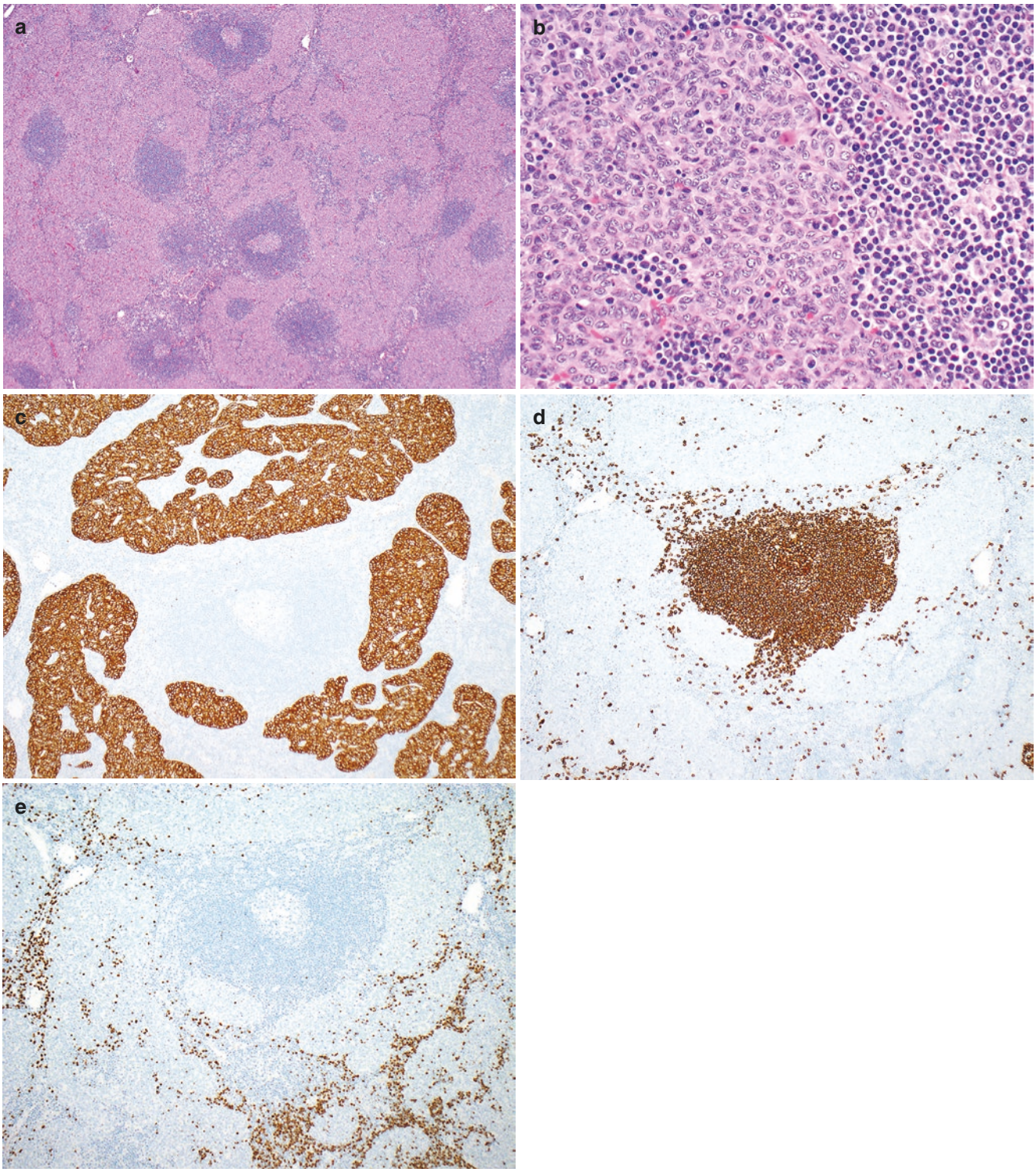


Fig. 7.71 Micronodular thymoma with lymphoid stroma: (**a**) at low magnification the tumor has a nodular appearance and shows pockets of lymphocytes with germinal centers. (**b**) The nodular areas (left) are comprised of bland-appearing small cells with round to oval nuclei and inconspicuous nucleoli. These cells are reminiscent of the neoplastic cells of type A thymoma. They mark with keratin AE1/AE3. (**c**) There is a rather abrupt demarcation from the lymphoid areas (right) which predominantly are comprised of small B-cells that mark with CD20 (**d**) and only scattered TdT-positive thymocytes (**e**) which are predominantly located at the interface between the epithelial and lymphoid cells. H&E ×40 (**a**), H&E ×400 (**b**), CD20, TdT, TdT ×100 (**c**–**e**). Courtesy of Dr. Anja C. Roden (Mayo Clinic Rochester, MN, USA)

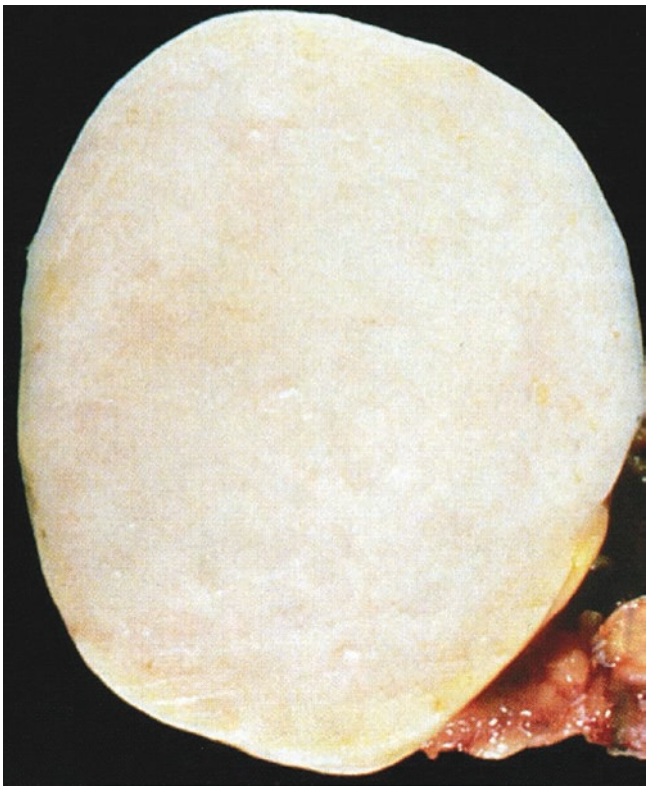


Fig. 7.72 Gross photograph of a sclerosing thymoma which on cut surface appears well circumscribed, light tan in color with a firm to hard consistency. Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

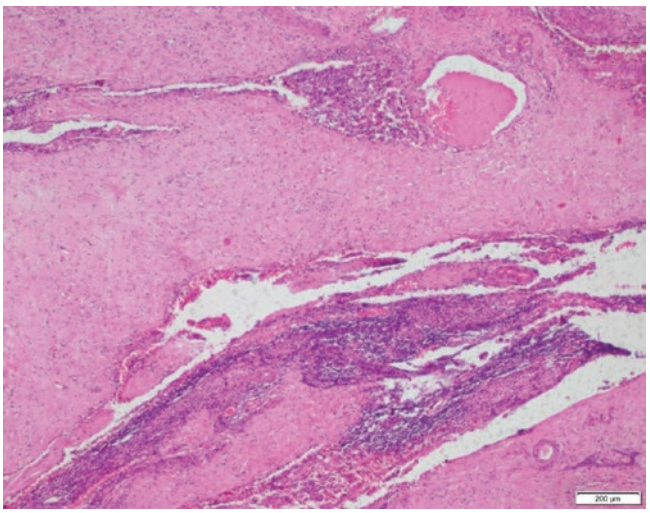


Fig. 7.73 Low power view of sclerosing thymoma showing predominantly sclerosed fibrotic stroma with foci of residual thymoma (H&E ×40)

- Difference between type B1 and B2 thymomas
- Type B1 and B2 thymomas are primarily differentiated by the predominance of thymic epithelial cells in the latter, while the former showing clusters of no more than three contiguous epithelial cells.

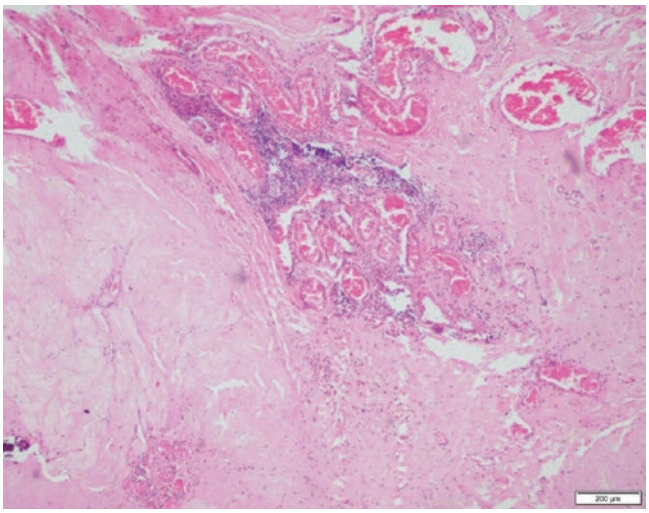


Fig. 7.74 Low power view of sclerosing thymoma showing predominantly sclerosis, hyalinization with few entrapped thymoma clusters, and proliferating blood vessels (H&E ×40)

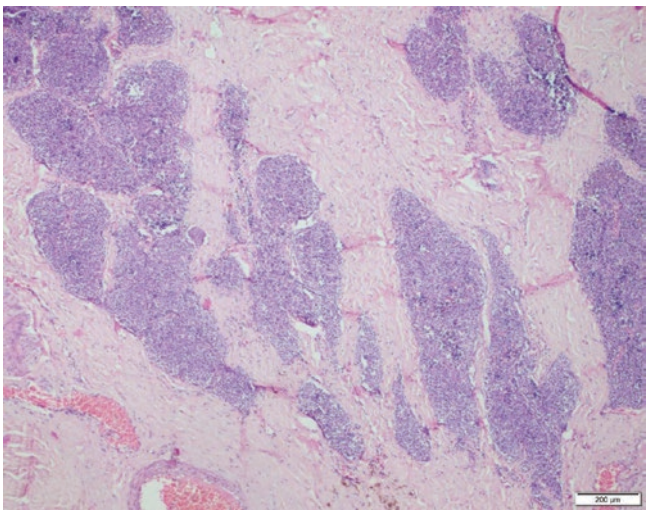


Fig. 7.75 Low power view of sclerosing thymoma showing islands of thymoma embedded in a predominantly sclerosed stroma (H&E ×40)

- Difference between type A and type B3 thymomas
- Both show predominance of epithelial cells with sparse lymphocytes but are differentiated based on the cytology of the epithelial cells being spindled and bland in the former with less common perivascular spaces and absent Hassall corpuscles whereas polygonal and more atypical cells in the latter.
- Difference between heterogeneous thymoma and type AB thymoma
- Type AB thymoma is not a heterogeneous thymoma with an admixture of type A and type B areas; rather is a type A thymoma with lymphocyte (TdT+) rich areas that harbor spindled epithelial cells.
- Difference between type AB thymoma and micronodular thymoma with lymphoid stroma

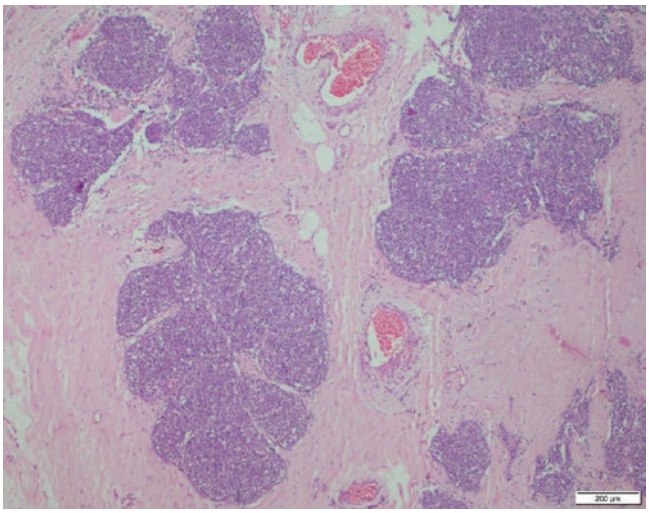


Fig. 7.76 Low power view of sclerosing thymoma showing islands of thymoma embedded in a predominantly sclerosed stroma (H&E ×40)

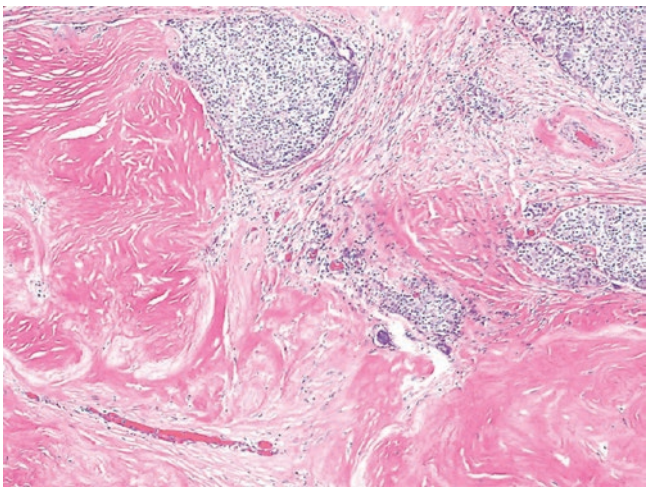


Fig. 7.77 Sclerosing thymoma with islands of type B areas. There is extensive hyalinization and sclerosis of the stroma (H&E ×100). Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

- Both type AB thymoma and micronodular thymoma with lymphoid stroma show islands of spindled thymic epithelial cells and lymphocyte rich areas; however, micronodular thymomas lack epithelial cells in the lymphocyte rich areas and show prominent lymphoid follicles with germinal centers immunopositive for CD20.
- Difference between type A thymoma and metaplastic thymoma
- Both show spindle cells; however, metaplastic thymoma is a biphasic neoplasm in which spindle cells are metaplastic fibroblast-like cells. These cells are vimentin-positive whereas spindle cells of type A thymoma are epithelial cells that are strongly positive for keratin stains and often CD20 positive.

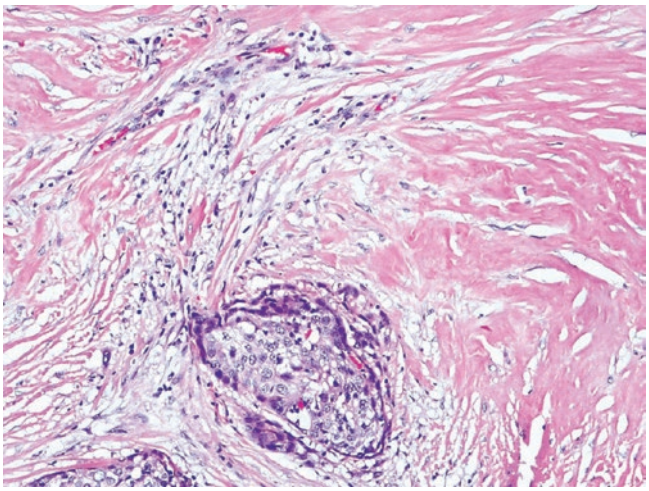


Fig. 7.78 High power view of sclerosing thymoma showing areas of epithelial cells intermixed with lymphoid cells surrounded by sclerosis (H&E x200). Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

7.11.2 Small Biopsies

- Distinction of type B1 thymoma from a T-lymphoblastic lymphoma (T-LBL) is primarily based on the morphology of the lymphocytes as their immunophenotype is the same. The lymphocytes in T-LBL may be atypical, monotonous with frequent mitoses and/or necrosis. Although the presence of epithelial cell network suggests diagnosis of thymoma, T-LBL can show cytokeratin positive epithelial cells from overrun thymus or entrapped mesothelial cells in small biopsies. Similarly, failure to recognize epithelial cells in a small biopsy of B1 thymoma may lead to spurious labeling of the case as T-LBL. In case a dilemma persists, a definite diagnosis should not be offered as the treatment of both the entities is different. Nevertheless, molecular analysis for T-cell receptor rearrangement, which is mostly monoclonal in T-LBL, may be done in difficult and equivocal cases for confirmation (See Chap. 13 for more details).
- Interpretation of small biopsies from anterior mediastinal masses requires careful examination and mandatory correlation with clinical and radiological features. Differentiating type B1 thymoma from thymic hyperplasia or T-LBL, type A thymoma from synovial sarcoma, hemangiopericytoma, neuroendocrine tumors, or even adenocarcinomas, can be very challenging and sometimes impossible even with appropriate immunohistochemistry.
- Similarly, subtyping of thymoma need not be attempted on small biopsies due to their heterogeneous morphology and a poor correlation with the final subtype on resection.

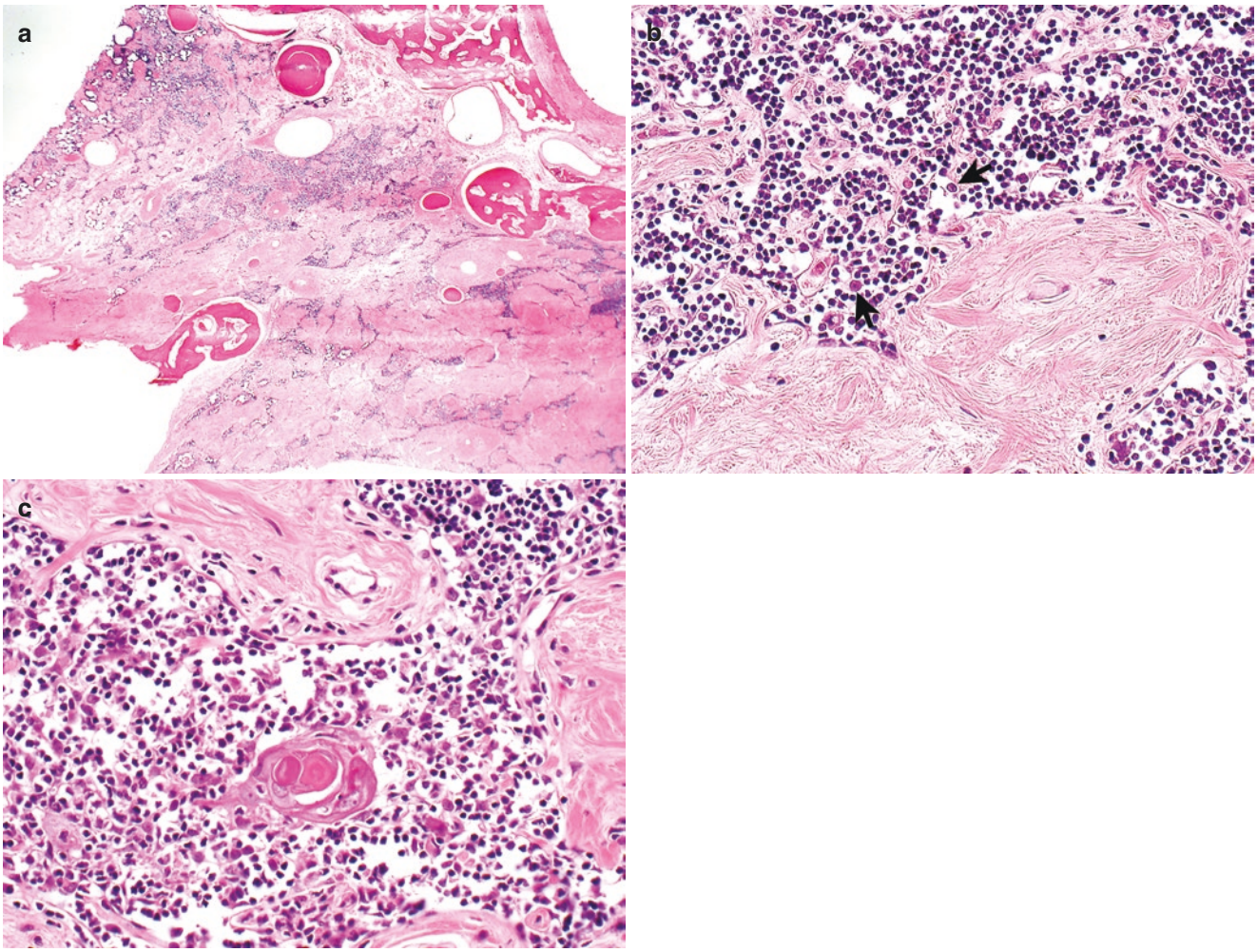


Fig. 7.79 Sclerosing and ossifying thymoma: (**a**) at low magnification there is a predominance of hyaline fibrosis and bony spiculae with intermixed cellular areas. (**b**) Hyaline fibrosis with adjacent small lymphocytes and scattered large epithelioid cells (neoplastic cells, arrows). (**c**) Hassel corpuscle-like structures are also identified. H&E ×12.5 (**a**), ×400 (**b, c**). Courtesy of Dr. Anja C. Roden (Mayo Clinic Rochester, MN, USA)

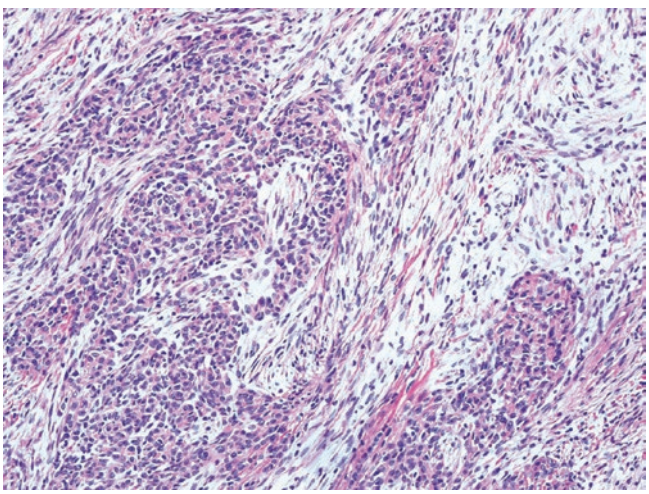


Fig. 7.80 A metaplastic thymoma showing a biphasic pattern with solid sheets of epithelial cells intermixed with a spindle cell component (H&E ×100). Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

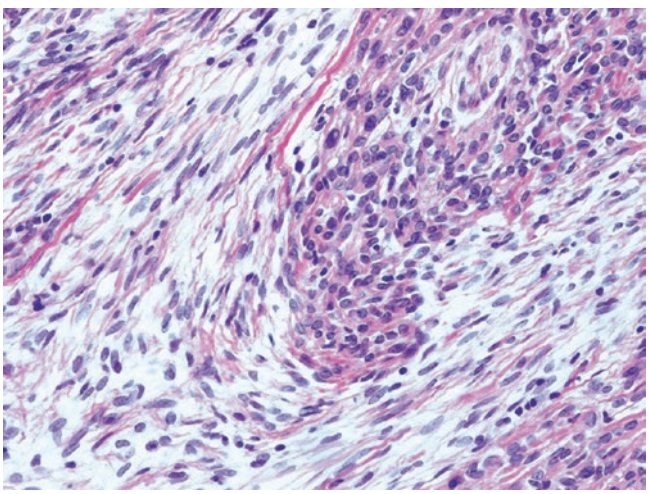


Fig. 7.81 A high power view of metaplastic thymoma showing co-existence of epithelial and mesenchymal components (H&E ×200). Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

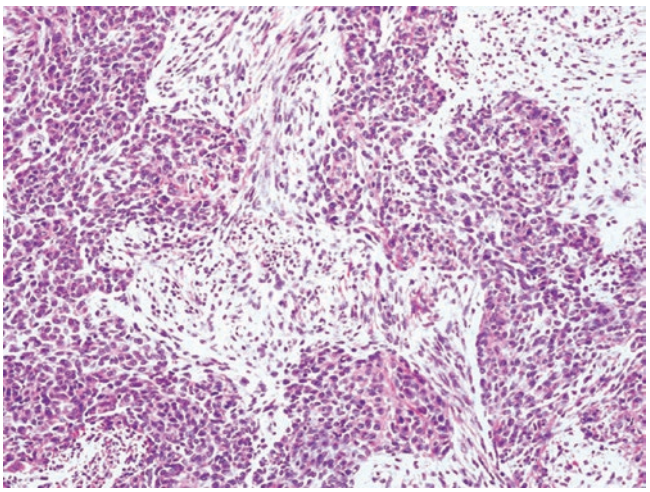


Fig. 7.82 Metaplastic thymoma with solid epithelial islands admixed with a cellular spindle cell stroma (H&E ×100). Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

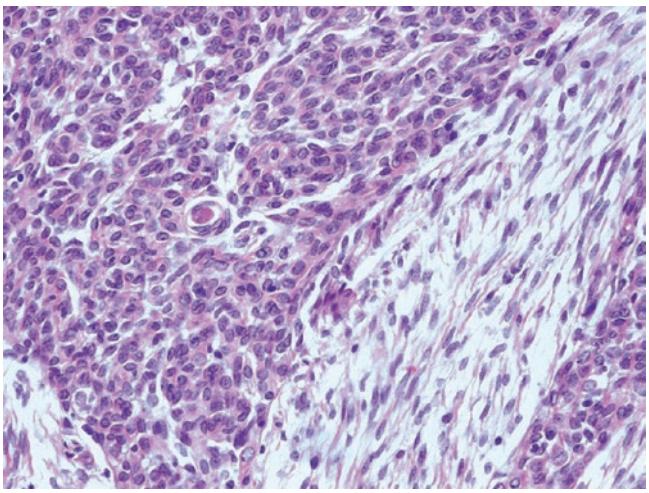


Fig. 7.84 High power view of metaplastic thymoma with epithelial and mesenchymal components. The epithelial cells exhibit mild nuclear pleomorphism (H&E ×200). Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

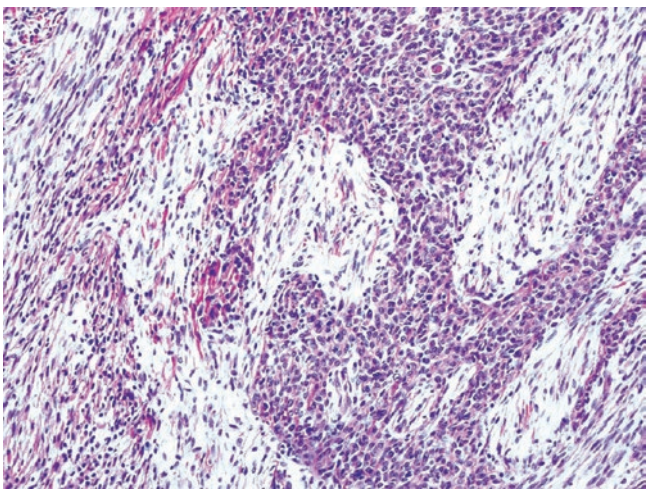


Fig. 7.83 Medium power view of metaplastic thymoma shows epithelial component present in solid sheet and trabeculae and the spindled mesenchymal component in the background with admixed inflammatory cells (H&E ×100). Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

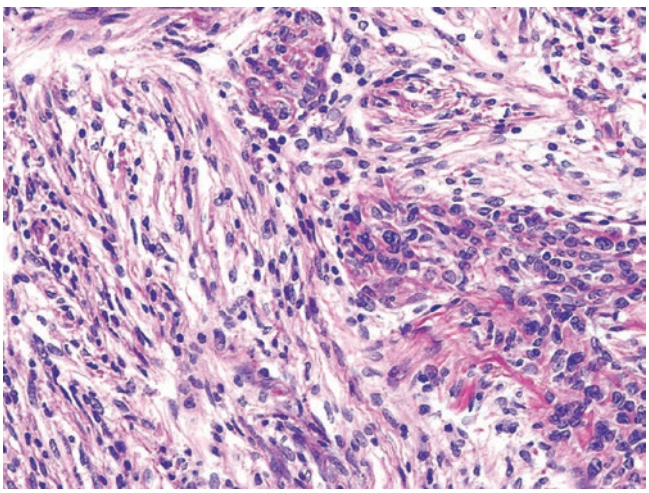
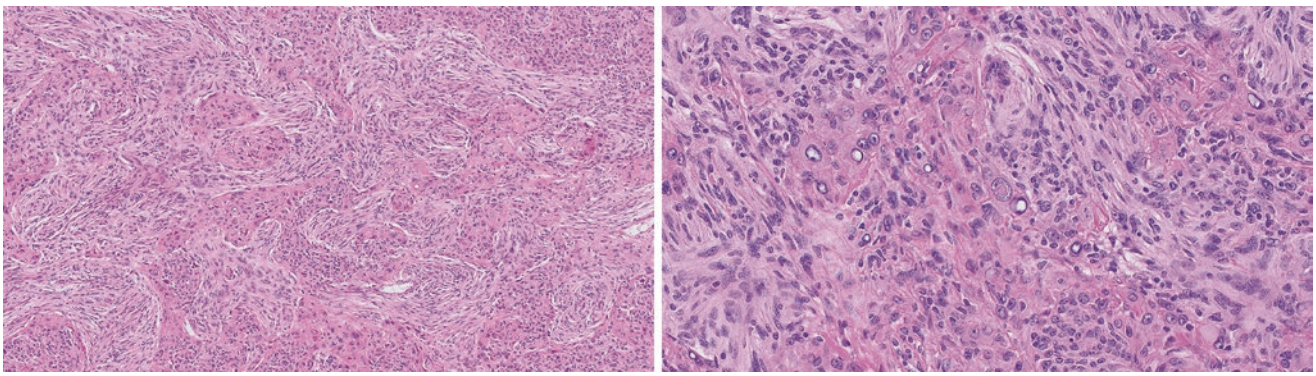


Fig. 7.85 High power view of a case of metaplastic thymoma with prominent lymphocytic admixture in the spindled areas (H&E ×200). Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine



Figs. 7.86 and 7.87 Low and medium magnification of a metaplastic thymoma. The tumor shows biphasic pattern composed of anastomosing islands of epithelial cells surrounded by spindle cell component. The epithelial cells are polygonal, oval, or round with abundant cytoplasm and sometimes present prominent atypia, nuclear pleomorphism, and pseudoinclusions. Spindle cells are bland looking without evident mitotic activity. Both components merge together in some areas. Lymphocytes are uncommon (H&E ×100 and ×200). Photograph courtesy: Dr. Mirella Marino IRCCS Regina Elena National Cancer Institute, Rome, Italy

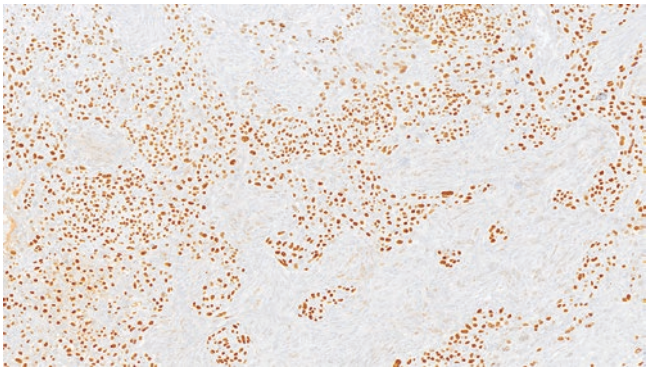


Fig. 7.88 Epithelial cells of metaplastic thymoma show nuclear reactivity for p63 (p63 ×100). Photograph courtesy: Dr. Mirella Marino IRCCS Regina Elena National Cancer Institute, Rome, Italy

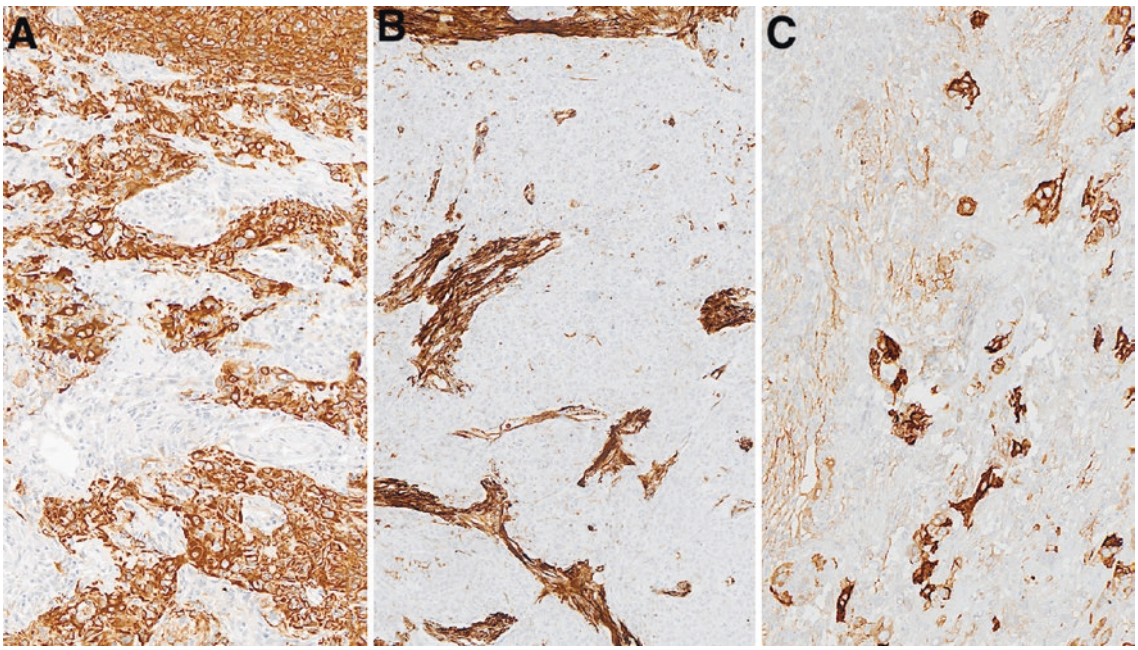


Fig. 7.89 Cytokeratin (**a**) is expressed only by epithelial cells and vimentin (**b**) by spindle cells while positive reaction for EMA (**c**) can be found in both components (AE1AE3 (**a**), vimentin (**b**), EMA (**c**), ×100). Photograph courtesy: Dr. Mirella Marino IRCCS Regina Elena National Cancer Institute, Rome, Italy

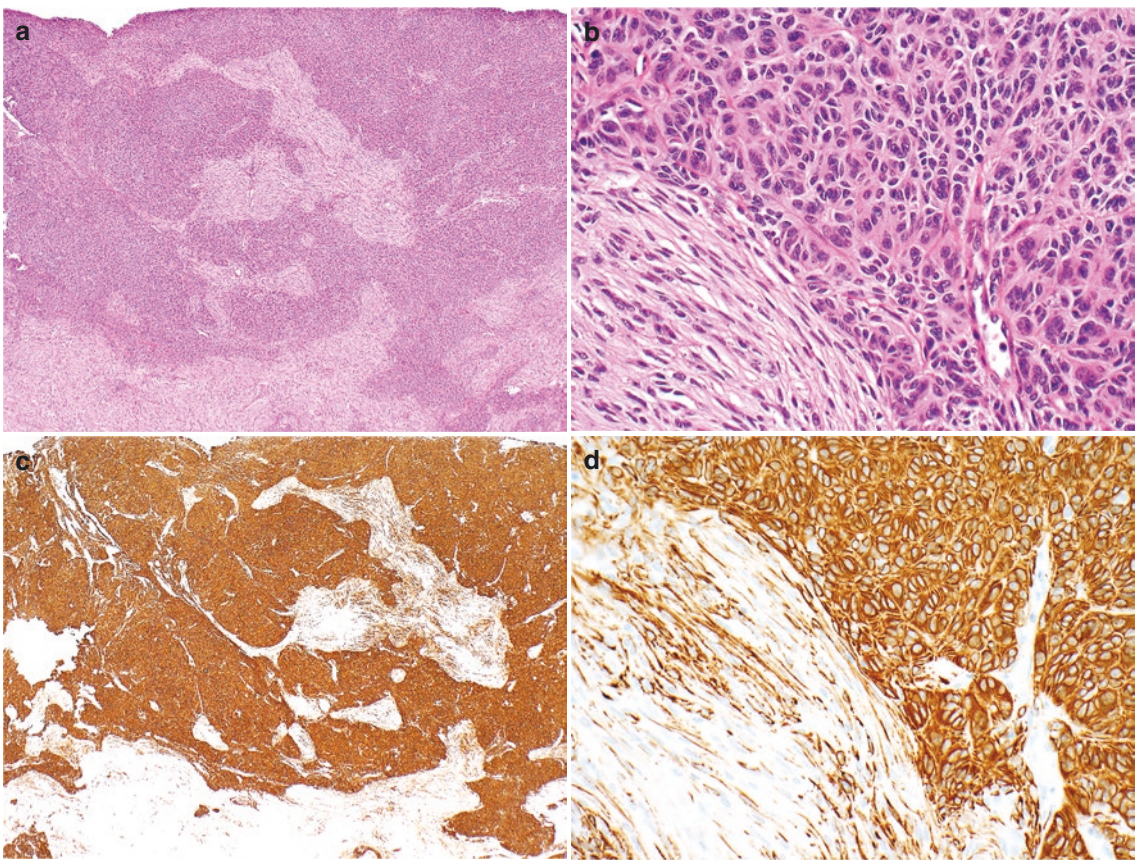


Fig. 7.90 (**a**) This is a biphasic neoplasm comprised of a darker pink neoplastic and a paler pink spindle cell component (H&E ×40). (**b**) The neoplastic component is comprised of oval to slightly elongated, bland-appearing cells with inconspicuous nucleoli (right side). There in abrupt transition to the bland-appearing spindle cell component (left) (H&E ×400). (**c, d**). Keratin AE1/AE3 stains strongly the neoplastic cells and may or may not mark the spindle cells. (Keratin AE1/AE3 ×40, ×400). Courtesy of Dr. Anja C. Roden (Mayo Clinic Rochester, MN, USA)

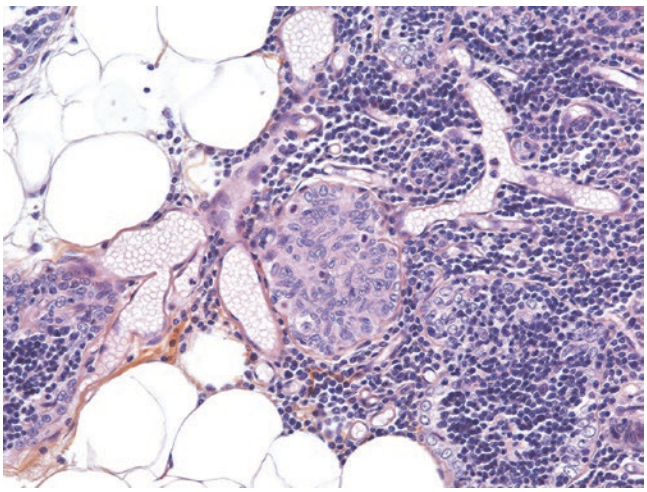


Fig. 7.91 Photomicrograph shows a small, well-demarcated but unencapsulated nodule of thymic epithelial cells in a normal thymus composed of adipocytes and lymphoid cells (H&E ×200). Photograph courtesy: Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

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