# Lymphomas and Other Rare Tumors of the Thymus

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Mirella Marino, Malgorzata Szolkowska, and Stefano Ascani

## 13.1 Introduction

The incidence of mediastinal masses in the general population is estimated to be one case per 100,000 persons per year, malignancy being more frequent in anterior mediastinal masses [1–3]. The distribution of the wide variety of tumors and of nonneoplastic lesions varies according to age and gender [4]. Moreover the anterior mediastinum (also named prevascular compartment) is the most common location of neoplasia (68%) in adults, whereas the posterior mediastinum is more frequently affected in children (52%) [5]. The most common abnormalities encountered in the prevascular compartment include benign thymic lesions (cysts, hyperplasia) and intrathoracic goiter. Malignancies include thymoma, thymic carcinoma, neuroendocrine thymic tumors (all together collectively indicated also as thymic epithelial tumors, TET), lymphoma, mesenchymal tumors and germ cell tumors (GCT), and metastatic tumors [6]. Frequencies are provided for the main entities among anterior mediastinal masses: thymic malignancy occurs in approximately 35%, lymphoma in approximately 25% , thyroid and other endocrine tumors in approximately 15%, benign teratoma in approximately 10%, malignant GCT in approximately 10% (seminoma, 4%, and non-seminomatous germ cell tumors (NSGCT), 7%), and benign thymic lesions in approximately 5% [7]. However, several other cell types and ectopic tissues in the mediastinum may give rise to a variety of other tumors rarer than TET.

Most of the tumors in the anterior mediastinum arise in the thymus. It may be very difficult to distinguish if an anterior mediastinal tumor has an extrathymic or intrathymic origin, particularly for large masses. Most of the thymic tumors arise from its main cellular components, epithelial and lymphoid.

Ectopic thymic tissue may be found along the embryonal route of descent as well as in different areas of the mediastinum/thoracic cavity which give rise to related tumors at these sites [8, 9]. Metastasis occurs in the thymus, although specific localization into thymus or anterior/middle mediastinal lymph nodes is difficult to demonstrate [10]. The metastases constitute the prevailing neoplastic pathology in the mediastinum [11].

## 13.2 Lymphoma of the Thymus/Anterior Mediastinum

Lymphomas occurring in the thymus belong both to T and B cell lineage or are Hodgkin lymphomas. They account for approximately 25% (13% of cases are Hodgkin lymphomas (HL) and 12% are non-Hodgkin lymphomas (NHL) of mediastinal tumors. However, only approximately 3% of HL and 6% of NHL arise as primary mediastinal malignancies. In fact, about 50% of HL and 20% of NHL involve the mediastinum in the framework of a systemic involvement [7]. In patients with a mediastinal component of generalized NHL, the involvement is mostly seen in mediastinal and hilar lymph nodes [12].

The two most common histologic subtypes that present with localized mediastinal involvement, primary mediastinal B lymphoma (PMBL) and T-lymphoblastic lymphoma (T-Lb), appear to arise from thymic tissue [13, 14]. The age-related specific subtype incidence is discussed in several papers [2, 15, 16].

A detailed classification and morphological/clinical overview of the different lymphoma types and their diagnosis can be accessed from various references [17–23].

In the subsequent section, examples of the most common mediastinal/primary thymic lymphoma, their main immunohistochemical markers, and morphological peculiarity/diag-

M. Marino (✉)
Department of Pathology, IRCCS Regina Elena National Cancer Institute, Rome, Italy
e-mail: mirella.marino@ifo.gov.it

M. Szolkowska
Department of Pathology, National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland

S. Ascani
Pathology Unit, Perugia University, Terni, Italy



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nostic pitfalls will be discussed. In addition, rare tumorlike lesions of relevant interest for their complex pathogenesis, heterogeneity of clinical features, constituting specific and rare biological entities such as Castleman disease occurring in the mediastinum [24–27] and in the thymus [28], and IgG4-related disease [29, 30] will be described.

## 13.3 Primary Lymphoma in the Anterior Superior Mediastinum

Lymphomas of immature precursor cells (T and B) and of peripheral T and B cells occur in the thymus. However, Hodgkin lymphoma of classic type (cHL), particularly the nodular sclerosis (NS) subtype, represents the most frequent mediastinal lymphoma. Among the lymphomas occurring in the mediastinum, T-cell lymphomas of precursor type predominate in pediatric age, whereas, in the adults, the most frequent lymphomas are of B cell origin, primary cHL of the thymus being rarely observed [15, 16, 31]. Table 13.1 lists the main immunophenotypical markers to characterize a suspect lymphoma in the mediastinum/thymus. Specific lymphomas arising or considered to derive from the thymus itself are as follows.

**Table 13.1** Main immunohistochemical markers useful to characterize lymphomas and hematological neoplasias/pseudotumors in the mediastinum

| Immunohistochemical markers of mediastinal lymphomas | Markers associated with hematological diseases/ neoplasms/pseudotumors |
|---|---|
| *Immature T-cell markers* | CD34 |
| CD1a, CD10, CD99, Terminal deoxynucleotidyl transferase (TdT) | Myeloperoxidase (MPO) |
| *Other T-cell markers* | Glycophorin |
| CD3, CD5 | CD61 |
| CD4/CD8 | Fact VIII |
| CD2, CD7 | CD68/PG-M1 |
| *Other markers of lymphoid cells* | CD68/KP1 |
| CD45 | LANA-1 (human herpesvirus 8 (HHV8) |
| LMO2 (LIM domain only 2) | CD138 |
| CD30 | IgG4 |
| CD15 | IgM |
| CD20 | |
| CD23 | |
| BCL2 | |
| PAX5 | |
| CD79a | |
| CD56 | |
| OCT-2/BOB.1 | |
| Mal (myelin and lymphocyte protein) | |
| Markers of germinal center differentiation: CD10, BCL6 | |
| Markers of activated B cells (ABC): | |
| MUM1 | |
| Epstein-Barr virus (LMP1) | |

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### 13.3.1 T-Lymphoblastic Lymphoma and Other T-Cell Lymphomas

The thymus is the main site of T-cell differentiation and education [17, 22]. During embryonic development, the T-cell lineage committed bone marrow progenitors enter the thymus via veins close to the corticomedullary junction and then migrate to the cortex. Thymopoiesis continues to occur in the thymus of human adults late in life despite the thymic involution [33].

Figure 13.1 shows the main characteristics of a T-Lymphoblastic Lymphoma. It should be noted that in the differential diagnosis of T-Lymphoblastic Lymphoma and a B1 thymoma, the evaluation of lymphoblast morphology is of little help, as they are similar in both tumors. Moreover, frequent mitosis and extensive necrosis are also seen in both tumors. Therefore, in an entirely necrotic tumor or in a small biopsy the diagnosis is often based on the evaluation of specific immunohistochemical markers targeting the neoplastic lymphoblasts, such as LMO2 [34, 35]. Previously, cyclin-dependent kinase-6 (CDK6) had been shown to stain only T-Lymphoblastic Lymphoma cells and subcapsular lymphoblasts in normal/hyperplastic thymuses [36]. Thymic remnant and epithelial cell (EC) networks, however, are very rarely found in T-Lymphoblastic Lymphomas, as the tumor growth is very destructive, in contrast to a B1 thymoma, where EC network may partially be seen even in necrotic tumors by appropriate immunohistochemical stains (cytokeratins).

As other rare T-cell lymphomas, mature, peripheral T-cell lymphomas have also been reported in the thymus/mediastinal lymph nodes [37]

### 13.3.2 Classic Hodgkin Lymphoma (cHL) and B Cell Lymphoma in the Thymus

Most lymphomas in the thymus derive from B cells. Thymic B cells, mainly located in the medulla or at the perivascular spaces, show a distinctive phenotype in comparison to other B cell subsets [38–40]; their relationship to peripheral B cell is still unclear [41]. These thymic B cells could give rise to B cell thymic lymphoma and to cHL of the thymus. In biopsies or surgical specimens of a lymphoid mass, it is difficult to find thymic remnants and other morphological findings that could indicate a thymic origin due to the fact that the neoplastic growth has a destructive action. However, when these remnants are seen they should be correctly recognized as such. Figure 13.2 shows a rare example of early phase of cHL in its intrathymic development.

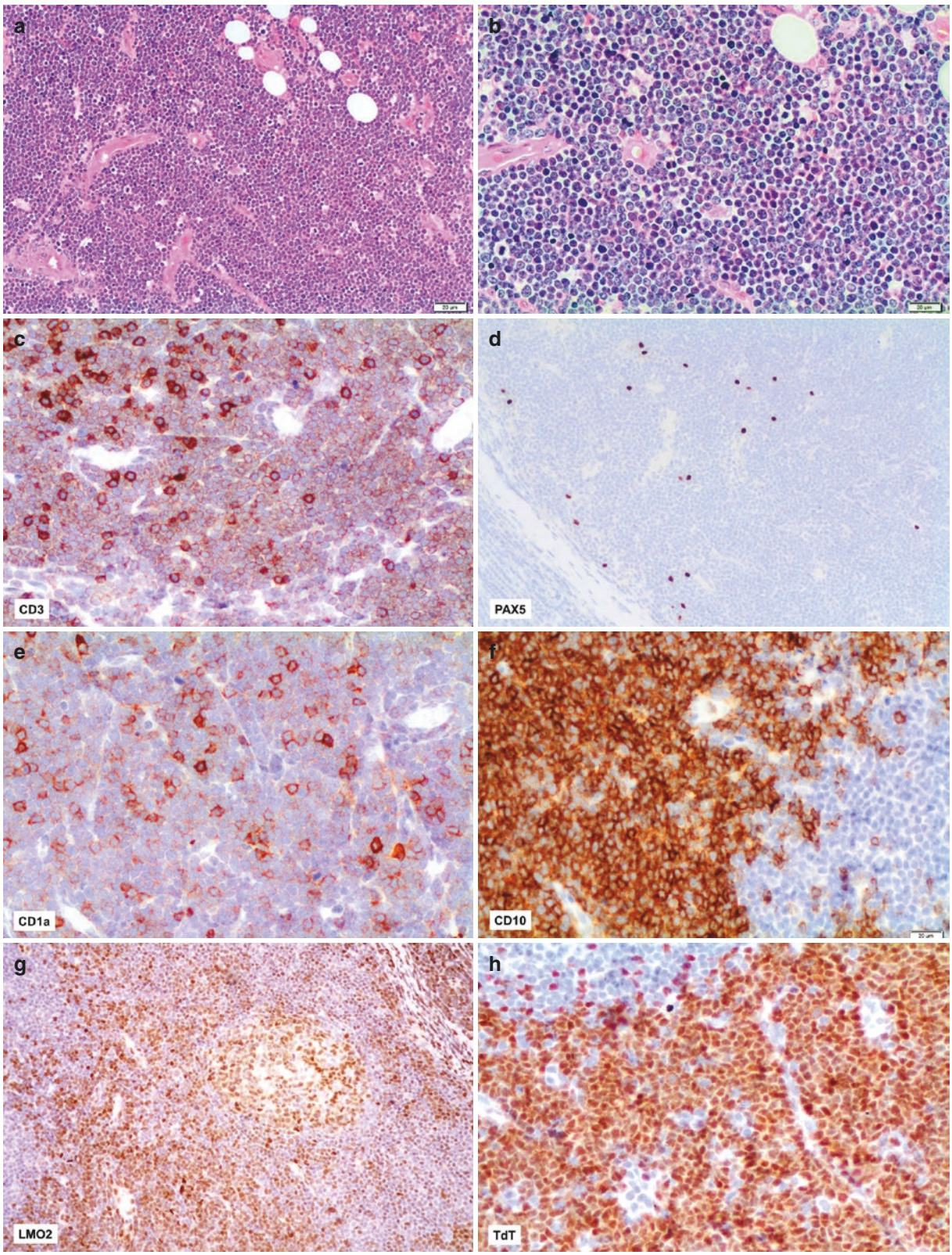


**Fig. 13.1** T-cell lymphoma, lymphoblastic (T-Lb lymphoma). (**a**) 22-year-old male, H&E, 200×; (**b**) H&E, 400×; (**c**) CD3, 400×; (**d**) Pax5, 200×; (**e**) CD1a, 400×; (**f**) CD10, 400×; (**g**) LMO2, 200×; (**h**) TdT, 400×. In the case shown, the monotonous, atypical neoplastic cells (**a–b**) are positive for CD3, CD1a, CD10, LMO2, and TdT (**c–e–f–g–h**) and negative for PAX5 (**d**). LMO2 is an interesting antibody which reacts mainly with malignant T-lymphoblastic cells, useful in the differential diagnosis with cortical thymocytes (adapted with permission from Ame Publishing Company) [32]

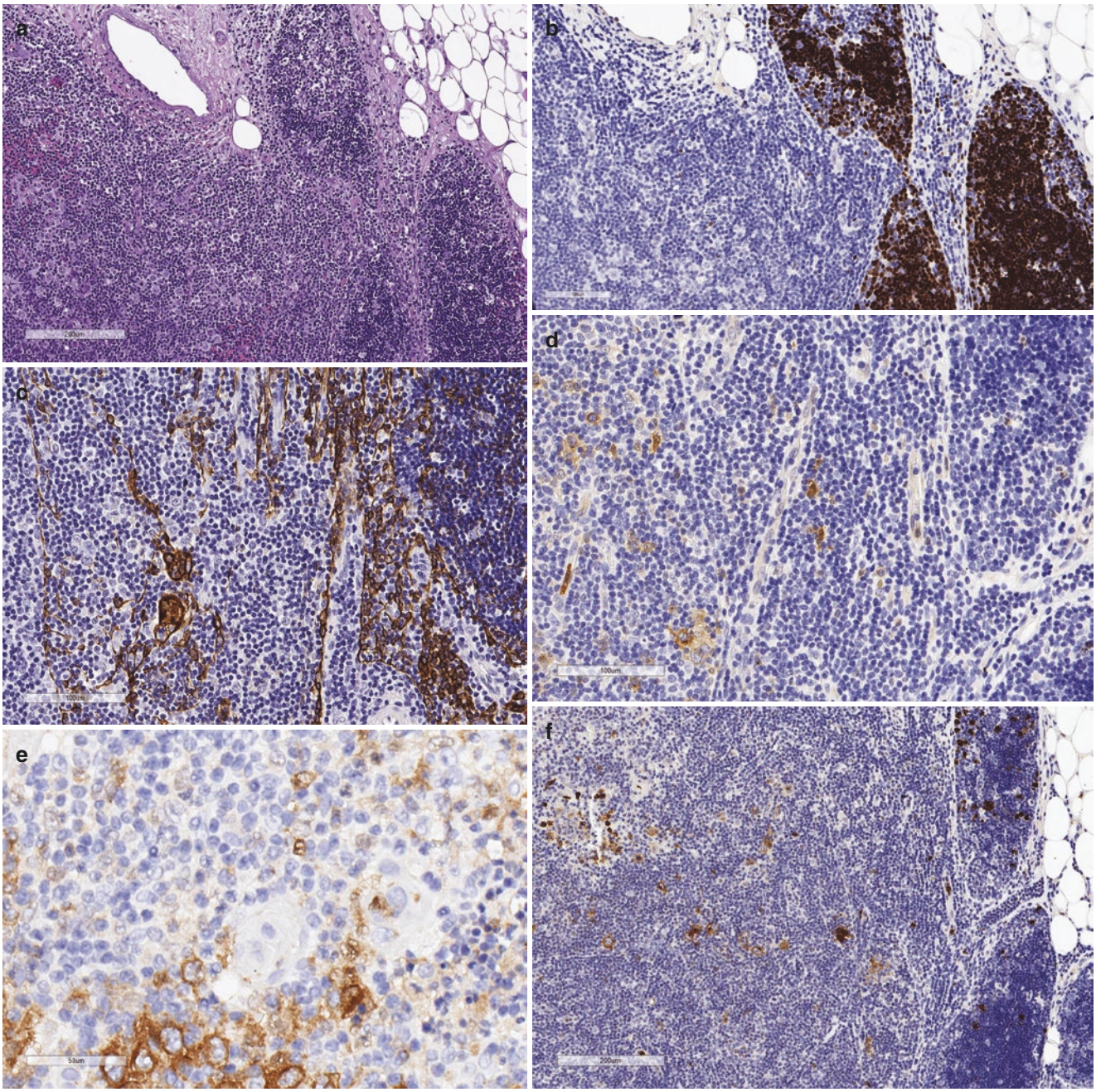


**Fig. 13.2** Early phase of Hodgkin lymphoma (HL) in the thymus. These pictures derive from the peripheral part of a mass surgically removed and found to be a thymic HL localization**.** (**a**) H&E 100×, the image is mainly focused to thymic medulla (M); lobules of cortex (C) are seen on the right. In the M sparse large atypical cells are seen; (**b**) TdT 200×, the stain underlines the C which is devoid of infiltration by large atypical cells; (**c**) CK MNF116 200×, normal cytokeratin pattern in a normal thymus; (**d**) CD30 200×, large CD30+ Hodgkin cells in the M, low magnification; (**e**) CD30 400×, large CD30+ Hodgkin cells in the M, high magnification; (**f**) CD15 100×, the large atypical Hodgkin cells are also CD15+

#### 13.3.2.1 Classic Hodgkin Lymphoma (cHL)

The most frequent subtype of cHL in the mediastinum is the nodular sclerosis (NS) variant [42], constituting about 50–70% of primary mediastinal lymphoma [43]. cHL-NS of the thymus is predominantly a tumor of the young age and primarily of females. In a sclerotic background with a polymorphic inflammatory population the demonstration of typical CD30+ cells, which are often very rare in the fibrous background (Fig. 13.3), is worthwhile to support the diagnosis. Reed-Sternberg cells (RS) are large with abundant

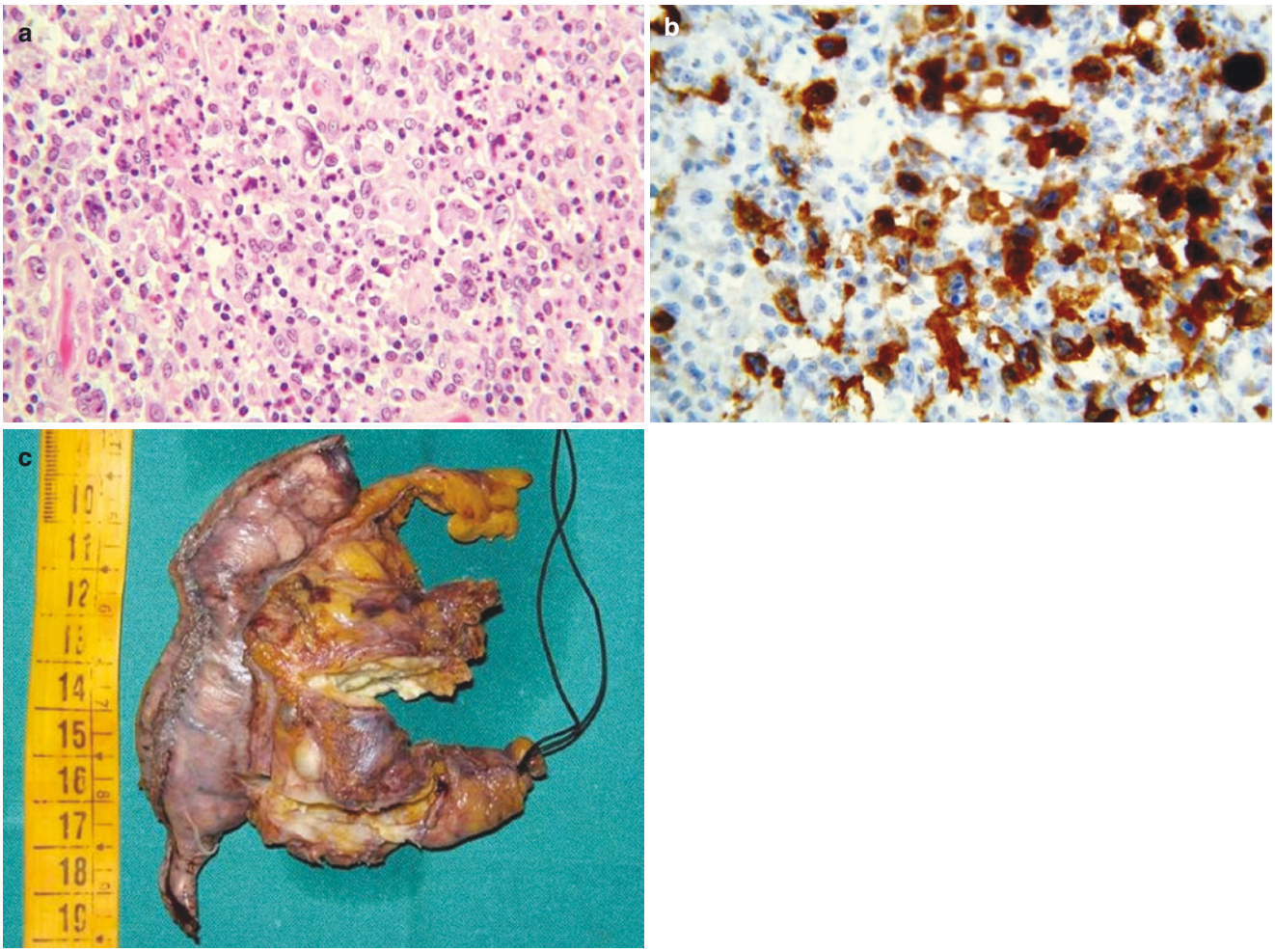


**Fig. 13.3** Classical Hodgkin lymphoma (cHL) of the thymus. (**a**) Polymorphic lymphoid cell population including scattered large atypical cells with the morphological features of Hodgkin's cells, H&E, 200×; (**b**) CD30 staining of large atypical Hodgkin's cells 200×; (**c**) macroscopy of a case of cHL in the thymus: mediastinal Hodgkin lymphoma is often cystic. In this case the mediastinal mass was adherent to lung parenchyma. Therefore extensive sampling of cystic mediastinal lesions is recommended (adapted with permission from Ame Publishing Company) [32]

eosinophilic cytoplasm, large double or multiple nuclei, and eosinophilic nucleoli; lacunar cells (LC) with small hyperlobated nuclei, small nucleoli, and clear, retracted cytoplasm are the cells more frequently associated to the NS subtype of cHL. As a specific pitfall, cHL induces reactive EC proliferation and/or cystic changes (Fig. 13.4) which may simulate a thymoma. Therefore, mediastinal cystic lesion should be extensively sampled because foci of cHL could be found in the wall [44–46]. The lymphoma usually forms large sclerotic masses with foci of necrosis and eosinophilic abscesses. cHL of the thymus is frequently mistaken with the primary mediastinal B cell lymphoma (PMBL), which also induces sclerotic reaction and may show RS-like cells. In fact, cHL-NS and PMBL have the same (B) cell origin [47, 48] and similar morphology and may show a similar clinical presentation.

#### 13.3.2.2 Primary Mediastinal B Cell Lymphoma (PMBL)

This lymphoma usually forms bulky, solid masses of > 10 cm, with local symptoms of rapid growth, invasion, and compression of vital structures. Tumor development may represent a hematological emergency. At the time of primary diagnosis, the tumor is limited to the thorax with no involvement of lymph nodes or other lymphoid organs (only supraclavicular nodes are eventually reached). During relapse, the subdiaphragmatic lymphoma extension is frequent. This lymphoma was first described as mediastinal B cell lymphoma with sclerosis, as it is associated with a distinctive fibrosis [49]. Neoplastic cells are of variable size, frequently of large or medium-large size, sometimes with pale clear cytoplasm in the central part of the tumor and

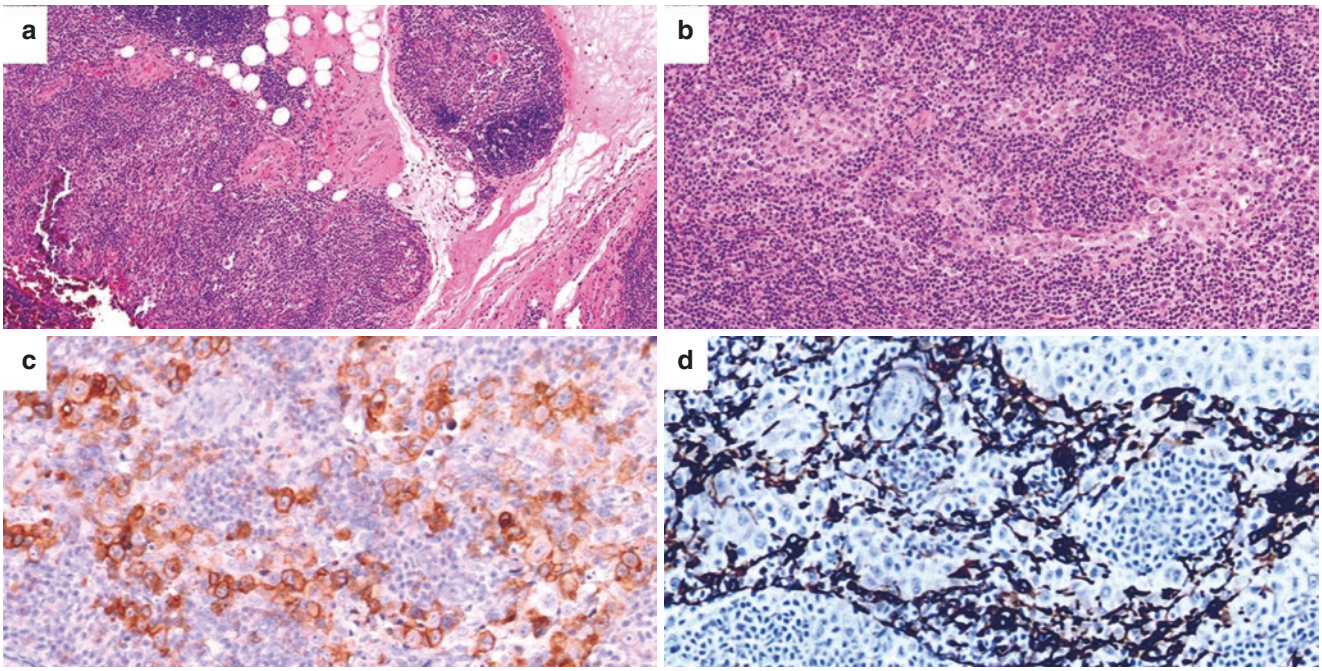


**Fig. 13.4** cHL panel: Hodgkin lymphoma in the thymus. The neoplastic lymphoid proliferation stimulates also EC network proliferation and therefore a thymoma. (**a**) Paracardiac anterior mediastinal mass occurring in a 22-year-old female, H&E staining, 100×; (**b**) H&E staining of the tumor, showing large cells with atypical nuclei in a lymphoid background, 200×; (**c**) IHC highlights CD30+ cells in the lymphoid background, 400×; (**d**) pankeratin immunostain reveals the presence of a disorganized EC network, 400× (courtesy of Prof. Lucia Anemona, Tor Vergata University, Rome, Italy). *EC* epithelial cells; *IHC* immunohistochemistry. (adapted with permission from Ame Publishing Company) [44]

peripherally distributed lymphocytes in the sclerotic background (Fig. 13.5). Neoplastic infiltrating CD20+ B cells have pleomorphic nuclei, ranging from regular, round nuclei to irregular, multilobulated forms [50]. In certain cases, neoplastic cells are large with prominent eosinophilic nucleoli, which resemble RS cells or variants. CD30 is weakly or focally expressed, with lesser intensity than in cHL but MAL, a protein involved in lymphocyte signal transduction, present on a minor subpopulation of thymic medullary B cells, is expressed by PMBL [51]. CD23 is also a PMBL marker [52]. However, in the differential diagnosis of these mediastinal lymphomas (cHL, PMBL, and the gray zone lymphoma (GZL)) use of a panel of antibodies is recommended [32, 53, 54].

#### 13.3.2.3 Gray Zone Lymphoma (GZL)

"Gray zone lymphoma" (GZL) or "B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma" [55] according to the 2017 WHO classification [23] originates in the mediastinum from a thymic medullary B cell [56]. GZL is a lymphoma of young patients (20 to 40 years) with a large anterior mediastinal mass, eventually involving the supraclavicular lymph nodes. Less frequently GZL occur in other localizations. GZL is a lymphoma with intermediate morphological and immunohistochemical characteristics (Fig. 13.6) between cHL and PMBL [48, 57]. In the case showed in Fig. 13.6, the large neoplastic cells coexpressed CD20, CD79a, CD30, PAX5, and the transcriptional factors OCT2 and BOB1. CD45 is negative. The genetical and epigenetic alterations reported show similarities and differences with those reported for PMBL and cHL. Consensus studies and updated diagnostic criteria were recently reported by Pilichowska et al. [58] and by Sarkozy et al., in the framework of the lymphoma study association (LYSA) [59] and in the recently published WHO classification of hematological malignancies [23]. A diagnostic scoring system was also proposed [60].

Table 13.2 shows comparison of main immunophenotypical characteristics of neoplastic lymphoid cells in cHL, PMBL, and GZL.

### 13.3.3 MALT Lymphoma of the Thymus

Among the peripheral B cell lymphomas occurring in the thymus, the most common is the mucosa-associated B cell lymphoma of MALT type or extranodal marginal zone lym-

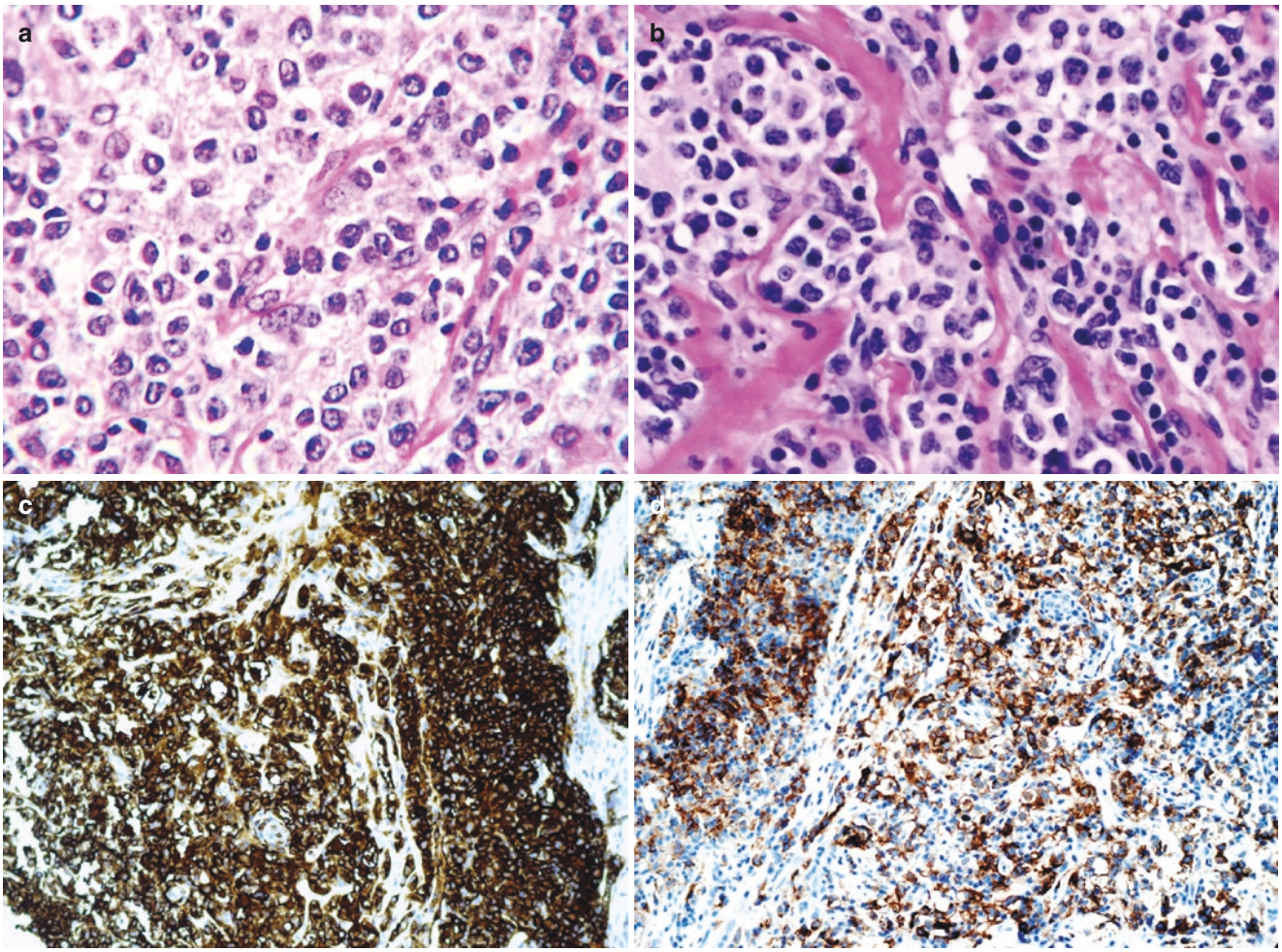


**Fig. 13.5** Primary mediastinal B cell lymphoma (PMBL): (**a**) H&E, 400×; (**b**) H&E, 400×; (**c**) CD20, 200×; (**d**) CD30, 200×. In (**a** and **b**), the sclerotic background is seen, as well as the irregular nucleus and the clear cytoplasm of the neoplastic B cells in PMBL. CD20 positivity is the hallmark of the disease, but CD30 is often coexpressed. A & B: courtesy of Prof. Fabio Menestrina (adapted with permission from Ame Publishing Company) [32]

phoma of MALT type [61]. This rare lymphoma type, often cystic, usually develops in association with autoimmune diseases [62] and is characterized by scant residual thymic EC network, lymphoepithelial (LE) lesions involving Hassall corpuscle (HC), and a monotonous infiltrate of marginal zone B cells [63] (Fig. 13.7).

### 13.3.4 Very Rare B Cell Lymphoma in the Mediastinum

In the setting of a systemic disease, B lymphoblastic lymphoma (B-Lb) may occur in the thymus. Rarely a primary mediastinal mass may also occur [64, 65], as shown in the Fig. 13.8, with B-Lb infiltrating the pericardium.

## 13.4 Neoplasms of Accessory Cells of the Lymphatic Tissue, with a Distinct Mention of Castleman Disease

Castleman disease (CD) is a morphological and clinically heterogeneous group of nonneoplastic lymphoproliferative disorder of the lymphoid tissue [24, 25, 27], occasionally giving rise to neoplasms of the constituting cells (both lymphoid and "accessory") [26, 66]. In the mediastinum, the most frequent type of CD is the hyaline vascular (HV) type. The reader is referred to several recent reports/reviews on this complex disease [67, 68]. The follicular dendritic cell sarcomas (FDCS), a neoplasm of accessory cells of the lymphoid tissue, may occur in the framework of CD [69].

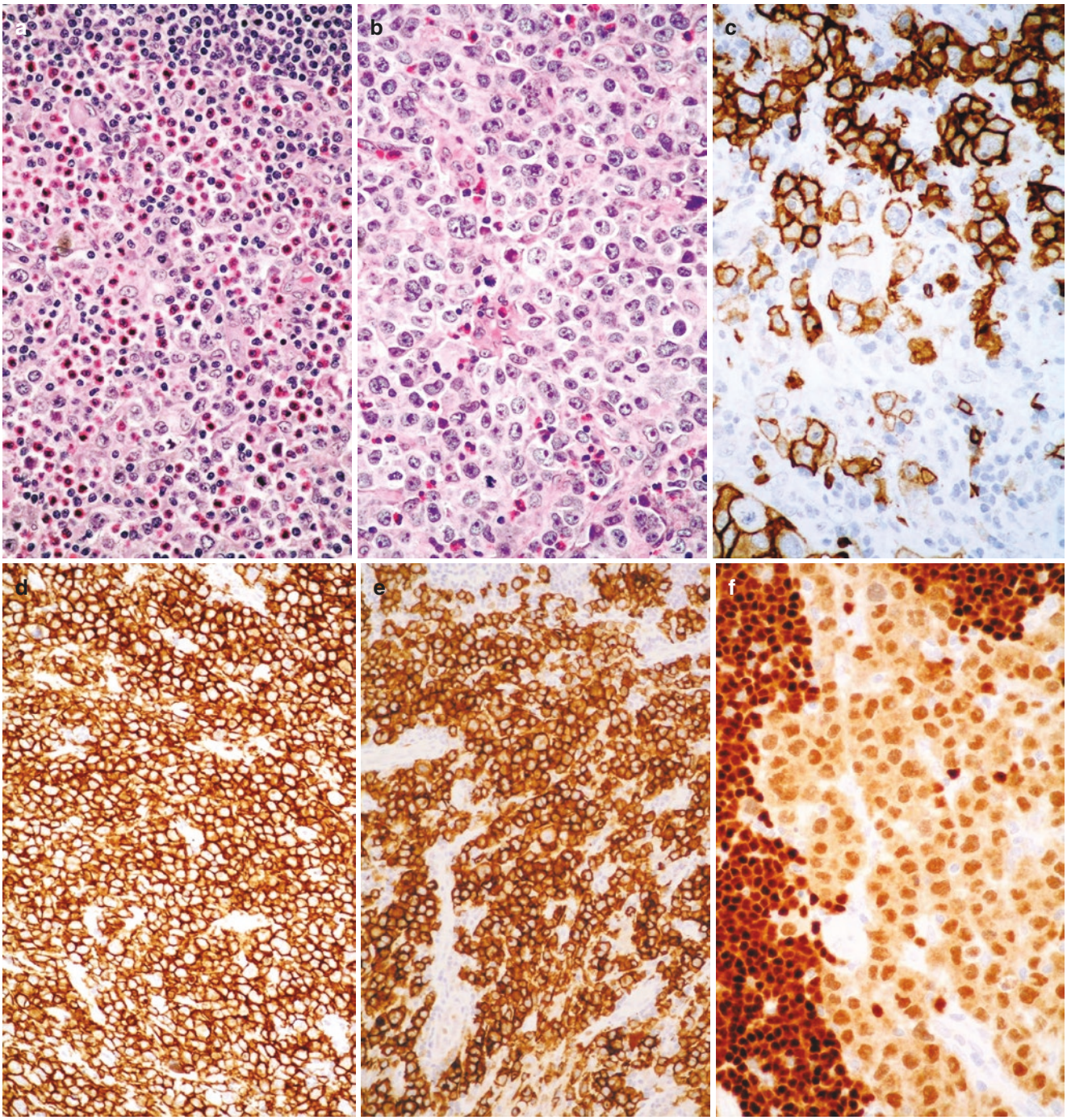


**Fig. 13.6** Gray zone lymphoma (GZL) is a lymphoma with morphological and immunohistochemical characteristics intermediate between cHL and PMBL—(**a**) H&E, 100×; (**b**) H&E, 200×; (**c**) CD20, 200×; (**d**) CD20, 100×; (**e**) CD30, 100×; (**f**) PAX5, 200×; (**g**) MUM1, 200×; (**h**) OCT2 200×. In the GZL case shown here neoplastic cells coexpress CD20, CD30, PAX5, and OCT2 (adapted with permission from Ame Publishing Company) [32]

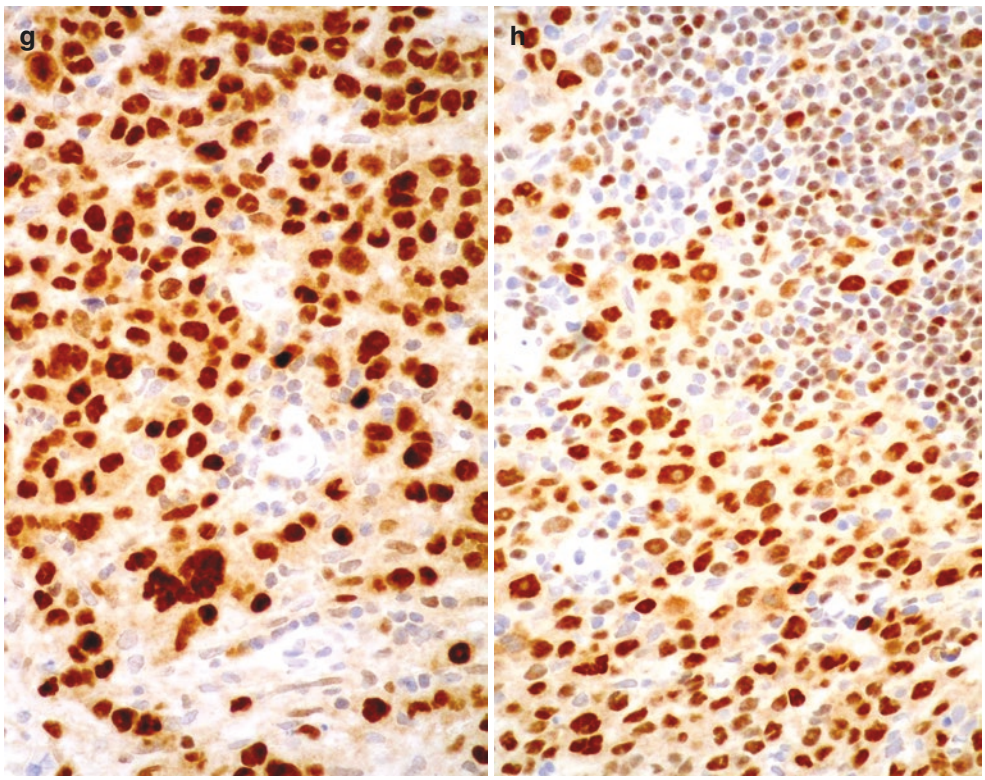


**Fig. 13.6** (continued)

**Table 13.2** Immunohistochemistry in the differential diagnosis of thymic cHL, PMBL, and GZL

| Antibodies | cHL | PMBL | GZL |
|---|---|---|---|
| CD30 | + (85–96%, Memb + Golgi area) | >80%, weak and heterogeneous | Usually + |
| CD15 | + (75–85%) | Usually – | May be expressed |
| CD45 | – | + | + |
| CD20 | <20–40% +, variable intensity | + | + usually |
| CD79a | Rarely + | + | + usually |
| PAX5 | *+ weak* | + | + usually |
| OCT2 | *–/+ usually* | + | + usually |
| BOB1 | – | + | + usually |
| MUM1 | + | + (75% of cases) | + usually |
| EBER (EBV) | *Only 10–25% of cases* | Mostly – | Mostly – |
| LMP-1 (EBV) | *19%* | Mostly – | Mostly – |
| MAL | *Negative* | Positive | + in a subset of cases |
| CD23 | *Negative* | + (70% of cases) | N.A. |
| BCL6 | *Negative* | + (45–100%) | Variably + |
| Cyclin E | *+ 79%* | Negative | N.A. |
| P63 | *N.A.* | Positive | N.A. |
| Fascin | *Positive* | Negative | N.A. |

Main immunohistochemical markers in the differential diagnosis of thymic cHL, PMBL, and MZL. The reactivity patterns reported are modified from the WHO classification of thymic epithelial tumors and from the WHO classification of lymphohematopoietic tumors ([14]; [23]) and from several reviews dealing with immunohistochemistry of mediastinal lymphoma to which the reader is referred for further details ([53]; [57]; [60]; [54]). Adapted with permission from AME Publishing Company [32]

*cHL* classical Hodgkin lymphoma, *PMBL* primary mediastinal B lymphoma, *GZL* gray zone lymphoma. See Ref. [32]-

*N.A.* data not available

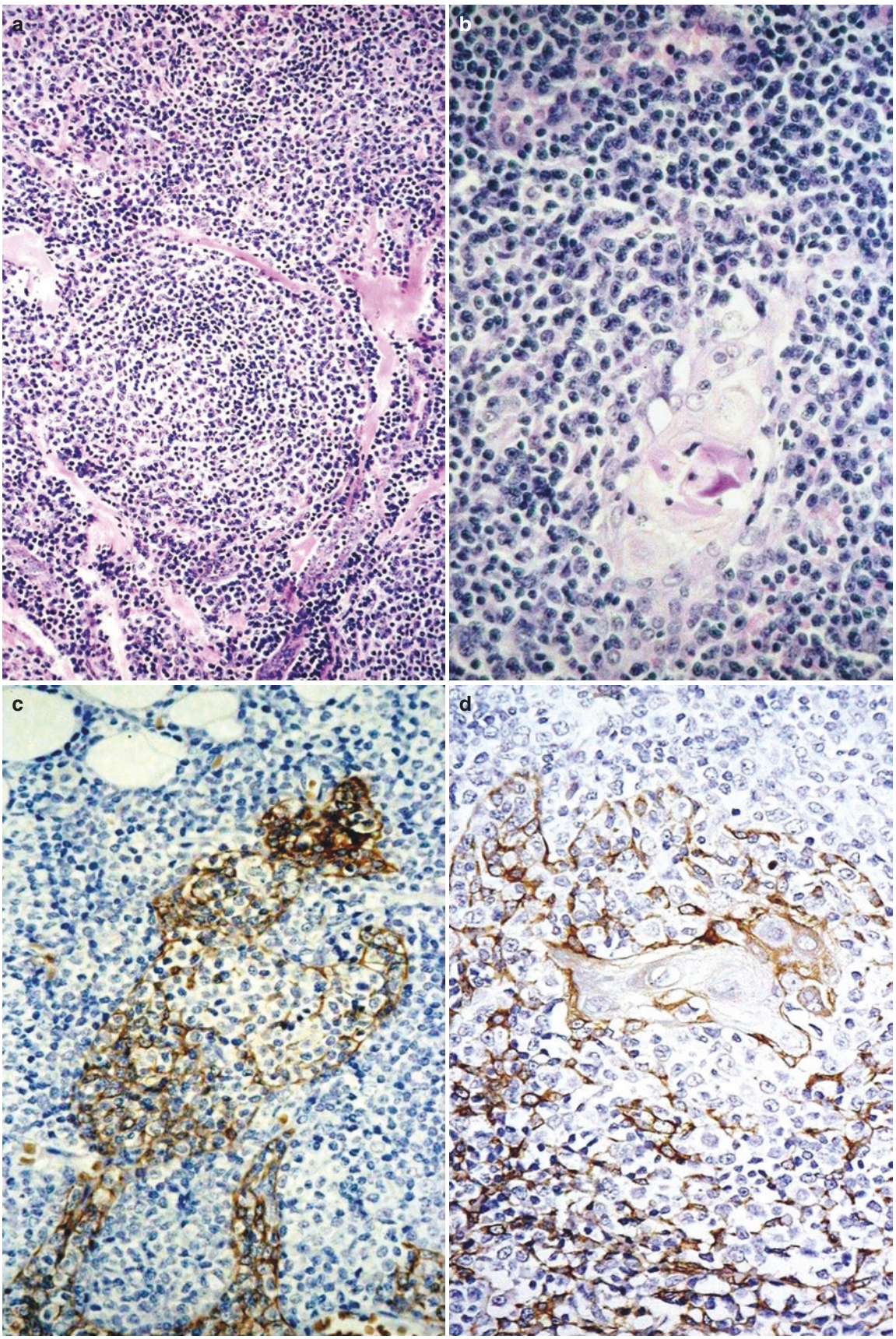


**Fig. 13.7** Mucosa-associated lymphoid tissue (MALT) lymphoma of the thymus—(**a**) H&E, 100×, a residual follicle is seen among the small monocytoid B cells. (**b**) H&E, 200×, Hassall corpuscle surrounded by neoplastic B cells. (**c**) Pancytokeratin stain, 200×: residual thymic epithelial structures in the lymphoid background. (**d**) Lymphoepithelial (LE) lesions in a Hassall corpuscle, pancytokeratin stain, 200× (adapted with permission from Ame Publishing Company) [32]

The heterogeneous group of very rare accessory cell neoplasms of the thymus includes those derived from Langerhans cells (Langerhans cell histiocytosis (Fig. 13.9) and Langerhans cell sarcoma) and Follicular dendritic cell sarcoma (FDCS); histiocytic sarcoma, interdigitating dendritic cell sarcoma, fibroblastic reticulum cell tumor, have been described in the mediastinum [23].

Accessory cell sarcomas have also been rarely reported to develop in GCT of the mediastinum [46, 70, 71]. Figure 13.10 represents the main features of a FDCS arising in CD.

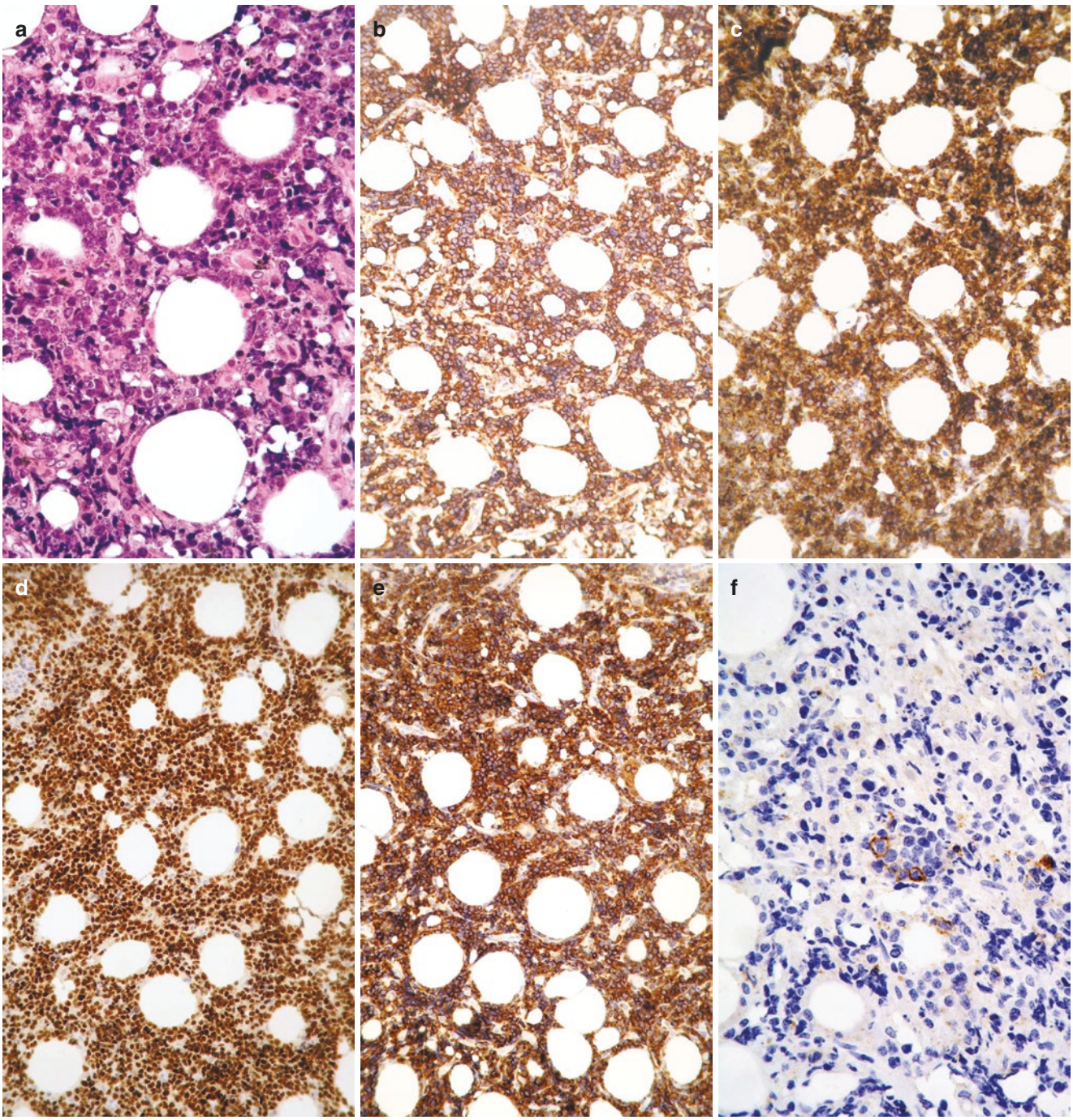


**Fig. 13.8** Lymphoblastic B (B-Lb) lymphoma, pericardium—(**a**) H&E, 200×; (**b**) CD34, 200×; (**c**) CD10, 200×; (**d**) PAX5, 200×; (**e**) CD79a, 200×; (**f**) CD20, 200×; (**g**) KI67, 200×. In the case shown, although CD20 (**f**) is negative, other B cell markers (**d–e**) are positive in the immature (**a**), CD34+, CD10+ (**b–c**) B lymphoblastic population. A very high proliferative activity is shown by the KI67 stain (**g**) (adapted with permission from Ame Publishing Company) [32]

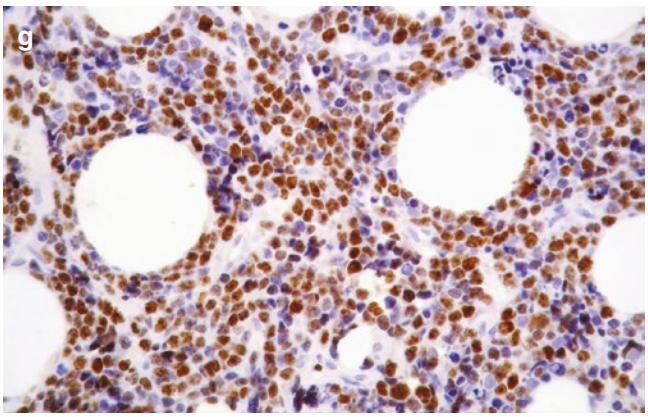


**Fig. 13.8** (continued)

## 13.5 Other Rare Hematological Neoplasias

In the framework of chronic myeloid leukemia (CML) a mediastinal mass and a blastic crisis may develop [72, 73]. Figure 13.11 shows the morphological features of cells infiltrating a sclerotic mediastinal stroma and results of the FISH for BCR/ABL. The cells were positive for CD45 and CD34. Subsequently, the FISH hybridization procedure confirmed that the blasts were BCR/ABL fusion positive. Moreover, hematological malignancies may arise also in the framework of GCT of the mediastinum [74–76].

## 13.6 Other Rare Tumors/Pseudotumors of the Mediastinum

### 13.6.1 Lymphadenoma

Lymphadenomas occur in salivary gland. Their thymic counterparts are rare and belong to benign salivary gland-type tumors of the thymus. These can be sebaceous or nonsebaceous. Microscopically, they show epithelial cells with or without sebaceous differentiation in the background of lymphoid stroma with germinal centers (Fig. 13.12). Epithelial cells show tubular or solid architecture, hence the term adenoma.

Thymoma should be considered in the differential diagnosis due to admixture of epithelial and lymphoid cells; however lack of characteristic tumor lobulation and irregular epithelial proliferation excludes thymoma.

### 13.6.2 Sclerosing Mediastinitis

Some of the fibrosing neoplasias/lymphomas previously described may simulate sclerosing (or fibrosing) mediastinitis (SM), a disease with immune/autoimmune pathogenesis, rarely affecting the mediastinum and the thymus [30, 77]. SM is part of the spectrum of IgG4-related disease (IgG4-RD) or it may be related to Histoplasmosis. This is an idiopathic fibroinflammatory disorder associated with hypergammaglobulinemia and increased serum levels of IgG, particularly IgG4. The newly formed fibrous tissue presents a marked IgG4+ plasma cell infiltrate [29, 78]. Figure 13.13 shows a case of IgG4-related disease developing in a salivary gland (Kuttner tumor) in an old woman. Cellular and storiform fibrosis; lymphoplasmacytic infiltration, with IgG4/IgG ratio of 40%; and >=50 IgG4 (+) cells/high power field (HPF) and obliterative phlebitis are among the diagnostic histological features of mediastinum and the other tissue localizations.

### 13.6.3 Mesenchymal Soft Tissue Tumors

Most of the mesenchymal tumors occurring in the anterior mediastinum show a thymic origin [79]. Mesenchymal soft tissue tumors of the mediastinum are similar in morphology and molecular features with their counterparts occurring in other sites. They account for 2% of all tumors in the mediastinum [79, 80]. A list of the histotypes more frequent in the anterior mediastinum is provided in a recent review [81]. Among soft tissue tumors**,** mediastinal sarcomas may either develop de novo or they may arise as "somatic-type" malignancy in a mediastinal GCT. The sarcomatous component develops more frequently in mediastinal GCT than in other sites [79]. Soft tissue tumors show a typical age and gender predilection or have specific associated diseases. Their diagnosis requires the use of immunohistochemistry by a specialized panel of antibodies, molecular testing, and the knowledge of the clinical setting [81].

#### 13.6.3.1 Neoplasms with a Lipomatous Component and Fibroblastic Tumors

**Liposarcoma**

Lipomatous tumors account for up to 10% of mediastinal masses. Liposarcoma, in particular, is the most common primary malignant soft tissue tumor of the mediastinum.

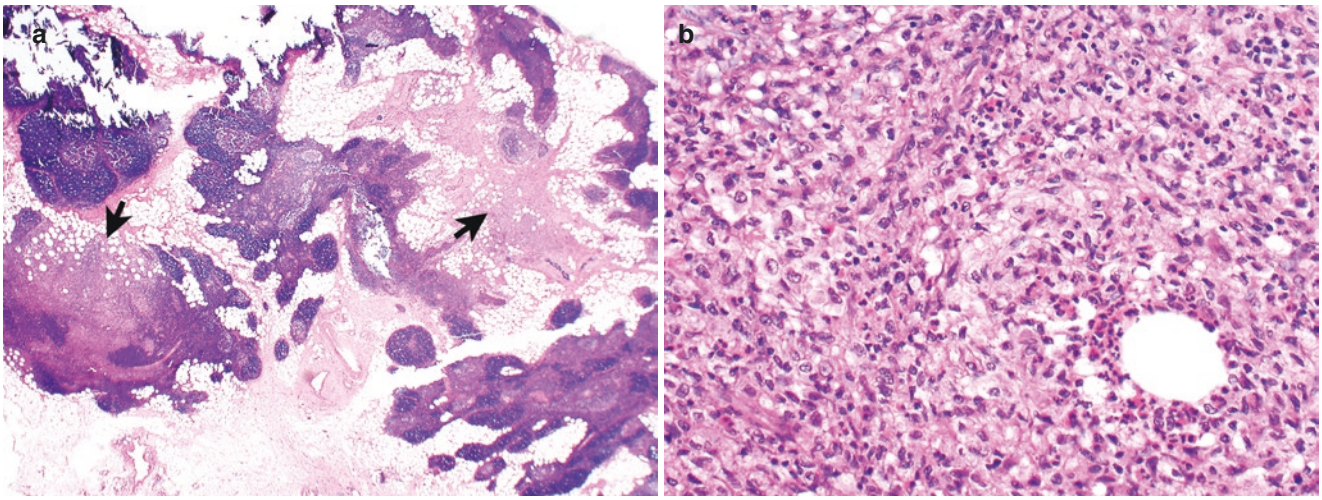


**Fig 13.9** Langerhans cell histiocytosis involving thymic gland. (**a**) The thymic gland shows a patchy cellular infiltrate focally in a more fibrotic background (arrows). (**b**) These infiltrates are comprised of large atypical epithelioid cells characterized by grooved and folded nuclei, some with more conspicuous nucleoli. These cells are marked with CD1a and langerin (not shown). Scattered eosinophils and neutrophils are also noted. Magnification x 20 (**a**), x 200 (**b**). Courtesy of Dr. Anja C. Roden (Mayo Clinic Rochester, MN, USA)

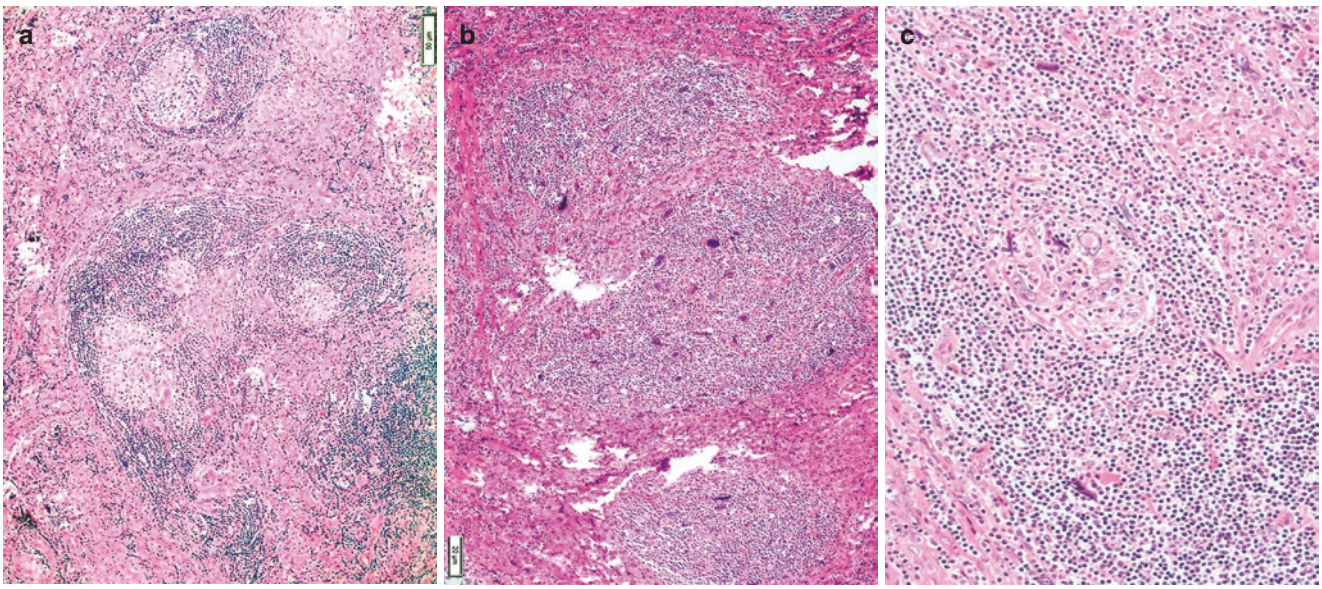


**Fig. 13.10** Follicular dendritic cell sarcoma (FDCS) arising in Castleman disease (CD). (**a**) H&E, 100×; (**b**) H&E, 100×; (**c**) H&E, 100×; (**d**) CD21, 100×; (**e**) EMA, 100×; (**f**) clusterin, 200×; (**g**) CD163, 200×; (**h**) S100. (**a–c**) Residual lymphoid follicles of CD surrounded by a polymorphic neoplastic population. (**d–g**) Neoplastic follicular dendritic cells are positive for CD21, EMA, clusterin, and CD163 and negative for S100 (**h**) (adapted with permission from Ame Publishing Company) [32]

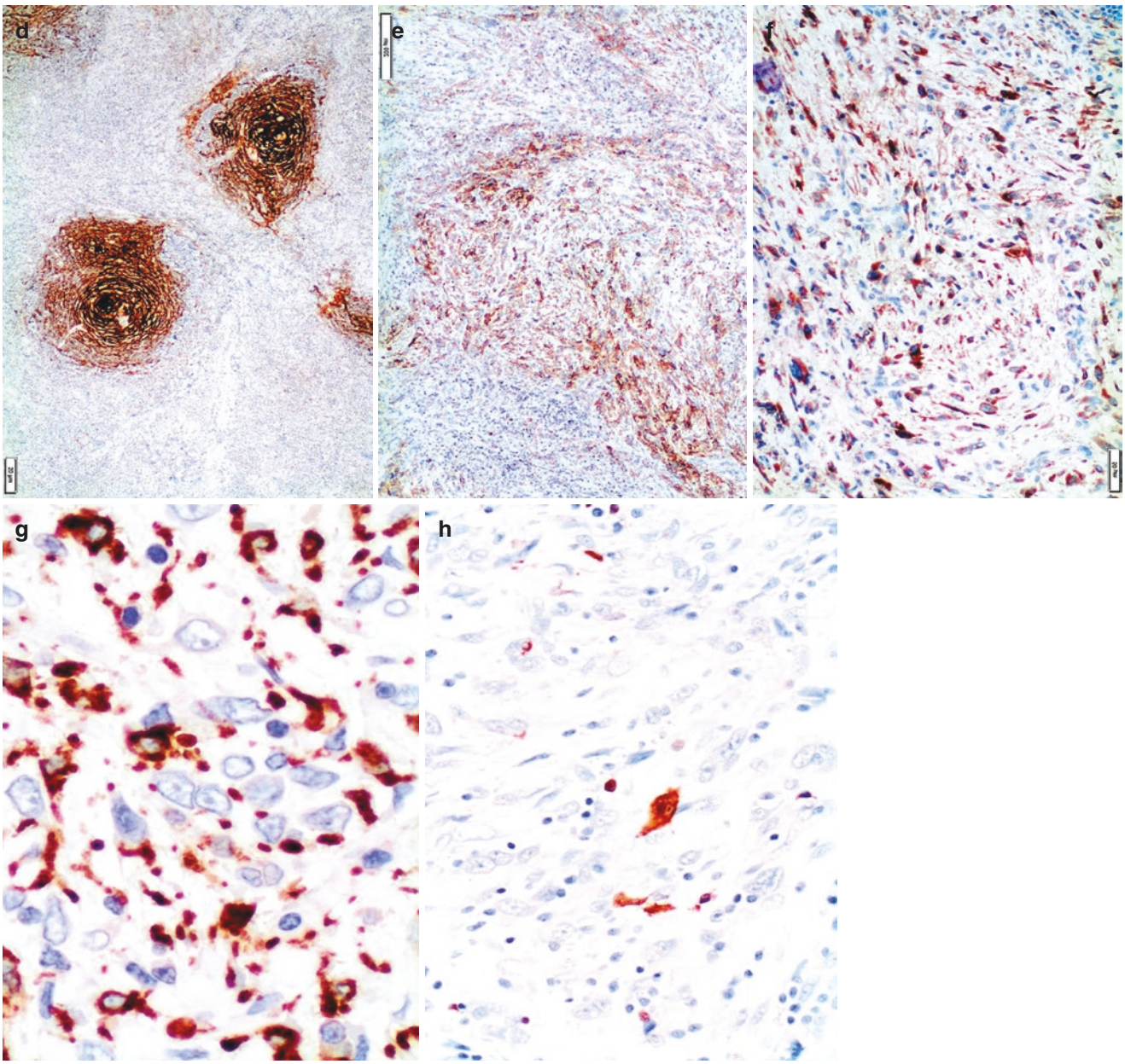


**Fig. 13.10** (continued)

A case of well-differentiated liposarcoma (Fig. 13.14) forms a huge tumor of 23 cm in diameter. The tumor shows a sclerosing pattern with focal loss of lipocytic differentiation; mature and immature (multivesicular) adipocytes embedded in fibro-myxoid (basophilic) stroma are seen. The lipoblasts contain several small fat droplets in the cytoplasm.

### Thymolipoma

These are rare mediastinal tumors with benign clinical course which are also called as lipothymomas or simply lipomas due to scant or absent thymic tissue respectively. Thymic tissue may not be seen in small biopsies due to limited sampling. These are associated with MG and other autoimmune diseases.

Grossly, as the name suggests, they are soft and yellow, well-outlined fleshy lobulated tumors. The size can be very large and weigh up to 2 kg. No necrosis or hemorrhage is present (Fig. 13.15).

Microscopically, these show variable proportions of adipose tissue and thymic tissue. Thymic tissue shows admixture of epithelial and lymphocytic cells including HC. No atypia is seen in thymic or lipomatous components of the tumor (Figs. 13.16 and 13.17). Rare rhabdomyoblastic, fibrous, sebaceous, and smooth muscle differentiation is noted.

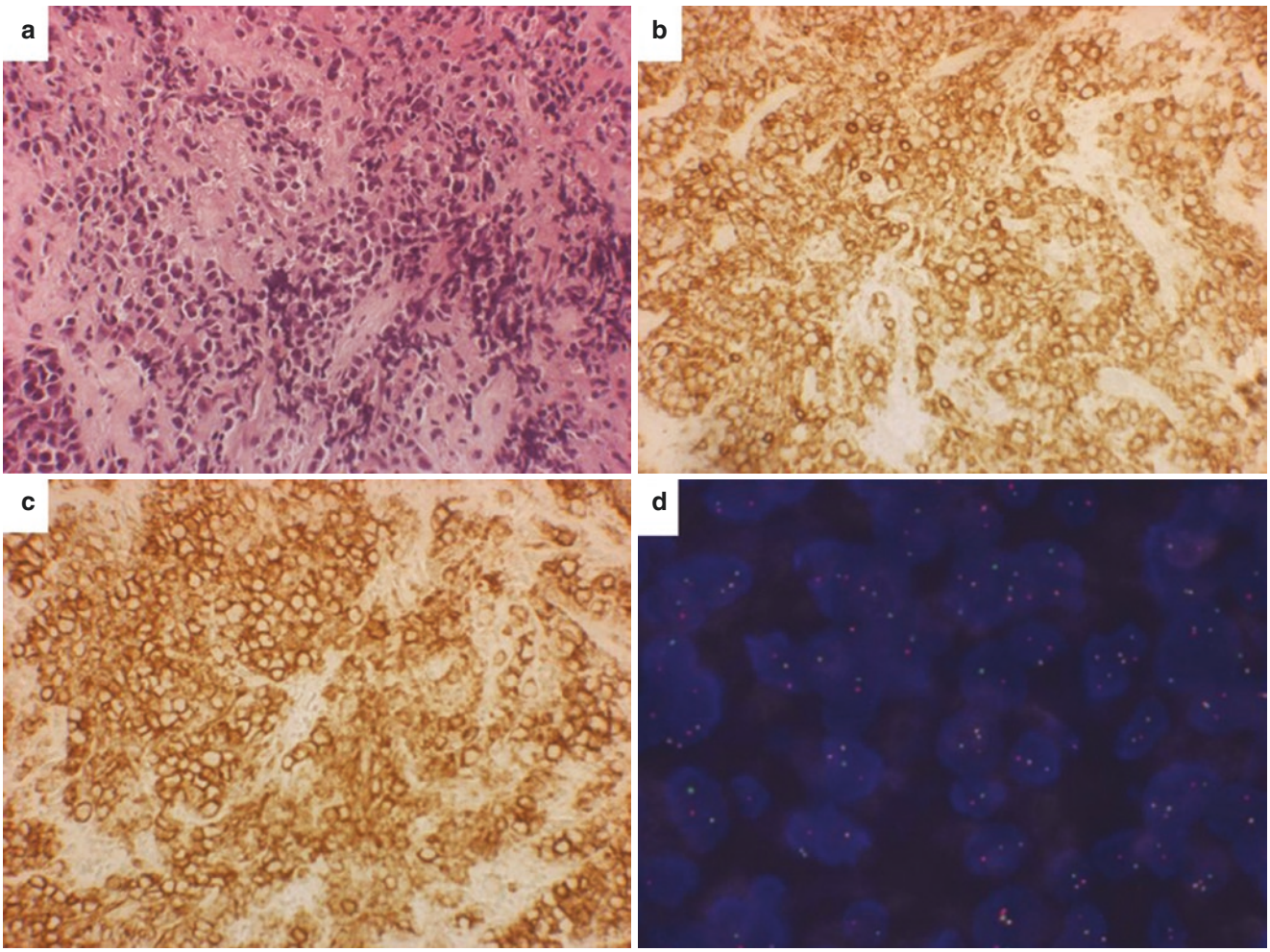


**Fig. 13.11** Mediastinal localization of blastic crisis in chronic myeloid leukemia (CML)—(**a**) H&E, 200×, sclerotic background infiltrated by an undifferentiated neoplasm; (**b**) CD45, 200×, the cells are CD45+; (**c**) CD34, 200×, positivity for CD34 is consistent with a blastic crisis occurring in the mediastinum in a male patient affected by CML; (**d**) FISH analysis, performed in FFPE sections. FISH *BCR-ABL* result in the mediastinal biopsy using LSI *BCR-ABL* dual color extra signal (Vysis, Abbott), 1000×: the LSI *BCR* probe labeled with spectrum green and LSI *ABL* probe labeled with spectrum orange. The presence of the yellow *BCR/ABL* fusion signal confirms the presence of t(9;22) translocation between *BCR* gene located on chromosome 22 and *ABL* located on chromosome 9 (courtesy of Dr Roberta Merola) (adapted with permission from Ame Publishing Company) [32]. Chronic myeloid leukemia (CML); formalin-fixed paraffin-embedded (FFPE); fluorescence in situ hybridization (FISH)

### Angiomyolipoma

These are incidentally found rare mediastinal tumors, mostly reported in anterior mediastinum (Fig. 13.18). Mediastinal angiomyolipomas do not show close association with tuberous sclerosis.

Grossly these are large, soft, and yellow-colored tumors (Fig. 13.19). Histomorphologically they are same as other angiomyolipomas which are constituted by variable proportion of adipose tissue, smooth muscle, and ectatic blood vessels (Fig. 13.20). Residual thymic tissue can be seen in the vicinity of the tumor.

### Lipofibroadenoma

It is a benign tumor of the thymus with only six case reports available in the literature [14, 82, 83]. It bears resemblance to fibroadenoma of the breast. They may arise de novo or in continuity with thymomas.

Grossly, the tumors are well-circumscribed and have a solid gray-white cut surface. Microscopically, the tumor has fibrotic and hyalinized stroma with entrapped epithelial cells and few interspersed TdT-negative lymphocytes (Fig. 13.21). Although differentiation from thymolipoma is based on predominance of adipose tissue in the thymolipoma and fibrous tissue in lipofibroadenoma, both may be considered in the spectrum of the same disease.

### Solitary Fibrous Tumor and Malignant Solitary Fibrous Tumor

Among fibrous/spindle cell mesenchymal tumors, solitary fibrous tumor (SFT) [84, 85] is a prototype in mediastinum.

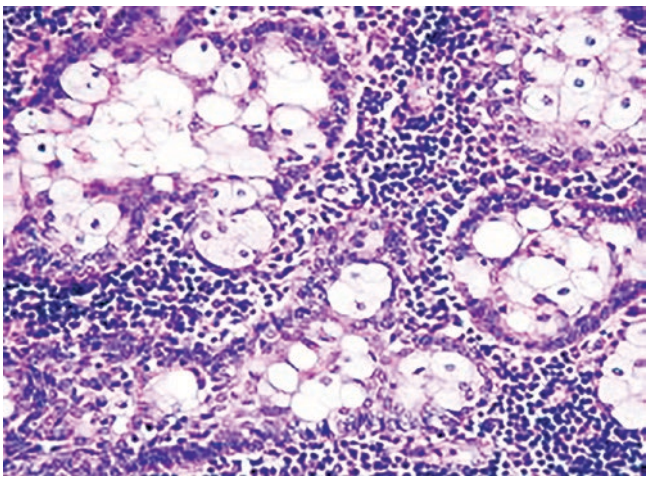

**Fig. 13.12** Photomicrograph shows solid nests of epithelial cells with sebaceous differentiation. The background shows lymphoid tissue (H&E ×400). Photograph courtesy: Dr Mark R Wick, Department of Pathology, UVA School of Medicine

SFT is, at present, considered a potentially malignant tumor even if morphology does not meet the criteria of the malignant SFT (Figs. 13.22 and 13.23). These tumors, considered to originate in the pleura, have a "patternless" architecture with randomly distributed hypocellular and hypercellular areas, sometimes embedded in keloid-like collagen. The criteria are same in mediastinum for predicting their malignant behavior, which include a high mitotic count (>4 mitoses per 2 $mm^2$), high cellularity, pleomorphism, and necrosis [86]. The SFT cells are cytologically benign spindle shaped with few mitoses and positive for CD34 (Fig. 13.22). In addition to CD34, the positivity for STAT6 (Fig. 13.23) is specific, as almost all SFTs harbor *NAB2-STAT6* fusion gene [87].

### Desmoid Tumors

Desmoid tumors (Fig. 13.24) should be suspected in case of spindle cell, "benign-looking" tumor without mitotic activity and necrosis but with a diffuse infiltration of surrounding tissues (fat tissue or skeletal muscles). These tumors prevail in

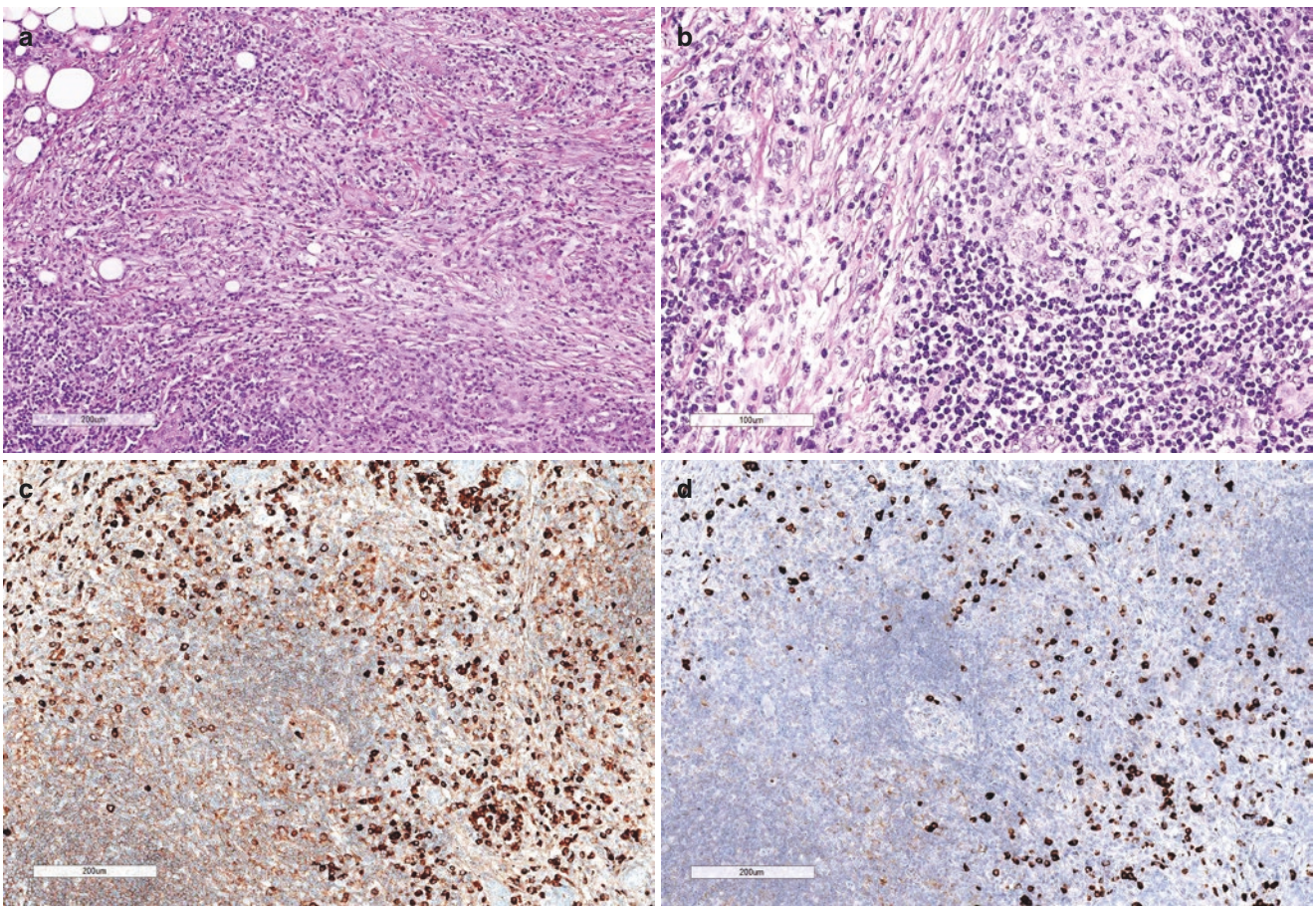


**Fig. 13.13** IgG4-related disease (IgG4-RD), an idiopathic fibroinflammatory disorder associated with hypergammaglobulinemia and increased serum levels of IgG4, produces pseudotumors, which develop in different organs/systems, including mediastinum: (**a**) H&E, 100×, fibroinflammatory infiltrate, rich in plasma cells; (**b**) H&E, 200×, many plasma cells are seen among the lymphoid cells, surrounding the reactive lymphoid follicle; (**c**) IgG, 100×, the plasma cells produce IgG; (**d**) IgG4, most plasma cells are IgG4 positive, 100× (adapted with permission from Ame Publishing Company) [32]

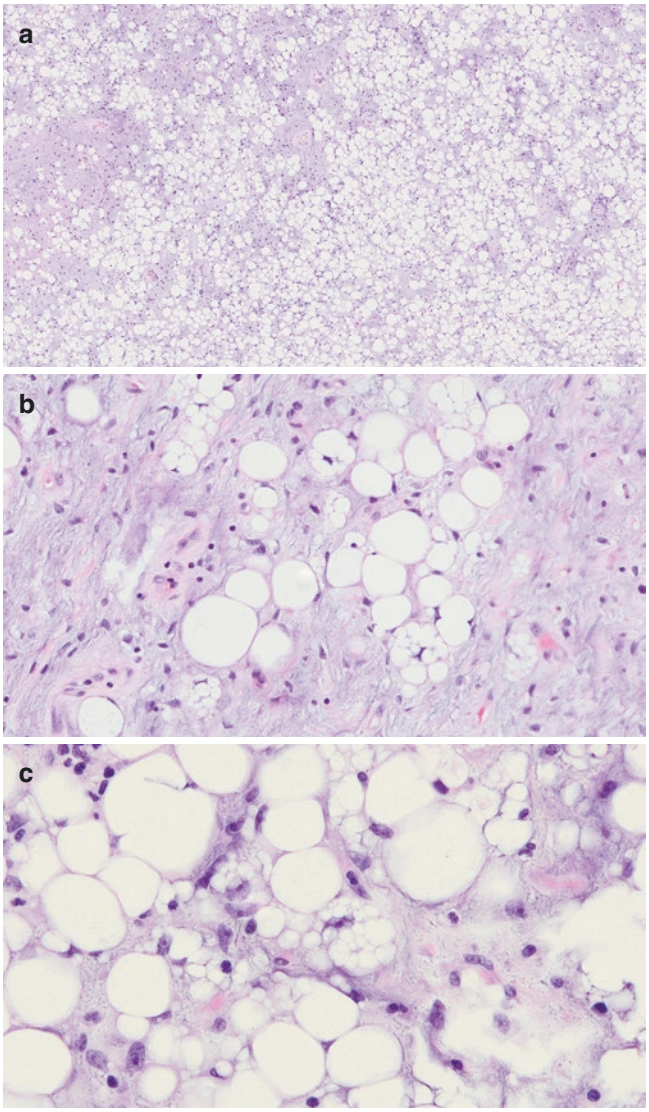


**Fig. 13.14** Liposarcoma: male, aged 73, huge tumor of the anterior mediastinum (up to 23 cm in the largest diameter) with several smaller satellite lesions. (**a**) The tumor was composed of fat tissue cells and fibro-myxoid component. H&E, 40×). (**b** and **c**) The lipoblasts contain several small fat drops in the cytoplasm instead of single big one. The nucleus is compressed and often located in the center of a cell. H&E, 200× and 400×

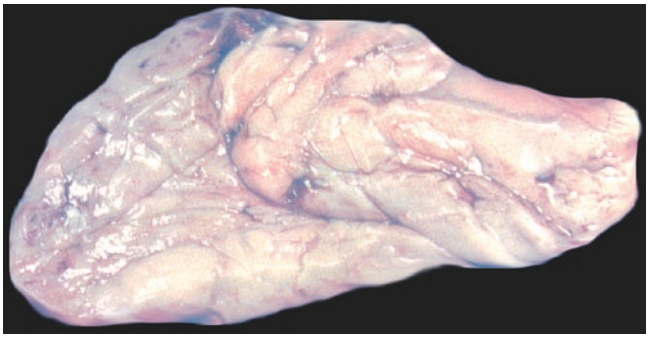

**Fig. 13.15** Gross photograph of thymolipoma which is a large, lobulated, soft, and yellow tumor. Photograph courtesy Dr Mark R Wick, Department of Pathology, UVA School of Medicine

woman under hormonal influence and are completely resected with difficulty, as they usually infiltrate much beyond macroscopic borders [88]. Desmoid tumors are driven by alterations of the Wnt/APC/β-catenin pathway [89]; mutations in the gene-encoding β-catenin, *CTNNB1*, are highly prevalent in sporadic desmoid tumors. Therefore, the β-catenin is an important marker in the diagnosis of these tumors [90].

### 13.6.3.2 Vascular Tumors

#### Hemangioma

The hemangioma depicted in Fig. 13.25 occurred in a patient with massive facial hemangiomatosis. Among benign vascular tumors, several types of hemangioma variants (capillary, cavernous) have been described in the mediastinum or in the thymus. Tumor size ranges from a few centimeters to 20 cm. In the series by Moran and Suster, associated histological features included fatty metaplasia, fibrosis, smooth muscle overgrowth, and inflammation [91].

#### Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma comes under vascular tumors with intermediate malignancy. Endothelial tumors of intermediate grade (hemangioendotheliomas) are characterized by local infiltrative growth and rare metastases (Fig. 13.26). These tumors show a spectrum of features with cells having abundant eosinophilic cytoplasm showing prominent vacuolization and intracellular lumen formation, few mitotic figures and myxoid changes in the stroma or more pronounced cytologic atypia, increased mitotic activity, and necrotic areas [92, 93].

#### Epithelioid Angiosarcoma

Epithelioid angiosarcoma (EAS) is a high-grade vascular neoplasm [94] characterized by high-grade cytology, necrosis, and abundance of mitosis (Fig. 13.27). Among vascular tumors, blood lakes, proliferation of slit-like vessels, and prominent nucleoli favor EAS. In the EAS series from Anderson et al. [95] *CAMTA1* rearrangement was negative in all cases, whereas a WWTR1 complex abnormality was found in rare cases. In EAS, the positivity of at least one vascular marker is reported, which allows differentiation from primary thoracic epithelial malignancies. However, as a potential pitfall with epithelial tumors, 25% of EAS show keratin expression. With regard to a possible thymic origin, in two cases from a series of angiosarcoma of the anterior mediastinum, Weissferdt reported the presence of a thymic tissue rim at the tumor periphery [96].

### 13.6.3.3 Lymphangioma or Vascular Lymphatic Neoplasms/Malformations

#### Lymphangioma

Lymphangiomas are not considered true neoplasms but rather malformations of the lymphatic vasculature of

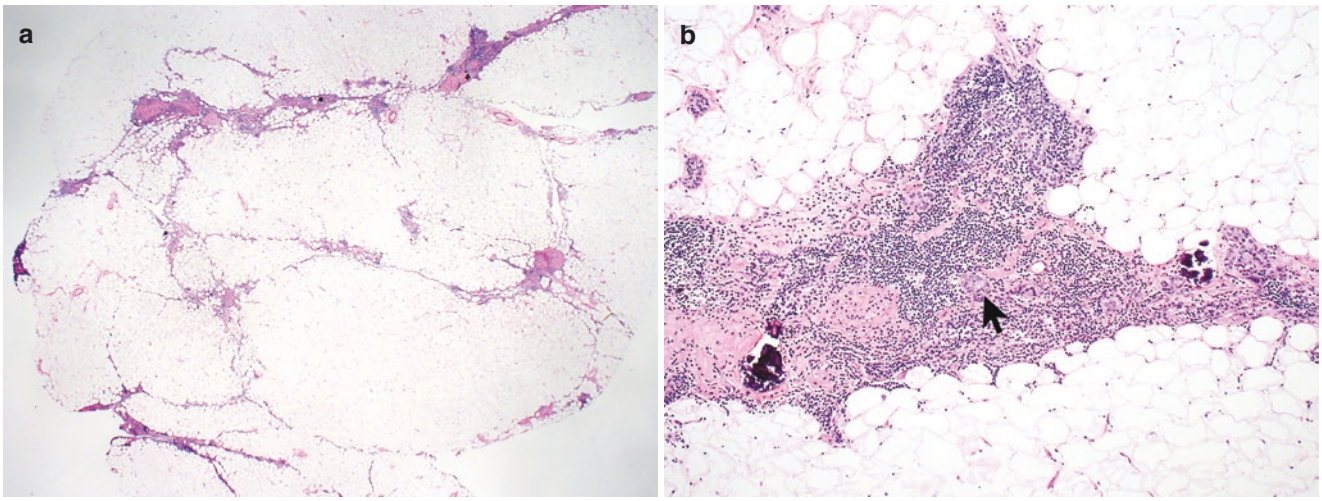


**Fig. 13.16** Thymolipoma. (**a**) At low magnification the lesion is largely comprised of benign adipose tissue intersected by strands of cellular and fibrotic tissue. (**b**) The intersecting tissue is comprised of small lymphocytes and usually small islands of bland-appearing epithelial cells (arrow). Calcified Hassall corpuscle are also present. Magnification ×12.5 (**a**), ×100 (**b**). Courtesy of Dr. Anja C. Roden (Mayo Clinic Rochester, MN, USA)

uncertain origin [97, 98]. A thymic example is shown here (Fig. 13.28).

#### Kaposiform Lymphangiomatosis

Mediastinal kaposiform lymphangiomatosis (KLA) is histologically similar to its soft tissue counterparts and is characterized by poorly circumscribed nodules of tightly packed small capillary-sized vessels, Kaposi sarcoma-like areas with spindled cells, and absence of human herpesvirus 8 (HHV-8) immunoreactivity. A component of larger lymphatic vessels is often seen (Fig. 13.29). These tumors are positive for CD31, CD34, and D2-40. In KLA, the spindle cells are distributed in sparse and poorly marginated clusters. Reported mediastinal KLA cases were usually seen in pediatric population, with almost equal sex distribution, and associated consumptive coagulopathy (Kasabach-Merritt syndrome) as a major cause of tumor-related fatality [99, 100].

## 13.7 Adamantinoma-Like Ewing Family of Tumors

The initial microscopic diagnosis of this case was that of thymic carcinoma with squamous cell differentiation and unusual expression of CD99. However, the translocation t(11;22) (q24;q12)*EWSR1-FLI1*$^{+}$ was found positive in tumor cells. This tumor shares the features of Ewing sarcoma (CD99 positivity, morphology of poorly differentiated component, and translocation) and squamous cell carcinoma (cytokeratin and squamous markers positive) (Fig. 13.30). This tumor is part of the Ewing family of tumors [80, 101, 102]. The t(11;22)(q24;q12) chromosomal translocation (*EWS-FLI1* gene fusion) is highly specific for ES/PNET, as >90% of the tumors show this gene rearrangement [103].

## 13.8 Germ Cell Tumors of the Mediastinum

The true incidence of mediastinal GCT is difficult to establish due to the rarity of these tumors, the scarcity of large series published, and the variable criteria chosen to consider this tumor group. The anterior mediastinum and retroperitoneum constitute the main sites of extragenital GCT development. It has been suggested that the GCT arise from ectopic germ cells diffused during embryogenesis [104] or that they derive from germ cells diffused through the body during embryogenesis to contribute to important regulatory, hematological, or immunological processes [70]. The hypotheses on the origin of extragonadal GCT have been extensively discussed by Oosterhuis et al. [105]. Recently the same researchers proposed a comprehensive developmental pathogenetic model for the origin of all GCT [106].

For a detailed description, the reader is referred to a recent review on GCT [71], other previous papers [107, 108], and on the data published by the 2015 WHO classification of tumors of the lung, thymus, and pleura [14].

1. Immature teratoma with embryonal carcinoma component of the mediastinum: two biopsies from the mass of a young man are shown. In the small first sample (surgical biopsy tissue) structures of different epithelial differentiation (glandular and squamoid) in a highly cellular undifferentiated stroma suggested immature teratoma (Fig. 13.31a). The second sample contained only small amount of tissue containing gland-like structures with numerous mitotic figures and karyorrhexis (Figs. 13.31b and 13.32). Immunophenotype of the cells of this sample corresponded to embryonal carcinoma. Mediastinal teratoma arising in the thymus has been reported and discussed elsewhere [109, 110].

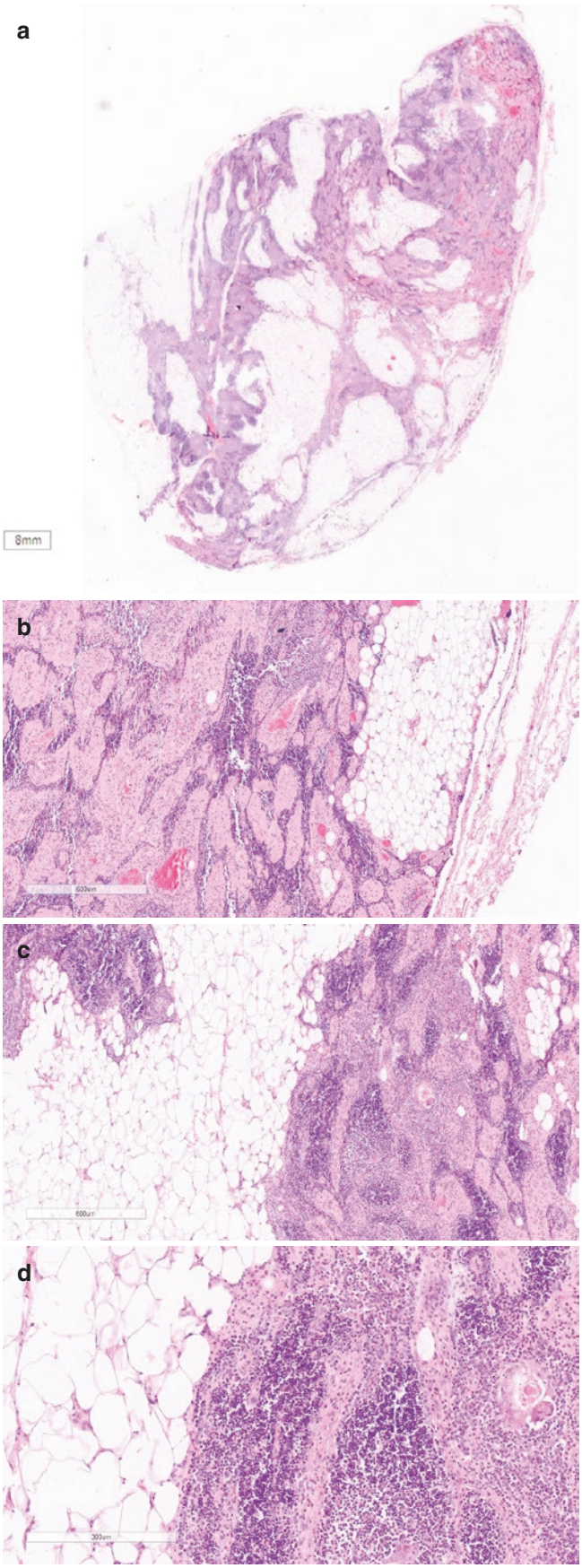


**Fig. 13.17** Another case of thymolipoma at low (**a**, **b**), medium (**c**), and high magnification (**d**)

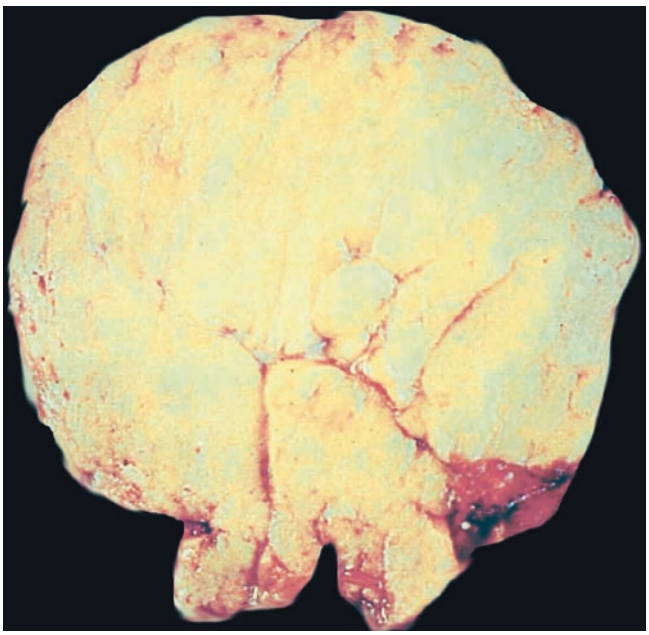

**Fig. 13.18** Gross photograph of angiomyolipoma. Photograph courtesy: Dr Mark R Wick, Department of Pathology, UVA School of Medicine

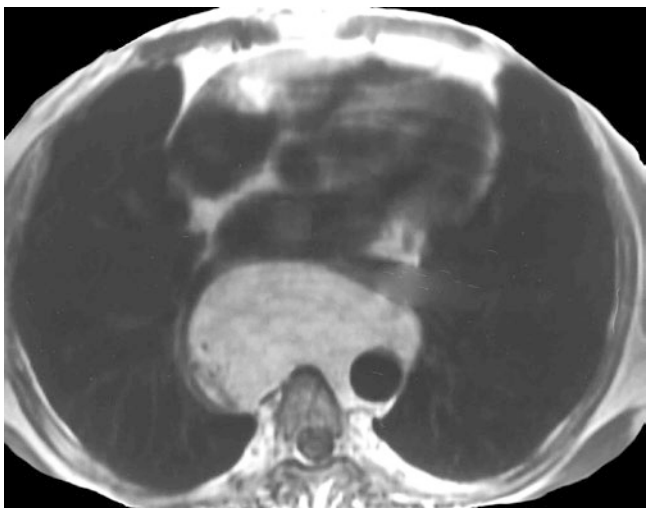

**Fig. 13.19** CT scan shows posterior mediastinal angiomyolipoma. Photograph courtesy: Dr Mark R Wick, Department of Pathology, UVA School of Medicine

2. Seminoma: case of a young man with a mediastinal tumor. A monotonous infiltrate composed of large lymphocyte-like cells with associated granulomatous reaction is seen. The neoplastic cells were PLAP, CD117, and D2-40 positive (Fig. 13.33). Several series of seminomas occurring in the mediastinum have been reported and discussed [111–113].
3. Yolk sac tumor: yolk sac tumor may present a variety of patterns including a pseudoadenocarcinoma pattern. Characteristic intracellular hyaline globules may be found in both yolk sac tumor and adenocarcinoma. A panel of immunohistochemical markers may allow the correct diagnosis. In this case the tumor cells were positive for

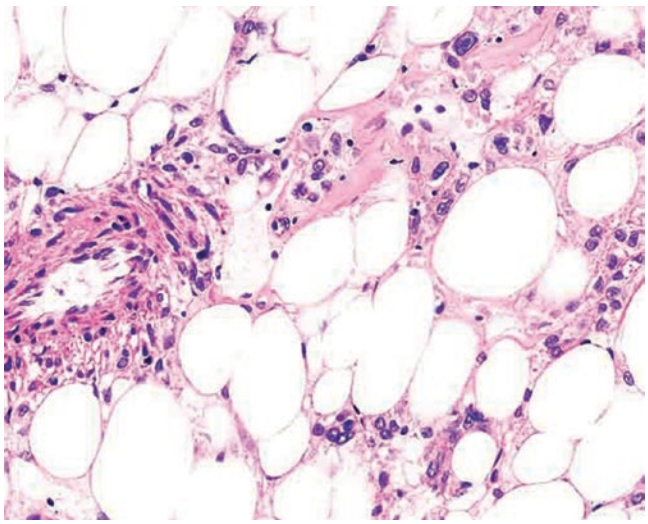

**Fig. 13.20** Angiomyolipoma: the photomicrograph shows admixture of adipocytes, ectatic vessels with smooth muscle proliferation. H&E, ×400

AFP (alpha-fetoprotein), negative for mucin, and positive for SALL-4 [113]. Markers for embryonal carcinoma and choriocarcinoma (CD30 and beta-H-CG) were negative (Fig. 13.34).

## 13.9 Metastases and Ectopic Tumors

### 13.9.1 Metastases

The incidence of thymic metastases from extrathymic tumors is difficult to establish, as at times perithymic lymph nodes are involved and thymus is secondarily involved by local extension of the disease. However, metastatic tumors in the mediastinum are very frequent [11]. Metastatic lung carcinomas involve the mediastinal lymph nodes more frequently than other tumors. Teratoma metastasized from the testis to the mediastinal lymph nodes is shown in Fig. 13.35. Melanoma metastasis has been also reported in the thymus (Fig. 13.36). Immunohistochemistry plays an important role in the identification or confirmation of the primary site [114]. The possibility of very unusual primary thymic neoplasms should also be considered, as primary thymic melanomas have been reported [115].

### 13.9.2 Ectopic Tumors

Among ectopic tumors, intrathymic ectopic parathyroid adenomas (Fig. 13.37) are reported. The occurrence of ectopic parathyroid tissue in the anterior mediastinum is rather

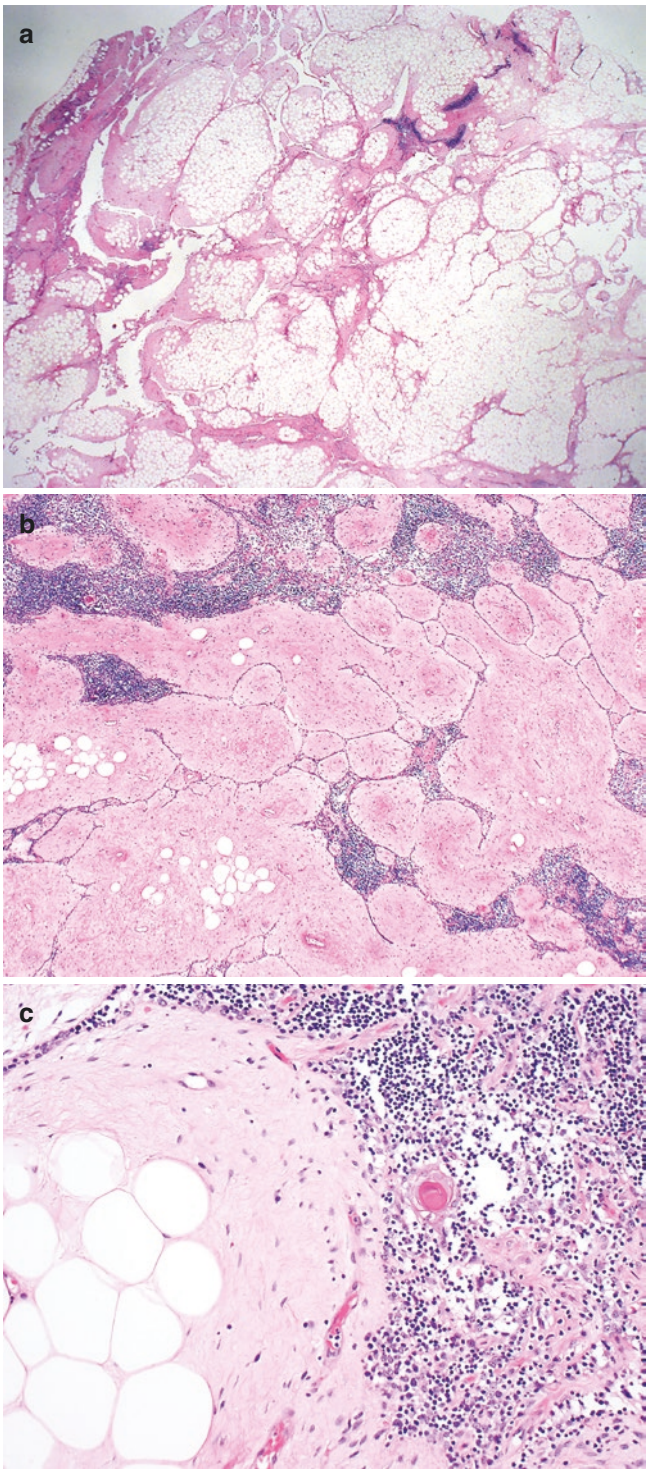


**Fig. 13.21** Lipofibroadenoma. (**a**) This lesion is comprised of benign adipose tissue intersected by strands of sclerosing fibrosis with a minimal cellular component. (**b**) In other areas the sclerosing and hyaline fibrosis is dominant with only small clusters of adipocytes and strands of cellular tissue. (**c**) The cellular areas are comprised of small lymphocytes, small vessels and some epithelioid cells. Hassall corpuscles are also present. Magnification ×12.5 (**a**), ×40 (**b**), ×200 (**c**). Courtesy of Dr. Anja C. Roden (Mayo Clinic Rochester, MN, USA)

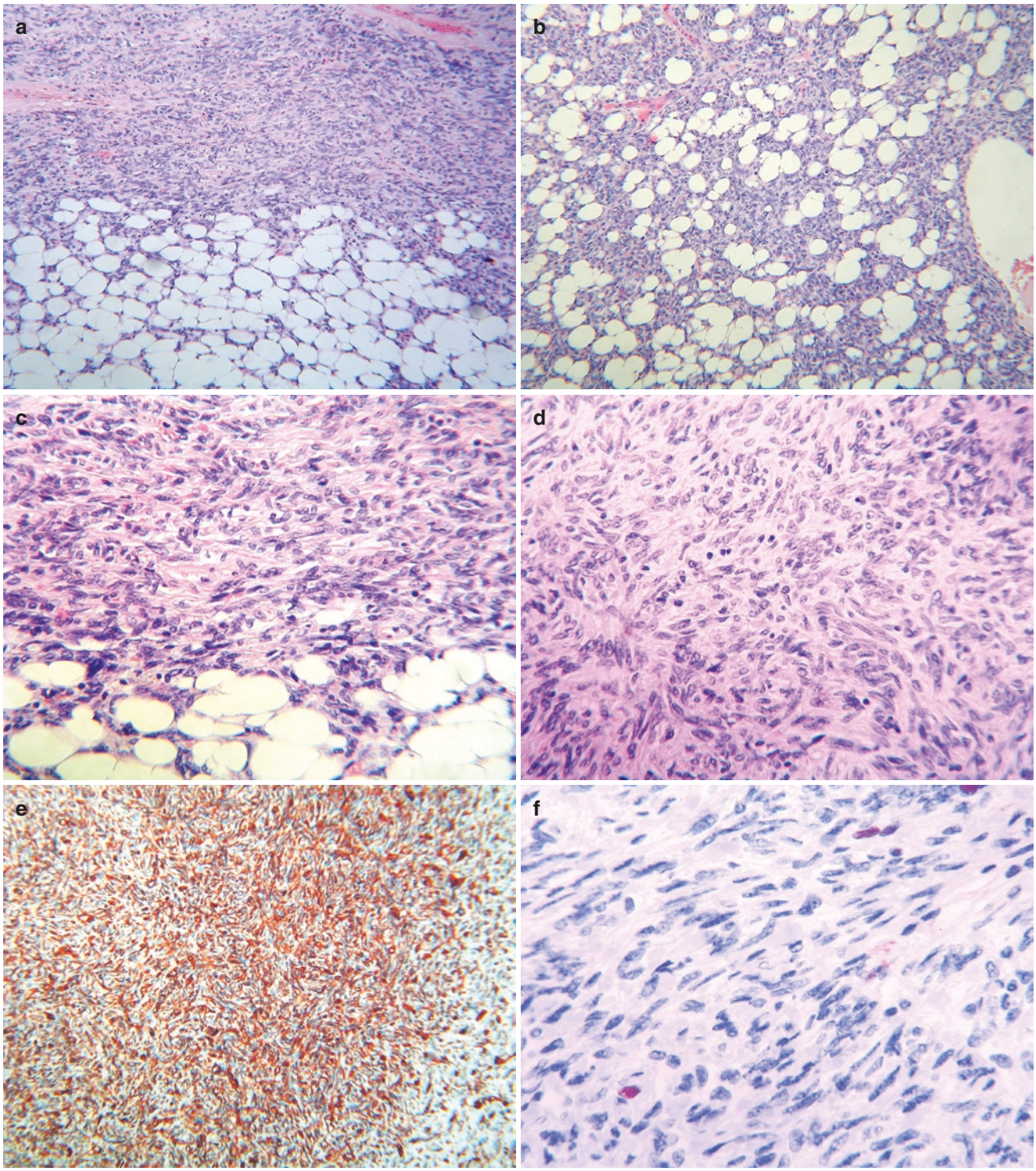


**Fig. 13.22** Solitary fibrous tumor (SFT) in a female, aged 63. SFT is a spindle cell intrathoracic tumor often derived from the stromal cells of the pleura and simulating a mediastinal tumor. SFT themselves cannot be regarded as "benign," as they are tumors of unknown malignant potential (or "potentially malignant"). (**a**) The tumor is composed of benign-looking spindle cells. In this case in several fields (**a**, **b**, **c**, **d**, H&E, respectively, 40×, 100×, 200×, 200×) no sign of malignancy was found; (**e**) CD34 stains the spindle cells as a characteristic finding in SFT (100×); (**f**) the KI67 stain highlights very few scattered nuclei (200×)

frequent and cases of parathyroid adenoma have been reported [116]. These ectopic tumors can be responsible for primary hyperparathyroidism. A case of primary juvenile sporadic hyperparathyroidism due to a parathyroid adenoma developing in a supernumerary fifth intrathymic parathyroid has been reported [117].

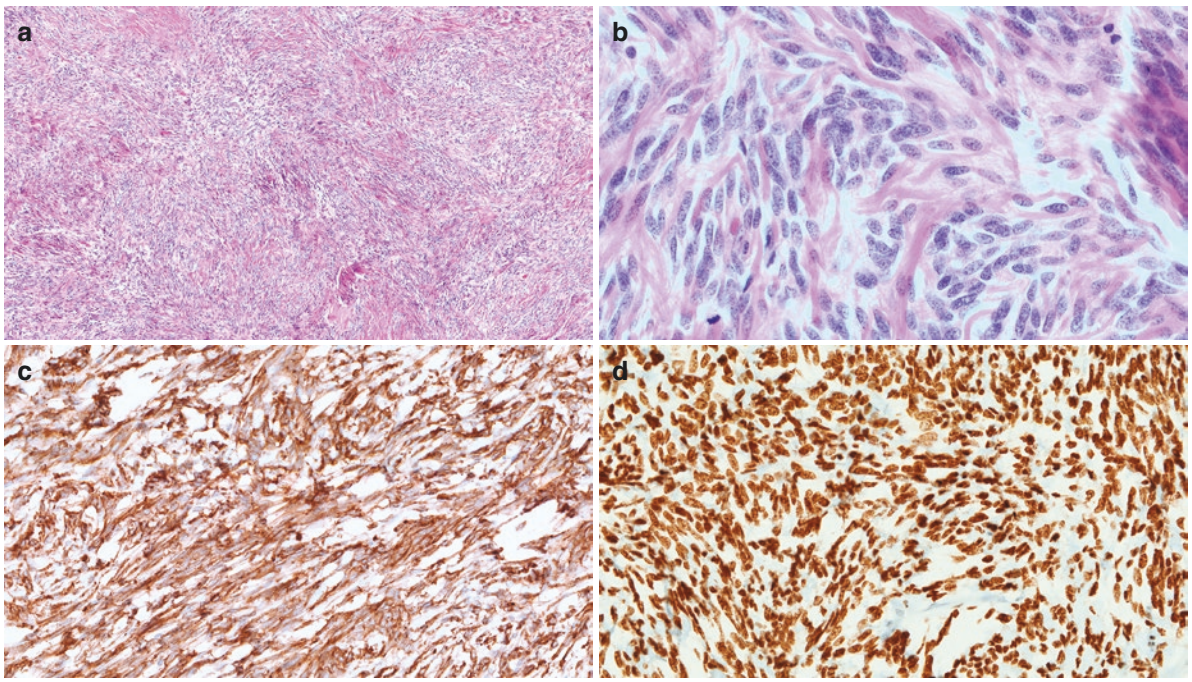


**Fig. 13.23** Malignant solitary fibrous tumor, female aged 65. According to WHO classification cellular-rich tumors with mitotic activity >4/10 HPF are named malignant SFT (MSFT). (**a**) Patternless architecture alternating hypocellular and hypercellular areas, 100×; (**b**) high magnification, 200×; two mitosis are seen; (**c**) CD34, 200×; (**d**) positive nuclear reaction for STAT-6, 200×. STAT6 stain is specific for SFT, as almost all SFT harbor an *NAB2-STAT6* fusion gene. S100 was also negative (not shown)

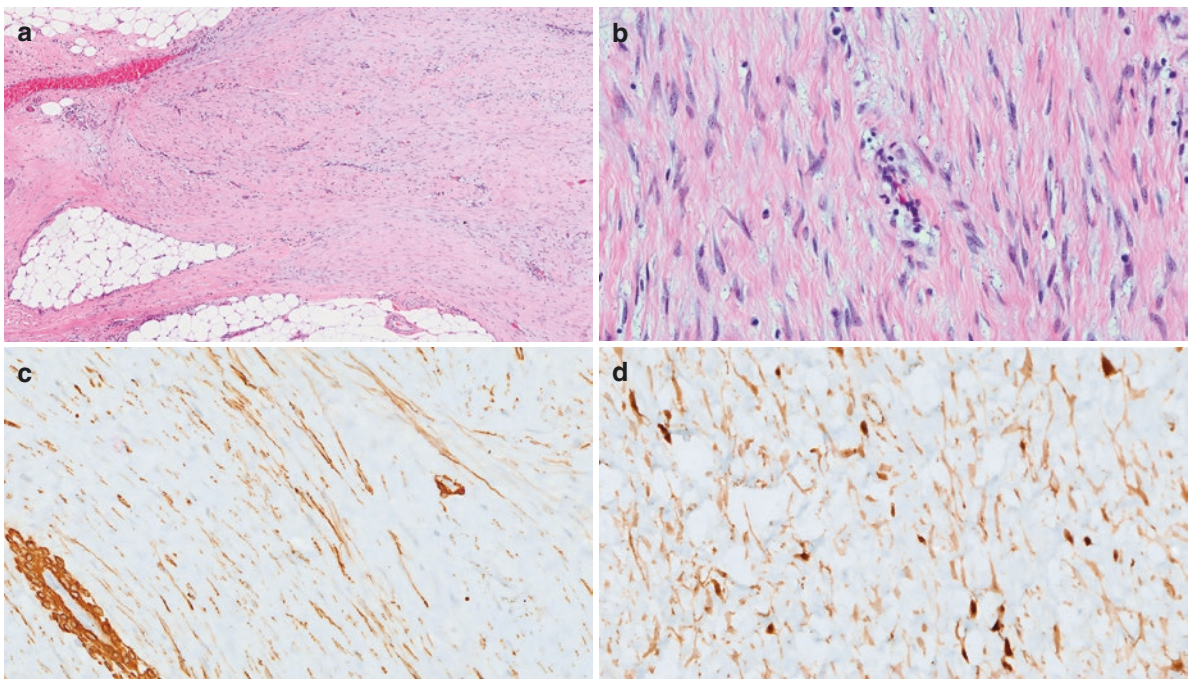


**Fig. 13.24** Desmoid tumor: female, aged 67. A tumor of the anterior mediastinum or pleura localized next to the pericardial sac without infiltration of the lung. Desmoids may resemble SFT. In the DD, IHC is decisive, as desmoids are positive for SMA and beta-catenin (nuclear reaction!) and may be positive for estrogen or progesterone receptors. The cells were also CD34 (-), CD99 (-), and Bcl-2 (-) (not shown). Despite "benign" cytology, prognosis is not good—desmoids usually infiltrate much beyond macroscopic borders. Complete resection is very difficult, so the tumors relapse many times but do not metastasize. (**a**) This tumor diffusely infiltrated fat tissue of the mediastinum, H&E, 40×; (**b**) spindle, bland-looking cells without atypia, mitotic activity, and necrotic areas. H&E, 200×; (**c**) cells were focally positive for SMA, 200×; (**d**) β-catenin, nuclear staining, 200×. Solitary fibrous tumors (SFT), differential diagnosis (DD), immunohistochemistry (IHC), smooth muscle actin (SMA)

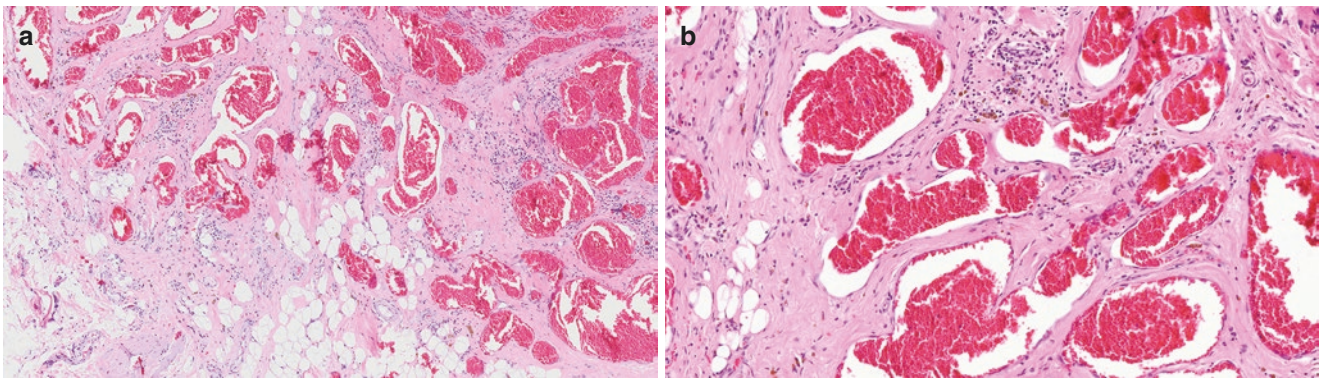


**Fig. 13.25** Hemangioma: female aged 73.This case occurred in a patient with massive facial hemangiomatosis and long-standing obstructive sleep apnea; the mediastinal tumor measured 2 cm in the largest dimension. The tumor was composed of vascular channels of different size, filled with blood, and lined by flat endothelial cells. The surrounding fibrotic stroma had hemosiderin deposits. (**a**) H&E, 100×; (**b**) H&E, 200×

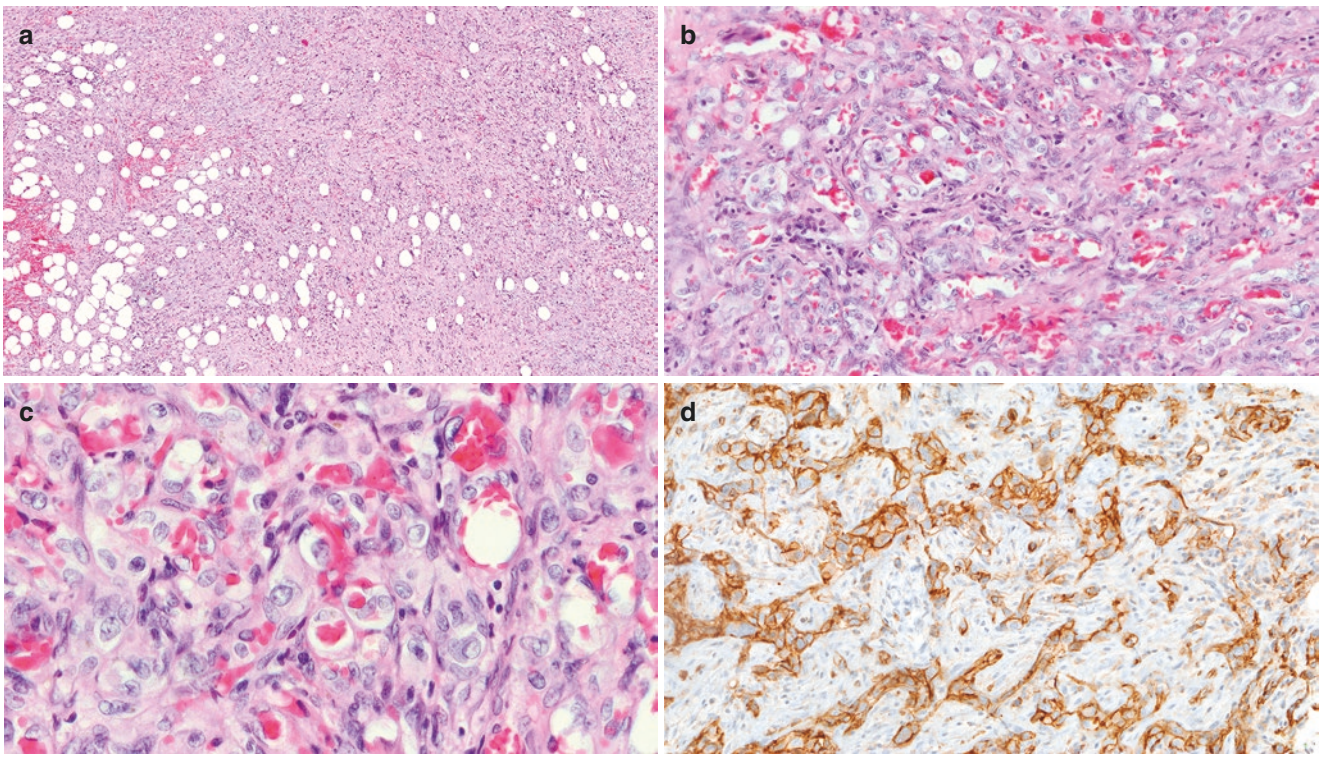


**Fig. 13.26** Hemangioendothelioma, epithelioid; female, aged 63. Tumor of mediastinum, 5 cm in the largest diameter, well-circumscribed, and encapsulated in MRI scans. Microscopic appearance on low magnification could suggest liposarcoma (dispersed adipocytic cells) but both higher magnification and immunohistochemistry results (CD31 +, CD34+, AE1AE3-, S-100 -, GLUT-1-, calretinin-) revealed that it was a vascular tumor. Atypia, diffuse, non-lobulated type of growth, elevated proliferation index, and negative reaction for GLUT-1 excluded hemangioma. Low mitotic index and lack of necrosis did not favor a diagnosis of angiosarcoma. Malignant pleural mesothelioma was considered in the DD but positive vascular markers and negative calretinin excluded this diagnosis. Proliferation index Ki-67 reached approximately 20% (not shown). (**a**) Infiltration of fat tissue by atypical neoplastic cells is seen. H&E, 40×. (**b–c**) On the medium and high magnification numerous small capillaries surrounded by epithelioid cells and filled with erythrocytes may be appreciated. Despite nuclear atypia neither necrosis nor increased mitotic activity was found (1 mitotic figure/10 HPF): H&E, (**b**) 200× and (**c**) 400×. (**d**) CD31 stained all cell membranes, 200×. Magnetic resonance imaging (MRI), differential diagnosis (DD)

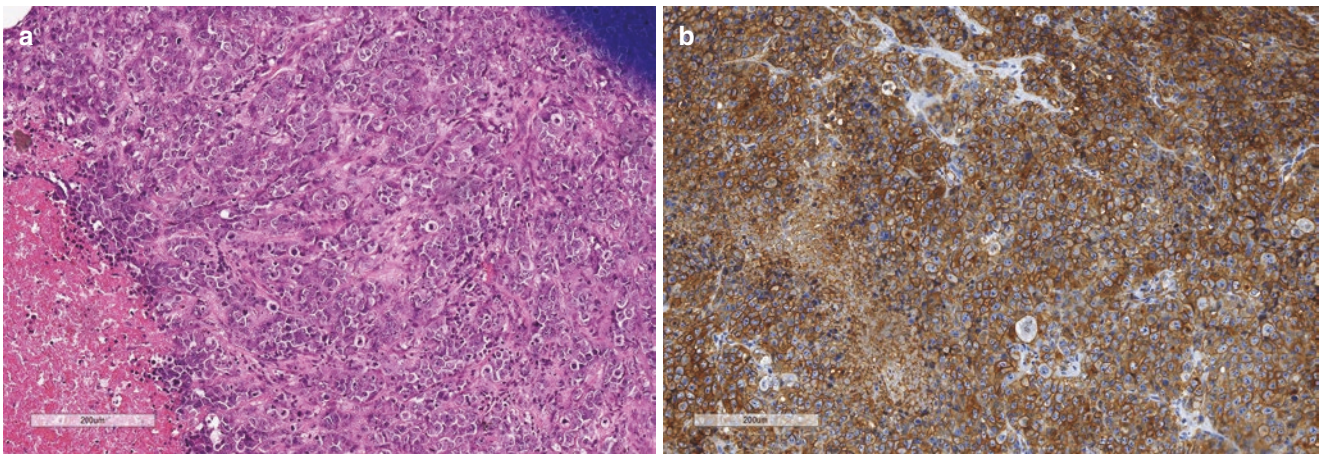


**Fig. 13.27** Epithelioid angiosarcoma with a mediastinal localization in a 28-year-old man. Epithelioid angiosarcoma is a highly aggressive endothelial cell origin tumor. Here pleomorphic epithelioid cells, with abundant eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli, are seen. CD34 positivity ranges in different series of epithelioid angiosarcoma. Factor VIII, CD31, Fli-1, and vimentin are usually also positive. Pancytokeratins may be also positive—(**a**) H&E, 200×, highly atypical cell population, necrosis; (**b**) CD34 positivity of neoplastic cells, 200× (adapted with permission from Ame Publishing Company) [32]

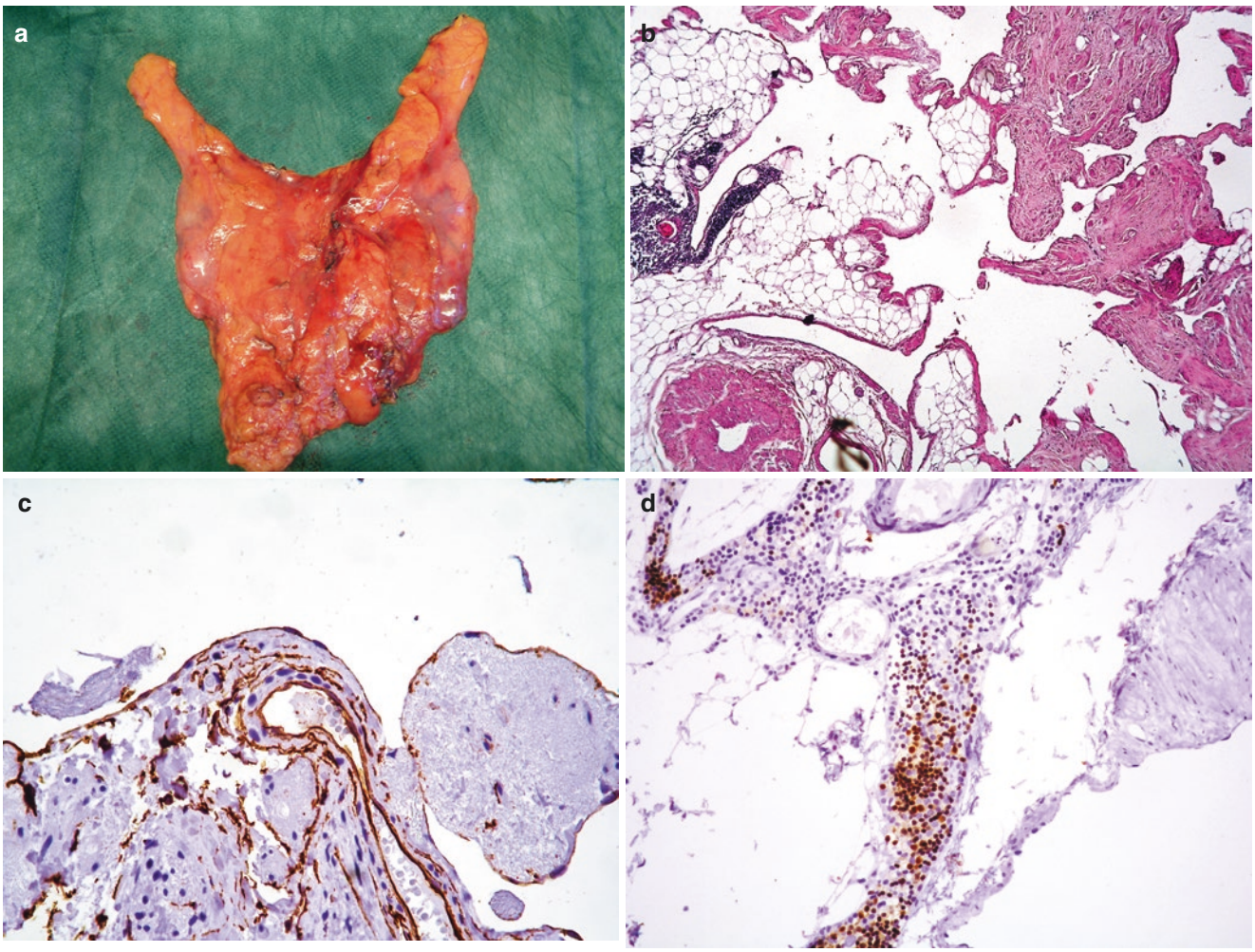


**Fig. 13.28** Lymphangioma. (**a**) Macroscopical picture of the tumor, recapitulating the thymus shape; (**B**) H&E stain of the tumor, 50×; (**c**) CD34 stain of lymphatic endothelium, 100×; (**d**) TdT positivity in thymic remnants, 100× (adapted with permission from Ame Publishing Company) [32]

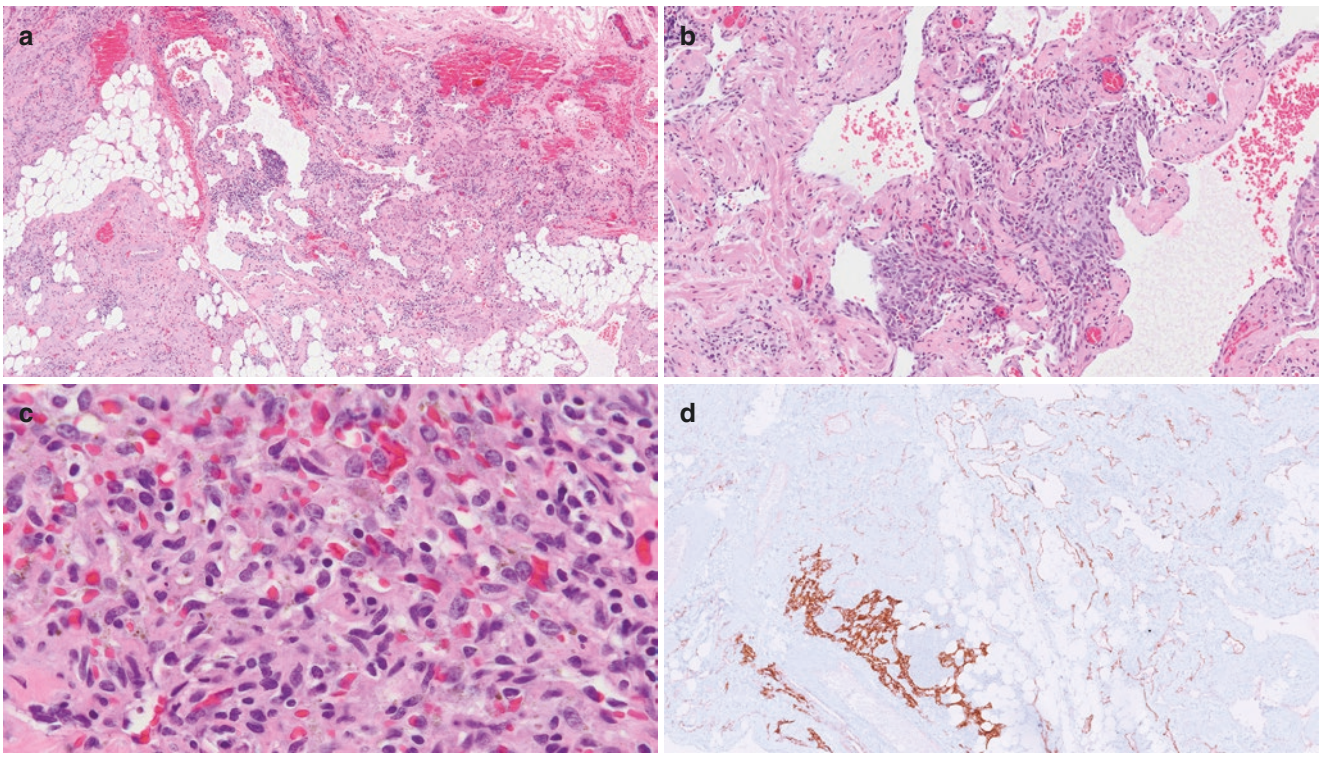


**Fig. 13.29** Kaposiform lymphangiomatosis (KLA): female, 21. Kaposiform lymphangiomatosis (KLA) is a newly classified clinicopathological entity—it is a variant of generalized lymphatic anomaly (GLA, previously named lymphangiomatosis) regarded as a malformation of lymphatic vessels with a concomitant failure of blood vessels, coagulopathy, and hemorrhages. The benign-looking spindle cells are positive for common vascular marker (CD34) and for markers of lymphatic endothelium: D2-40 or, e.g., PROX-1. Hemosiderin deposits are a proof of small hemorrhages. The tumor of mediastinum was associated to multiple additional lesions in the lungs and spleen and one osteolytic lesion in a sacral bone. The patient suffered from persistent cough and reported an episode of hemoptysis two years before admission to the hospital. Blood analysis revealed elevated D-dimer level (>14,000 ng/mL [reference value: <500 ng/ml]). (**a–b**) The tumor was composed of a number of dilated, thin-walled irregular vessels infiltrating the fat tissue. Vessels were either empty or filled with blood. (**a**) H&E, 40×; (**b**) H&E, 100×. (**c**) Small foci of spindle cells without atypia and mitotic activity could be found occasionally, representing endothelia of densely packed slit-like capillaries. H&E, 400×. (**d**) Both the endothelial cells covering dilated vessels and spindle cells forming capillaries were positive for D2-40 (and for CD34, not shown) (D2-40 40×)

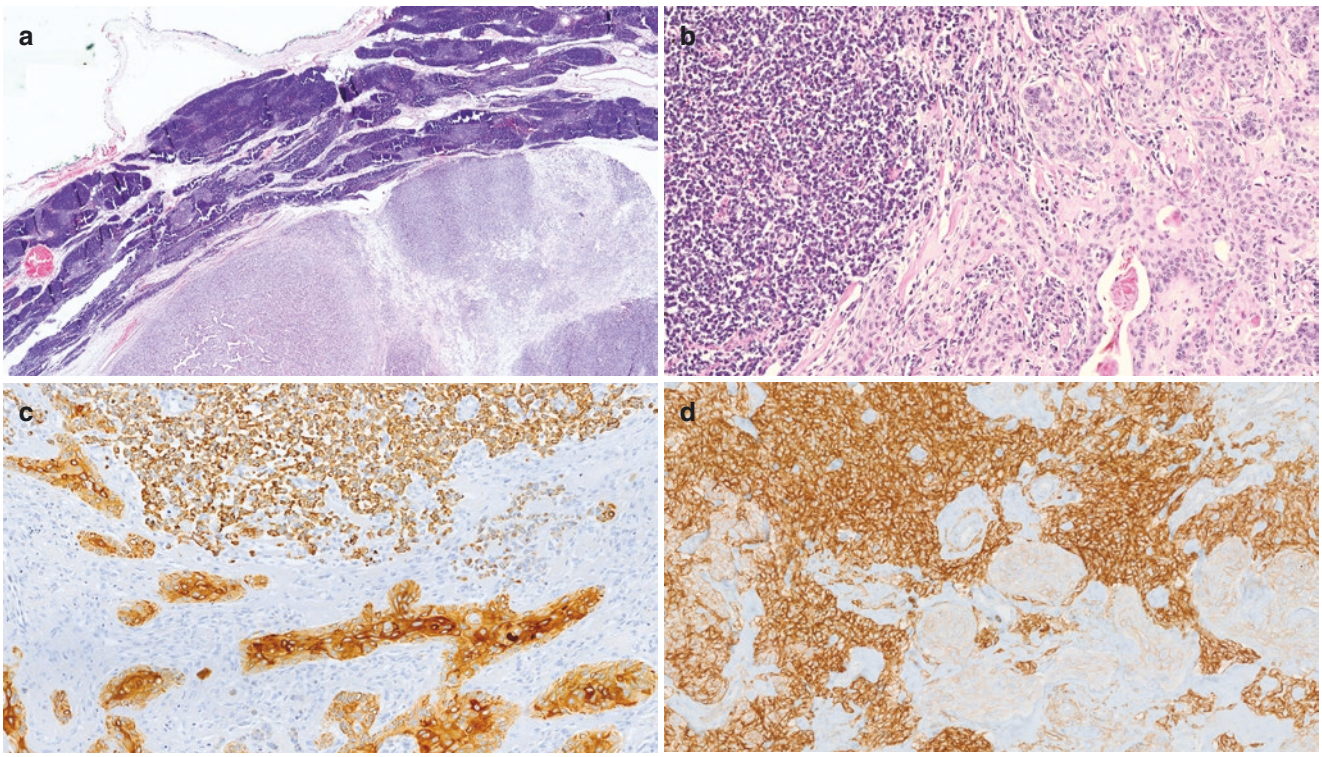


**Fig. 13.30** Adamantinoma-like EWS: female, 21. A tumor of anterior mediastinum, 12 cm in the largest dimension compressing the right lung. A right hydrothorax was additionally found. Initial symptoms were dry, persistent, exhausting cough and increasing breathlessness. The initial microscopic diagnosis was thymic carcinoma with squamous cell differentiation and unusual expression of CD99. The translocation t(11;22) in tumor cells was found by FISH analysis (Courtesy of: Andrzej Marszalek, MD, PhD, Department of Cancer Pathology and Prophylaxis, Poznan University of Medical Sciences, Greater Poland Cancer Center, Poznan, Poland). Low magnification of a thymus (upper left) with a well-circumscribed tumor (lower right). H&E, 10×. (**b**) The major component of the tumor was composed of small, blue, undifferentiated cells, but about 25% of the tumor revealed a squamous cell keratinizing component. H&E 200); (**c**) CK AE1/AE2 stain, all cells reacted. The reaction in squamous cell component was strong and diffuse (lower part) while the reaction in undifferentiated component varied according to the areas considered, 100× (**d**). All components were positive for CD99 but undifferentiated component showed distinct, strong reaction (left) while the reaction in squamous cell component was very weak (right). CD99, 100×. The NUT stain was negative (not shown). A tumor that shares the features of Ewing sarcoma (CD99, morphology of poorly differentiated component and translocation) and squamous cell carcinoma (cytokeratin and squamoid markers in immunohistochemistry) is classified as adamantinoma-like Ewing sarcoma. Currently Ewing sarcoma and PNET belong to the same group: Ewing family of tumors

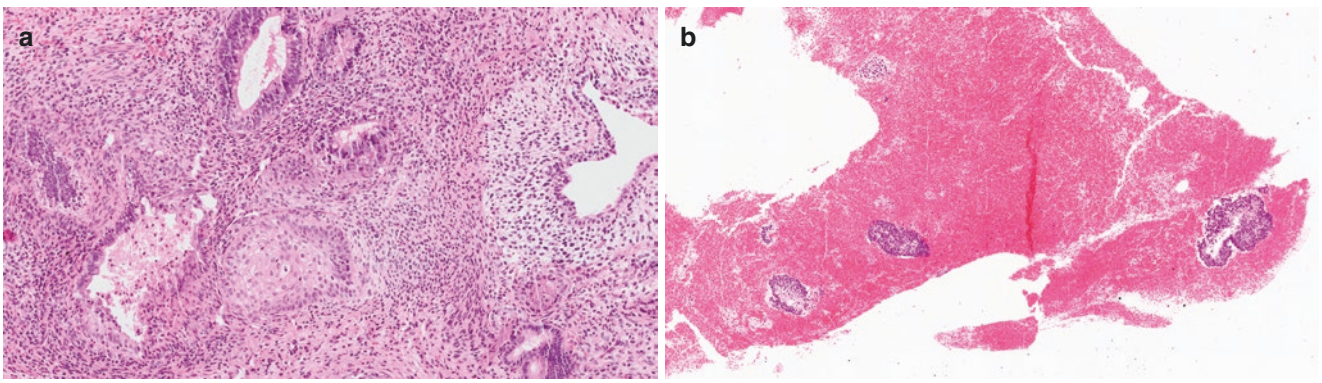


**Fig. 13.31** Teratoma with embryonal carcinoma component: male, 25. A tumor of anterior and superior mediastinum. Initial symptom was the persistent, paroxysmal cough. (**a**) One of the samples contained immature mesenchymal stroma with epithelial component of glandular and squamous cell type. The glands were CD30 negative. The first sample (**a**) contained the tissue with glandular formations lined by ciliated epithelial cells, focal squamoid differentiation, and highly cellular, undifferentiated stroma. The tissue with structures of different differentiation (glandular and squamoid) suggested an immature teratoma. H&E, 200×. The second sample (**b**) contained small amount of neoplastic tissue with glandular differentiation belonging to the embryonal carcinoma component, low power. H&E, 40×

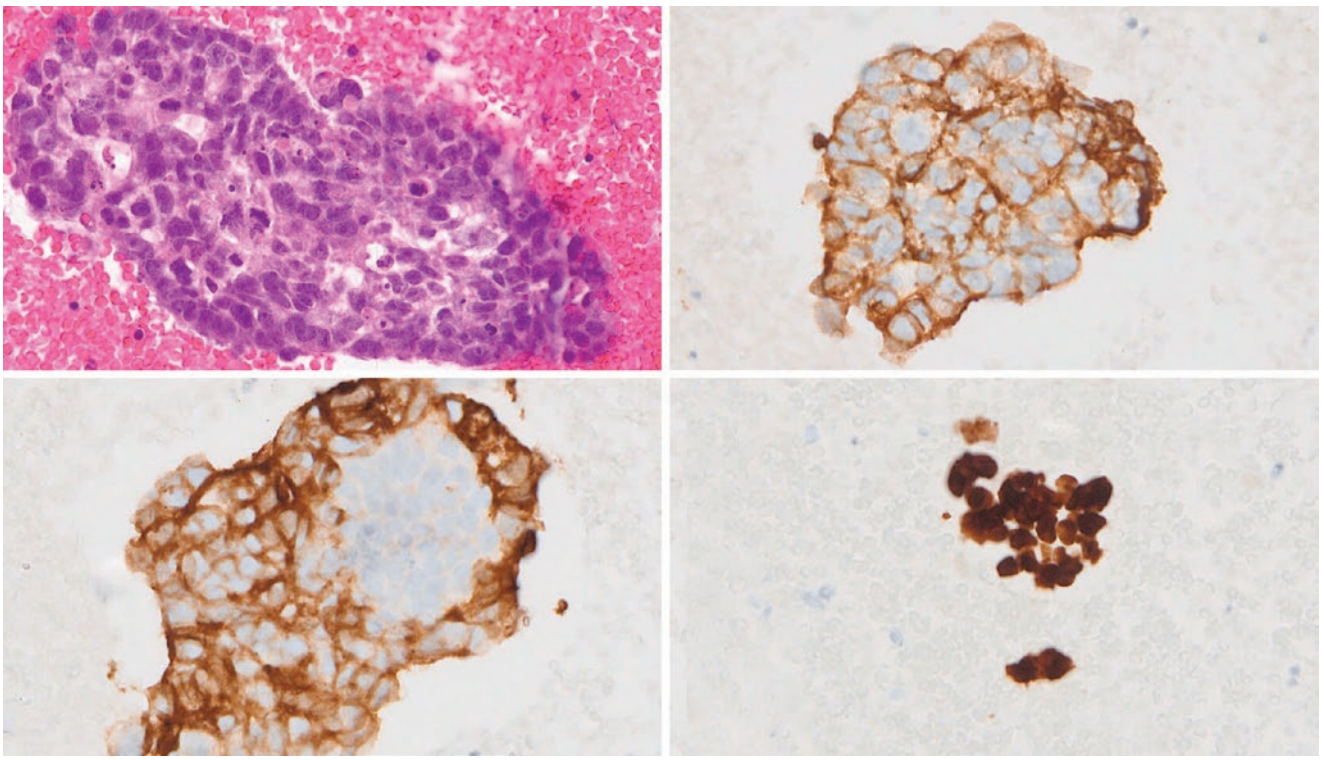

**Fig. 13.32** Teratoma with embryonal carcinoma component (same case as in Fig. 13.31): embryonal carcinoma characterization. In the context of clinical data (young man, aged 25) and of an immature teratoma, an embryonal carcinoma component has to be taken into consideration. Positive anti-cytokeratin, anti-CD30, and anti-SALL-4 reaction confirmed the diagnosis. The reaction anti-AFP was negative (not shown). High power of the glandular high-grade component, H&E, 200× (upper left). It was positive for cytokeratin (upper right), 200×, CD30 (lower left) (200×), and SALL-4 (lower right) (200×). Immunophenotype of the tissue corresponded to embryonal carcinoma

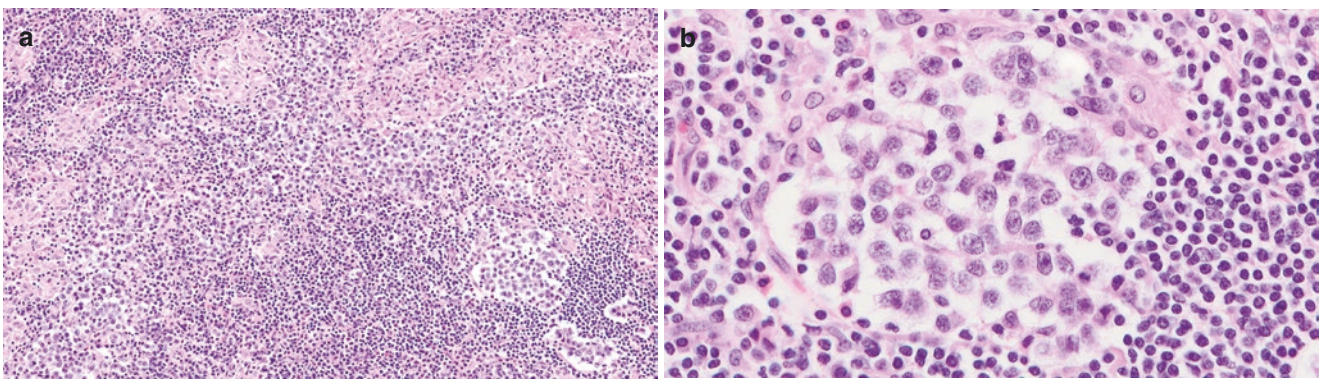


**Fig. 13.33** Seminoma: male, 26. A tumor of the anterior mediastinum found on CT scans performed due to the hemoptysis. The tumor measured up to 11 cm and was well-circumscribed. Neoplastic cells were loosely packed (**a**, H&E, 100×); at higher magnification neoplastic cells were surrounded by numerous lymphocytes; epithelioid granulomas were also seen (**b**, H&E, 400×). (**c**) Positive reaction for PLAP (200×). (**d**) CD117 (200×). (**e**) D2-40 (podoplanin) (200×). (Other staining not shown: CK PAN−, CEA−, AFP−, PAS+)

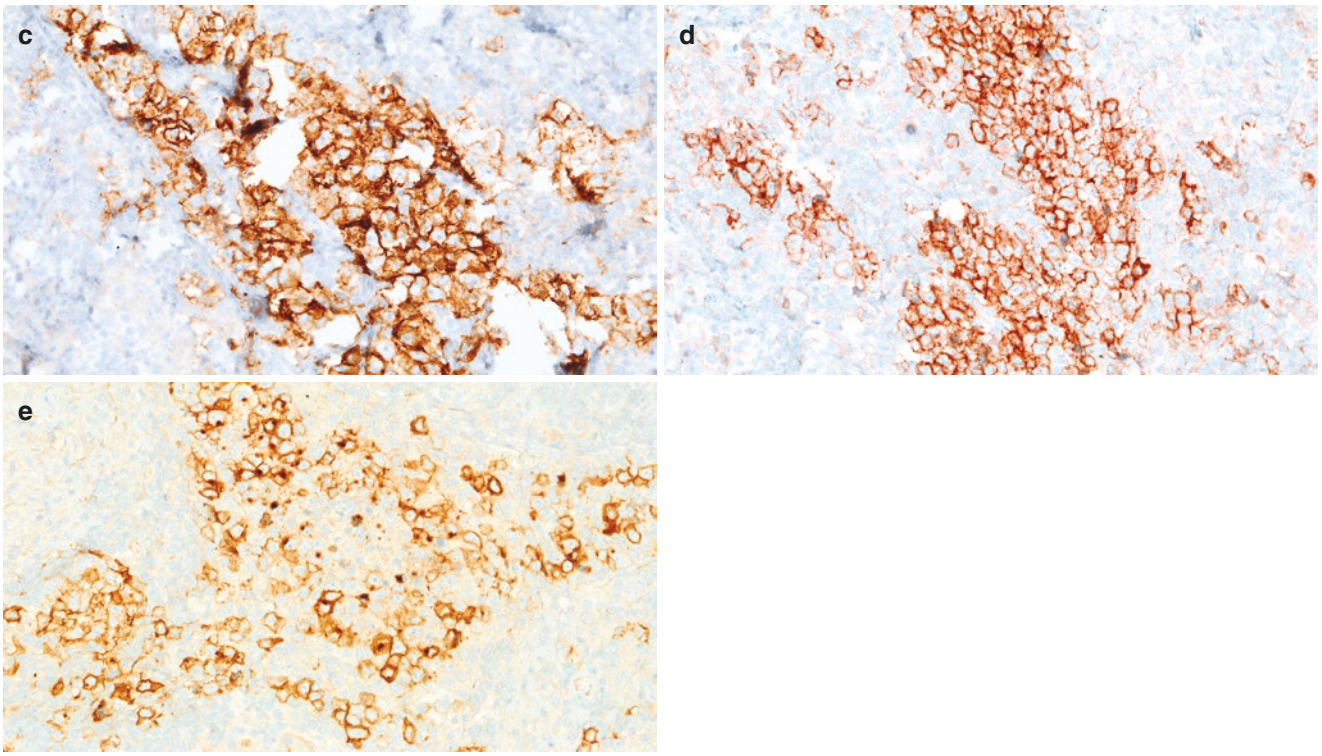


**Fig. 13.33** (continued)

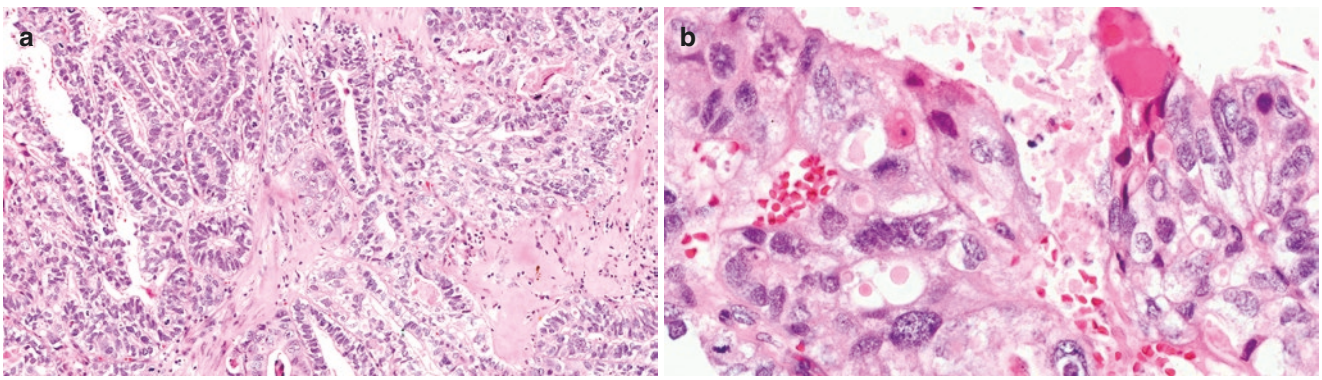


**Fig. 13.34** Yolk sac tumor: male, 19. Tumor of mediastinum and right lung hilum, 9 cm in the largest diameter. The tumor compressed SVC. AFP level in the serum was elevated. The tumor was resected after neoadjuvant chemotherapy. (**a**) Numerous pseudoglands lined by cuboidal cells with subnuclear vacuoles. This pattern may resemble secretory endometrium (H&E, 100×). (**b**) Solid area of a tumor with intracellular hyaline globules. H&E, 400×. (**c**) Positive reaction for cytokeratin in all neoplastic cells (AE1AE3, 200×). (**d**) Heterogenous but positive nuclear reaction for SALL-4 (200×); (**e**) reaction for AFP was positive in single cells. Hyaline globules were strongly accentuated (200×). (**f**) A certain number of cells revealed positive nuclear reaction for CDX-2 (CDX-2 200×). Yolk sac tumor may present very different features including pseudoadenocarcinoma pattern. Characteristic intracellular hyaline globules may be found in both yolk sac tumor and adenocarcinoma, but in this case they were positive for AFP (alpha-fetoprotein) and negative for mucin. The tumor cells were also positive for SALL-4, which is a good marker for germ cell tumors regardless of the subtype. There were no elements of teratoma. Elevated serum level of AFP was also strongly suggestive for yolk sac tumor. Results of other IHC tests: AE1AE3 (+), beta-catenin (−), TTF-1 (+ in singular cells), chromogranin (−), synaptophysin (−), PLAP (−), CDX-2 (+). Mucicarmine (+), PAS (+). Superior vena cava (SVC), alpha-fetoprotein (AFP)

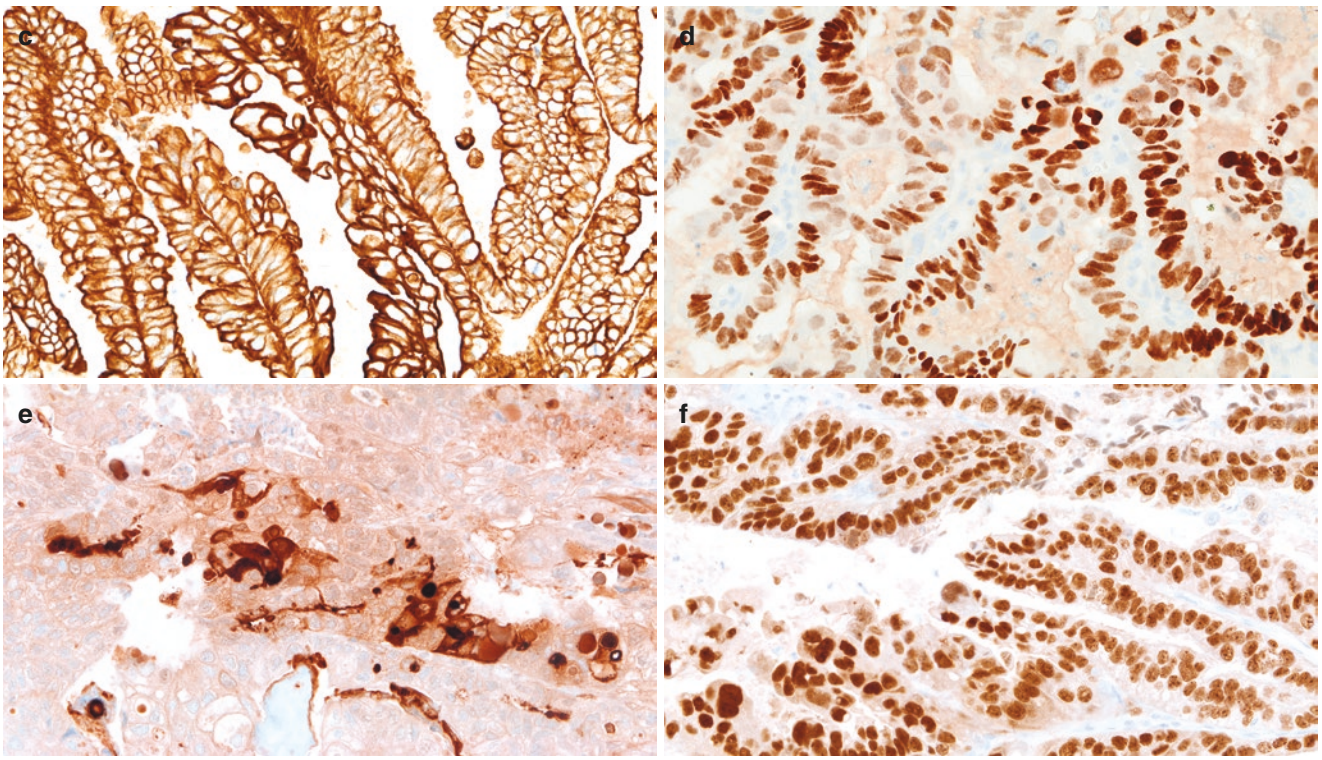


**Fig. 13.34** (continued)

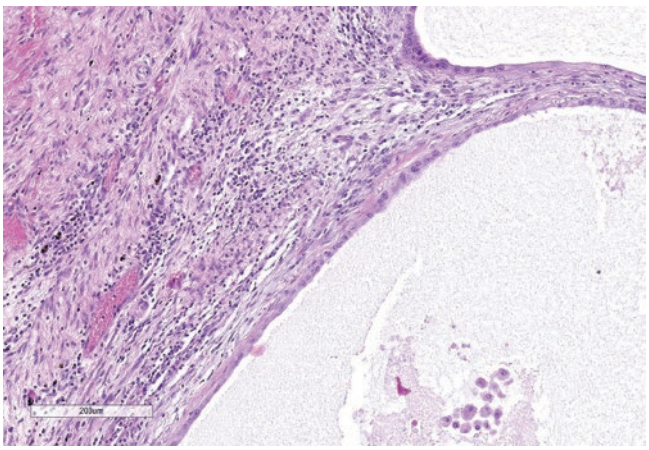

**Fig. 13.35** Testicular teratoma metastasis in a mediastinal lymph node, H&E, 100× (adapted with permission from Ame Publishing Company) [32]

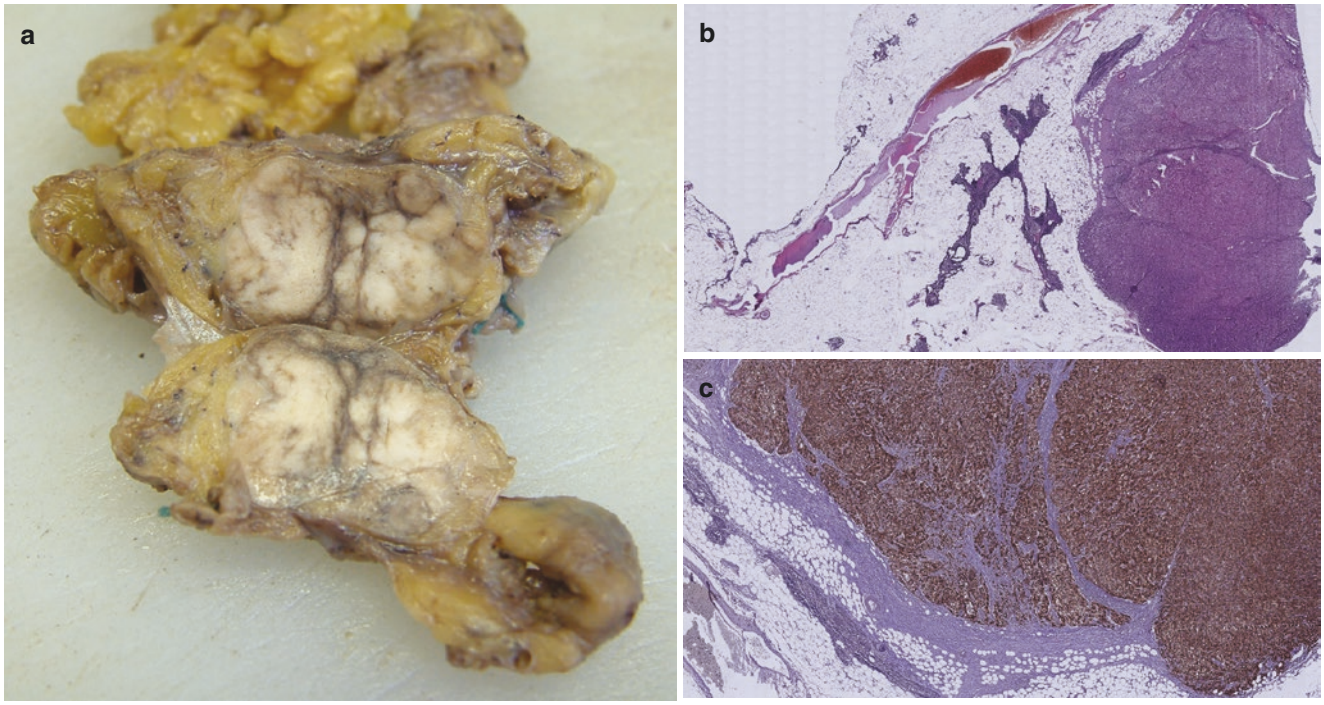


**Fig. 13.36** Melanoma metastasis in thymus: (**a**) thymic metastasis of melanoma, surgical specimen; (**b**) H&E, 50×, the melanoma metastasis is located in the thymic tissue; residual thymus is clearly seen also outside the tumor, on the left with respect to the metastasis; (**c**) melanoma metastasis in the thymus, HMB45 stain, 100× (adapted with permission from Ame Publishing Company) [32]

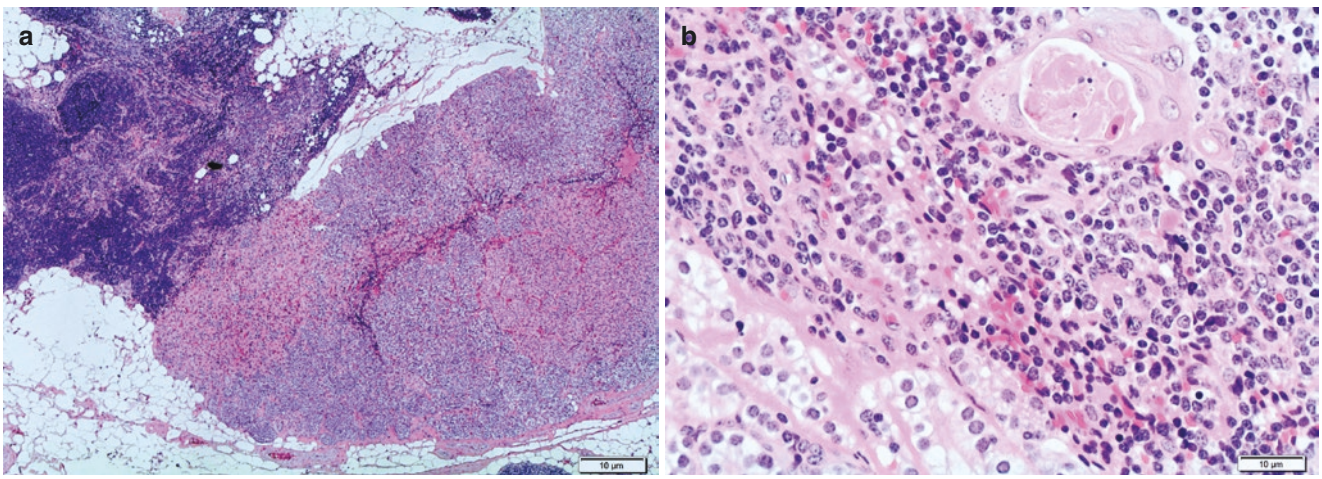


**Fig. 13.37** Intrathymic ectopic parathyroid adenoma: (**a**) at low magnification, the thymus is clearly seen (H&E, 40×); (**b**) a very rare image of intrathymic ectopic parathyroid adenoma: epithelial cells of the adenoma surround a Hassall corpuscle (H&E 200×)

## 13.10 Conclusions

Considering the examples shown here, which represent only a limited part of the infinite histotypes so far described, the diagnosis of tumors of the mediastinum requires experience and a multidisciplinary approach of pathologists and clinicians. Use of multiple immunohistochemical markers is essential to establish the correct diagnosis. Thoracic pathologists, pediatric pathologists, hematopathologists, soft tissue tumors pathologists, thoracic surgeons, and endocrinologists should contribute to this challenging field of diagnostics. Search for genomic changes/chromosomal translocations should also become part of the routine investigations in some cases. The referral to center of expertise in mediastinal/thoracic rare tumors and the recent development of networks in thoracic oncology (such as in Europe the network established in EURACAN) (http://euracan.ern-net.eu) is expected to provide better integration of diagnosis, clinical care, and research.

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**Conflicts of Interest** The authors have no conflicts of interest to declare.

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