Pathology of Thymic Carcinoma

9

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9.1 Introduction

Thymic carcinomas are rare and less common than thymomas. They usually occur in the prevascular (anterior) mediastinum. In general, they behave more aggressively than thymomas with high rates of metastases and recurrences even after resection (41–50%) [1, 2]. The median time to death ranges from 2 to 3.6 years, and 10-year survival ranges from 0 to 67% [3–5]. Most patients are diagnosed at high stage, Masaoka stages III or IV [1, 6], precluding primary resection [6]. Therefore patients commonly (38–44%) undergo neoadjuvant therapy [1, 6]. Complete resection has been reported in 21 to 87.5% [1, 2, 4–10]. Larger studies show that complete resection and lower Masaoka-Koga stage are associated with better overall survival [4, 5]. Moreover, although the National Comprehensive Cancer Network (NCCN) guidelines [11] recommend chemotherapy followed by surgery or more chemotherapy with or without radiation for locally advanced disease, only a proportion of thymic carcinomas responds to such therapy. For instance, in one study, complete pathologic response was only seen in 14% and rare viable tumor cells in 19% of thymic carcinomas after neoadjuvant therapy [12]. Other studies have not found complete pathologic response to neoadjuvant therapy in any thymic carcinomas and percent viable tumor ranged between 1 and 95% post-neoadjuvant treatment [13, 14].

Therefore, the pathologist is often confronted with a small biopsy of such a tumor before neoadjuvant therapy is initiated as is also recommended by the NCCN guidelines [11]. The distinction between thymic carcinoma and thymoma, specifically type B3 thymoma and occasionally even type A thymoma, can be problematic [15], particularly on small biopsies. In addition, differentiating between primary and metastatic disease can be a challenge as the morphology of thymic carcinomas resembles that of carcinomas elsewhere in the body. While thymomas are usually not subtyped on small biopsies given their potential morphologic heterogeneity, subtyping of thymic carcinomas on biopsies can be important as some subtypes behave overall more aggressively than others. In resection specimens tumor staging, resection margins, and subtype of thymic carcinoma are important to report for treatment and management of the patient. Furthermore, besides separately submitted lymph nodes, lymph nodes also need to be dissected off the main specimen and evaluated.

This chapter will address some of the challenges in the diagnosis of thymic carcinomas and their distinction from metastatic disease.

9.2 Epidemiology and Clinical Features

Thymic carcinomas are rare neoplasms, encompassing 2 to 28% of all thymic epithelial tumors [3] with an incidence of one to five cases per million population per year [16]. The median or mean age at diagnosis is 59.6 and 53 years, respectively, although the age range is wide (19–82 years) [1, 6]. There is a slight male predominance (56–62%). Most patients are symptomatic (52–86%) and most commonly present with chest pain, shortness of breath, and/or superior vena cava syndrome [1, 2, 7]. In contrast to thymomas, thymic carcinomas in general are not associated with a paraneoplastic syndrome [1, 6, 8]. Only occasional cases of thymic carcinoma associated with a paraneoplastic syndrome including myasthenia gravis, polymyositis, or dermatomyositis are reported in the literature [2, 7, 17, 18].

9.3 Gross Findings

Thymic carcinomas are often large with a median or mean size of 6 to 7 cm and 9.6 cm (range, 2–19 cm) [1, 2, 6, 7]. They commonly grow in an infiltrative pattern. Like other

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D. Jain et al. (eds.), *Atlas of Thymic Pathology*, https://doi.org/10.1007/978-981-15-3164-4_9

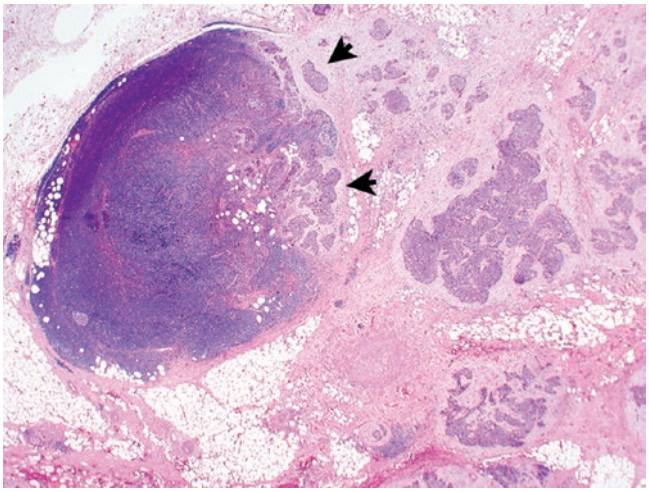

Fig. 9.1 A thymic carcinoma directly invades into a perithymic lymph node (arrows) corresponding to pN1 and at least stage IVA in the eighth AJCC/UICC TNM staging. Magnification ×20

carcinomas they have a firm cut surface with a heterogeneous appearance. They lack the lobulated gross appearance of thymomas. As the eighth AJCC/UICC staging (TNM classification) requires microscopic review of lymph nodes, these should be dissected off the resection specimens. Studies show that 27 to 46% of resected thymic carcinomas have lymph node involvement (Fig. 9.1) [1, 2, 19].

9.4 Histopathology

Thymic carcinomas are characterized by a distorted architecture (Fig. 9.2a). They lack the lobulation of thymomas. They usually invade into the surrounding adipose tissue (Fig. 9.2b) and sometimes into adjacent structures and organs. Often thymic carcinomas are comprised of sheets, nests, or sometimes single tumor cells in a background of a desmoplastic stromal reaction (Fig. 9.2c). In general, there is overt cytologic atypia and increased mitotic activity (Fig. 9.2d, e). Necrosis is commonly seen (Fig. 9.2f). Cystic changes might occur. In the background, there are various numbers of chronic inflammatory cells, specifically mature B and T lymphocytes. Clusters of TdT-positive thymocytes are not present.

Thymic carcinomas are morphologically subtyped according to the WHO (Table 9.1) [20]. While squamous cell carcinomas are usually the most common subtype of thymic carcinomas, many other subtypes are described in the mediastinum. The pathologist needs to be aware of these subtypes as some might be treated differently. The prognostic significance of various histologic subtypes of thymic carcinomas is still somewhat controversial in the literature. This might be, at least in part, due to the, in general, low number of cases in these studies. However, there is some suggestion that adenocarcinomas, "poorly differentiated carcinomas," clear cell carcinomas, NUT carcinomas, and lymphoepithelioma-like carcinomas have worse outcomes than squamous cell carcinomas and mucoepidermoid carcinomas [7].

Most studies show that stage is a prognostic parameter in thymic carcinomas. Patients with higher Masaoka stage have a worse prognosis, specifically Masaoka stage IV-patients having a worse overall survival and stage I and II patients having the best survival [2, 5, 7, 17].

As alluded to earlier, thymic carcinomas have no unique histopathologic features. Based on the subtype, their histologic features mimic carcinomas of the same subtype elsewhere in the body. Immunohistochemistry might be helpful in some circumstances (Table 9.2); however, ultimately, radiologic correlation and correlation with clinical history is important and usually required to exclude metastatic disease.

The distinction of thymic carcinomas, specifically well or moderately differentiated squamous cell carcinomas, from WHO type B3 thymoma or even type A thymomas can occasionally be challenging. The lack of clusters of thymocytes might be useful in the distinction of thymic carcinomas from thymomas; however, some B3 and A thymomas also lack thymocytes. Therefore, the absence of thymocytes is not specific to thymic carcinomas but their presence is indicative of thymomas. Furthermore, evidence suggests that a Ki-67 labeling index of over 14% of tumor cells only occurs in carcinomas and not in thymomas; a Ki-67 LI of ≤5% has not been seen in carcinomas [25]. However, many carcinomas have a Ki-67 labeling index between 5 and 14% and in these cases this measurement will not be useful to distinguish carcinoma from thymoma. Some studies have suggested that the expression of CD5 and/or CD117 might aid in the distinction of thymic carcinomas from thymomas. Studies comparing B3 thymomas with thymic carcinomas show that CD5, CD117, and monoclonal CEA are most specific for thymic squamous cell carcinomas with sensitivities of 67–84%, 77–90%, and 75%, respectively [26–28]. Only rare B3 thymomas have been reported to express CD5 or CD117 (6% and 17%, respectively, in one study) [27]. CD1a appears specific for type B3 thymomas, staining lymphocytes (thymocytes) in 87.5% of cases. Thymoproteasome subunit beta5t is expressed in B3 thymomas but not in thymic carcinomas; however, this marker is not widely available [27, 28].

In rare instances thymic carcinomas arise in thymomas [29]. If a thymic carcinoma and a thymoma are observed together, according to the WHO, the term "combined carcinoma" should be used and the carcinoma component should

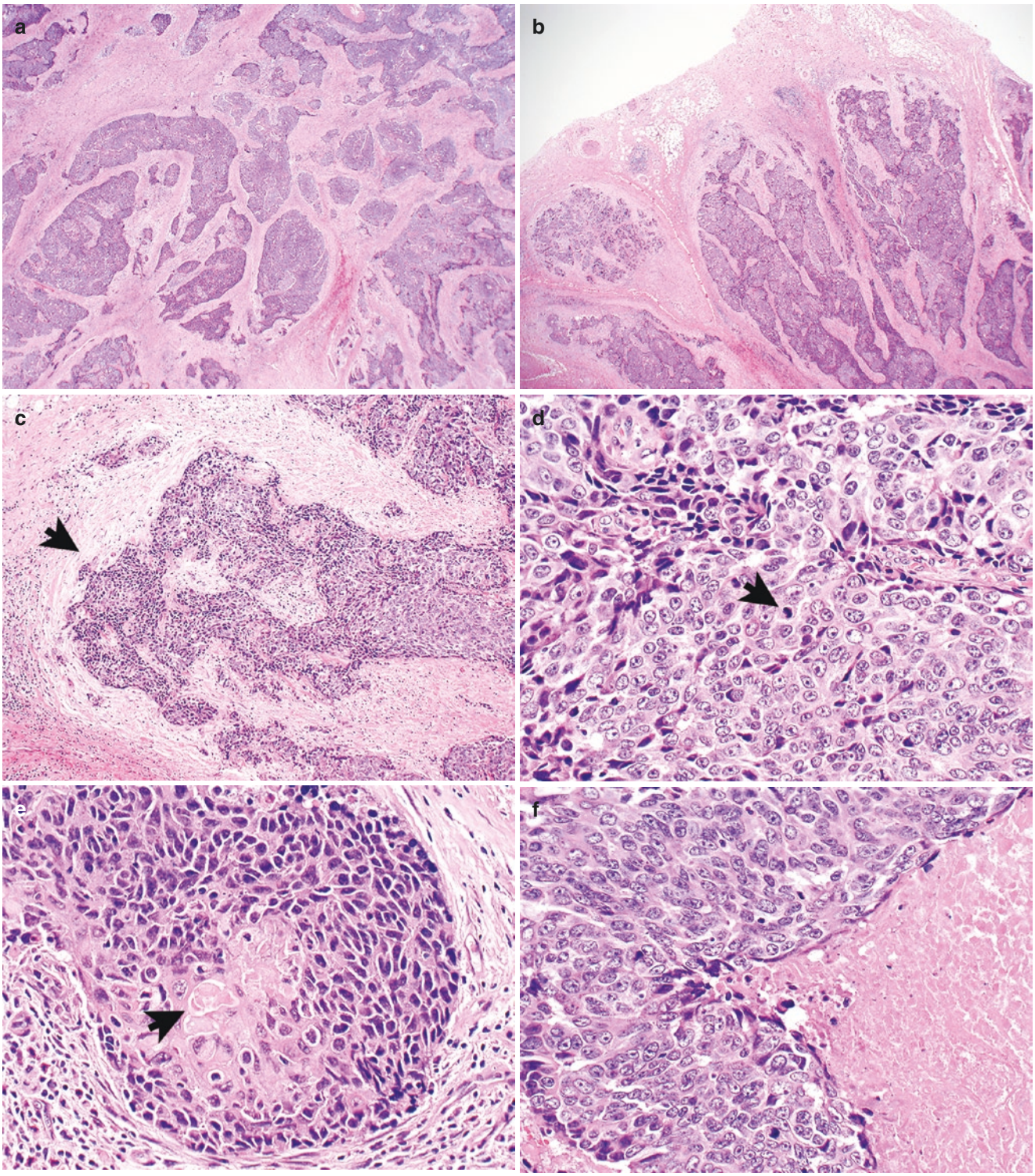

Fig. 9.2 Poorly differentiated squamous cell carcinoma. (**a**) Irregular nests and small sheets of tumor cells are growing in a fibrotic background. (**b**) The neoplastic cells are invading into the adjacent adipose tissue. (**c**) The tumor cells are in a desmoplastic stromal reaction (arrow). (**d**) The tumor cells exhibit high-grade cytology with conspicuous nucleoli. Increased mitotic activity (arrow) is noted. (**d**) The tumor cells have eosinophilic cytoplasm; foci of keratinization (arrow) are noted. (**e**) Areas of necrosis are present. (**f**) The tumor cells are positive for p40 supporting squamous differentiation. (**g**) The tumor cells coexpress CD5 (**h**) and CD117 (**i**) suggestive of thymic origin of the tumor which was confirmed by clinico-radiologic correlation. Magnification, ×12.5 (**a, b**), ×100 (**c**), ×400 (**d–i**)

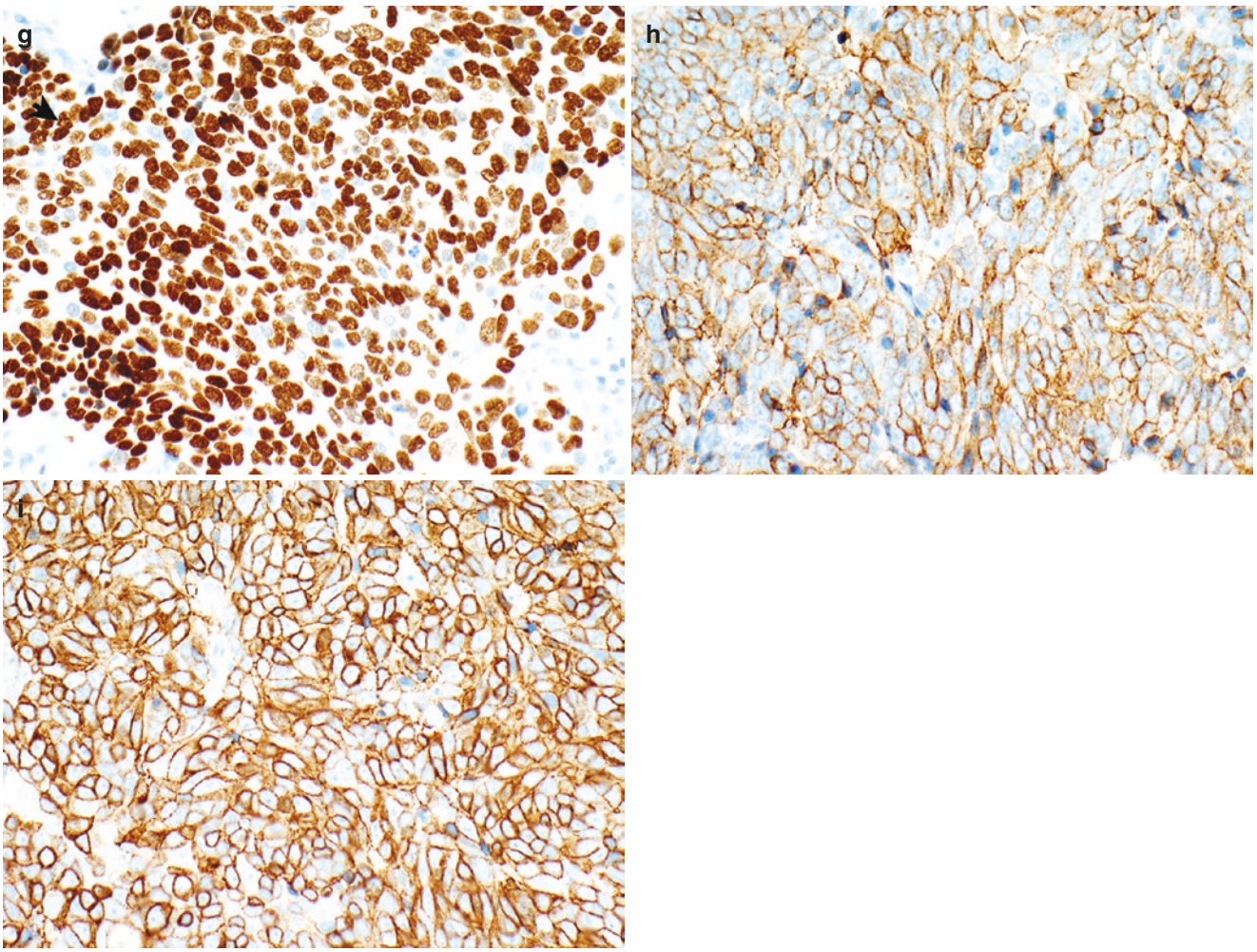

Fig. 9.2 (continued)

Table 9.1 WHO classification of thymic carcinomas [20]

WHO classification
Squamous cell carcinoma
Basaloid carcinoma
Mucoepidermoid carcinoma
Lymphoepithelioma-like carcinoma
Clear cell carcinoma
Sarcomatoid carcinoma
Adenocarcinoma
NUT carcinoma
Undifferentiated carcinoma
Other rare thymic carcinomas
Adenosquamous carcinoma
Hepatoid carcinoma
Thymic carcinoma, NOS
Combined thymic carcinoma

be reported first followed by the thymoma component(s) independent of the proportion of the carcinoma component [20]. The percent of each component should be estimated in 10% increments. Thymic carcinomas can also occur in combination with carcinoid tumors.

Table 9.2 Immunostains that might help to distinguish thymic carcinomas from metastases

Immunostain	Thymic carcinoma (% positive cases)	Non-lymphoid metastases (% positive cases)
CD5	20–100	0–34[a]
CD117	60–87	20–100[b]
CD5 and CD117 [21–23]	54–65	0[c]
CD205 [23]	52–76	4–27
FoxN1 [23]	59	13
PAX8 [23, 24]	0–69[d]	0–6[c,d]
PAX8 and CD117 [23]	69	0
PAX8 and CD5 [23]	46	0

[a]Adenocarcinoma of gastrointestinal tract, breast, lung, gynecologic organs, epithelioid sarcoma, mesothelioma, urothelial carcinoma; *clone dependent*

[b]Squamous cell carcinoma of lung, gastrointestinal stromal tumor, germ cell tumors

[c]Squamous cell carcinoma of the lung

[d]Clone dependent (0 for monoclonal PAX8, 58–69% [thymic carcinoma], and 2.4–6% [lung carcinomas] for polyclonal PAX8)

9.4.1 Squamous Cell Carcinoma

Squamous cell carcinomas are the most common thymic carcinomas encompassing 29 to 79% of all thymic carcinomas [1, 2, 4–8, 17]. Morphologically, they are similar to squamous cell carcinomas elsewhere. They can be keratinizing (Fig. 9.2e) or non-keratinizing. Necrosis is often identified (Fig. 9.2f). They usually express markers of squamous differentiation such as p63, p40 (Fig. 9.2g), desmoglein-3 (DSG-3), and CK5/6 [30] and coexpress CD5 and CD117 (Fig. 9.2h and i).

9.4.2 Basaloid Carcinomas

Basaloid carcinomas are unusual thymic carcinomas with basaloid features. Most of these tumors are incidentally discovered on imaging studies. Grossly, these are often multicystic tumors (Fig. 9.3a). Histopathology shows small- to medium-sized cells with rounded, occasionally elongated nuclei, scant cytoplasm, and inconspicuous or prominent nucleoli growing in cystic papillary-glandular or nesting growth patterns with peripheral palisading (Fig. 9.3b–d). Focal squamous differentiation and comedo-type necrosis

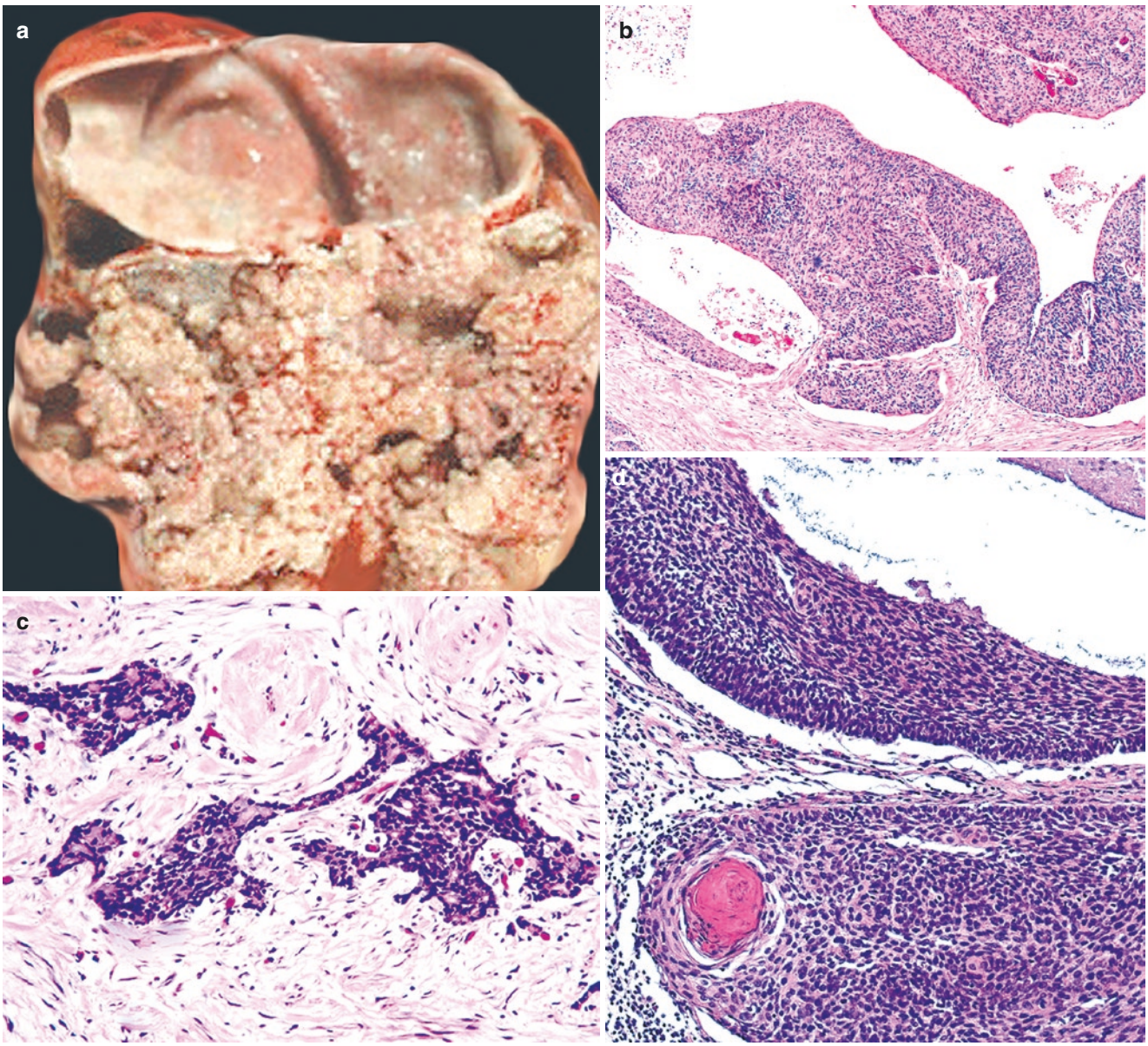

Fig. 9.3 Basaloid carcinoma. (**a**) Gross photograph shows an irregular lesion (lower half) associated with a cyst (upper half). (**b**) Medium-sized, oval to slightly elongated tumor cells are growing along a cyst wall. (**c**) Tumor cell nests are in a desmoplastic stroma. (**d**) Prominent peripheral palisading and focal keratin pearls are present. Magnification, ×100 (**b**), ×200 (**c**), ×400 (**d**). Figures are courtesy of Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

may be seen. Mitotic activity in general is low with up to four mitoses per 2 mm^2 although mitotic activity has been described up to 35 mitoses per 2 mm^2 [31, 32].

The tumor cells express pancytokeratin, and most cases also express CD117, p63/p40, and p53 (88%), an immunophenotype that makes the distinction from basaloid squamous carcinomas difficult [31]. These tumors are negative for TTF-1, S100, and synaptophysin.

9.4.3 Mucoepidermoid Carcinoma

Mucoepidermoid carcinomas are rare subtypes of thymic carcinoma. They morphologically resemble mucoepidermoid carcinomas in other organs (Fig. 9.4a). These tumors are comprised of epidermoid (squamous), intermediate, and mucus cells (Fig. 9.4b, c). According to the WHO, in the mediastinum, they are graded as low- and high-grade mucoepidermoid carcinomas dependent on the degree of cytologic atypia and mitotic activity [20]. As in other anatomic sites, there is a strong association between mucoepidermoid carcinoma and t(11;19)(q21;p13) (*MECT1-MAML2* fusion transcript) which is not observed in thymic squamous cell carcinomas or adenosquamous carcinomas [33].

The differential diagnosis of mucoepidermoid carcinomas includes adenosquamous carcinoma and adenocarcinoma; both can arise in the thymic gland/anterior mediastinum.

Other salivary gland-type tumors are even more rare in the mediastinum but can occur and should be considered in the differential diagnosis [34].

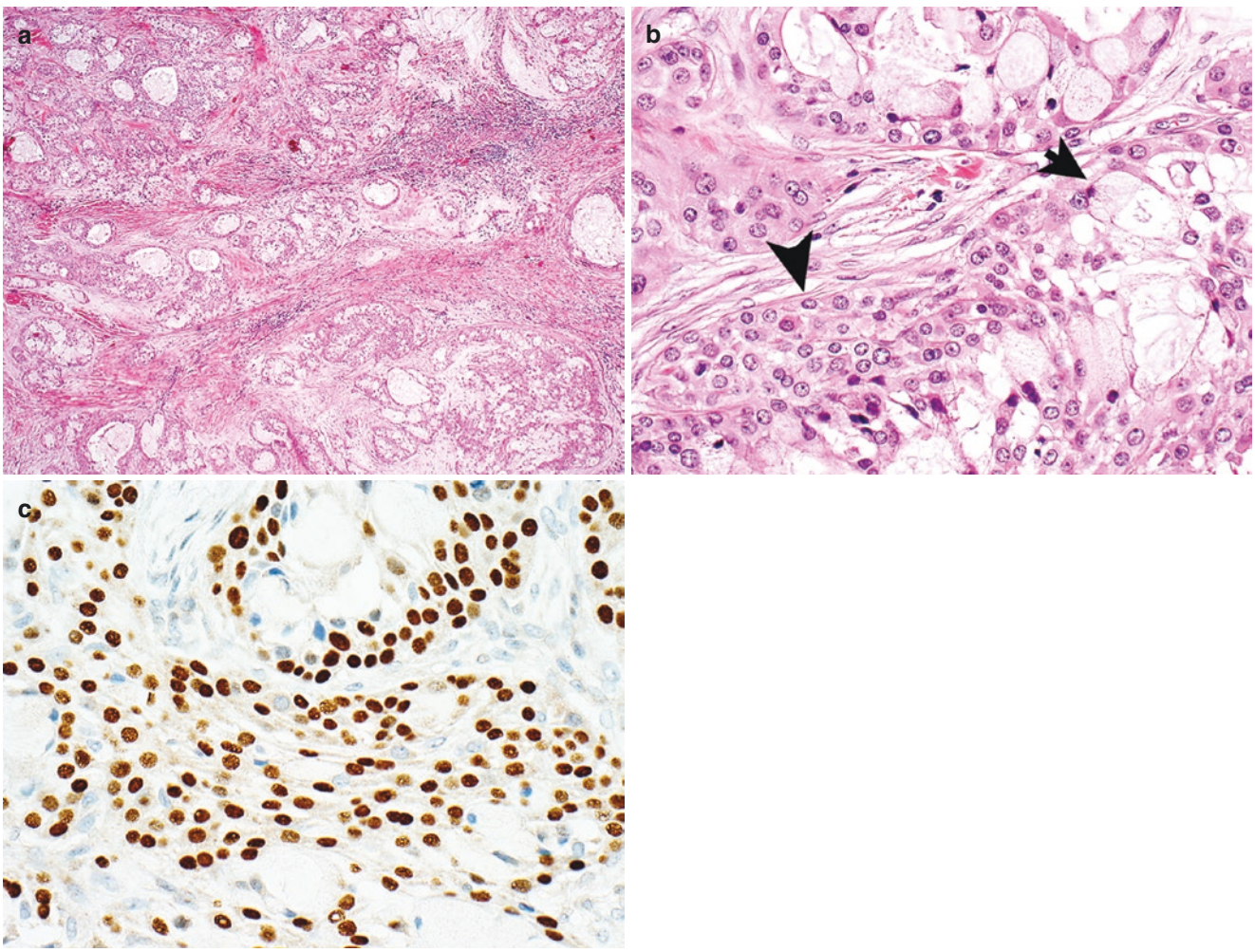

Fig. 9.4 Mucoepidermoid carcinoma, low grade. (**a**) The tumor is comprised of a glandular component and foci of solid tumor areas. (**b**) Tumor cells with cytoplasmic mucin (arrow) are intimately associated with epidermoid cells (arrowhead), the latter expressing p40 (**c**). Mitotic activity or cytologic atypia is not appreciated. The diagnosis was confirmed by *MAML2* rearrangement. Magnification, ×40 (**a**), ×400 (**b, c**)

9.4.4 Lymphoepithelioma-Like Carcinoma

The tumor is characterized by sheets, nests, and cords of cytologically high-grade epithelioid cells with cellular borders and prominent nucleoli (Fig. 9.5a, b). The tumor cells are often growing in a syncytial pattern. The background usually is characterized by a marked mixed chronic inflammatory infiltrate. However, occasionally, the chronic inflammatory infiltrate might be relatively mild. The tumor cells express keratin and frequently markers of squamous differentiation such as p40 and CK5/6 (Fig. 9.5c). Although many of the background lymphocytes are of T-cell phenotype, they are mature and do not mark with TdT. EBV in situ hybridization will help in the diagnosis of these tumors as approximately half of these cases are associated with EBV (Fig. 9.5d) [20].

Lymphoepithelioma-like carcinomas are very aggressive tumors [35]. They occur at a median age of 41 to 49 years old but the age range is wide (4–76 years). The estimated mean survival is only 16 months in 88% of patients [20].

9.4.5 Clear Cell Carcinoma

Clear cell carcinomas are very rare tumors comprising less than 3% of all thymic carcinomas. Due to their aggressive behavior and distinct histomorphology, they are classified as

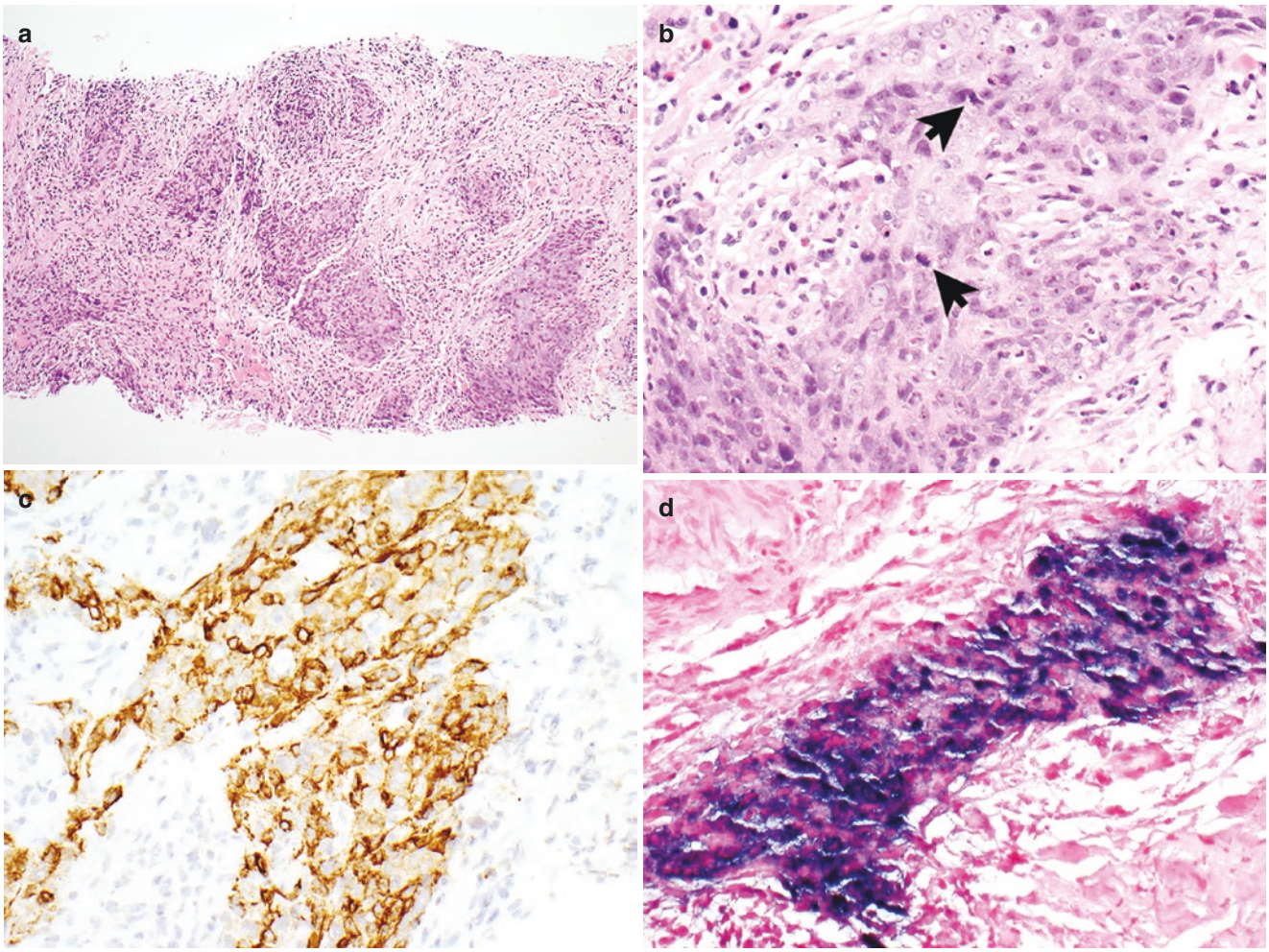

Fig. 9.5 Lymphoepithelioma-like carcinoma. (**a**) Irregular nests and small sheets of tumor cells are within a marked chronic inflammatory background. (**b**) The tumor cells are of high-grade cytology with a slightly streaming growth pattern and prominent nucleoli. High mitotic activity (arrows) is noted. The inflammatory background is comprised of lymphocytes, plasma cells, and scattered eosinophils. The tumor cells express CK5/6 (**c**) and are positive for EBV by in situ hybridization (**d**). Magnification, ×100 (**a**), ×400 (**b–d**)

a separate entity. On microscopy these tumors are characterized by fibrous and hyalinizing stroma analogous to hyalinizing clear cell carcinomas of salivary glands (Fig. 9.6) [36]. The tumor cells contain cytoplasmic glycogen which can be highlighted with periodic acid Schiff stain. These tumors are positive for markers of squamous differentiation such as p40 and CK5/6. An *EWSR1* translocation has been reported in these tumors; however, larger studies are required to confirm this finding and to establish their exact genetic abnormalities.

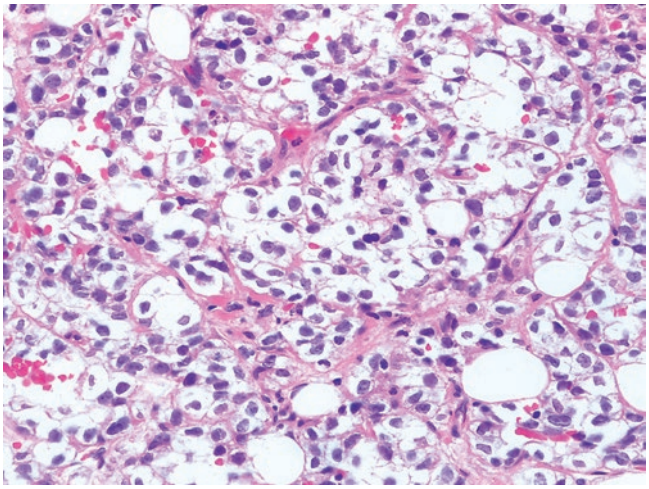

Fig. 9.6 Clear cell carcinoma. Large polygonal tumor cells have abundant clear cytoplasm and are embedded in vascularized and hyalinized stroma (not shown here). Magnification, ×400. Figure is courtesy of Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

9.4.6 Sarcomatoid Carcinoma

Sarcomatoid carcinoma is composed of sarcoma-like areas with possible heterologous components such as rhabdomyoblastic or cartilaginous differentiation (Fig. 9.7). The differential diagnosis of sarcomatoid carcinoma includes synovial sarcoma of the mediastinum [37]. Identification of t(X;18)(p11.2;q11.2), *SYT-SSX1*, or *SYT-SSX2* gene fusion can help to confirm the diagnosis of synovial sarcoma.

9.4.7 Adenocarcinoma

Thymic adenocarcinomas encompass 4 to 10% of thymic carcinomas (Figs. 9.8a–d and 9.9a, b) [1, 21]. They are morphologically similar to adenocarcinomas elsewhere and can be of mucinous, non-mucinous, or papillary morphology. Adenocarcinomas with signet ring cells or goblet cells also occur [21, 38]. The tumors in general express an intestinal immunophenotype including CK20 (Fig. 9.9c) and CDX2 (Fig. 9.9d) while being negative for TTF-1 and PAX8 (clone BC12). In addition, they expressed MUC2 and CEA. CK7 expression is variable (Fig. 9.9e) [21, 39]. Unlike in thymic squamous cell carcinomas, the combined expression of CD5 and CD117 might not be helpful to distinguish thymic adenocarcinomas from metastatic adenocarcinomas of the lung as approximately 4% of lung adenocarcinomas coexpress these markers (CD5 clone SP19, not provided in other reference) [22, 40].

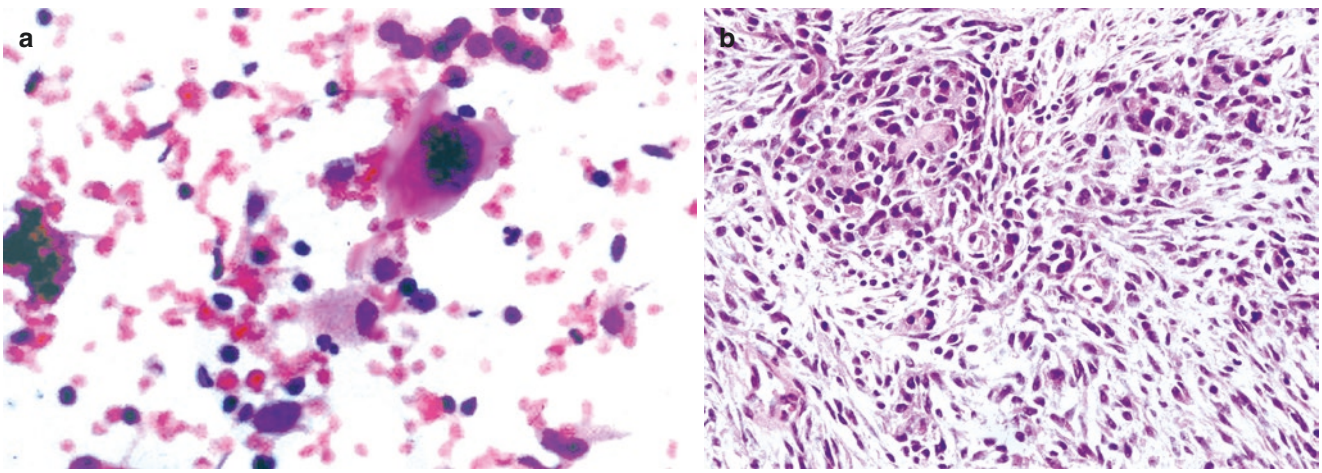

Fig. 9.7 Sarcomatoid carcinoma. (**a**) Cytology smear shows pleomorphic tumor cells (**b**) A biphasic sarcomatoid carcinoma shows spindle and epithelioid tumor cells. Magnification, ×400 (**a**), ×200 (**b**)

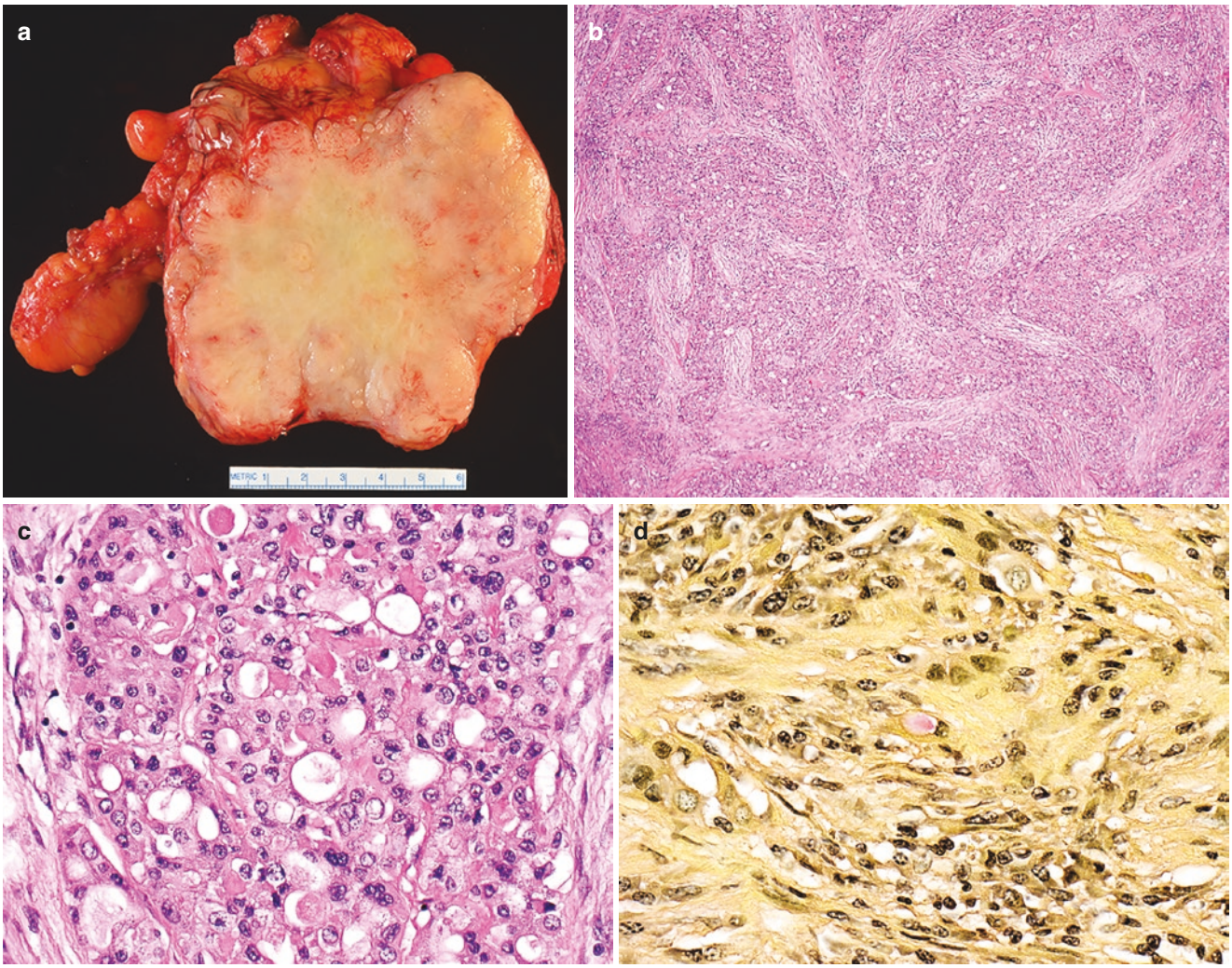

Fig. 9.8 Poorly differentiated thymic adenocarcinoma. (**a**) The cut surface shows an irregular tan mass. (**b**) Sheets and nests of tumor cells grow in a desmoplastic stromal reaction. (**c**) Vague gland formation is apparent. Occasional tumor cells contain cytoplasmic mucin which is confirmed by a mucicarmine stain (**d**). Magnification, ×40 (**b**), ×400 (**c**), ×600 (**d**)

9.4.8 NUT Carcinoma

NUT carcinomas are rare and very aggressive tumors [41, 42].

Morphologically they are characterized by sheets of undifferentiated but usually monotonous tumor cells that are characterized by round nuclei with open chromatin and conspicuous nucleoli (Fig. 9.10a, b). Mitotic activity and necrosis are readily apparent. Especially in larger specimens abrupt squamous differentiation might be identified (Fig. 9.10c, d).

Fifty-one to 67% of patients have metastases at time of presentation. The outcome of this tumor is usually fatal with a median overall survival of 4.7 to 6.7 months with only rare patients surviving for several years [43, 44]. These tumors have a midline predominance (90%) and occur most commonly in the thorax (57–67%) followed by head and neck. Patients with thoracic tumors present with pleuritic chest pain, nonproductive cough, shortness of breath, and/or weight loss. There is no sex predilection. The median age ranges between 16 and 50 years old but these tumors have been reported over a wide age range (0.1–78 years).

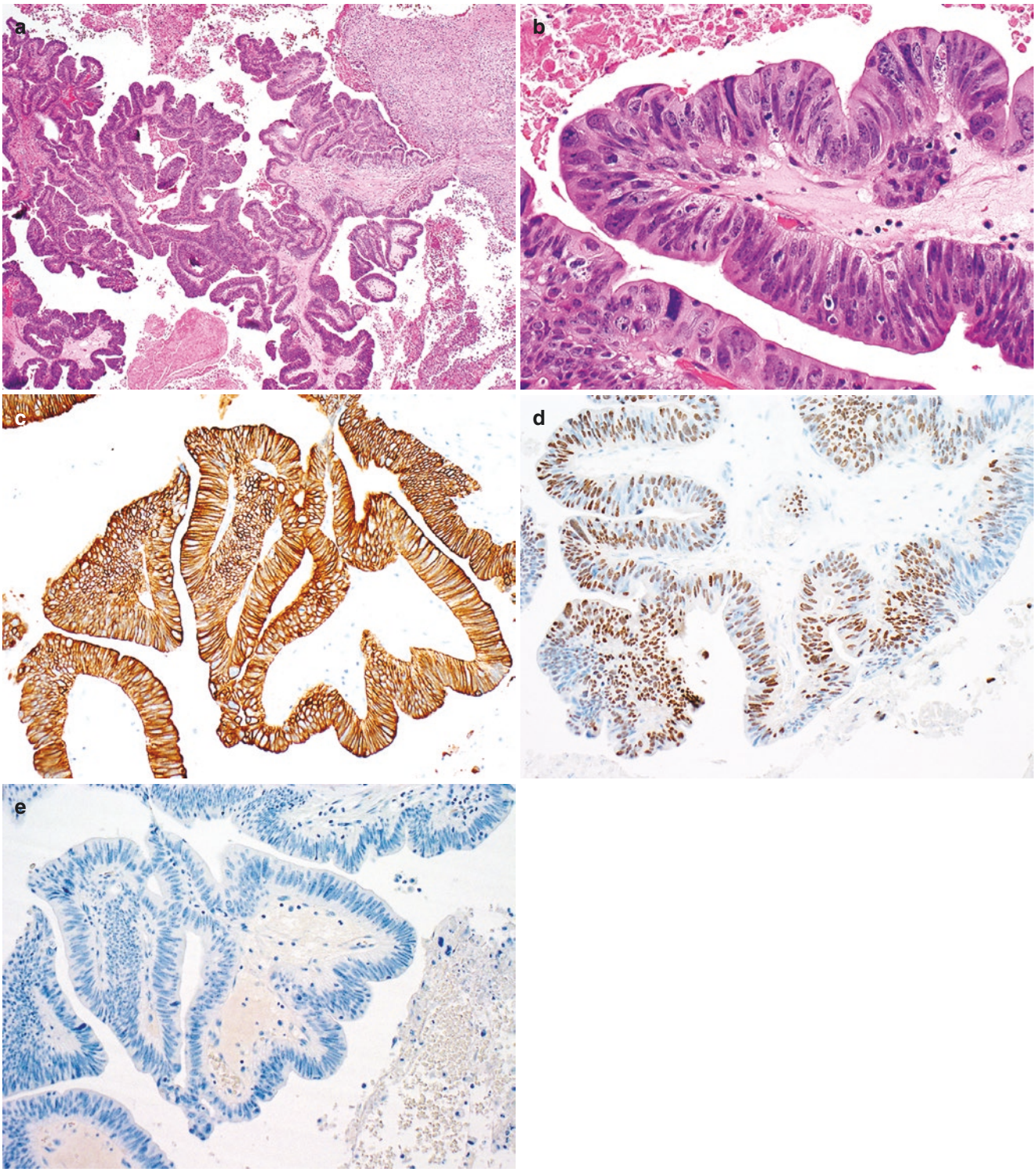

Fig. 9.9 Moderately differentiated thymic adenocarcinoma with papillary features. (**a**) Tumor cells line papillae. (**b**) Many tumor cells are of columnar cytology. Mitotic activity is increased. This adenocarcinoma exhibits an intestinal phenotype expressing CK20 (**c**) and CDX2 (**d**) and lacking expression of CK7 (**e**). Besides a mediastinal mass no other tumors were identified by imaging studies or history. Magnification ×40 (**a**), ×400 (**b**), ×200 (**c–e**)

NUT carcinomas are considered an aggressive subset of squamous cell carcinomas. Therefore, these tumors commonly express markers of squamous differentiation such as p40 (Fig. 9.10e) and CK5/6 [45–48]. They might also express TTF-1 (Fig. 9.10f) and/or CD34. Occasionally NUT carcinomas are negative for all markers tested. Their karyotype is simple in contrast to most solid malignancies. These tumors are characterized by rearrangement and translocation of the *NUT (NUTM1)* gene, most commonly *BRD4-NUT*t(15;19)(q14;p13.1) (70%) but also *BRD3-NUT* or NUT variant fusions. NUT (nuclear protein in testis) immunostain shows a nuclear speckled staining pattern that is specific (100% specificity if germ cell tumors, specifically seminomas, have been excluded) and sensitive (87% sensitivity) for NUT carcinoma if expressed in more than 50% of tumor cells (Fig. 9.10g) [49]. Therefore, if a tumor shows NUT expression, a diagnosis of NUT carcinoma can be established without the need for molecular or cytogenetic testing. If the tumor is NUT negative but the suspicion based on morphology and/or clinical presentation is high for the disease, FISH studies, RT-PCR, or karyotyping might be helpful.

Complete surgical resection and/or initial radiotherapy might be associated with increased survival [43, 50]. Clinical trials have been performed or are ongoing using BET (bromodomain

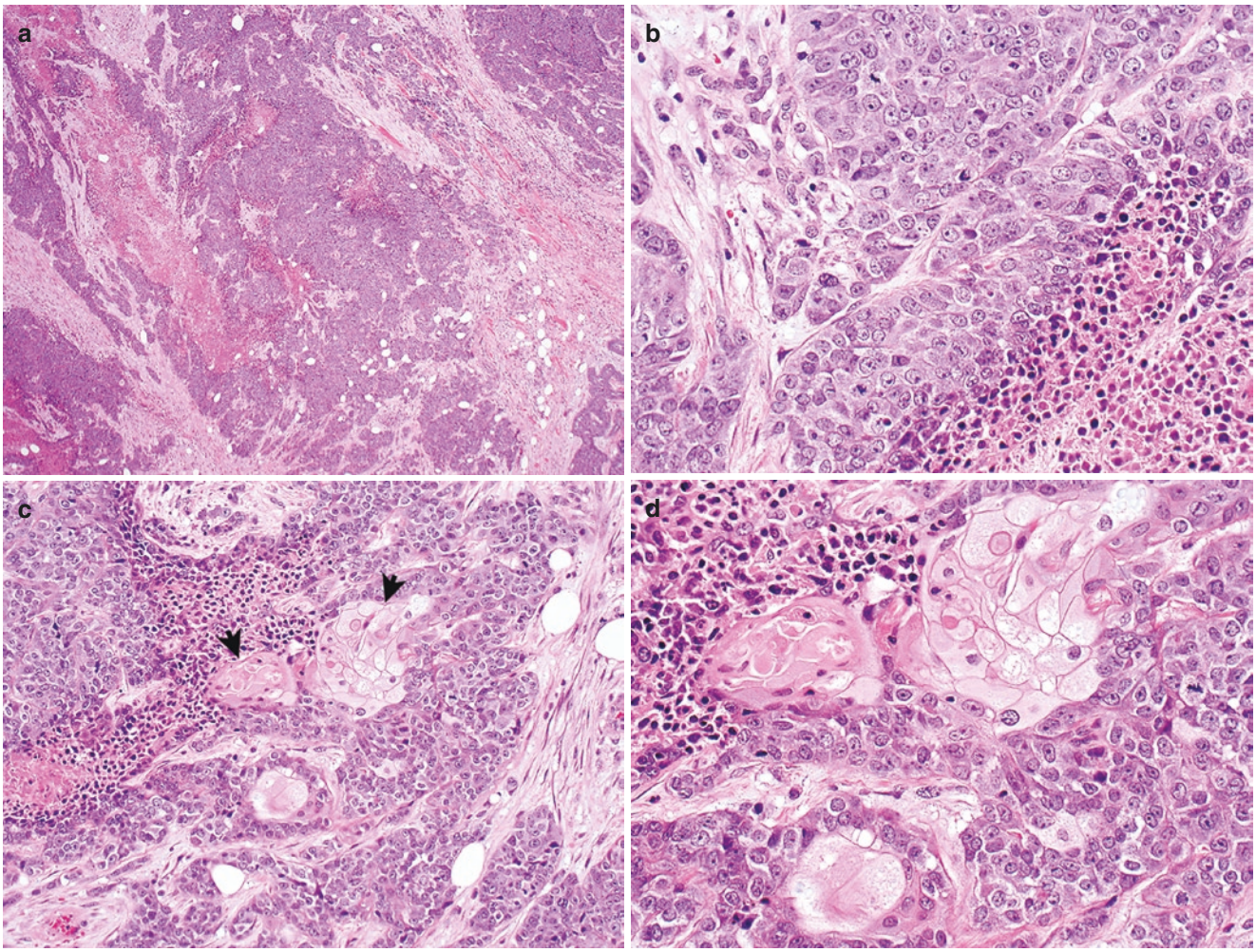

Fig. 9.10 NUT carcinoma. (**a**) Tumor cells are growing in sheets. Large areas of necrosis are present. (**b**) Although the tumor cells appear to be monotonous, they are of undifferentiated cytology as characterized by high nuclear-to-cytoplasmic ratio and conspicuous nucleoli. High mitotic activity and necrosis are readily identified. (**c, d**) Abrupt squamous differentiation is apparent (arrows, **c**). The tumor cells express p40 (**e**) and TTF-1 (clone SPT24) (**f**). (**g**) NUT immunostain shows a speckled nuclear staining pattern in virtually all tumor cells. Magnification, ×40 (**a**), ×400 (**b**, **d–g**), ×200 (**c**)

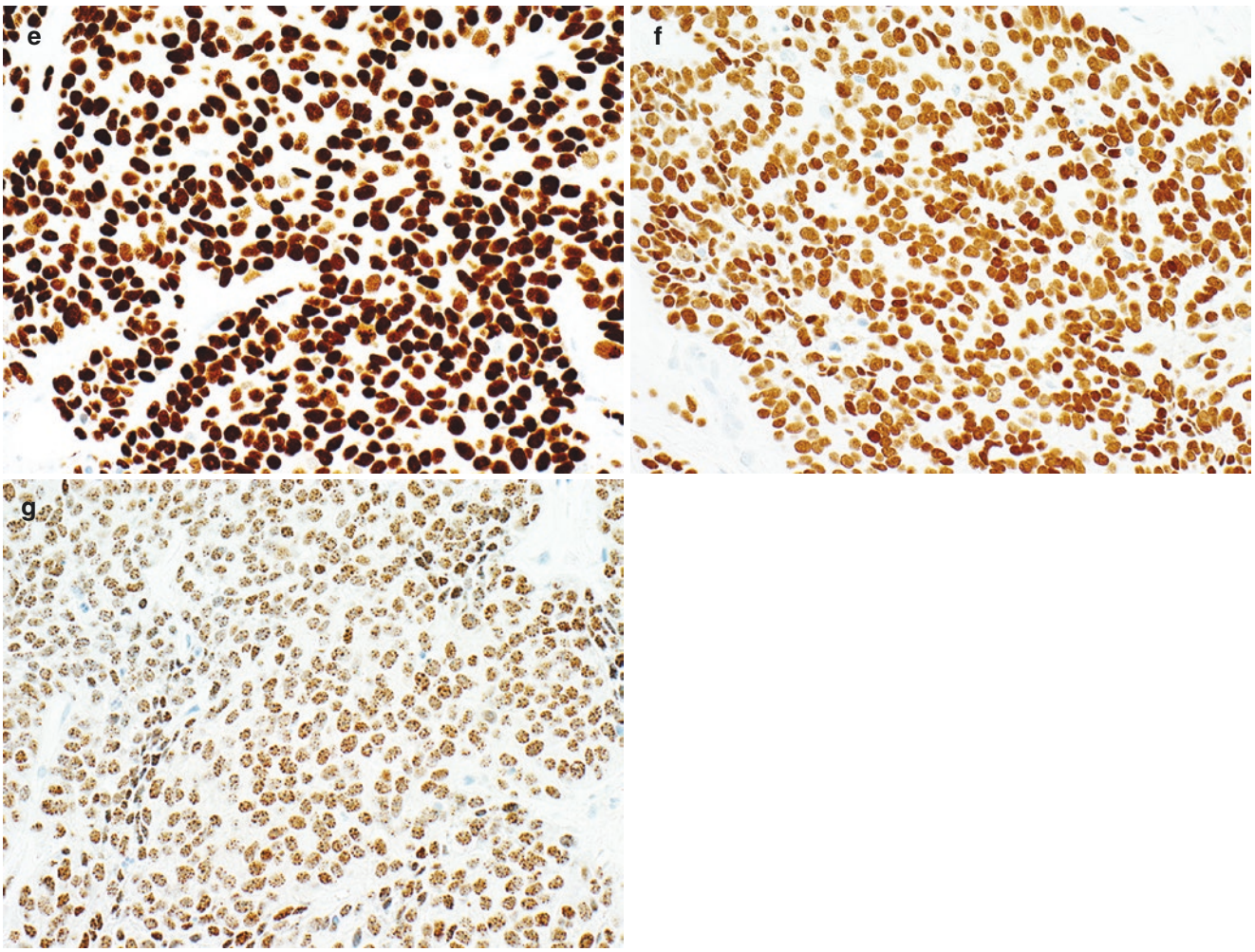

Fig. 9.10 (continued)

and extraterminal domain family) or HDAC (histone deacetylase) inhibitors to target the BRD4-NUT protein [51, 52].

9.4.9 Undifferentiated Carcinoma (Anaplastic Carcinoma)

Undifferentiated carcinomas are rare tumors with an aggressive clinical course. These tumors lack any morphologic and immunophenotypic differentiation except for expression of keratin suggestive of epithelial differentiation. Expression of CD5, CD117, and/or PAX8 has been reported in a subset of cases [53, 54]. Histologically, these carcinomas are poorly differentiated and can be comprised of tumor cells with marked cytologic atypia, pleomorphic and giant cells, and atypical mitotic figures (Fig. 9.11) [55]. The diagnosis is that of exclusion of other thymic carcinomas, sarcomas, germ cell tumors, and malignant melanoma.

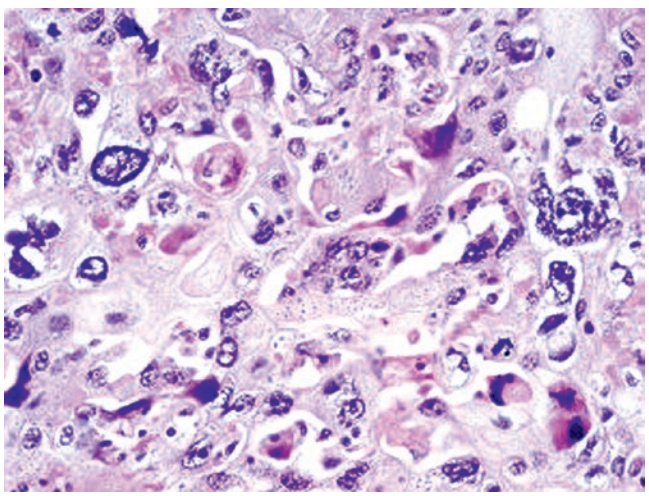

Fig. 9.11 Undifferentiated (anaplastic) carcinoma. High power magnification shows pleomorphic, slightly spindled tumor cells. Magnification, ×600. Figure courtesy of Dr. Mark R Wick, Department of Pathology, UVA School of Medicine

9.4.10 Rare Thymic Carcinomas

Micronodular thymic carcinomas with lymphoid stroma, similar to micronodular thymomas with lymphoid stroma, have a vague nodular appearance of the tumor cells intermixed with lymphoid follicles on low power microscopy (Fig. 9.12a). In a series of five cases [56], it has been shown that the tumor nodules might coalesce to form sheetlike, elongated, or solid areas. On high magnification, the neoplastic epithelial cells exhibit cytologic atypia with large, round to oval nuclei with conspicuous nucleoli and abundant cytoplasm or fusiform appearance of nuclei with punctate nucleoli (Fig. 9.12b, c). These tumors lack the bland and spindle appearance of the tumor cells of micronodular thymoma with lymphoid stroma, type A, or type AB thymomas. Focal keratinization has been described. In addition, increased mitotic activity of the neoplastic cells (5 to 14 mitoses per ten high power fields, reportedly [56]) is observed. Dense lymphoid infiltrates with lymphoid follicles with germinal centers are in between the areas of neoplastic cells. The lymphoid component is mainly composed of mature B lymphocytes and numerous mature CD3-positive, TdT-negative T lymphocytes. Plasma cells are polytypic. However, immature TdT-positive thymocytes are lacking, another distinction from micronodular thymoma, type A (although some type A thymomas also lack thymocytes), and AB thymomas.

The tumors measure between 3 and 10 cm and infiltration into lung or pleura is described in a subset of cases [56]. In the series of five cases (three men), the mean age was 64 years (range, 42–78 years). Only two of the five patients were symptomatic (chest pain, dyspnea) and none of the patients had metastatic disease at time of presentation. All patients underwent complete surgical resection. Four patients were alive without evidence of disease during

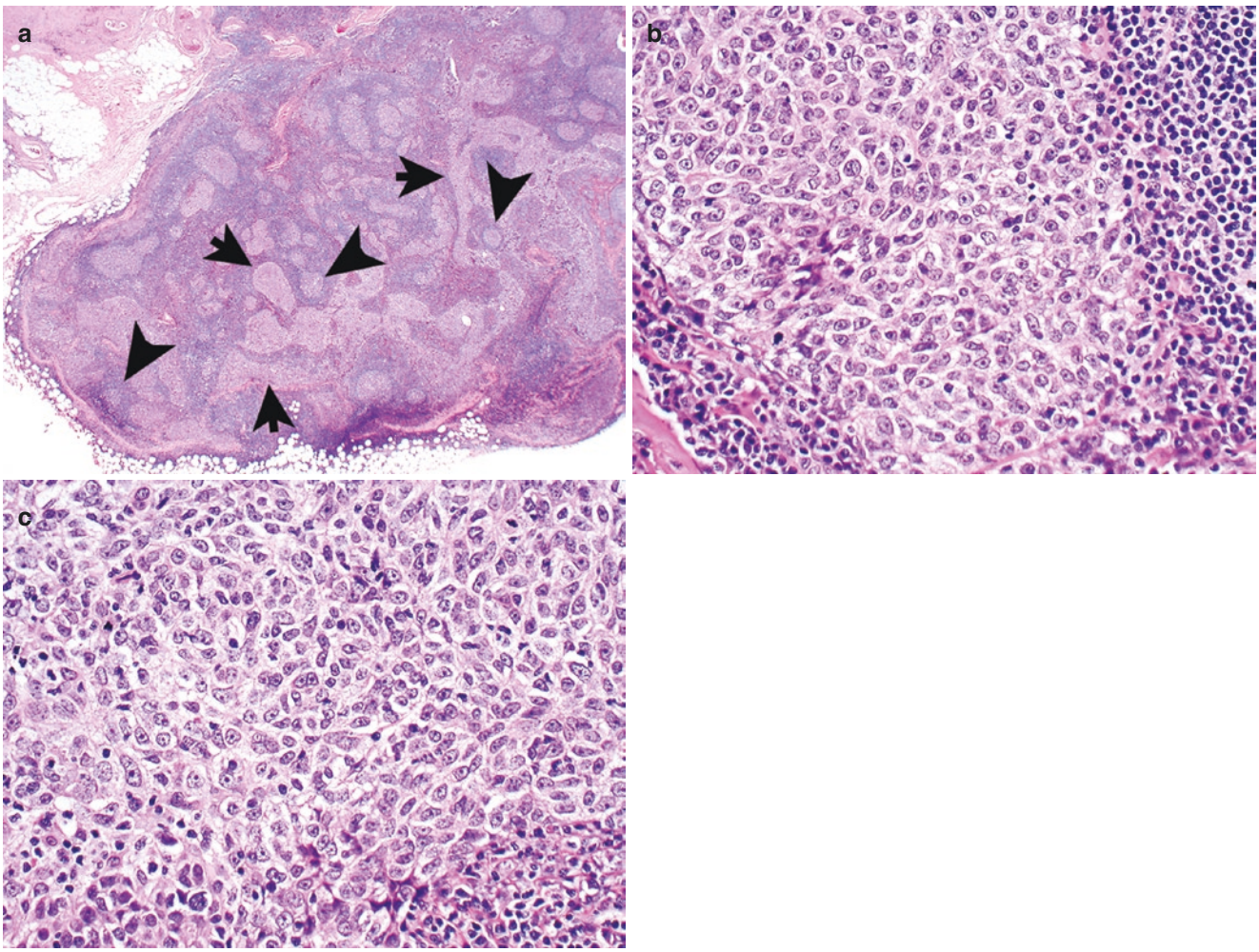

Fig. 9.12 Micronodular thymic carcinoma with lymphoid stroma. (**a**) The tumor is comprised of nodules and strands of tumor cells (arrows) in a lymphocytic background with lymphoid follicles harboring germinal centers (arrowheads). (**b, c**) The tumor cells are cytologically atypical with round to oval nuclei with open chromatin and prominent nucleoli. Mitotic activity is increased. Magnification, ×20 (**a**), ×400 (**b, c**)

a follow-up of 3 to 26 months; one patient died of disease 21 months after the diagnosis.

SMARCA4-deficient thoracic tumors are in general aggressive neoplasms. *SMARCA4* encodes BRG1 which is one of the two catalytic subunits of the SWI/SNF chromatin-remodeling complex that acts as tumor suppressor, regulates transcription, and promotes cell differentiation. Loss of BRG1 expression can be used as a surrogate marker for *SMARCA4* deficiency. *SMARCA4*-deficient thoracic sarcomas are morphologically undifferentiated tumors often with at least focal rhabdoid morphology (Fig. 9.13a, b) [57]. In a study of 40 undifferentiated thoracic tumors with rhabdoid morphology, 12 (30%) showed loss of BRG1 expression, 39% of which were mediastinal tumors, 25% pleural tumors, and 21% lung tumors [57]. Cytokeratin was expressed in rare neoplastic cells in 83% of the cases (Fig. 9.13c). Rarely, TTF-1 was expressed in a few tumor cells. INI-1 expression was retained; CD34 and SALL4 were seen in a subset of cases while the tumors were negative for desmin, NUT, and S100. BRG1 expression is lost (Fig. 9.13d).

The median or mean age of patients with thoracic *SMARCA4*-deficient sarcomas ranges between 48 to 59 years and 39 years, respectively (range, 27–90 years) with a male predominance [57–59]. Reported median survival is 6 to 7 months. The 2-year survival is significantly worse in *SMARCA4*-deficient thoracic sarcomas than in patients with BRG1-retained tumors (12.5% vs 64.4%).

It is important to recognize these tumors given their dismal prognosis [58]. *SMARCA4* deficiency is not restricted to mediastinal tumors and has also been described in small cell carcinomas of the ovary, hypercalcemic type, a subset of atypical teratoid-rhabdoid tumors of the CNS, and carcinomas of various sites including the lung.

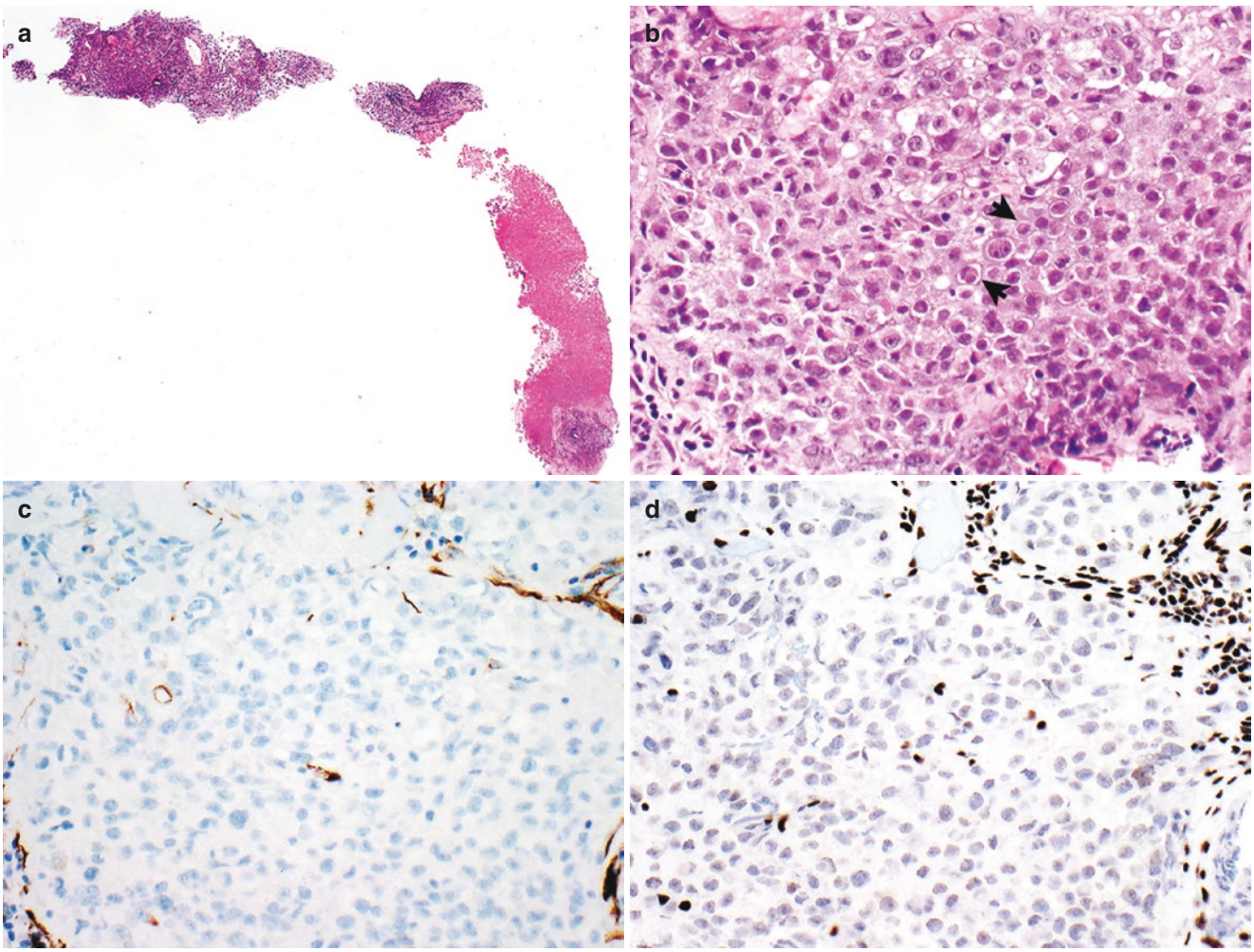

Fig. 9.13 *SMARCA4*-deficient thoracic sarcoma. (**a**) The tumor is hypercellular (upper left hand side) with large areas of necrosis (right side). (**b**) The tumor cells have an increased nuclear-to-cytoplasmic ratio and are round to oval with prominent nucleoli. Some cells have eosinophilic cytoplasm and a lateralized nucleus suggestive of rhabdoid cytology (arrows). (**c**) The neoplastic cells are negative for OSCAR keratin. (**d**) The tumor cells lack expression of BRG1 (note BRG1 expression in lymphocytes and endothelial cells serving as positive internal control). Magnification, ×40 (**a**), ×400 (**b–d**)

9.5 Immunohistochemistry of Thymic Carcinomas

No immunohistochemical marker is specific for thymic origin. Therefore, a battery of immunomarkers, for instance, CD5, CD117, and PAX8 (polyclonal), might be performed to distinguish thymic carcinomas from metastatic disease (Table 9.2) [21–24]. However, the sensitivity of this combination of markers is relatively low for thymic carcinomas. Furthermore, the antibody clone is important as certain clones have different sensitivities and specificities for thymic tumors. For instance, while polyclonal PAX8 might be helpful in the identification of a primary thymic epithelial tumor, monoclonal PAX8 usually is negative in these tumors.

The coexpression of CD5 and CD117 has been shown to be specific to thymic carcinomas (Fig. 9.2h, i) when compared to lung squamous cell carcinomas. However, the combination of these immunohistochemical markers has not been thoroughly tested in squamous cell carcinomas of other sites. Furthermore, the clone for CD5 is important as different clones have different specificities and sensitivities for thymic carcinomas.

As mentioned earlier, most of the thymic carcinomas are of squamous cell subtype. Therefore, not surprisingly, thymic carcinomas in general express markers of squamous differentiation including p40, CK5/6, and DSG 3. For instance, a study showed that p40 and DSG3 are expressed in 100% and 83% of thymic squamous cell carcinomas and 50% and 0% of undifferentiated thymic carcinomas, respectively [30].

9.6 Molecular Alterations

Only little is known about molecular abnormalities of thymic carcinomas. The recent TCGA study was predominantly comprised of thymomas and only contained very few thymic carcinomas [60]. Homozygous deletion of *CDKN2A* has been shown in 18 to 38% of thymic carcinomas [61–63]. While the *GTF2I* mutation appears to play a role in thymomas, this mutation is only found in 8% of thymic carcinomas [20, 64]. *KIT* mutations were identified in 6 to 20% of thymic carcinomas [61, 65]. *TP53* and *ATM* gene deletions were found in 32 and 8% of thymic carcinomas, respectively. Mutations were also identified in *FGFR3*, *ALK*, *ERBB4*, and *NRAS* in a few cases [61].

9.7 Summary

Thymic carcinomas are rare tumors that in general behave more aggressively than thymomas. Thymic carcinomas lack the lobulated architecture of thymomas and show more cytologic atypia, architectural distortion, and desmoplastic stromal reaction. These tumors lack specific morphologic findings and indeed exhibit morphologies that can be seen in malignancies elsewhere in the body. Although immunostains might be helpful in the distinction between primary thymic carcinoma and metastatic disease, ultimately, clinicoradiologic correlation is required for that distinction. Larger studies, possibly multi-institutional studies, are still needed to better characterize the behavior of many of these tumors.

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