# Thymic Carcinoma

8

## Introduction

In this chapter, we will discuss the entity known as thymic carcinoma; however, some thymic carcinomas are discussed under tumors of salivary gland origin (mucoepidermoid carcinoma, basaloid carcinoma, and others), while neuroendocrine carcinomas are presented in the chapter on neuroendocrine neoplasms. Therefore, this chapter will contain exclusively non-neuroendocrine and non-salivary gland origin neoplasms. In addition, this chapter will not include the so-called well-differentiated thymic carcinoma [1]. Such a tumor is the equivalent to atypical thymoma (WHO type B3), and it is discussed in the chapter on thymoma in this book. Also, the staging of thymic carcinoma and thymoma is presented in a separate chapter in this text.

The entity known as thymic carcinoma is a clinicopathological condition that until recently has generated more interest, essentially because of its separation from the more common thymic tumor: thymoma. Even though the tumor is likely to have existed long before it became recognized as a different tumor from thymoma, it is also known that thymic carcinoma in general is a rare thymic tumor. In the first series of fascicles of the Armed Forces Institute of Pathology (AFIP) [2] on the tumors of the thymus gland, the author of this important document stated "one should occasionally see a primary squamous cell carcinoma in the anterior mediastinum" and provided one illustration of such an occurrence. The tumor the author described was a well-circumscribed tumor in a patient without evidence of primary tumor elsewhere. In essence, such description and careful evaluation of the possible tumor elsewhere have constituted one of the most important definitions for the entity of thymic carcinoma. In 1975, the second series of fascicles from the AFIP [3] were presented; a few important aspects are worth highlighting: (1) the table of contents of the fascicle does not include any entry on the entity "thymic carcinoma"; (2) in the thymoma section, thymic carcinoma, among other terms, appears as a synonym of thymoma; (3) several of the illustrations are labeled as "malignant thymoma," and it is uncertain whether the authors meant *invasive thymoma* or *thymic carcinoma*; and (4) the illustration presented under the heading of squamous cell carcinoma is exactly the same one published in the earlier first series of fascicles of the AFIP. However, this second series does include thymic carcinoid as a separate entity (now considered a neuroendocrine carcinoma). Thus, based on those two highly important publications, one can gather that the entity known as thymic carcinoma had not been properly recognized and likely lumped in with other cases of thymoma. However, other anecdotal cases of thymic squamous cell carcinoma similar to the one described by Castleman [1] in the AFIP fascicle also were reported by Frank and colleagues [4] in a case with concurrent esophageal leiomyoma and by Watson and colleagues [5].

The first original description of a series of cases of squamous cell carcinomas of the thymus is credited to Shimosato and colleagues [6]. The authors described eight cases of thymic squamous cell carcinomas in seven men and one woman between the ages of 39 and 65 years with no associated paraneoplastic syndrome. Interestingly, in this initial report, one can argue that in six of the cases reported, the tumor extended to the lung, thus raising some concerns about the thymic origin. In one other case, the tumor extended to soft tissue and lymph nodes, while in only one case the tumor was limited to the thymus. Nevertheless, the authors concluded that squamous cell carcinomas of the thymus should be separated from ordinary thymoma and that squamous cell carcinoma involving both the thymus and the lungs should be carefully examined for the primary site.

Since this original description of primary thymic carcinoma, numerous original contributions have been reported, and numerous reviews on the subject have been advanced with different aims but with the goal of advancing the knowledge of thymic epithelial tumors. In 1982, Snover and colleagues [7] described a small series of thymic carcinoma with five different histological variants: mixed small cell undifferentiated/squamous cell carcinoma, basaloid carcinoma, mucoepidermoid carcinoma, clear cell carcinoma,



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and sarcomatoid carcinoma. The authors stated that none of the reported patients had tumors elsewhere, which was used as criteria for inclusion as thymic carcinoma. In addition, the authors stated that "occasional thymomas are unequivocally malignant on cytologic grounds, and those are designated as 'thymic carcinoma.'" Interestingly, when the authors estimated the occurrence of these tumors in the mediastinum, a range of 7–33% is given for the generic term of "malignant thymomas." This report of five cases clearly illustrates the issue that thymic carcinomas are also heterogeneous tumors beyond squamous cell carcinomas. However, this description raises another concern, and that is "cytologic atypia," which oftentimes is difficult to define, and clearly not so well defined in terms of separating thymoma and thymic carcinoma, unless the case is straightforward. In 1998, Suster and Moran [8], in a review manuscript on the spectrum of differentiation and histologic types, stated that, in addition to the previously mentioned features by Snover and colleagues [6] regarding cytologic atypia, it is also important to add the presence of loss of organotypical features of thymic differentiation. Furthermore, the authors stated that there is nothing distinctive or pathognomonic about the histology of thymic carcinoma, making it difficult to determine whether a given tumor represents a primary thymic carcinoma or a metastasis from a different source. In addition, the authors emphasize the spectrum of differentiation that can be seen in these tumors that may range from well-differentiated to poorly differentiated to anaplastic malignancies with different growth patterns. The authors also commented on the overall survival rate of these tumors and stated it to be approximately 33% at 5 years. However, they also noted that the survival is related to the staging of the tumor at the time of diagnosis. In 2005, Suster [9] once again emphasized previously reported concepts on thymic carcinoma, and 10 years later, Moran and Suster [10] stated a similar definition about thymic carcinoma: (1) overt cytologic features of malignancy and (2) absence of organotypical features of differentiation of the thymus. However, the authors added that complete clinical and radiological studies are needed to demonstrate the absence of an occult tumor elsewhere, as there is nothing distinctive or pathognomonic about this histology of thymic carcinoma. The authors also stated that, up to 2008, approximately 200 cases of thymic carcinoma have been reported in the literature. One important fact that needs to be highlighted is that, in many reviews or original presentation of cases, the issue of the incidence of this tumor is rather obscured by the fact that most of those publications also include either invasive thymomas or neuroendocrine carcinomas. Ritter and Wick [11], in 1999 also in a review on primary thymic carcinomas, arrived at a similar conclusion in terms of the definition of the diagnosis. The authors agreed that such diagnosis requires detailed clinical and radiographic information and that the histopathology of these tumors is also varied. Suster and Moran [12], in a conceptual approach to the classification of thymic epithelial tumors, stated that the cytological atypia and the identification organotypical features of differentiation are important clues in separating thymoma from thymic carcinoma. The authors further stated the importance of clinical staging for these tumors. More recently, Weiss [13] reviewed the subject of thymic carcinoma and stated that thymoma and thymic carcinoma have a combined incidence of 0.2–1.5% of all tumors, which may account for 50% of all tumors of the anterior mediastinum. The authors further estimated that thymic carcinoma represents 1% of thymic malignancies, with an estimated incidence of 500 cases per year in the USA.

Based on the different publications on this subject, it is important to highlight that the diagnosis of thymic carcinoma must meet the following criteria:

1. Cytologic atypia
2. Loss of organotypical features
3. Clinical and radiological evidence of absence of tumor elsewhere

Regarding the etiology and pathogenesis of thymic carcinoma, there are two speculative hypotheses to account for their occurrence. The first is that the tumor is a separate entity from thymoma and the tumor arises de novo from cellular precursor either from thymic remnants or from misplaced epithelial elements in the mediastinum. The second hypothesis and the one that we believe more likely explains the occurrence of thymic carcinoma is that thymic carcinoma is part of a spectrum of thymic epithelial neoplasms, having in one end a better differentiated neoplasm with high degree of organotypical differentiation simulating the normal thymus (thymoma) and, at the other end, a tumor that has lost the organotypical features of differentiation and in addition shows cellular atypia (thymic carcinoma). This latter hypothesis is based on the occurrence of thymic epithelial tumors that showed in the same lesion a degree of differentiation that expands from classical thymoma to thymic carcinoma [14, 15]. (See diagrammatic illustrations in the chapter on thymoma.)

## Clinical Features

The literature of thymic carcinoma compared to the literature on thymoma is rather limited due to the infrequency of the occurrence of thymic carcinoma. Due to those limitations, large series of thymic carcinomas have been reported, but there are only a few. The majority of reports on thymic carcinoma are small series of cases or isolated case reports.

Wick and colleagues [16], in a retrospective study of 75 years, collected 20 patients that the authors concluded

represented thymic carcinomas. The patients were 14 men and 6 women between the ages of 4 and 72 years (average 47.6 years). Clinically, none of the patients reported had any associated condition such as myasthenia gravis (MG), Cushing's syndrome, hypogammaglobulinemia, or aregenerative anemia. The symptoms described for these patients were essentially non-specific and included cough, chest pain, fever, fatigue, night sweats, weight loss, anorexia, and superior vena cava syndrome. Two patients in this study were asymptomatic. In 13 patients, the tumor was totally or subtotally resected by thoracotomy; 18 patients received additional radiation therapy, and 8 patients received chemotherapy. Metastatic disease to the liver, lung, lymph nodes, adrenal glands, and bone was documented in 13 patients. Histologically, 13 tumors corresponded to poorly differentiated carcinomas (lymphoepithelioma-like), two tumors were labeled as spindle cell squamous cell carcinoma, one was labeled as "sarcomatoid" carcinoma, and four tumors were labeled as small cell carcinoma. Fifteen patients died of massive local tumor growth, metastases, or both. The overall average postoperative survival of patients who died of thymic carcinoma was 20 months. In addition, the authors documented two cases in which the patients were alive with recurrence or metastasis 18 and 43 months after surgery. Shimizu and associates [17] reported five thymic carcinomas in four men and one woman between the ages of 50 and 69 years who clinically presented with non-specific symptoms such as chest pain and cough. Interestingly, in three cases, the initial biopsy material was interpreted as thymoma and one as mesothelioma. Complete surgical resection was accomplished only in one patient. Histologically, four cases corresponded to squamous cell carcinomas and one case to small cell carcinoma. The five patients were also treated with radiation and chemotherapy, and metastatic disease to the liver, bone, lymph node, and lung was documented in three patients. Three patients died in a period of 7–38 months, while one was reported to be alive with disease at 9 months, and one additional patient was disease-free at 60 months. Truong and associates [18] also reported 13 cases of thymic carcinoma in 7 men and 6 women between the ages of 30 and 74 years (mean age, 54.2 years) who presented with non-specific symptoms related to mediastinal compression by the tumor. None of the patients described had any paraneoplastic syndrome. Eleven tumors were described as invading adjacent structures, while two tumors were described as "encapsulated." Histologically, seven tumors were labeled as lymphoepithelioma-like, four as small cell carcinomas, one as clear cell, and one additional case as "adenosquamous" carcinoma. Six patients died in a period of 3–36 months due to recurrence or metastasis, and three patients died postoperatively, while four patients were alive without disease at 2–60 months. Similar numbers of cases were also reported by Kuo and associates [19] in nine men and four women between the ages of 19 and 64 years (median age, 40 years), who presented with non-specific symptoms and no history of paraneoplastic syndromes. The authors documented five different histological categories including lymphoepithelioma-like (two cases), clear cell (one case), mixed squamous and small cell carcinoma (two cases), mixed adenosquamous and small cell carcinoma (two cases), and squamous cell carcinoma (six cases). The authors identified that all patients with pure squamous cell carcinoma were alive with a median survival of 27 months and, based on that observation, stated that the prognosis of patients with pure thymic squamous cell carcinoma is better. Hartmann and associates [20], in a review of 20 years, identified 5 cases of thymic carcinoma among 54 mediastinal tumors. The tumors were identified in three women and two men between the ages of 38 and 68 years who presented with non-specific symptoms, and no paraneoplastic syndrome was identified. Histologically, three tumors corresponded to lymphoepithelioma-like, one squamous cell carcinoma, and one "undifferentiated" carcinoma. The five patients died of tumor in a period of no more than 20 months. Hsu and associates [21], in a retrospective review of 10 years (1982–1992), reported 20 cases of thymic carcinoma in 9 men and 11 women between the ages of 34 and 70 years (mean, 51.4 years). The presence of MG was not reported in any patient but no additional clinical symptomatology was provided for this group of patients. Histologically, eight tumors were squamous cell carcinomas, seven "undifferentiated" carcinomas, one lymphoepithelioma-like carcinoma, one clear cell, one mucoepidermoid carcinoma, and two carcinoid tumors. The authors documented an overall cumulative survival of 45.9% at 3 years and 34.4% at 5 years, while the median survival times for patients with complete and incomplete resection were 39 months and 14 months, respectively. Patients who received postoperative radiation therapy had a median survival time of 39 months, while those who did not receive radiation therapy had a median survival time of 15 months. Regarding histological features, the authors estimated a median survival time for squamous cell carcinoma and undifferentiated carcinoma at 25 and 11 months, respectively. The authors concluded that complete surgical resection, postoperative radiation therapy, and squamous cell histology do not offer significant favorable prognosis even though those features are associated with longer median survival times. Chalabreysse and associates [22] also reported 19 primary thymic carcinomas in 13 men and 6 women between the ages of 29 and 75 years who presented with symptoms of chest pain or superior vena cava syndrome. The histological features of the cases studied are similar to those previously reported in other studies, and the authors also included among these 19 carcinomas 6 neuroendocrine carcinomas and 1 mucoepidermoid carcinoma. Surgical resection was performed in 10 patients, and only in 2 patients was the resection complete; 16 patients received

radiation therapy, and 11 received chemotherapy. In 12 patients, the authors documented local or metastatic disease, while 10 patients died due to tumor. The overall survival rate was 14.5% at 5 years. Based on their analysis, the authors concluded that thymic carcinoma has an aggressive behavior and had poor overall prognosis. Yano and associates [23], in a collective retrospective study at a single institution, evaluated 30 thymic carcinomas in 16 men and 14 women between 33 and 84 years (mean: 59 years) who presented with varied non-specific symptomatology but with no paraneoplastic syndrome. Thirteen patients were inoperable, and those patients received either radiation therapy or chemotherapy, while seven patients had complete surgical and ten patients had incomplete surgical resection. Seventeen patients died between 2 and 78 months, while 13 patients were alive between 6 and 232 months (average, 64 months). The authors estimated a 5-year survival rate of 47.5% and a median survival time of 49 months. The authors concluded that resectability was the only prognostic factor, as the authors observed significant better prognosis in cases with total resection. Takeda and associates [24] had a similar experience in their report of 15 patients with thymic carcinoma in which the authors concluded that complete resection is the mainstay of therapy when possible. In this report – which included 12 squamous cell carcinomas, 2 undifferentiated carcinomas, and 1 adenocarcinoma – the median survival was 13 months for patients without resection and 57 months for patients with complete surgical resection. The total 3- and 5-year survival rate was estimated at 51.9% and 39%, respectively. Tomita and coworkers [25] arrived at a similar conclusion in a report of eight thymic carcinomas in two men and six women between the ages of 19 and 67 years (mean: 54.8). No paraneoplastic syndromes or MG was associated with any patient. The histologies observed were five squamous cell carcinomas, one adenosquamous carcinoma, one clear cell carcinoma, and one small cell carcinoma. In a review of 20 years, Liu and coworkers [26] evaluated 614 cases of anterior mediastinal tumors and identified 38 cases that the authors coded as thymic carcinomas, representing in their experience approximately 6.2% of all anterior mediastinal tumors. The tumors were identified in 26 men and 12 women between the ages of 28 and 80 years. Of the 38 patients, 15 had surgical procedures performed; complete resection was done in 8 patients (all these patients had low-grade histology – squamous cell carcinoma), while debulking was performed in the other 7 patients. The remaining 23 patients were treated either with partial resection or only biopsy. Interestingly, three patients were also diagnosed with MG. The histologies of the tumors are similar to those reported in other series of cases. The mean survival time in 35 patients was estimated to be 53 months, with a median of 24 months, while the overall cumulative survival rate was 38% at 3 years and 27% at 5 years. The authors concluded that tumor grade, stage, and resectability influence patients' survival. In a different study focused on the treatment of thymic carcinoma, Ogawa and coworkers [27] evaluated 40 patients who have been diagnosed with thymic carcinoma; 27 patients were treated with complete surgical resection followed by radiotherapy with or without chemotherapy, while 13 were treated with radiation therapy with or without chemotherapy. The overall survival rates at 5 and 10 years for all patients were estimated at 38% and 28%, respectively. Twenty-seven patients (68%) died of tumor, and 13 patients were alive during a period ranging from 44 to 193 months (median, 87 months). The authors concluded that multimodal treatment – complete surgical resection and postoperative radiation therapy with or without chemotherapy – is *curative* therapy for thymic carcinoma. In that regard, unusual cases of thymic carcinoma with KIT and VEGF positivity have been described in which the patient has responded to a molecular targeted-based therapy [28].

One of the largest series of primary thymic carcinomas is the one reported by Suster and Rosai [29], who encountered 60 cases in 36 men and 24 women between the ages of 10 and 76 years. The majority of tumors occurred in patients in the fourth decade of life. Clinically, two patients had a history of MG, and no other paraneoplastic syndromes were identified. Histologically, the cases were separated into low- and high-grade malignancies: 20 cases belong to low-grade tumors (mucoepidermoid carcinoma, basaloid carcinoma, and keratinizing squamous cell carcinoma), while 40 cases belong to high-grade tumors (lymphoepithelioma-like carcinoma, small cell carcinoma, undifferentiated/anaplastic carcinoma, sarcomatoid carcinoma, clear cell carcinoma). In addition, correlations were made by the infiltrative nature of the neoplasm, whether well-circumscribed to the mediastinum or infiltrative. Based on this experience, the authors identified overall survival rates at 1, 3, and 5 years of 56%, 40%, and 33%, respectively. Furthermore, 88% of the patients with infiltrative tumors died of their tumor compared to 16% of patients with well-circumscribed tumors; 84% of patients with high-grade tumors died of tumor, while none of the patients with low-grade tumors died. In addition, the authors concluded that the morphological features of the tumor correlate well with clinical behavior, and that histological type constitutes the most reliable and important predictor of prognosis. In a more recent publication [30] in what constitutes up to now the largest series of cases of thymic carcinoma – this series of cases excluded neuroendocrine carcinomas as their behavior is different – the authors analyzed 65 thymic carcinomas: 38 squamous cell carcinomas (including 3 basaloid carcinomas), 12 undifferentiated carcinomas, 4 lymphoepithelioma-like carcinoma, 3 spindle cell carcinoma, 2 mucinous adenocarcinomas, 2 papillary carcinomas, 2 clear cell carcinomas, 1 rhabdoid carcinoma, and 1 anaplastic carcinoma. Based on this experience, the authors

concluded not only that the Masaoka staging system does not reliably predict prognosis but also that the most important parameter to predict prognosis is the lymph node status, regardless of the location of the lymph node. (See staging of thymic carcinoma in the respective chapter on staging.) Follow-up information was documented in 62 patients over a period ranging from 3 to 126 months (mean, 51 months); it was found that 36 patients (58%) were alive, while 26 patients (42%) had died over a period of 1–165 months (mean survival, 47.5 months). The overall survival rate at 3 and 5 years was estimated to be at 76.6% and 65.7%, respectively. The findings lead the authors to propose a different staging system from the one adapted from Masaoka, and to argue that such findings suggest that thymic carcinoma may have a better outcome than previously believed. However, it is also important to note that staging and particularly the presence of lymph node involvement plays a very important role in prognosis.

## Pathological Features

### Macroscopic Features

The tumor size of thymic carcinoma varies from 2 to more than 10 cm in greatest diameter. The tumors may be well circumscribed or have an infiltrative pattern compromising adjacent structures, including the pleura, pericardium, or lung. The tumors are generally described as tan to white with firm consistency, while areas of hemorrhage and necrosis may also vary from case to case (Fig. 8.1a–c). In some cases, cystic changes may also be identified. The presence of extensive necrosis is commonly associated with high-grade histology.

### Histopathological Features

The tumors described in this section will not include mucoepidermoid carcinoma and basaloid carcinoma, as they are presented in the chapter on salivary gland-type tumors, while neuroendocrine carcinomas are presented in the chapter on neuroendocrine neoplasms. In addition, the entity described as "low grade metaplastic carcinoma of the thymus" [31] will not be discussed in this chapter as we consider such designation incorrect because it represents a change in name only from the original description of thymoma with pseudosarcomatous stroma [32], and as such it is discussed in the chapter on thymomas. Therefore, the histology of the tumors discussed herein will be that of non-neuroendocrine tumors and non-salivary gland-type neoplasms. Nevertheless, the spectrum of histopathological growth patterns that has been documented in thymic carcinoma is varied and as such will be presented in this section.

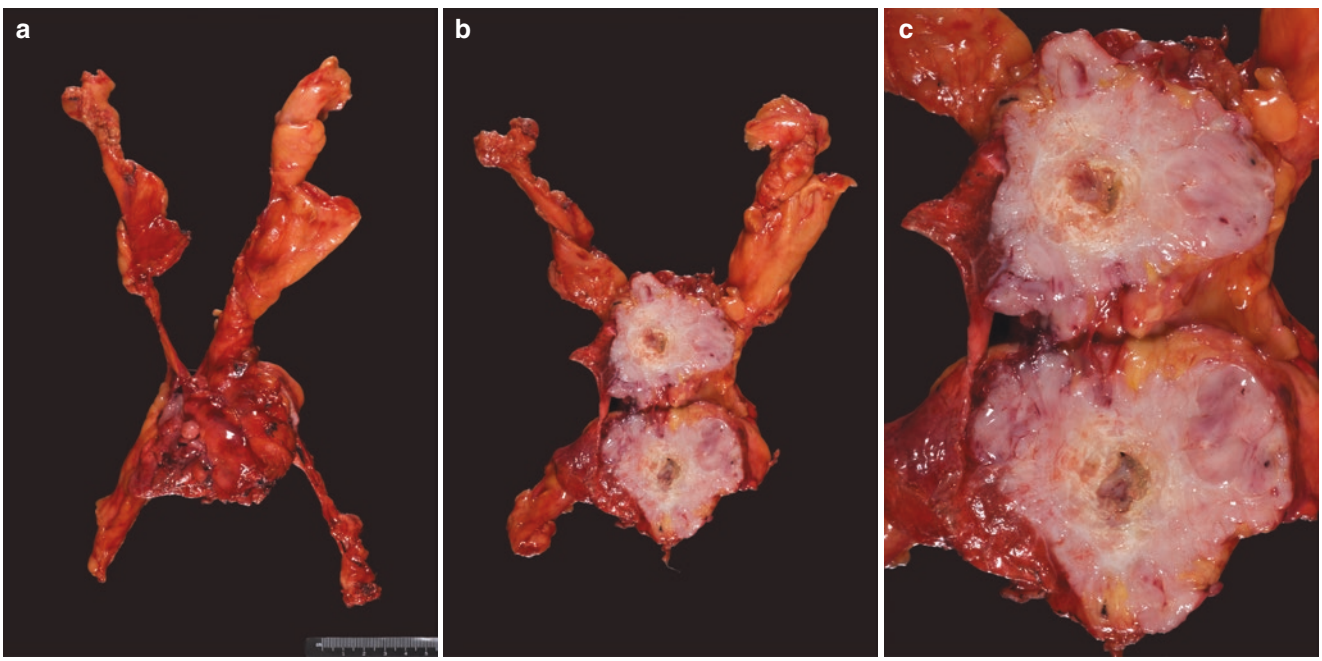


**Fig. 8.1** (**a**) Surgical resection of thymic carcinoma; note the presence of a mass within the thymic gland. (**b**) Bisected thymic carcinoma showing infiltrating borders. (**c**) Thymic carcinoma showing focal central necrosis

### Squamous Cell Carcinoma

As stated earlier in this chapter, credit for the description of these tumors is given to Shimosato [6], who reported a small series of cases. However, even though the original description emphasizes the well-differentiated nature of these tumors, the fact is that, among squamous cell carcinoma, there is a spectrum that may vary from well to moderately to poorly differentiated squamous cell carcinoma.

In the well-differentiated squamous cell carcinoma, the tumor may show a lobular architecture with varying size islands of tumor cells (Fig. 8.2a–c), which are composed of round or polygonal cells, vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm (Fig. 8.3a–f). Areas of keratinization with the presence of intercellular bridges are often encountered (Fig. 8.4a–c). The tumor may show cystic changes, and in some cases, the cystic changes are similar to those seen in multilocular thymic cyst (Fig. 8.5a–g). The presence of thymic carcinomas with associated multilocular thymic cyst has been specifically reported in the literature, and this feature is rather unusual. In addition, a variant of cystic well-differentiated squamous cell carcinoma of the thymus has been reported in which the tumors are pre-

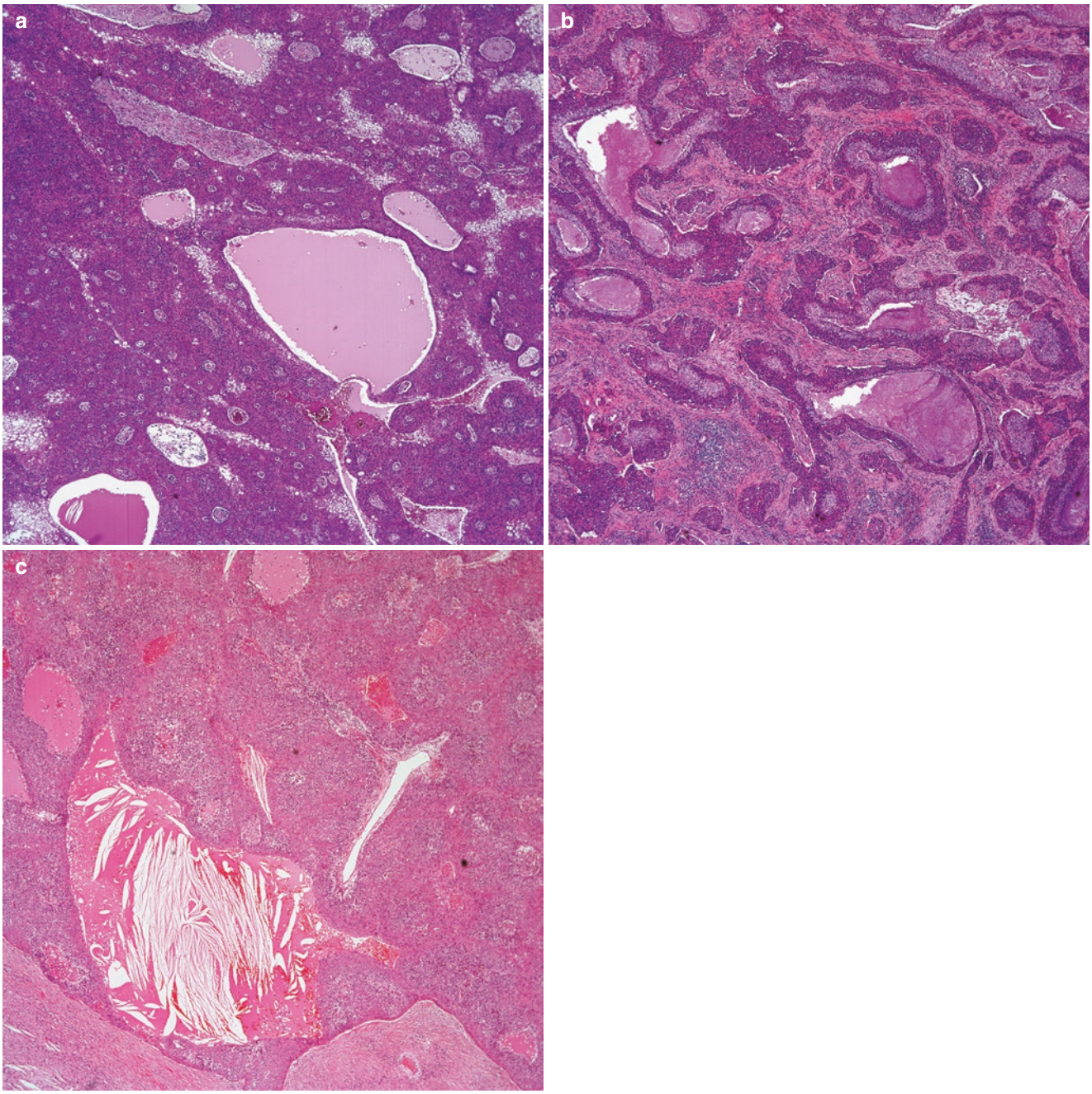


**Fig. 8.2** (**a**) Low power view of a thymic carcinoma showing microscopic cystic changes. (**b**) Different growth pattern of a thymic carcinoma with areas of come-like necrosis. (**c**) Sheets of neoplastic cells with focal cholesterol cleft granuloma

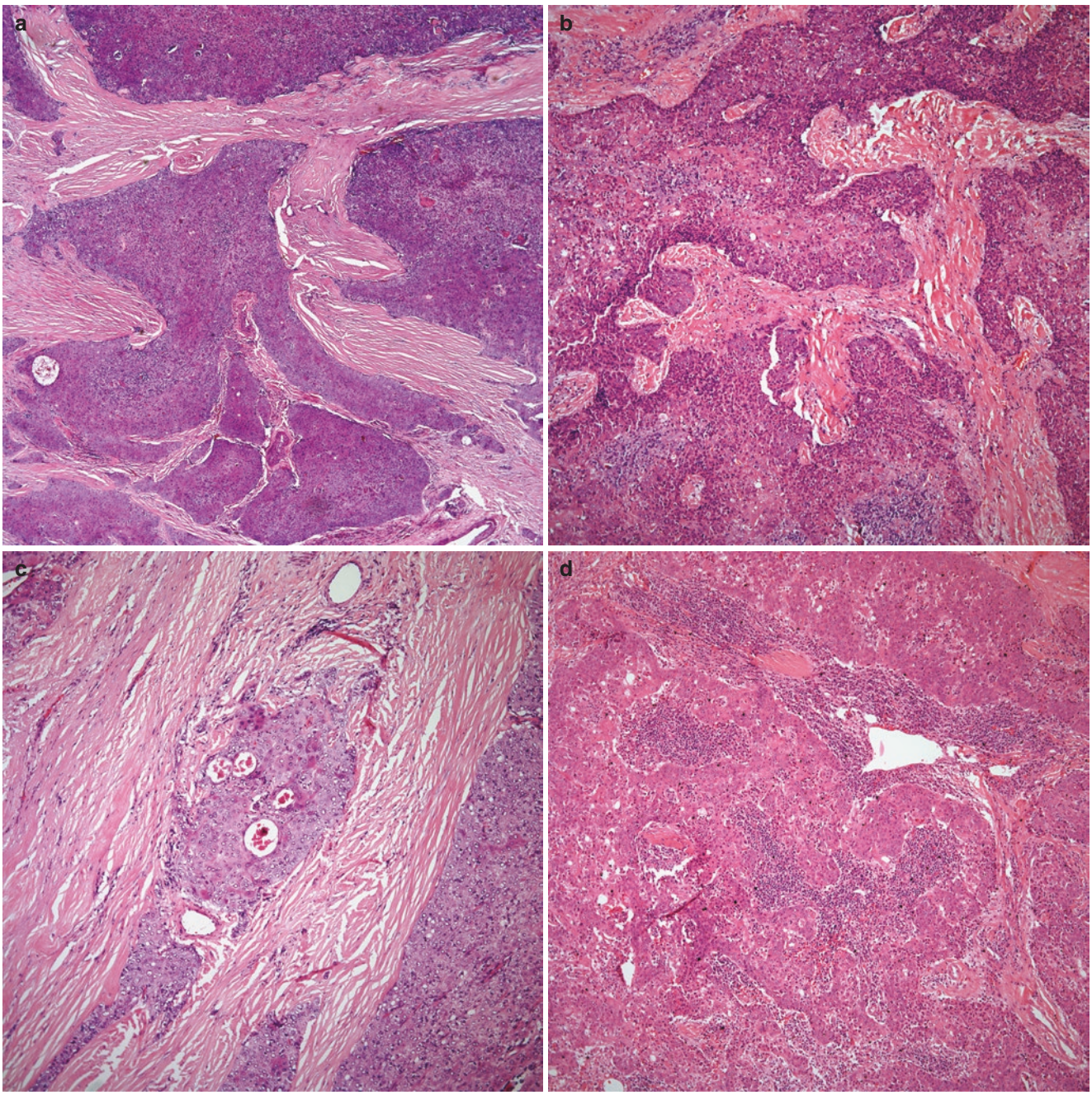


**Fig. 8.3** (**a**) Thymic carcinoma showing irregular islands of tumor cells. (**b**) Thymic carcinoma showing sheets of malignant cells without increased mitotic activity. (**c**) Islands of tumor cells embedded in fibroconnective tissue. (**d**) Mixed areas of tumor cells and inflammatory reaction

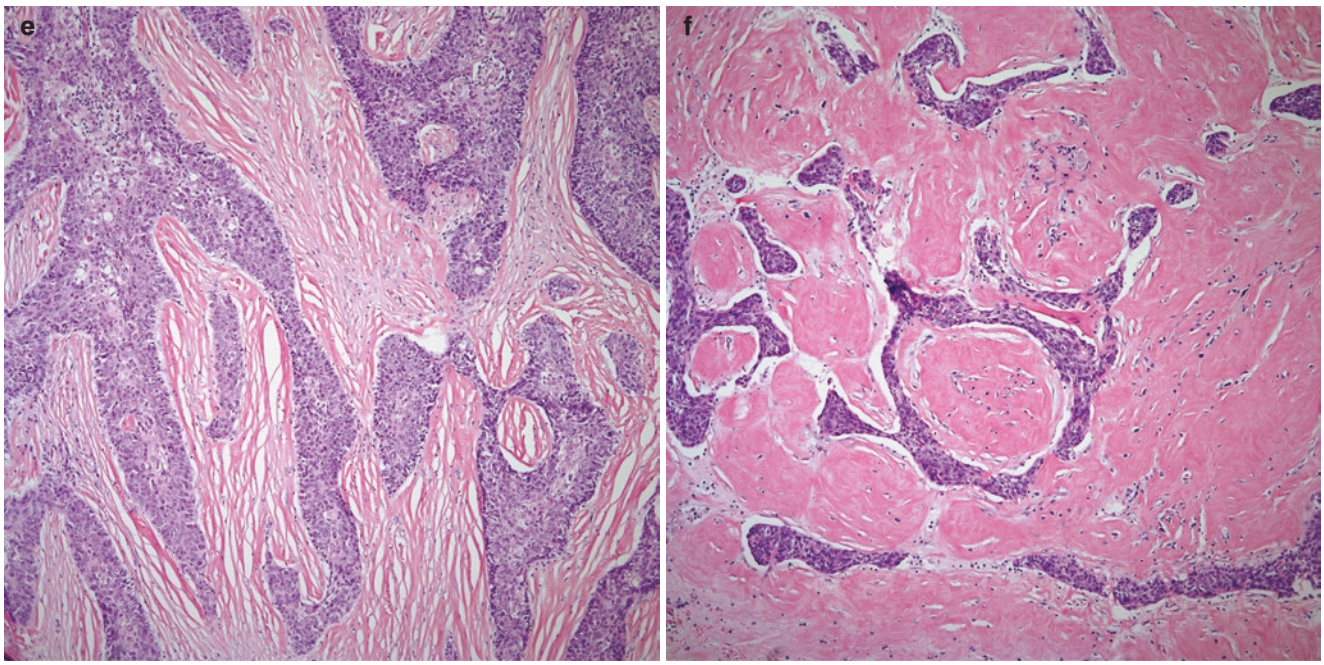


**Fig. 8.3** (continued) (**e**) Increased areas of fibroconnective tissue and strips of tumor cells. (**f**) Marked presence of fibroconnective tissue

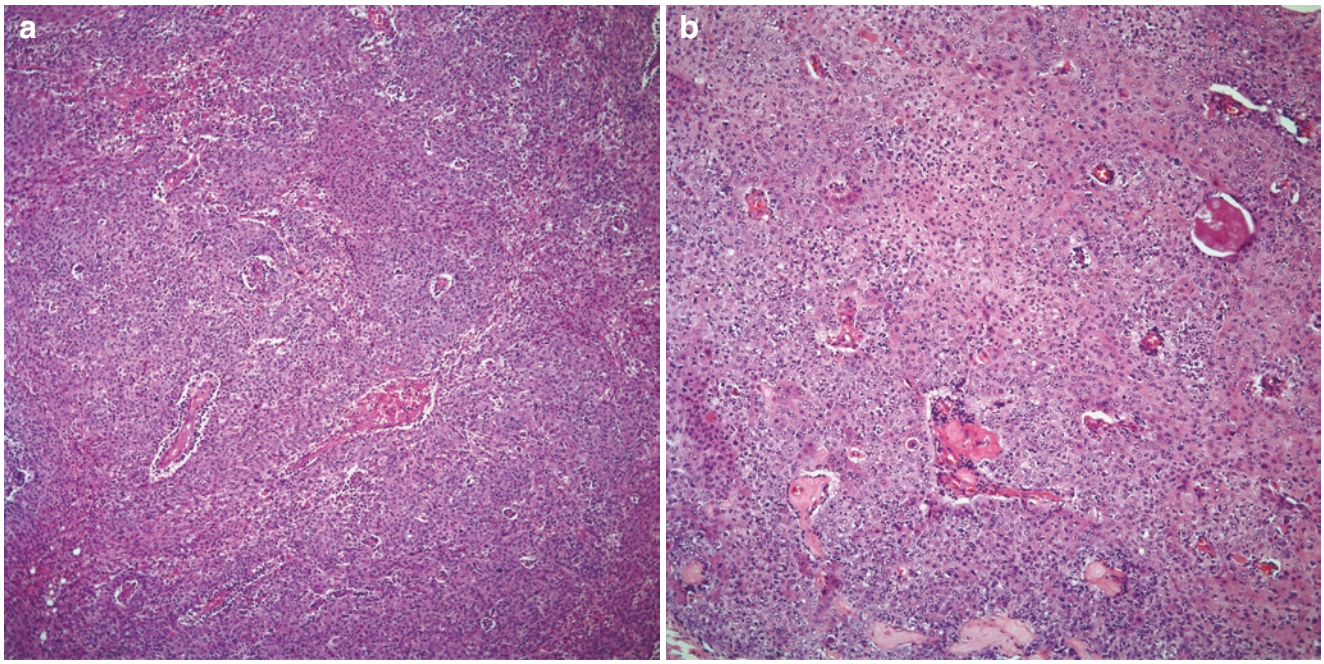


**Fig. 8.4** (**a**) Sheets of epidermoid cells in thymic carcinoma. (**b**) Homogeneous cellular proliferation without increased in mitotic activity

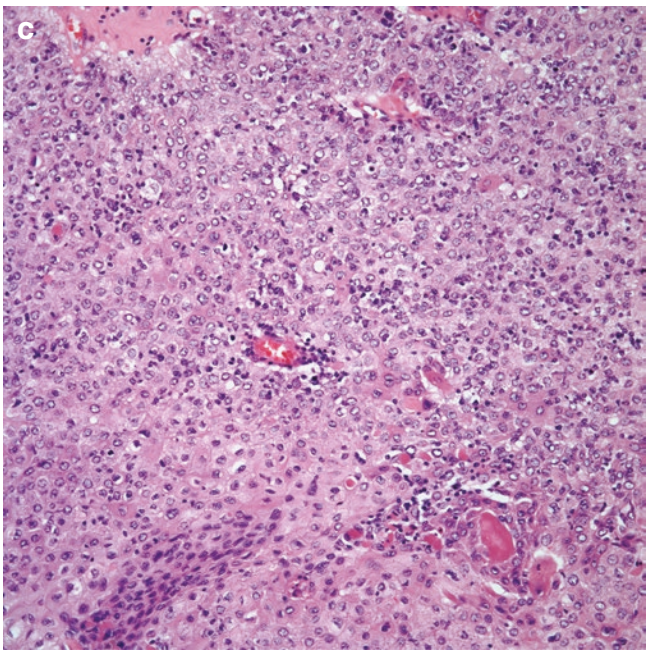


**Fig. 8.4** (continued) (**c**) Higher magnification showing mild nuclear atypia and apoptotic nuclei

dominantly cystic with alternating solid areas and evidence of keratinization [33, 34] (Fig. 8.6a–c). Mitotic activity in these tumors (well-differentiated) may be present but usually is not high (Fig. 8.7a–c). Areas of hemorrhage or necrosis are not common (Fig. 8.8a–c).

On the other hand, tumors belonging to the moderately and poorly differentiated categories may be more common in comparison to those of low-grade histology. The low power view of these tumors may also show different growth patterns, which include infiltrating borders (Fig. 8.9), cystic changes, small islands of tumors cells separated by fibroconnective tissue, areas of comedo-like necrosis, tumor necrosis with single cell necrosis, and calcifications (Fig. 8.10a–e). In addition, the tumor may also show irregular lobular architecture, ribbons of tumor cells with abortive germinal centers, extensive hyalinization, and prominent inflammatory changes where the malignant cells can be easily overlooked (Fig. 8.11a–e). Higher magnification of thymic carcinomas shows a neoplastic cellular proliferation composed of medium size cells with round nuclei and prominent nucleoli, mitotic activity is easily identified, areas that can be easily misconstrued as small cell carcinoma may also be present,

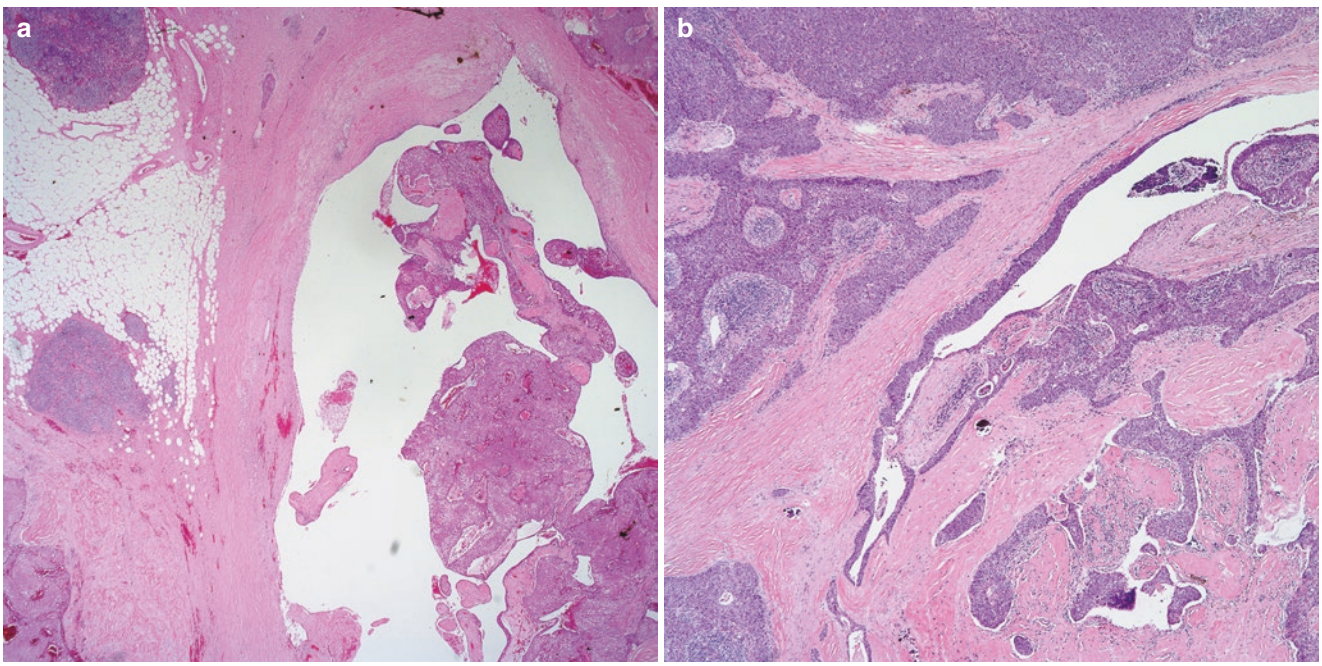


**Fig. 8.5** (**a**) Thymic carcinoma with prominent cystic changes. (**b**) Cystic areas showing irregular strips of tumor cells

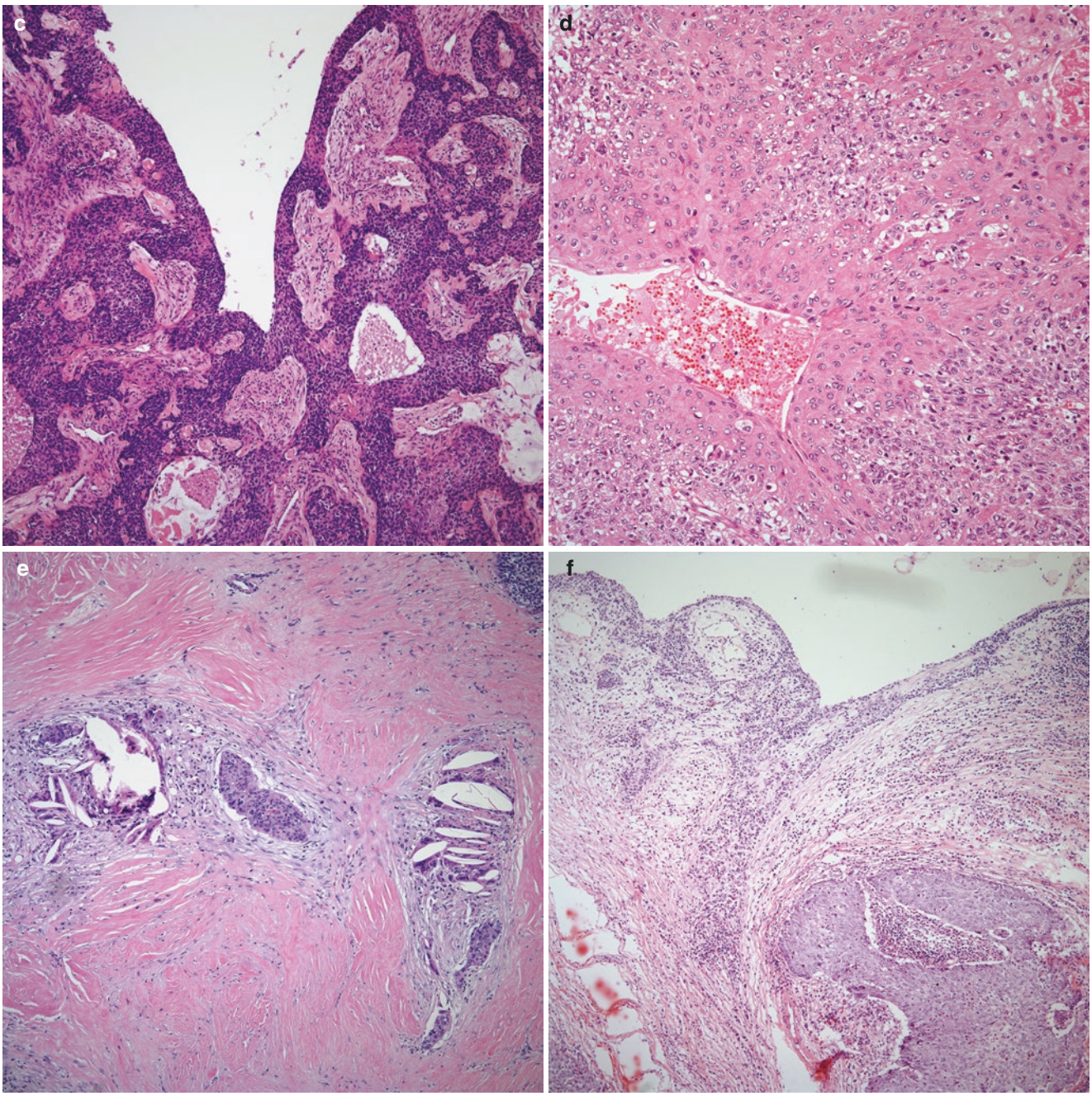


**Fig. 8.5** (continued) (**c**) The lining of the cystic area is also involved by carcinoma. (**d**) The wall of a vascular structure is also involved by carcinoma. (**e**) Extensive areas of fibrosis with cholesterol cleft granulomata and small island of tumor cells. (**f**) Cystic areas similar to those seen in multilocular thymic cyst; the wall is involved by carcinoma

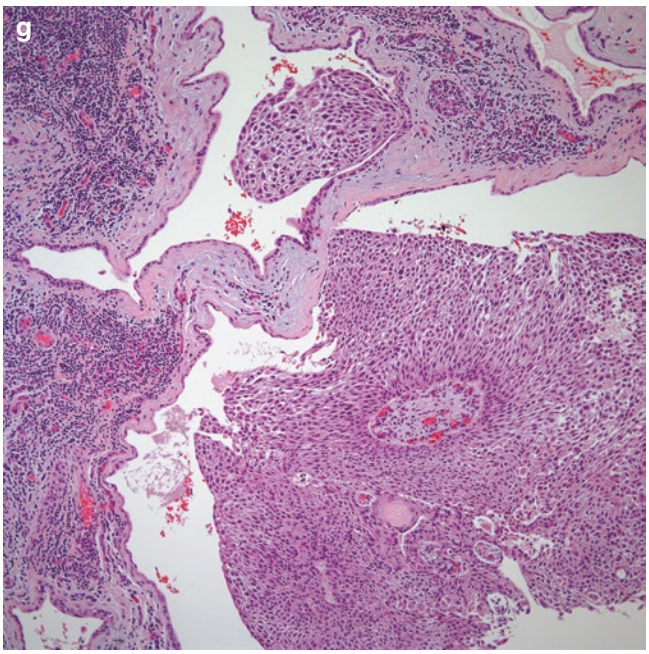


**Fig. 8.5** (continued) (**g**) Cystic spaces also involved by carcinoma

and extensive necrosis with only small islands of tumor cells may also be seen (Fig. 8.12a–d). In addition, the presence of keratinization may be seen only focally or may not be present at all. In general terms, the spectrum of thymic squamous cell carcinomas may represent approximately 50–60% of all thymic carcinomas.

### Sarcomatoid Carcinoma

Even though this morphological variant of thymic carcinomas has been mentioned in earlier literature, the most comprehensive series of cases is the one presented by Suster and Moran [35] in a description of 16 cases of 7 women and 9 men between the ages of 23 and 82 years. However, the tumor has been documented in other series of cases, and may represent approximately 5% of all thymic carcinomas. The clinical and surgical presentation of these cases is similar to that described in other variants of thymic carcinoma. However, the histopathological features are those of a spindle cell proliferation with varying spectrum of cellular atypia, which in some areas may resemble spindle cell thymoma and in other areas a frank sarcomatoid carcinoma. The tumors show infiltrative pattern, may retain some lobular architec-

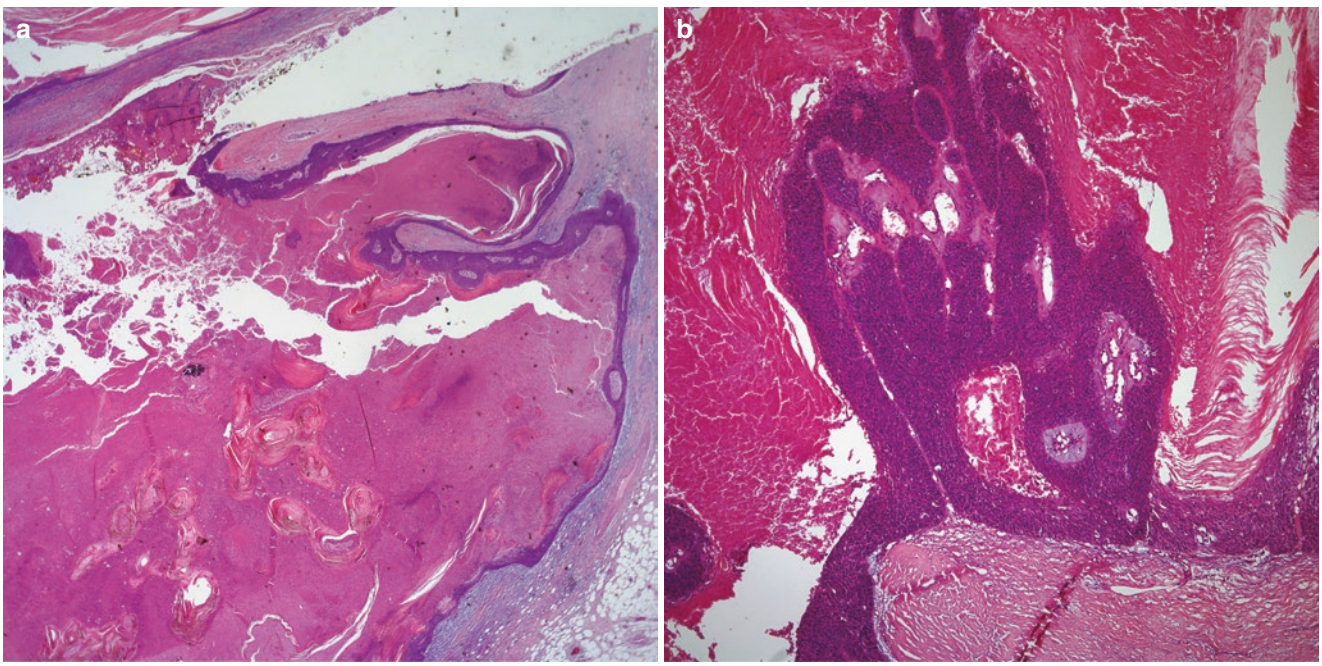


**Fig. 8.6** (**a**) Low power view of a cystic keratinizing squamous cell carcinoma. (**b**) Extensive keratinization and verrucous-like proliferation

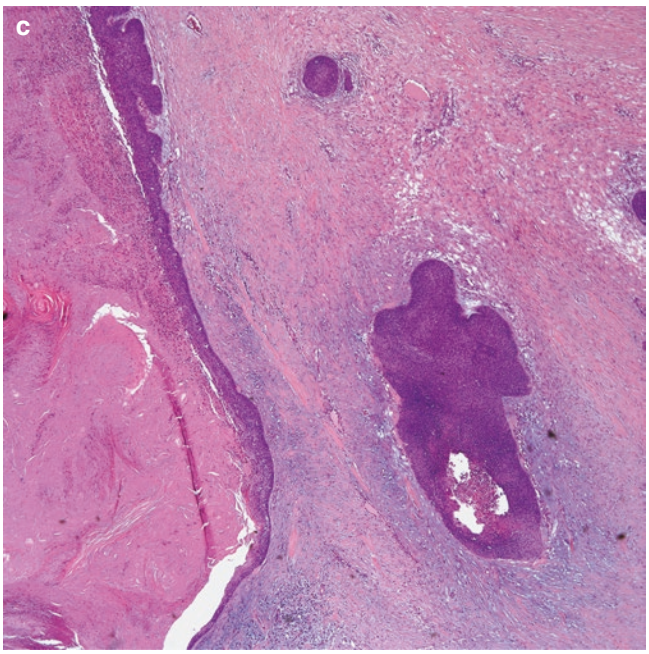


**Fig. 8.6** (continued) (**c**) Squamous carcinoma present in the wall of cystic structure

ture, or present with cystic changes similar to those seen in multilocular thymic cyst (Fig. 8.13a–d). The tumor may also show some versatility in the different growth patterns including neural-like, smooth muscle-like, carcinosarcoma-like, and synovial sarcoma-like, among others (Fig. 8.14a–d). Higher magnification of these tumors shows spindle cells with oval nuclei, scant cytoplasm, and prominent nucleoli, while mitotic activity in these tumors may vary from 3 to 10 × 10 hpf (Fig. 8.15a, b). Areas of necrosis and hemorrhage are commonly present. Recently, descriptions of sarcomatoid carcinoma arising in metaplastic thymoma have been reported [36, 37]. However, two issues arise in those cases: (1) the term metaplastic that was coined for these tumors was within thymic carcinoma and not thymoma, as the original description is thymoma with pseudosarcomatous stroma [31, 32], and (2) it appears that this description is a hybrid of two different terms for the same tumor, which in our opinion is thymoma but not metaplastic. However, if we take these reports at face value, then the reported cases belong in the spectrum of thymic epithelial tumors that shares features of thymoma and thymic carcinoma. In that regard, Suster and Moran [14] presented the largest series up to now with 22

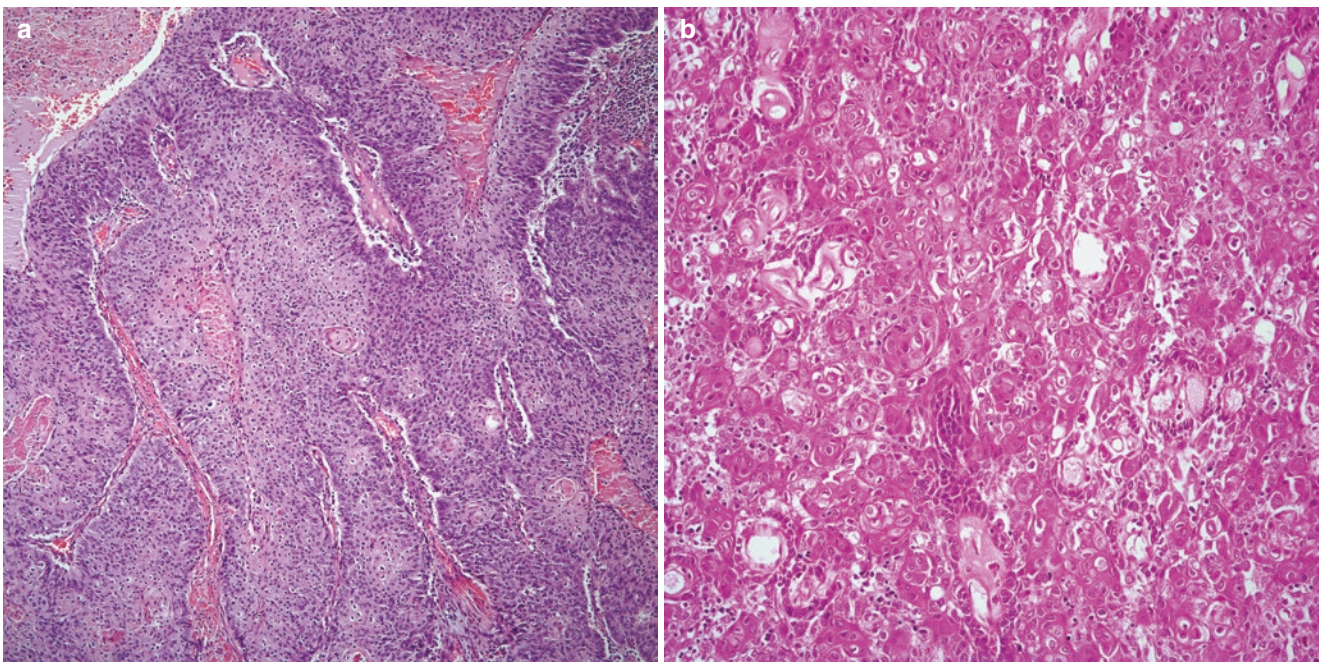


**Fig. 8.7** (**a**) Thymic squamous carcinoma with focal areas of keratinization. (**b**) More extensive keratinization

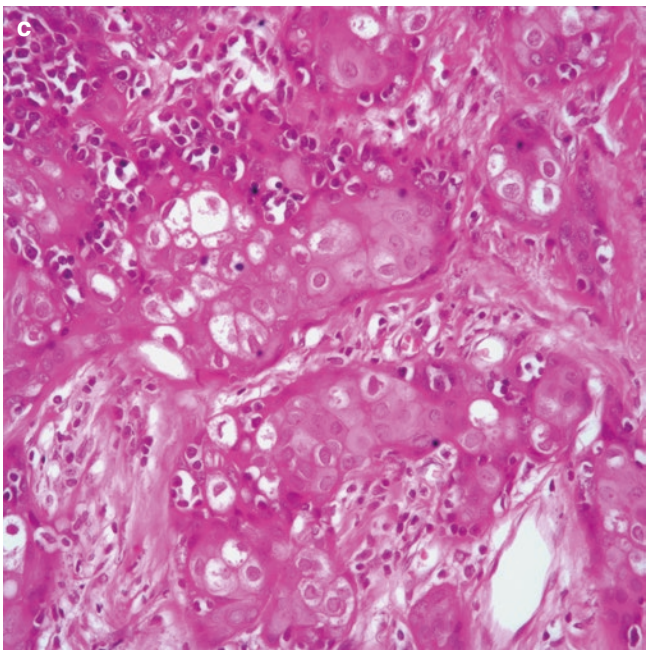


**Fig. 8.7** (continued) (**c**) Higher magnification showing keratinizing areas with mild nuclear atypia and absent mitotic activity

patients: 16 men and 6 women between the ages of 23 and 83 years. The cases reported included several different permutations between thymoma and thymic carcinoma in different proportions. Therefore, those cases of sarcomatoid carcinoma arising in metaplastic thymoma only expand the spectrum of such associations.

### Undifferentiated Carcinoma

This type of thymic carcinoma represents a minority of the cases; however, it may represent approximately 15% of all thymic carcinomas. Essentially, the tumor is composed of sheets or islands of neoplastic cells without any morphological differentiation toward squamous cell or neuroendocrine carcinomas. The tumors show marked cellular atypia and increased mitotic activity of more than 10 × 10 hpf (Fig. 8.16a–e). In addition, areas of necrosis and hemorrhage are commonly seen. Nonaka and coworkers [38] reported five cases of this type of carcinoma in which the tumor was associated with what the author designated as "Castleman's disease-like reaction." Interestingly, the authors also stated that this type of carcinoma might have an indolent behavior, as their five patients were alive after a period ranging from 1

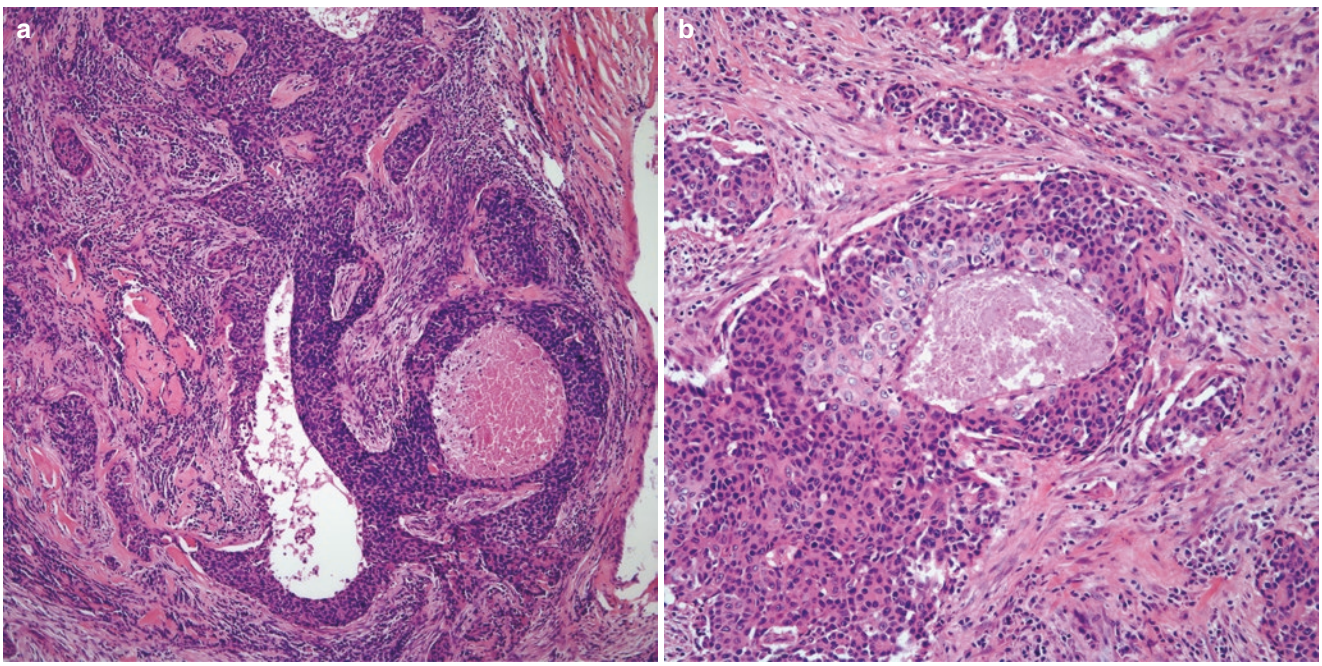


**Fig. 8.8** (**a**) Thymic carcinoma with focal areas of necrosis and inflammatory reaction. (**b**) Focal comedo-like necrosis

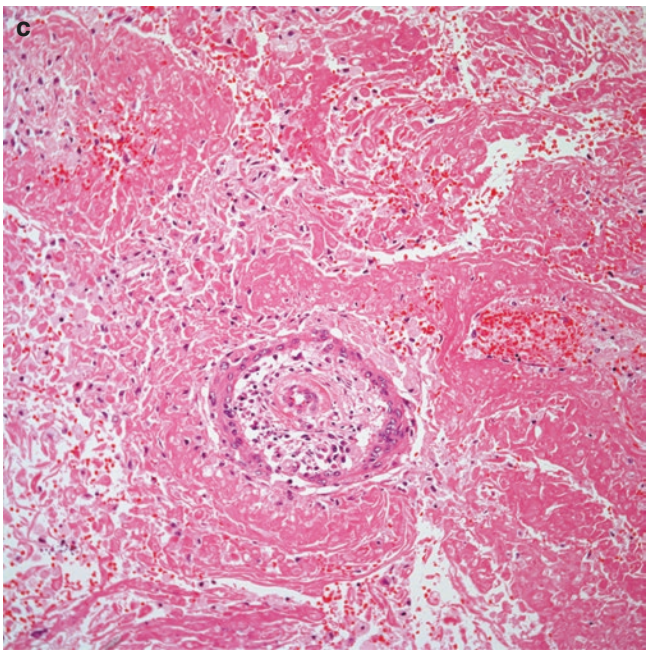


**Fig. 8.8** (continued) (**c**) Extensive keratin debris with little viable tumor

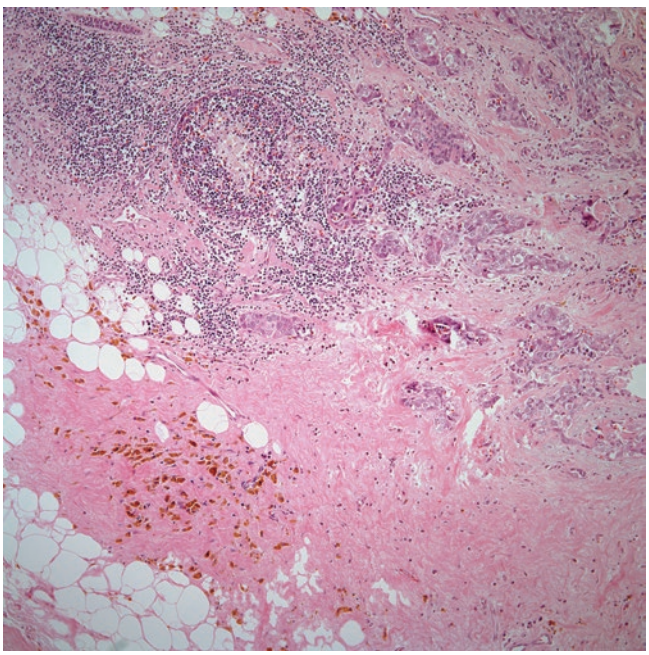

**Fig. 8.9** Thymic carcinoma showing infiltrative growth pattern into adipose and perithymic tissue

to 22 years. However, it is important to mention that in four of those patients, the tumor was limited to the anterior mediastinum and complete surgical resection was performed. In one other patient, only biopsy material was done followed by radiation therapy, but no tumor extension outside of the mediastinum was documented. Therefore, it is possible that it is not that this histology follows a good clinical course, but rather the extent of disease, which in these cases appears to be limited to the anterior mediastinum. Thus, this speaks more in favor of staging rather than histology as the driver of the clinical course. We have encountered similar tumors in which the histology is more worrisome, as the tumors may show focal areas of spindle cells admixed with round cells and prominent germinal centers, some of them with a vessel crossing the germinal center in a manner that mimics the hyaline vascular type of Castleman's disease (Fig. 8.17a–c).

### Lymphoepithelioma-Like Carcinoma

This particular variant of thymic carcinoma may represent approximately no more than 10% of all thymic carcinomas. The tumors characteristically show a syncytial growth pattern composed of large cells with ill-defined borders, vesicular nuclei, and prominent nucleoli. The tumor cells or islands of tumor cells are embedded in an inflammatory stroma composed predominantly of lymphocytes with scattered plasma cells. Areas of necrosis and hemorrhage are not prominent in these tumors, while the mitotic activity is variable and may range from <10 × 10 hpf to >10 hpf (Fig. 8.18a–g). It is of interest to highlight that reports of this type of thymic carcinoma associated with Epstein-Barr virus (EBV) have been reported in the literature. Dimery and coworkers [39] reported a case of thymic carcinoma in a 30-year-old woman who had serological evidence of infection with EBV, and Southern blot analysis showed the presence of the viral genome in the tissue. Leyvraz and coworkers [40] described a similar occurrence in a 19-year-old young man with thymic carcinoma. The authors concluded that the presence of EBV-associated nuclear antigen (EBNA) in the carcinoma cells and the high level of viral genome detected in the DNA suggest a role of the EBV in the genesis of this type of thymic carcinoma, similar to that seen in nasopharyngeal carcinoma.

### Papillary Carcinoma

Even though this tumor is presented here as specific variant of thymic carcinoma, it is very likely that it is part of the spectrum of thymic adenocarcinoma, as we have reported; (see the section on adenocarcinoma in this chapter). However,

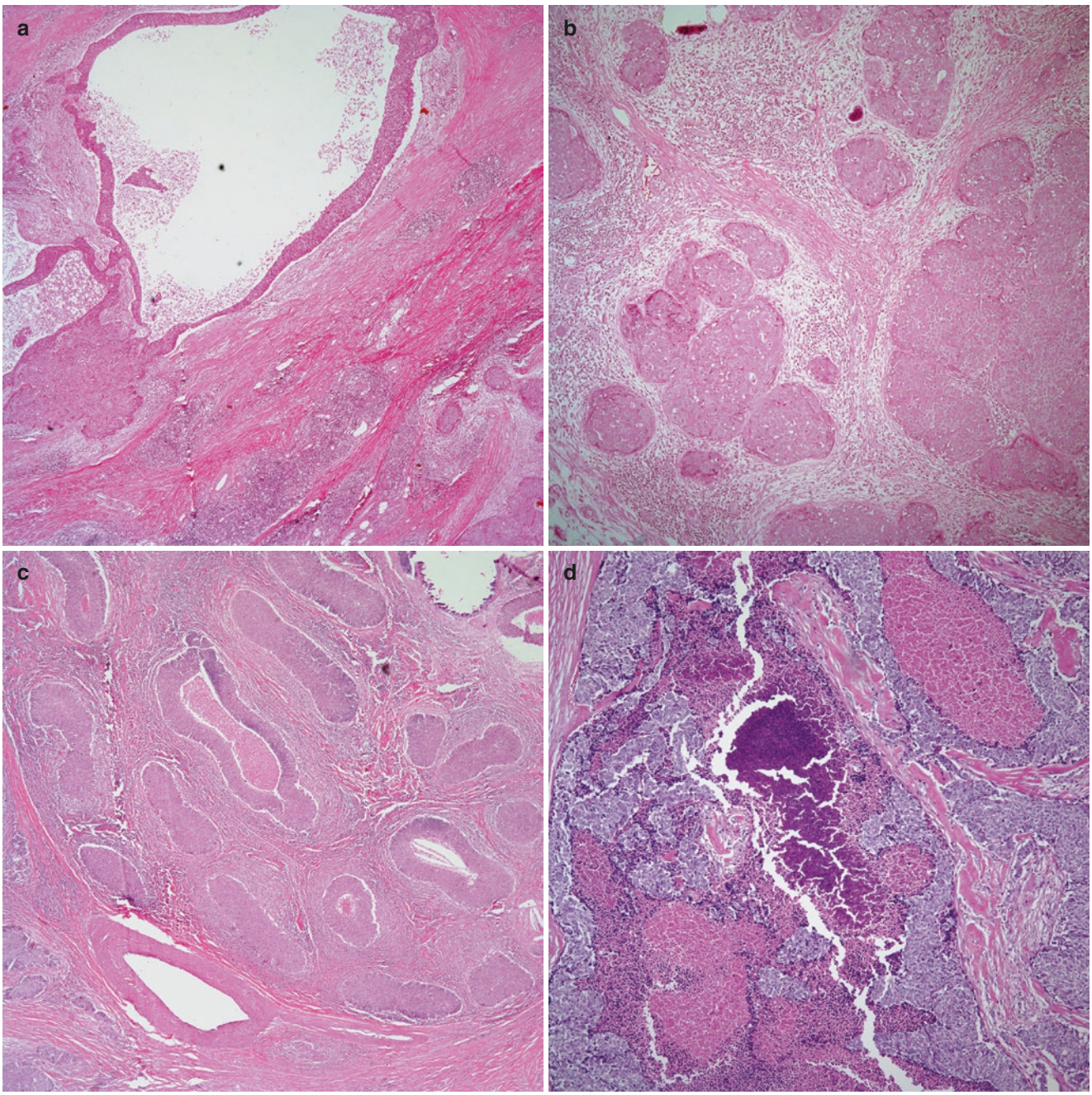


**Fig. 8.10** (**a**) Thymic carcinoma with cystic changes. (**b**) Small islands of tumors cells separated by fibroconnective tissue and inflammatory reaction. (**c**) Thymic carcinoma with comedo-like necrosis and inflammatory reaction. (**d**) Thymic carcinoma with extensive necrosis and single cell necrosis

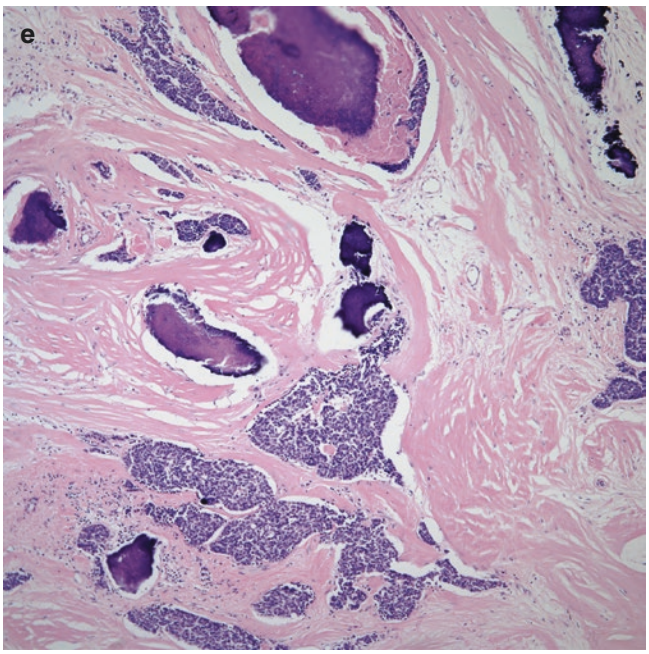


**Fig. 8.10** (continued) (**e**) Thymic carcinoma with numerous calcifications

this is another type of carcinoma that – even though it has been reported in some series of cases – credit for a report highlighting this type of thymic carcinoma is due to Matsuno and coworkers [41], who reported a small series of four cases with this histology. The low power view is of a well-circumscribed tumor that may be bordered by remnants of thymic tissue. Other histological features include a complex papillary growth pattern, papillary structures containing foamy histiocytes, loose and well-formed papillary structures, and solid-like areas in which the papillary structures are compressed (Fig. 8.19a–e). The papillary growth pattern may be formed by papillary structures without a fibrovascular core, with a fibrovascular core, with a mixture of these and compressed, and with a complex pattern (Fig. 8.20a–d). At higher magnification, these papillary structures can be lined by low cuboidal epithelium, columnar epithelium, clear cells with nuclear atypia, and/or columnar-like type of epithelium (Fig. 8.21a–d). Nuclear atypia and mitotic activity are variable, but in general the tumor does not show increased mitotic activity. Some cases have been reported in which the tumor also shows combined features of thymoma and thymic

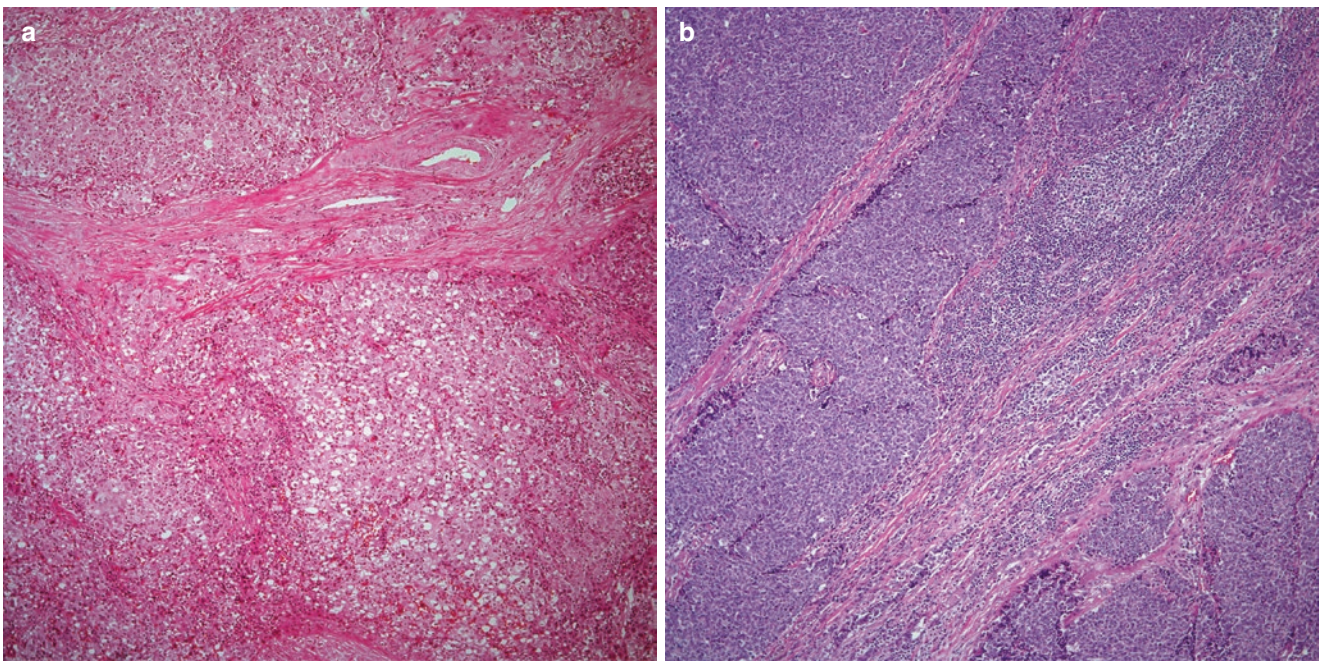


**Fig. 8.11** (**a**) Thymic carcinoma with irregular lobules of tumor cells. (**b**) Thymic carcinoma with sheets of tumors cells and presence of abortive germinal center

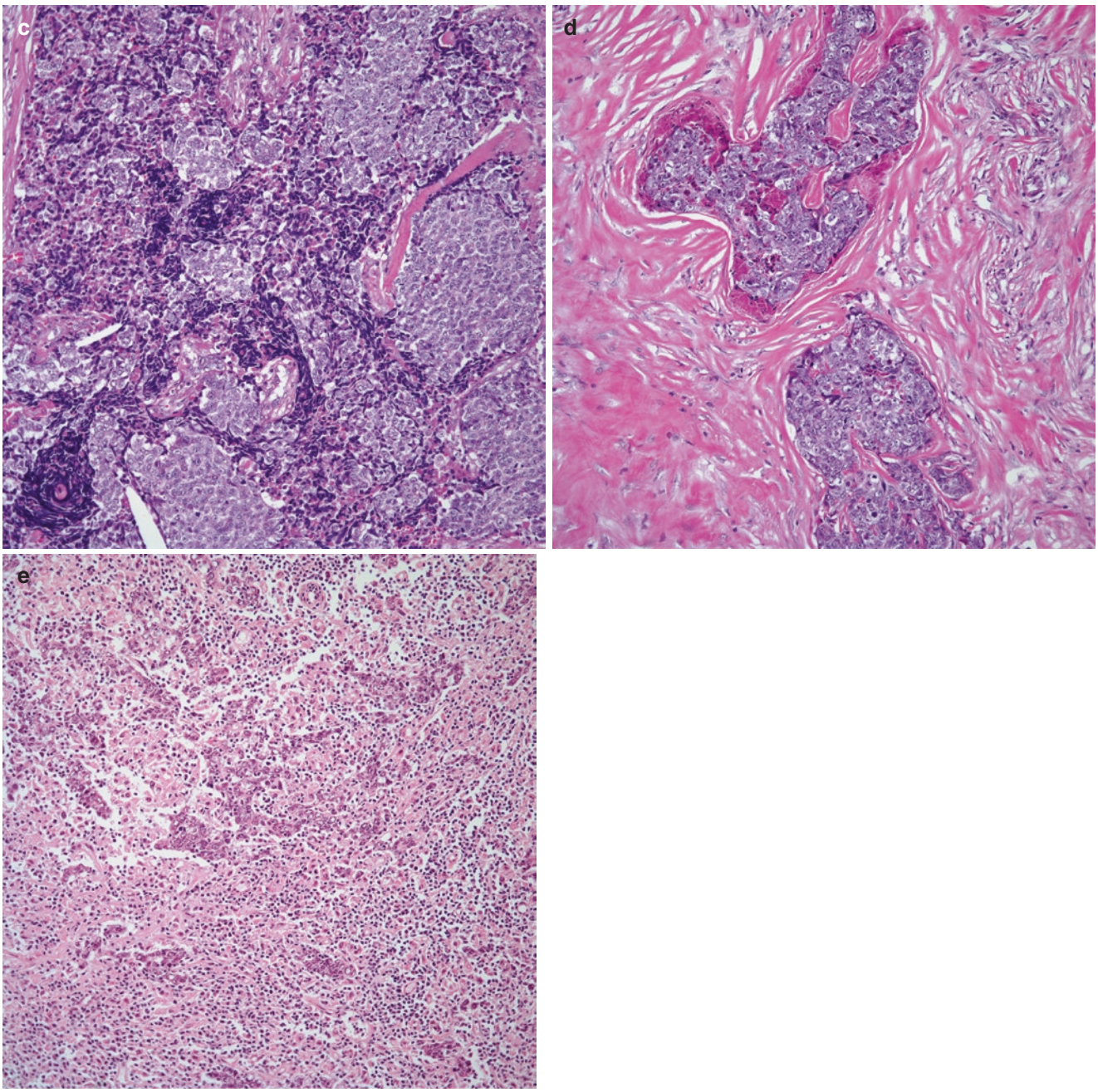


**Fig. 8.11** (continued) (**c**) Thymic carcinoma with areas of crush artifact. (**d**) Thymic carcinoma with extensive hyalinization. (**e**) Thymic carcinoma with extensive inflammatory reaction

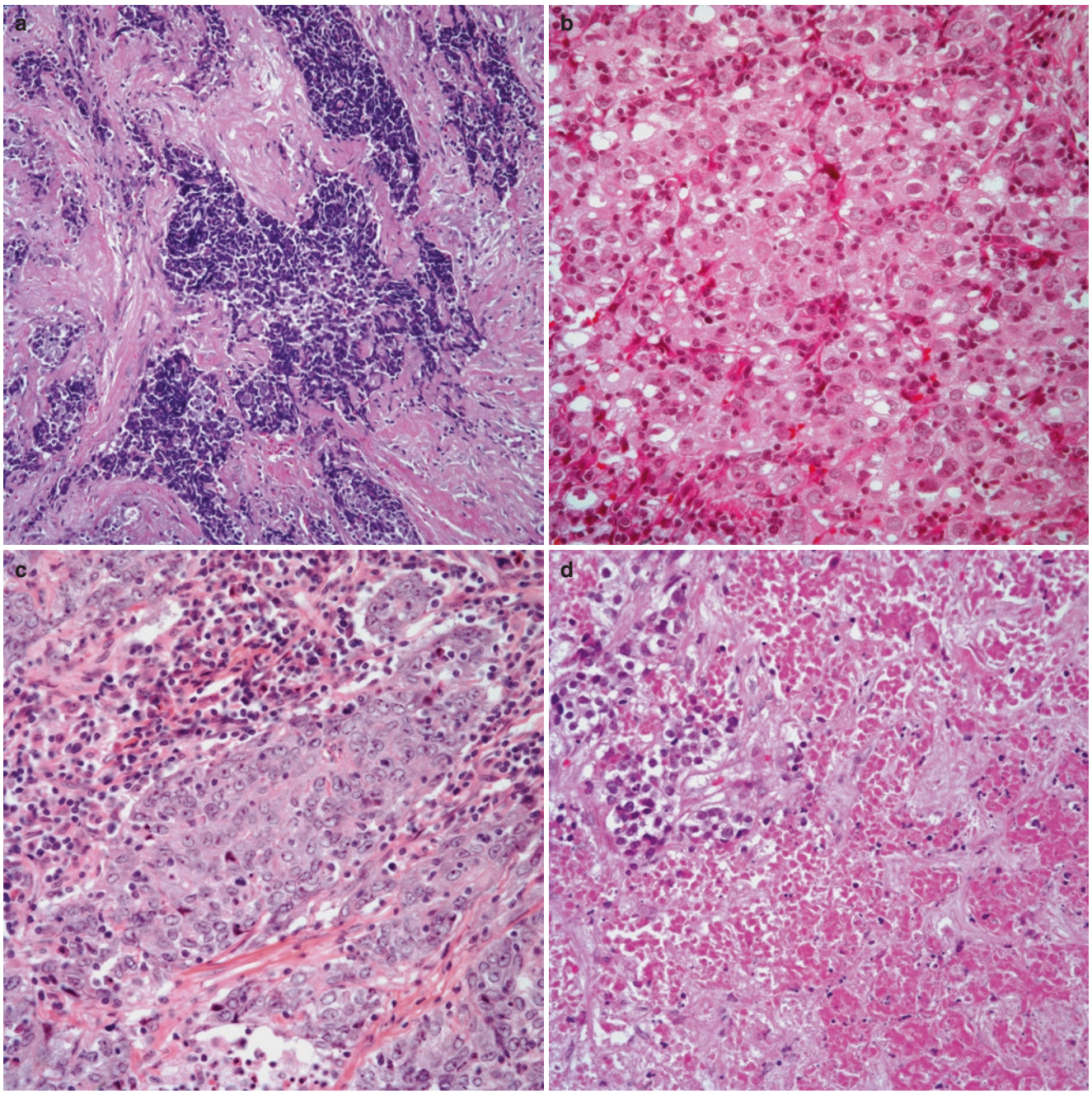


**Fig. 8.12** (**a**) Thymic carcinoma with areas mimicking small cell carcinoma. (**b**) Higher magnification of a thymic carcinoma showing medium size cells with round nuclei and prominent nucleoli. (**c**) Thymic carcinoma showing mitotic activity. (**d**) Thymic carcinoma with extensive areas of necrosis

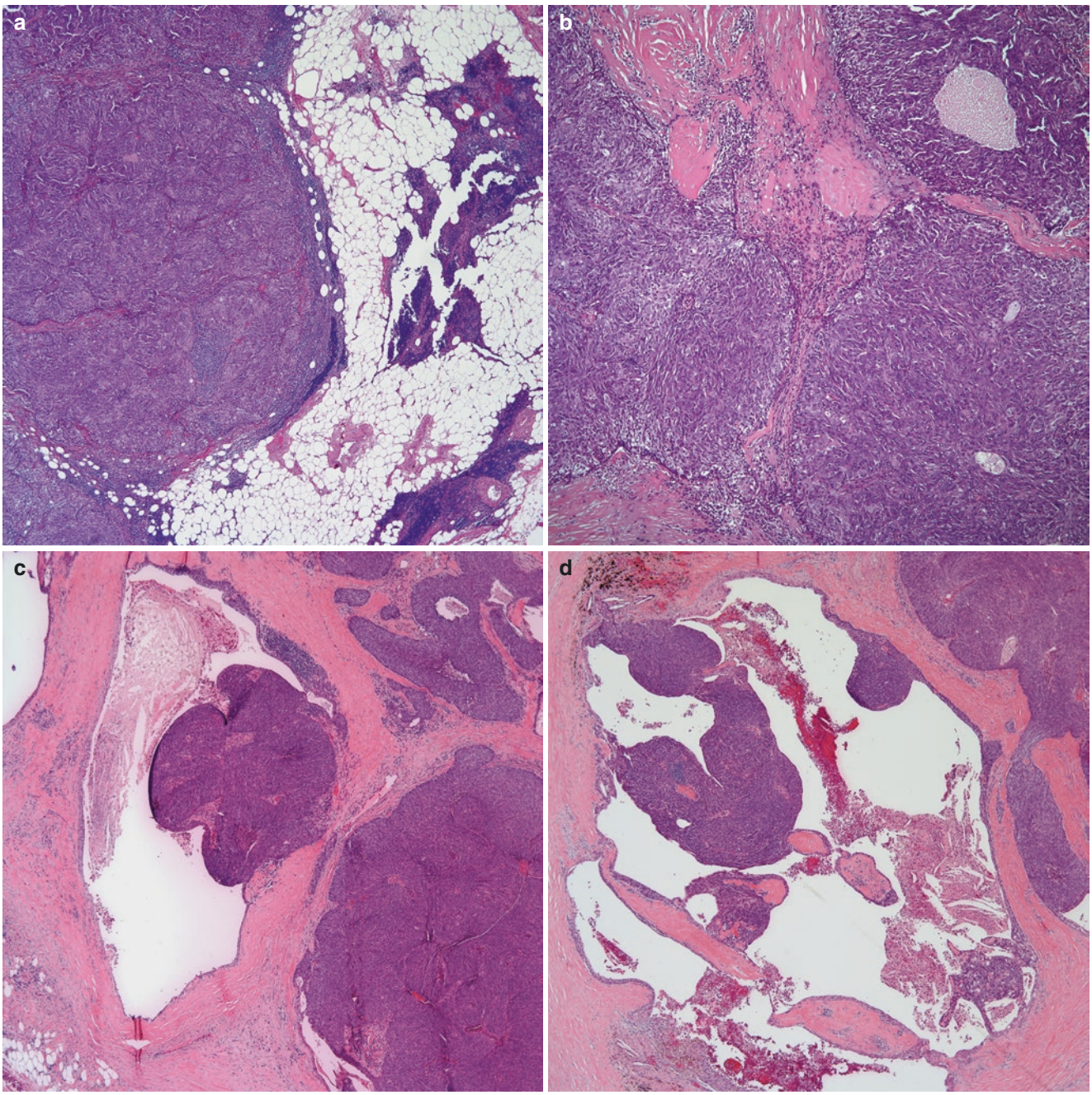


**Fig. 8.13** (**a**) Spindle cell thymic carcinoma penetrating perithymic adipose tissue. (**b**) Spindle cell thymic carcinoma preserving some lobular architecture. (**c**) Spindle cell thymic carcinoma with cystic changes. (**d**) Cystic changes similar to those in multilocular thymic cyst

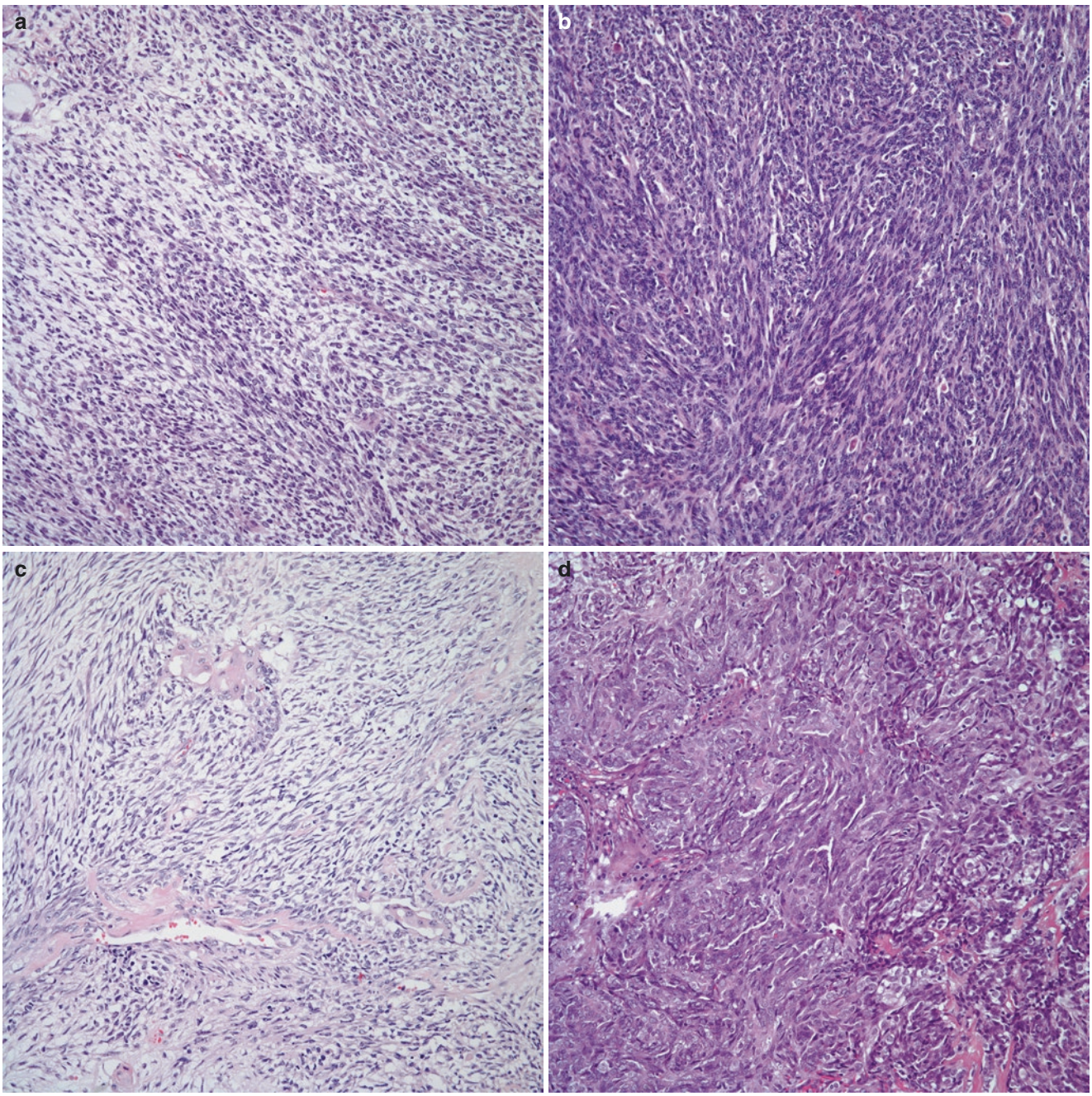


**Fig. 8.14** (**a**) Spindle cell thymic carcinoma with a subtle neural-like pattern. (**b**) Spindle cell thymic carcinoma with a smooth muscle-like pattern. (**c**) Spindle cell thymic carcinoma with carcinosarcoma-like pattern; note the presence of an island of classic squamous cell carcinoma. (**d**) Spindle cell thymic carcinoma with synovial sarcoma-like areas

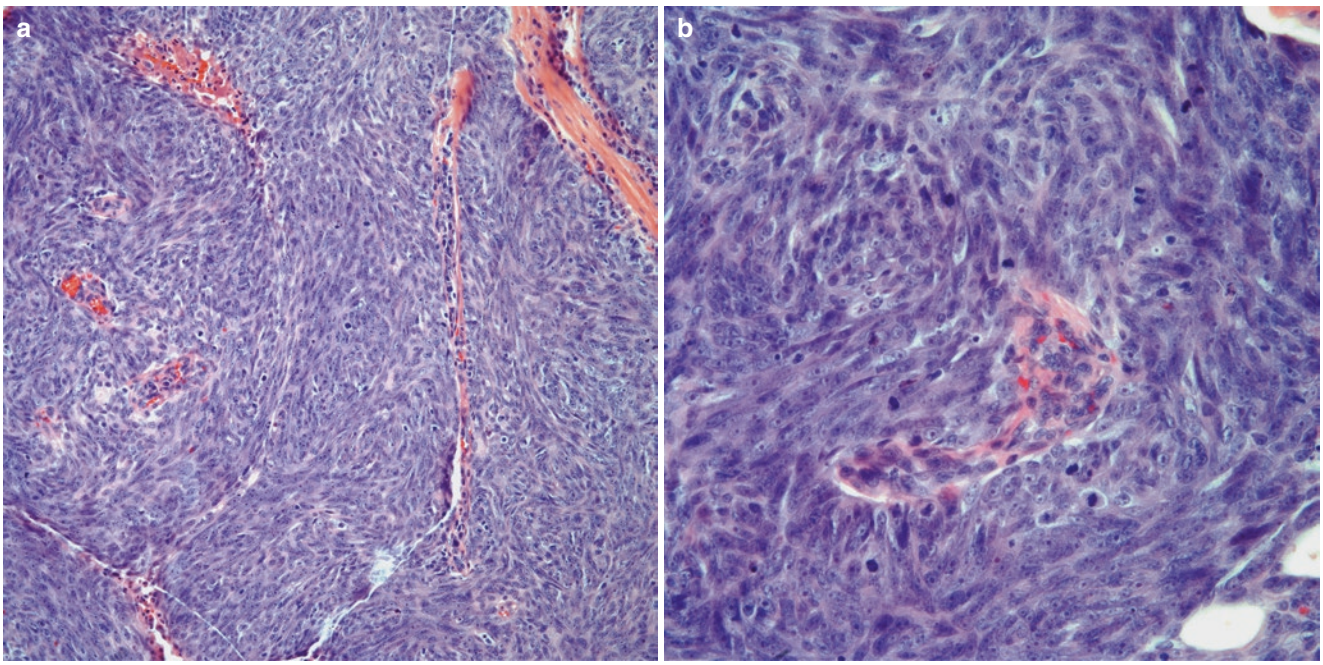


**Fig. 8.15** (**a**) Higher magnification of spindle cell thymic carcinoma showing fusiform cells, with scant cytoplasm, oval nuclei, and prominent nucleoli. (**b**) Spindle cell thymic carcinoma with mitotic activity

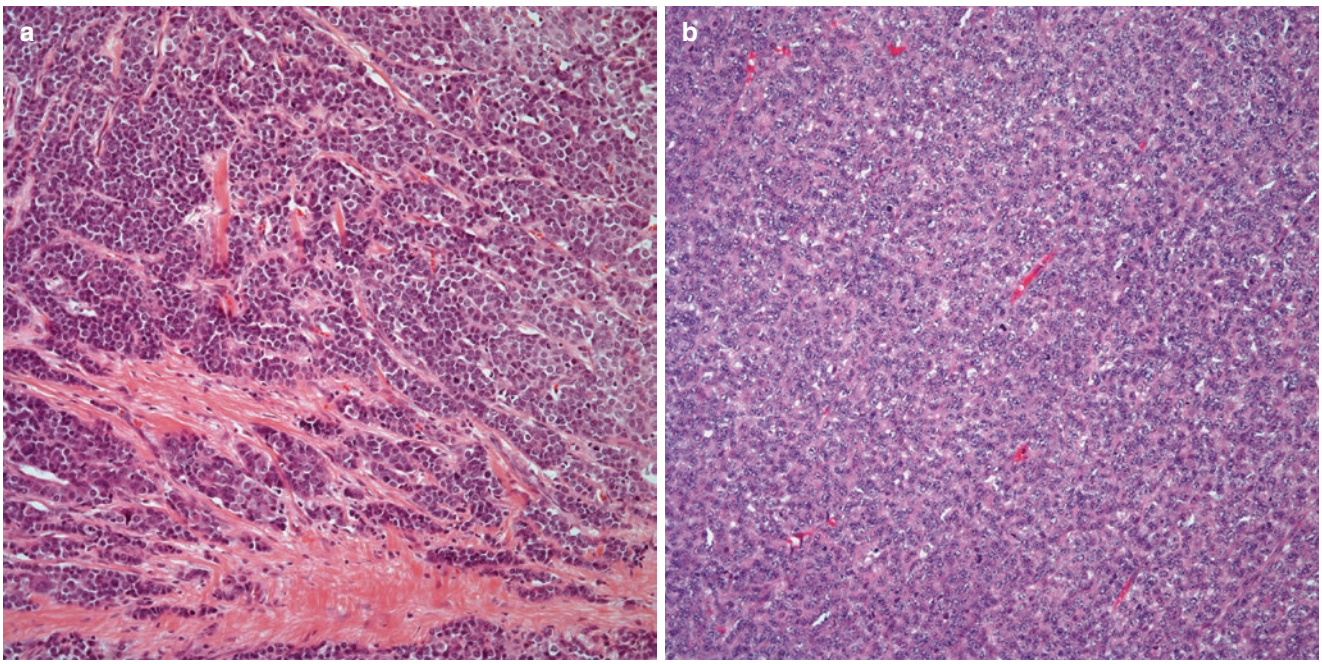


**Fig. 8.16** (**a**) Undifferentiated thymic carcinoma showing ribbons of tumor cells. (**b**) undifferentiated thymic carcinoma showing sheets of neoplastic cells

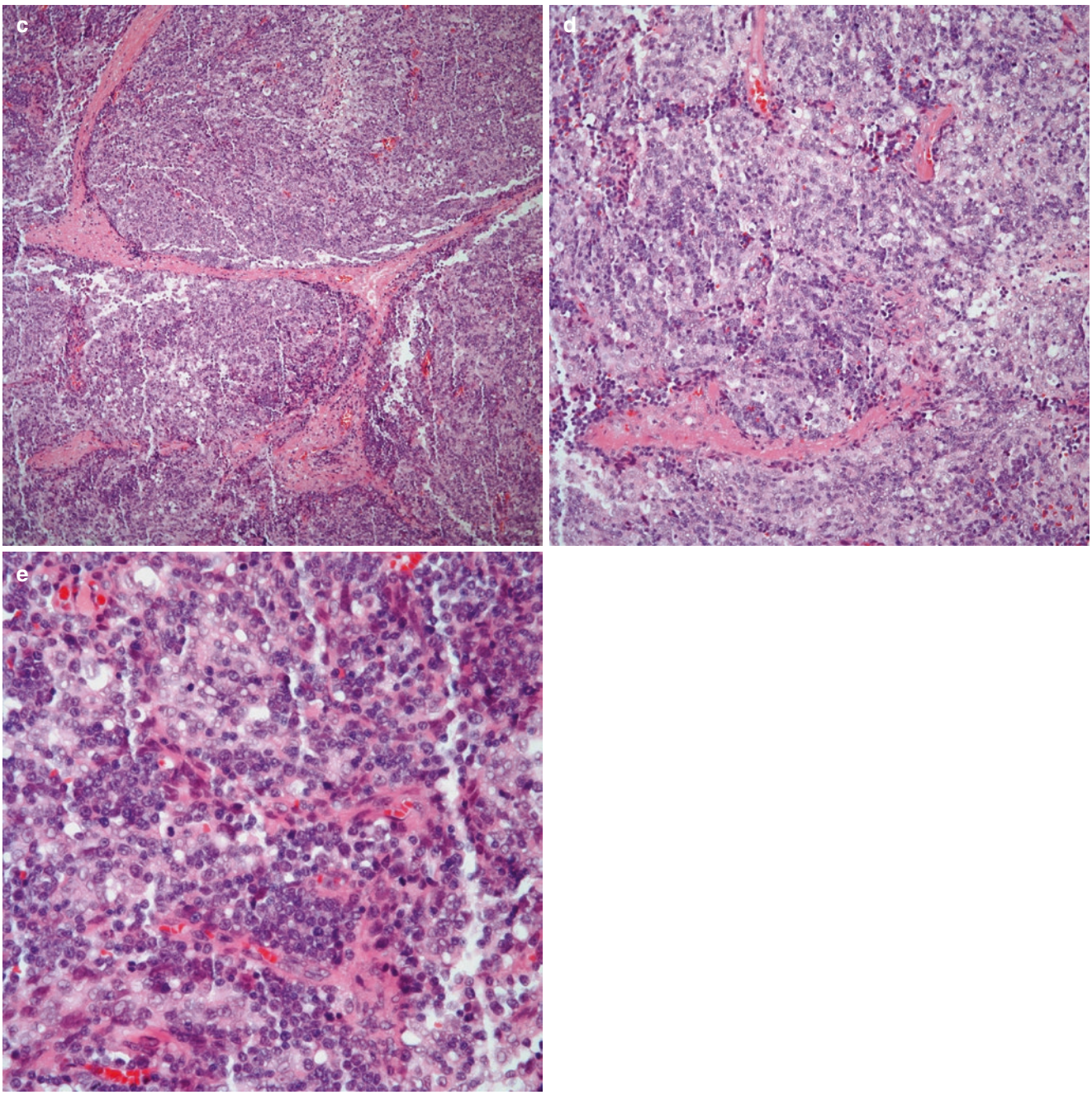


**Fig. 8.16** (continued) (**c**) Low power view of an undifferentiated thymic carcinoma showing lobulation. (**d**) Cellular atypia and absence of an inflammatory reaction in undifferentiated thymic carcinoma. (**e**) Mitotic figures are easily encountered

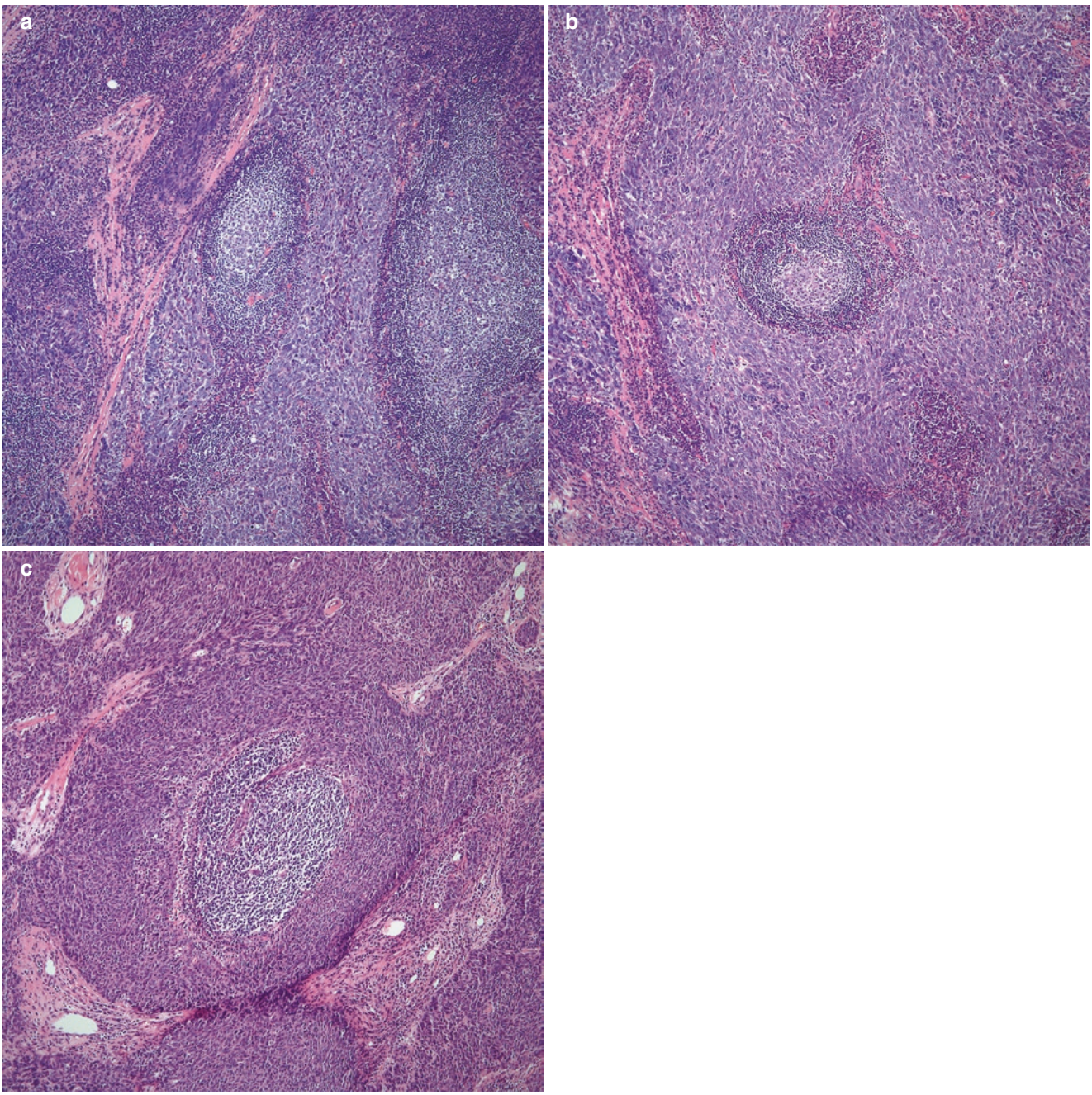


**Fig. 8.17** (**a**) Undifferentiated thymic carcinoma with prominent germinal centers. (**b**) Undifferentiated thymic carcinoma with mixture of round and spindle cells circling a germinal center. (**c**) Similar area of prominent germinal center with features mimicking Castleman's disease

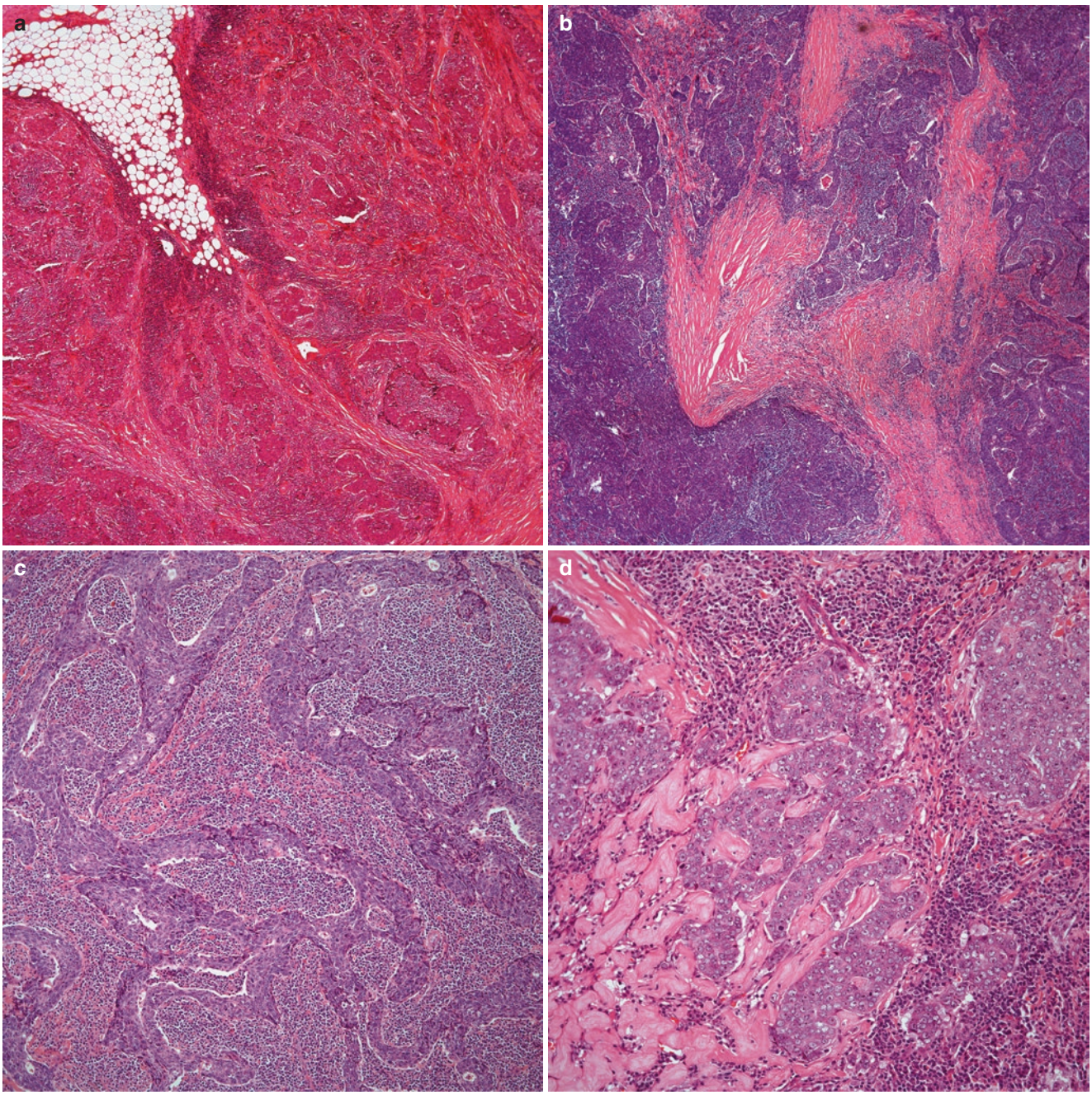


**Fig. 8.18** (**a**) Low power of a lymphoepithelioma-like carcinoma of the thymus infiltrating thymic and adipose tissue. (**b**) Lymphoepithelioma-like carcinoma with islands of tumor cells. (**c**) Ribbons of tumor cells embedded in an inflammatory background. (**d**) Tumor cells embedded in amyloid-like reaction admixed with inflammatory cells

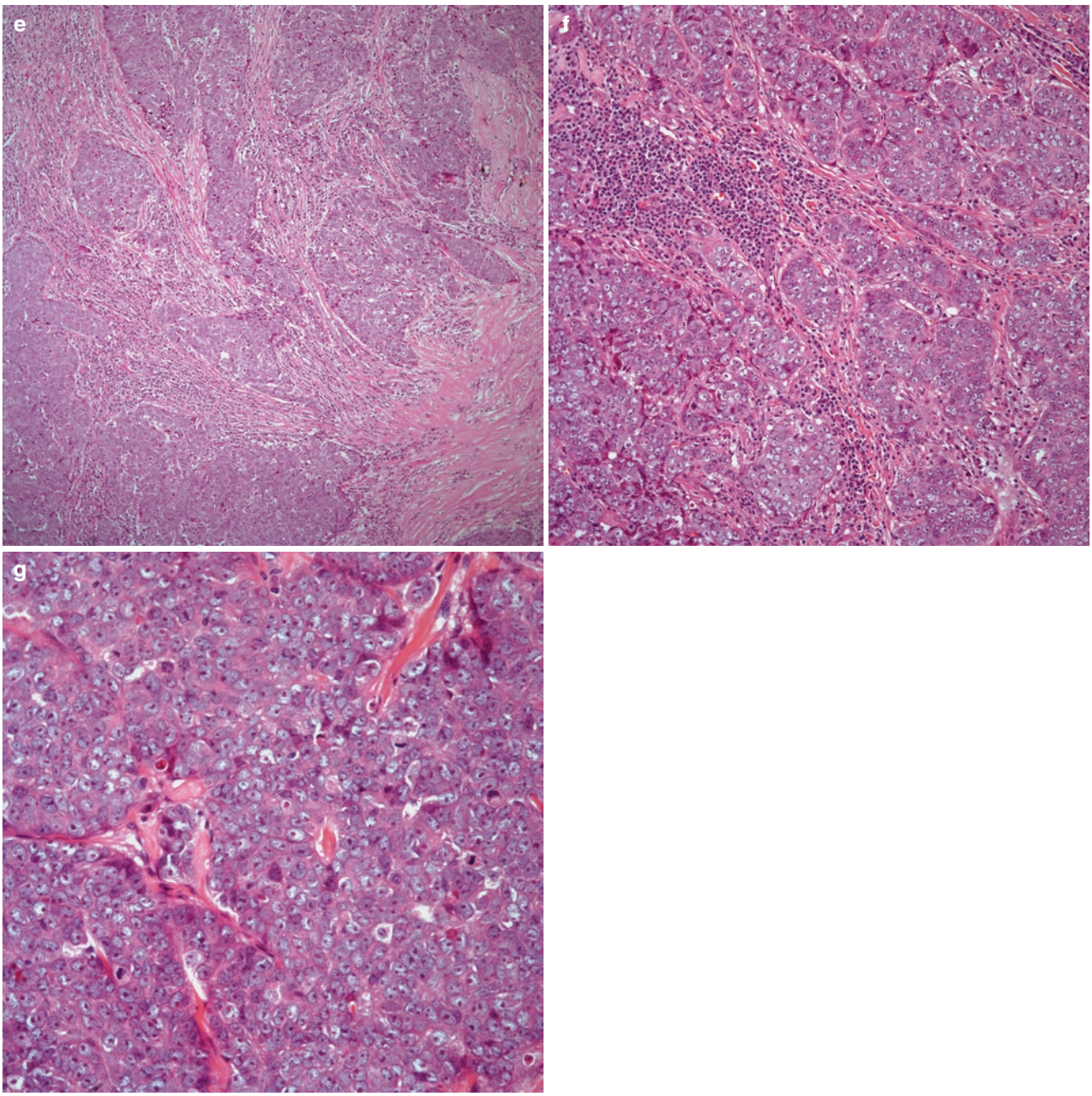


**Fig. 8.18** (continued) (**e**) Tumor islands infiltrating fibroconnective tissue in an irregular growth pattern. (**f**) Tumor composed of medium-sized cells with round nuclei and prominent nucleoli. (**g**) Mitotic activity is easily encountered

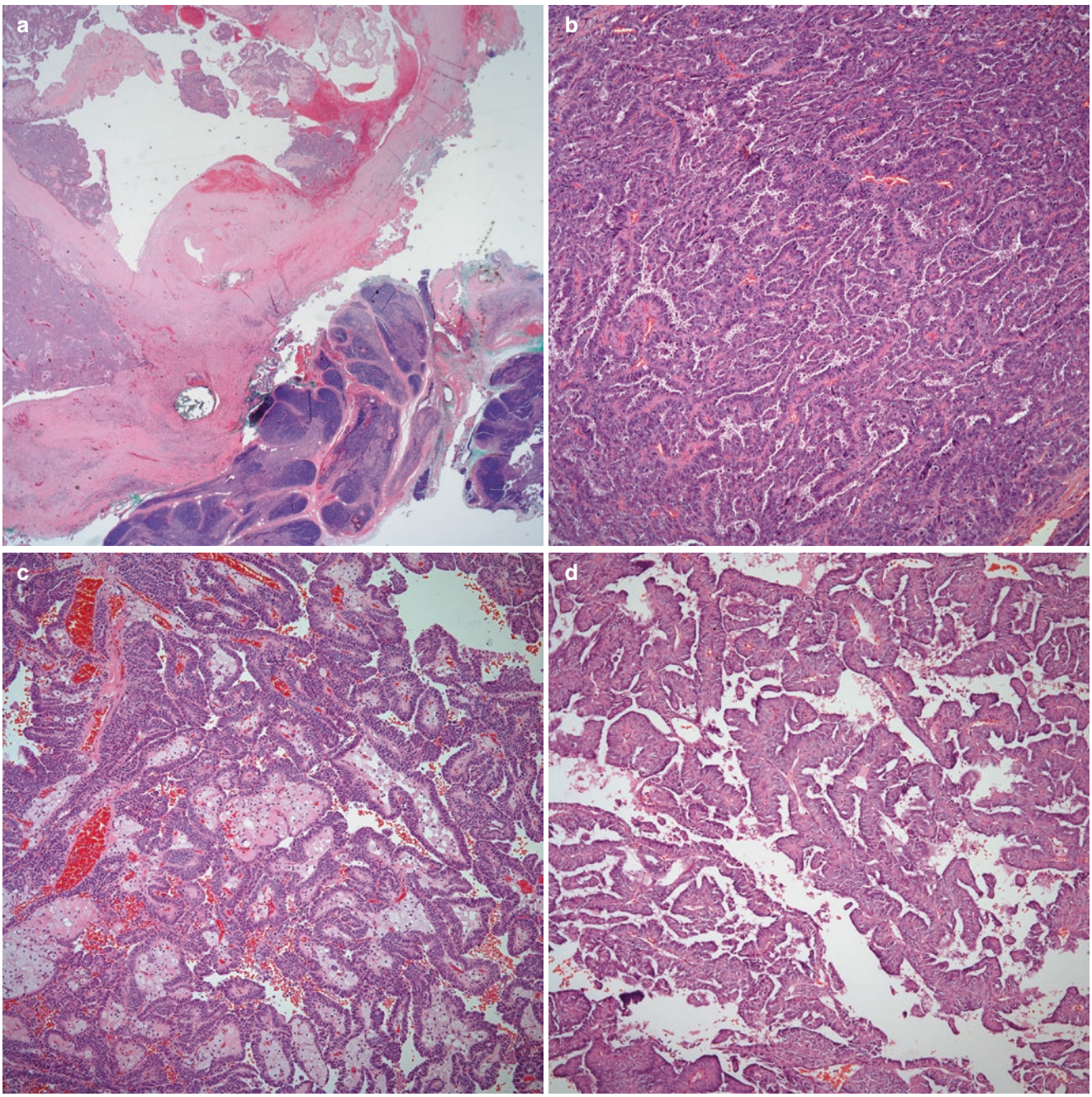


**Fig. 8.19** Different growth patterns of papillary thymic adenocarcinoma. (**a**) Cystic tumor with a rim of thymic tissue in the periphery. (**b**) Tightly packed papillary structures arranged in a complex pattern. (**c**) Papillary structures filled with foamy macrophages. (**d**) Slimmed papillae with fibrovascular cores

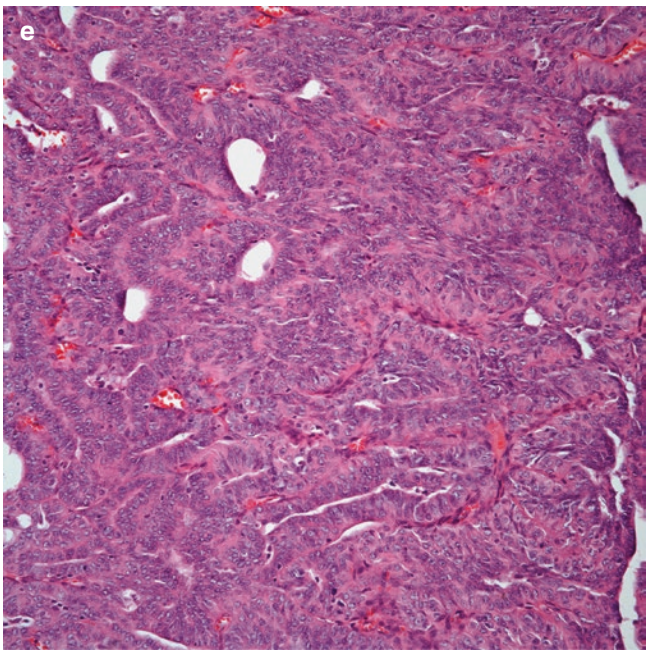


**Fig. 8.19** (continued) (**e**) Solid-like areas in which the papillae are compressed

carcinoma. In general terms, thymic papillary carcinomas are rare and account for no more than 2–3% of these tumors. In addition, we have reported another variant in a recent publication on thymic adenocarcinomas in which the tumor shows a micropapillary growth pattern. Characteristically, micropapillary structures are floating in empty spaces separated by thin fibroconnective tissue. Psammoma bodies are common, and the micropapillae are lined by low cuboidal epithelium. Mitotic activity, nuclear atypia, and necrosis are generally absent (Fig. 8.22a–c).

### Clear Cell Carcinoma

Snover and Rosai originally mentioned this type of thymic carcinoma in their publication on the "five distinctive histological variants," as the authors reported one case among others [7]. In addition, it has been anecdotally recorded in other series of thymic carcinomas as well as in case reports [42, 43]. The case described by Wolfe and colleagues [42] was in a 33-yer-old man with symptoms of fatigue and weight loss who showed an anterior mediastinal mass upon thoracic imaging. The case reported by Stephens and colleagues [43]

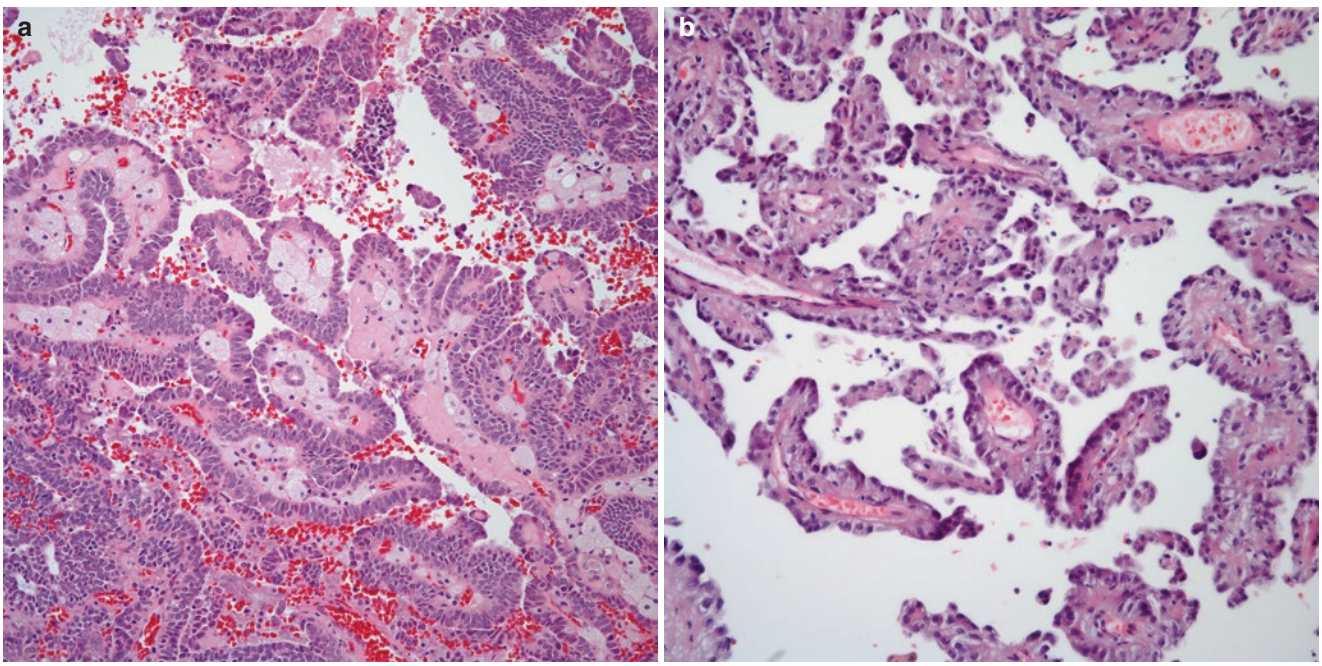


**Fig. 8.20** Intermediate view of papillary thymic adenocarcinoma. (**a**) Papillary structures without significant nuclear atypia or mitotic activity. (**b**) Papillary structures of different sizes and shapes with fibrovascular core

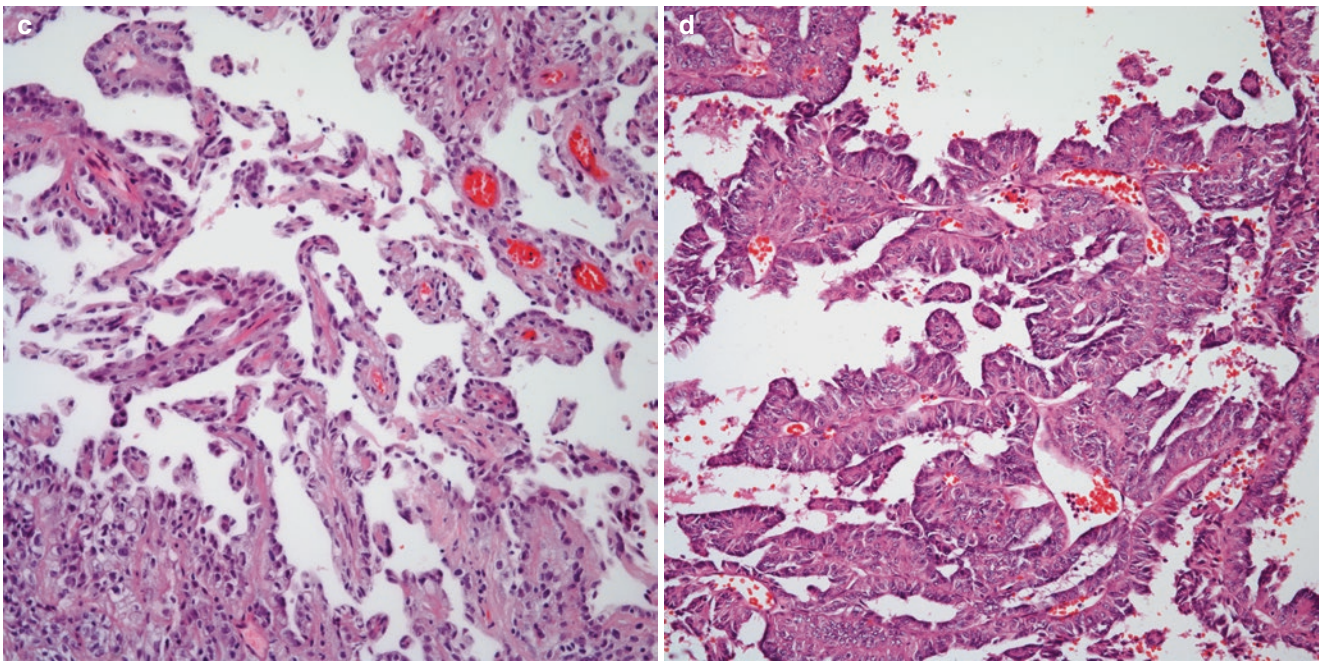


**Fig. 8.20** (continued) (**c**) Elongated and compressed papillary structures. (**d**) Well-formed papillary structures with fibrovascular core

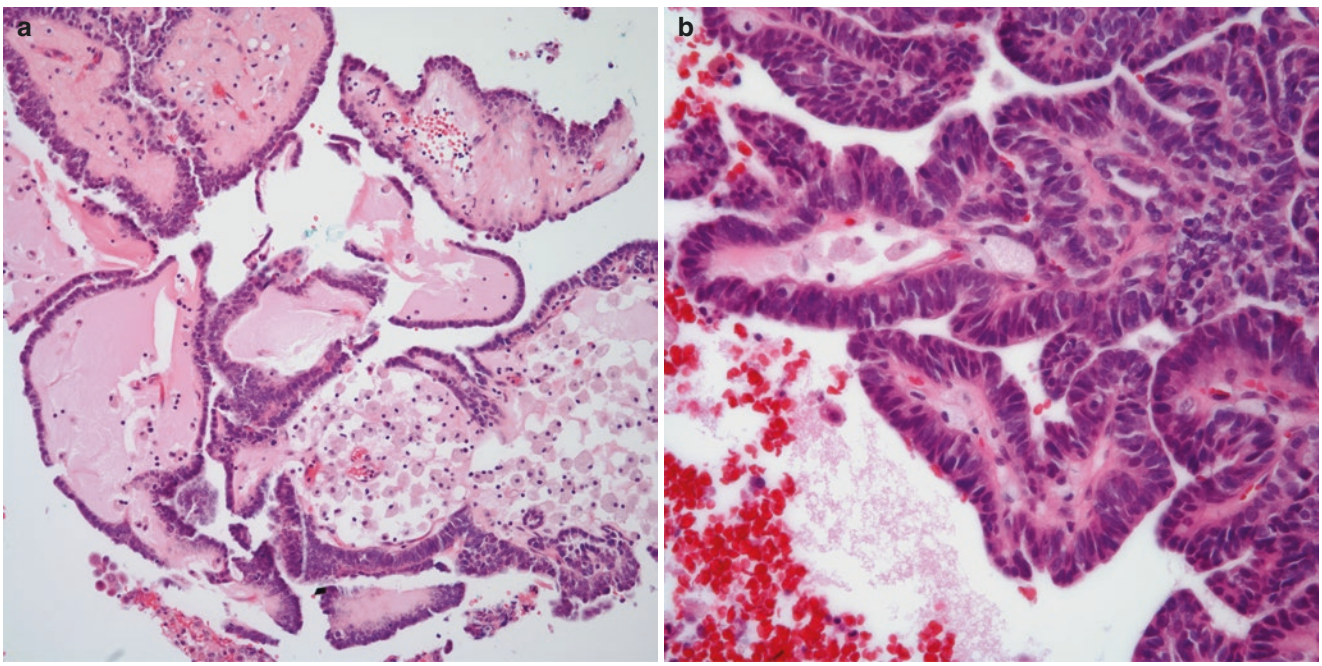


**Fig. 8.21** High power view of papillary thymic adenocarcinoma. (**a**) Papillae lined by low cuboidal epithelium with minimal nuclear atypia and absent mitotic activity. (**b**) Papillary structures lined by columnar epithelium

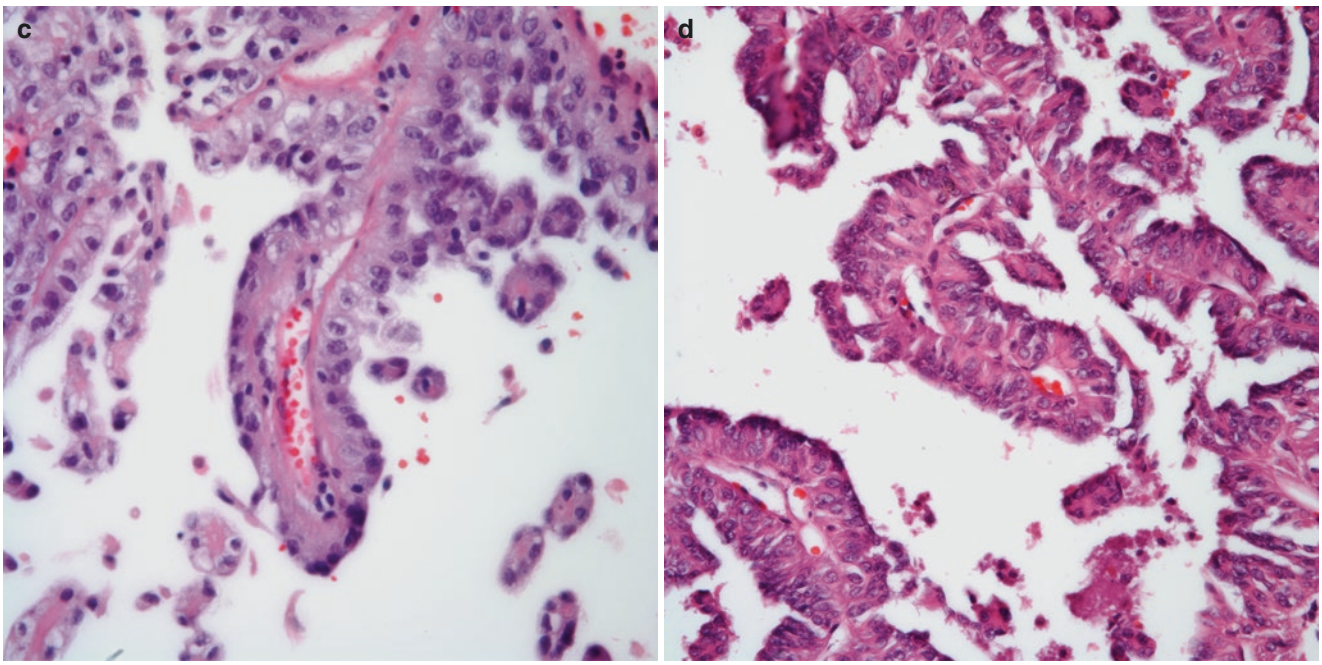


**Fig. 8.21** (continued) (**c**) Papillary structures lined by cells with clearing of the cytoplasm and showing nuclear atypia. (**d**) Papillary structures lined with columnar-like type of epithelium

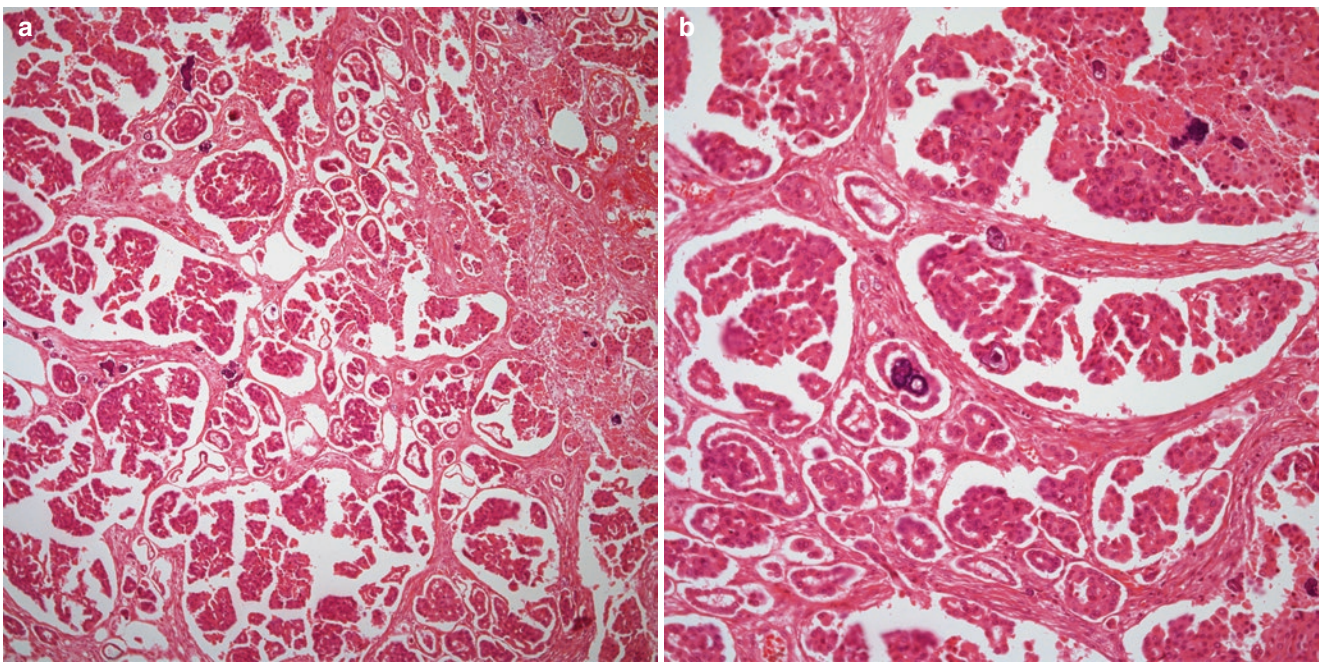


**Fig. 8.22** Thymic micropapillary adenocarcinoma. (**a**) Micropapillae floating in empty spaces. (**b**) Micropapillae with scattered psammoma bodies

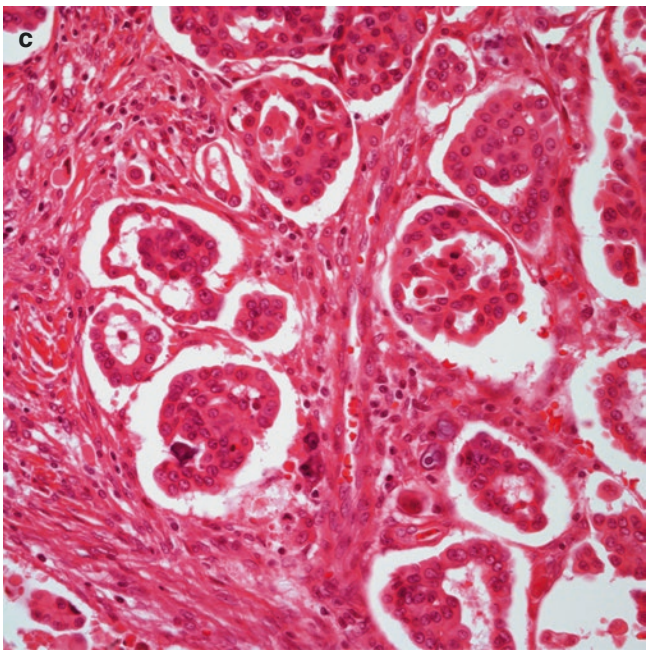


**Fig. 8.22** (continued) (**c**) Micropapillae lined by low cuboidal epithelium with absent nuclear atypia or mitotic activity

was in a 72-year-old man who was asymptomatic, and the mediastinal mass was encountered during routine imaging. Hasserjian and colleagues [44] reported the largest series of thymic carcinomas with clear cell features in a report of eight cases: five men and three women between the ages of 36 and 84 years (mean, 52 years). Two patients were asymptomatic, and the remaining patients showed non-specific symptoms including dyspnea and chest pain. Follow-up information showed that four patients had died, while one additional patient had persistent disease. Even though it is not clear what the exact stage of the tumor was at the time of diagnosis, the authors estimated a median survival for patients who died of tumor at 13 months (range, 4–24 months).

The histopathological features of these tumors in all the cases reported appear to be fairly similar. In our experience with this type of histology, we have observed that the tumor at low power view may preserve some of the lobular architecture in which the tumor cells are arranged in irregular nests of tumor cells with areas of necrosis and separated by fibroconnective tissue (Fig. 8.23a, b). The tumor shows sheets or cords of neoplastic cells, composed of round to oval cells with clear cytoplasm, round nuclei, and inconspicuous nucleoli (Fig. 8.24a–c).

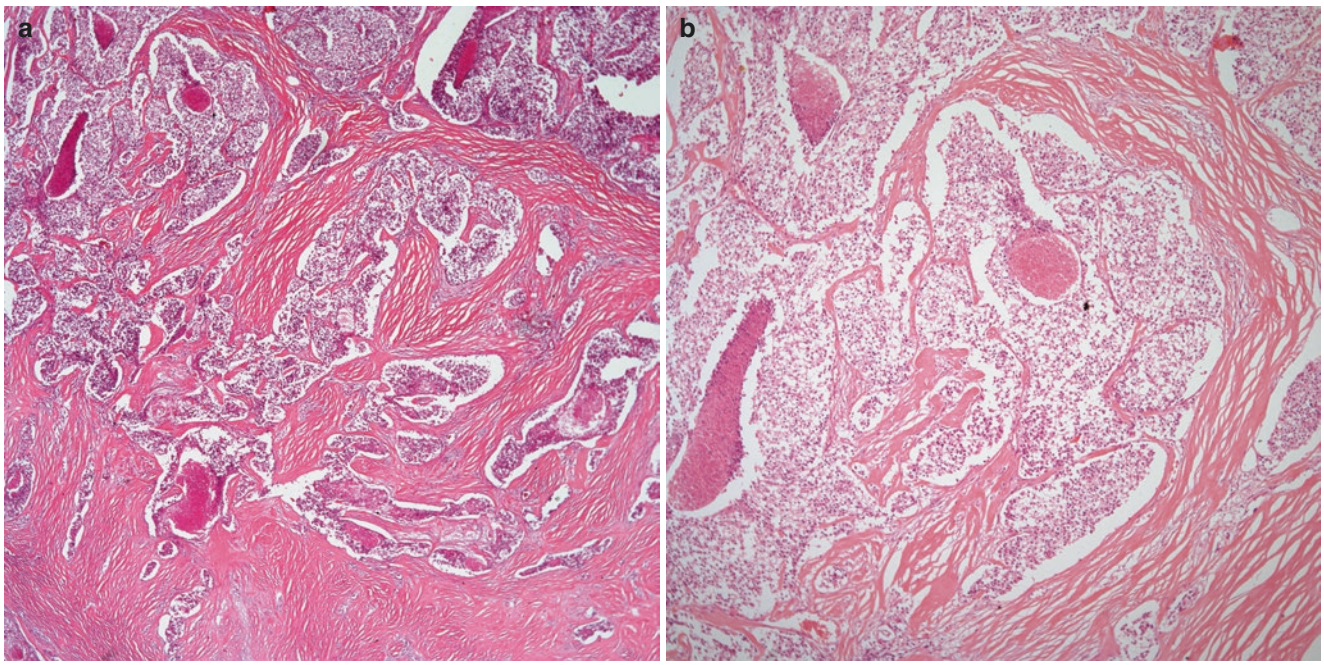


**Fig. 8.23** Low power view of thymic carcinoma with clear cells features. (**a**) Tumor still preserves some lobular architecture, form by irregular nests of tumor cells. (**b**) Nests of tumor cells with necrosis, separated by fibroconnective tissue

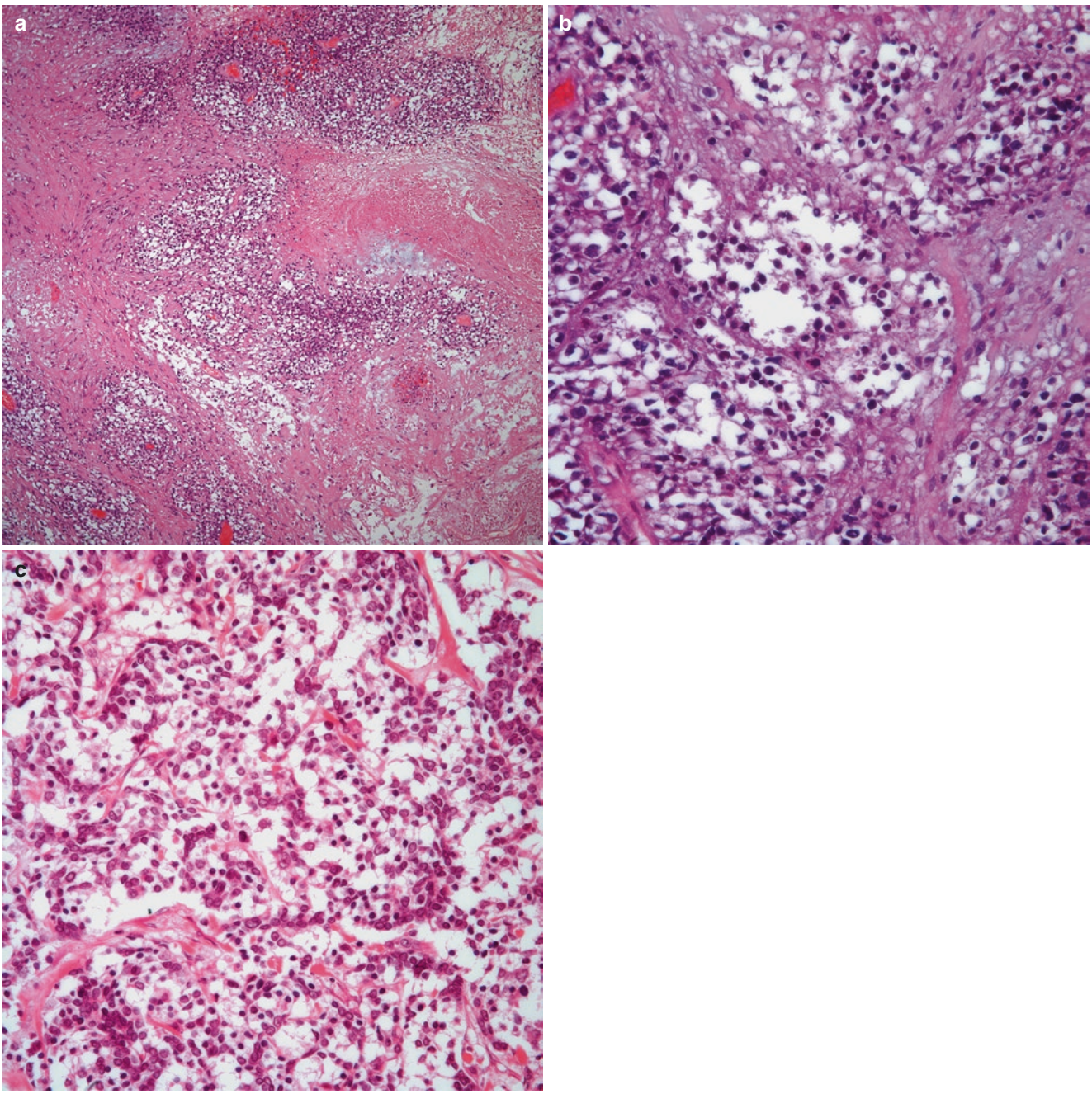


**Fig. 8.24** Intermediate power view of thymic carcinoma with clear cell features. (**a**) Sheets of tumor cells admixed with necrotic areas. (**b**) Small nests of tumor cells with apoptotic nuclei. (**c**) Fairly homogeneous cellular population with mild nuclear atypia

Cellular atypia is not marked, and mitotic activity is variable and can be as high as 10 × 10 hpf (Fig. 8.25a–c). The tumor does not show glandular differentiation nor the presence of goblet cells. A focus of squamous cell differentiation has been reported in a single case. Lymphocytes are scant and generally admixed with tumor cells. Histochemical stain for periodic acid-Schiff (PAS) shows the presence of intracellular glycogen, while mucicarmine histochemical stain is generally negative for intracellular mucin. In general, thymic carcinomas with clear cell features account for no more than 3% of all thymic carcinomas.

### Rhabdoid Carcinoma

This is a rare variant of thymic carcinoma representing no more than 1% of all these tumors. Tropani and colleagues [45] in 2003 reported what appears to be the first documentation of this unusual variant in a 67-year-old man who presented with chest pain and hemoptysis and who, upon chest imaging, was shown to have an anterior mediastinal mass. A radical thymectomy was performed, obtaining an 8 cm tumor mass, which histologically showed a solid proliferation of neoplastic cells arranged in nests and sheets of large pleomorphic cells with large nuclei and prominent nucleoli. The most salient feature of these tumors is the presence of intracytoplasmic paranuclear inclusions displacing the nuclei to the periphery of the cell. Mitotic activity is variable but easily identifiable. In our experience with these growth patterns, we have seen only a few of these types of cases with similar features as those described by Tropani and colleagues [45] in which the tumor shows a prominent neoplastic cellular proliferation composed of rhabdoid cells arranged in sheets of neoplastic cells (Fig. 8.26a–c).

### Hepatoid Carcinoma

This variant of thymic carcinoma was documented by Franke and colleagues [46] in a case report of a 70-year-old woman with symptoms of dyspnea, who was found to have an anterior mediastinal mass. Resection of the mediastinal mass was performed, and the tumor was described as well circumscribed, measuring more than 10 cm in greatest diameter. Histologically, the tumor was described as solid or trabecular sheets of neoplastic cells with a subtle nodular pattern, composed of medium-sized, round cells with round nuclei and prominent nucleoli. Mitotic activity was described as present but not increased. Intraepithelial lymphocytes were not observed. It is possible that this variant of thymic carcinoma may merge with other tumors that in other series of cases have been termed "undifferentiated large cell" carcinoma. In our experience with this type of histology, we have observed a similar growth pattern that is characteristically nodular, and separated by thin fibroconnective tissue with inflammatory cells. These nodules are composed of polygonal cells with ample eosinophilic cytoplasm, round nuclei, and nucleoli. At higher magnification, the tumor cells may have intranuclear inclusion and also show the presence of intracytoplasmic hyaline globules (Fig. 8.27a–d).

### Anaplastic Carcinoma

This variant is also rare and may account for approximately 1% of all thymic carcinomas. Once again, this type of carcinoma has been recognized in other series of cases and may be related to tumors that have been coded under different terminology, such as large cell undifferentiated or pleomorphic carcinoma. In 2012, we reported six cases of such a tumor under the designation of "anaplastic carcinoma" [47]. The tumors were described in five women and one man between the ages of 42 and 72 years (mean, 62 years) who presented with non-specific symptoms including cough, dyspnea, and chest pain. Histologically, the tumors are characterized by the presence of islands of tumor cells composed of large polygonal cells with distinct cell borders, basophilic cytoplasm, marked nuclear pleomorphism, and prominent nucleoli. Presence of atypical multinucleated giant cells is often seen haphazardly placed between tumor cells. Mitotic activity is easily identifiable but is not dramatically increased. Follow-up was available in only four of the six cases described and showed that three patients had died between 14 and 63 months after initial diagnosis. It was concluded that thymic anaplastic carcinoma has an aggressive behavior (Fig. 8.28a–c).

### Micronodular Carcinoma with Lymphoid Hyperplasia

This variant represents the malignant counterpart of micronodular thymoma with lymphoid hyperplasia described by Suster and Moran in 1999 [48] (see the chapter on thymoma). This thymic carcinoma variant [49] was reported in five patients, three men and two women between the ages of 42 and 78 years (mean: 64 years). Three patients were asymptomatic, while two patients presented with non-specific symptoms of dyspnea and chest pain. Histologically, the tumor characteristically grows in a micronodular fashion with islands of epithelial cells embedded in a lymphoid-rich stroma, which shows florid lymphoid hyperplasia with presence of germinal centers. The epithelial islands, contrary to the thymoma counterpart, show a marked atypical cellular proliferation composed of spindle, round, or oval cells with vesicular nuclei, prominent nucleoli, and moderate eosinophilic cytoplasm. In addition, increased mitotic activity is usually present. Focal keratinization may be seen in some cases. Necrosis may be present, but it is not extensive, when present, it may be in the form of comedo-like type of necrosis (Fig. 8.29a–g).

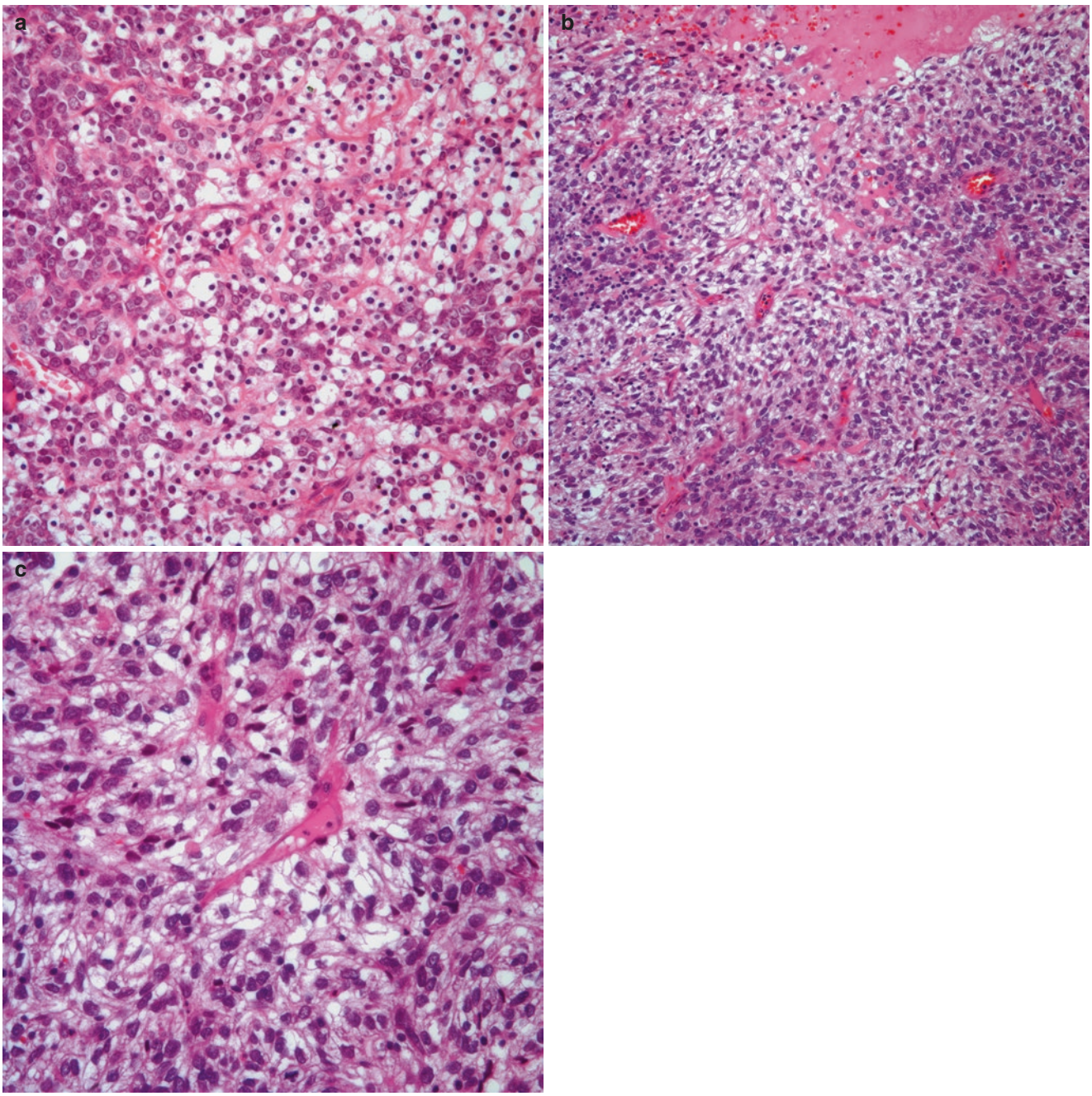


**Fig. 8.25** High power view of thymic carcinoma with clear cell features. (**a**) Medium-sized cells with round nuclei, some cells with prominent nucleoli and clear cytoplasm. (**b**) Sheets of tumor cells with clear cytoplasm and a discrete fibrovascular network. (**c**) Moderate nuclear atypia and mitotic activity

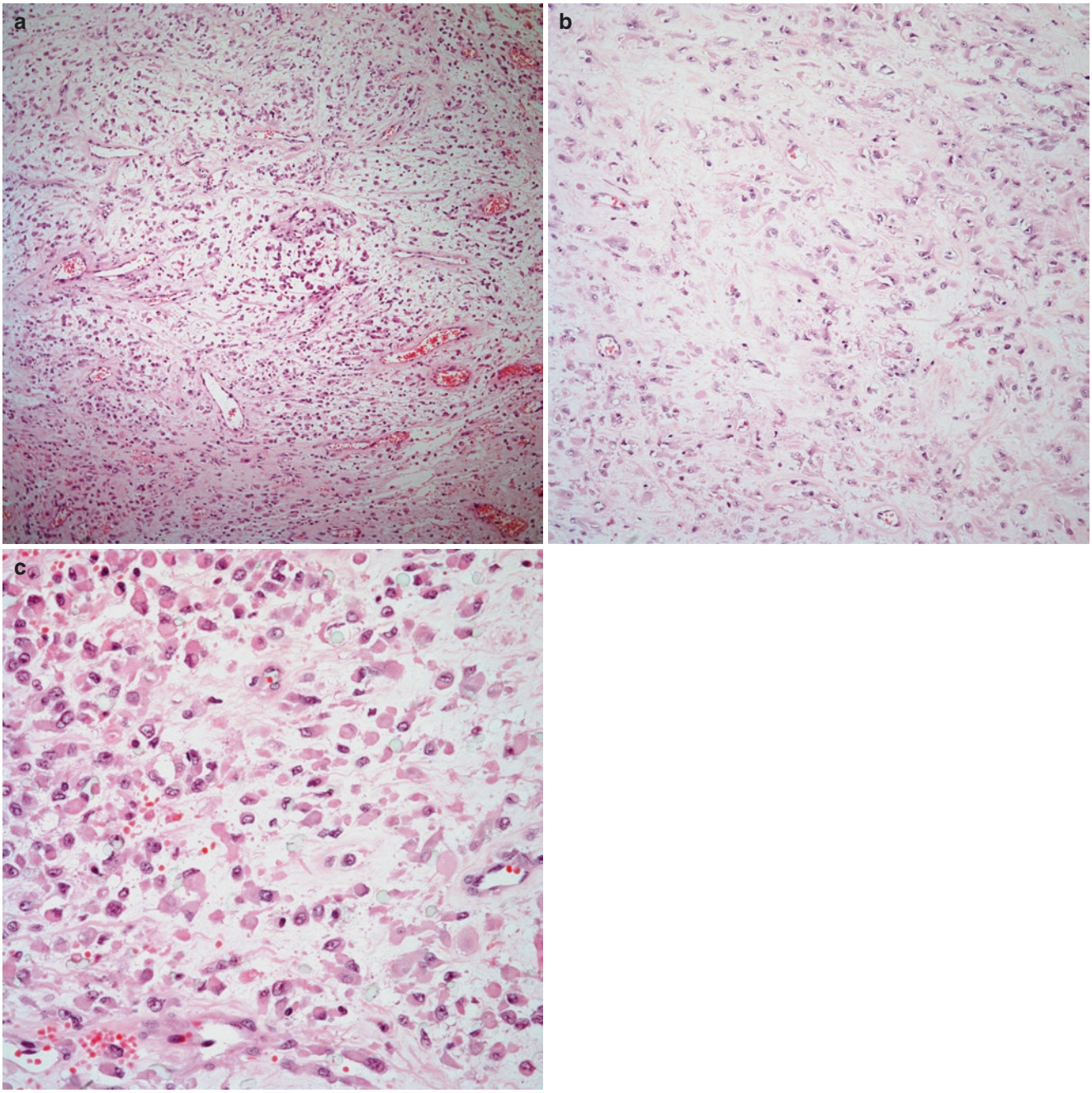


**Fig. 8.26** (**a**) Low power view of a primary thymic rhabdoid carcinoma. (**b**) Sheets of tumor cells embedded in a collagenous stroma. (**c**) Tumor cells showing a rhabdoid appearance

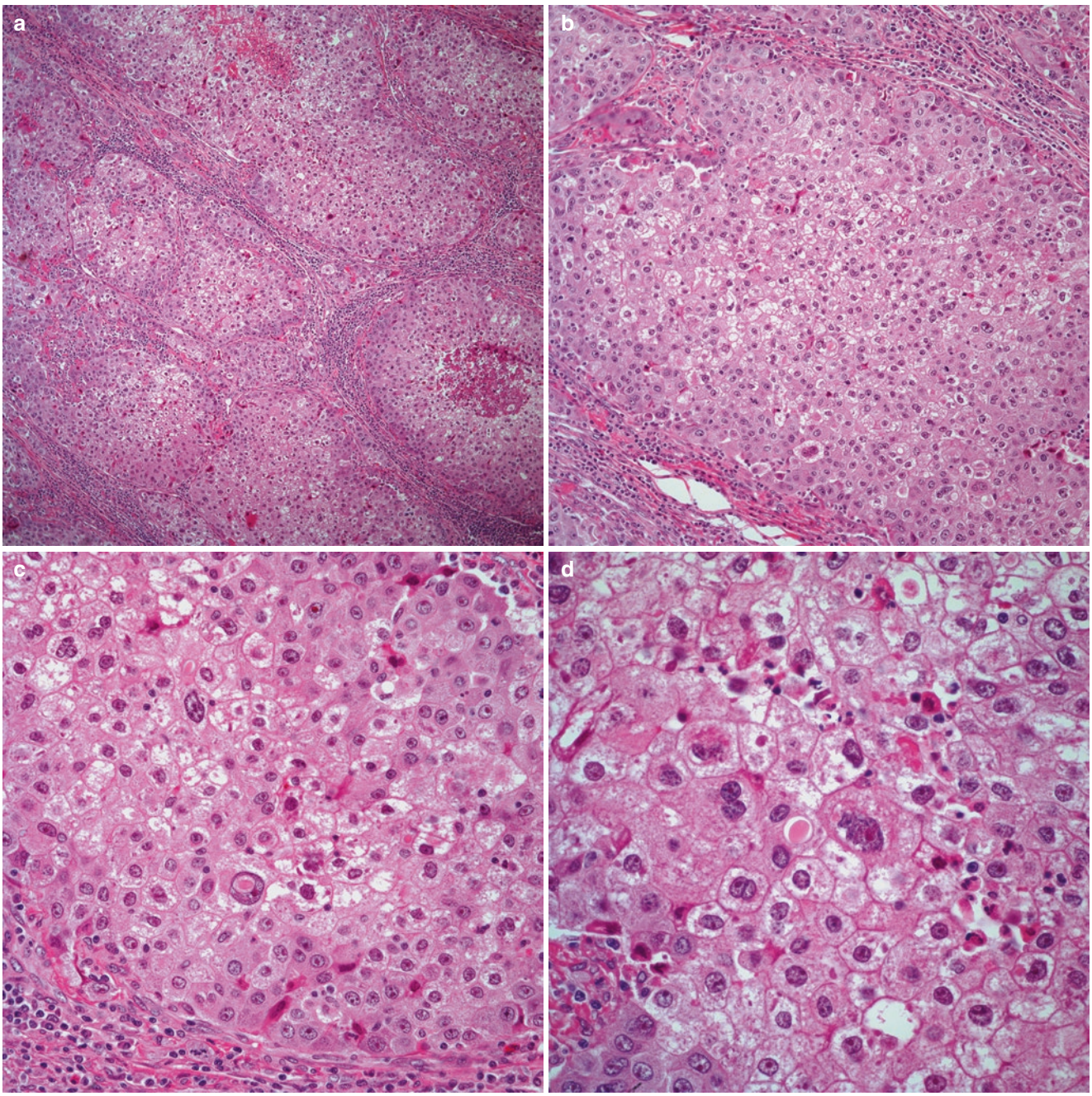


**Fig. 8.27** (**a**) Low power view of a hepatoid thymic carcinoma showing a nodular pattern. (**b**) Polygonal cells with ample eosinophilic cytoplasm. (**c**) Presence of intranuclear inclusion. (**d**) Atypical cells with prominent nucleoli and the presence of intracytoplasmic hyaline globules

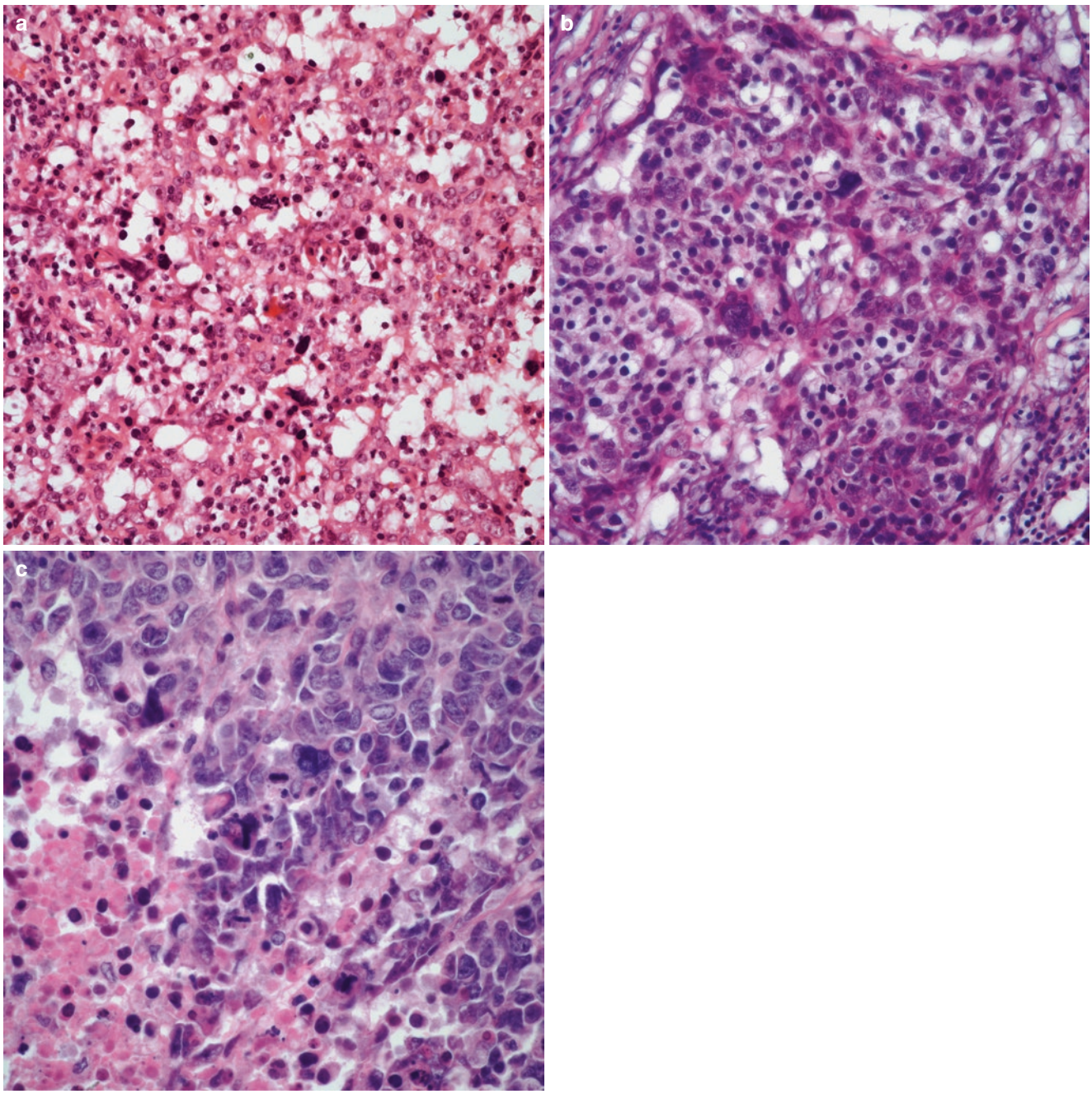


**Fig. 8.28** (**a**) Thymic anaplastic carcinoma showing atypical mitotic figures and scattered multinucleated giant cells. (**b**) Multinucleated giant cells with prominent nucleoli. (**c**) Necrosis, multinucleated giant cells, and mitotic activity

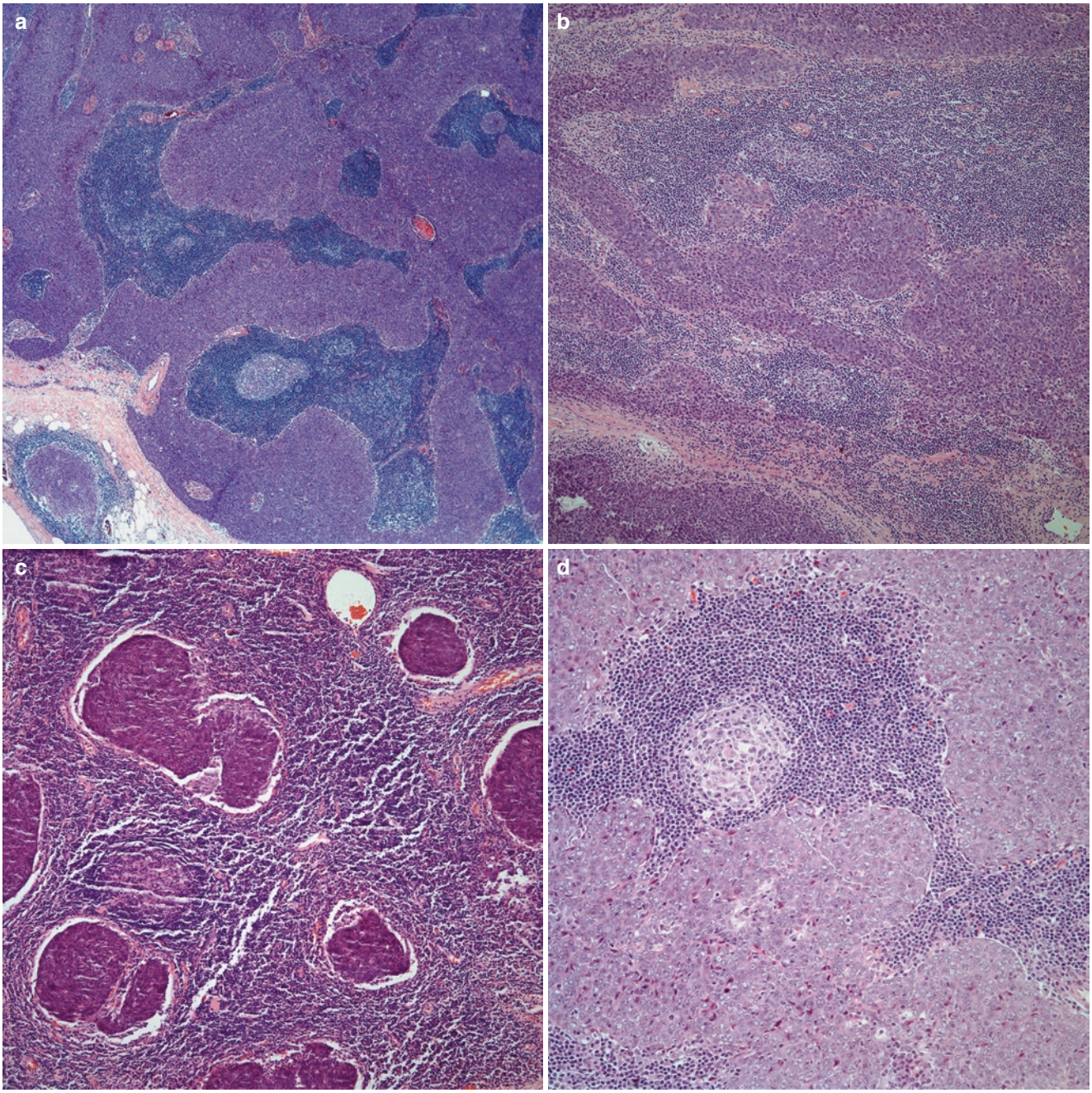


**Fig. 8.29** (**a**) Micronodular thymic carcinoma showing nodules of tumor cells with prominent lymphoid hyperplasia. (**b**) Tumor cells growing in ribbons. (**c**) Tumor cells appear to be floating in empty spaces. (**d**) Contrast between the tumor cells and the presence of a germinal center

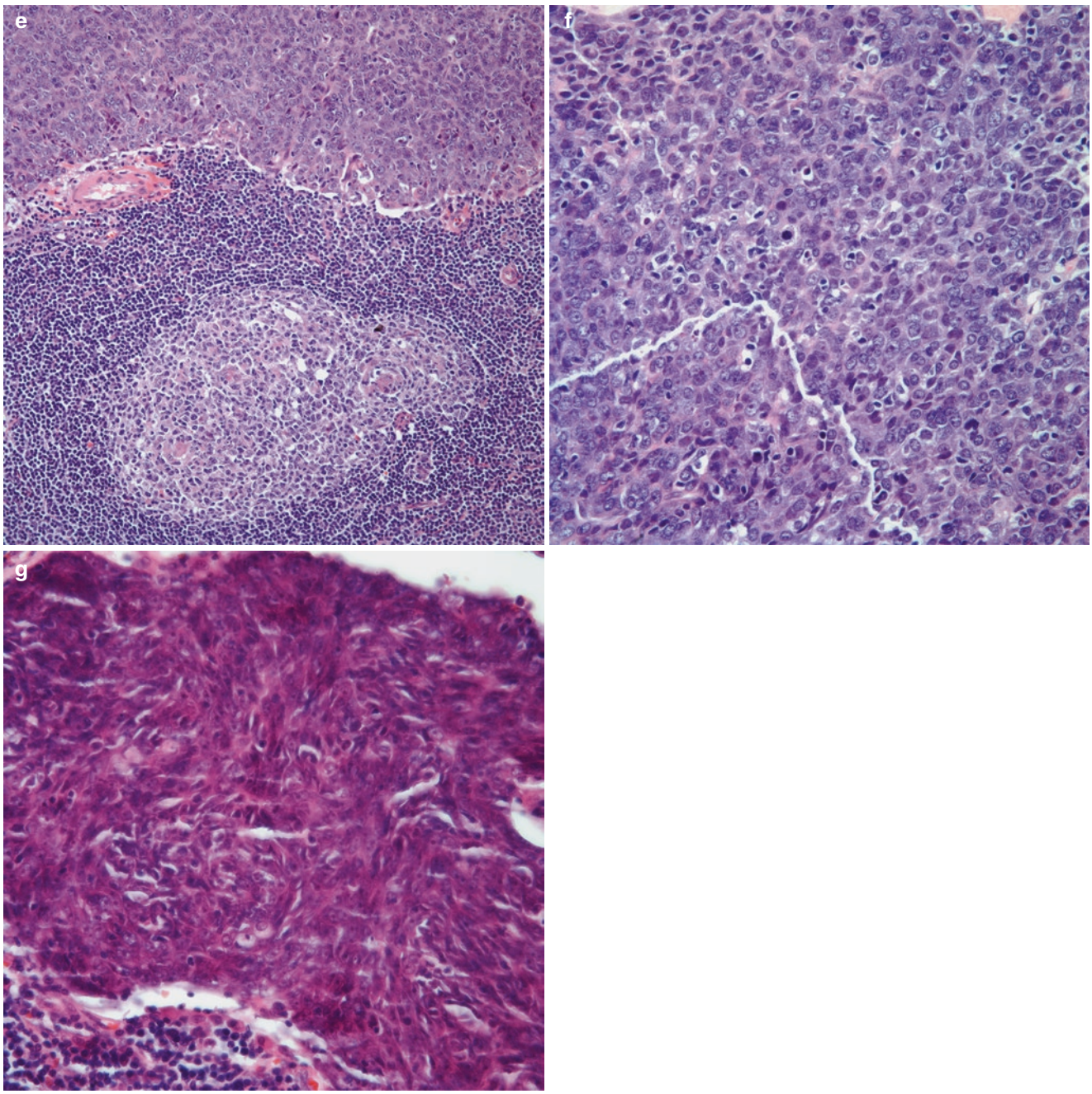


**Fig. 8.29** (continued) (**e**) Prominent germinal center and adjacent tumor with cellular atypia and mitotic activity. (**f**) Higher magnification of the tumor cells composed of oval cells with round nuclei, prominent nucleoli, and mitotic activity. (**g**) Tumor cells showing spindle cell features

### Other Unusual Variants

Two other additional variants of thymic carcinoma have been described as isolated case reports. However, we have been able to identify additional such cases: thymic carcinoma with rhabdomyomatous component and thymic carcinoma with neuroblastoma. The former unusual variant of thymic carcinoma was described by de Queiroga and colleagues [50] in a description of a 70-year-old woman with a posterior mediastinal mass. Histologically, the tumor showed a high-grade malignancy composed of islands of atypical cells with vesicular nuclei, prominent nucleoli, and increased mitotic activity in association with extensive areas of necrosis. In addition, the malignant epithelial component was associated with a conspicuous cellular proliferation composed of cells with bright eosinophilic cytoplasm and small, round, eccentrically placed nuclei (rhabdomyomatous component) (Fig. 8.30a, b). On the other hand, Alguacil-Garcia and Halliday [51] reported a 60-year-old man who, during a surgical heart procedure, was found to have a small nodule in the left lobe of the thymus. Histologically, the tumor was described as a conventional carcinoma with scattered islands of solid, small round or oval clusters of cells with occasional pseudorosettes embedded in an eosinophilic fibrillary background (neutrophil). Recently, we had the opportunity to see such an occurrence in an adult individual in which the main tumor mass was that of a thymic carcinoma with a separate area of neuroblastoma. In addition, the tumor also showed cystic changes (Fig. 8.31a–d). These two variants of thymic carcinoma are rare and may pose significant problems in interpretation.

### Adenocarcinoma

Contrary to the fact that the great majority of thymic carcinomas are represented by squamous cell carcinomas of the different grades of differentiation, the occurrence of thymic adenocarcinoma is unusual, and poses significant problems not only in the diagnosis of the tumor but also in assigning the thymus as the primary site. It is known that in the thoracic cavity, adenocarcinomas are by far more common in the lung, and if to that fact we add that many adenocarcinomas of extrathoracic origin often metastasize to the lung, then the interpretation of primary adenocarcinoma of the thymus requires a more complete clinical and radiological correlation excluding not only a pulmonary adenocarcinoma but also excluding an adenocarcinoma of extrathoracic origin. Nevertheless, primary adenocarcinomas of the thymus have been reported, and rare cases have been included in several series of thymic carcinoma, as other variants of thymic carcinoma. However, in actuality, the reports specifically addressing the issue of thymic adenocarcinoma are limited to a single or three case reports [52–67]. However, it is also important to highlight that many cases that have been coded under the term *papillary carcinoma* may also be grouped under the designation of papillary adenocarcinomas of the thymus, which is a more appropriate terminology. Tumors with that particular histology have already been addressed above. Clinically, thymic adenocarcinomas appear to have a slight predilection for men rather than women in a proportion of 1.5:1 and have been described in young patients as well as in older individuals, ranging in age from 15 to more than 80 years. The symptomatology is varied and non-specific and would include chest pain, shortness of breath, and cough. Even though in several reports the authors have concluded that these tumors with this histology follow an aggressive behavior, there are also reports of patients who have survived 10 years or more without evidence of recurrence or metastasis. In cases in which the tumor has shown an aggressive behavior, the tumor has metastasized to the lung, the liver, or bone.

In general, the frequency of these tumors as primary thymic adenocarcinomas is rare, and up to now there are reports of approximately 50 cases in the literature. However, the histopathological growth patterns described including the papillary growth pattern, have been varied. We recently analyzed 16 primary thymic adenocarcinomas [68] in 9 men and 7 women between the ages of 22 and 68 years. Clinically, the patients presented with non-specific symptoms of cough, chest pain, and dyspnea. Diagnostic imaging in these patients showed an anterior mediastinal mass, and surgical resection of the tumor was performed in those patients. Macroscopically, the tumor size varied between 5 and 14 cm, and some tumors were described as having mucoid changes, while others were described as necrotic or cystic. However, the most important findings of this study were to identify several main growth patterns in these tumors:

- Mucin-rich adenocarcinoma of the so-called colloid carcinoma: in this variant, the tumors show extensive areas of mucinous material in which there may be floating clusters of malignant cells. In some areas, the tumor also shows cystic changes, while in focal areas the tumor may show signet-ring cell appearance (Fig. 8.32a–f).
- Non-mucinous adenocarcinoma: this tumor is characterized by either a proliferation of small to medium size glands or the presence of an intestinal-like growth pattern. In both of these patterns, it is possible to observe well-formed glands with focal areas of necrosis, tumor infiltrating adipose tissue, and cellular atypia with increased mitotic activity. In some cases, one can identify the presence of small glandular proliferation with marked cellular atypia and mitotic activity dissecting fibroconnective and adipose tissue (Fig. 8.33a–h).
- Papillary/micropapillary adenocarcinoma: this tumor is characterized by the presence of well-formed papillary structures with complex arrangement and separated by a delicate network of fibroconnective tissue. Cellular atypia

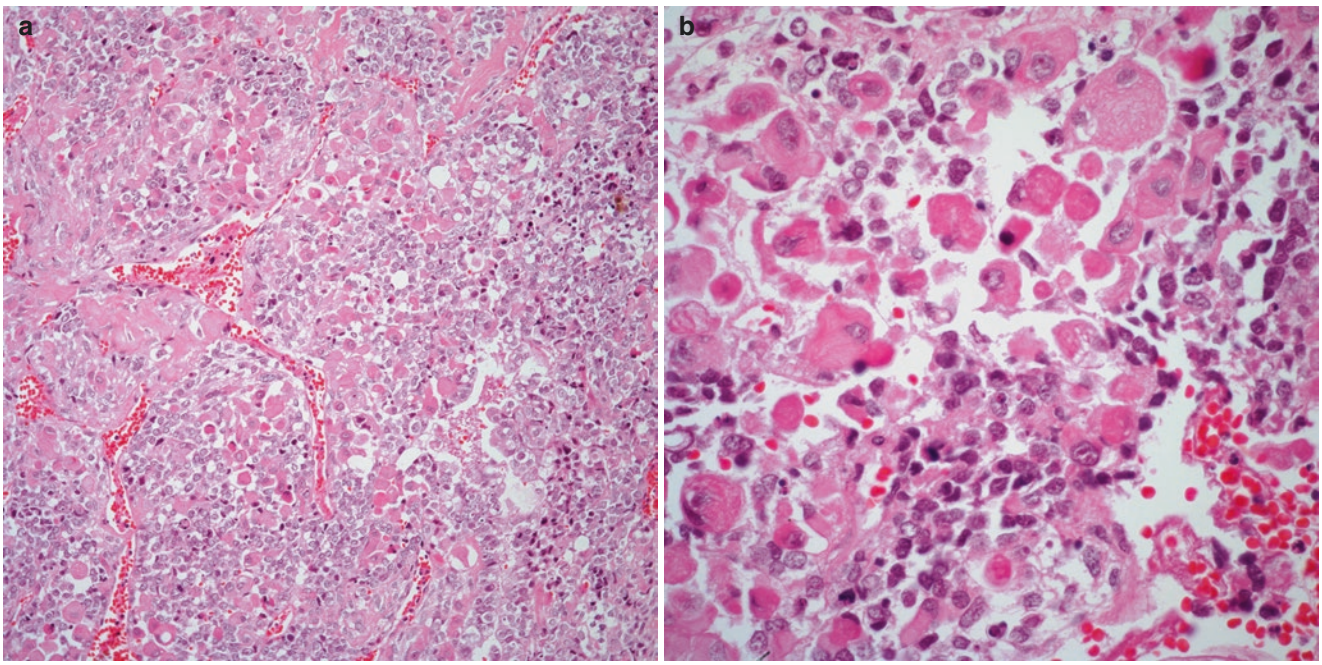


**Fig. 8.30** (**a**) Low power view of a rhabdomyomatous thymic carcinoma showing the two different populations of cells. (**b**) Closer view at the rhabdomyomatous component

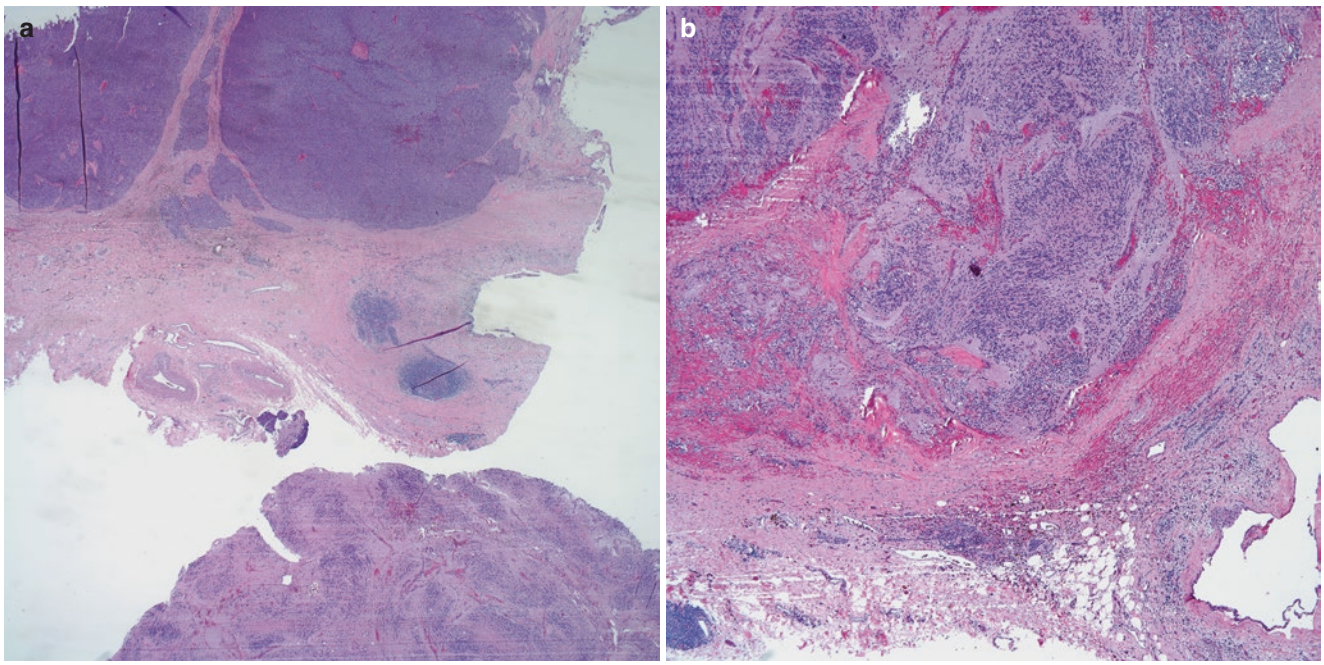


**Fig. 8.31** (**a**) Low power view of a mixed thymic carcinoma and neuroblastoma. (**b**) Neuroblastoma with adjacent thymic cystic changes

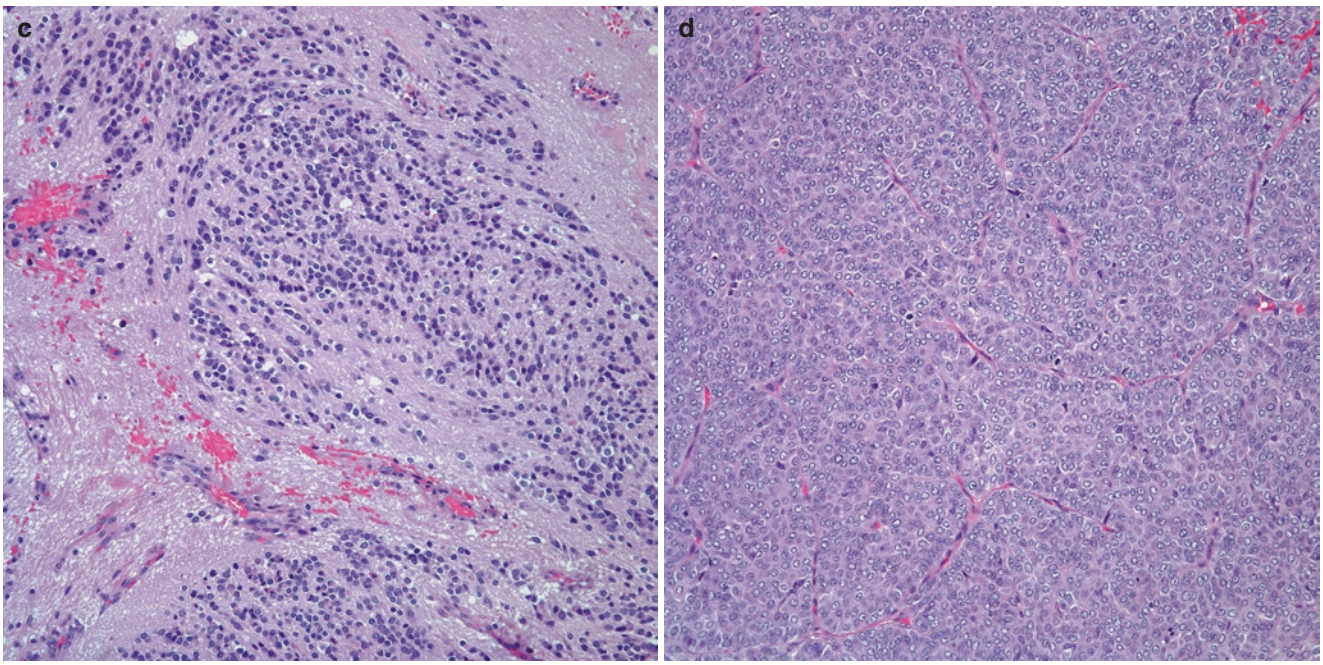


**Fig. 8.31** (continued) (**c**) Closer view at the neuroblastomatous component with presence of neurophil. (**d**) Closer view at the thymic carcinoma showing nuclear atypia and mitotic activity

and mitotic activity are easily identifiable. In the micropapillary growth pattern, the tumor appears to be in spaces separated by fibroconnective tissue. The tumor cells are filling those spaces, and psammoma bodies are often present. In this variant, the tumor does not have prominent nuclear atypia or increased mitotic activity; also see papillary carcinoma above.

– In addition, we were able to identify some minor growth patterns that may accompany the main histology of the tumor. These minor patterns include solid areas in which the tumor does not show any glandular differentiation. Also, the minor growth patterns demonstrated the association of thymoma and thymic adenocarcinoma.

Even though we are proponents of the staging of these tumors as the best way to predict prognosis, it is important to highlight that in some cases in which the tumor may show metastatic spread at the time of diagnosis, the clinical follow-up has not been that of a fatal disease. Therefore, it is possible that there may be other mechanisms that may trigger a more rapid course in these cases.

It is also important to highlight the differences that may be observed with the use of immunohistochemical stains in thymic adenocarcinomas. Even though some of these results may correlate with the different histologies present in these tumors, we observed positive staining in tumor cells for keratin 7, keratin 20, CD5 (Fig. 8.34a), CDX2, and CD117 (Fig. 8.34b). Also, important to highlight is that PAX-8 and TTF1 are generally negative in these tumors.

## Immunohistochemical and Molecular Features

Due to the rarity of thymic carcinomas, there is somewhat limited information regarding the immunohistochemical profile that those tumors may have. Nevertheless, numerous publications on the subject have been presented, mainly with the idea of attempting to separate thymic carcinomas from others carcinomas of different origin.

Fukai and colleagues [69], in a comparative study of lung carcinoma and thymic carcinoma, analyzed both of these tumors using cytokeratin 7 and 13 and identified that thymic squamous carcinomas were positive for cytokeratin 7 (monoclonal antibody RCK 105) (9/9 cases), while lung carcinomas were negative. Hishima and associates [70], in a study attempting to separate thymic carcinoma from thymoma, studied 23 thymic epithelial tumors, separating them into thymoma, atypical thymoma, and thymic carcinoma. The authors identified CD5 (receptor molecule that signals cell growth in T-cells) as a good marker to separate thymic carcinoma from thymoma; however, the authors also found that CD5 was also expressed in atypical thymomas. Additionally, the authors performed double labeling of tumor cells with CD5 and cytokeratin. In this study, the authors stated that CD5 was not identified in other carcinomas including breast, esophagus, stomach, colon, and uterus. Following this publication, several other studies have documented similar findings. Dorfman and associates [71] evaluated CD5 staining in 24 thymic carcinomas, identifying 16 cases with immunoreactivity to CD5. This staining was seen more often in squamous cell carcinoma (9/16) and less in other types of

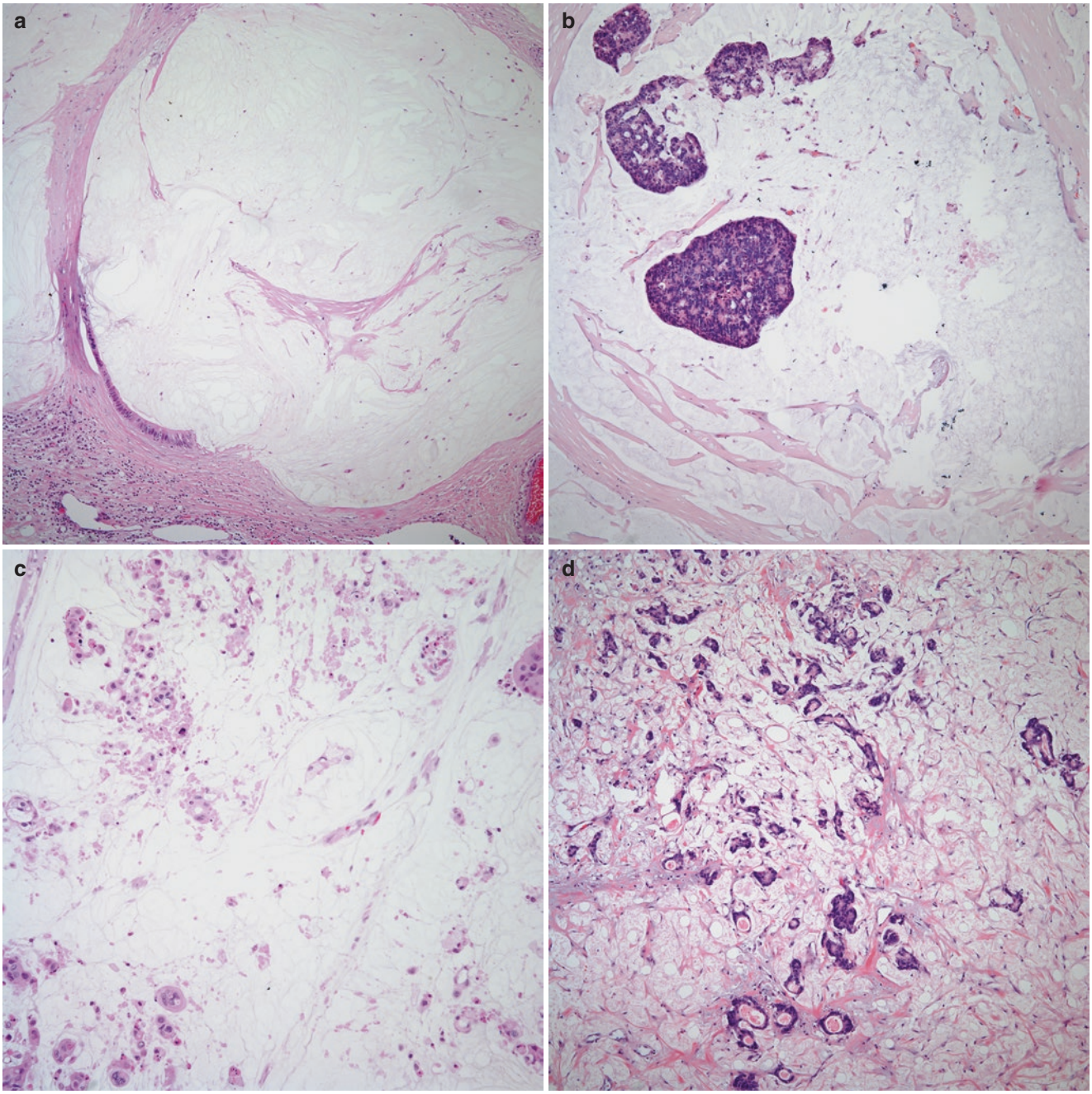


**Fig. 8.32** (**a**) Mucinous adenocarcinoma of the thymus showing extensive mucin deposition and only a rim of mucinous epithelium. (**b**) Small islands of malignant cells embedded in mucinous pools. (**c**) Single malignant cells floating in a mucinous pool. (**d**) Well-formed malignant glands embedded in mucinous stroma

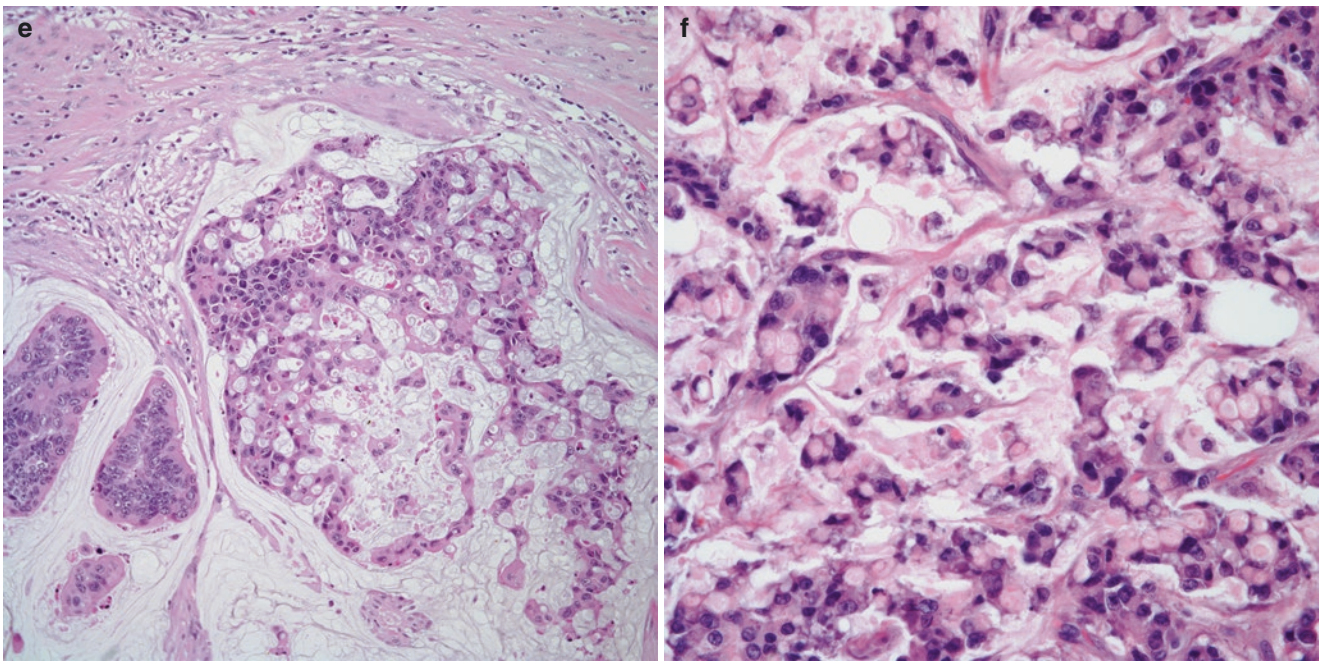


**Fig. 8.32** (continued) (**e**) Intra- and extracellular mucinous areas. (**f**) Signet ring-cell areas in a mucinous adenocarcinoma

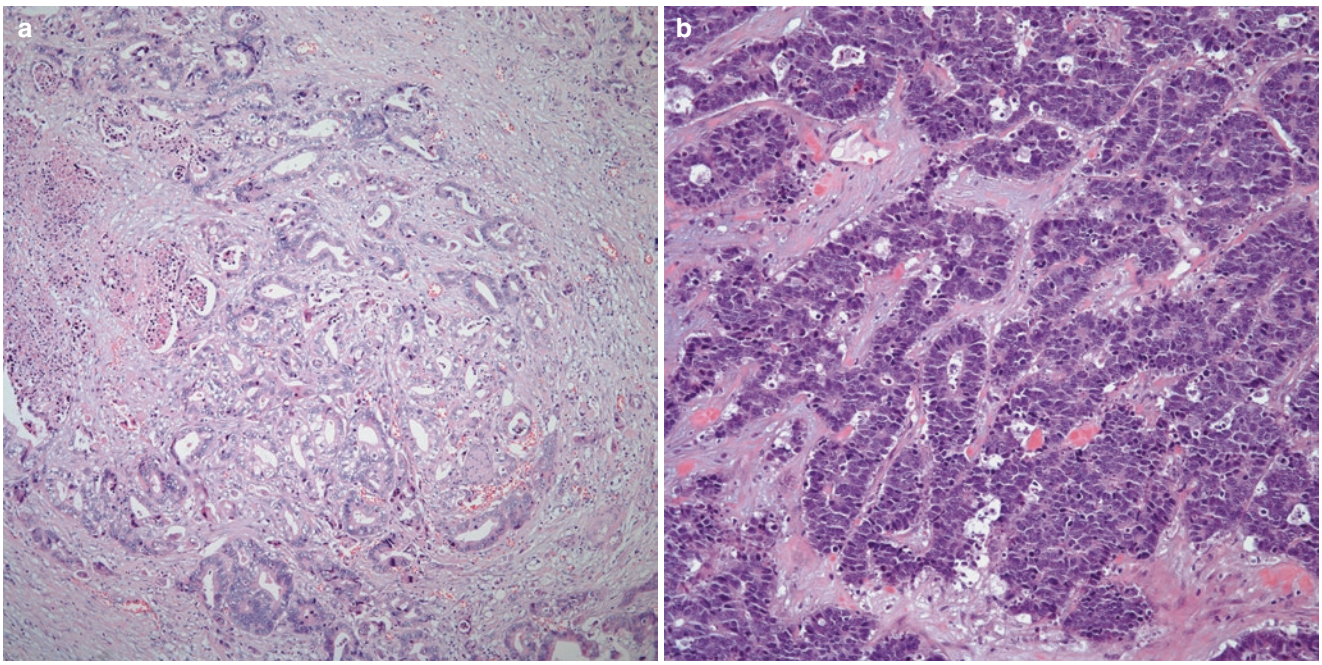


**Fig. 8.33** (**a**) Low power view of non-mucinous adenocarcinoma showing a malignant glandular proliferation. (**b**) Small glandular proliferation dissecting fibroconnective tissue

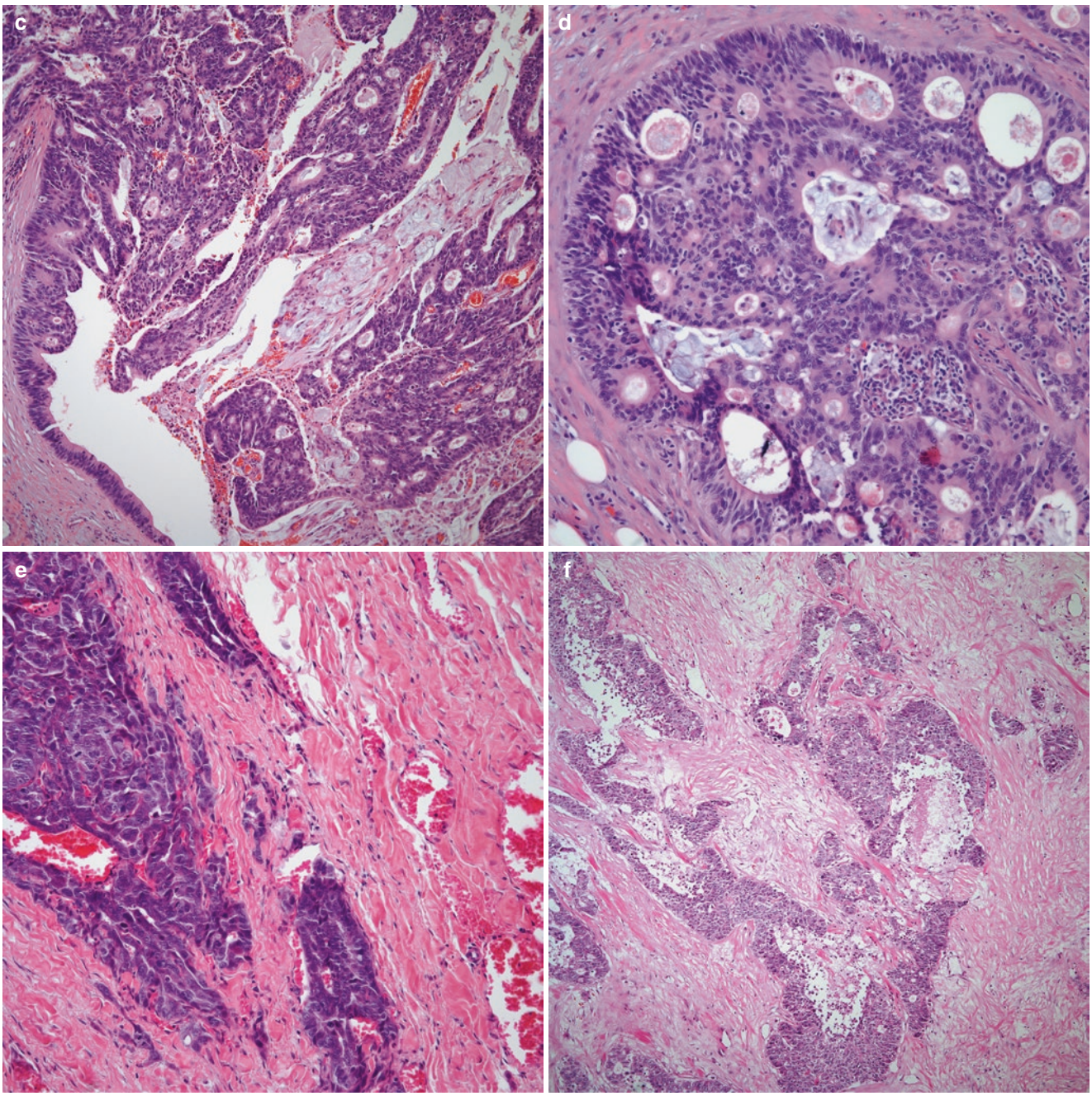


**Fig. 8.33** (continued) (**c**) Thymic adenocarcinoma with colonic-like features. (**d**) Malignant gland with luminal mucin. (**e**) Malignant glands with adjacent solid area. (**f**) Irregular islands of malignant cells with glandular formation

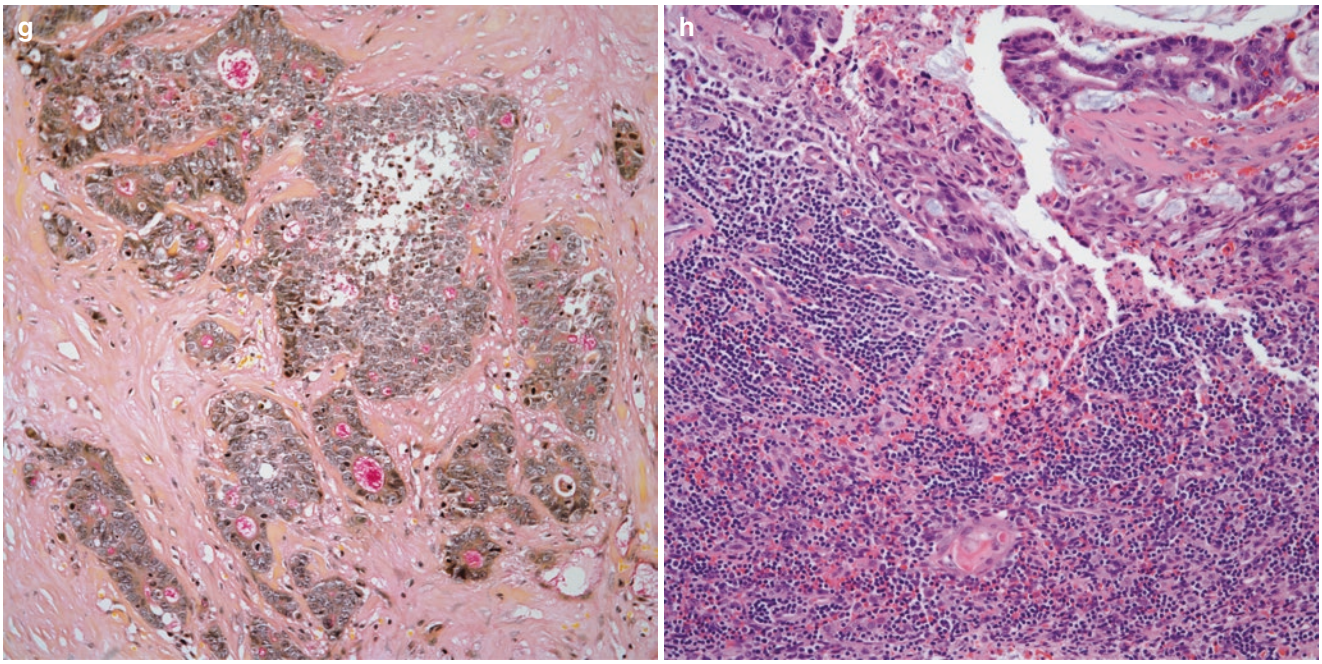


**Fig. 8.33** (continued) (**g**) Mucicarmine stain shows intra- and extracellular mucin. (**h**) Adenocarcinoma involving remnant of thymic tissue; note the presence of Hassall's corpuscle

histologies. In addition, the authors stated than none of the 17 thymomas showed any reactivity to CD5 as well as 61 cases of carcinoma of different origin. The authors concluded that CD5 is a useful marker for primary thymic carcinoma. On the other hand, Kornstein and Rosai [72] evaluated 109 thymic tumors and 423 other neoplasms using two different monoclonal antibodies: clone CD5/54/B4 labeled 7/24 thymic carcinomas and none of the other types of tumors, while clone 4C7 labeled 15/24 thymic carcinomas, 2/84 thymomas, and 14/386 other epithelial tumors. In a different study evaluating CD5 (monoclonal antibody CD5-4C7) immunoreactivity, Tateyama and associates [73] stained 73 tumors of different organs including 22 thymomas and 7 thymic carcinomas. All thymic carcinomas showed membranous staining, while four cases of atypical thymoma also showed focal positive staining, and none of the other types of thymoma showed any staining. The authors also documented that positive intracytoplasmic staining was identified in cases of mesothelioma.

Contrary to the emphasis on CD5 as a discriminator of thymoma and thymic carcinoma or thymic carcinoma from other types of carcinomas, more general immunohistochemical panels have been performed in thymic carcinomas. Pomplum and associates [74] evaluated the staining pattern of cytokeratin 7, CD5, CD10, CD1a, and TTF1 in 20 thymic tumors (thymoma, atypical thymoma, and thymic carcinoma) against 10 primary squamous cell carcinomas and 10 large cell carcinomas of the lung. The authors identified 3/10 large cell carcinomas positive for TTF1, while CD5 was positive in 3/6 thymic carcinomas and 1/14 thymomas, with only focal staining in 1/20 lung carcinomas. The staining of CK7 and CD10 did not help in distinguishing thymic or lung origin. In a different study by Pan and associates [75] on thymic carcinoma and thymoma, the authors evaluated 22 thymic carcinoma and 35 thymomas for the staining pattern of calretinin, mesothelin, cytokeratin 5/6, thrombomodulin, HBME-1, Wilms' tumor (WT-1), Ber-Ep4, MOC-31, BG-8, B72.3, CEA, CD15, TTF-1, p63, and CD5. The authors identified that about 33% of thymic carcinomas were positive for calretinin and/or mesothelin, both thymic carcinomas and thymomas were positive for keratin 5/6, HBME-1 was positive in four thymic carcinomas and ten thymomas, and WT-1 was seen positive in one thymic carcinoma. Also, about 70% of thymic carcinomas were positive for Ber-Ep4,

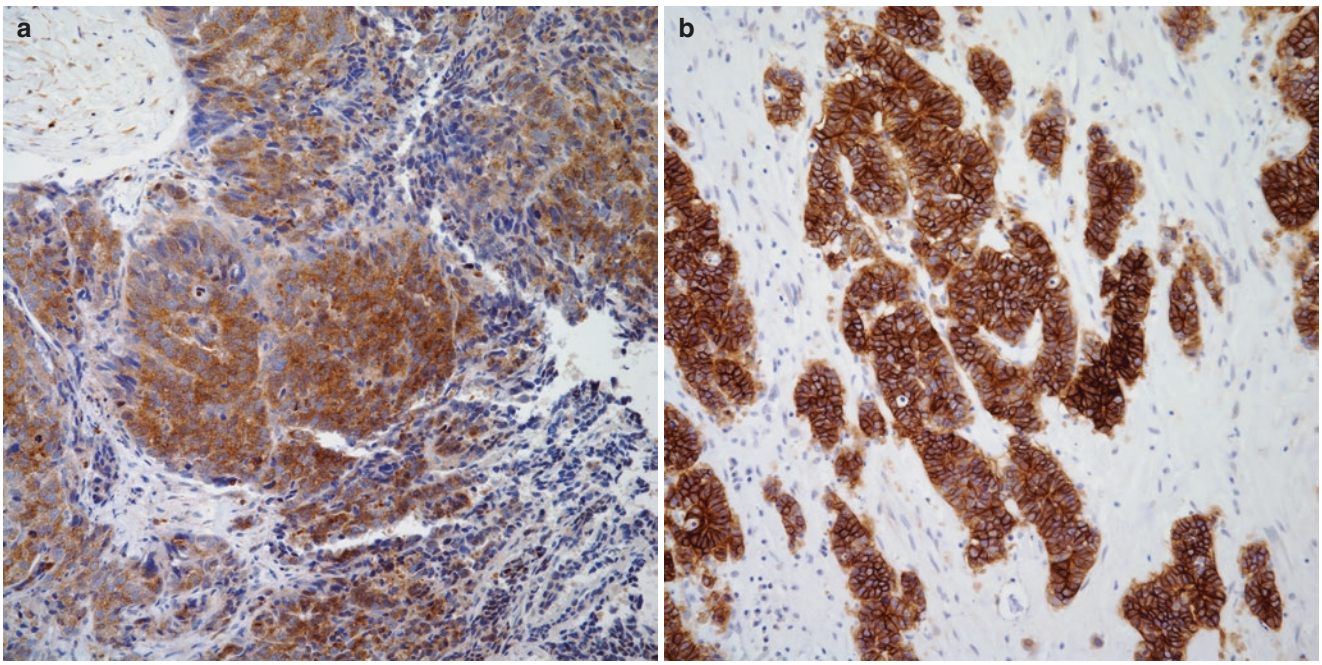


**Fig. 8.34** (**a**) Immunohistochemical stain for CD5 showing positive staining in a thymic adenocarcinoma. (**b**) Immunohistochemical staining for CD117 showing positive staining in a thymic adenocarcinoma

BG-8, and CD15. In addition, positive staining in thymic carcinomas was seen for CEA, B72.3, and MOC-31. P63 was positive in all the cases, while CD5 was positive in 9/22 thymic carcinomas. Thrombomodulin and TTF1 were negative in all cases. Nonaka and associates [76] evaluated 58 thymomas and 17 thymic carcinomas using Foxn1 and CD205 (DEC205) and encountered that Foxn1 was diffusely expressed in thymoma, mainly those with lymphocytic component, while it was only focally expressed in thymic carcinoma. Also, CD205 cytoplasmic expression was strong and diffuse in all thymomas, with focal variable intensity in thymic carcinoma. The authors concluded that Foxn1 is a better marker for thymoma and thymic carcinoma than CD5 and CD117. Kojika and associates [77] evaluated the expression of GLUT-1 as a discriminant of atypical thymoma and thymic carcinoma. The authors, using tissue microarray, evaluated 12 thymic carcinomas and 7 atypical thymomas, concluding that GLUT-1 is a good marker to separate atypical thymoma from thymic carcinoma, especially in biopsy specimens.

Also important to highlight is the fact that several authors have identified neuroendocrine differentiation in thymic epithelial tumors [78, 79]. Ishima and associates [78] evaluated nine thymic carcinomas identifying positive staining in seven cases for synaptophysin. Libero and associates [79], in a study of 19 thymic carcinomas, encountered that 10 of the 19 cases (53%) showed immunoreactivity for synaptophysin. In addition, the authors also identified six cases in which there were scattered cells positive for chromogranin. More recently, other markers have been observed to show positive staining in thymic carcinomas, including p63, keratin 5/6, keratin 7, CDX2, FoxN1, CD117, CD205, and calretinin [30]. In addition, thymic carcinomas have shown significant immunohistochemical expression for EGFR, pEGFR, HER2, HER3, TGF alpha, amphiregulin, and epiregulin [80].

Regarding molecular studies on thymic carcinoma, there have been a few attempts to analyze different aspects of this tumor, and a few reviews on this subject have been written [81, 82]. Hirabayashi and associates [83] evaluated thymomas and thymic carcinomas for mutation in p53 and CDKN2 genes using PCR-SSCP and did not identify any mutations of those genes. However, the authors identified one case of thymic carcinoma with hypermethylation in the promoter region of CDKN2. Also, HER gene amplification by FISH and increased EGFR and HER2 gene copy numbers have been reported in thymic carcinomas [80]. Yamaguchi and associates [84] have also reported a single case of thymic carcinoma in which the authors identified deletions in exon 19 of EGFR with PCR method, and also three point mutations, G719A in exon 18, T790M in exon 20, and L858R in exon 21. On this subject, Meister and associates [85] evaluated 20 thymic epithelial tumors (17 thymomas and 3 thymic carcinomas), and even though the authors identified EGFR-positive staining in the majority of cases by immunohistochemistry, none of the cases had sequence alteration in the tyrosine kinase domain of EGFR similar to that seen in lung carcinoma. Yoh and associates [86] evaluated the mutational status of EGFR and KIT in 24 thymomas and 17 thymic carcinomas in which the authors were not able to identify EGFR mutations in thymic carcinoma, while the mutational analysis

for KIT showed only missense mutation in exon 11 of a single case of thymic carcinoma. In a similar study of EGFR and KIT in 38 thymomas and 7 thymic carcinomas, Girard and associates [87] identified KIT mutations in thymic carcinomas but no mutations in the EGFR kinase domain. Perhaps more importantly is the fact that in this study squamous cell carcinomas of the thymus and lung were compared, and the findings appear to show a difference, which potentially could be of aid in separating these two tumors. Zettl and coworkers [88], in a study on recurrent genetic aberrations in thymoma and thymic carcinoma, concluded that atypical thymoma (WHO type B3) and thymic squamous cell carcinoma partially share genetic aberrations. Watanabe and coworkers [89] provided their experience with expression of telomerase activity in thymic epithelial neoplasms, namely, thymoma and thymic carcinoma, and identified telomerase activity in these tumors. However, the authors stated that the activity was higher in thymomas than in thymic carcinoma, which could be explained by the presence of immature lymphocytes in thymomas.

## NUT Carcinoma

In 1991, Kees and coworkers [90] reported a single case of an intrathoracic poorly differentiated carcinoma in an 11-year-old girl in which the authors performed a chromosomal analysis identifying a translocation t(15;19), which the authors determined had not been previously recorded in the literature. In the same year, Kubonishi and coworkers [91] also described a thymic carcinoma in a 22-year-old female in which the authors also identified a chromosomal translocation t(15;19)(q15;p13) and also arrived at the same conclusion that such translocation had not been previously reported. It is important to highlight that these two publications, although highly important, appear not to have gotten the attention of diagnostic pathologists in general as it took two additional years for another case to be published. In 1993, Lee and coworkers [92] described a disseminated mediastinal carcinoma in a 5-year-old boy who followed a fatal course. In this case, the authors, as in the previous cases, performed a cytogenetic study identifying a chromosomal abnormality t(15;19)(q12;p13.1), concluding that this translocation may be specific for thymic carcinoma and may indicate an aggressive tumor.

In 2001, French and coworkers [93] evaluated 13 carcinomas in patients ranging in age from 3 to 53 years, including 3 thymic, 3 mucoepidermoid, 2 laryngeal, 1 nasopharyngeal, and 4 sinonasal. The goal as explained in the report was to "map" the chromosome 15 and 19 translocation breakpoints by FISH. Interestingly, of the 13 cases studied, the authors detected t(15;19) in only 1 out of the 4 cases of sinonasal carcinoma, while it was not detected in 3 thymic, 3 mucoepidermoid, and 2 laryngeal carcinomas. The authors concluded that their findings reveal a novel oncogenic mechanism in which the chromosome 19 translocation breakpoint interrupts the coding sequence of a bromodomain gene, BRD4, thus implicating BRD4 as a potential partner in a t(15;19)-associated fusion oncogene. Vargas and coworkers [94] also reported similar findings of t(15;19) chromosomal translocation in two young patients, one a 13-year-old with an epiglottic tumor and the other in a 12-year-old with a nasopharyngeal mass. In both of these patients, the tumor followed an aggressive behavior. The authors concluded that these findings are part of a distinct clinicopathological entity characterized by midline carcinoma with rapid fatal course. Sait and coworkers [95] also reported a thymic carcinoma with chromosomal translocation t(1;8)(p13;p11); however, the patient was a 38-year-old man with a tumor characterized by "giant cell features," while Toretsky and coworkers [96] reported another thymic carcinoma in a 15-year-old boy with a complex three-way translocation t(11;15;19). In 2003, French and coworkers [97], following their initial work on BRD4, demonstrated that the chromosome 15 translocation rearranges the novel gene NUT (nuclear protein in testis), resulting in a BRD4-NUT fusion oncogene. The authors added that their finding is the first known fusion oncogene in a highly malignant epithelial neoplasm. In 2008, Stelow and coworkers [98], in a study of 31 cases of undifferentiated carcinomas of the upper aerodigestive tract, introduced the term "NUT midline carcinoma." In this study, 5 of 28 cases showed rearrangements of the NUT and BRD4 genes by FISH, while 3 of the 5 cases also showed diffuse nuclear staining for NUT by immunohistochemistry. In addition, 23 other tumors were also evaluated for NUT immunohistochemistry, which showed mainly focal nuclear staining. The authors concluded that about 20% of these tumors not associated with EBV showed NUT rearrangement by FISH. In addition, the authors were able to document this finding in adult patients and stated that the use of NUT by immunohistochemistry may be a useful method to identify similar tumors. Needless to say, cases outside of the midline have also been encountered to show similar chromosomal translocation. Mertens [99] identified one of these cases in a 10-year-old child with a bone tumor, and den Bakker [100] identified another case in the parotid gland of a 15-year-old male. Based on available literature on this rare type of carcinoma, it is possible that NUT midline carcinoma may account for somewhere between 5% and 20% of poorly differentiated carcinomas, mainly in the midline (Fig. 8.35a, b). However, it is important to highlight that, although most tumors are reported in young patients, adult individuals may also show the chromosomal translocation. Nevertheless, it is difficult to determine which cases need to be tested based on histology alone, and the occurrence of a poorly differentiated carcinoma in the midline in a young patient is the most likely scenario, which triggers the investigation of the translocation. In a recent

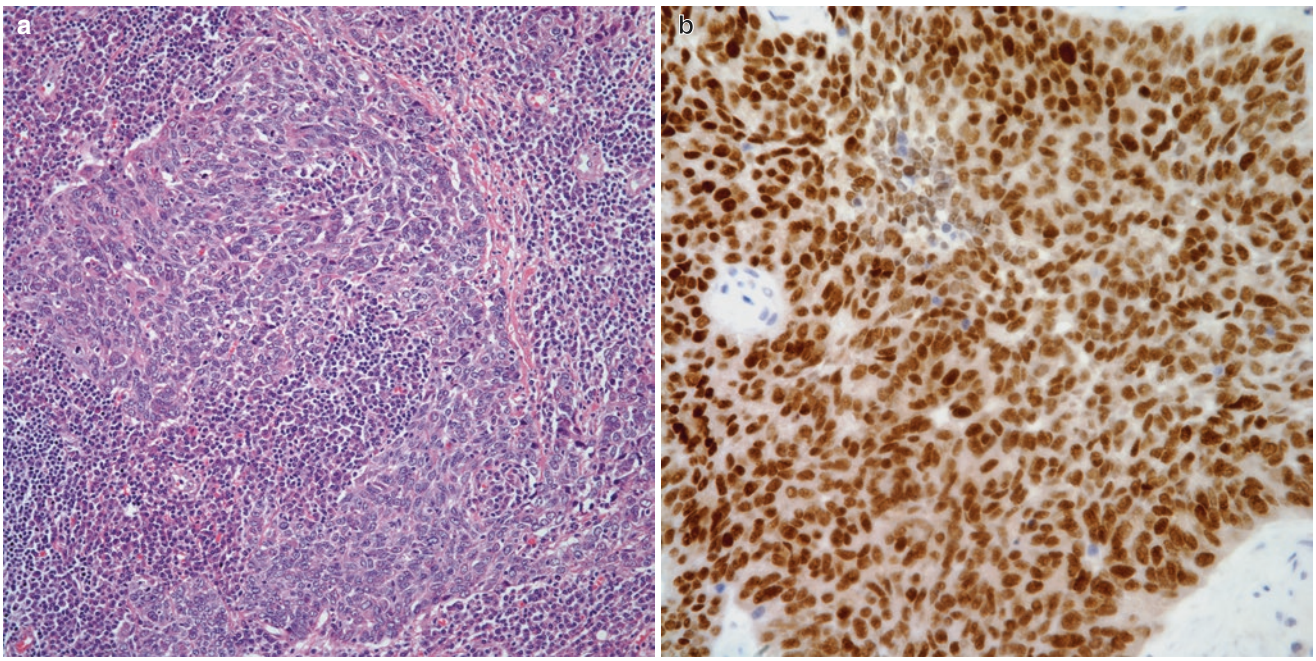


**Fig. 8.35** (**a**) Poorly differentiated thymic carcinoma. (**b**) Immunohistochemical staining for NUT showing strong nuclear staining

review on NUT midline carcinomas, French [101] advanced the hypothesis that these tumors may arise from primitive neural crest. However, such a suggestion needs to be properly confirmed.

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