Germ Cell Tumors

10

Introduction

Mediastinal germ cell tumors (MGCT) are an unusual group of tumors that share similar histopathological features with those occurring in the gonads or along the midline line. By far, germ cell tumors occur more often in the gonads. However, they also can occur in the pineal gland, retroperitoneum, and sacral area [1–4]. In several series [5–8], extragonadal germ cell tumors have accounted for approximately 1–15% of mediastinal tumors in adults and 25% in children.

Because of their putative origin from germ cells and their rarity in extragonadal locations, the very existence of primary GCT outside the gonads has been questioned in the past, and their presence was invariably attributed to metastases from occult or "burned-out" gonadal primary. Nevertheless, the existence of mediastinal germ cell tumors has been known for more than one century. The first description of what is today considered a mediastinal teratoma is attributed to Gordon [9], who, in 1823, described a mediastinal neoplasm containing teeth and hair in an autopsy of a 21-year-old female. Toward the end of the eighteenth century, Hare [10] reviewed the current literature and found ten cases of teratomatous lesions, and Hertzler [11] in 1916 had compiled 72 case reports of teratomatous lesions. It was not until the middle of the twentieth century that other non-teratomatous mediastinal germ cell tumors were recognized [12, 13]. In view of the similarities that germ cell tumors share regardless of the anatomic site, it is essential that a careful clinical evaluation be undertaken prior to diagnosing a tumor as primary in the mediastinum. This will be of importance not only for proper determination of the primary site but also for staging and treatment purposes. Despite the histopathological similarities displayed by both gonadal and extragonadal germ cell tumors, certain subtle differences have been observed, which may carry important diagnostic and prognostic implications. For instance, mediastinal non-seminomatous GCT are often seen in association with Klinefelter's syndrome, hematologic malignancies, and secondary development of high-grade sarcomas. However, in general, mediastinal non-teratomatous GCT have been associated with diverse clinical conditions. Table 10.1 depicts some of the different clinical conditions associated with mediastinal non-teratomatous GCT.

The true incidence of MGCT is difficult to assess. Some estimates consider that in general GCT account for 1–5% in the mediastinum [14], while others estimate that MGCT account for approximately 10–20% of all mediastinal tumors [15, 16]. Mullen and Richardson [7] evaluated 702 adults with primary anterior mediastinal tumors and found that 15% of them corresponded to MGCT. In addition, the authors also evaluated 179 children with primary anterior mediastinal masses and found that 24% of these neoplasms were MGCT. Davis and colleagues [6] reviewed 2399 cases of mediastinal tumors between the years of 1952 and 1973 and found 72 cases (3%) of MGCT. Unfortunately, most available figures are based on relatively short series of cases or from studies that included benign cysts and other types of neoplasms. One important conclusion that can be drawn from previous studies is the fact that MGCT are more common in young men. In our experience with 322 cases of MGCT, we were able to observe a dramatic predominance of men in a proportion of 9:1 [17]. The few cases of MGCT that we were able to see in women were teratomatous lesions. We also noted that teratomatous lesions represent the most common MGCT. Figures 10.1 and 10.2 show the different distributions of mediastinal GCT by age groups and by histological types. Based on those distributions, it is clear that the most common mediastinal GCT is teratoma. Also important to highlight is that among the teratomatous tumors, mature teratomas are more common, while immature teratomas account for less than 5% of all teratomatous tumors (Fig. 10.3). Among the non-teratomatous tumors, seminomas are the most common, while among the non-seminomatous, non-teratomatous tumors; yolk sac tumor is the most common (Fig. 10.4). However, the bulk of mediastinal GCT is made of teratomas and seminomas, leaving the rest of GCT to account for no more than 25% of all mediastinal GCT [17].

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Several theories have been presented in order to explain the presence of GCT in the mediastinum. Although some of these theories are provocative and interesting, the puzzle of the origin of GCT of the mediastinum is still far from solved. Whether the cell or cells of origin are ectopically misplaced or represent an integral normal component of this region, the bulk of the evidence seems to point in the direction of a thymic origin [18–23].

Classification

Although for the most part the classification system used for MGCT is similar to that proposed by the World Health Organization (WHO) [24], we have introduced a few modifications in order to provide more histopathological information on these tumors [17]. Tables 10.2 and 10.3 provide the classification schema devised for these tumors. Those changes are mainly in the area of teratomatous tumors. Terms such as teratocarcinoma and malignant teratoma are rather non-specific and in many circumstances misleading; thus, we have proposed abandoning such terminology. The concept of separating teratomatous lesions based on the presence of specific cellular components with the respective percentage may lead to more specific therapy, which may also be translated into an improve clinical response for these patients.

Table 10.1 Clinical conditions associated with non-teratomatous MGCT

Tumor type	Associated Condition
Seminoma	Ventricular septal defect
	Congenital absence of thoracic hemivertebra
	Pulmonic stenosis
	Gynecomastia
	SVC syndrome
Yolk sac tumor	Klinefelter's syndrome
	Idiopathic thrombocytopenia
	Acute megakaryoblastic leukemia
	Malignant histiocytosis
	SVC syndrome
Embryonal Carcinoma	Idiopathic thrombocytopenia
	Klinefelter's syndrome
Choriocarcinoma	Gynecomastia
	SVC syndrome
	Klinefelter's syndrome

Staging

A staging system has been devised as an attempt to properly identify the anatomic distribution of GCT and also to stratify those patients who may benefit from any additional therapy [17]. This staging system was developed after an analysis of 322 cases of mediastinal GCT including all the different histological types. The staging schema is depicted in Figs. 10.5, 10.6, 10.7, and 10.8, and it is as follows:

- Stage I – well-circumscribed tumor with or without focal adhesion to the pleura or pericardium but without microscopic evidence of invasion into adjacent structures (Fig. 10.5).
- Stage II – tumor confined to the mediastinum with macroscopic and/or microscopic evidence of infiltration into adjacent structures (such as pleura, pericardium, and great vessels) (Fig. 10.6).
- Stage III – Tumor metastases:
  - IIIA – with metastases to intrathoracic organs (lymph nodes, lung, etc.) (Fig. 10.7)
  - IIIB – with extrathoracic metastases (Fig. 10.8)

Following this schema, we encountered that mature and immature teratomas were the only tumors that invariably were in stage I, while the remaining tumors were found in different

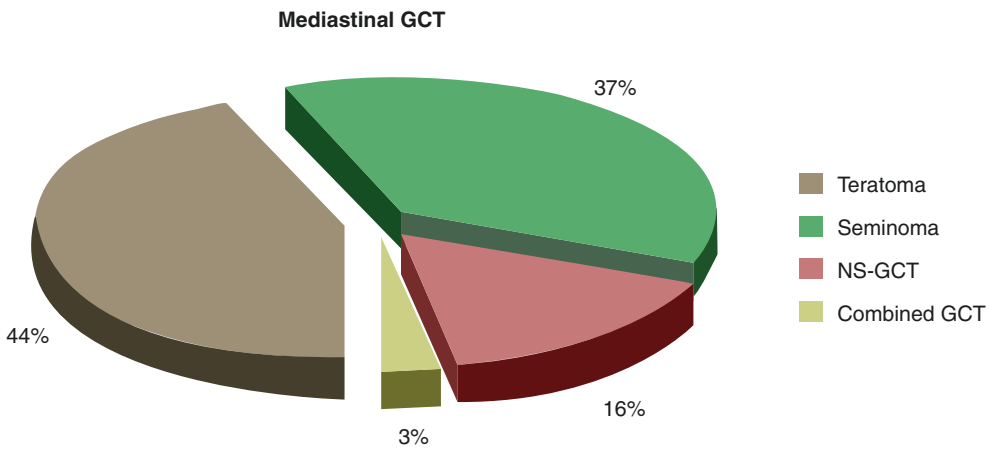

Fig. 10.1 Distribution of mediastinal germ cell tumors by histological type. (Adapted with permission of John Wiley and Sons from Moran and Suster [17])

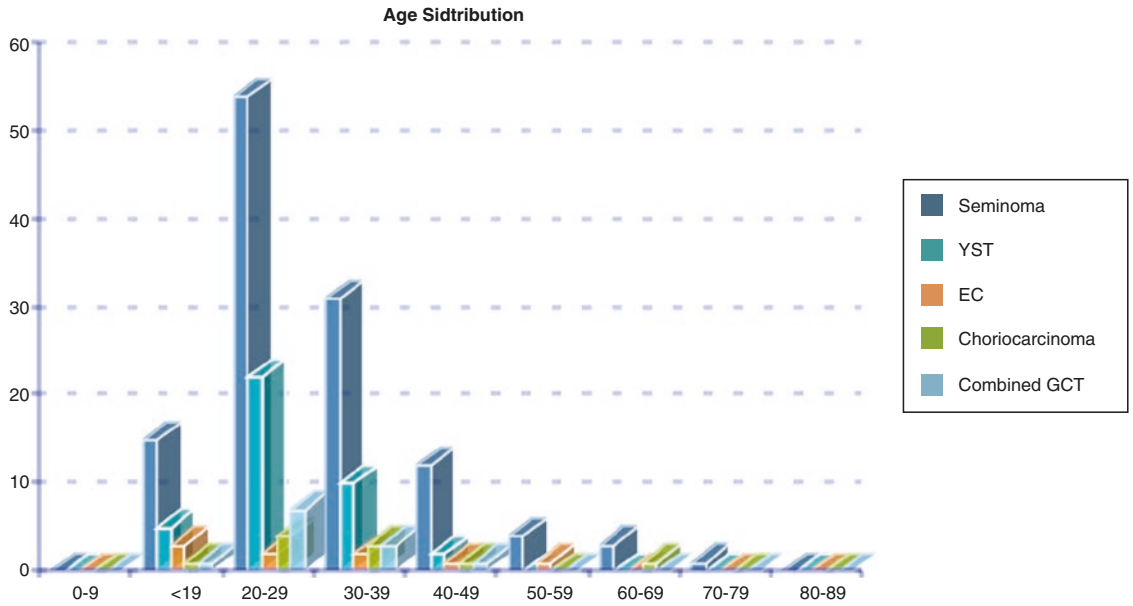

Fig. 10.2 Distribution of mediastinal germ cell tumors by age group. (Adapted with permission of John Wiley and Sons from Moran and Suster [17])

Fig. 10.3 Distribution of mediastinal teratomatous lesions. (Adapted with permission of John Wiley and Sons from Moran and Suster [17])

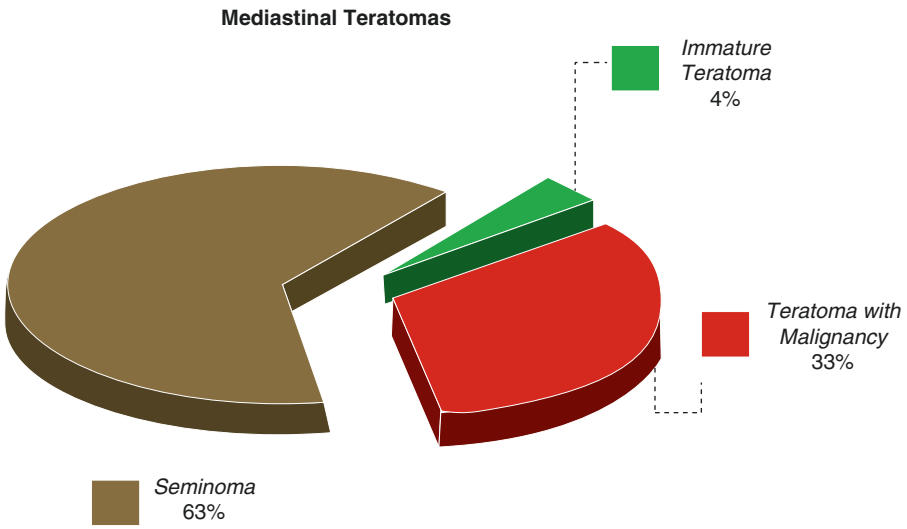

Fig. 10.4 Distribution of mediastinal non-seminomatous germ cell tumors

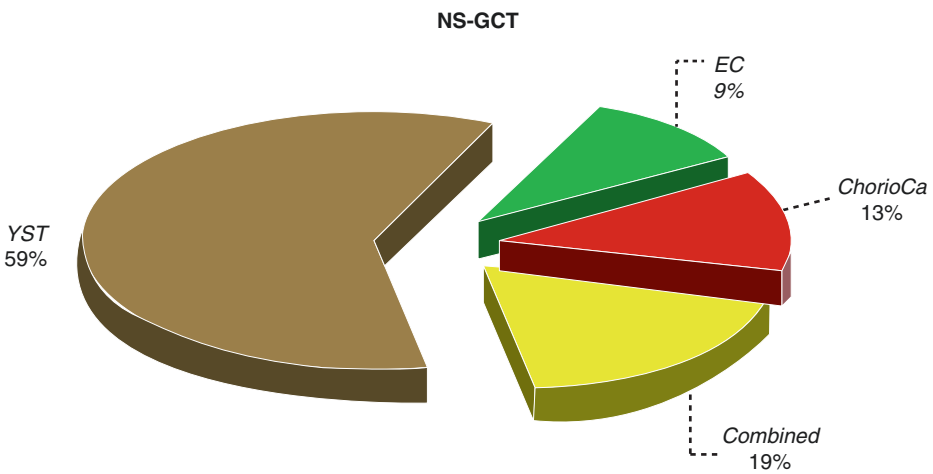

Table 10.2 Classification of MGCT

Teratoma
Mature
Immature
With Malignant component
Type I: with another GCT, i.e., seminoma, YST, EC, etc.
Type II: with a malignant epithelial neoplasm, i.e., adenocarcinoma, squamous cells carcinoma, etc.
Type III: with a malignant mesenchymal component, i.e., rhabdomyosarcoma, angiosarcoma, etc.
Type IV: with any combination of previous types
Seminoma
Embryonal carcinoma
Yolk sac tumor (endodermal sinus tumor)
Choriocarcinoma
Combined germ cell tumor

A combination of any of the above tumors without teratomatous elements
Adapted with permission of Wiley and Sons from Moran and Suster [17]

Table 10.3 Distribution by histologic type of 138 mediastinal teratomas

Mature teratoma	87 cases	63%
Immature teratoma	6 cases	4%
With malignant component	45 cases	33%

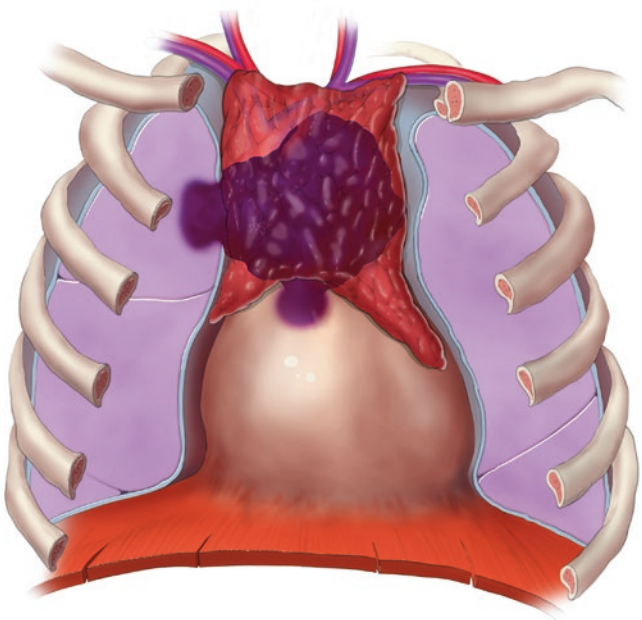

Fig. 10.6 Stage II in mediastinal germ cell tumors. (Copyright © 2012 with permission from Dr. Kalhor and Moran)

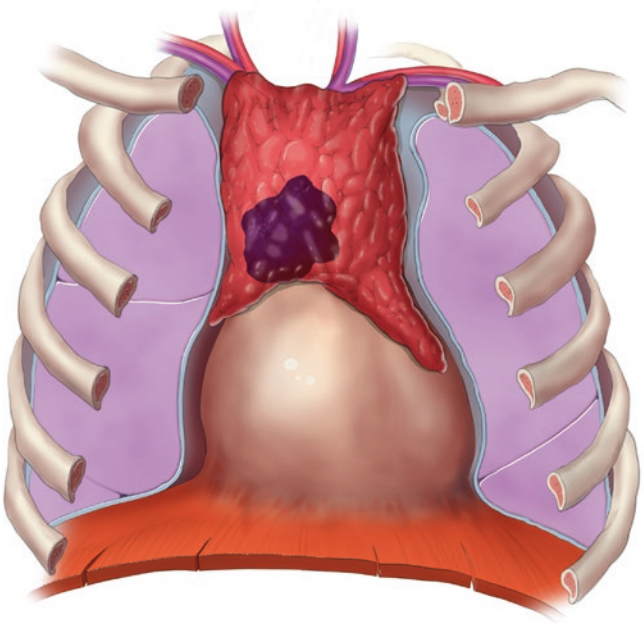

Fig. 10.5 Stage I in mediastinal germ cell tumors. (Copyright © 2012 with permission from Dr. Kalhor and Moran)

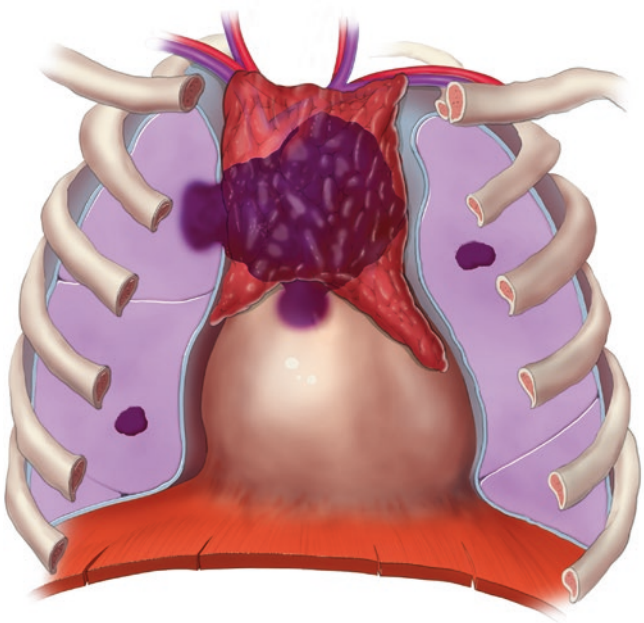

Fig. 10.7 Stage IIIA in mediastinal germ cell tumors. (Copyright © 2012 with permission from Dr. Kalhor and Moran)

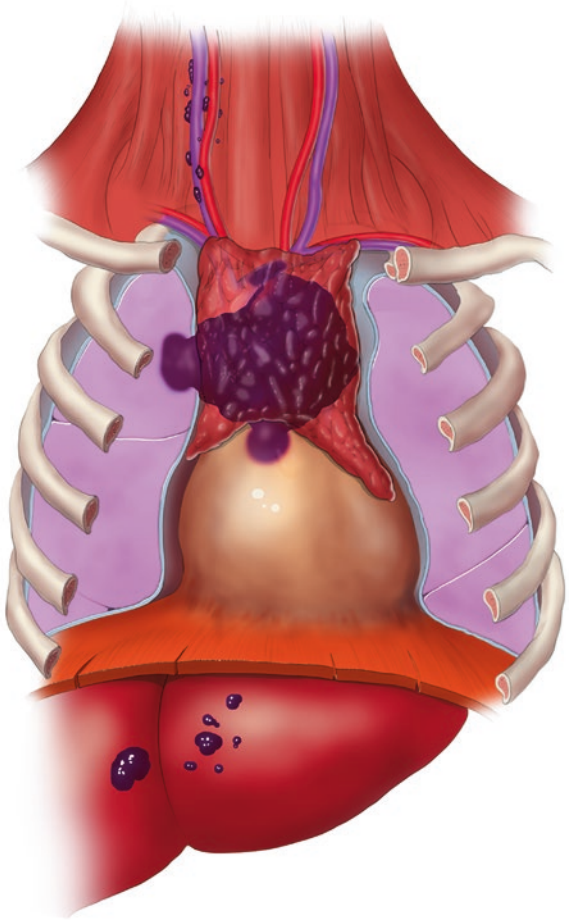

Fig. 10.8 Stage IIIB in mediastinal germ cell tumors. (Copyright © 2012 with permission from Dr. Kalhor and Moran)

stages. It is considered that the stratification of cases following such schema may be used not only to determined additional therapy but also to estimate possible outcome in these patients.

Teratomas

Teratomas are defined as tumors showing tissues derived from all three germ cell layers. However, a tumor may be accepted as teratoma, if at least two of the germ cell layers are represented. Those tumors composed exclusively of tissues derived from ectoderm are often termed "dermoid" cysts and have been variously regarded as monodermal teratomas. Mediastinal teratomas represent the most commonly reported MGCT and have accounted for up to 80% of all primary MGCT in different series [2, 4, 8, 18, 19, 21, 25–65].

Mature Teratoma

Mature teratoma appears to represent the most common MGCT. Undoubtedly, it is the most often reported and also the earliest one to have been recognized in the literature. Short series of cases or large series of cystic tumors of the mediastinum including cystic lesions not related to teratomatous lesions have been commonly presented in the literature [6, 8, 18, 19, 25–29]. Interestingly, in all those published series of cases, the tumors appear to be present in men and women in almost equal proportion, the great majority of patients were treated with surgical resection, and the follow-up was that of an indolent process. Clinically, the reported symptomatology includes cough, chest pain, dyspnea, and hemoptysis. However, in some series, up to 36% of the patients were asymptomatic [28]. More recently, Dulmet and colleagues [15] reviewed a 30-year experience and found 98 cases of MGCT. Fifty were mature teratomas; 38 tumors were in women and 12 in men. All these patients were treated with surgical resection, and the survival rate after 15 years was approximately 95%. On the other hand, teratomas in children appear not to be as common as in adults. In a few large series [30–34], the number of cases reported in children is dramatically less than those in adults. However, the treatment and prognosis appear to be similar as that reported for adult patients.

In our experience with 87 cases of mature teratomas, we found a male/female ratio of approximately 2:1, in contrast to other reported series of 1:1 [18]. Interestingly, when we separate teratomas with malignant component from mature teratomas, there appears to be a high predominance of male patients in the former [17]. Nevertheless, teratomas are more commonly seen in the anterior mediastinum with sporadic cases reported in the posterior mediastinal compartment [35, 36].

Based on our experience and that collected from the literature, one can conclude that the treatment of choice for these tumors is complete surgical resection, and the outcome in these patients appears to be good. However, reported cases of mature teratomas with metastasis showing frank malignant component have been reported [37]. In these cases, it is difficult to determine whether the malignant component was present from the outset. These instances may represent examples of incompletely resected tumors or inadequate sampling.

Clinical Features

The symptomatology in these patients is related to the size of the tumor. In small tumors, the patients may be completely asymptomatic, while in patients with larger tumors,

symptoms of cough, chest pain, shortness of breath, etc. may be present. In some cases, Klinefelter's syndrome has been associated [38]. However, the symptomatology present does not allow a separation between mature teratomas and other types of teratomatous tumors. Unusual symptoms including hemoptysis and pericarditis [39, 40] may be present. In this context, mediastinal teratomas should be distinguished from intrapericardial teratomas [41]. Also, endocrine abnormalities such as production of insulin have been reported [42].

Radiologically, mature teratomas may show extension toward one side of the midline. Calcifications can be seen and have been reported in about 20–40% of the cases; teeth and the presence of fat-fluid level are considered specific for teratoma [43]. Nonetheless, there is no radiological characteristic that can separate mature teratoma from teratomatous tumors with malignant component.

Gross Features

The tumors can vary in size from a few centimeters to over 15 cm in greatest diameter. They are usually soft, ill defined, and surrounded by thin membranous tissue. The tumors can show predominantly a cystic appearance with presence of abundant sebaceous material, hair, and teeth. On the other hand, teratomas can present as solid lesions or as combination of solid and cystic areas (Figs. 10.9a, b and 10.10). Because of the large size that these tumors may have, it is highly important to properly sample these lesions in order to fully determine if the components present are mature tissues. Even though there is not a "magic" number of sections that one must take, it is recommended to take a reasonable number of sections equivalent to one section per centimeter of tumor; however, close attention should be paid to suspicious

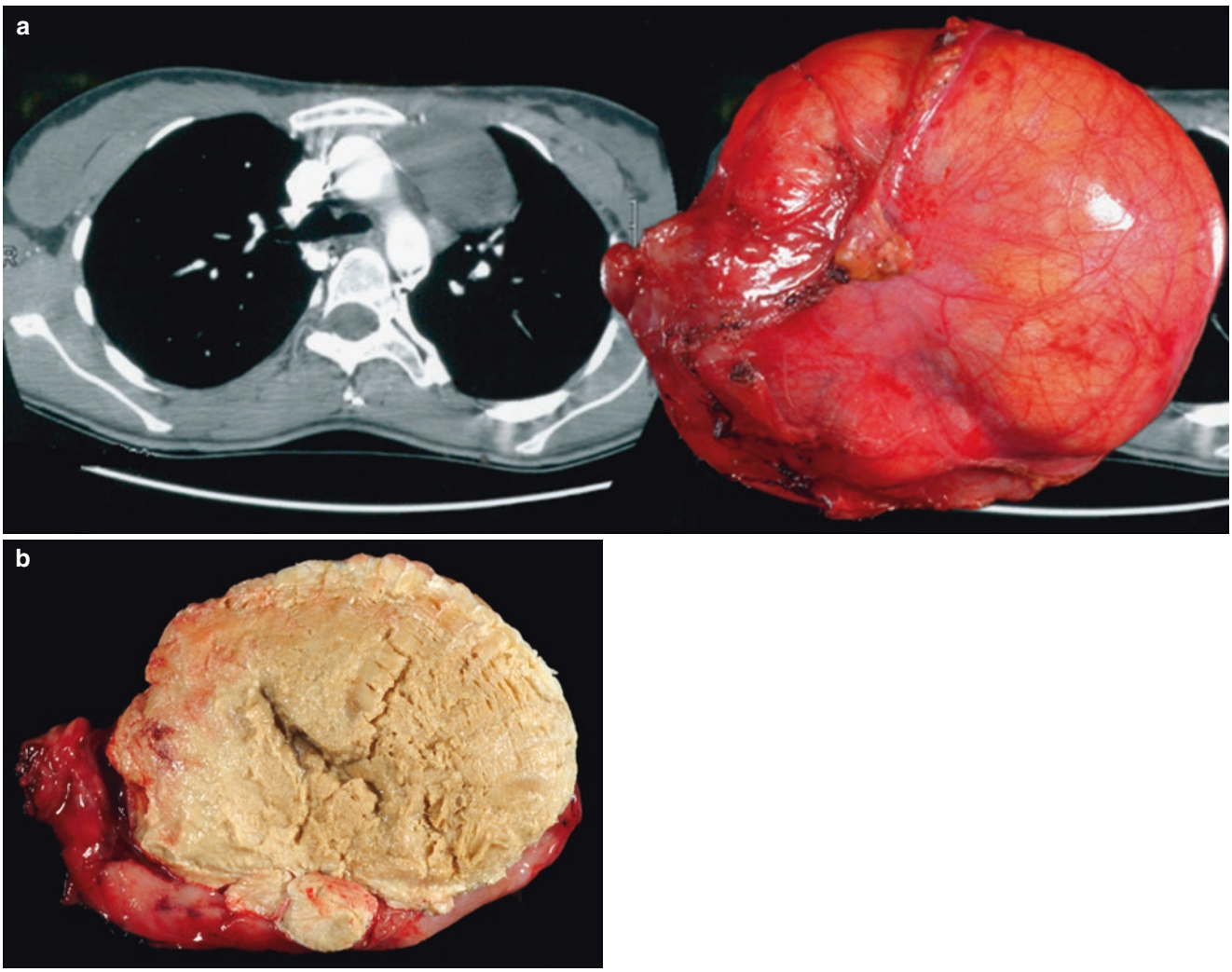

Fig. 10.9 (**a**) Mediastinal mature teratoma compared to the CT image of the tumor. (**b**) Mediastinal teratoma showing sebaceous material

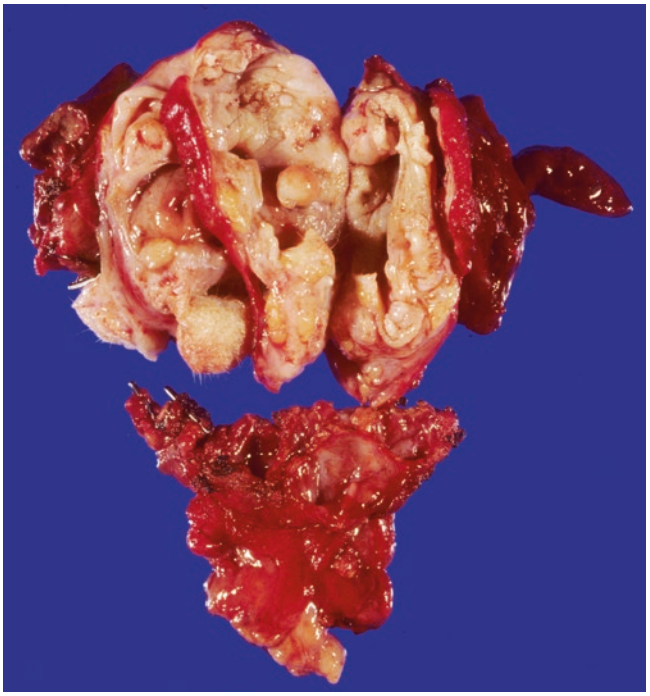

Fig. 10.10 Mediastinal mature teratoma showing classic cystic structures

solid areas of the tumor, and, if needed, extensive sampling should be performed.

Histological Features

The classical features of mature teratoma are the presence of cystic structures lined by columnar epithelium admixed with areas of fibroconnective tissue, cartilage, skin appendages, keratinization, and areas of mature glial tissue. In some areas, cystic structures lined by squamous epithelium are commonly seen. The cystic structures are generally filled with sebaceous or keratinous material. The cysts may occasionally rupture provoking an intense inflammatory reaction that may extend outside the confines of the lesion into the pleura or pericardium, simulating an infiltrative process. A wide variety of mature tissues may be observed in mature teratomas; however, pancreatic tissue appears to be one of the most commonly encountered [44, 45]. Absence of immature elements or malignant component is necessary in order to arrive at the diagnosis of mature teratoma (Figs. 10.11, 10.12, 10.13, 10.14, and 10.15).

Immunohistochemical Features

The use of immunohistochemical markers in the diagnosis of mature teratomas is limited. Essentially, the diagnosis is made on standard H&E sections. The use of neuroendocrine markers may be useful for identification of a variety of neuropeptides in cases in which pancreatic tissue is present and clinically functioning.

Differential Diagnosis

The diagnosis of mature teratoma is in the great majority of cases fairly simple and straightforward. Since the presence of immature neural tissue or foci harboring a malignant component may significantly alter the prognosis, adequate sampling of the tumor is of the utmost importance. Thorough extensive sampling is therefore recommended.

Immature Teratoma

This term is reserved for those tumors in which, in addition to the mature teratomatous elements, the tumor also shows areas of immature neuroepithelium. Because of the lack of a standard nomenclature for teratomas, it is difficult to determine the incidence or prevalence of these tumors in the mediastinum. However, they appear to be quite rare. It is possible that cases of immature teratomas may have been reported along with other cases of teratoma with malignant component in previous studies; conversely, tumors showing the criteria for immature teratoma have been included in reports dealing with other germ cell tumors of the mediastinum. In one study, it was estimated that immature teratomas might account for approximately 1% of all mediastinal teratomas [46]. Different series of MGCT in which immature teratomas have been included have been presented in the literature [5, 15, 32, 33, 46–48]. Most of the cases corresponding to immature teratomas have been described in relatively younger individuals or in children. The documented outcome from those series of cases is variable; however, it is possible that immature teratomas in children have a better outcome than in adults. Nevertheless, the most important element is the sampling process, which needs to be adequate. The determination of the amount (percentage) of immature elements present in a particular tumor needs to be made.

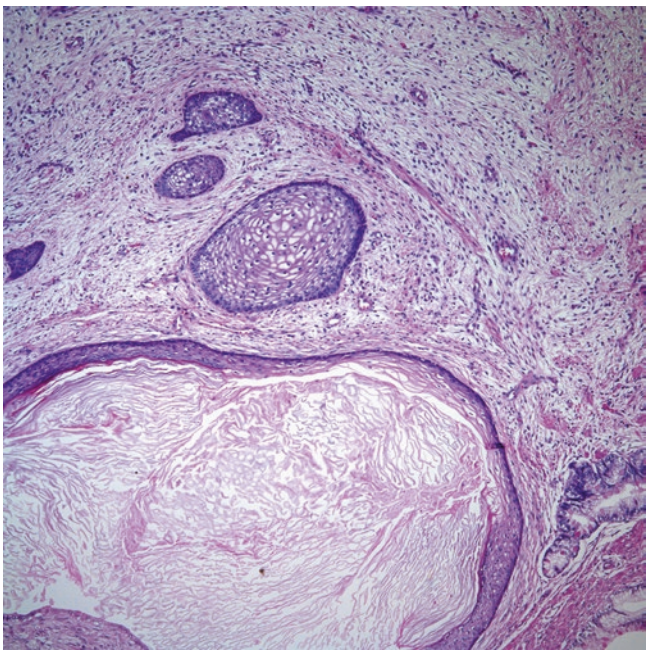

Fig. 10.11 Mediastinal mature teratoma showing dermal appendages and cystic structures

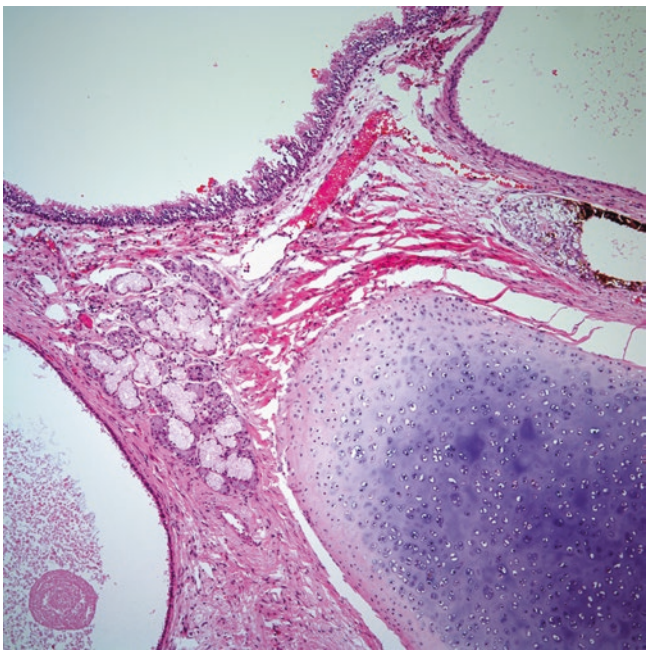

Fig. 10.13 Mature teratoma showing mature cartilage and cysts lined by low columnar epithelium

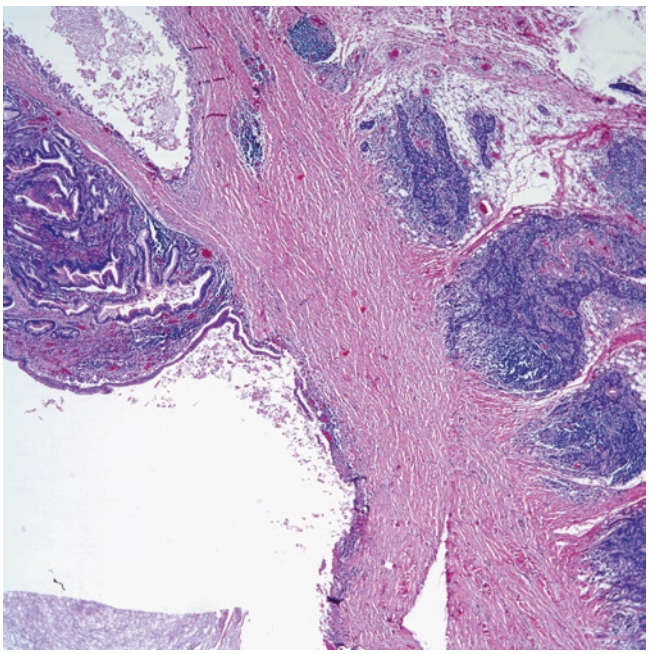

Fig. 10.12 Mediastinal mature teratoma showing remnants of thymic tissue and mature glandular proliferation

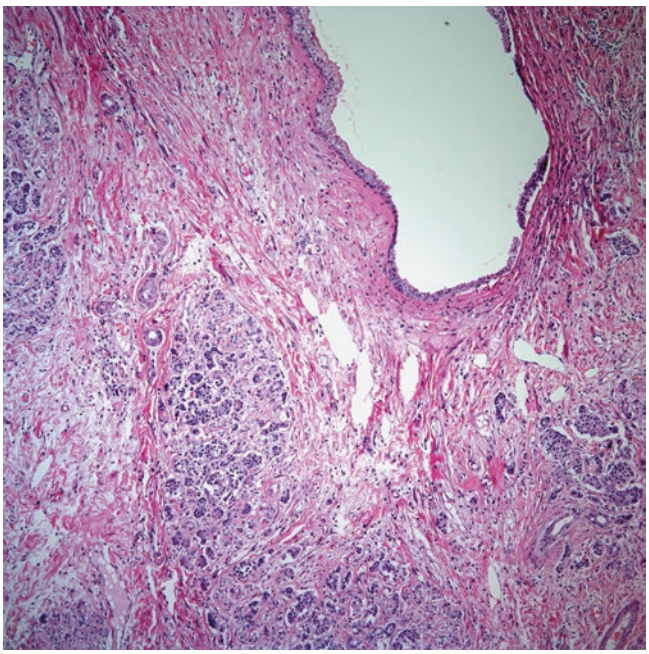

Fig. 10.14 Mediastinal mature teratoma showing pancreatic tissue

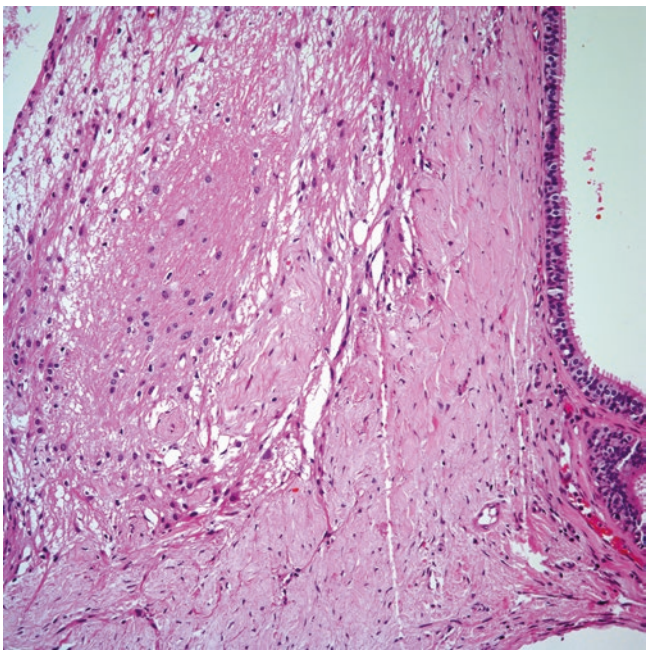

Fig. 10.15 Mediastinal mature teratoma showing mature glial tissue

Clinical Features

The clinical manifestations of patients with immature teratomas are essentially indistinguishable from those of mature teratomas. The patients may present with cough, fever, and/or chest pain, or with respiratory distress related to the size of the mass, which can compromise adjacent mediastinal structures.

Gross Features

The tumors can be partially cystic with solid areas. The outer surface is generally lobulated and fairly well delimited. On cut surface, the tumor may show clear fluid or areas of induration within the cyst walls. In the solid component, the tumor may show a soft, tan, and homogeneous appearance. The size of these tumors, the same as that of mature teratoma, can vary from a few centimeters to over 10 cm in greatest diameter (Fig. 10.16).

Histological Features

The classical feature of immature teratoma is the presence of foci of immature neuroepithelium. This latter component may comprise over 80% of the tumor, while in some cases its presence may be limited to focal areas. Morphologically, it is characterized by the presence of neuroepithelial tubules and

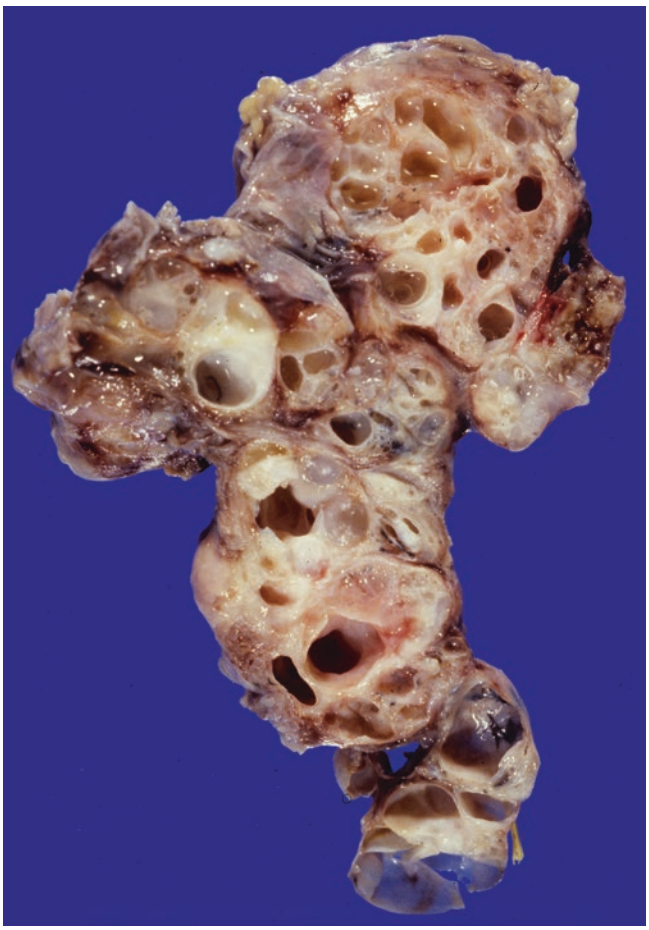

Fig. 10.16 Immature teratoma showing solid and cystic areas

rosettes. These structures may be embedded in an immature neuroepithelial background (neurophil), while in other areas the neural structures may be admixed with cartilage or other mature elements. Closer view of the cellular proliferation will show spindle or oval cells with dark nuclei, inconspicuous nucleoli, and scant cytoplasm. Mitoses are rare, and the appearance of the cellular proliferation is more reminiscent of an embryonic type of epithelium (Figs. 10.17, 10.18, 10.19, and 10.20a, b).

Immunohistochemical Features

The use of immunohistochemical markers in these tumors is limited to neural markers such as S-100 protein, neurofilaments, glial fibrillary acidic protein (GFAP), and neuron-specific enolase (NSE). In the majority of cases, the diagnosis can be reached on morphological grounds, leaving the use of immunohistochemical stains for cases in which the immature component is not apparent.

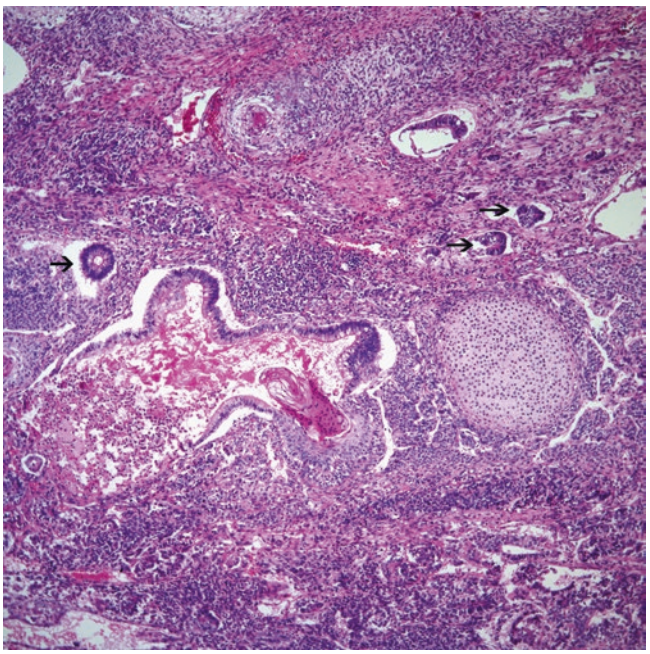

Fig. 10.17 Mediastinal teratoma showing predominantly mature elements with only focal immature component (see arrow)

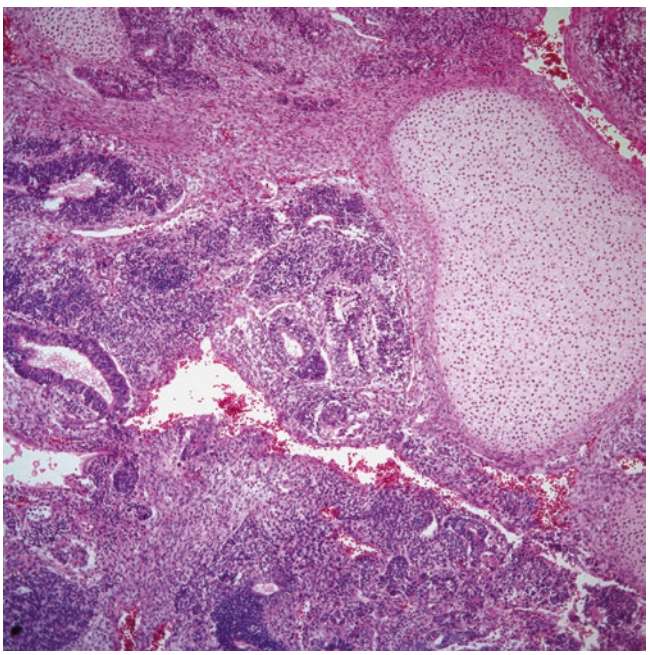

Fig. 10.18 Immature teratoma showing also mature cartilaginous component

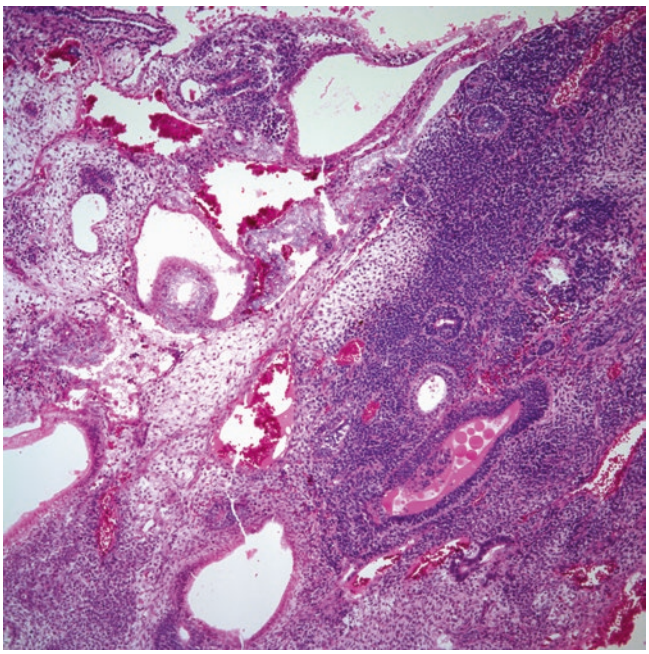

Fig. 10.19 Epithelial cystic mature structures admixed with immature teratoma in the form of neuro-rosettes and solid areas

Differential Diagnosis

The diagnosis of immature teratoma is rather straightforward, if there is enough material available for evaluation. However, in small biopsies, sampling error may obscure the diagnosis. Alternatively, when only neuroepithelium is present, the possibility of other tumors that may show neural differentiation may be entertained. Malignant peripheral nerve sheath tumors, Schwannomas, and extraskeletal Ewing's sarcoma may be a consideration in small biopsies. Correlation with clinical and radiographic findings may be of help in narrowing down the differential diagnosis in such instances.

Teratoma With Malignant Component

This term encompasses several types of teratomatous lesions, which may show a variety of malignant components [4–6, 8, 19, 26, 27, 29, 32, 34, 48–67]. In the past, terms such as teratocarcinoma and malignant teratoma were variously employed for these tumors. Whether the malignant component arises from malignant transformation of the benign mature teratomatous elements, represents a collision tumor, or originates from multidirectional differentiation of primi-

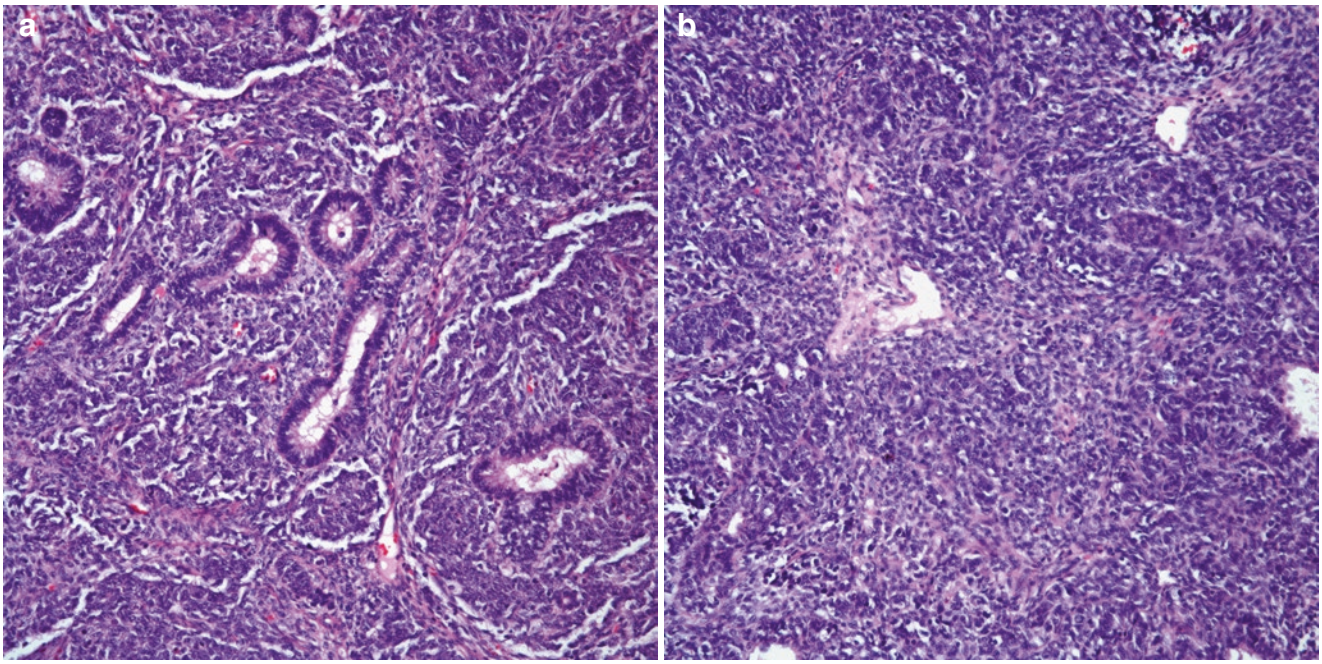

Fig. 10.20 (**a**) Immature teratoma showing classical features of neurotubules embedded in solid immature neural component. (**b**) Immature teratoma showing solid areas of neural component

tive stem cells is a question that remains unanswered. Because of the uncertainty as to the exact pathogenesis of these tumors, we prefer the descriptive term "teratoma with malignant component" to those previous terminologies. We have further subdivided these tumors into four distinct categories:

- Type I – teratoma admixed with another type of MGCT (seminoma, yolk sac tumor, embryonal carcinoma, choriocarcinoma)
- Type II – teratoma admixed with another type of epithelial neoplasm (squamous cell carcinoma, adenocarcinoma, small cell carcinoma, large cell carcinoma, etc.)
- Type III – teratoma admixed with a mesenchymal neoplasm (rhabdomyosarcoma, angiosarcoma, chondrosarcoma, osteosarcoma, etc.)
- Type IV – teratoma admixed with two or more of the above

Although in general the treatment for these patients is surgical resection followed by adjuvant therapy, the prognosis is rather poor in comparison with that of mature teratomas. However, we consider that by providing a more specific diagnosis for the malignant component, therapeutic efforts can be more beneficially tailored toward the different specific types of malignant components present, thereby improving the patients' chances for better survival.

Clinical Features

The symptoms of patients with teratoma with malignant component are similar to those of other teratomas. The symptoms will depend on the size of the lesion and the compromised adjacent structures. The vast majority of patients are asymptomatic, and the tumors are found to be unresectable at the time of exploratory thoracotomy. Teratomas with malignant component ("malignant teratoma," "teratocarcinoma") represent approximately 20% of all mediastinal teratomas [6, 68]. Teratomas with malignant component have been associated with hematological conditions such as lymphoblastic leukemia, megakaryoblastic leukemia, hemophagocytic syndrome, histiocytosis, and other medical conditions such as precocious puberty and Klinefelter's syndrome [58, 69–79]. Chromosomal abnormalities have also been observed in cases of malignant teratomas of the mediastinum. Tricot [80] documented 5q-anomalies in the bone marrow in patients with mediastinal teratoma with malignant transformation.

Although teratomas with malignant component can occur in all age groups, there is a tendency for this tumor to occur in the third and fourth decades of life. We do not know of any case in which a mediastinal teratomatous lesion with malignant component has given rise to mature teratomatous metastases as has been described for testicular tumors [5].

There are no specific radiographic features that can separate mature teratomas from teratomas with malignant component. The diagnosis should be strictly based on histopathological examination.

Gross Features

The gross features of teratomas with malignant component are similar to those of other teratomas (Fig. 10.21). These tumors can show extensive cystic changes as well as more solid areas. The tumors are usually poorly circumscribed and infiltrative and may be surrounded by thin membranous tissue. Their size may vary from a few centimeters to over 12 cm in greatest diameter.

Histopathological Features

- *Type I* – this type may show one or more of the other types of germ cell tumors, including seminoma, yolk sac tumor, embryonal carcinoma, and/or choriocarcinoma. In our experience, this type represents the most common form of teratoma with malignant component. The admixture of mature teratomatous elements such as the hair, skin, bone, and cartilage, with areas showing other types of germ cell tumor such as seminoma, etc., characterizes the histologic features of these tumors (Figs. 10.22a, b and 10.23).
- *Type II* – teratomatous elements are admixed with other differentiated malignant neoplasms of epithelial origin. Adenocarcinoma or squamous cell carcinomas are the most frequent types observed in these lesions. The features of the malignant component observed in this type will be those of conventional adenocarcinoma or keratinizing squamous cell carcinoma. In rare occasions, the malignancy will be of a large cell carcinoma or small cell carcinoma (Fig. 10.24a, b).
- *Type III* – a variety of malignant mesenchymal neoplasms such as rhabdomyosarcoma, liposarcoma, and/or angiosarcoma can be seen in association with mature teratoma. In some cases, the mature teratoma may be associated with an undifferentiated mesenchymal neoplasm. The features of the sarcomatous elements will be those seen in the conventional soft tissue counterparts of these tumors (Fig. 10.25a, b).
- *Type IV* – this is an unusual phenomenon in which a teratoma may show areas of mature or immature teratoma associated with carcinoma, sarcoma, and/or another germ cell tumor. We have documented cases of this unusual phenomenon [17].

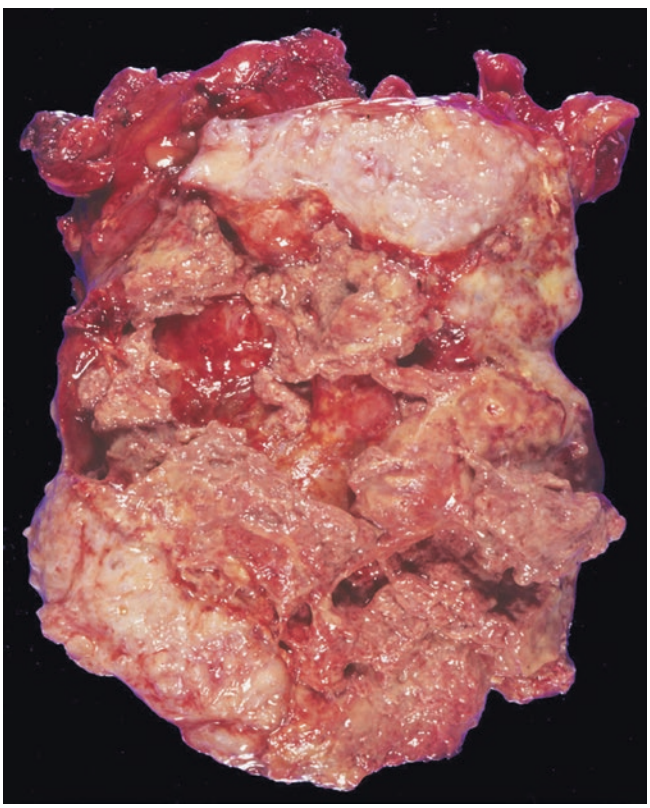

Fig. 10.21 Teratoma with malignant component. At the macroscopic level, there is no pathognomonic feature that will discriminate this tumor from other teratomatous lesion

Histochemical, Immunohistochemical, and Ultrastructural Features

The use of specific markers may be of help for identifying the different neoplastic components of these tumors. Germ cell markers such as placental-like alkaline phosphatase (PLAP), alpha-fetoprotein (AFP), SALL-4, Glypican 4, OCT4, TCL1, and human chorionic gonadotrophin (HCG) may be of aid in separating germ cell elements from other malignant epithelial neoplasms. The use of keratins, vimentin, actin, desmin, and S-100 protein may be of aid in identifying specific features of differentiation in pleomorphic and spindle cell elements in these tumors. The use of these special markers should therefore be guided to identify the different specific components. The role of electron microscopy is more limited due to the sampling difficulties inherent to these tumors. However, ultrastructural examination may be of aid in adequately sampled cases for differentiating sarcomatous from anaplastic carcinomatous and germ cell elements.

Differential Diagnosis

Teratomas are easily recognizable tumors that do not pose a problem for diagnosis. However, because malignant components may be small and focal, caution should be exercised before rendering an unequivocal diagnosis of mature teratoma

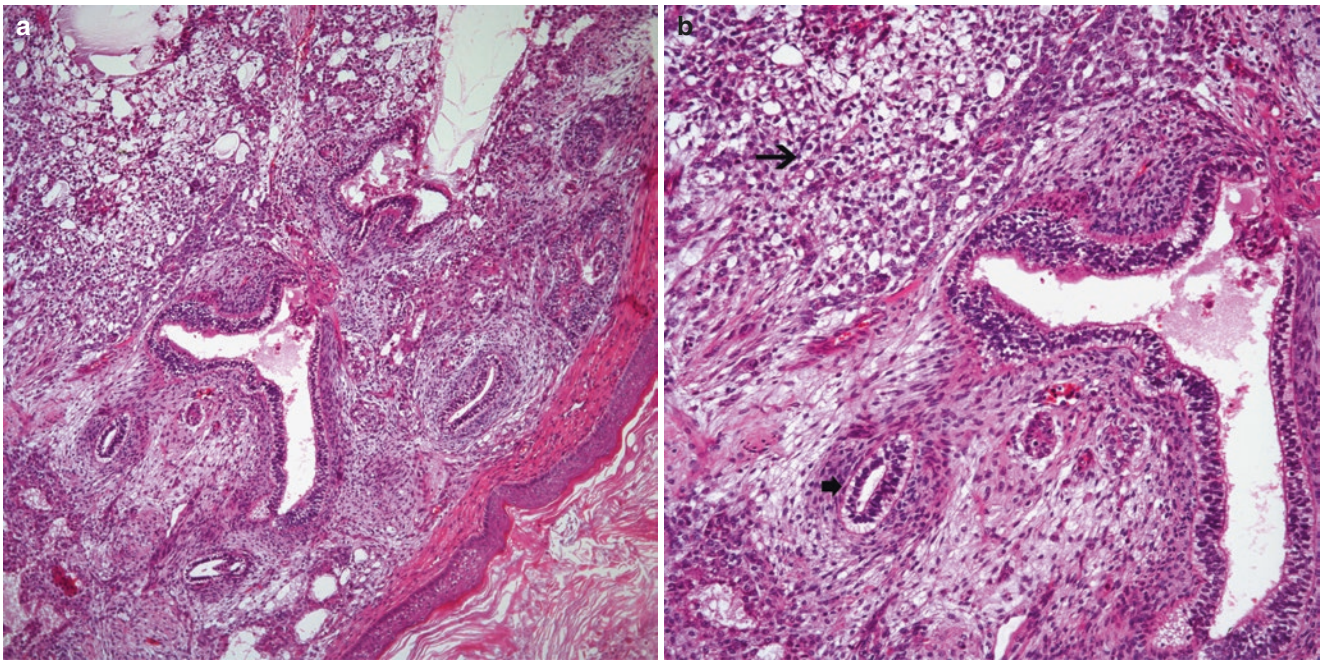

Fig. 10.22 (**a**) Type I mediastinal teratoma displaying mature, immature, and malignant component in the form of yolk sac tumor. (**b**) Close magnification of the immature component (neurotubules and rosettes) and yolk sac tumor (see arrows)

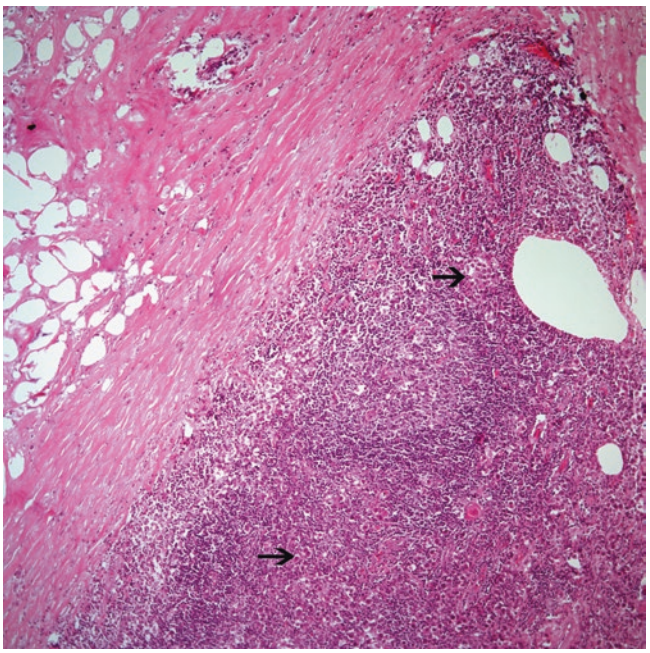

Fig. 10.23 Type I mediastinal teratoma with malignant component in which there is another germ cell tumors associated, in this case seminoma (see arrows)

in small biopsy specimens. By the same token, a small biopsy of an anterior mediastinal mass may show only mesenchymal elements with rhabdomyosarcomatous or liposarcomatous features that may be part of a teratoma. Such cases should be separated from pure mesenchymal tumors, which have also been described in the anterior mediastinum [81, 82]. Because of the possibility that even mature lesions may harbor an additional malignant component, complete excision and extensive sampling of these tumors are recommended for accurate diagnosis.

Seminoma

Primary mediastinal seminomas are neoplasms that have been well recognized for over 50 years [12, 83–86]. The first description of a pure seminoma in the anterior mediastinum is attributed to Woolner and colleagues [12] in 1955, who described two seminomas (germinomas) arising in the anterior mediastinum. It is important to note that previous descriptions of teratomatous germ cell tumors of the mediastinum had already mentioned the presence of seminomatous component [21, 67]. There appears to have been some reluctance in the past to accept the existence of seminomas as primary mediastinal tumors; hence, mediastinal seminomas were designated by other names such as "seminoma-like tumor," "seminomatous thymoma," and "pseudo-seminome, thymome" [85, 86]. In 1962, Lattes [86], in an analysis of 107 cases of thymomas and other tumors of the thymus, alluded to four cases of seminoma-like tumors of the mediastinum in young males and concluded that morphologically the tumors were indistinguishable from those seen in the male and female gonads. However, he cautioned about the danger of lumping together other pathological entities under the term "thymic seminoma" and "pseudo-seminomatous thymoma." Today, the existence of these tumors occurring primarily in the mediastinum is well-established [5, 6, 14, 29, 50, 51, 61, 62, 87–108].

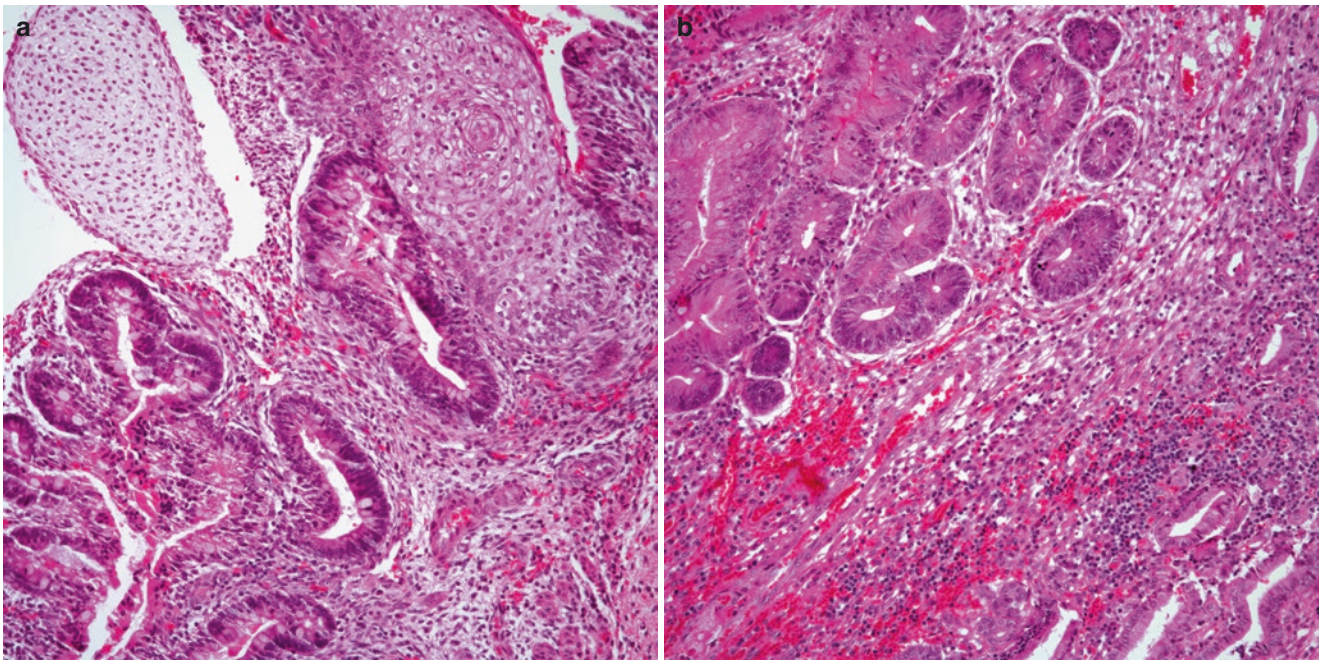

Fig. 10.24 Type II teratoma with malignant component. (**a**) In this case note the presence of cartilage and adenocarcinoma. (**b**) Adenocarcinoma embedded in a fibrous inflammatory stroma

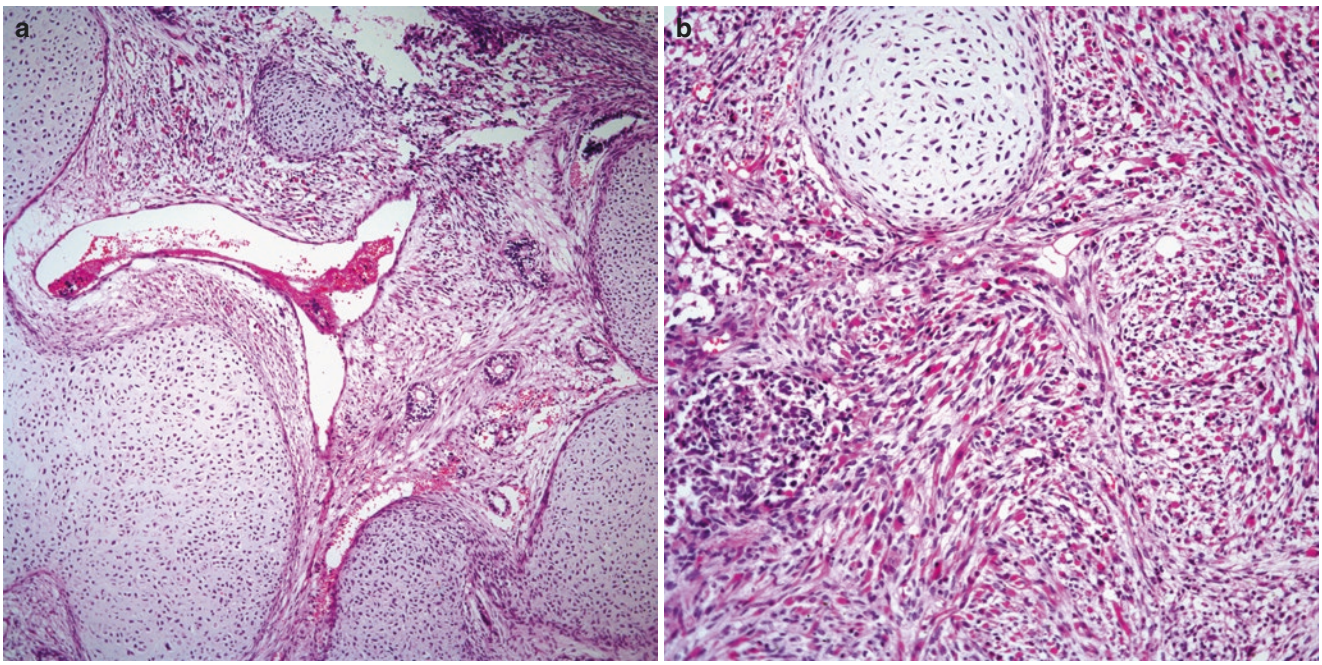

Fig. 10.25 Type III, mediastinal teratoma with malignant component. (**a**) In this case note the presence of cartilage and rhabdomyosarcoma. (**b**) Closer view of the rhabdomyosarcomatous component

Although seminomas occur often in the anterior mediastinum, cases of seminomas in the posterior mediastinal compartment have been also described [88].

Because of the rarity of this neoplasm and the lack of more comprehensive studies of these tumors, it is difficult to determine the exact incidence of mediastinal seminomas in the general population. However, in our experience, pure seminomas of the anterior mediastinum represent the second most common germ cell tumor after teratomatous lesions. Seminomas have been estimated to account for approximately 37% of all mediastinal germ cell tumors [109]. Although in our material we did not find any cases of seminomas occurring in women, such an association has been cited in the literature [62, 83, 100, 107]. It has been stated that seminomas are tumors more commonly seen in young adults. Interestingly, in our review of 120 cases of primary anterior mediastinal seminomas, the ages ranged from 14 to 79 years with an average of 46.5 years. Nevertheless, seminomas are more common in the third and fourth decade of life (Fig. 10.26a, b).

Clinical Features

The symptoms of patients with seminomas of the anterior mediastinum depend largely on the size of the tumor. Symptoms are mostly related to compression of adjacent organs. These symptoms include cough, chest pain, hemoptysis, and/or dyspnea. In some instances, the patients may present with superior vena cava syndrome [50, 83, 94]. The latter symptom has been estimated to occur in approximately 10–25% of the cases of anterior mediastinal seminomas [88, 95, 102, 110]. Interestingly, in some patients, a history of testicular trauma, orchitis, or maldescended testis has been documented [88]. However, a good number of patients with anterior

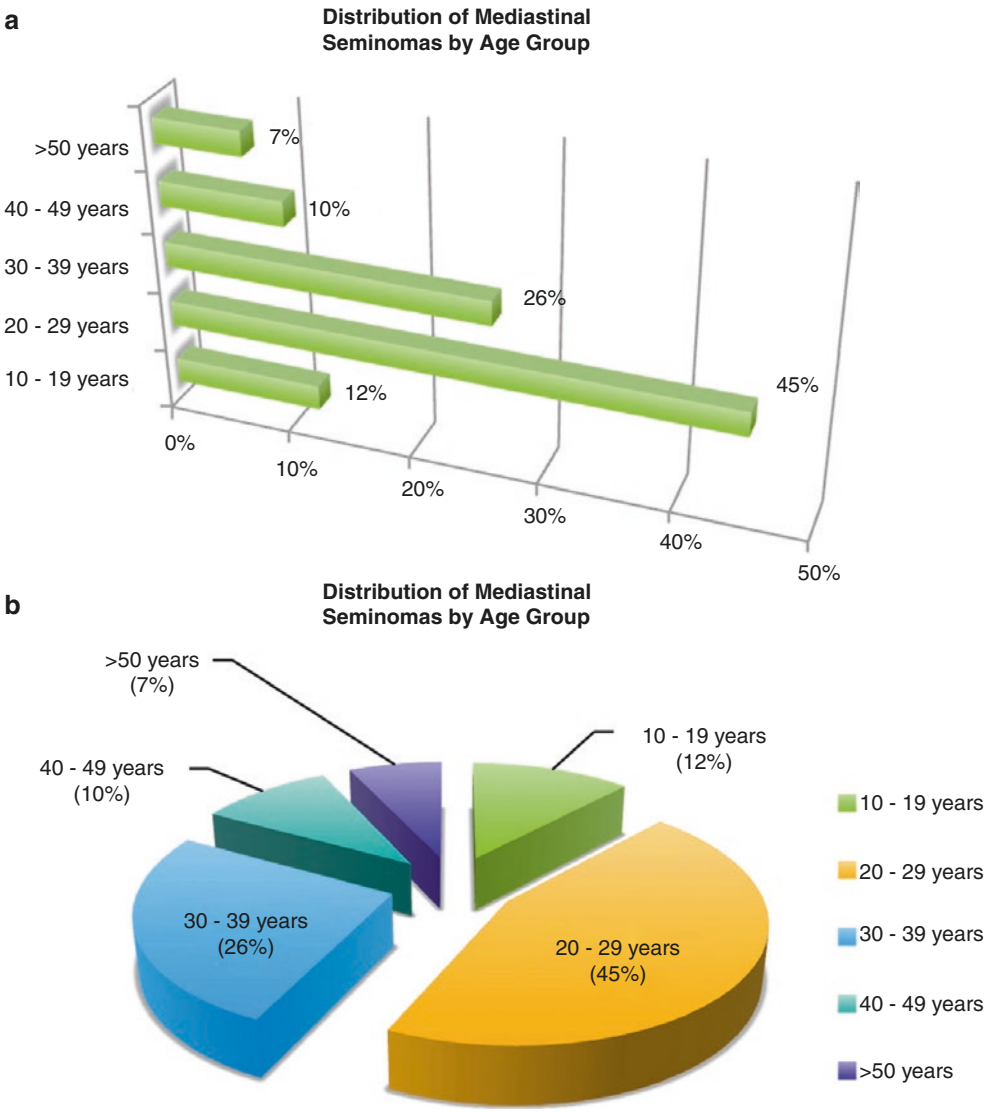

Fig. 10.26 (**a**) Distribution of seminomas per age group. (**b**) It is the respective % of seminomas per age group

Table 10.4 Common and uncommon symptoms in mediastinal seminomas

Symptoms
Chest pain
Shortness of breath
Superior vena cava syndrome
Cough
Dysphagia
Arm pain
Upper respiratory infection
Vocal cord paralysis
Hoarseness
Asymptomatic

mediastinal seminomas are asymptomatic, and the tumor is detected during a routine physical examination or chest radiographs. Table 10.4 depicts some of the common and uncommon symptoms associated with mediastinal seminomas.

Several clinical syndromes and unusual clinical conditions have been observed in association with seminomas. Raghavan and Barret [101] described a 13-year-old boy with mediastinal seminoma in association with ventricular septal defect and congenital absence of thoracic hemivertebra. Kinding and Tavel [98] described a 43-year-old man with acquired pulmonic stenosis due to an anterior mediastinal seminoma, which resolved after resection of the tumor. Nagi and colleagues [87] described a young man who presented with a history of painful gynecomastia and was found to have an anterior mediastinal seminoma with increased serologic levels of β-HCG.

Perhaps the most important question regarding seminomas is whether they are primary in the mediastinum or represent metastases from occult primary testicular tumors. This topic has been debated for quite some time. In the past, due to the reluctance to accept mediastinal seminomas as primary neoplasms, the discovery of such tumors was invariably followed by testicular biopsies. Although the results appear to some extent controversial, important knowledge was obtained from those studies. Azzopardi and Hoffbrand [111] cautioned against the uncritical acceptance of extragonadal germ cell tumor. The authors documented a case of viable metastases from a retrogressed testicular seminoma and reviewed six similar cases from the literature. In addition, the authors concluded that great caution is necessary before making a diagnosis of primary retroperitoneal seminoma; interestingly, in this review, one patient had also mediastinal seminoma. Contrary to Azzopardi's observations, Abell and colleagues [112] documented ten cases of primary retroperitoneal seminomas in patients without evidence of testicular involvement. Buskirk and colleagues [113] in a more recent study described 12 cases of primary seminoma of the retroperitoneum in the absence of testicular involvement. However, there have been some authors who have argued against the acceptance of extragonadal germ cell tumors without proper histologic evaluation of testicular biopsies [114]. In actuality, testicular seminomas rarely metastasize to the anterior mediastinum. In a review of 16 patients with extragonadal germ cell tumors and negative testicular tumor at palpation, Bohle and coworkers [115] found that 10 of 12 patients with retroperitoneal tumors had an occult testicular primary, whereas in four patients with MGCT, none had evidence of an occult testicular primary. Luna and Valenzuela-Tamaris [51] also documented a study of 20 autopsy cases of mediastinal germ cell tumors of various histologies. In all 20 cases, the testes were carefully step-sectioned, and the authors were able to find only two cases in which the testes contained an occult tumor or a well-defined testicular scar. Interestingly, the histology of the mediastinal tumors in those cases was that of a non-seminomatous tumor. The authors cited two studies from large series of testicular germ cell tumors, one by Johnson and coworkers [116], who in a review of 78 autopsies of patients with testicular germ cell tumors found no metastases to the anterior mediastinal region without involvement of mediastinal nodes, and another by Lynch and Blewett [117], who quoted a publication by Houghton of a study of 220 cases of metastasizing testicular tumors with no documented metastases to the mediastinum. However, rare metastases to the mediastinum from testicular germ cell tumors have been described. White and coworkers [118] were able to document pericardial metastasis from a testicular seminoma. Also, Man-Cha [90] reported a case of simultaneous retroperitoneal and mediastinal seminoma in an 18-year-old boy who underwent left orchiectomy without any evidence of a testicular tumor. On the other hand, there are reports of the development of testicular seminomas several years after the patient has been diagnosed and treated for a mediastinal seminoma [28, 88]. In these cases in particular, it may be possible to argue that the testicular tumor had already been present; however, based on the length of appearances of both tumors, a second primary is most likely.

Germ cell tumors (GCT) can display distinctive chromosomal abnormalities. Bosl and coworkers [119] in a study of 29 cases of different primary sites (including mediastinum) found that the isochromosome of chromosome 12[1(12p)] is a useful marker of GCT in males. However, because of similar histologic features displayed by these tumors in either mediastinal or testicular location, there have been attempts to

further analyze these tumors for more discriminant features. In this regard, Oosterhuis and coworkers [120] studied the ploidy in 19 primary MGCT, encountering that the ploidy of mediastinal tumors was remarkably different from that of testicular tumors of adults and closer to those of children. MGCT share similar features with childhood testicular GCT in terms of both being diploid; nevertheless, diploid testicular GCT are rare. Seminomas are usually hypertriploid, while non-seminomatous tumors are usually hypotriploid. The authors proposed that the pathogenesis of malignant MGCT is probably different from that of testicular tumors of adults and stated that ploidy studies in questionable cases may be of help in elucidating the site of origin of these tumors when the clinical setting is obscured. More recently, we analyzed the expression of p53 and K-ras-2 oncogene in 13 cases of primary mediastinal seminomas. We found that the k-ras-2 genotype was normal in approximately 92% of the cases, and also identified a single mutation in codon 13. This latter finding may be of help in distinguishing mediastinal from testicular tumors since most testicular tumors show abnormalities of codon 12 rather than codon 13 [121].

The radiological features of these tumors have been well defined. Rosado-de-Christenson and coworkers [43] found that seminomas are typically large and bulky, well-marginated, lobulated masses, which may extend to both sides of the midline. On CT scans, seminomas appear large and coarsely lobulated with a homogeneous attenuation equal to that of soft tissue. Seminomas enhance slightly after the administration of contrast material. Areas of low attenuation may also be detected [122]. Extension of the tumor into the midline and posterior mediastinal compartments can also occur. Ringlike and stippled calcifications within a mediastinal seminoma on CT studies have been reported [123].

Seminomas are eminently radiosensitive tumors [64, 102, 124–127]. However, it is also known that approximately 20–30% of advanced germ cell tumors will fail to achieve a durable complete response to chemotherapy [128]. Medini and coworkers [129] evaluated the follow-up of eight patients with extragonadal seminomas, including five patients in whom the tumors were primary in the mediastinum, and found that 50% of the patients died within a period ranging from 2 months to 16 years; 25% of these patients died of unrelated conditions, and, in one patient, metastases to the brain were documented. The remaining 50% of the patients were alive and well after a period of 5–17 years. Hurt [95] followed 17 patients with primary mediastinal seminoma of whom 16 had received radiation therapy after initial diagnosis, concluding that possible factors that may influence the progression of disease include age (older than 35 years), presentation with fever, superior vena cava syndrome, supraclavicular or cervical adenopathy, and roentgenographic evidence of hilar disease. Hainsworth and coworkers [130] also studied 32 patients with extragonadal GCT (17/32 MGCT; 6/32 seminomas), concluding that extragonadal GCT can be as curable as testicular GCT when treated with intensive chemotherapy and surgical resection. In a study of exclusively MGCT (28 cases; 11/28 seminomas), Economou [63] found 82% of the patients free of tumor after a period ranging from 6 months to 15 years. The primary treatment for these patients was radiation therapy, except in one patient who received chemotherapy for metastatic disease. Green and coworkers [131] encountered similar findings in a study of 17 retroperitoneal seminomas and 1 mediastinal seminoma. However, it is important to note that cardiac disease that may be the source of much morbidity and mortality may appear after mediastinal irradiation for seminoma [132]. In a study of 27 patients with primary MGCT including 13 patients with pure seminomas treated with radiation therapy alone, it was found that the most important factor was the histology of the tumor. The 5-year survival rate for all of the patients with pure seminoma was of 100%, whereas tumors showing non-seminomatous features displayed a worse prognosis. On the other hand, late recurrences have been reported after many years of successful remission [133]. A recent study by Rodney and coworkers [134] addressing the survival outcomes in 34 men with mediastinal GCT including 27 with non-seminomatous GCT (NS-GCT) and 7 with pure seminomas showed that 41% with NS-GCT were alive with a median overall survival of 33.5 months. Patients with seminoma were treated with platinum-based chemotherapy and did invariably well.

Although a good number of seminomas are limited to the anterior mediastinal region without invasion into adjacent structures, metastases of mediastinal seminomas to other organs can occur. In our experience, we have observed metastatic lesions from mediastinal seminomas to the lung, brain, lymph node, pleura, liver, and bone [109]. Serum tumor markers have also been studied to further determine staging and prognosis of GCT. In a study of 111 patients with GCT of the testicle, Scardino and coworkers [135] found that 33% of patients with testicular seminoma had elevated CEA levels; however, CEA levels did not correlate with the course of disease.

Follow-up information obtained in 65 patients with primary mediastinal seminomas studied by us disclosed that 49 patients were alive and well after a period ranging from 1 to 19 years (mean: 10 years). Sixteen patients died during the same period of time. We were not able to find a statistically meaningful correlation between aggressive behavior and any clinical or histopathological feature in these tumors.

Gross Features

Seminomas vary in size from a few centimeters to over 16 cm in greatest diameter (Fig. 10.27). The outer surface may be smooth and glistening or may show a lobulated appearance. The cut surface can show either a coarsely lobular or a discrete nodular pattern. The color may vary from white to light tan, and the consistency is rather soft. In some cases, solid areas may alternate with large cystic areas containing necrotic material, while in other areas the tumor may have the appearance of an entirely cystic mass. In some cystic tumors, it is possible to observe indurated areas within the walls of the cysts.

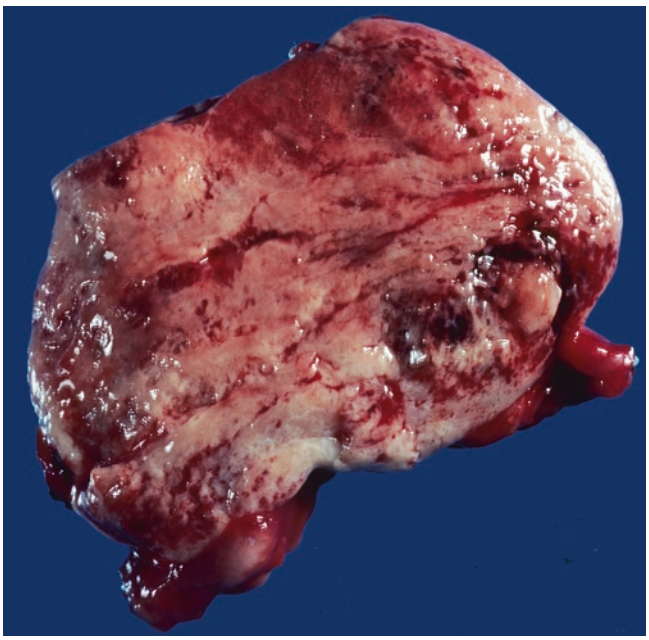

Fig. 10.27 Mediastinal seminoma showing a solid tumor mass

Histologic Features

The histology of primary mediastinal seminomas is similar to those described for their gonadal counterparts. On scanning magnification, the neoplastic cells may be arranged in sheets or forming a discrete nesting pattern-containing uniform round to oval tumor cells (Fig. 10.28a–d). In cases in which the neoplastic cells are arranged in a nesting pattern separated by thin fibrovascular septa, the fibrovascular septa will be characteristically infiltrated by a large number of lymphocytes; however, the presence of lymphocytes may vary as, in some cases, despite the presence of areas of hyalinization, the inflammatory component is not present (Fig. 10.29a–c). In some other cases, the lymphoid component is completely admixed with the neoplastic component (Fig. 10.30). However, this phenomenon may obey to the normal lymphocytic component of the thymus. In some unusual cases, mediastinal seminomas may show focal or extensive areas of "crush artifact," which may obscure the true nature of the neoplasm (Fig. 10.31a, b). On higher magnification, the neoplastic cells are composed of large, round to polygonal cells with pale cytoplasm; round nuclei and prominent nucleoli may or may not be apparent (Fig. 10.32). Mitotic figures are usually present but not in large numbers (Fig. 10.33). Seminomas can also show foci containing large giant cells of syncytiotrophoblast type. In our experience, this feature was observed in less than 5% of the cases. Although most of the cases described in the literature belong to the classical type of seminoma, there are a few reports of anaplastic seminoma in the anterior mediastinum [103]. Other microscopic features that may be associated with mediastinal seminomas include (A) presence of thymic remnants, which can be seen in approximately 27% of the

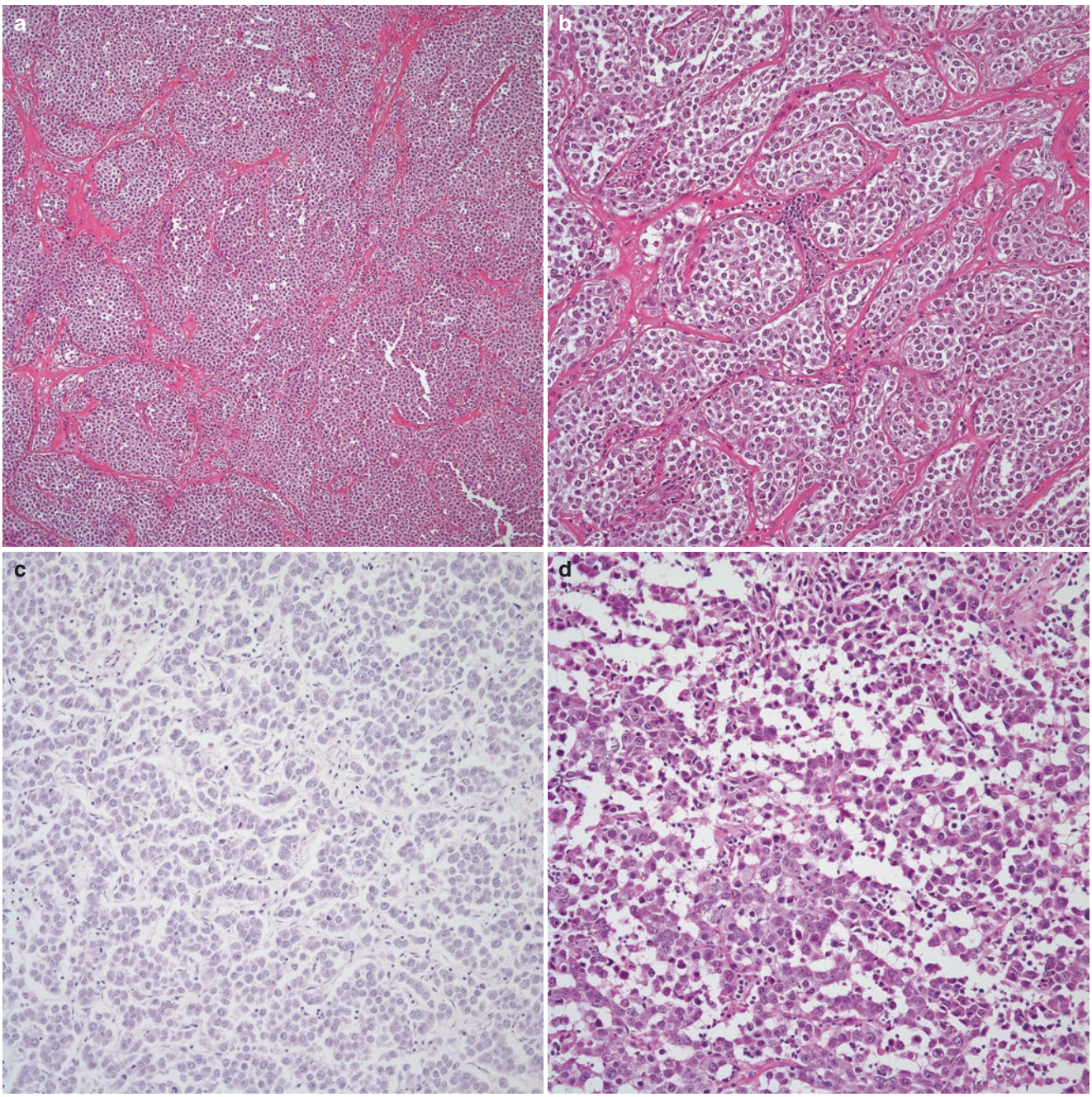

Fig. 10.28 (**a**) Mediastinal "thymic" seminoma showing a discrete nested pattern of growth; (**b**) intermediate magnification showing a subtle nested pattern. (**c**) Seminoma showing ribbons of neoplastic cells. (**d**) Seminoma showing sheets of neoplastic cells

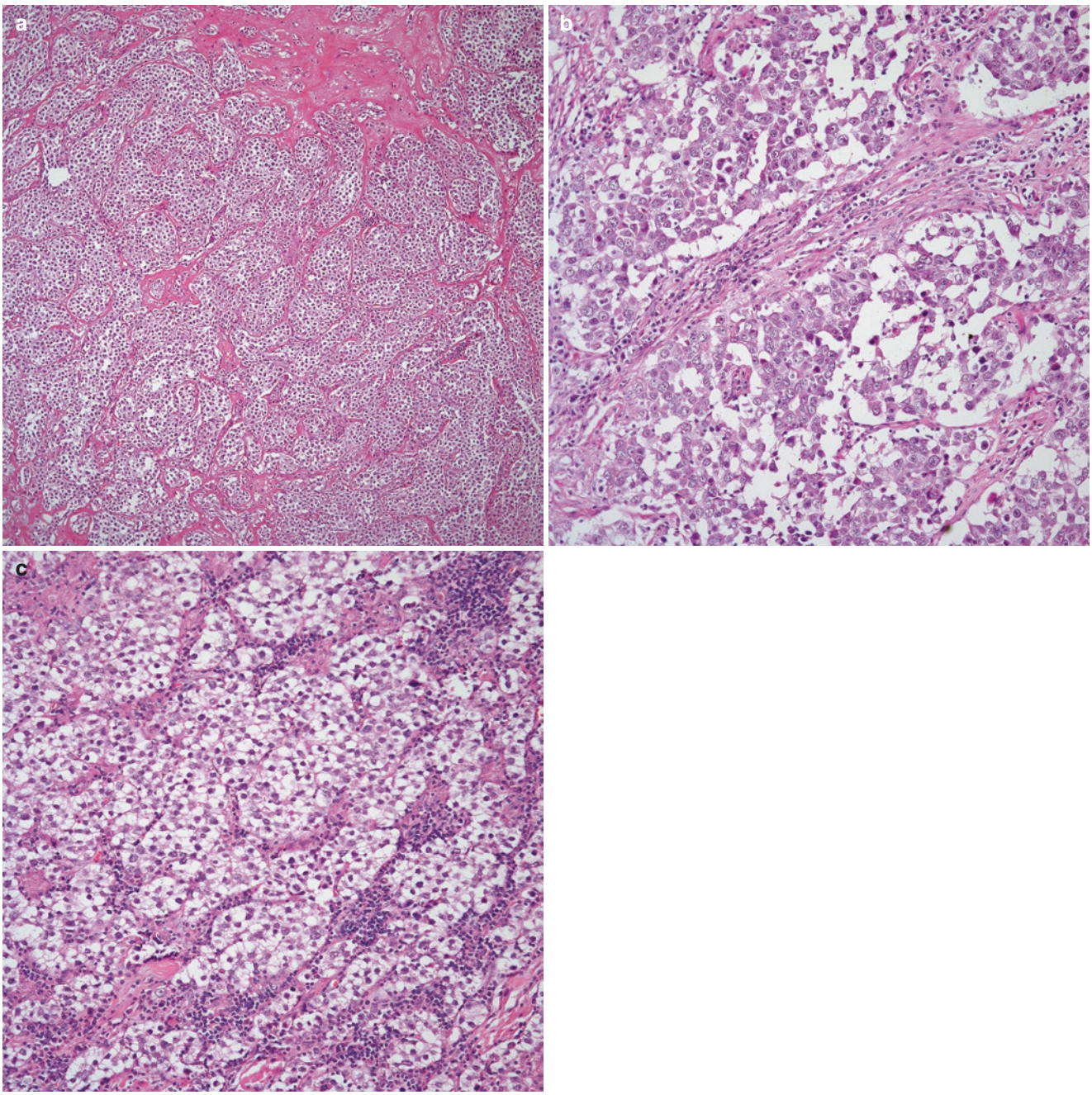

Fig. 10.29 (**a**) Seminoma showing discrete presence of hyalinization with no presence of lymphocytes. (**b**) Seminoma with mild presence of lymphocytes in the fibroconnective tissue. (**c**) Seminoma with more lymphocytic component

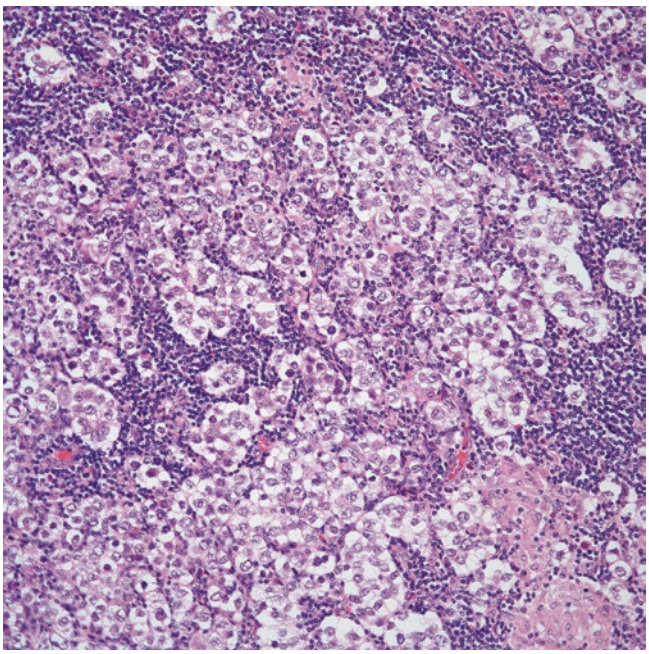

Fig. 10.30 Seminoma admixed with abundant lymphocytic component

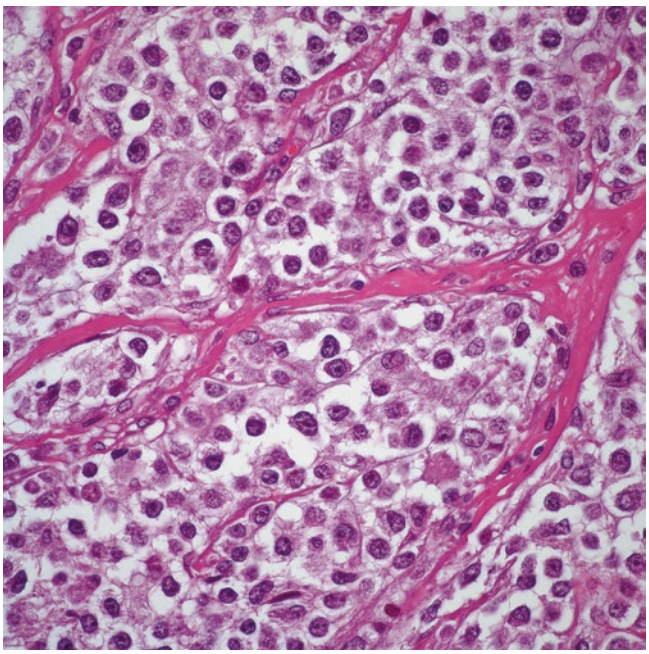

Fig. 10.32 High-power magnification of seminoma showing round to oval tumor cells with distinct cell borders round to oval nuclei, and in some cells prominent nucleoli is present

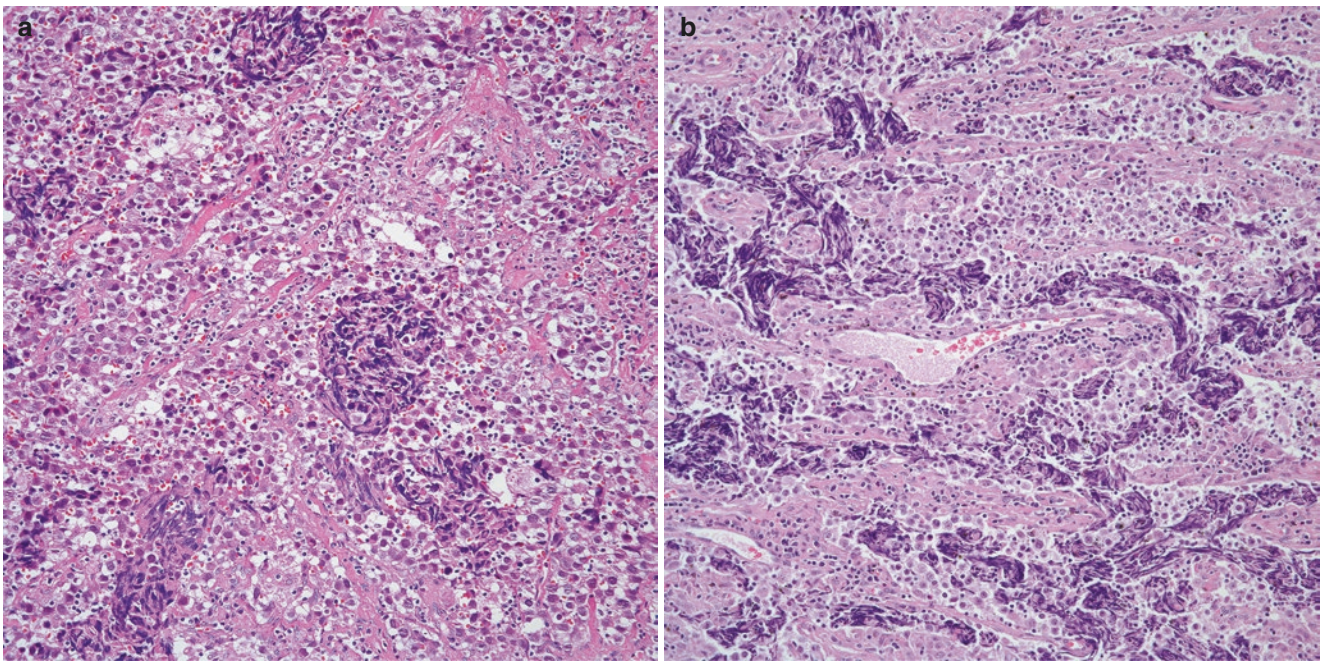

Fig. 10.31 (**a**) Seminoma with focal areas of crush artifact. (**b**) Seminoma with more extensive areas of crush artifact

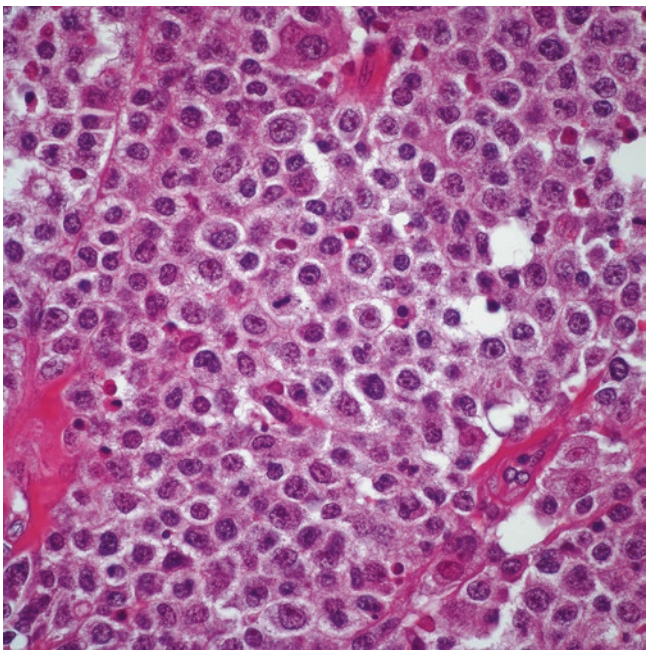

Fig. 10.33 High-power magnification of a seminoma showing scattered mitotic figures

tumors (Fig. 10.34a–c); (B) granulomatous reaction, which can be seen in the form of isolated giant cells admixed with the neoplastic cells to full blown florid non-caseous granulomas inflammation in about 46% of the cases (Fig. 10.35a–e); and (C) necrosis, which can be focal or extensive, making in some cases difficult the identification of neoplastic cells (Fig. 10.36a–c). Mediastinal seminomas may also show other unusual features including lymphoid hyperplasia with the presence of prominent germinal centers and tumors characterized by a predominantly cystic appearance. The two latter features are present in less than 10% of the tumors and have been reported separately as uncommon morphological features associated with these tumors in the mediastinal region.

In our experience with cystic seminomas, the tumors were reported as grossly cystic tumors, and, histopathologically, they mimic multilocular thymic cyst [136]. These tumors characteristically show areas of lymphoid hyperplasia, cysts lined by squamous epithelium and cholesterol cleft granulomas. The seminomatous component is found growing along the cystic walls of the tumor (Fig. 10.37a, b). In cases in which there is a predominantly cystic tumor, extensive sampling becomes necessary in order to determine the presence of seminoma. On the other hand, seminomas may also show extensive florid follicular lymphoid hyperplasia, which may pose a problem in separating this tumor from a lymphoproliferative tumor in the anterior mediastinum. In these cases, seminomas show at low power a striking lymphoid hyperplasia with prominent germinal centers. The tumor cells are placed in between the germinal centers (Fig. 10.38a, b). This unusual histological feature has been described in fewer than 10% of the cases, and the clinical and demographic features of the cases reported are similar to those described for mediastinal seminomas. The reported cases include male patients between the ages of 24 and 31 years who presented with non-specific clinical symptoms, and the presence of florid follicular lymphoid hyperplasia does not appear to influence the outcome of these patients [137].

One other additional unusual feature of seminomas is its association with another non-GCT. We have described the presence of seminoma in a case of primary leiomyosarcoma of the anterior mediastinum [138]. More recently, we described the association of a thymic seminoma with a thymoma [139]. In these two particular scenarios, the final diagnosis is likely to be reached after complete surgical resection has taken place. It is important to highlight that, in a small mediastinoscopic biopsy, it is likely that only one of the tumors in question may be represented, which may lead to important treatment decisions. However, once the surgical resection is available, in cases in which the seminoma may be associated with another mesenchymal neoplasm like in the case of leiomyosarcoma, it is likely that one should be able to distinguish the two processes on morphological grounds. However, in the case that a seminoma is associated with a thymoma, the diagnosis may pose more challenges. In either of these situations, it is prudent to perform additional immunohistochemical stains that may aid in separating the seminomatous component from either leiomyosarcoma or

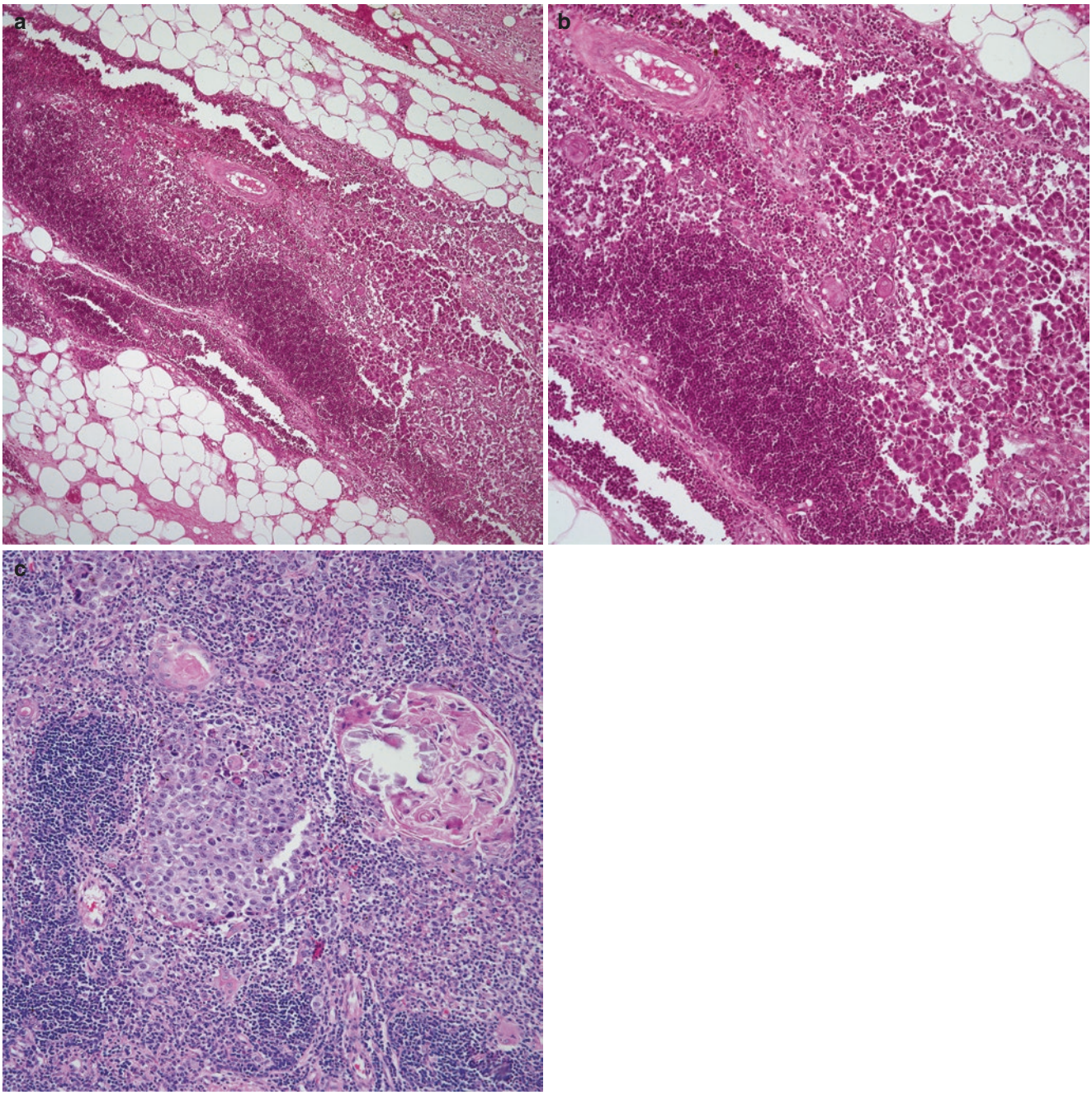

Fig. 10.34 (**a**) Seminoma involving portion of the thymic gland. (**b**) Seminoma adjacent to Hassall's corpuscles. (**c**) Dilated Hassall's corpuscle adjacent to areas of seminoma

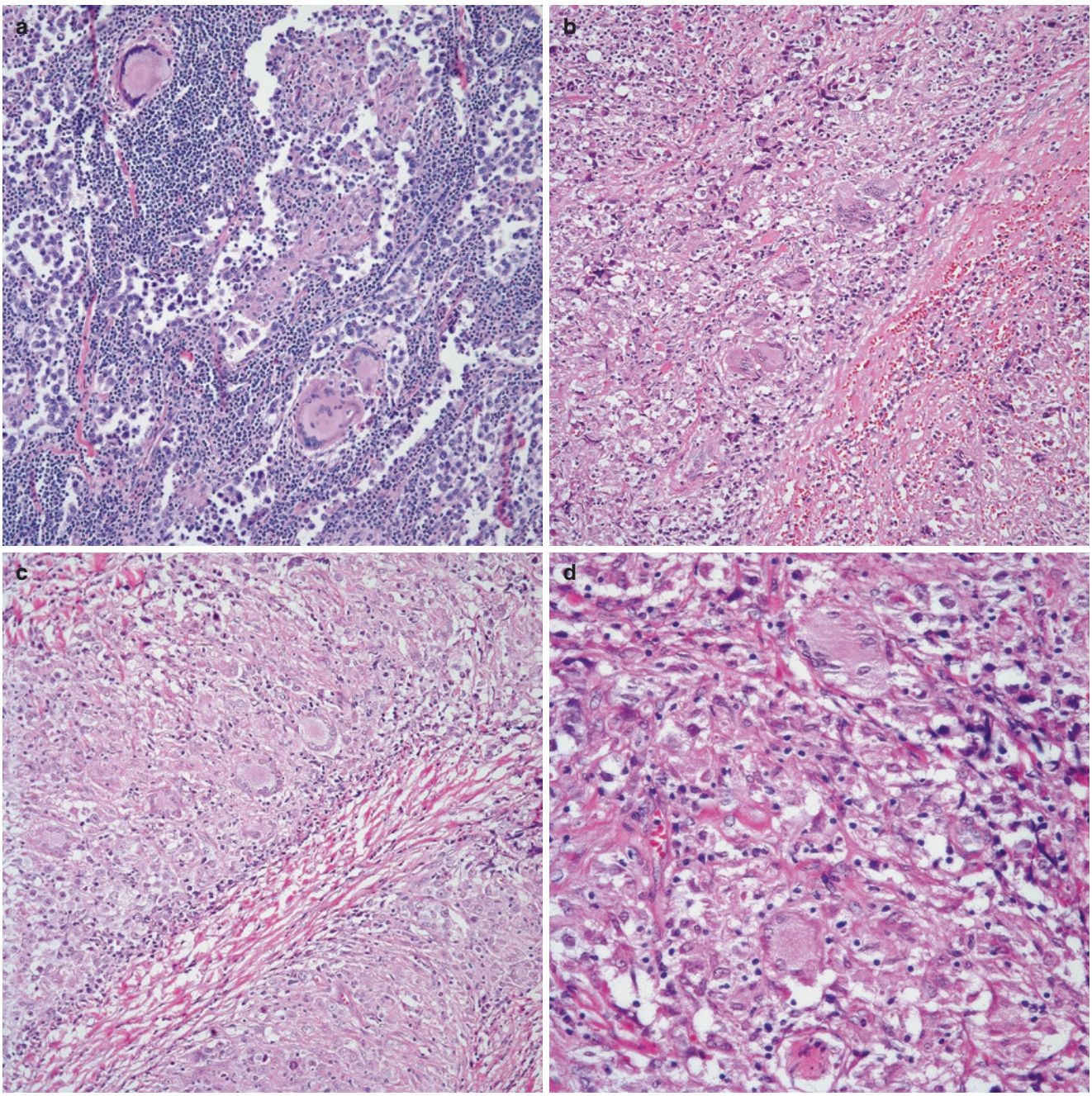

Fig. 10.35 (**a**) Seminoma with presence of scattered giant cells. (**b**) Numerous multinucleated giant cells with some viable tumor cells. (**c**) Florid granulomatous reaction. (**d**) Multinucleated giant cells with only focal viable tumor cells.

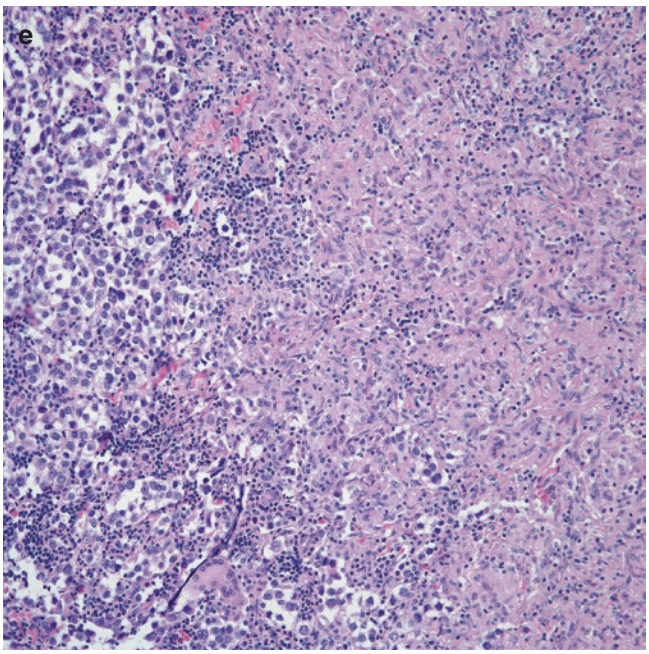

Fig. 10.35 (continued) (**e**) Seminoma with non-caseating granulomatous inflammation

thymoma. The careful use of immunohistochemical stains in these settings is highly advised. Table 10.5 depicts some of the most important histopathological features of mediastinal seminomas.

The most important histochemical stain in seminomas is the use of periodic acid-Schiff (PAS) to demonstrate the presence of glycogen within the neoplastic cells (Fig. 10.39). The neoplastic cells are negative for intracellular mucin using mucicarmine and D-PAS.

Mediastinal seminomas just like any other malignant neoplasm may spread within the thoracic cavity or invade below the diaphragm or above the thoracic inlet (Fig. 10.40a, b). The prognosis of these tumors, although good in general terms, is in great part determined by the stage of the tumor at the time of diagnosis. A common current practice is the medical treatment of these tumors prior to surgical resection. However, once medical treatment has been provided to a patient in whom the biopsy shows the presence of germ cell tumor, the surgical resection may just show extensive areas of necrosis and histiocytic reaction without any remaining viable tumor.

Immunohistochemical Features

Most of what is known about the immunohistochemical features of GCT is drawn from studies in testicular tumors. Beckstead [140] studied 32 cases of gonadal GCT using alkaline phosphatase and found that this antibody showed strong plasma membrane positivity in all 9 cases of seminoma in his study. The author suggested that alkaline phosphatase reaction is a useful adjunct in the diagnosis of GCT. Battifora and associates [97] studied the presence and distribution of keratin in 34 cases of GCT, including 18 seminomas. The authors found that all cases of seminomas gave negative results and suggested that the presence or absence of keratin can be helpful in distinguishing seminoma from other GCT such as embryonal carcinoma, which may show at least focal positive staining. Niehans and associates [141] studied 121 cases of GCT of diverse sites including gonadal and extragonadal primaries, using several antibodies including cytokeratin, vimentin, epithelial membrane antigen (EMA), placental-like alkaline phosphatase (PLAP), S-100 protein, leukocyte common antigen (LCA), CD-45 (T-and B-cell markers), LN-2, carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), chromogranin A, Leu-7, alpha-fetoprotein (AFP), alpha-1-antitrypsin (AAT), and the beta-subunit of HCG. The authors concluded that the presence of PLAP-positive staining and negative EMA appeared to be a staining pattern unique for GCT in general. In addition, the authors also found that cytokeratin was helpful in distinguishing seminomas from non-seminomatous germ cell tumors. However, the authors acknowledged the presence of focal or diffuse-positive reaction for cytokeratin in approximately 10% of seminomas. NSE immunostaining was positive in about 75% of all GCT, while vimentin was found to be positive in approximately 30% of seminomas.

We have studied 50 cases of primary mediastinal seminomas using antibodies against PLAP, CAM 5.2 (low molecular weight keratin), wide-spectrum keratin, HCG, EMA, CEA, and AFP. Our results parallel those of other studies in that positive membrane and cytoplasmic staining for PLAP was observed in 80% of the cases. However, we also observed strong dot-like paranuclear positivity with CAM 5.2 in 75% of the cases using a microwave antigen retrieval technique. In addition, broad-spectrum keratin also showed weak cytoplasmic positivity in approximately 70% of the cases. The discrepancy with previous studies concerning keratin immunoreactivity in these tumors

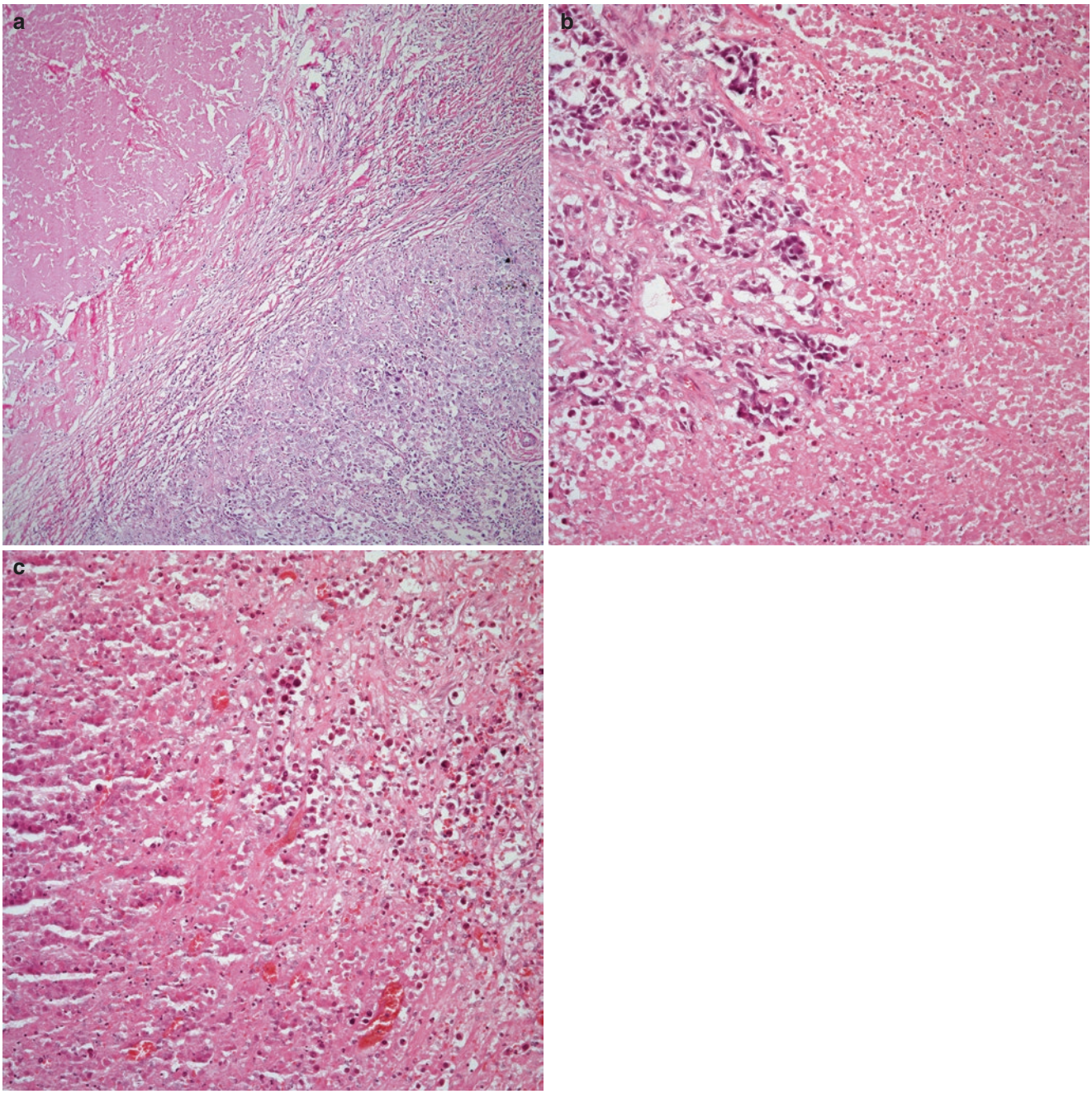

Fig. 10.36 (**a**) Seminoma showing areas of necrosis; however, the tumor cells are easily identified. (**b**) Seminoma with more extensive necrosis and only focal areas of viable tumor cells. (**c**) Extensive necrosis with only scattered tumor cells

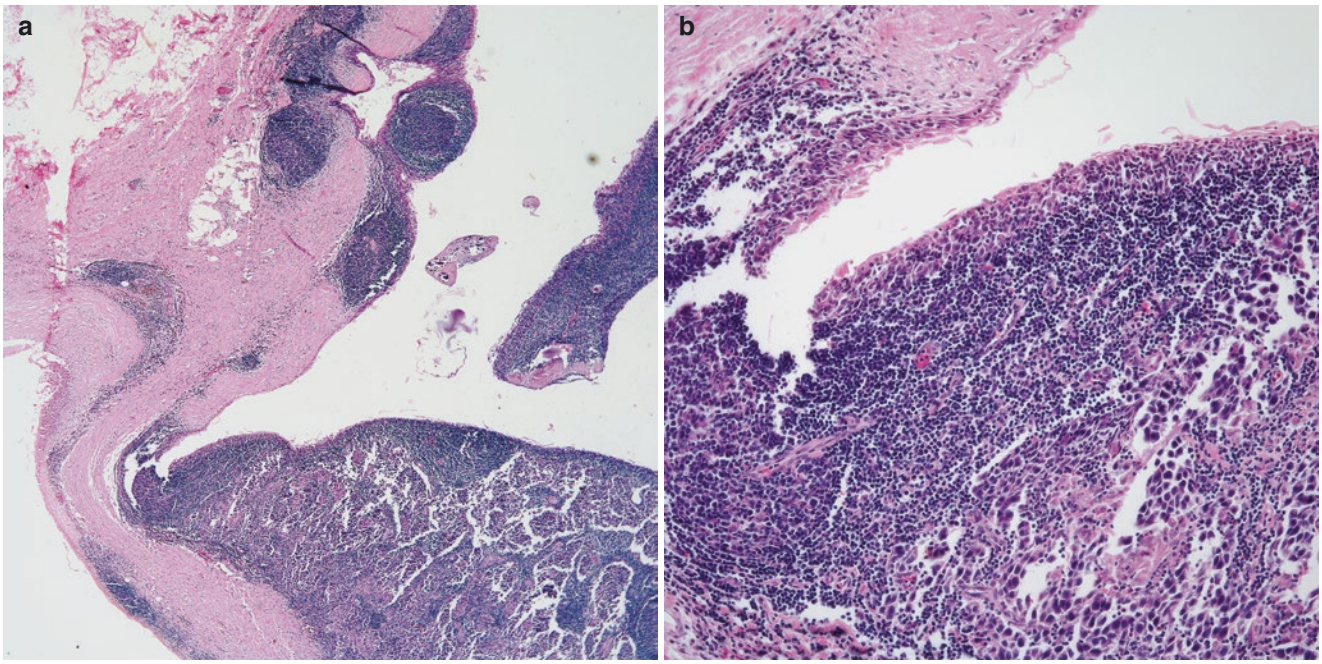

Fig. 10.37 (**a**) Predominantly cystic seminoma. (**b**) Higher magnification of a cystic seminoma showing conventional tumor cells

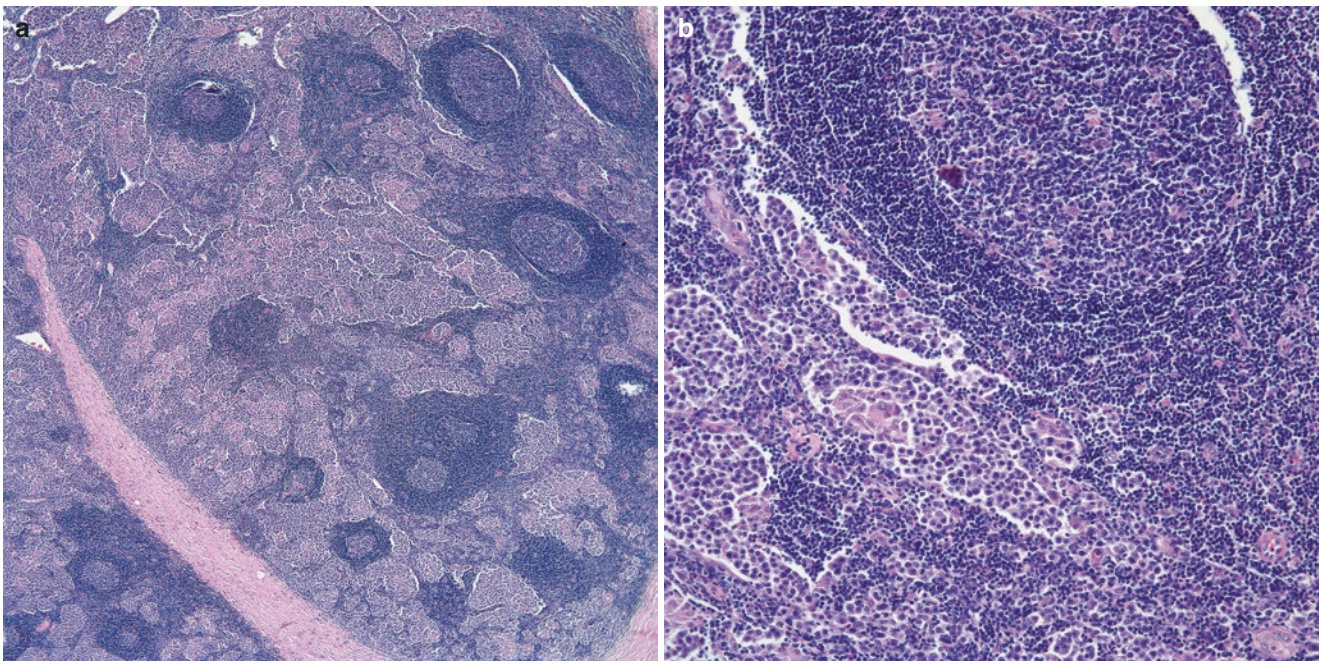

Fig. 10.38 (**a**) Seminoma with prominent lymphoid hyperplasia and presence of germinal centers. (**b**) Seminomatous areas adjacent to a germinal center

Table 10.5 Common histologic findings in 120 mediastinal seminomas

Granulomatous reaction	45%
Remnants of thymic tissue	27%
Necrosis	25%
Scattered giant cells	12%
Lymphoid follicular hyperplasia	<10%
Cystic changes	<10%
Trophoblastic giant cells	<5%

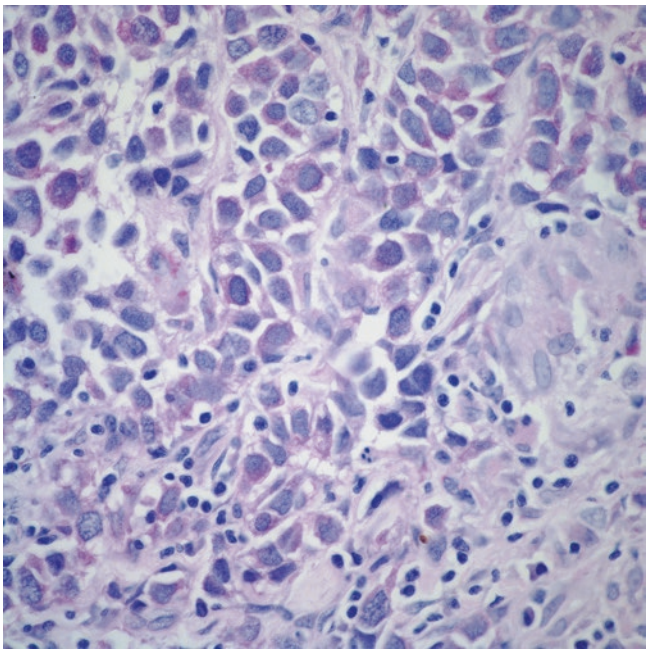

Fig. 10.39 Periodic acid-Schiff histochemical stain showing areas of intracellular glycogen in tumor cells

may be explained on the basis of improved antigen retrieval methods. Vimentin also showed positive staining in 50% of our cases; and HCG showed scattered, focal positivity of isolated single cells in 15% of the cases. Other immunohistochemical studies including CEA, EMA, and AFP were negative in all the cases studied. In a separate study comparing testicular and mediastinal germ cell tumors, we were able to detect some differences between these two groups [142]. In addition, immunohistochemical studies with p53 tumor suppressor gene protein in adult germ cell testicular tumors have shown expression of this protein in 90% of seminomatous tumors [143]. A different study showed that a mutation of the p53 gene is involved in the development of human testicular seminoma [144]. One other development worth mentioning is the recent availability of an anti-seminoma monoclonal antibody, which has been reported to be of value in the diagnosis of these neoplasms [145]. Also, seminomas have been investigated with the use of new markers including c-kit (CD-117) and the stem cell markers SALL4, OCT4, NANOG, UTF1, TCL1, and SOX2. Some of these markers have been reported to stain 100% of seminomas; c-kit may show positive staining in about 74% of the cases, while SOX2 has been consistently negative [146–148]. More recently, we performed an immunohistochemical study of 32 cases of primary mediastinal seminomas with emphasis on novel markers. We identified that 97% of tumor expressed SOX17, 91% showed positive staining for SALL4 and OCT3/4, and 88% stain positively for MAGEC2 and CAM5.2, while only 6% showed positive staining for polyclonal PAX8 and 3% for TCL1 (Fig. 10.41a–d). None of the tumors show positive staining for keratin 5/6, GATA-3, SOX3, and glypican 3 [149]. Table 10.6 depicts the immunohistochemical features more commonly associated with mediastinal seminomas.

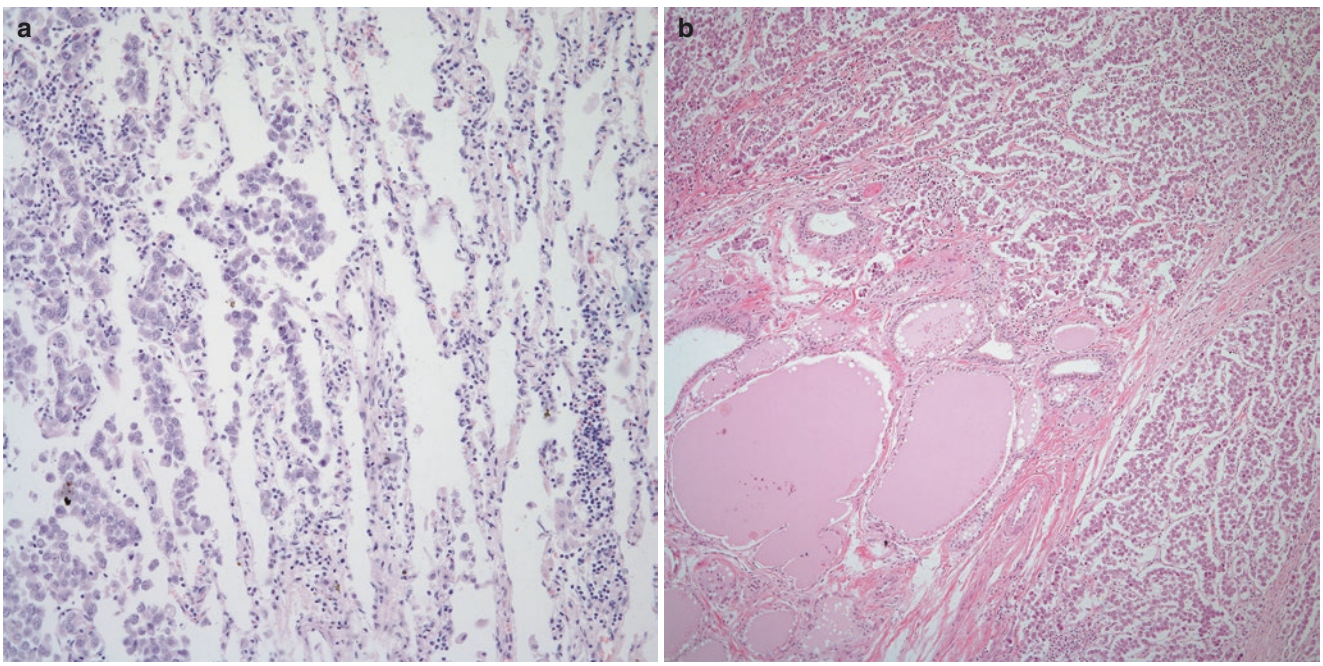

Fig. 10.40 (**a**) Seminoma invading lung parenchyma. (**b**) Seminoma invading the thyroid gland

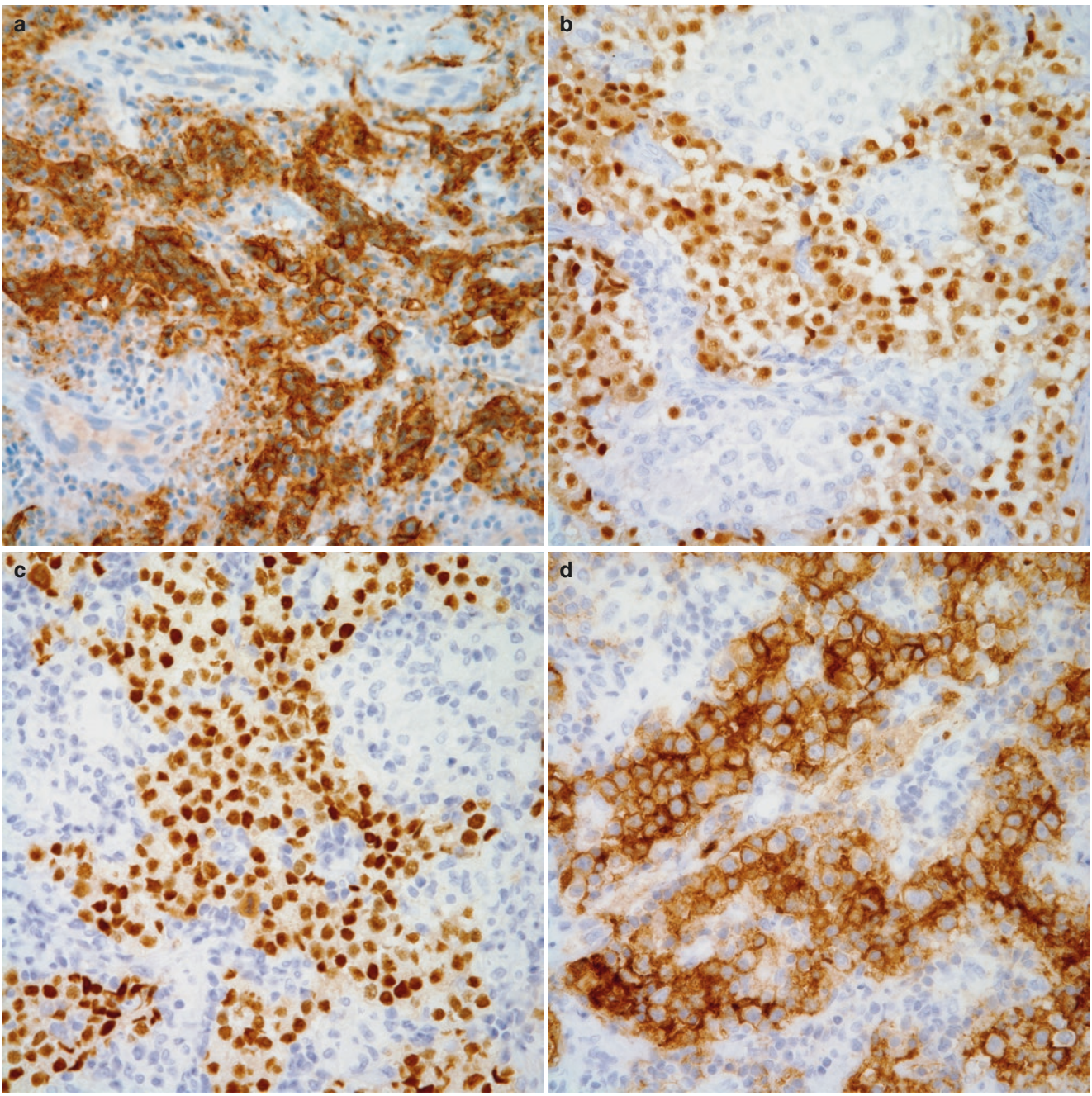

Fig. 10.41 (**a**) Seminoma showing positive staining for CD117. (**b**) Seminoma showing positive reaction in tumor cells for OCT 3/4. (**c**) Seminoma showing positive staining in tumor cells for SALL4. (**d**) Placental-like alkaline phosphatase showing positive reaction in tumor cells

Table 10.6 Immunohistochemical profile of MGCT

Tumor	PLAP	AFP	CAM5.2	HCG	SALL4	Glypican	OCT3/4	CD30	CD117
Seminoma	++	–	++	–	++	–	–/+	–	++
YST	–	++	++	–	++	+	–	–	+
E.C.	–	++	++	–				++	
ChorioCa	–	–	+	++	–	–	–	––	––

Ultrastructural Features

There are a few reports of ultrastructural studies of primary mediastinal seminomas. Levine [106] described the ultrastructural features in a case of primary mediastinal seminoma and concluded that these tumors shared similar features with their gonadal counterpart. The most salient ultrastructural features of mediastinal seminomas include the presence of large, round nuclei with smooth contours and fine, evenly dispersed nuclear chromatin, abundant cytoplasm poor in organelles, and abundant glycogen particles forming small glycogen rosettes or arranged in focal clusters (Fig. 10.42). Another rather distinctive feature in seminoma, although by no means pathognomonic, is the presence of loose, elongated rope-like nucleolonema within the nuclei of the cells. The cell membranes are generally round and smooth and voided of specialized organelles such as microvilli, complex interdigitating, or well-developed cell junctions. Rudimentary junctions and occasional desmosomes may be seen.

Differential Diagnosis

The most important differential diagnosis is with metastatic seminoma from a gonadal primary, even though such occurrence is highly unusual. Nevertheless, a careful clinical history and physical examination is always important. Other tumoral conditions that should be considered in the differential diagnosis include metastatic melanoma, thymic carcinoma, and malignant lymphoma, especially Hodgkin's lymphoma and large cell lymphoma. The use of immunohistochemical studies can help in solving this problem, as melanomas would show positive staining using antibodies for S-100 protein, HMB-45, and Pan Mel. The same applies to lymphoma and thymic carcinoma. In the former studies for LCA, B- and T-cell markers, Leu-M1 (CD-15), and CD-30 can be helpful, while in the latter the use of PLAP can lead to a correct interpretation. Nonetheless, the issue in a small biopsy can be more challenging, and a careful study of the morphology of the tumor becomes of utmost importance. Important to highlight is the unusual association of seminoma with another non-GCT, which may be difficult to diagnose in a small mediastinoscopic biopsy, which in turn may also affect treatment decisions. Some of these tumors' treatment of choice may depend on the initial interpretation of the mediastinal tumor. Finally, in cases of cystic seminomas, judicious sampling is highly important in order to identify diagnosable areas of seminoma.

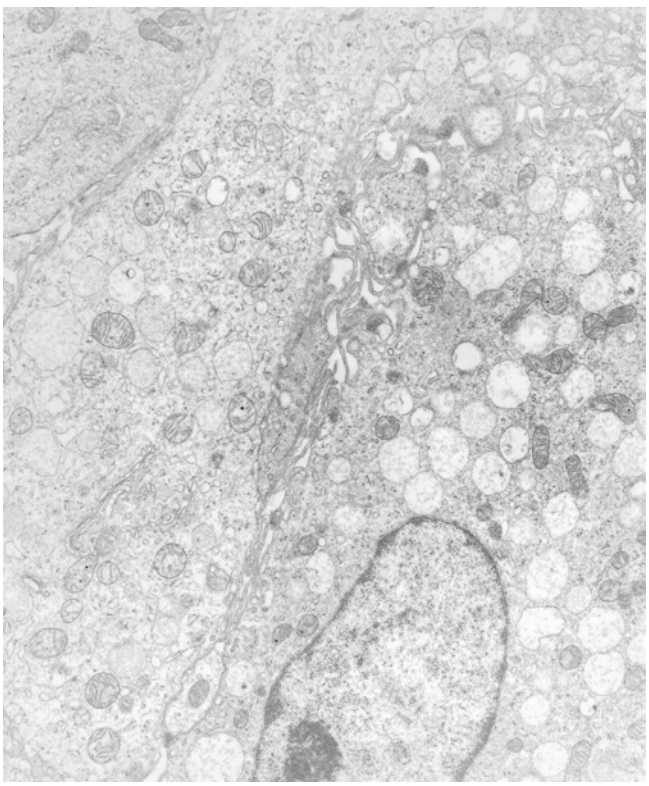

Fig. 10.42 Ultrastructural study of a mediastinal seminoma showing abundant glycogen droplets, classical of seminoma

Non-seminomatous Germ Cell Tumor

The term non-seminomatous germ cell tumor as used in this chapter refers to a group of tumors that encompasses yolk sac tumor (endodermal sinus tumor), embryonal carcinoma, and choriocarcinoma. As a group, non-seminomatous germ cell tumors are still outnumbered by seminoma as primary malignant germ cell tumors of the mediastinum. When NS-GCT occurs in the anterior mediastinum, these tumors show striking predilection for males in the third and fourth decades of life, just the same as seminomas. However, unlike mediastinal seminomas, these neoplasms have a clearly documented association with non-germ cell malignancies and Klinefelter's syndrome. Serum tumor markers for AFP and β-HCG are elevated in over 80% of patients with non-seminomatous germ cell tumors and may be of aid for diagnosis and for monitoring treatment. Elevated serum AFP may be seen with either yolk sac tumor or embryonal carcinoma, whereas marked elevation of β-HCG will be highly suggestive of choriocarcinoma. Antibodies specific for these peptide markers are of great value for histopathologic diagnosis.

Yolk Sac Tumor

Yolk sac tumor (YST) is also known as embryonal carcinoma infantile type or endodermal sinus tumor. YST in the mediastinum is a rare neoplasm. This tumor appears to be a common testicular GCT in childhood, while in adults it

is more often associated with other GCT [150]. Teilum [151] in 1959 first described this neoplasm and observed that a mixture of undifferentiated neoplastic "mesoblastic cells" and irregular spaces closely resembling the endodermal sinuses of Duval, characteristic of the rat's placenta, were features of YST. In Teilum's opinion, this tumor represented a proliferation of entirely undifferentiated embryonal cells differentiating toward extraembryonic membrane structures such as the mesoblast and yolk sac endoderm.

In 1967, Teilmann and associates [13] were the first to describe an example of YST in the anterior mediastinum in a 33-year-old man. At autopsy, the tumor showed extensive metastases; however, the testes did not show any evidence of neoplasm. The authors therefore concluded that the mediastinal region was the primary site for this tumor.

YST in extragonadal location and more specifically in the mediastinum is rare [152–164]. Although these tumors occur more frequently in the third and fourth decades of life, YST may also occur in infants [155]. These tumors appear to predominate in males; however, there are a few reports of these tumors in females [152, 155, 162]. To assess a specific incidence is rather difficult in view of their rarity. In our experience, YST is the most common non-seminomatous/non-teratomatous malignant GCT of the mediastinum, and accounts for approximately 12% of all MGCT [17]. In our study, these tumors were more prevalent in the third and fourth decades of life, with only sporadic cases found in the second and fifth decades of life [165]. We did not find any cases of YST in females.

Clinical Features

The clinical presentation of these tumors will be directly related to their size. Larger tumors are likely to compress adjacent structures, and the patients may present with symptoms of dyspnea, cough, chest pain, or superior vena cava syndrome. On the other hand, some patients may be completely asymptomatic [156]. An unusual presentation for YST is mimicking pericardial effusion [154]. The presence of increase levels of alpha-fetoprotein in the serum is a feature highly suggestive of YST [166, 167].

Interestingly, a few other medical conditions have been associated with mediastinal YST. Sogge and associates [168] documented a case of mediastinal YST in a 26-year-old man in association with Klinefelter's syndrome. The patient had a buccal smear with about 20% of Barr bodies, small testes, without palpable masses, and no gynecomastia. Similar findings of YST in association with Klinefelter's syndrome and Klinefelter's syndrome with sexual precocity were described by Nichols and associates and Floret and associates, respectively [169, 170].

Hematologic disturbances have also been associated with YST. Garnick and associates [171] found an association between idiopathic thrombocytopenia and mediastinal non-seminomatous GCT. The authors stated that the presence of thrombocytopenia might be an adverse prognostic feature for patients with extragonadal GCT. Nichols and associates [172] in 1990 reported 16 additional cases of hematologic neoplasms associated with primary mediastinal GCT and reviewed 27 similar cases reported in the literature. The median time between the diagnosis of GCT and the development of hematologic neoplasia was about 5 months. In 13 of the patients, both conditions occurred simultaneously, leading the authors to suggest that the development of hematologic neoplasia in this setting is not the result of chemotherapy for the GCT. The association of hematologic neoplasia and GCT appears to be more intimately related with tumors showing yolk sac elements. The most common lymphoproliferative lesion associated with YST appears to be acute megakaryoblastic leukemia and malignant histiocytosis. It is of interest that, in one patient with this association, a cytogenetic abnormality of the chromosome i12p was found in the GCT and in the leukemic blasts, thus suggesting a common progenitor cell for both processes. Nonetheless, the authors stated that the cytogenetic abnormalities were not consistent. Most recently, Orazi and associates [173] stated that hematopoietic precursor cells within the yolk sac tumor component are the source of secondary hematopoietic malignancies in patients with MGCT.

Another unusual event in these tumors is the secondary development of sarcomatous elements. Some authors have claimed that the pluripotential nature of the mesenchyme-like component of YST may give rise to sarcomas occurring in some patients with treated germ cell neoplasms [174, 175]. Ulbright and associates [176] documented such experience in 14 patients with GCT.

The radiologic findings displayed by YST are by no means pathognomonic of this tumor. The same as with other non-seminomatous GCT, radiographically, the tumor may be smooth or lobulated, well circumscribed, or ill defined. On CT scans, the tumor may show heterogeneous attenuation. Large central regions of low attenuation may occupy up to 50% of the lesion and correspond to areas of necrosis and/or hemorrhage [43].

The treatment and prognosis of non-seminomatous GCT in general have changed over the years. The median survival rate for these tumors in the older literature was about 8 months [152]. However, many patients included in those studies may not have benefited from the more modern treatment protocols presently available. In 1976, Kurman and Norris [177] analyzed 71 cases of yolk sac tumors of the ovary documenting only 9 survivors among 65 patients in whom follow-up was available. The survival rate after 3 years was 13%, while in 93% of the cases the neoplasm

recurred within 1 year after diagnosis. Interestingly, about 90% of the deaths occurred within 2 years after diagnosis. The authors concluded that size and stage of the tumor had prognostic significance. In the mediastinal location, it has been estimated that 27% of the patients will have metastatic disease at the time of the presentation [152]. The most common sites for metastases of mediastinal YST include the lymph node, liver, lung, and brain. The apparently high incidence of metastases at presentation suggests a rapid growth of the tumor.

In Hainsworth's experience with 32 patients with extragonadal GCT, the authors concluded that intensive chemotherapy (cis platinum-based) and surgical resection offer the best results in the management of these tumors [130]. In this study, 89% of the patients survived after a follow-up period of 30 months. Economou and associates [63] reported 28 patients with mediastinal GCT, including 17 patients with non-seminomatous tumors showing only 18% survival after a period between 6 months and 15 years. The authors concluded that non-seminomatous GCT treated with cisplatin-bleomycin chemotherapy had a median survival of 14 months, while those treated with different modalities showed a survival rate of 4 months. However, long-term survival can also occur in patients treated with surgery and combination of chemotherapy and radiation therapy [159]. Another useful parameter for evaluating the prognosis of non-seminomatous GCT of the mediastinum is the return to normal of serum levels of tumor markers (AFP, HCG) after cisplatin therapy [178]. Most authors agree that the most adequate treatment needs to be aggressive including surgical resection and chemotherapy [64, 179–183]. In general, the 5-year survival rate for non-seminomatous GCT varies from 8% to 58% in different series [64, 127, 183].

Our experience mirrors that of the literature: out of 38 cases of YST of the mediastinum that we were able to follow, only 13% of the patients survived 2 years after diagnosis, while approximately 45% of them died of tumor within the same period of time. However, most of our cases included patients who were diagnosed and treated prior to the advent of more modern therapeutic modalities. The use of the current more aggressive germ cell treatment protocols should favorably impact on the outcome of these patients.

Gross Features

These tumors tend to be unencapsulated, large, soft tissue masses with a tendency to invade adjacent structures. The size of the tumors varies from a few centimeters to 20 cm in greatest dimension. Areas of hemorrhage and/or necrosis may be evident (Fig. 10.43). However, there are no distinct gross features that allow distinction from seminomas or other non-seminomatous tumors.

Histologic Features

The histopathological features of YST are quite distinctive, and a diagnosis can be made in the majority of instances with relative ease on routine microscopy. However, it is important to highlight that YST is probably the most versatile GCT in

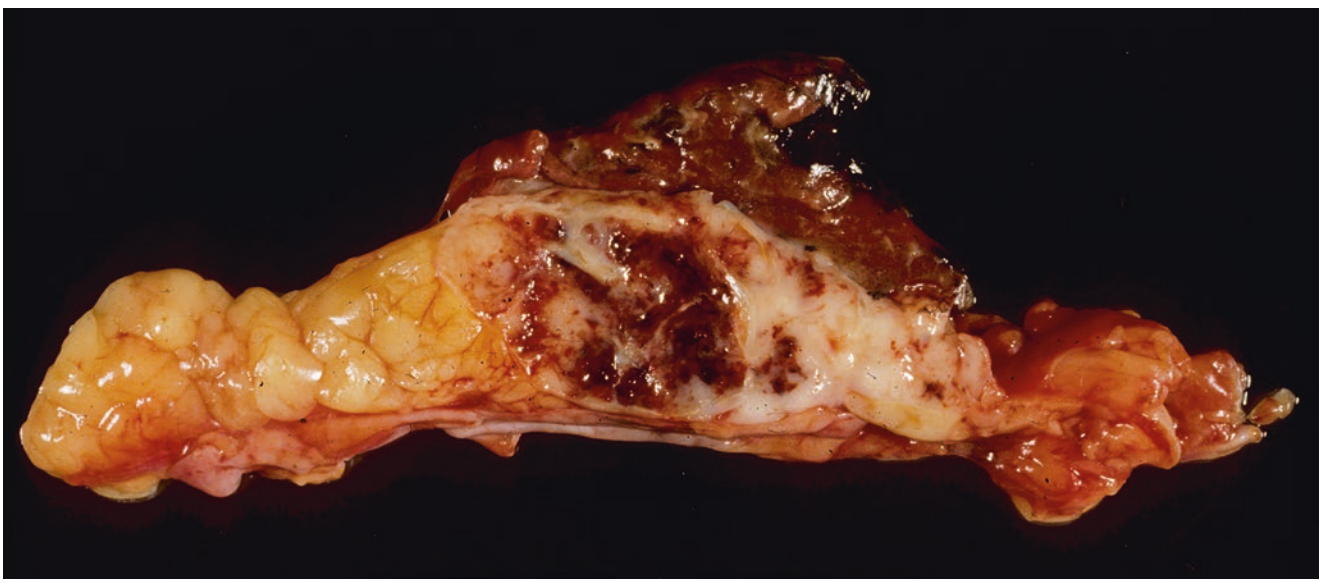

Fig. 10.43 Mediastinal yolk sac tumor showing non-encapsulated, partially hemorrhagic tumor mass

the anterior mediastinum. A variety of growth patterns have been described for these tumors in the gonads, including the reticular, vitelline, pseudo papillary, solid, myxomatous, sarcomatoid, macrocystic, and hepatoid [150]. In our experience, all those histopathologic growth patterns are also recapitulated in mediastinal yolk sac tumors [184–186].

The low-power magnification of these tumors may show different growth patterns, thus the importance to keep this tumor in the differential diagnosis of the different neoplasms that may seed the anterior mediastinum. In some cases, the tumor may be just adjacent to thymic tissue, which lends support to the notion that the tumor is likely to originate from the thymic gland (Fig. 10.44). In some unusual cases, the tumor may be adjacent to areas of thymic tissue showing areas similar to those described as multilocular thymic cyst (Fig. 10.45). The tumor may also show more common growth patterns including reticular, myxoid, glandular, papillary, the so-called intestinal-like growth pattern, solid, hepatoid, pseudovascular, spindle cell, or a combination of them (Fig. 10.46a–j). The most common appearance of these tumors is the reticular pattern, which is characterized by areas containing a loose meshwork of glandular or ductal structures that are lined by low columnar to flattened epithelial cells resulting in microcystic intercellular spaces, separated by basement membrane-like material. In many cases, the neoplastic cellular proliferation may show a prominent myxoid background. However, in other areas, the neoplastic cellular proliferation may adopt a more prominent macrocystic appearance. In some areas, the neoplastic cells may alternate with areas showing an edematous stroma. The neoplastic cells can be disposed in sheets interspersed with cystic areas, while in other areas the tumor may show a papillary configuration alternating with more solid foci. However, in some cases, the neoplastic cells appear to be around sclerotic vessels (Fig. 10.47a–c). The presence of Schiller-Duval bodies characteristic of yolk sac tumors will greatly facilitate the diagnosis. These structures consist of papillary projections lined by primitive epithelial cells that extend into the microcystic spaces and contain a single central blood vessel. Another distinctive feature of YST is the presence of brightly eosinophilic PAS-positive, diastase-resistant hyaline globules scattered within the stroma and intracellularly (Fig. 10.48). These hyaline globules have been shown to be composed of aggregates of alpha-fetoprotein and other plasma proteins. Focal areas in these tumors may show striking cellular atypia with presence of bizarre mitotic figures and large hyperchromatic nuclei. In other areas, the neoplastic cellular proliferation may show a prominent perivascular arrangement. In some tumors, focal areas in which there is a marked spindling of the neoplastic cells can be identified. However, the reticular pattern characterized by ribbons of neoplastic cells, presence of intra and extracellular hyaline droplets, and Schiller-Duval bodies is

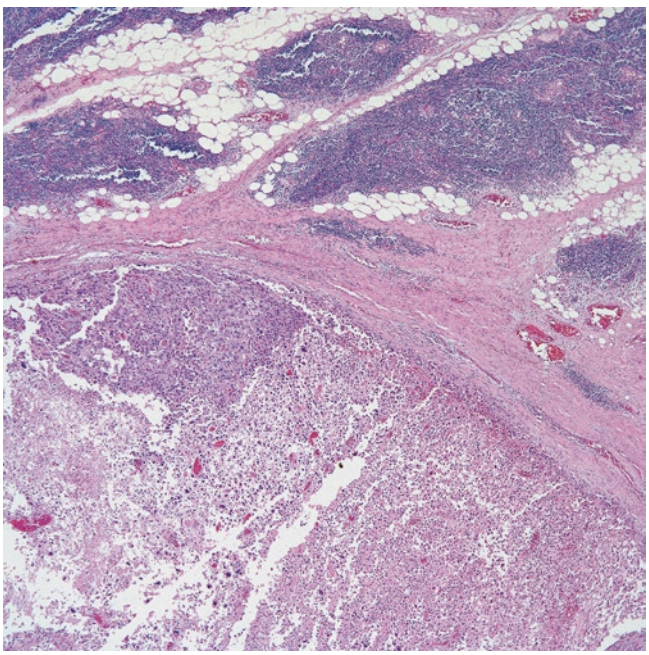

Fig. 10.44 Yolk sac tumor adjacent to thymic gland

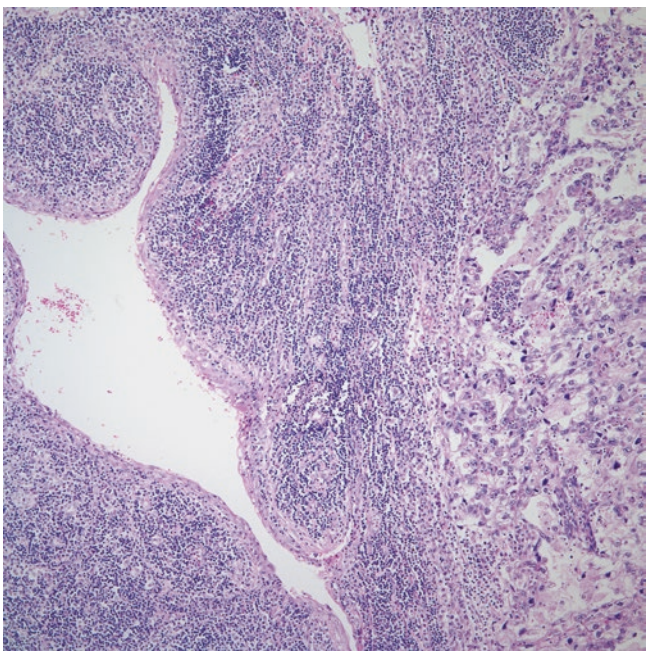

Fig. 10.45 YST adjacent to cystic thymic areas similar to those described in multilocular thymic cyst

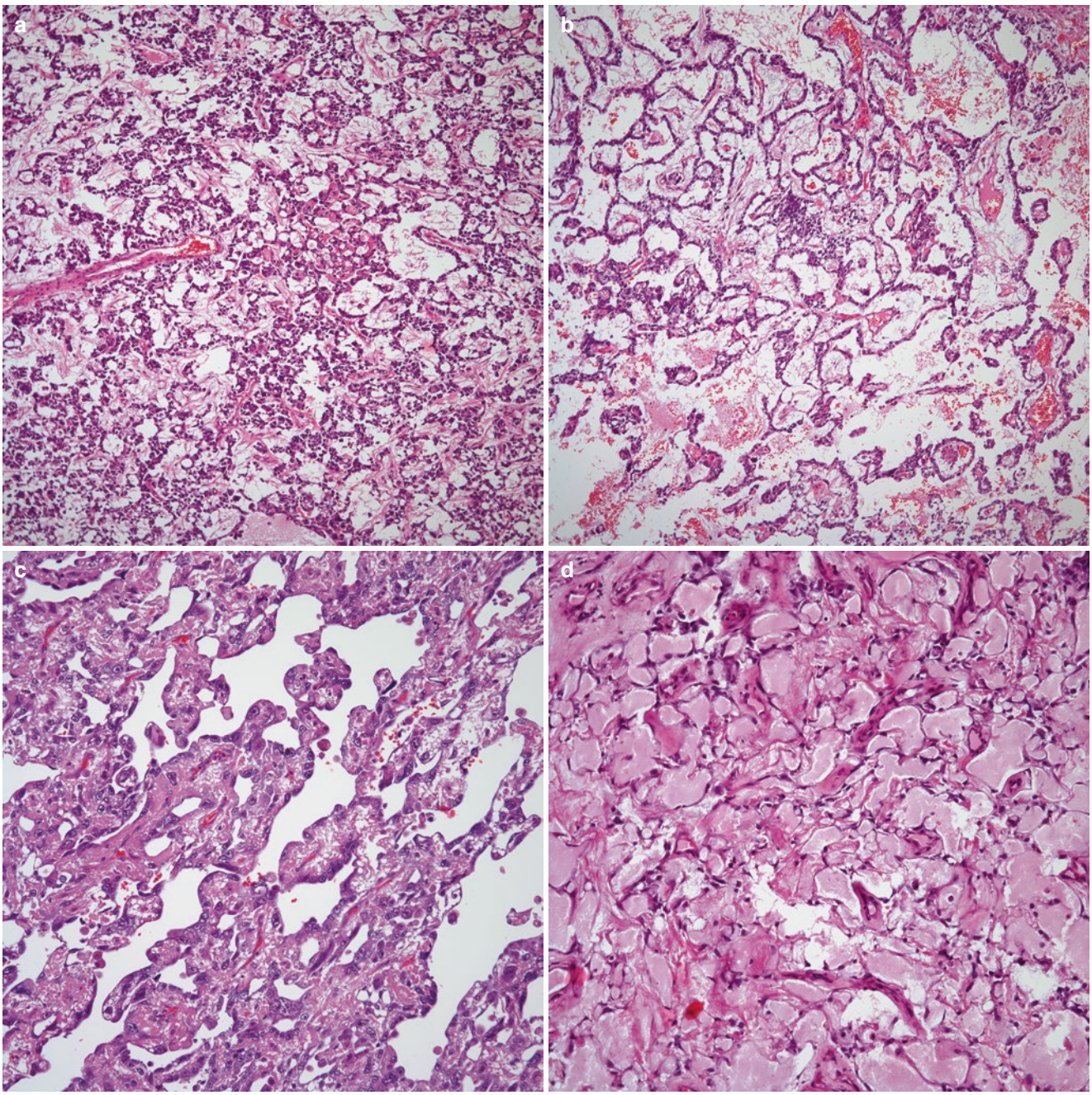

Fig. 10.46 (**a**) YST tumor shows a reticular growth pattern; (**b**) YST showing a microcystic growth pattern; (**c**) YST showing a pseudovascular pattern; (**d**) YST with prominent edematous "myxoid" change

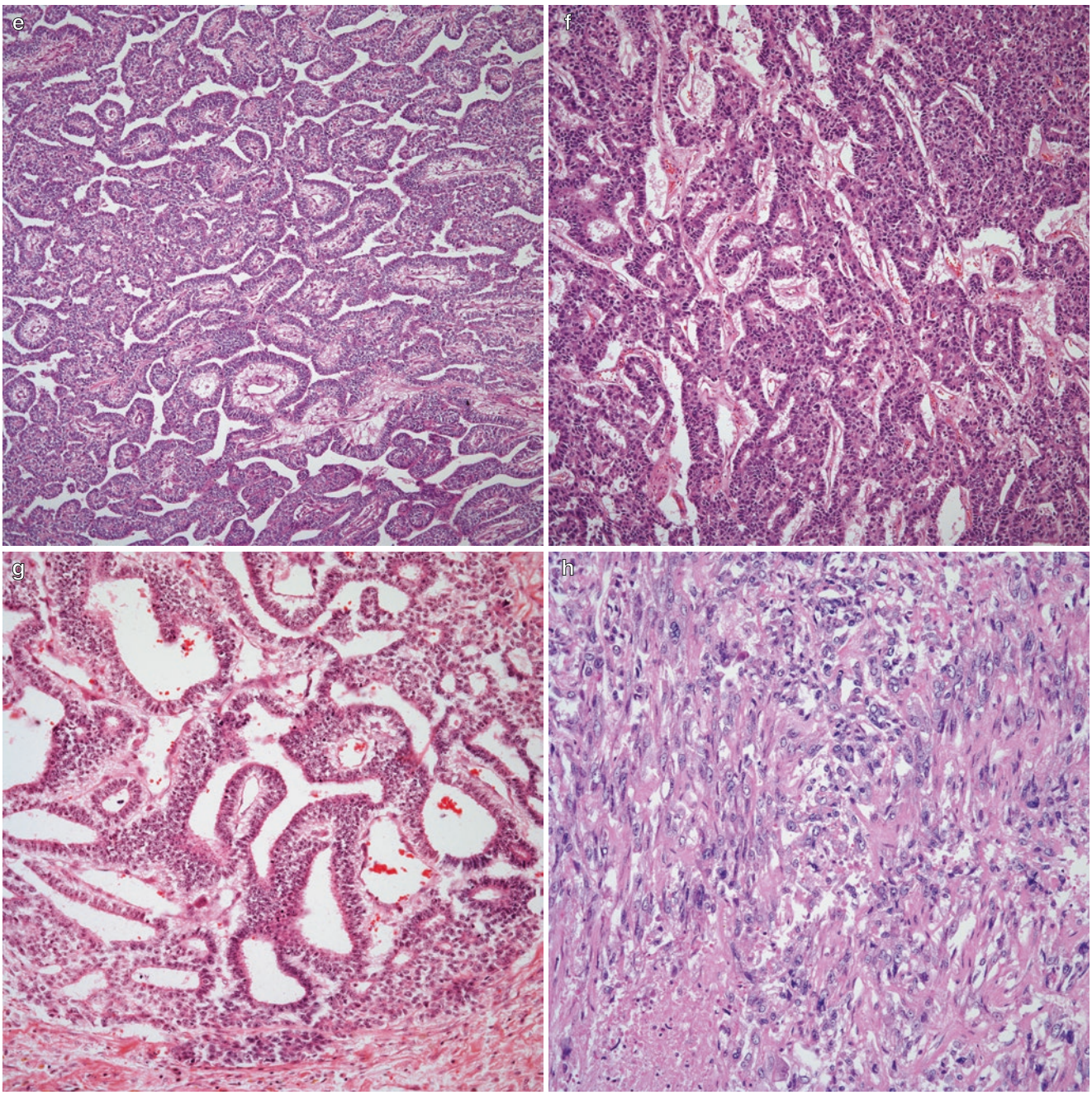

Fig. 10.46 (continued) (**e**) YST with a pseudoglandular appearance; (**f**) YST with glandular-like appearance; (**g**) YST with more "embryonic glandular appearance"; (**h**) YST with spindle cell features

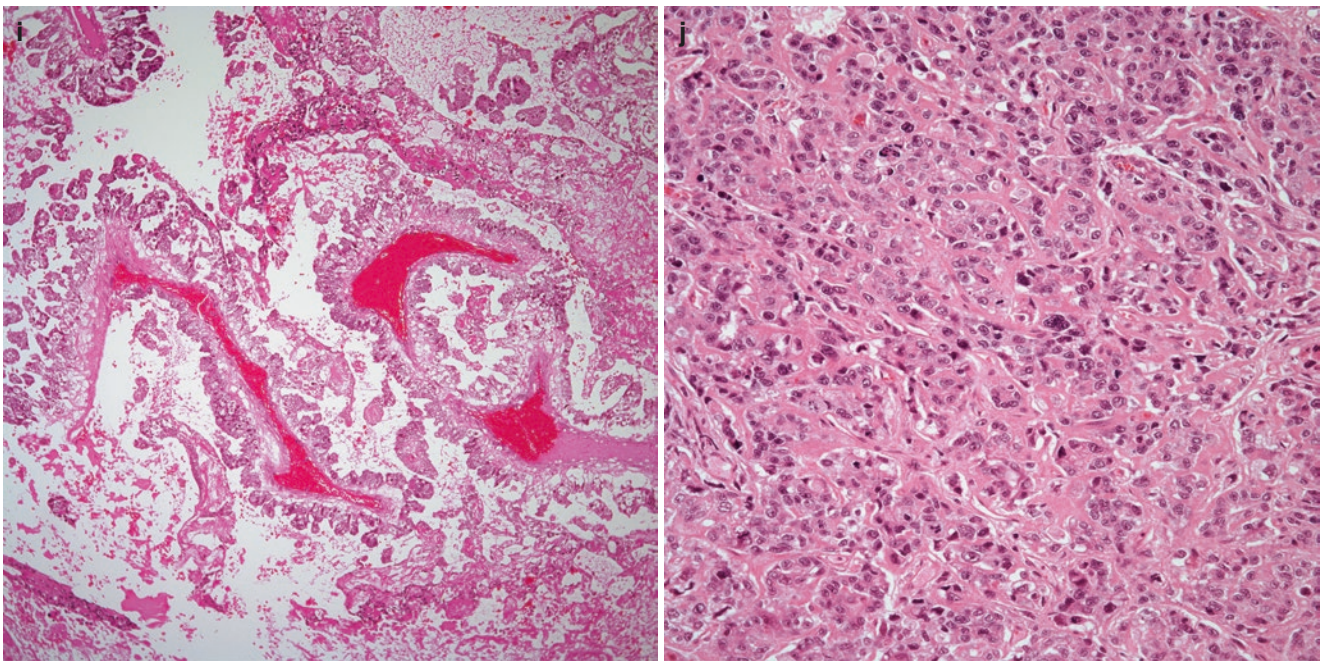

Fig. 10.46 (continued) (**i**) YST with the so-called "intestinal" growth pattern; (**j**) YST with solid growth pattern

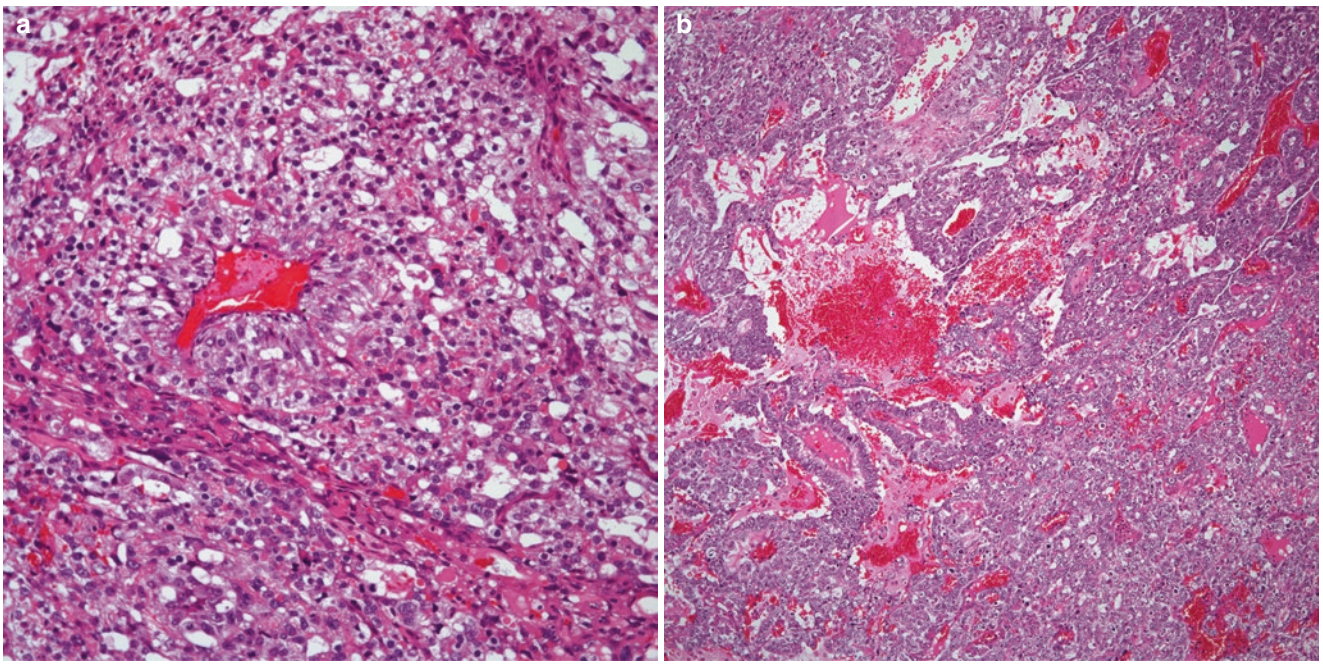

Fig. 10.47 (**a**) YST showing a Schiller-Duval body in a solid clear cell pattern. (**b**) Several Schiller-Duval bodies are present in this rather solid growth pattern

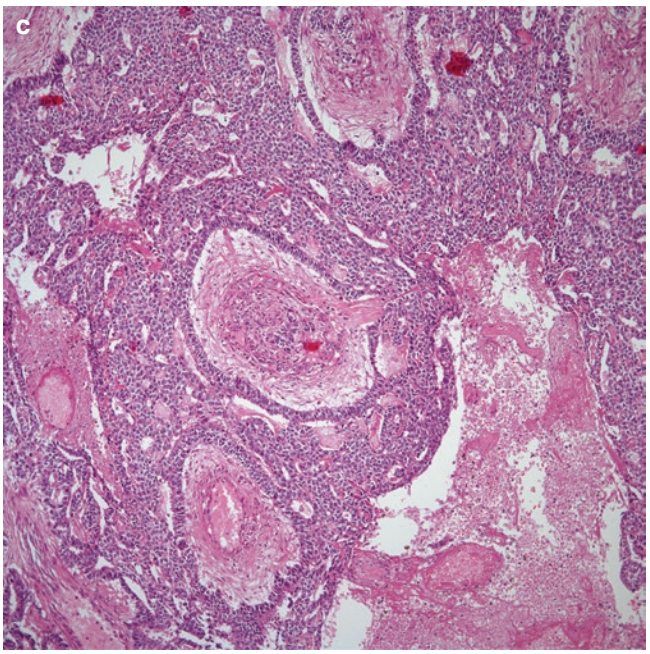

Fig. 10.47 (continued) (**c**) In some cases, the tumor cells are arranged around fibrotic or sclerotic vessels

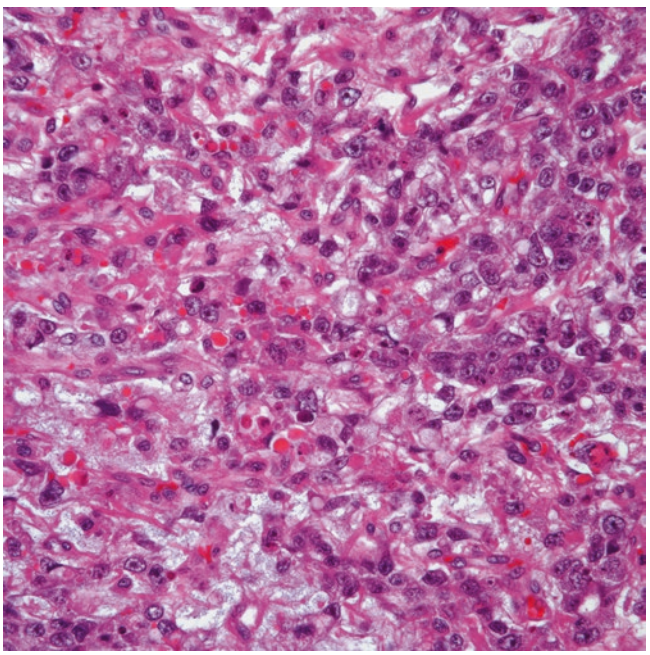

Fig. 10.48 Higher magnification of a YST tumor showing numerous hyaline globules

the most classic presentation of yolk sac tumors. In general, the high cytological features of YST are those of a proliferation of rather small cells, with round to oval nuclei and inconspicuous nucleoli (Fig. 10.49a–d). In some cases, the neoplastic cells may show prominent clear cytoplasm (Fig. 10.50a, b). Mitotic figures and areas of necrosis and hemorrhage may also be present (Fig. 10.51a–d). An unusual histopathologic growth pattern of yolk sac tumors that can be observed in the mediastinum is the so-called hepatoid variant, which is characterized by a tightly cohesive, solid neoplastic proliferation of cells with abundant cytoplasm that resembles liver tissue. In this growth pattern, it is also possible to observe cellular atypia and mitotic figures (Fig. 10.52a–d). Occasionally, more differentiated tissues of endodermal origin may be present in YST, including enteric-like glands or endometrioid-like areas. Another relatively unusual feature of YST that we have observed in the mediastinum is the presence of prominent cystic changes similar to those seen in multilocular thymic cysts and cystic seminomas [136]. In our experience, this unusual presentation accounts for less than 5% of these tumors.

Just like with other malignant neoplasm, the tumor may also invade adjacent organs such as the pleura, pericardium, or lung (Fig. 10.53). Also, the tumor may invade other structures below the diaphragm or above the thoracic inlet.

The current practice of treating patients with MGCT with chemotherapy followed by surgical resection in many cases does not provide enough viable tumor to confidently determine the percentage of tumor that may be present.

Immunohistochemical Features

The use of immunohistochemistry has shown that these tumors may display positive staining for AFP, CEA, keratin, and alpha-1-antitripsin (AAT) [97, 152, 187]. Stains for PLAP, EMA, NSE, Leu-7, and vimentin have also shown some variable positivity [139]. In our experience, in addition to the above mentioned stains, we also noted a strong positive reaction of the tumor cells with low molecular weight keratin CAM 5.2 [165]. Also, we have seen YST showing strong positive reaction for SALL4, while CD117 and Glypican may show only focal positive staining in tumor cells (Fig. 10.54a–e). The most reliable and consistent stain supporting the diagnosis of YST, however, is AFP.

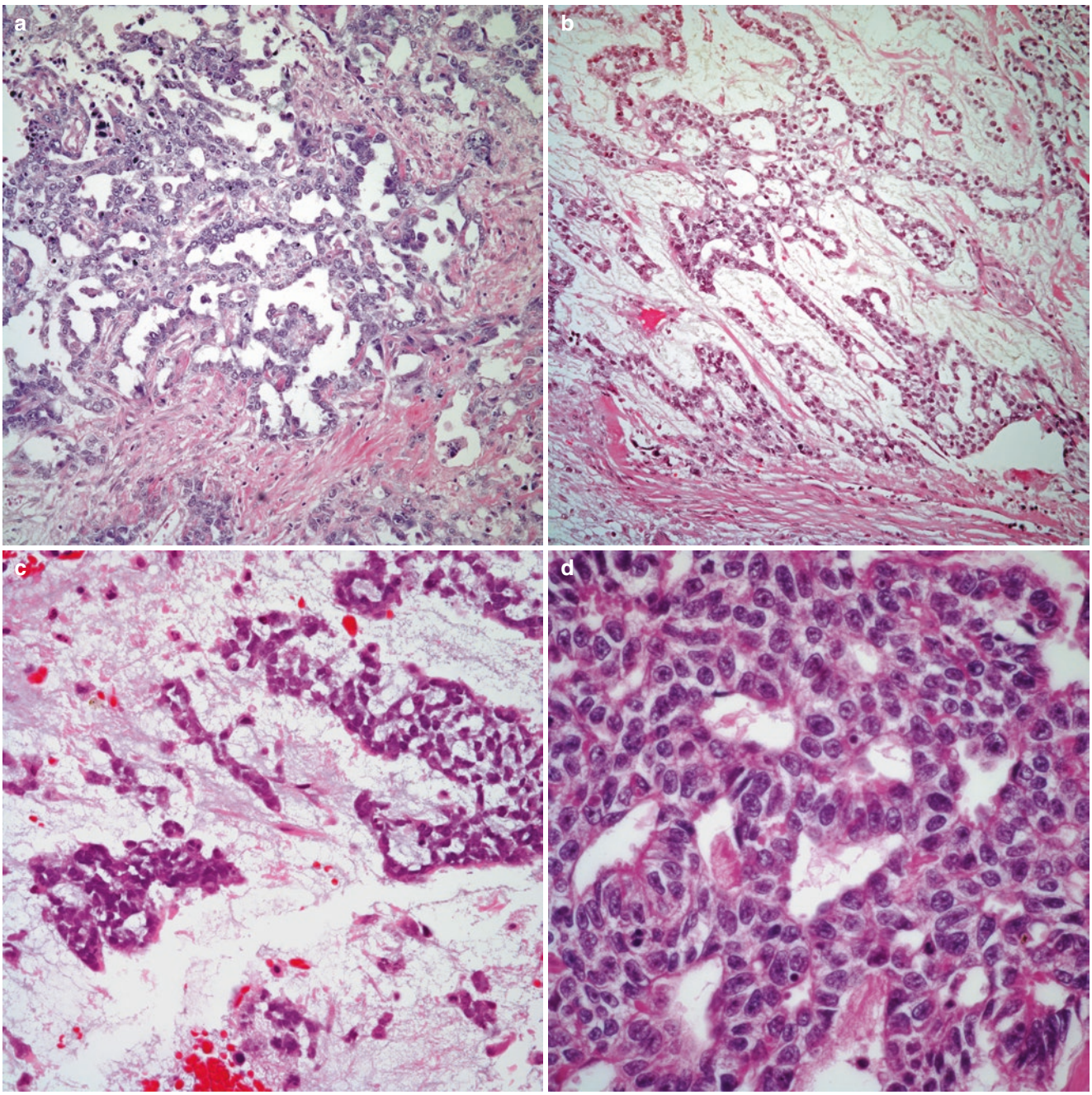

Fig. 10.49 (**a**) YST showing a neoplastic cellular proliferation composed of rather small cells without marked nuclear atypia or mitotic activity. (**b**) Ribbons of neoplastic cells embedded in a myxoid stroma without increased mitotic activity or nuclear atypia. (**c**) Clusters of small cells embedded in a mucinous stroma. Note the absence of increase mitotic activity. (**d**) High-power view of the small cells with round to oval nuclei and inconspicuous nucleoli

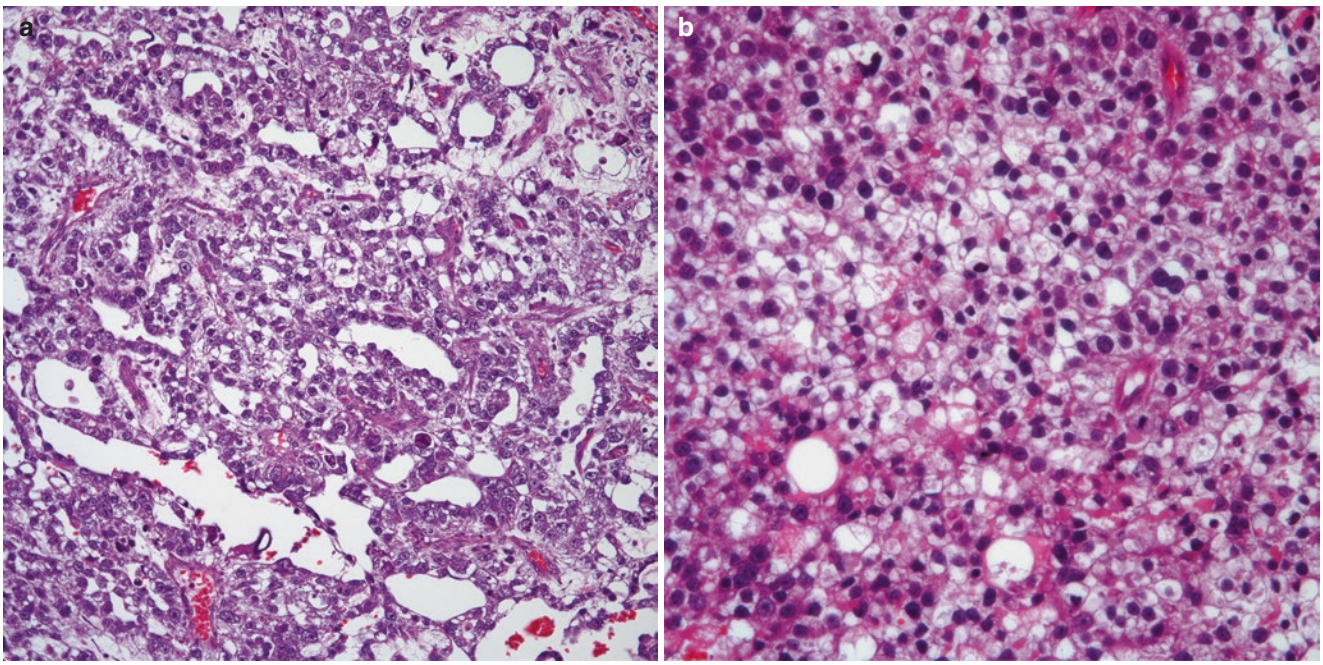

Fig. 10.50 (**a**) YST tumor showing cells with clear cytoplasm. (**b**) High-power magnification showing YST composed of rather small cells with clear cytoplasm

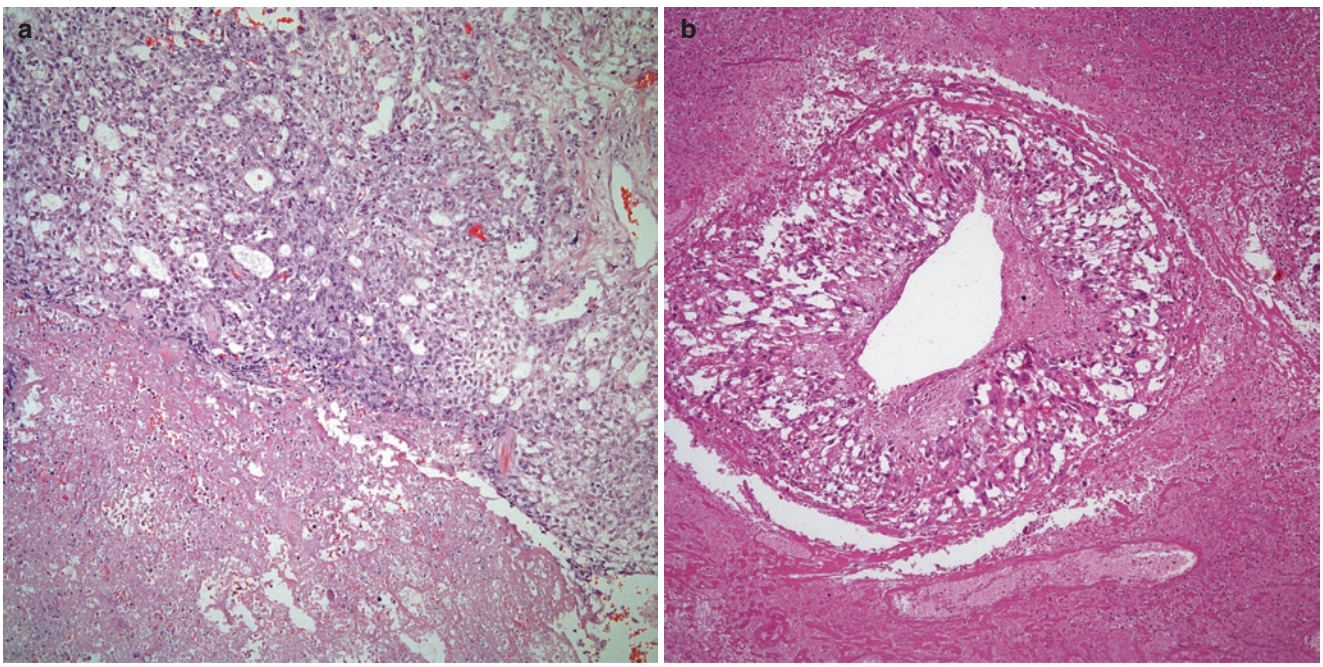

Fig. 10.51 (**a**) YST showing areas of necrosis. (**b**) Extensive necrosis is present with only focal areas of YST; note the Schiller-Duval body

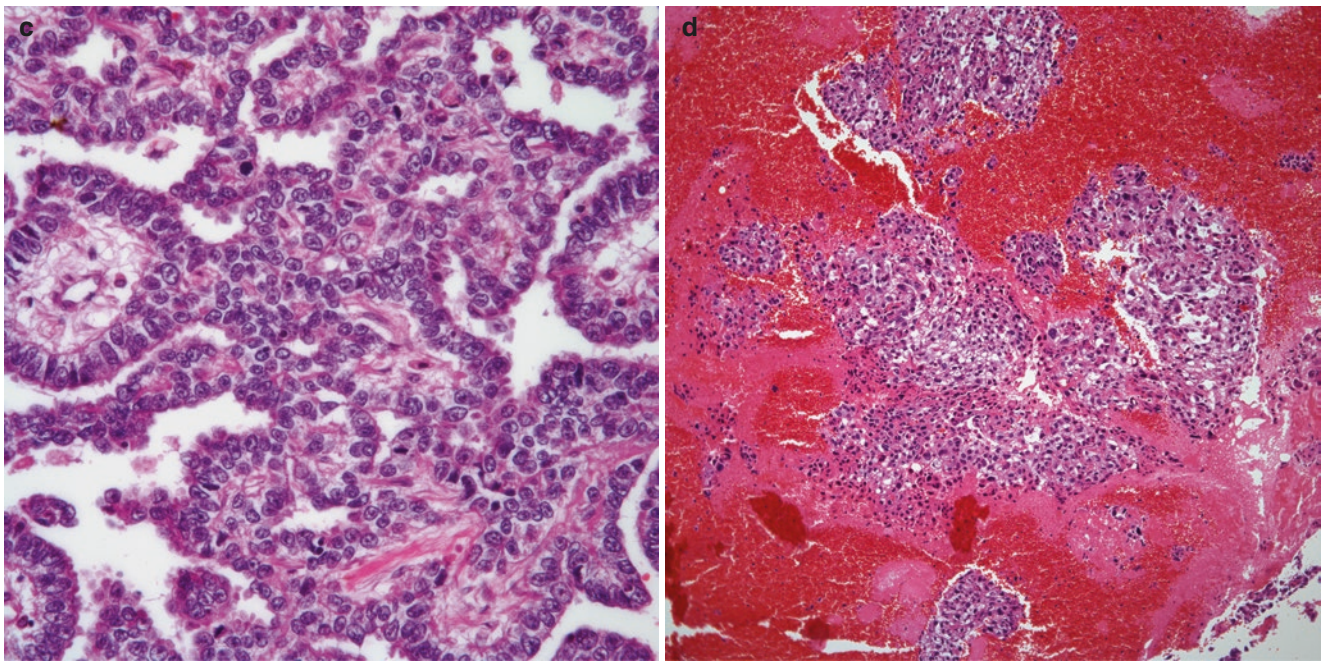

Fig. 10.51 (continued) (**c**) Solid growth pattern of YST showing numerous mitotic figures. (**d**) YST showing areas of hemorrhage

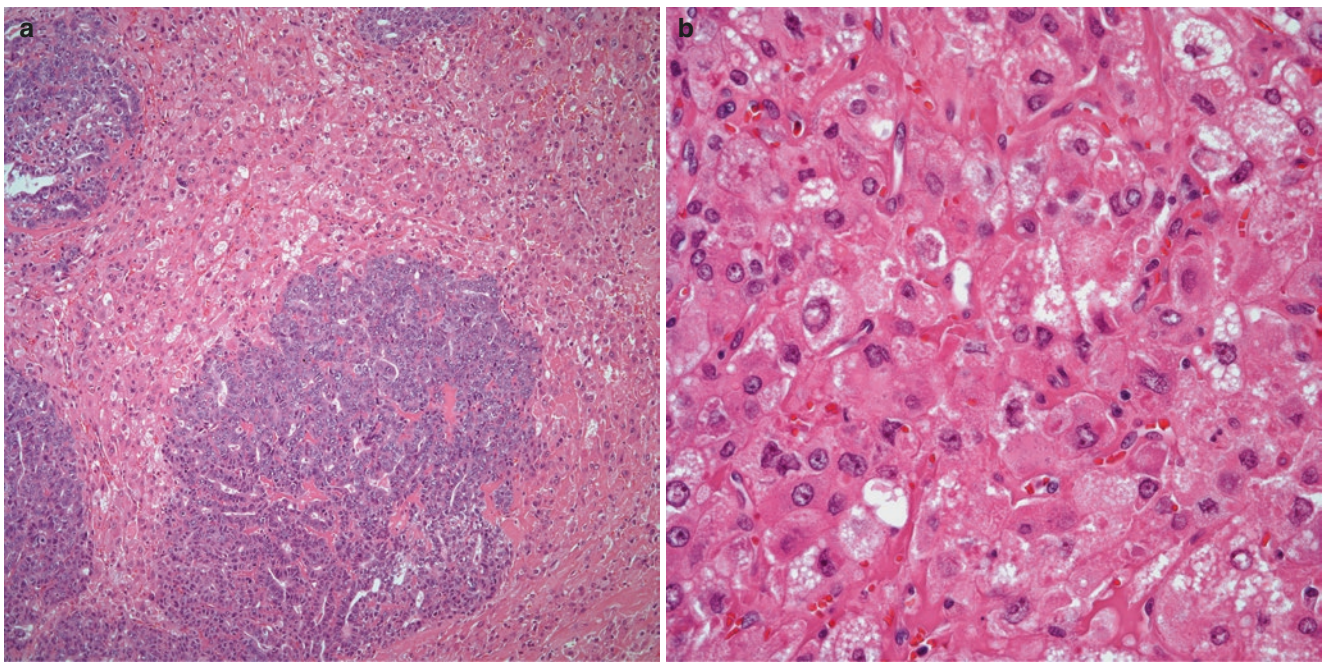

Fig. 10.52 (**a**) YST showing focal conventional areas admixed with hepatoid growth pattern. (**b**) Higher magnification of the hepatoid variant showing large cells with eosinophilic cytoplasm

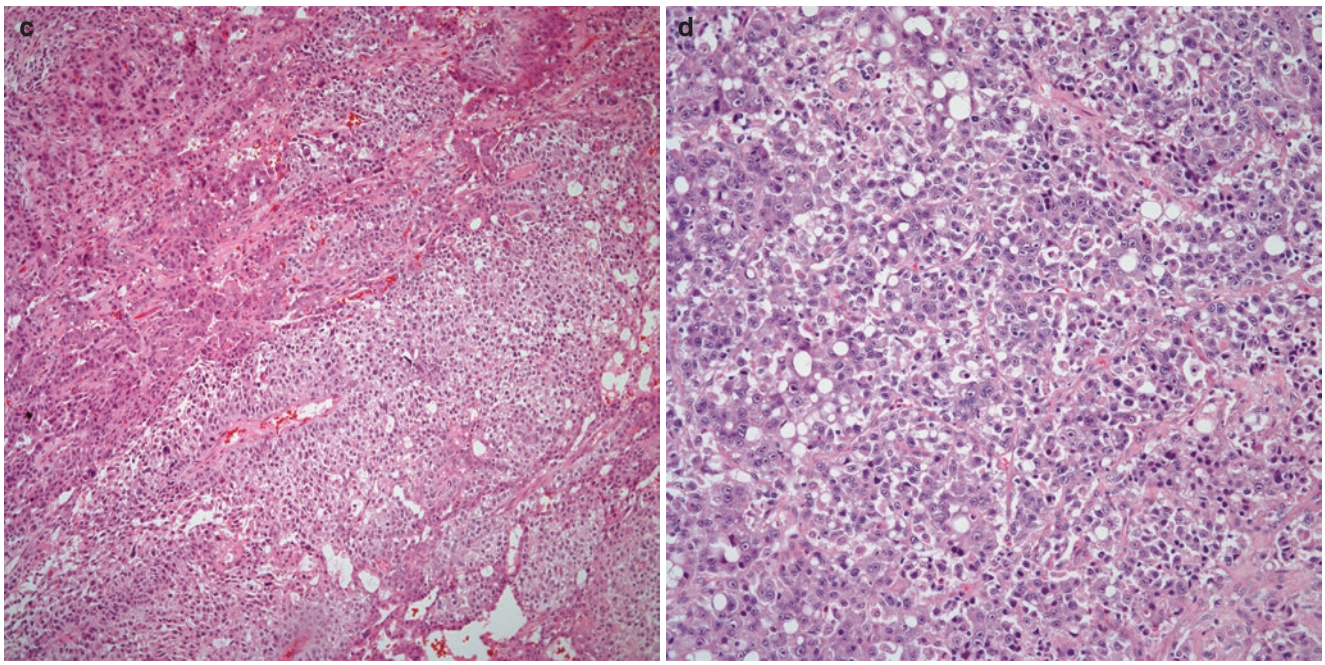

Fig. 10.52 (continued) (**c**) Conventional areas of YST adjacent to areas of hepatoid pattern composed of ribbons of neoplastic cells. (**d**) High magnification of the hepatoid variant showing areas similar to "fat droplets"

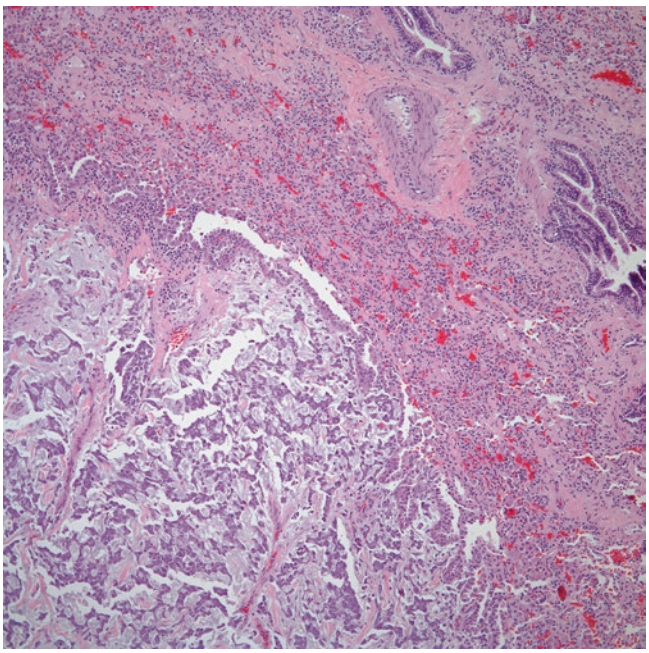

Fig. 10.53 Yolk sac tumor invading lung parenchyma

Ultrastructural Features

YST may show the presence of abundant extracellular electron-dense basement membrane material surrounding the cell membranes and electron-dense spheroidal bodies lying free in the cytosol. The cytoplasm of the cells may contain prominent rough endoplasmic reticulum with dilated cisternae, numerous uniform mitochondria, free ribosomes, and a well-developed Golgi apparatus. Glycogen granules and/or large lysosomes may be present. The cell membranes are joined by frequent small desmosomes, while glandular and ductular structures with true lumens displaying short microvilli may also be present. The electron-dense spheroidal bodies corresponding to the hyaline globules seen by light microscopy may be occasionally found lying free in the cytosol or may be present in extracellular location (Fig. 10.55).

Differential Diagnosis

The diagnosis of YST – when the tumor presents classical microcystic growth pattern, hyaline globules, and Schiller-Duval bodies – is straightforward. However, in some instances, clear separation from embryonal carcinoma may not be quite that simple. Another problem lies with the fact that the two tumors may coexist. Metastatic poorly differentiated carcinoma to the mediastinal region may also be confused with the solid variant of YST, while YST with prominent papillary features may be mistaken for a metastatic papillary neoplasm from other sites. In the latter two cases, the presence of areas displaying more characteristic features such as hyaline globules or Schiller-Duval bodies will be of aid in arriving at a correct interpretation. In addition, the presence of AFP in serum and/or its demonstration in tissue sections represents an added valuable tool for diagnosis.

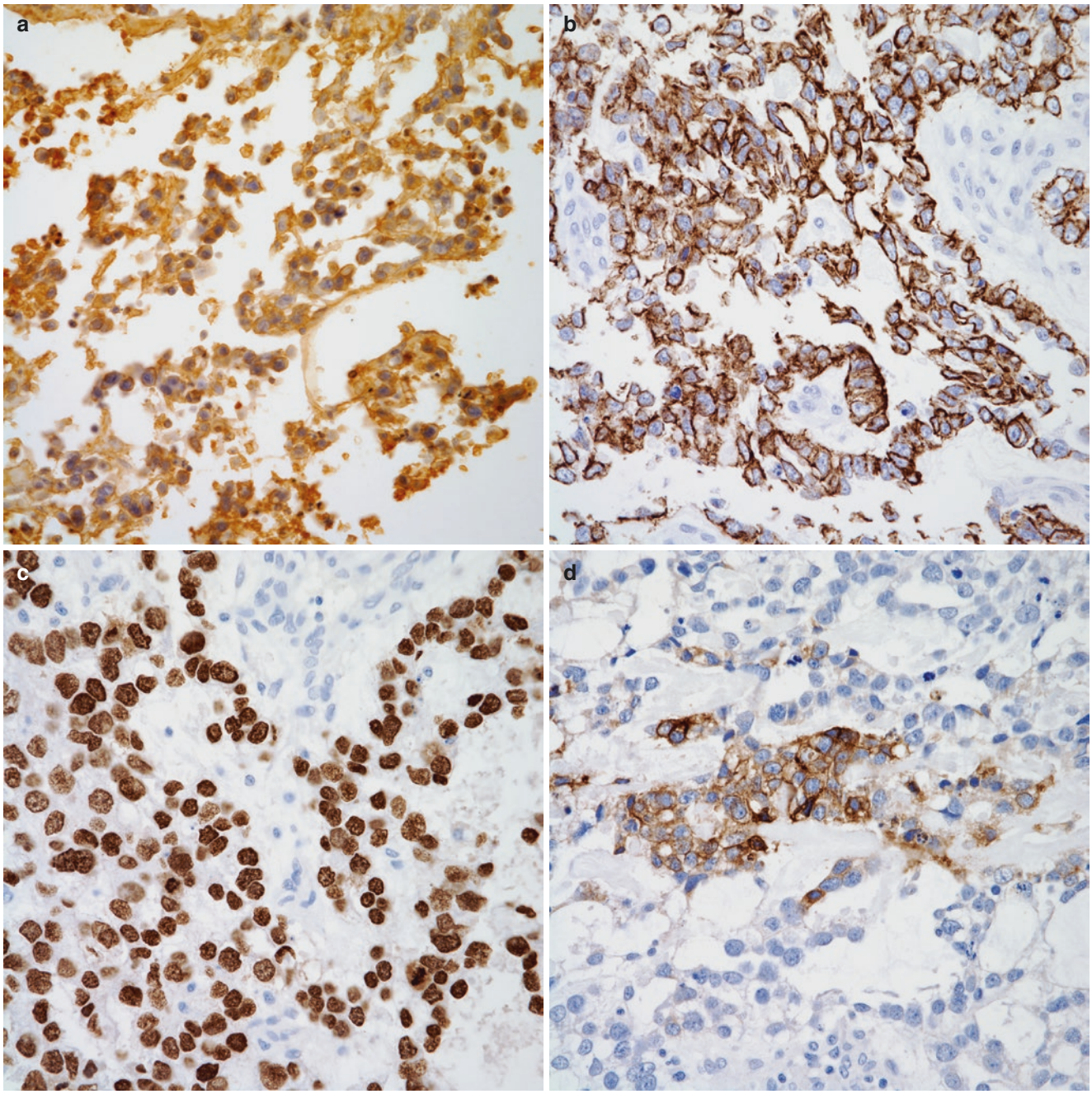

Fig. 10.54 Immunohistochemical stains in YST. (**a**) Positive staining for AFP. (**b**) CAM5.2 shows positive staining in tumor cells. (**c**) SALL4 showing strong nuclear positive staining in YST. (**d**) YST showing focal staining for glypican

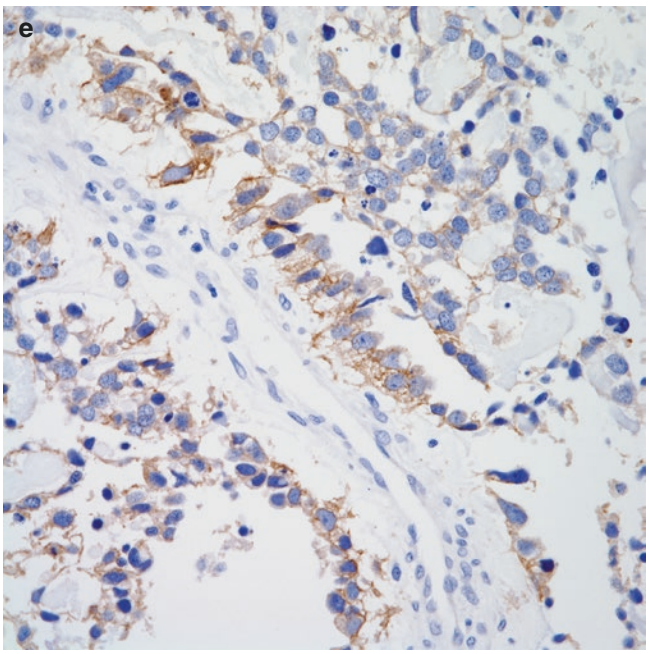

Fig. 10.54 (continued) (**e**) YST showing focal positive staining for CD117

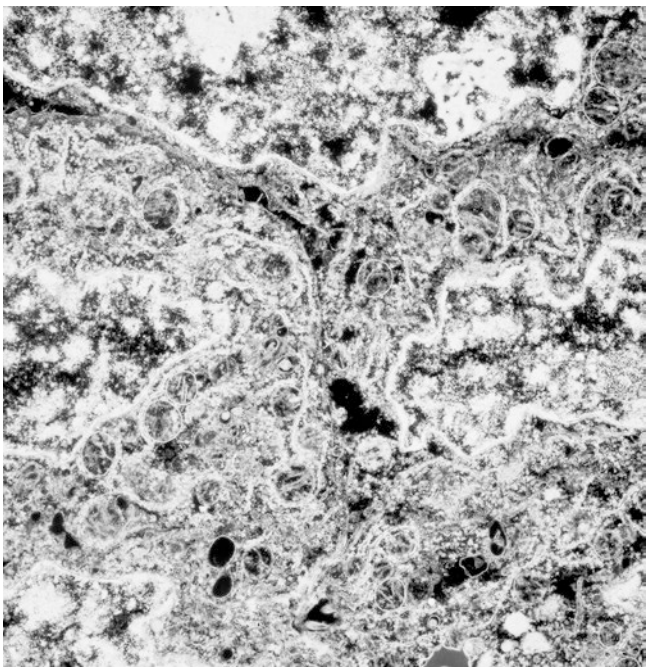

Fig. 10.55 Ultrastructural study of M-YST showing cells with irregular nuclei, tight junctions, numerous mitochondria, and lysosomes

Embryonal Carcinoma

Embryonal carcinoma (EC) is one of the most unusual MGCT. It rarely presents in its pure form [32, 153], and in most instances it is associated with another GCT [188–191]. In the past, these tumors were also known as the "adult type" of embryonal carcinoma to differentiate this tumor from the "infantile type," which is now currently known as YST.

Clinical Features

The true incidence of this tumor in the general population is difficult to estimate due to its rarity in its pure form. In our experience [165], EC accounts for approximately 10% of all MGCT. The same as with YST, embryonal carcinoma is more common in men in the third and fourth decades of life. However, cases of EC in women and in older individuals have been described [32, 188, 190].

The clinical manifestations of primary mediastinal EC are similar to those described for YST. Essentially, the symptomatology is linked to the size of the tumor mass. When these tumors reach a large size, they will compress adjacent structures and produce symptoms including shortness of breath, dyspnea, and chest pain. Similarly to YST, embryonal carcinomas have been associated with hematologic abnormalities such as idiopathic thrombocytopenia [171] and chromosomal abnormalities such as Klinefelter's syndrome [191].

The radiological appearance of EC is similar to that of YST. The most important feature is the presence of a large smooth or lobulated mass, which may be well circumscribed or may have irregular margins that pushes into the adjacent lung parenchyma. Evidence of metastatic tumor in the lung fields is commonly seen. However, there are no radiologic features that will allow distinction between EC and other non-seminomatous GCT.

The treatment for patients with these tumors is similar to that described for YST. Essentially, both neoplasms have been grouped under the heading of non-seminomatous GCT, and have been treated the same way in the majority of studies in the literature. The treatment consists of a cis-platinum-based chemotherapy with or without surgical resection of the tumor [63, 64, 130, 159, 179–183].

Gross Features

The tumors are usually large, ill defined, and soft, with or without extensive areas of necrosis and/or hemorrhage. They can measure from a few centimeters to over 10 cm in greatest dimension (Fig. 10.56). There are no gross features helpful in distinguishing these tumors from any other MGCT.

Histologic Features

On scanning magnification, the tumor may show a solid growth pattern mimicking an undifferentiated epithelial neoplasm (Fig. 10.57a–d). On closer view, the tumor may

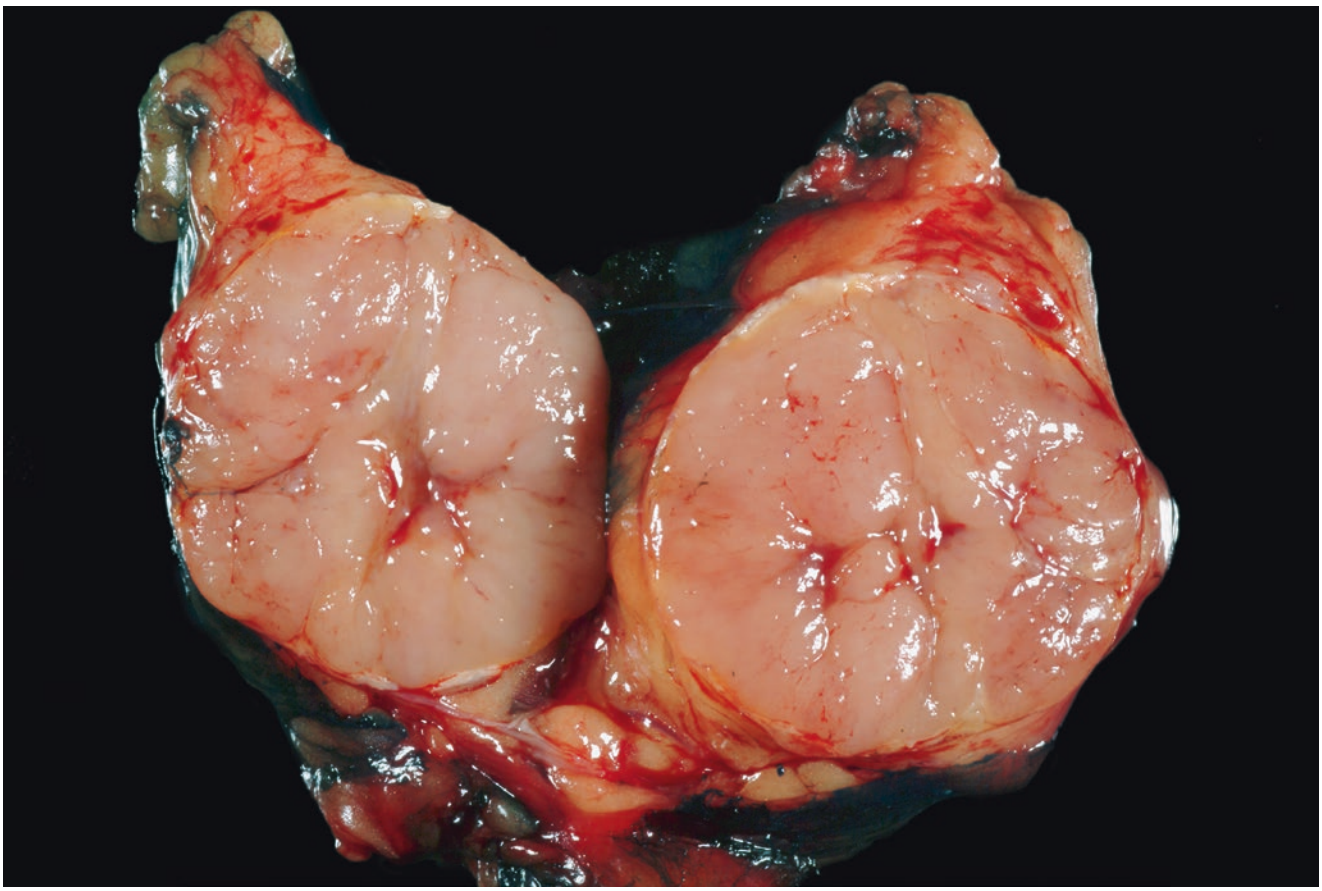

Fig. 10.56 Mediastinal embryonal carcinoma showing an ill-defined tumor mass with focal areas of hemorrhage

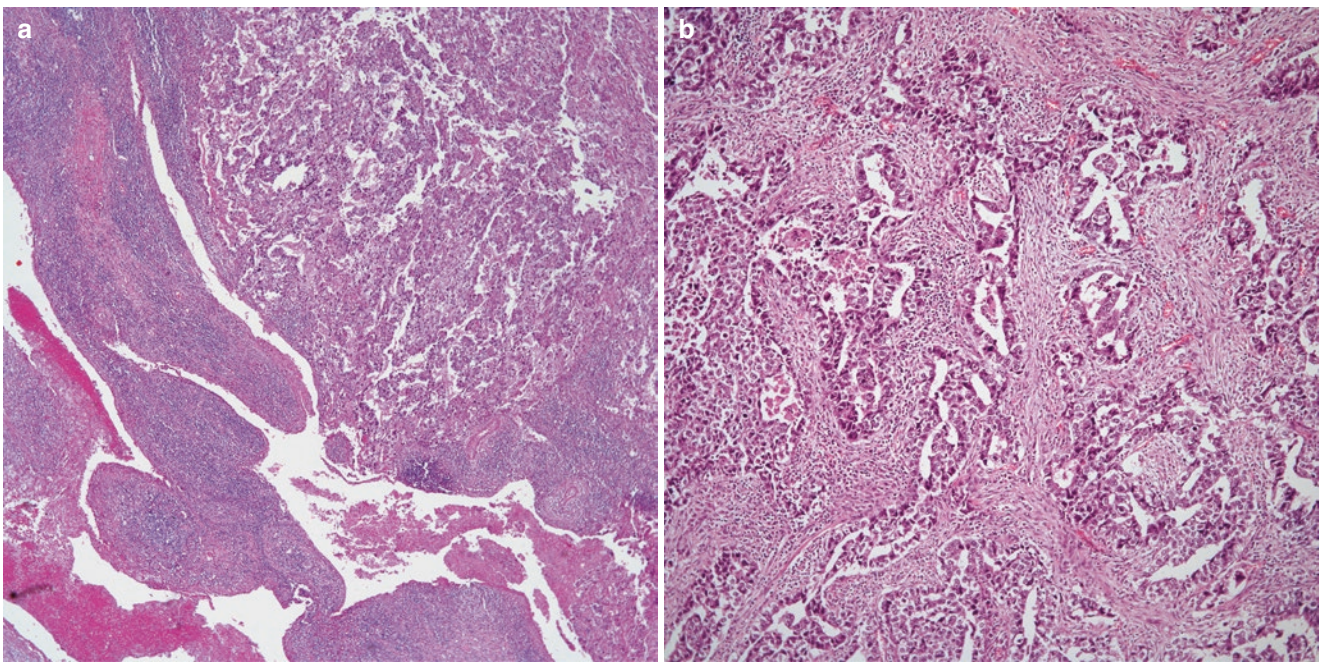

Fig. 10.57 (**a**) Embryonal carcinoma adjacent to areas of thymic tissue. (**b**) Embryonal carcinoma showing glandular component dissecting fibroconnective tissue

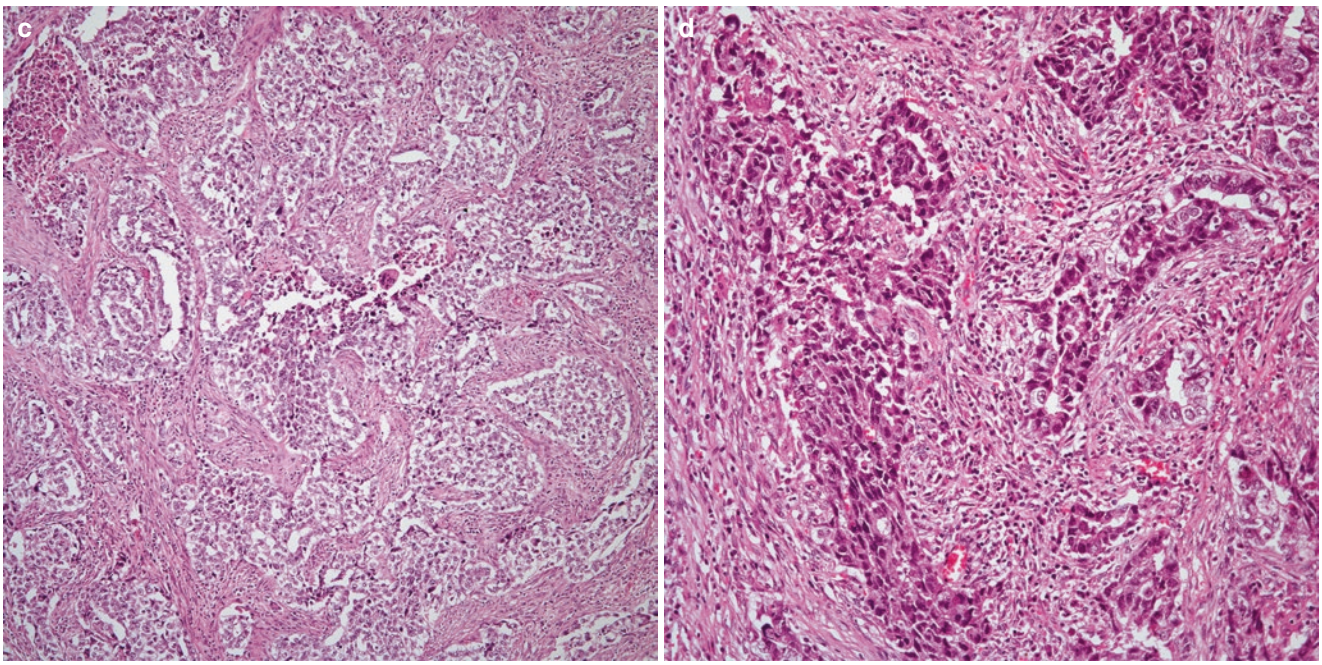

Fig. 10.57 (continued) (**c**) Solid areas alternating with poorly formed glands. (**d**) Poorly formed glands dissecting fibroconnective tissue with mixed inflammatory reaction

disclose a more glandular appearance (Fig. 10.58). However, the tumor may show a solid pattern with haphazard distribution of the neoplastic cells (Fig. 10.59a, b). The neoplastic cellular proliferation is composed of relatively large, primitive-appearing cells with round to oval nuclei and prominent nucleoli (Fig. 10.60a–d). The cytoplasm can be either clear or slightly eosinophilic. In some areas, it is possible to identify ill-defined glandular structures admixed with a more undifferentiated neoplastic cellular proliferation. The tumor may be overshadowed by extensive areas of necrosis in which there may be glandular structures embedded within the necrotic debris (Fig. 10.61a, b). More undifferentiated areas are commonly seen showing an increase number of mitoses and cytologic atypia as well as the presence of scattered syncytiotrophoblast-type multinucleated giant cells. Often, the tumor infiltrates into adjacent organs such as the pericardium and pleura.

The use of histochemical stains is mainly to rule out the possibility of a poorly differentiated adenocarcinoma, in which case the D-PAS and mucicarmine stains will show intracellular mucin, unlike EC in which no intracellular mucin is evident.

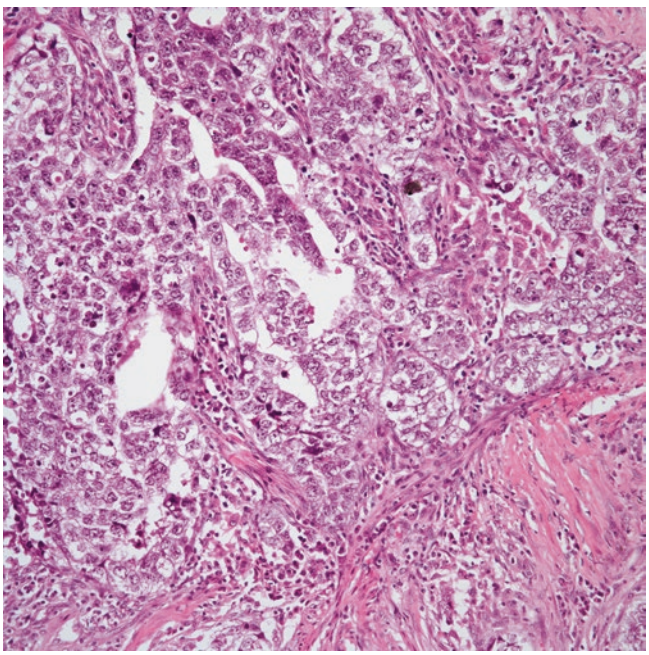

Fig. 10.58 E.C. showing poorly formed glands composed of larger cells with clearing of the nuclei and conspicuous nucleoli

Immunohistochemical Features

EC shares some of the immunohistochemical features with YST. They may show positive staining using antibodies against AFP, PLAP, NSE, Leu-7, Keratin, and vimentin [141]. Unlike AFP immunoreactivity in YST and PLAP immunoreactivity in seminomas, the positivity for these markers in EC will be more patchy and focal. The low molecular weight cytokeratins, such as CAM 5.2, are more often present in these tumors than the broad-spectrum type and will stain strongly and diffusely the neoplastic elements.

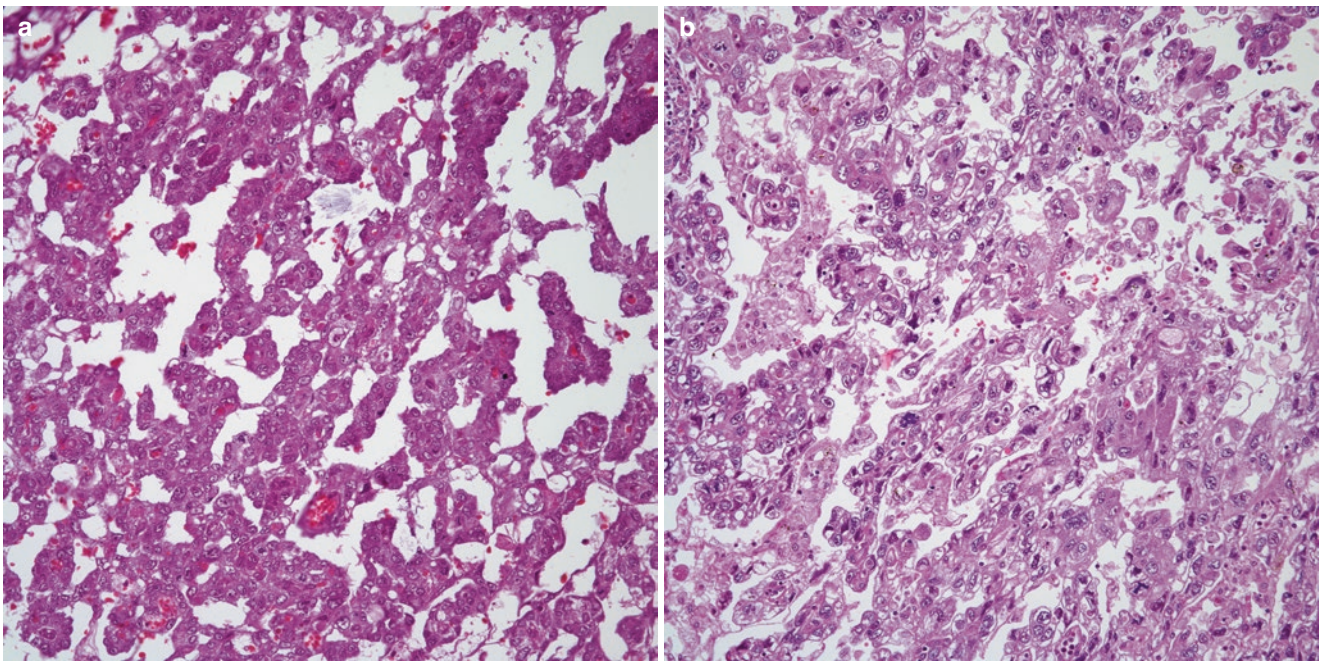

Fig. 10.59 (**a**) E.C. showing sheets of neoplastic cells. (**b**) E.C. composed of larger cells with vacuolization of the cytoplasm, large nuclei with prominent nucleoli

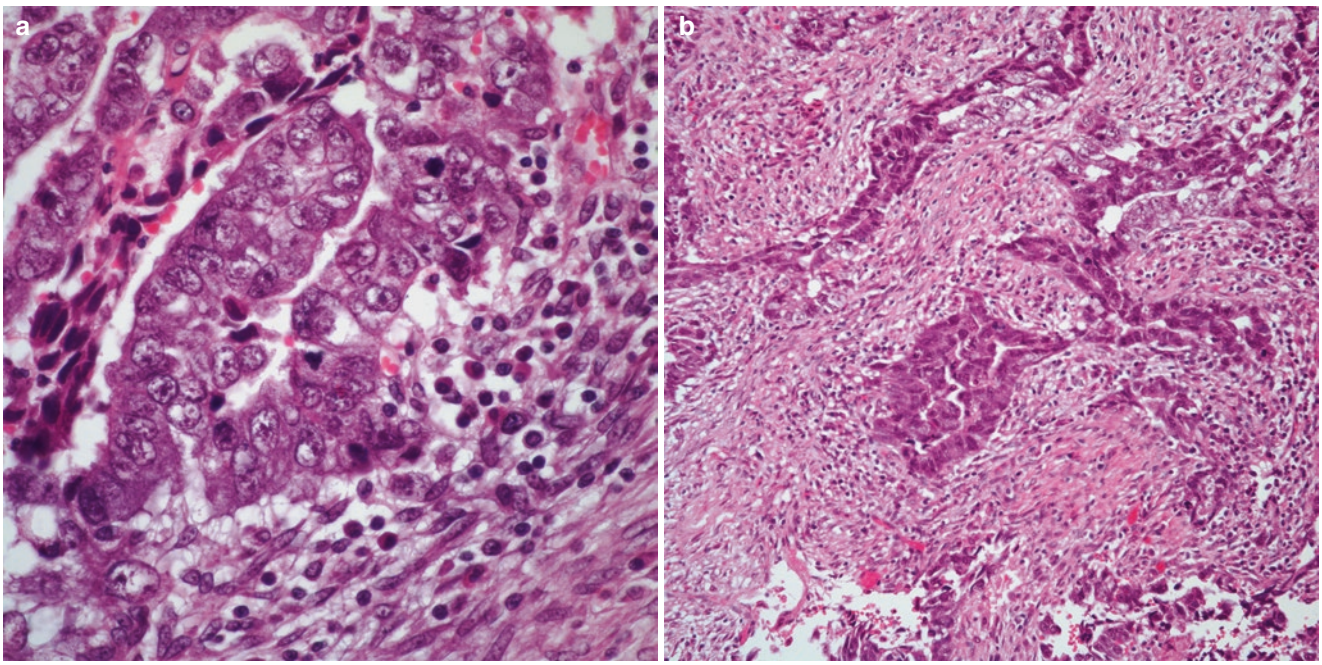

Fig. 10.60 (**a**) Higher magnification of E.C. showing larger cells with clear nuclei and prominent nucleoli; mitotic figures are also present. (**b**) Collapsed glandular structures infiltrating fibroconnective tissue

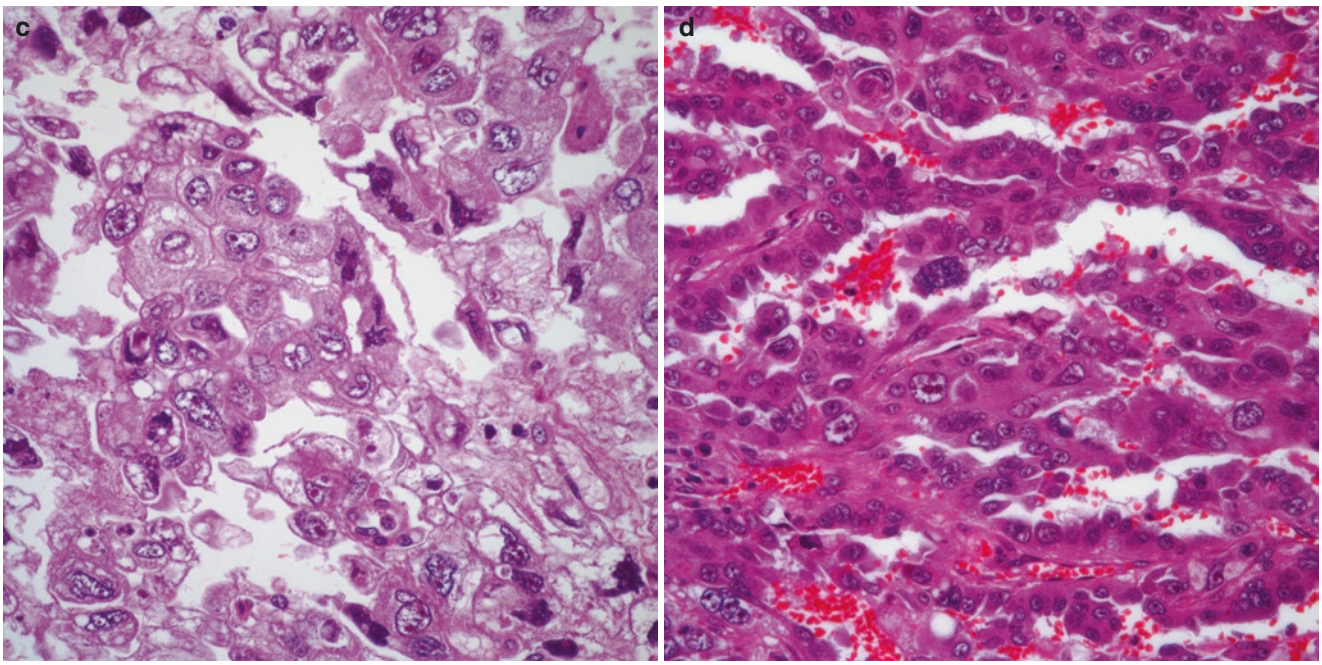

Fig. 10.60 (continued) (**c**) E.C. showing large cells with ample cytoplasm, round to oval nuclei and prominent nucleoli. (**d**) E.C. showing ribbon and glands composed of large cells with eosinophilic cytoplasm, round nuclei, and prominent nucleoli

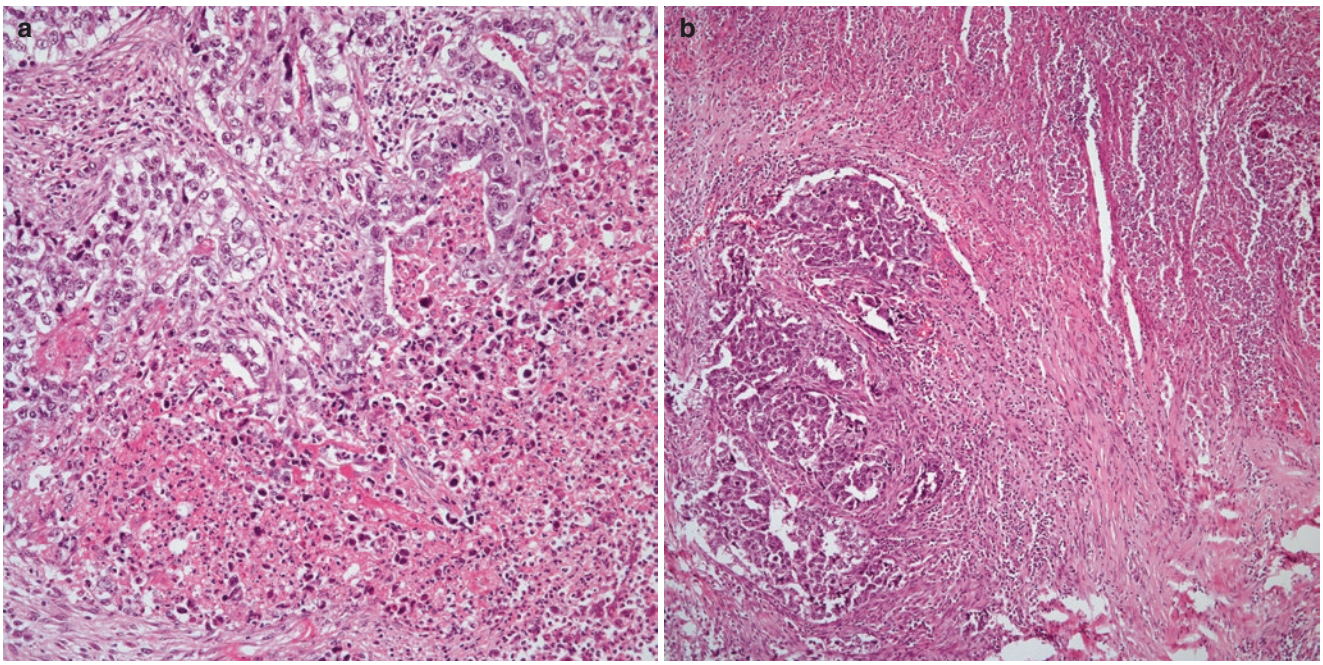

Fig. 10.61 (**a**) E.C. showing discrete areas of necrosis in which neoplastic cells are also evident. (**b**) E.C. with more extensive areas of necrosis and only focal areas of viable tumor

Interestingly, EC also shows positive staining with CD-30 [192]. This latter characteristic is not shared by any other GCT and may be of potential value for differential diagnosis (Fig. 10.62a, b).

Ultrastructural Features

There are no distinctive ultrastructural features for this neoplasm. The tumor is composed of solid sheets of primitive, undifferentiated epithelial cells with large nuclei and prominent electron-dense nucleoli (Fig. 10.63). However, one can observe desmosomal intercellular junctions, bundles of cytokeratin filaments, and occasional lumen formation. The presence of cytoplasmic AFP globules can occasionally be observed in close association with rough endoplasmic reticulum, indicating areas of presumed yolk sac differentiation. In an ultrastructural study reported by Ulbright and associates [193], the authors stated that long-tight junctions and telolysosomes were found in all cases of EC, whereas they were generally less well developed in carcinomas of teratomatous origin.

Differential Diagnosis

The most important issue in the differential diagnosis of embryonal carcinoma is with metastasis from an undifferentiated large cell carcinoma or a poorly differentiated adenocarcinoma. Primary lung carcinomas can often metastasize to the mediastinum. In this setting, a proper clinical and radiological evaluation is essential. The diagnosis is aided by recognition of the primitive, immature appearance of the glands and cellular elements in embryonal carcinoma. Extensive sampling is also important to exclude the possibility of a combined GCT. Two important aspects that can be of help are the fact that the overwhelming majority of patients with EC are young with a bulky anterior mediastinal mass. In addition, EC commonly shows positive staining for CD30, which would be unusual in carcinoma of lung origin.

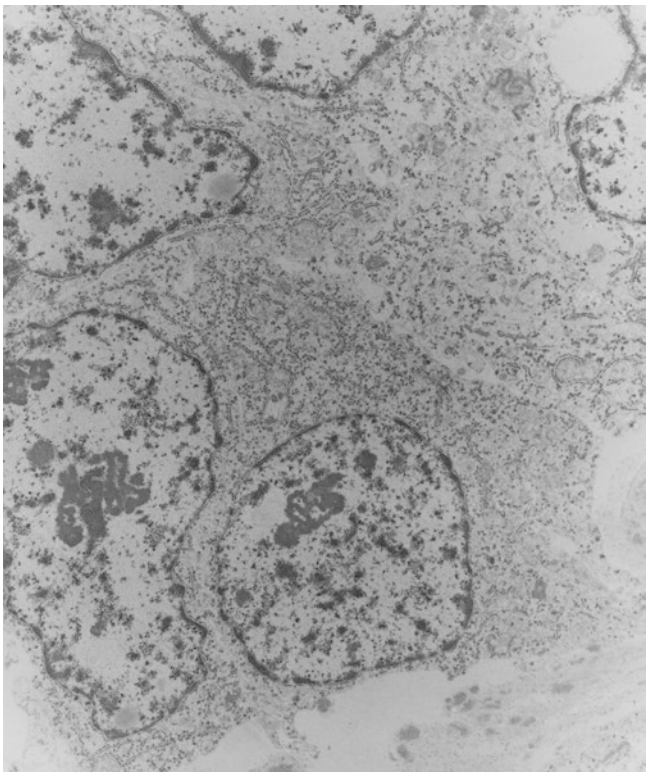

Fig. 10.63 Ultrastructural study of E.C. showing larger cells with round to oval nuclei and dense nucleoli

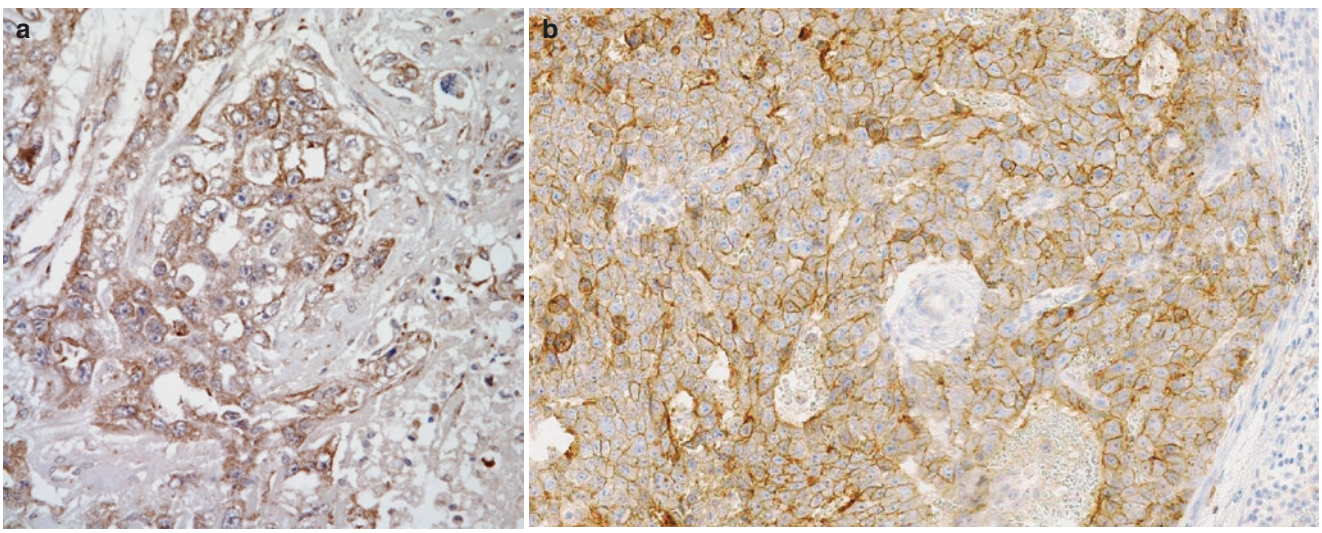

Fig. 10.62 (**a**) E.C. showing strong positive staining for keratin. (**b**) E.C. showing strong positive staining for CD-30

Choriocarcinoma

Extragonadal choriocarcinomas are not only rare but also probably the most debatable GCT to occur outside of the gonads. Part of the controversy surrounding the existence of primary extragonadal choriocarcinomas is the fact that small testicular tumors can give rise to widespread metastatic lesions. On the other hand, it has been stated that in some instances the primary lesion may undergo complete regression, therefore casting doubts over the real existence of primary mediastinal choriocarcinomas.

In 1961, Azzopardi and associates [194] studied 17 patients with widespread metastases of GCT. Eight of the cases were compatible with choriocarcinoma. The authors found that, in all cases, a distinct and well-defined testicular scar was found, which the authors interpreted as the primary site of origin. In addition, in 13 cases, the authors noted the presence of "peculiar amorphous hematoxylin-staining deposits" in dilated seminiferous tubules. These deposits were shown to consist of phospholipid, protein debris, and DNA, as well as mucoid substances and calcium phosphate, which were believed to result from tumor necrosis. The authors concluded that the presence of these deposits was consistent with a "burned-out" primary testicular tumor. Similar findings had already been described in a single case by Prim as cited by Azzopardi [194]. Therefore, it was proposed that before rendering the diagnosis of primary extragonadal choriocarcinoma, a careful search for a testicular scar or microscopic neoplasm must be undertaken. In 1953, Lynch and Blewett [117] reported a case of choriocarcinoma in the mediastinal region and cited Ritchie as the first to describe such a tumor in the anterior mediastinum. The authors analyzed previously reported cases and found great disagreement regarding the concept of primary choriocarcinoma of the mediastinum and concluded that the best manner to establish the diagnosis of primary choriocarcinoma of the mediastinum requires serial sectioning of the testes and hormonal studies of the urine and of the tumor. Based on these criteria, the number of cases accepted as primary choriocarcinoma of the mediastinum is definitely low. Interestingly, the authors noted a tendency to interpret testicular scars as representing the origin of choriocarcinoma without considering that the scar themselves might be secondary reaction. On the other hand, some authors have questioned the so-called spontaneous healing of primary choriocarcinoma. In any event, the issue is merely of academic interest since the finding of a small, burned-out, or regressed primary tumor in the gonads is unlikely to alter the prognosis or clinical behavior of the tumor.

Clinical Features

The true incidence of choriocarcinomas arising primarily in the mediastinum is extremely difficult to assess. Although numerous single cases of choriocarcinomas arising in the mediastinum have been reported [4, 5, 61, 64, 117, 168, 195–202], the presence of an anterior mediastinal mass in the absence of testicular lesion on palpation is not necessarily an indication that the case represents a primary mediastinal choriocarcinoma, and some of the reported cases may have corresponded to metastases to the mediastinum from an occult or regressed primary. These tumors predominantly affect men in the third and fourth decades of life and constitute a small percentage of MGCT. In our experience, this tumor accounts for less than 5% of all MGCT [203].

Choriocarcinomas presenting as anterior mediastinal masses usually produce symptoms of cough, shortness of breath, dyspnea, gynecomastia, chest pain, and/or superior vena cava syndrome [168, 198, 199]. It is of interest to note that, in the great majority of the cases reported, by the time the diagnosis is established, the tumor has already spread outside the mediastinal compartment and is usually found involving the lungs.

There are no radiological characteristics that can help separate choriocarcinoma from other non-seminomatous MGCT. However, in most of the cases reported, the radiological features correspond to those of a more advanced tumor with multiple tumoral nodules in the lungs or in other areas such as the liver. Therefore, the presence of an anterior mediastinal mass suspected clinically of being a GCT, which is already involving lung and/or other viscera, should be highly suggestive of choriocarcinoma.

The prognosis for patients with mediastinal choriocarcinoma as reported in the literature is dismal. In most of the reported cases as well as in our experience, at the time of diagnosis, the tumor had already spread within the thoracic or extrathoracic area. The tumors appear to metastasize widely and rapidly to other organs such as liver and brain. In most of the early cases described in the literature, treatment was ineffectual. However, in a few cases, the patients experienced survival rates of several years after treatment with chemotherapy [168, 200]. Nevertheless, the clinical course is that of rapid deterioration and death within few months.

Gross Features

In the majority of cases, the tumors appear as non-encapsulated masses that may occupy a good portion of the

anterior mediastinum involving pericardium, pleura, lungs, and/or heart. However, in a few cases, the tumors appear to be better circumscribed without evidence of involvement of adjacent structures [168, 198, 200].

Histologic Features

At scanning magnification, choriocarcinomas show extensive areas of hemorrhage and/or necrosis (Fig. 10.64). Closer view of the tumor shows areas displaying two different cell types: cytotrophoblastic and syncytiotrophoblastic cells. Large polygonal cells showing abundant clear cytoplasm, central round to oval nuclei, and distinct cell borders characterize the cytotrophoblastic proliferation. On the other hand, large, multinucleated giant cells with abundant eosinophilic cytoplasm characterize the syncytiotrophoblastic component. Mitoses and bizarre cellular features are also common findings (Fig. 10.65a–f).

Histochemical studies may be of value to determine the presence of intra- and extracellular mucin and may serve to rule out the possibility of a primary large cell carcinoma of the lung.

Immunohistochemical Features

The hallmark of choriocarcinoma is the presence of HCG immunoreactivity in the syncytiotrophoblastic component of the tumor (Fig. 10.66). However, antibodies for PLAP, EMA, AFP, CEA, and keratins may also display focal positivity in these tumors [141].

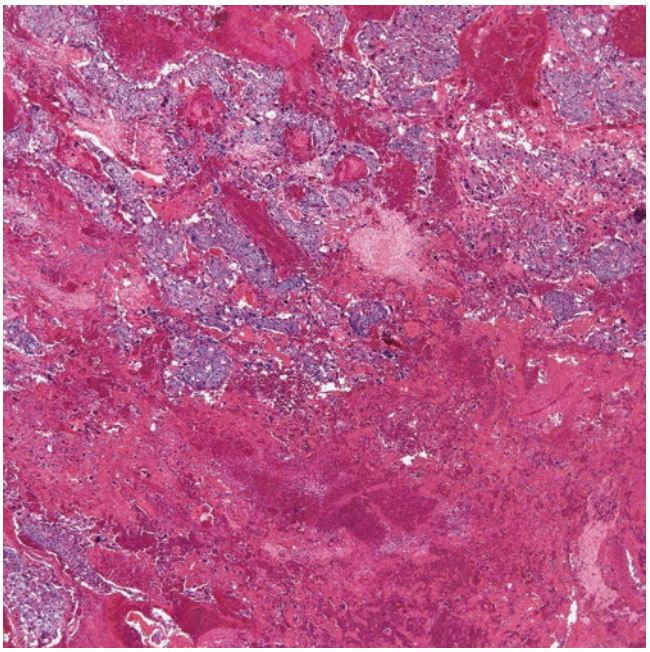

Fig. 10.64 Low-power view of a mediastinal choriocarcinoma showing extensive areas of hemorrhage

Ultrastructural Features

Electron microscopic studies in choriocarcinoma of the mediastinum are not available. However, in those occurring in the testicular region, it has been noted that the cytotrophoblastic component may closely resemble embryonal carcinoma.

Differential Diagnosis

The most important differential diagnosis lies in distinguishing a primary from a metastatic choriocarcinoma. A number of other tumors may show prominent areas composed of multinucleated malignant giant cells that may be confused with syncytiotrophoblastic cells. In particular, primary lung neoplasms such as pleomorphic carcinoma [204] may metastasize to the mediastinum. In addition, pleomorphic carcinomas or large cell carcinomas occurring primarily in the lung may also show ectopic production of HCG, making the distinction from choriocarcinoma a challenge for the pathologist. The presence of a dual cell population comprising both cyto- and syncytiotrophoblast would be more in keeping with a primary choriocarcinoma, whereas the presence of a concomitant, single large intrapulmonary mass would be highly suggestive of a metastasis from a lung primary. Although most cases of primary mediastinal choriocarcinoma involve the lung at the time of diagnosis, such involvement is usually characterized by the presence of multiple pulmonary tumor nodules rather than a single, large solitary mass. In addition, primary mediastinal choriocarcinomas appear to affect more commonly young men while pleomorphic lung carcinomas predominantly affect an older age group.

Combined Germ Cell Tumors

This term is used in this text to describe tumors showing combinations of seminoma, embryonal carcinoma, YST, and/or choriocarcinoma, in the absence of teratomatous components. We prefer such designation instead of the term “mixed tumors” in view not only of the existence of neoplasms in other systems that are known by this designation but also because of its lack of specificity. In addition, we consider that tumors showing teratomatous components should be grouped with teratomas rather than be included under the heading of combined germ cell tumors [205].

Clinical Features

In our experience with 322 cases of MGCT, we were able to identify 12 cases that fulfill these criteria, which we diagnosed as combined GCT. Therefore, these neoplasms represented approximately 5% of all mediastinal GCT. These

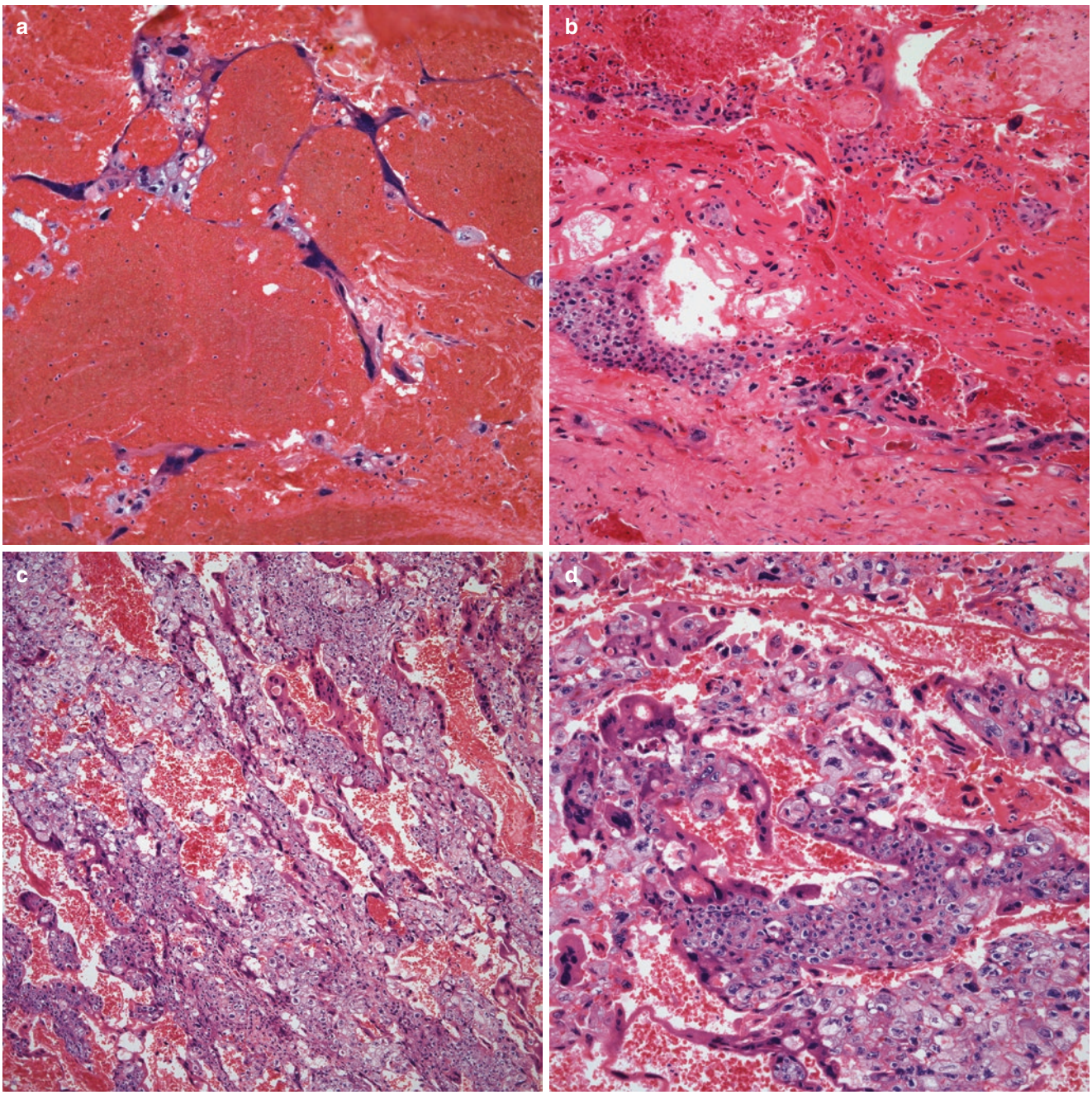

Fig. 10.65 (**a**) Choriocarcinoma with extensive areas of hemorrhage and the outlines of syncytiotrophoblastic cells. (**b**) Syncytiotrophoblastic and cytotrophoblastic cells admixed with hemorrhage. (**c**) Choriocarcinoma with classic cellularity of cyto- and syncytiotrophoblastic cells. (**d**) Dual component formed by multinucleated syncytiotrophoblastic cells and mononuclear cytotrophoblastic cells

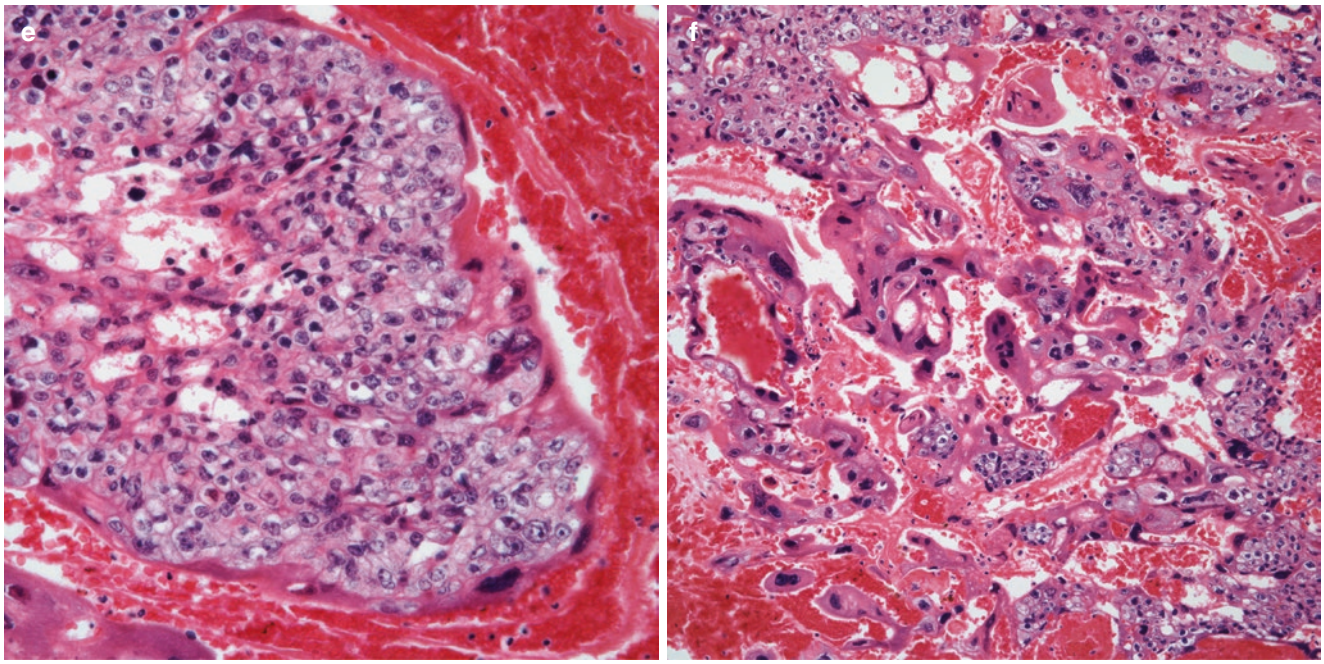

Fig. 10.65 (continued) (**e**) Choriocarcinoma with predominant cytotrophoblastic component. (**f**) Choriocarcinoma with predominant syncytiotrophoblastic component

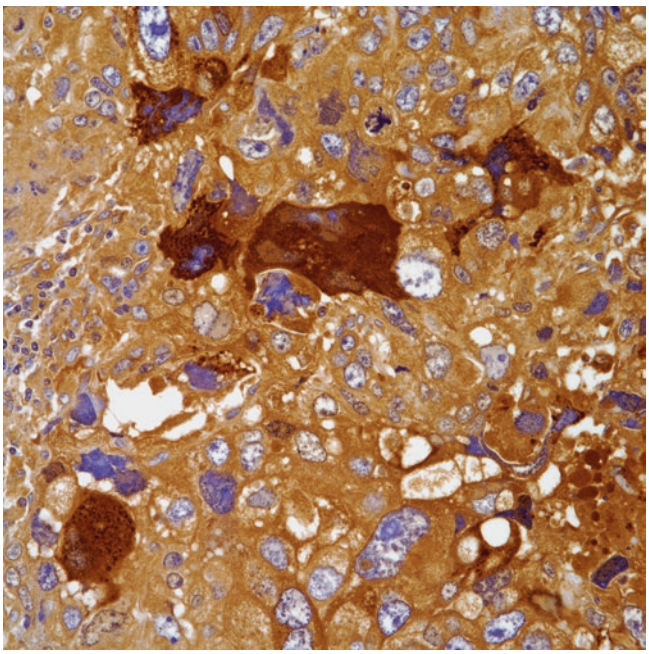

Fig. 10.66 Immunohistochemical stain for HCG showing positive staining in the syncytiotrophoblastic component

tumors predominantly affect males in their third and fourth decades of life. However, female patients with this type of tumor have also been described [188].

The clinical features shown by patients are similar to those described for other GCT, namely, chest pain, cough, and shortness of breath. In our experience, none of these tumors was associated with hematologic or chromosomal abnormalities. Nonetheless, such abnormalities have been previously reported [169, 206]. There is no radiologic feature which can separate combined GCT from other GCT. Therefore, histologic examination is the only way to arrive at a specific diagnosis.

The treatment and prognosis for these tumors will depend on the amount (percentage) of a particular germ cell component and the extent of the disease at the time of diagnosis.

Gross Features

These tumors may vary in size from small to very large tumors (>10 cm in diameter). The outer surface may be glistening and surrounded by membranous tissue. The cut surface shows a firm, slightly nodular tan to whitish appearance. Areas of hemorrhage and/or necrosis may be seen.

Histologic Features

A combination of the different tumors already described may be seen. In essence, these tumors may show any combination among seminoma, YST, EC, and/or choriocarcinoma [32, 188–190]. In our experience, seminomas are the tumor component more often present as part of these tumors (Fig. 10.67a–c). The histologic features of each of those tumors have already been described. The histochemical, immunohistochemical, and ultrastructural features of these tumors will depend on the particular components present.

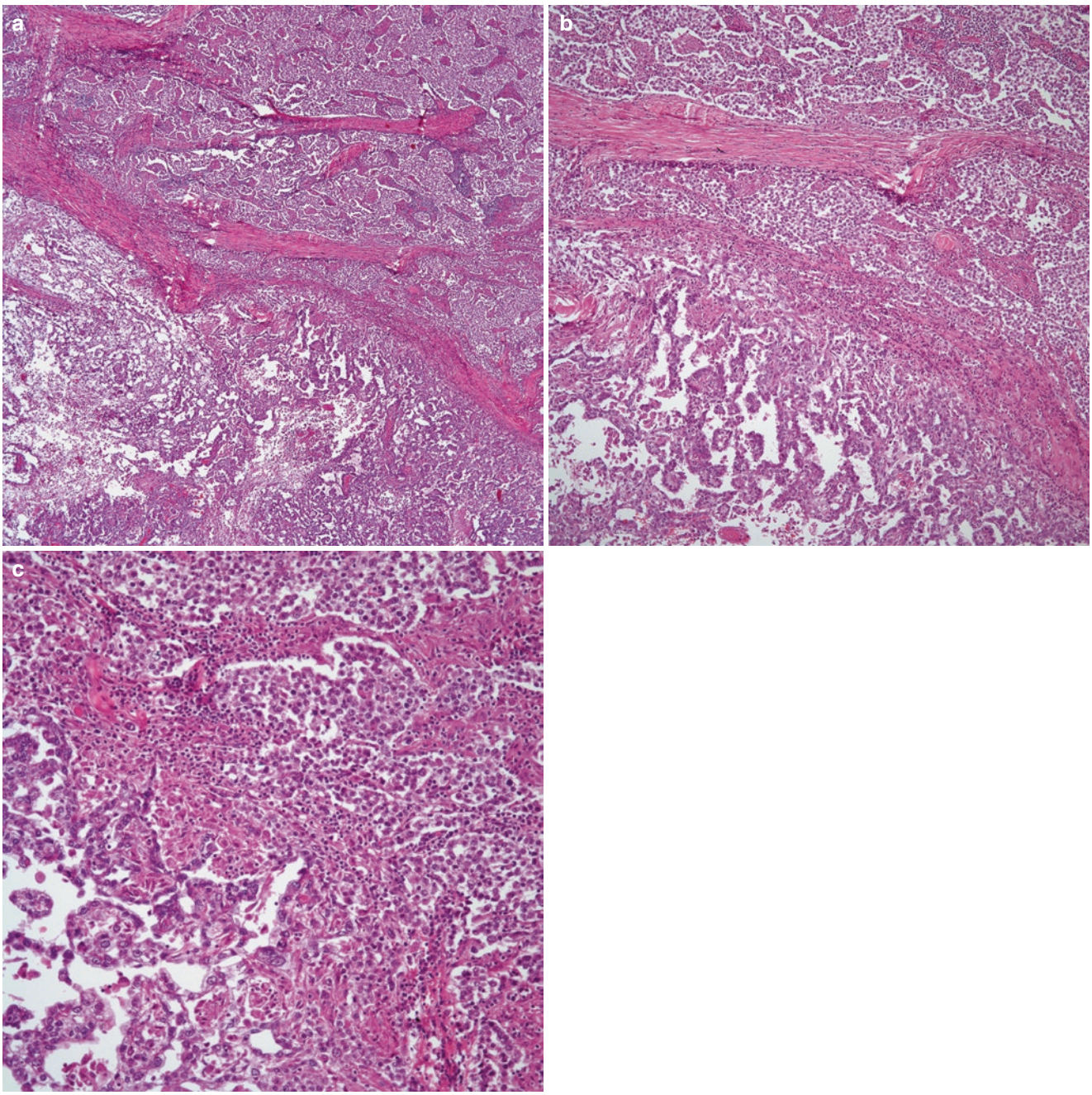

Fig. 10.67 (**a**) Combined GCT showing sharp separation of YST and seminoma. (**b**) YST and seminoma separated by a thin fibroconnective tissue with inflammatory reaction (**c**) YST and seminoma with very discrete transition

Summary

Mediastinal GCT represent an important group of tumors that need to be carefully evaluated, as current therapeutic modalities over the years have made a significant difference in their treatment and prognosis. Even though mature teratomas may represent the most common mediastinal GCT, the need for proper sampling in order to properly exclude other tumors that may need a different approach beyond complete surgical resection should be underscored. Among the non-teratomatous tumors, seminomas are by far the most common, while among the NS-GCT, yolk sac tumor is the more common. Special attention should be given to providing approximate percentages of the different components that may be present in MGCT.

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