Testis and Paratesticular Lesions

6

Debra L. Zynger and Charles C. Guo

List of Frequently Asked Questions

What Is the Difference Between Prepubertal and Postpubertal Testicular Germ Cell Tumors?

There are critical differences between prepubertal and postpubertal testicular germ cell tumors.

- Postpubertal testicular germ cell neoplasms have as their precursor germ cell neoplasia in situ (GCNIS). These tumors characteristically demonstrate 12p abnormalities (isochromosome formation, increase in copy number) and have an increased risk with cryptorchidism.
- GCNIS is not a precursor for prepubertal tumors.
- Prepubertal germ cell tumors are composed of pure teratoma, pure yolk sac tumor, or very rarely a mixture of teratoma and yolk sac tumor. Pure teratoma in the prepubertal population is an indolent lesion with teratoma composed of neuroendocrine tumor with atypical features such as necrosis and mitoses being the possible exception.
- Teratoma in the postpubertal population is malignant.
- Epidermoid cysts (squamous lined cysts filled with keratin debris) and dermoid cysts (squamous lining with dermal structures such as adnexa) are lesions that are not associated with GCNIS and are cured with complete excision.
- It is imperative to carefully evaluate the surrounding testicular parenchyma for GCNIS or scarring that could indicate a regression of other germ cell tumor components in a postpubertal patient before rendering a diagnosis of an epidermoid cyst.

D. L. Zynger (✉)
Department of Pathology, The Ohio State University Medical Center, Columbus, OH, USA
e-mail: debra.zynger@osumc.edu

C. C. Guo
Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

The remainder of the text describing germ cell tumors will refer to the postpubertal population unless otherwise indicated.

What Is the Most Common Type of Germ Cell Tumor? What Are Other Components of Germ Cell Tumors?

A germ cell tumor can be comprised of one ("pure") or multiple subtypes (Table 6.1). Pure seminoma is more common than mixed germ cell tumor. A tumor with multiple components is called a mixed germ cell tumor. Common subtypes found within mixed germ cell tumors are seminoma, embryonal carcinoma, teratoma, yolk sac tumor, and choriocarcinoma. Rare types include teratoma with somatic-type malignancy and the nonchoriocarcinomatous placental tumors placental site trophoblastic tumor, epithelioid trophoblastic tumor, and cystic trophoblastic tumor.

- Pure seminoma accounts for approximately 60% of testicular germ cell tumors.
- Within mixed germ cell tumor, embryonal carcinoma is the most frequent tumor type followed by teratoma, yolk sac tumor, seminoma, and least frequently choriocarcinoma.

Reference: [1]

Table 6.1 Invasive testicular germ cell tumor components

Seminoma
Embryonal carcinoma
Yolk sac tumor
Teratoma
Teratoma with somatic-type malignancy
Choriocarcinoma
Placental site trophoblastic tumor
Epithelioid trophoblastic tumor
Cystic trophoblastic tumor

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What Is the Significance of Different Germ Cell Tumor Types? In which Specimens Is It Required to List Each Germ Cell Tumor Type and Providing Percentages of Each? How Can the Estimation Percentage of Each Tumor Type Be Performed?

Diagnosing a tumor as pure seminoma impacts pT categorization and treatment. Amounts of embryonal carcinoma, choriocarcinoma, yolk sac tumor, and teratoma have been correlated with other adverse pathological features and outcome. Histologic features can be used to estimate percentages. Immunohistochemistry can be used as an aid to corroborate the histologic impression of tumor type. Tumor percentages should be documented for all germ cell tumor specimens including orchiectomy, retroperitoneal lymph node dissection, and distant metastasis.

- Size is a prognostic parameter of pure seminoma that is reflected in the subclassification of pT1a (≤3 cm) and pT1b (>3 cm), although 4 cm is a more cited and studied size threshold.
- Lymphovascular invasion is the most robust prognostic indicator in nonseminomatous tumors and in these patients retroperitoneal lymph node dissection or adjuvant chemotherapy can be considered. In patients with nonseminomatous tumors undergoing active surveillance, relapse occurred in 44% of those with lymphovascular invasion compared to 14% without.
- Presence of teratoma within a primary tumor increases the likelihood of residual teratoma in a postchemotherapy retroperitoneal mass.
- Presence of teratoma in a retroperitoneal metastasis suggests consideration of resection of all lung metastases as histologic concordance of retroperitoneal and lung metastases is high (75%).
- It is recommended that all residual retroperitoneal masses >1 cm be resected unless the primary tumor was pure seminoma.
- Predominance or pure choriocarcinoma portends aggressive behavior.
- Higher amounts of embryonal carcinoma and lower amounts of teratoma and yolk sac tumor are associated with worse pathologic features.
- The presence of teratoma with somatic-type malignancy, particularly in a metastasis, is correlated with a worse outcome.

References: [2–24]

What Is the Clinical Presentation of Seminoma Compared to a Nonseminomatous Germ Cell Tumor?

Seminoma presents at a mean age of 35–37 years with 72–80% clinical stage I. Serum lactate dehydrogenase is often elevated with normal to modestly increased serum human chorionic gonadotropin and normal alpha fetal protein levels. Mean tumor size is 3.9–4.3 cm. In patients diagnosed over 60 years of age, most germ cell tumors (82%) are seminoma.

Patients with nonseminoma have a mean age of 28–31 years and more frequently present at higher stage (60% clinical stage I). Serum levels of human chorionic gonadotropin and alpha fetal protein can be markedly elevated depending upon presence and amount of choriocarcinoma and yolk sac tumor, respectively. Mean tumor size is 4.1–4.7 cm. Within clinical stage I, relapse is more common in nonseminomatous germ cell tumors (19%) compared to seminoma (13%).

References: [1, 10, 13, 15, 25–28]

What Are the Key Histologic Clues to Diagnose GCNIS? What Is the Expression Profile of GCNIS?

GCNIS is the precursor lesion of postpubertal germ cell tumors. Within seminiferous tubules, seminoma-like cells are seen.

- The key histologic feature is the location of these cells in that they are found against the basement membrane (within the spermatogonial niche) rather than dispersed throughout the tubule (Table 6.2; Fig. 6.1a).
- Other important histologic features include vacuolated cytoplasm, nucleomegaly, and hyperchromatic nuclei with occasional prominent nucleoli.

Table 6.2 Features and differential diagnosis of germ cell neoplasia in situ (GCNIS)

	Location in seminiferous tubule	Tubule appears filled with cells/necrosis	Cells within tubule are homogenous	OCT3/4
GCNIS	Against basement membrane	No	No	+
Intratubular seminoma/embryonal carcinoma	Dispersed	Yes	Variable	+
Germ cells with delayed maturation	Dispersed	Yes	No	+
Sertoli-only tubules	Against basement membrane	No	Yes	–

- Tubules with GCNIS typically lack spermatic maturation and thus the tubules appear predominately empty or have lumens with mostly flocculent pink cytoplasm rather than nucleated cells.

Immunohistochemical stains can corroborate the diagnosis of GCNIS:

- Positive: SALL4, PLAP, CD117/c-kit, D2-40/podoplanin, and OCT3/4 (Fig. 6.1b, c).
- Negative: CD30, WT1, inhibin.

References: [29–32]

What Is Intratubular Tumor and How Is It Different Than GCNIS? What Are Other Mimickers of GCNIS?

Other types of intratubular neoplasia such as intratubular seminoma, intratubular embryonal carcinoma, and intratubular teratoma are much less common than GCNIS.

- These lesions can be differentiated from GCNIS as these lesions fill the lumen of the seminiferous tubule with tumor cells or necrosis rather than exist only against the basement membrane (Table 6.2).
- Intratubular seminoma will have an identical immunophenotype as GCNIS.
- Intratubular embryonal carcinoma will have weaker expression of PLAP, minimal expression of CD117/c-kit, and D2-40/podoplanin and will be positive using CD30.
- Germ cells with delayed maturation as can be seen in cryptorchid testes mimic GCNIS.
- These cells are also OCT3/4 positive but occur sprinkled throughout the seminiferous tubule.
- Tubules containing only Sertoli cells can mimic GCNIS.
- A tubule with GCNIS usually contains cells that appear less homogenous than a Sertoli-only tubule.
- Sertoli cells will show positivity for inhibin and WT1 and negativity for SALL4 and OCT3/4.

References: [29–32]

What Are the Histologic Features and Immunohistochemical Expression Pattern of Seminoma?

Seminoma is unencapsulated with a border that sometimes shows growth between tubules (Fig. 6.2a). The tumor can look nodular at low power with expansile sheets of cells separated by fibrous bands containing lymphocytes (Fig. 6.2b; Table 6.3). Cells are monotonous with cleared out to pale, eosinophilic cytoplasm (Fig. 6.2c). The cleared-out cytoplasm, attributable to glycogen, with the remaining nuclei gives rise to a "fried egg" appearance. Nonoverlapping cells and the empty cytoplasm yield a fine, sharp cell membrane, and a polygonal shape to cells. Nuclei have clumped chromatin and prominent nucleoli. Mitotic figures are frequent.

The immunoprofile of seminoma is (Table 6.4):

- Positive: SALL4, PLAP, CD117/c-kit, D2-40/podoplanin, and OCT3/4.
- Negative: AE1/3, CD30, glypican 3, AFP, GATA3, CK7, HCG, inhibin.
- Seminoma can mimic other germ cell tumor types and other lesions.

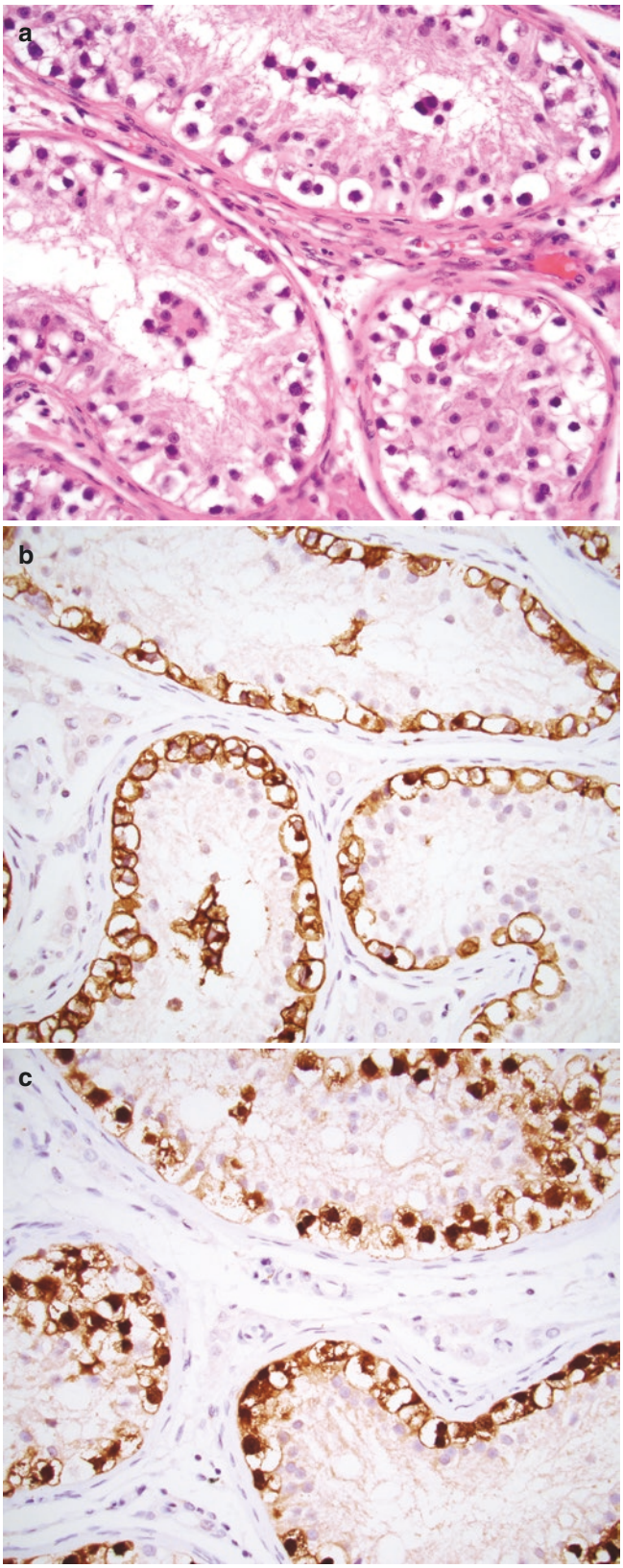

Fig. 6.1 GCNIS. (**a**) GCNIS displays atypical, vacuolated cells lined up against the basement membrane of the seminiferous tubule. (**b**) GCNIS expresses CD117/c-kit in a predominately membranous pattern. (**c**) GCNIS expresses strong, diffuse nuclear OCT3/4

- Pseudoglandular growth or poorly fixed specimens can mimic embryonal carcinoma.
- A microcystic growth patterns resembles yolk sac tumor (Fig. 6.2d).
- Seminoma can have abundant granulomatous inflammation, masking tumor cells, mimicking granulomatous orchitis.
- Nongerm cell tumors to be considered include diffuse large B-cell lymphoma (positive CD20/negative OCT3/4), particularly in an older man, and Sertoli cell tumor (positive inhibin/negative OCT3/4), both of which are readily differentiated from seminoma using immunohistochemistry.

References: [33–36]

What Are Syncytiotrophoblastic Cells in Seminoma and What Is the Clinical Significance of Their Presence?

Syncytiotrophoblastic cells are present in approximately 15% of seminomas. These are typically are seen in scattered clusters near capillaries. The cells are large, have multiple nuclei, and vary from ample cytoplasm to more abundant nuclei ("mulberry" type cells) (Fig. 6.3). These cells usually express HCG and keratin and the presence of these cells has been correlated with detectable increases in serum HCG.

If identified, these tumors can be diagnosed as "seminoma with syncytiotrophoblast cells" and should not be diagnosed as a choriocarcinoma component. Admixture with cytotrophoblasts required for a diagnosis of choriocarcinoma in contrast to seminoma with syncytiotrophoblast cells in which the cells are encountered intermixed with seminoma cells. Their presence does not change clinical management. There is minimal published on this phenomenon in the literature from the past 30 years. Other multinucleate cells, such as Langerhans type giant cells with peripheral nuclei and no expression of HCG or keratin, may be seen.

References: [35–38]

What Is the Significance of a High Mitotic Rate in Seminoma?

Seminoma with high mitotic rate (so called "anaplastic seminoma") has no known prognostic significance and does not impact management. It has been recommended that these diagnostic modifiers not be used to avoid confusion and inappropriate treatment.

References: [31, 39–41]

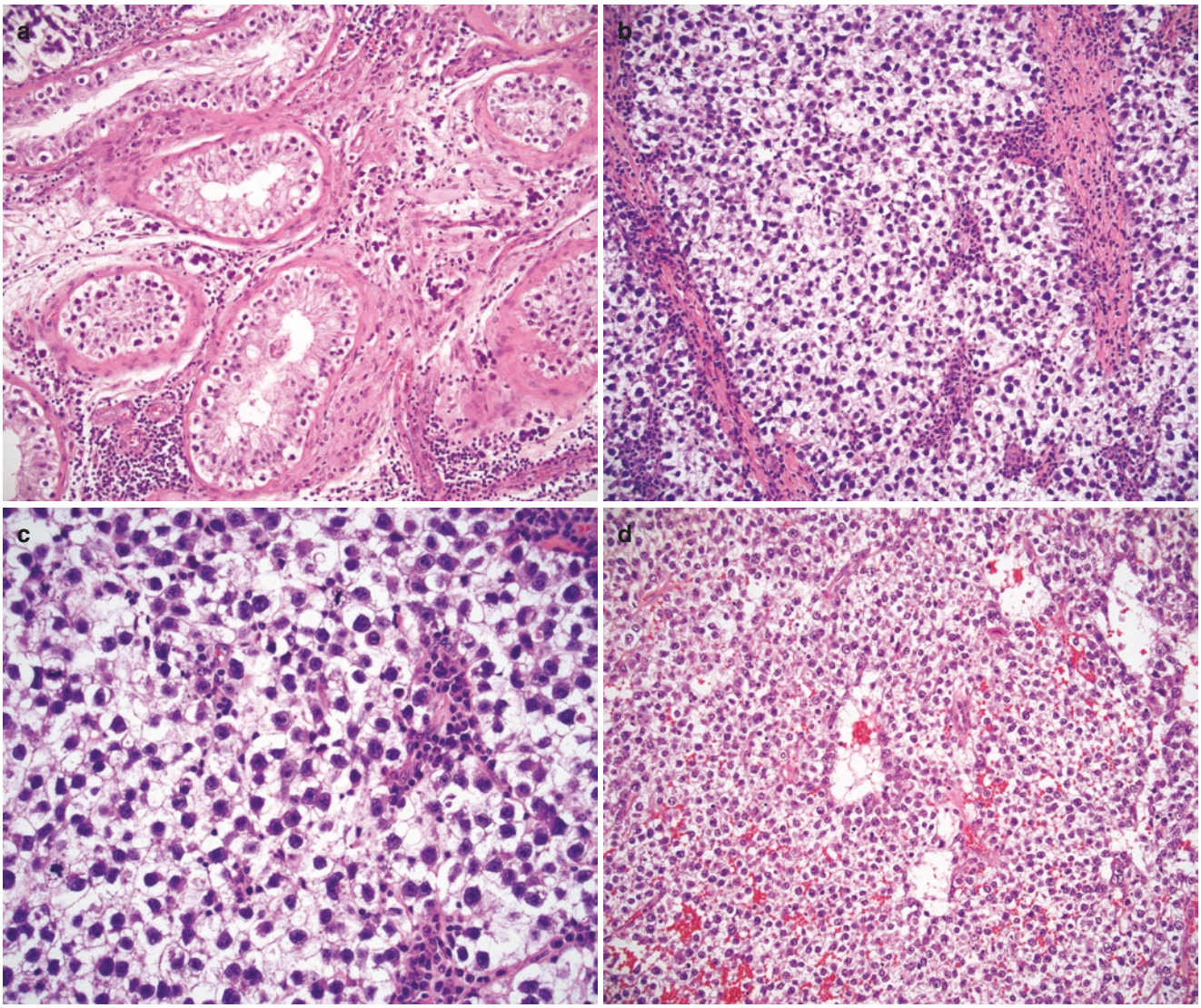

Fig. 6.2 Seminoma. (**a**) Seminoma with tumor infiltrating between tubules at the periphery of the tumor (intertubular growth). (**b**) Fibrous bands containing lymphocytes are characteristic of seminoma. (**c**) Seminoma is composed of sheets of distinctive, monotonous cells with prominent cell membranes and cleared-out cytoplasm. (**d**) Microcystic growth in seminoma can mimic yolk sac tumor

Table 6.3 Histologic features of germ cell tumor subtypes

	Architecture	Distinct cell borders/no cellular overlap	Cytology	Most important germ cells tumor mimics
Seminoma	Expansile nodules separated by fibrous bands containing lymphocytes	Yes	Monotonous cells with pale to cleared-out cytoplasm	Embryonal carcinoma, yolk sac tumor
Embryonal carcinoma	Sheet-like, glandular and papillary growth predominate	No	Pleomorphic, high-grade cells	Seminoma, yolk sac tumor
Yolk sac tumor	Microcystic/reticular pattern most common	No		Seminoma, embryonal carcinoma
Teratoma	Variable	Variable	Variable	Yolk sac tumor
Choriocarcinoma		No-syncytial cells Yes-mononucleate cells		Embryonal carcinoma

Table 6.4 Immunohistochemical expression of common germ cell tumor types

	Seminoma	Embryonal carcinoma	Yolk sac tumor	Choriocarcinoma	Teratoma
SALL4 (nuclear)	+	+	+	+	Variable
PLAP	+	+/weak	–	–	–
CD117/c-kit	+	–/weak	–	–	–
D2-40/podoplanin	+	–/weak	–	–	Variable
OCT3/4 (nuclear)	+	+	–	–	–
CD30	–	+	–	–	–
AE1/3	–/weak	+/weak	+	+	Variable
Glypican 3	–	–	+	+	Variable
AFP	–	–	+	+	Variable
GATA3 (nuclear)	–	–	+	+	Variable
CK7	–	–	–/focal	+	Variable
HCG	–	–	–	+	–
Inhibin	–	–	–	+ (syncytial cells)	–
WT1 (nuclear)	–	–	–	–	–
Calretinin	–	–	–	–	–

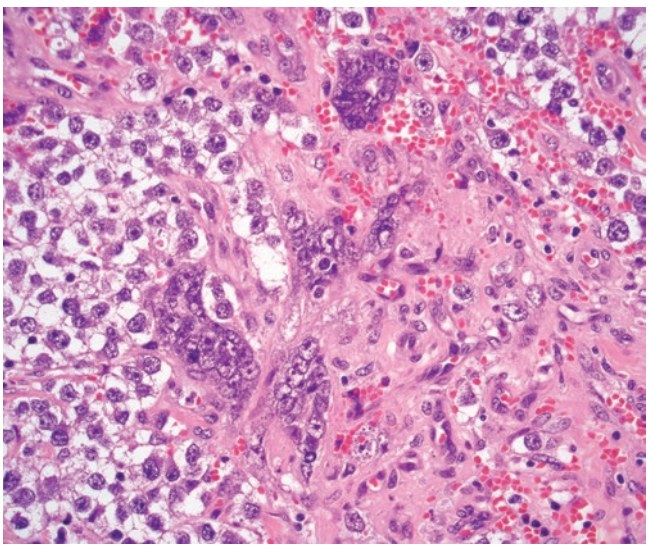

Fig. 6.3 Seminoma with syncytiotrophoblast cells. Multinucleated cells are clustered together

What Are the Histologic Features and Immunohistochemical Expression Pattern of Embryonal Carcinoma?

Embryonal carcinoma is a primitive, high-grade tumor. The most common growth pattern is diffuse, sheets of cells (55%), but numerus other growth patterns can be seen, and glandular (175) and papillary (11%) patterns are frequent (Fig. 6.4a–c; Table 6.3). Cells are large and overlapping with indistinct cell borders. There is a moderate amount of amphophilic cytoplasm. Nuclei are pleomorphic with prominent nucleoli and frequent mitotic figures present. Necrosis and hemorrhage are frequent. Lymphovascular invasion is often present.

The immunoprofile of embryonal carcinoma is (Table 6.4):

- Positive: SALL4, OCT3/4, CD30.
- Positive/weak: PLAP, AE1/3.
- Negative/weak: CD117/c-kit, D2-40/podoplanin.
- Negative: glypican 3, AFP, GATA3, CK7, HCG, inhibin.
- Embryonal carcinoma can mimic other germ cell tumor types and other lesions.
- Diffuse growth mimics poorly fixed seminoma, especially if admixed with lymphocytes (Fig. 6.4d).
- Degenerative areas and areas with hemorrhage mimics choriocarcinoma.
- Papillary and glandular patterns mimic yolk sac tumor and teratoma (Fig. 6.4b, c).
- In the metastatic setting, embryonal carcinoma is a mimicker of poorly differentiated carcinoma.

References: [33–36, 38, 42, 43]

What Are the Histologic Features and Immunohistochemical Expression Pattern of Yolk Sac Tumor?

Yolk sac tumor has a vast array of growth patterns in which multiple can coexist in the same tumor (Table 6.5).

The most common is microvesicular/reticular in which haphazard, varying-sized, anastomosing small cysts are present (Fig. 6.5a, b). The cysts are lined by cuboidal to flattened cells, which can appear lipoblast-like or signet ring. Hyaline globules and wispy myxoid material can be seen in the cyst spaces. Cells are blander than other types of germ cell tumors and mitotic figures, while present, are more difficult to appreciate.

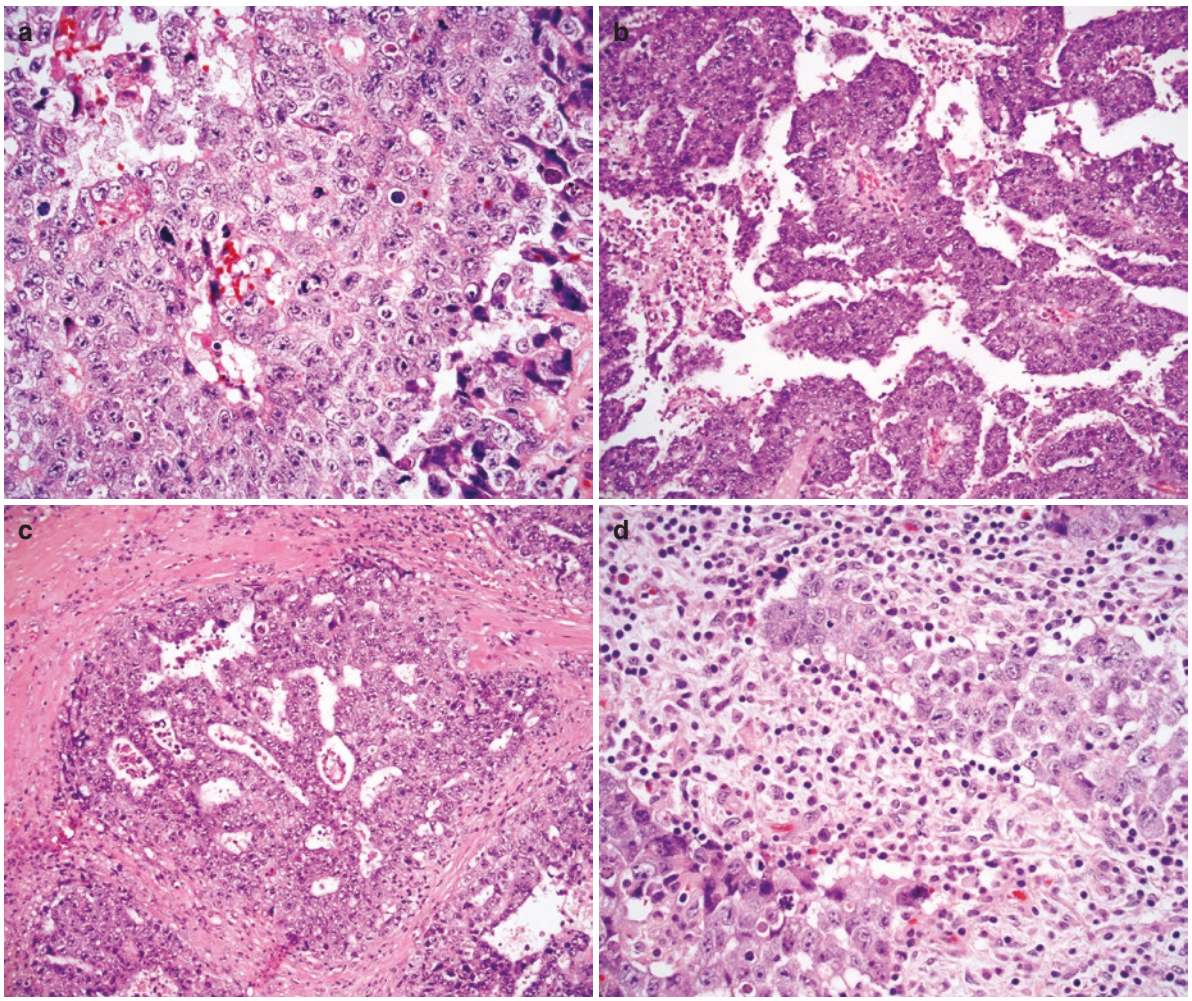

Fig. 6.4 Embryonal carcinoma. (**a**) Embryonal carcinoma usually has a sheet-like growth. Cells are crowded with amphophilic cytoplasm, macronucleoli, and frequent mitotic figures. (**b**) Papillary growth can minim yolk sac tumor. (**c**) Pseudoglandular or cystic growth can mimic yolk sac tumor. (**d**) Embryonal carcinoma admixed with lymphocytes mimics seminoma

Table 6.5 Growth patterns of yolk sac tumor

Yolk sac tumor growth patterns	Features
Microcystic/reticular	Most common
Myxomatous	Myxoid background
Macrocystic	Large cysts
Solid	Sheets of larger cells, mimicker of seminoma
Glandular/alveolar	Simple, complex, or secretory endometrial appearing; mimics adenocarcinoma and teratoma
Endodermal sinus/perivascular	Shiller-Duval bodies
Hepatoid	Recapitulates liver, including expression
Papillary	Thin fibrovascular cores or micropapillary clusters
Sarcomatoid/spindle cell	Mimics sarcoma or teratoma with somatic-type malignancy
Parietal	Intervening eosinophilic basement membrane
Polyvesicular vitelline	Prominent microcysts, classically pear shaped

The myxomatous pattern has similar morphology with more abundant myxoid stroma and cords or strands of cells throughout (Fig. 6.5c). Larger cysts are seen in the macrocystic pattern. The solid pattern has sheets of cells that are monotonous, have well-delineated cell membranes and a moderate amount of pale to cleared-out cytoplasm (Fig. 6.5d). Simple or anastomosing gland like structures can be seen in the glandular/alveolar pattern as can glands resembling secretory endometrium with supra- and subnuclear vacuolization (Fig. 6.5e). The endodermal sinus patter is uncommon and displays a central papillary core surrounded by cuboidal tumor cells (Shiller-Duval bodies) within a background of microcysts (Fig. 6.5f). The cells in the hepatoid pattern grow in nests and cords, have abundant eosinophilic cytoplasm, and express liver markers (Fig. 6.5g). Papillary pattern has thin fibrovascular cores or clumps of micropapillary tumor clusters lacking fibrovascular cores (Fig. 6.5h). Sarcomatoid or spindle cell growth has diffuse growth of somewhat bland, stellate cells. Recent research has shown that some high-

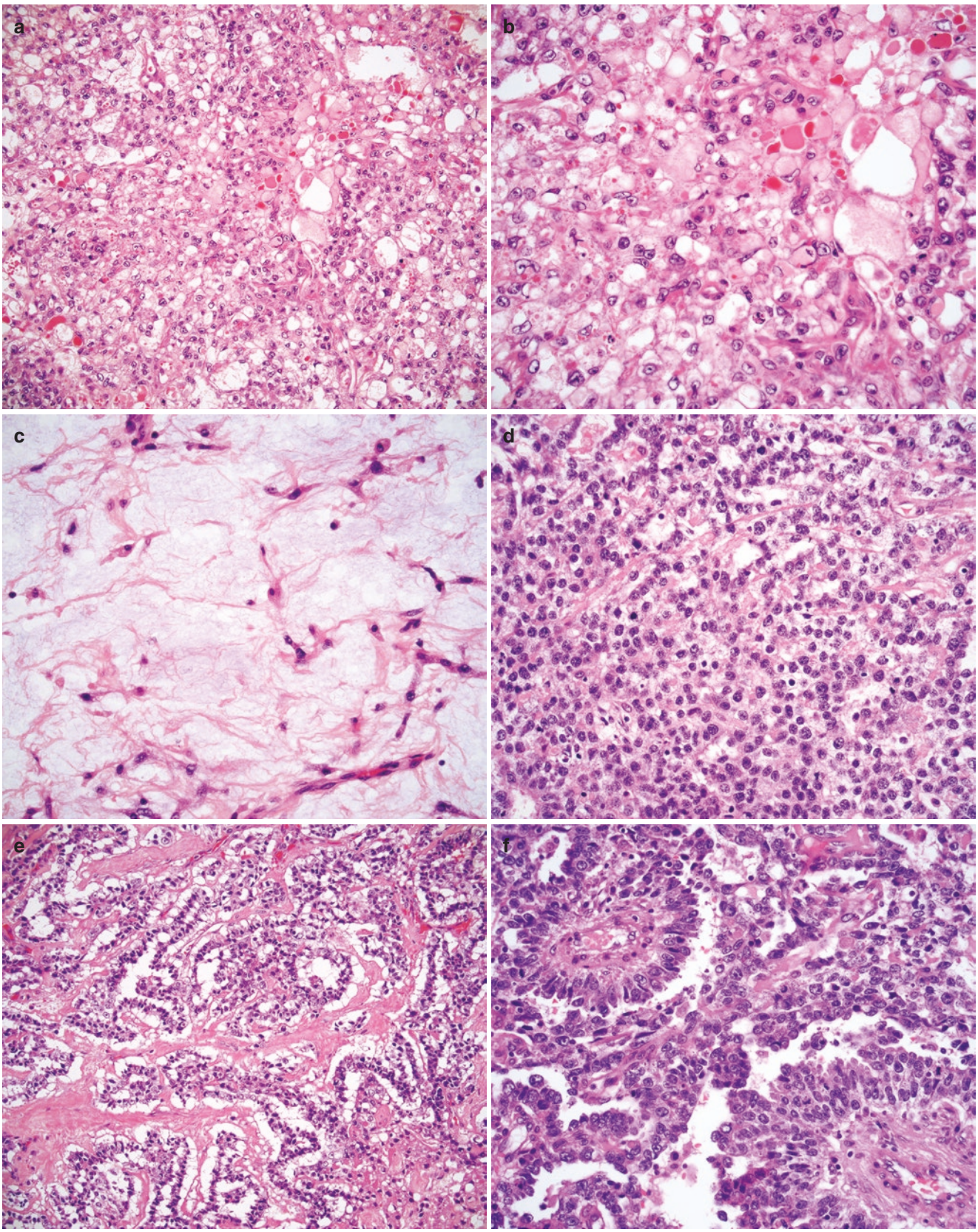

Fig. 6.5 Yolk sac tumor. (**a**) The microcystic/reticular pattern is most common. (**b**) Cells appear flattened and bland. Hyaline globules are seen. (**c**) The myomatous pattern is easily overlooked. (**d**) Solid growth mimics seminoma. (**e**) Glandular/alveolar has an appearance of adenocarcinoma. (**f**) The endodermal sinus pattern has Shiller-Duval bodies (upper left and lower right). (**g**) Hepatoid pattern. (**h**) Papillary pattern

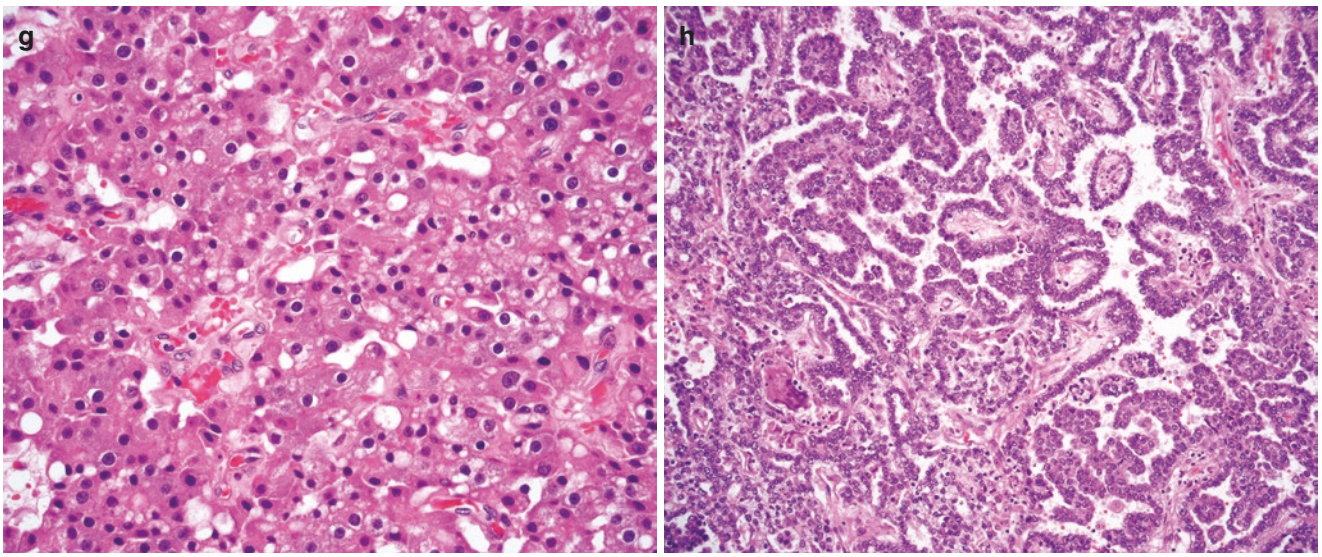

Fig. 6.5 (continued)

grade sarcomatoid tumor that were previously thought to be teratoma with somatic-type malignancy, especially in post-chemotherapy metastases, are actually high-grade sarcomatoid yolk sac tumor. The parietal pattern refers to tumor with eosinophilic clumps or bands of basement membrane material typically between areas with microvesicular/reticular growth. Polyvesicular vitelline pattern has microcysts lined by cuboidal to flattened cells in a hypocellular, edematous to densely cellular background. The microcysts range from pear shaped to irregular and anastomosing.

The immunoprofile of yolk sac tumor is as follows (Table 6.4):

- Positive: SALL4, AE1/3, glypican 3, AFP, GATA3.
- Focal/negative: CK7.
- Negative: PLAP, CD117/c-kit, D2-40/podoplanin, OCT3/4, CD30, HCG, inhibin.
- Yolk sac tumor can mimic other germ cell tumor types and other lesions (Table 6.3).
- Solid yolk sac tumor mimics seminoma (Fig. 6.5d).
- Sarcomatoid yolk sac mimics primary sarcoma and teratoma with somatic-type transformation.
- Glandular yolk sac tumor mimics adenocarcinoma and teratoma (Fig. 6.5e).

References: [17, 33–35, 42–45]

What Is Polyembryoma and How Should It Be Diagnosed in a Pathology Report?

Polyembryoma is the intimate co-mingling of embryonal carcinoma and yolk sac tumor to form structures that resemble the early presomite embryo (embryoid-bodies) (Fig. 6.6a, b).

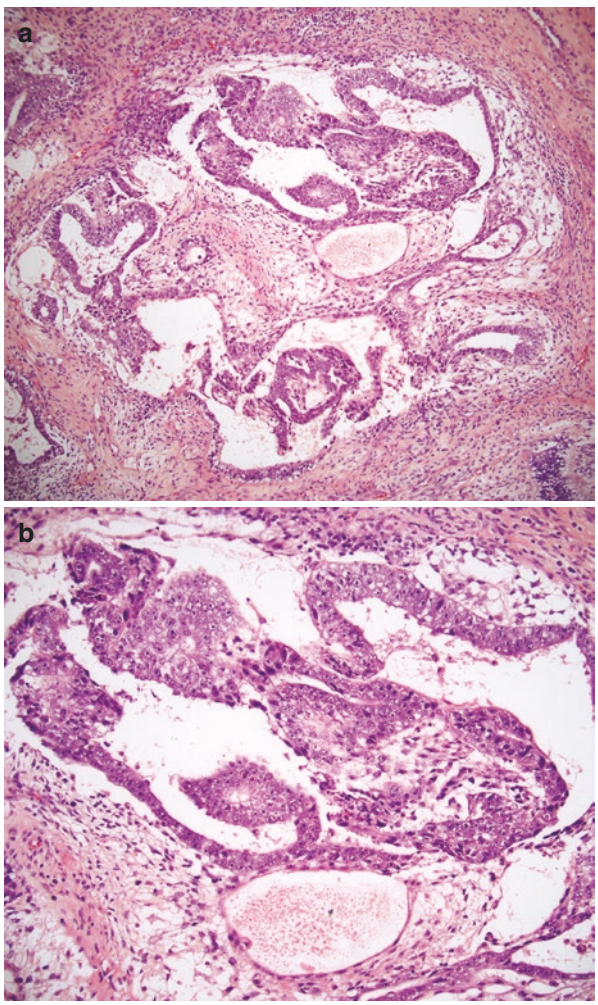

Fig. 6.6 Polyembryoma. (**a**) Numerous embryoid bodies. (**b**) Embryoid body. Basophilic cells are embryonal carcinoma and wispy cells are yolk sac tumor

- A cuplike shape is seen lined by cuboidal to columnar embryonal carcinoma cells.
- Cells within and around the cup lining are made of yolk sac tumor with reticular or myxomatous growth.
- Polyembryoma exists alongside other germ cell tumor types and therefore is a part of a mixed germ cell tumor.
- It is not necessary to mention polyembryoma growth in a pathology report but rather to recognize the structures in order to correctly identify and quantify each germ cell tumor type that is present.

References: [42, 46]

What Are the Histologic Features and Immunohistochemical Expression Pattern of Choriocarcinoma?

Choriocarcinoma is composed of syncytial cells, called syncytiotrophoblasts, and mononucleated trophoblasts (cytotrophoblasts and intermediate trophoblasts). These cells grow admixed and are usually associated with adjacent hemorrhage (Fig. 6.7a). Classically, the syncytiotrophoblasts grow as a cap overlying the mononucleated trophoblasts (Fig. 6.7b). Syncytiotrophoblasts are large cells with multiple pleomorphic, hyperchromatic nuclei. They have abundant, dense, eosinophilic cytoplasm and indistinct cell borders. Mononucleated trophoblasts are medium sized with pale eosinophilic cytoplasm with distinct cell borders (Fig. 6.7c).

The immunoprofile of choriocarcinoma is shown in Table 6.4.

- Positive: SALL4, AE1/3, glypican 3, AFP, GATA3, CK7, HCG, inhibin (syncytiotrophoblasts), p63 (cytotrophoblasts).
- Negative: PLAP, CD117/c-kit, D2-40/podoplanin, OCT3/4, CD30.
- Choriocarcinoma can mimic other germ cell tumor types and other lesions (Table 6.3).
- Small foci admixed with other tumor types can mimic seminoma with syncytiotrophoblasts or embryonal carcinoma with syncytiotrophoblasts.
- As the syncytial cells are large and pleomorphic, small foci can mimic embryonal carcinoma.
- Post chemotherapy, it can be difficult to discern choriocarcinoma from other types of trophoblastic tumors including cystic trophoblastic tumor, epithelial trophoblastic tumor and placental site trophoblastic tumor.

References: [4, 22, 46, 47]

What Are the Histologic Features and Immunohistochemical Expression Pattern of Teratoma?

Teratoma can form any mature or fetal cell type. Common tissue types include spindled mesenchymal stroma, squamous epithelium, respiratory epithelium, intestinal epithelium, cartilage (often with cytologic atypia), and immature neural elements (Fig. 6.8a, b). Spindled smooth muscle or fibroblastic areas of teratoma are easily overlooked but should be included in the diagnosis and quantification of teratoma.

The diagnosis of teratoma is almost always made by recognition of multiple tissue types and the expression pattern is highly variable, depending on the tissue that is recapitulated. SALL4 expression is inconsistent and cannot be relied upon to rule out the presence of teratoma in limited biopsy specimens.

The immunoprofile of choriocarcinoma is as follows (Table 6.4):

- Variable: SALL4, AE1/3, glypican 3, AFP, GATA3, CK7, D2-40/podoplanin.
- Negative: PLAP, CD117/c-kit, OCT3/4, CD30, HCG.

Reference: [33]

Does Immature Teratoma Need to Be Diagnosed Separately from Mature Teratoma?

Both immature and mature teratoma elements are malignant in a postpubertal tumor (Fig. 6.8b). There is no clinical relevance to the presence of immature teratoma in a postpubertal tumor, and therefore only the presence and amount of teratoma, inclusive of mature and immature teratoma, need to be included in a pathology report.

Reference: [33]

How Is Teratoma with Somatic-Type Malignancy Diagnosed?

Teratoma with somatic-type malignancy is defined as overgrowth of one teratoma element occupying a 4×-magnification field or 0.5 cm. It is most frequent in metastases and has a corresponding poor prognosis as the patients usually have a relapse. Presence in a primary tumor may not yield a worse prognosis. Teratoma with somatic malignancy must be differentiated from sarcomatoid yolk sac tumor or glandular

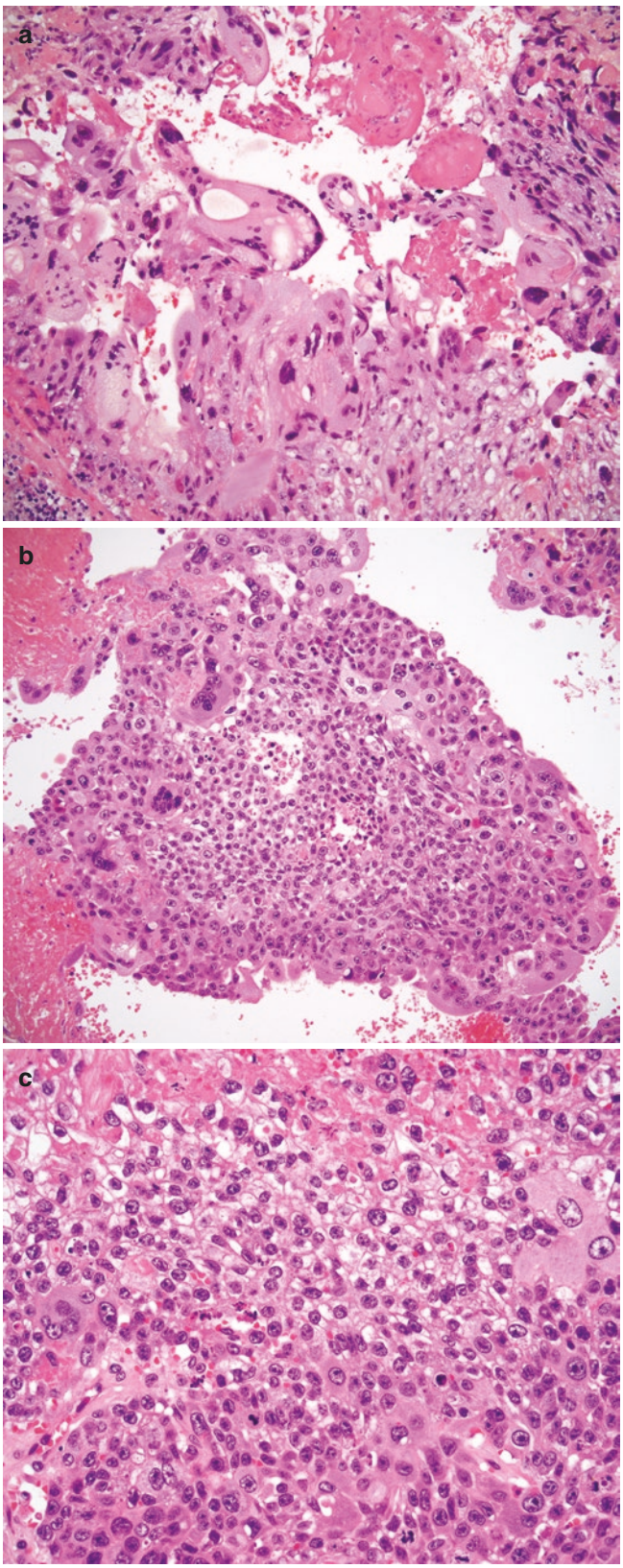

Fig. 6.7 Choriocarcinoma. (**a**) Syncytiotrophoblasts predominate with associated hemorrhage and peripheral mononucleated trophoblasts. (**b**) Characteristic capping of the syncytiotrophoblasts over the trophoblasts is more apparent in areas with greater numbers of mononucleated cells. (**c**) The solid growth of mononucleated trophoblasts mimics seminoma and embryonal carcinoma

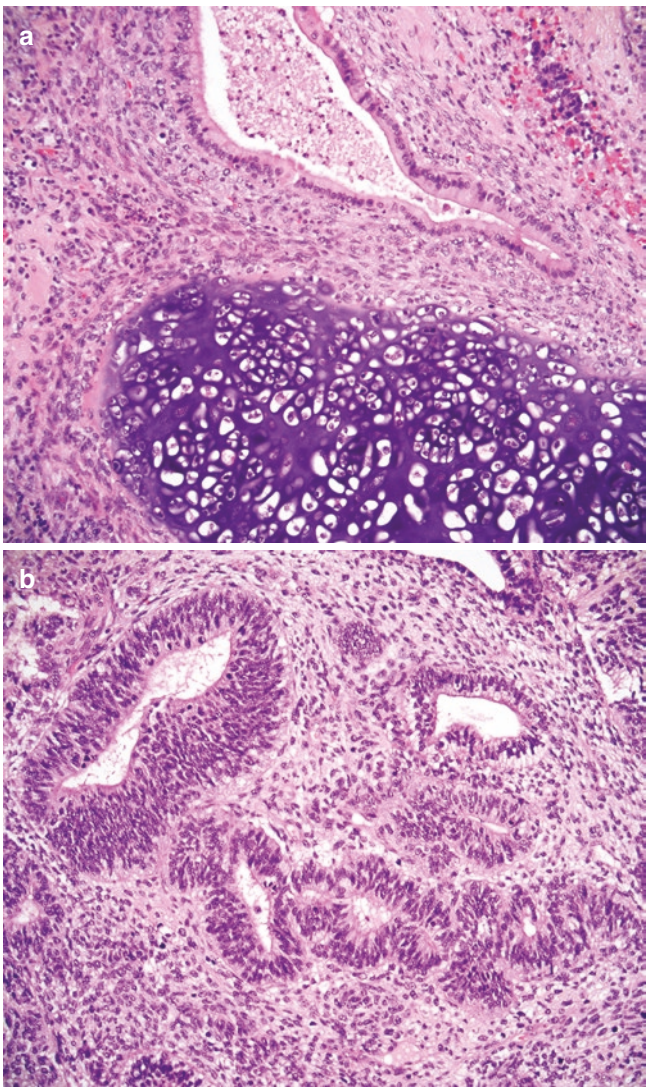

Fig. 6.8 Teratoma. (**a**) Cartilage, glandular epithelium and spindled mesenchymals cells. Spindled cells are easily overlooked but should be included in the diagnosis and quantification of teratoma. (**b**) Immature neural elements. This is included in teratoma as there is no distinction between immature and mature teratoma made in postpubertal testicular germ cell tumors

yolk sac tumor, frequent mimickers in postchemotherapy metastases.

Teratoma with somatic-type malignancy can mimic other germ cell tumor types and other lesions.

- Teratoma with somatic sarcoma can mimic sarcomatoid yolk sac tumor.
- Teratoma with somatic adenocarcinoma can mimic glandular yolk sac tumor.
- Teratoma with somatic squamous cell carcinoma can mimic choriocarcinoma and other nonchoriocarcinomatous germ cell tumor types.

- Metastasis from nongerm cell tumor such as primary sarcoma, adenocarcinoma, and squamous cell carcinoma must be excluded in metastases.

References: [17, 45, 48–50]

What Are the Most Common Forms of Teratoma with Somatic-Type Malignancy?

Types of somatic type malignancy vary in prevalence (Table 6.6). The majority are sarcoma (63%). The presence of sarcoma may indicate a worse prognosis than other types.

The most common types in order of decreasing frequency are as follows:

- Rhabdomyosarcoma (35%) (Fig. 6.9a, b)
- Sarcoma, not otherwise specified (24%) (Fig. 6.9c)
- Adenocarcinoma
- Primitive neuroectodermal tumor (lacks t(11;22) translocation, medulloepithelioma appearance) (Fig. 6.9d)
- Neuroglial tumor (lacks consistent results with *ATRX*, *IDH*, *BRAF*) (Fig. 6.9e)
- Squamous cell carcinoma

References: [48–53]

How Can Seminoma Be Differentiated from Embryonal Carcinoma?

Both seminoma and embryonal carcinoma can have solid growth. Seminoma has fibrous septae admixed with lymphocytes that is not present in embryonal carcinoma. Seminoma is composed of uniform cells while embryonal carcinoma is more pleomorphic. Seminoma cells are not overlapping while cells are more crowded and cell borders are less distinct in embryonal carcinoma. The cytoplasm in seminoma is usually much paler than is seen in embryonal carcinoma.

Table 6.6 Most common types of teratoma with somatic-type malignancy

Somatic type	Features
Rhabdomyosarcoma (35%)	
Sarcoma, not otherwise specified (24%)	Must exclude sarcomatoid yolk sac tumor
Adenocarcinoma	Must exclude glandular yolk sac tumor
Primitive neuroectodermal tumor	Lacks t(11;22) translocation, medulloepithelioma appearance
Neuroglial tumor	Lacks consistent results with *ATRX*, *IDH*, *BRAF*
Squamous cell carcinoma	Must exclude cystic trophoblastic tumor

Seminoma expresses CD117/c-kit and D2-40 while embryonal carcinoma is positive for CD30 (Fig. 6.10a, b). Both can express PLAP, but reactivity is stronger in seminoma. Adjacent GCNIS can serve as an excellent internal control for staining that is consistent with seminoma.

References: [34, 35]

How Can Seminoma Be Differentiated from Yolk Sac Tumor?

Both seminoma and yolk sac tumor can have solid or microcystic growth. Yolk sac tumor lacks fibrous septae containing lymphocytes as is seen in seminoma. Seminoma nuclei are larger and more uniform. Microcysts in yolk sac tumor have well-defined lumens dispersed haphazardly. The cells lining the microcysts are flattened whereas in microcystic seminoma the cells remain polygonal and the cysts form in areas that appear discohesive. Cells in solid yolk sac lack prominent cell borders that are characteristic of seminoma.

Seminoma expresses PLAP, CD117/c-kit, D2-40 and OCT3/4, while yolk sac tumor is positive using AE1/3, glypican 3, AFP, and GATA3.

References: [34, 35]

How Can Embryonal Carcinoma Be Differentiated from Yolk Sac Tumor?

Glandular and papillary structures can be seen in both embryonal carcinoma and yolk sac tumor. The cells of embryonal carcinoma are larger and are infrequently flattened compared to yolk sac tumor. The cytoplasm of embryonal carcinoma is denser and more basophilic and the nuclei are larger and have increased pleomorphism. Mitoses are easier to identify in embryonal carcinoma.

Embryonal carcinoma expresses OCT3/4 and CD30 while yolk sac tumor is positive using glypican 3 and AFP (Fig. 6.11a–c).

References: [34, 35]

How Can Choriocarcinoma Be Differentiated from Other Common Types of Germ Cell Tumor?

Choriocarcinoma is easily overlooked as it grows in conjunction with other tumor types often as minute foci and is further obscured by the association with hemorrhage (Fig. 6.12a–e). A key finding in addition to hemorrhage is the large syncytiotrophoblast with indistinct cell borders capping mononucleated cytotrophoblasts. Mononucleated

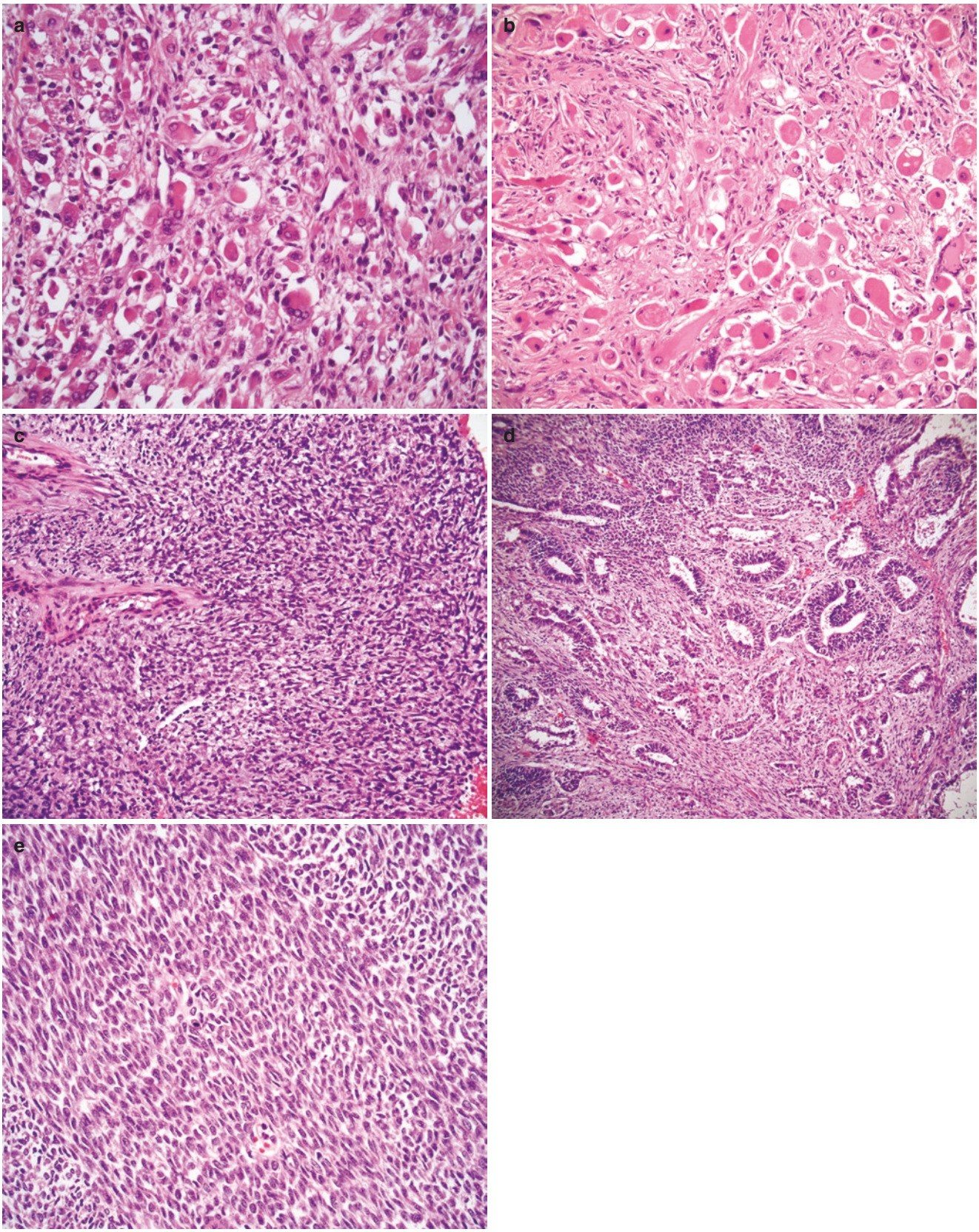

Fig. 6.9 Teratoma with somatic-type malignancy. (**a**) Rhabdomyosarcoma within a testicle. This is the most common somatic-type malignancy. (**b**) Rhabdomyosarcoma in a lung metastasis. Somatic-type malignancy is more frequent in metastases than primary tumors. (**c**) Sarcoma not otherwise specified in a mediastinal metastasis. (**d**) Primitive neuroectodermal tumor within a testicle. Primitive neural elements occupied over 2 cm. (**e**) Spindle cell malignancy with neural differentiation (NGFR positive) in a retroperitoneal metastasis

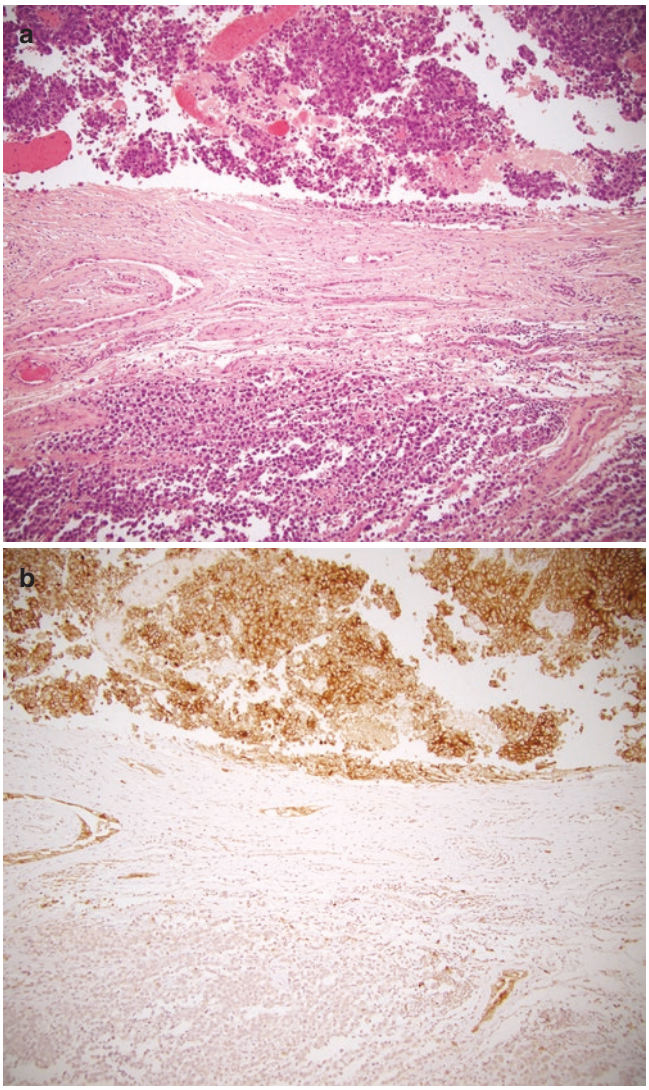

Fig. 6.10 Seminoma and embryonal carcinoma. (**a**) Solid growth and poor tissue preservation makes differentiating seminoma (bottom) from embryonal carcinoma (top) difficult. (**b**) CD30 is positive in embryonal carcinoma and negative in seminoma

cytotrophoblasts can mimic embryonal carcinoma and seminoma. Compared to embryonal carcinoma, mononucleated cytotrophoblasts have paler cytoplasm and have prominent cell membranes. Compared to seminoma, mononucleated cytotrophoblasts have irregular nuclear contours while seminoma nuclear contours are smooth.

Choriocarcinoma expresses GATA3, CK7, HCG, inhibin (syncytiotrophoblasts) and p63 (cytotrophoblasts) while seminoma expresses PLAP, CD117/c-kit, D2-40/podoplanin, and OCT3/4 and embryonal carcinoma has robust reactivity for as OCT3/4 and CD30 (Fig. 6.12a–e).

References: [34, 35]

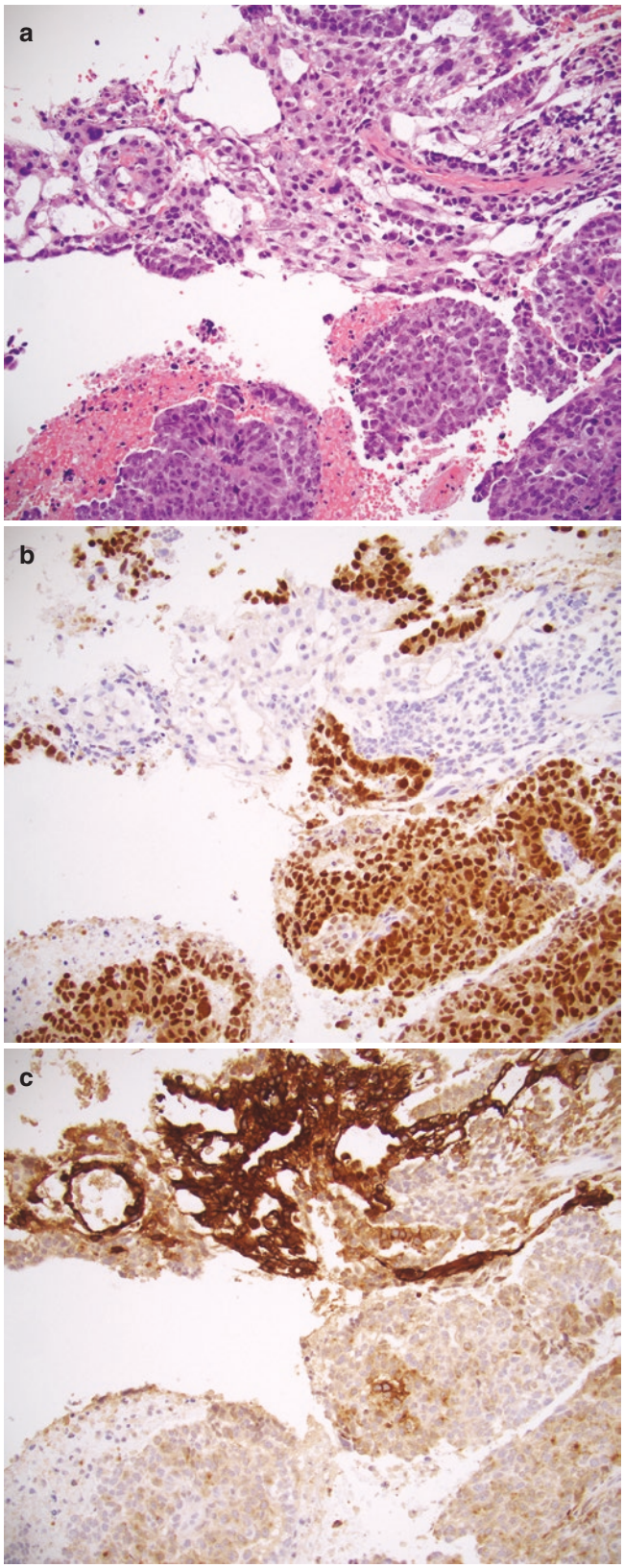

Fig. 6.11 Embryonal carcinoma and yolk sac tumor. (**a**) In this brain metastasis minute amounts of fragmented tumor make diagnosing the embryonal carcinoma (bottom) and yolk sac tumor (top) difficult. (**b**) OCT3/4 is positive in embryonal carcinoma and negative in yolk sac tumor. (**c**) Glypican 3 is positive yolk sac tumor and weak in embryonal carcinoma

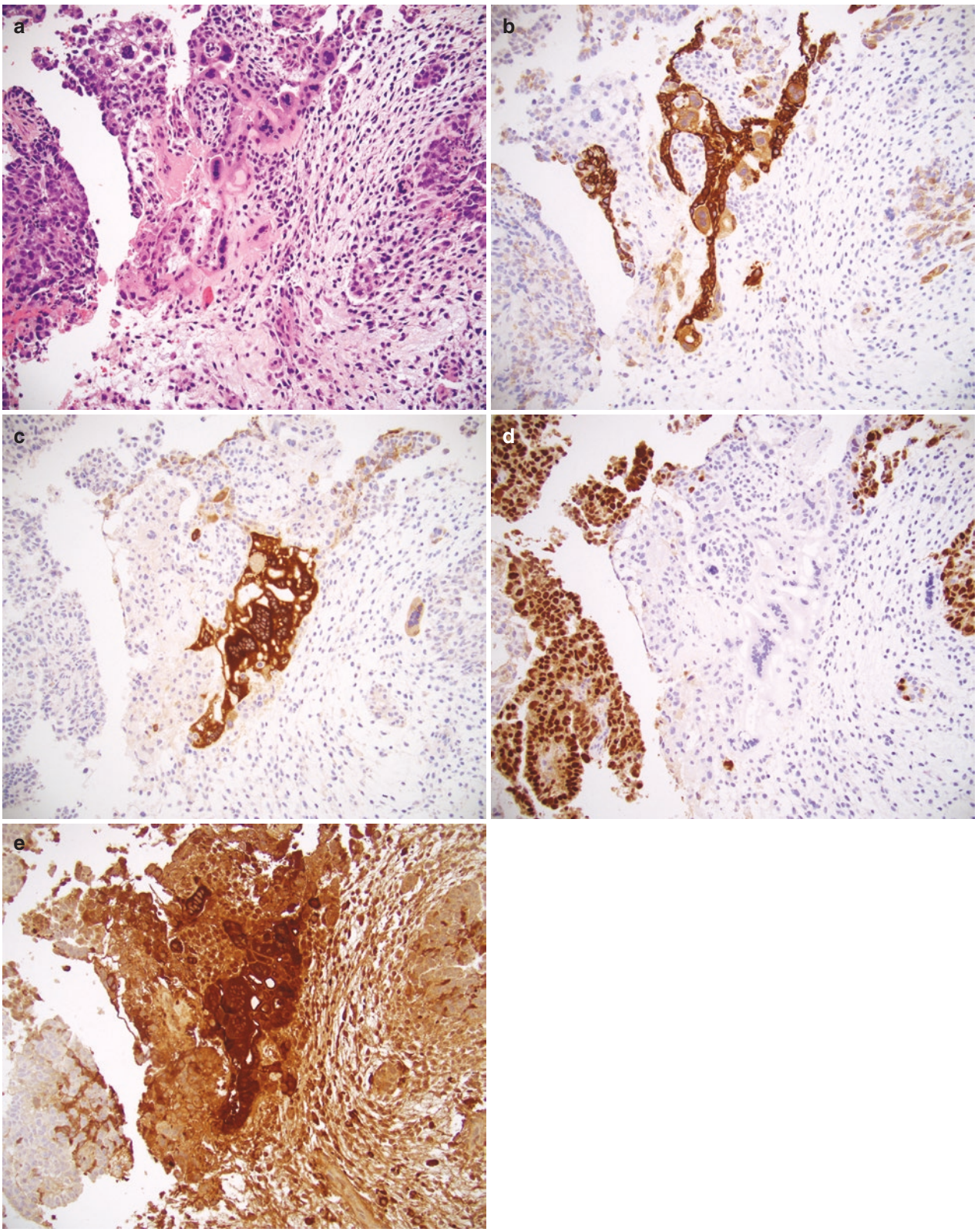

Fig. 6.12 Choriocarcinoma admixed with embryonal carcinoma and teratoma. (**a**) Minute amounts pf choriocarcinoma (center, predominately syncytiotrophoblasts), in a background of teratoma (spindle cells) and embryonal carcinoma (left and far right). (**b**) CK7 os positive in choriocarcinoma and weak to negative in embryonal carcinoma and the spindle cell component of teratoma. (**c**) Inhibin is positive in syncytiotrophoblasts of choriocarcinoma and is negative in embryonal carcinoma and the spindle cell component of teratoma. (**d**) OCT3/4 is positive in embryonal carcinoma and negative in choriocarcinoma and teratoma. (**e**) HCG is positive in choriocarcinoma but due to bleed artifact is a subpar marker

What Are the Histologic Features of Uncommon Placental Subtypes of Germ Cell Tumor, Placental Site Trophoblastic Tumor, Epithelioid Trophoblastic Tumor, and Cystic Trophoblastic Tumor?

Placental site trophoblastic tumor, epithelioid trophoblastic tumor, and cystic trophoblastic tumor are nonchoriocarcinoma gestational trophoblastic tumors that can occur in testicular germ cell tumors. Cystic trophoblastic tumor is usually found in post-chemotherapy retroperitoneal lymph node dissections and has the same prognosis and management as residual tumor composed only of teratoma. Placental site trophoblastic tumor and epithelioid trophoblastic tumor occur in both the untreated, primary setting as well as in distant, late metastases.

Placental site trophoblastic tumor is composed of discohesive sheets of large, mononucleated trophoblasts with abundant eosinophilic cytoplasm, very large pleomorphic nuclei, prominent nucleoli, numerous mitoses, apoptotic figures, and vascular invasion.

Epithelioid trophoblastic tumor of cohesive sheets of large, squamoid cells with well-defined cell membranes, abundant, dense, eosinophilic cytoplasm, intracytoplasmic vacuoles containing debris, pleomorphic nuclei with prominent nucleoli, mitoses, and occasional multinucleation (Fig. 6.13).

Cystic trophoblastic tumor grows in conjunction with teratoma and always has a cystic growth. Large irregular-shaped cysts are lined one to multiple layers of squamoid cells (Fig. 6.14a, b). Cells are mostly mononucleate with occasional multinucleation seen. Cells can be vacuolated with eosinophilic debris in the vacuoles. Nuclei are hyperchromic and often appear smudged or degenerative. Mitoses are not identified. As cystic trophoblastic tumor is managed similar to teratoma, it is imperative not to mistaken it for a squamous cell carcinoma somatic malignancy within teratoma.

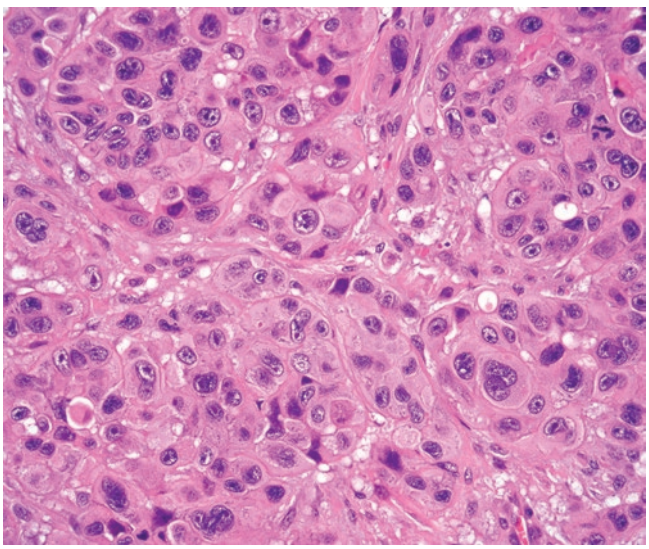

Fig. 6.13 Epithelioid trophoblastic tumor (chest metastasis). Sheets of squamoid cells are seen

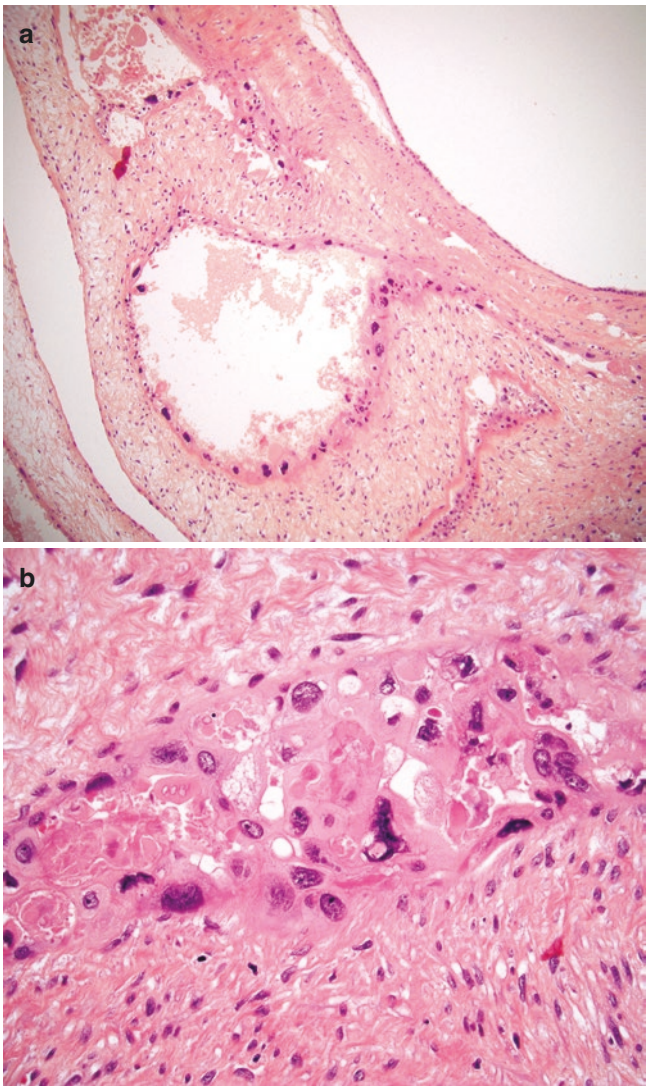

Fig. 6.14 Cystic trophoblastic tumor (postchemotherapy retroperitoneal lymph node mass in which teratoma was also present). (**a**) Variable-sized cysts are present lined by hobnailed to flattened squamoid cells. (**b**) Nuclei are smudgy, degenerative, and occasionally multinucleated

References: [30, 31, 53–55]

What Is the Expression Profile of Placental Site Trophoblastic Tumor, Epithelioid Trophoblastic Tumor and Cystic Trophoblastic Tumor?

The immunoprofile of testicular nonchoriocarcinoma gestational trophoblastic tumors is not well studied and shows expression overlap.

Placental site trophoblastic tumor expresses the following:

- Positive: HCG, GATA3, human placental lactogen (HPL).
- Negative: PLAP, p63.

Epithelioid trophoblastic tumor expresses the following:

- Positive: PLAP, CK7, inhibin, GATA3, p63.
- Variable HCG.
- Negative: HPL.

Cystic trophoblastic tumor expresses the following:

- Positive: glypican 3, GATA3, inhibin (focal).
- Variable: HCG, p63.
- Negative: HPL.

References: [30, 47, 53, 54]

What Is a Regressed Germ Cell Tumor and What Are the Characteristic Findings?

Testicular germ cell tumors can present with spontaneous complete or partial regression of the primary tumor. Patients most commonly present with a retroperitoneal metastasis. There is no apparent difference in prognosis between complete and partial regression. Currently, there is no data comparing the prognosis of regressed versus nonregressed testicular germ cell tumors.

Within the testicle, a grossly identifiable scar is seen (Fig. 6.15a). Adjacent to a fibrotic scar with admixed lymphoplasmacytic inflammation, seminiferous tubules are atrophic and have peritubular fibrosis (Fig. 6.15b, c). Half of cases contain GCNIS (Fig. 6.15d). Large coarse calcifications are less common but if an intratubular pattern is seen, this is consistent with tumoral regression. Pure seminoma (40%) is the most common tumor type identified within the testicle in tumors with incomplete regression.

References: [56, 57]

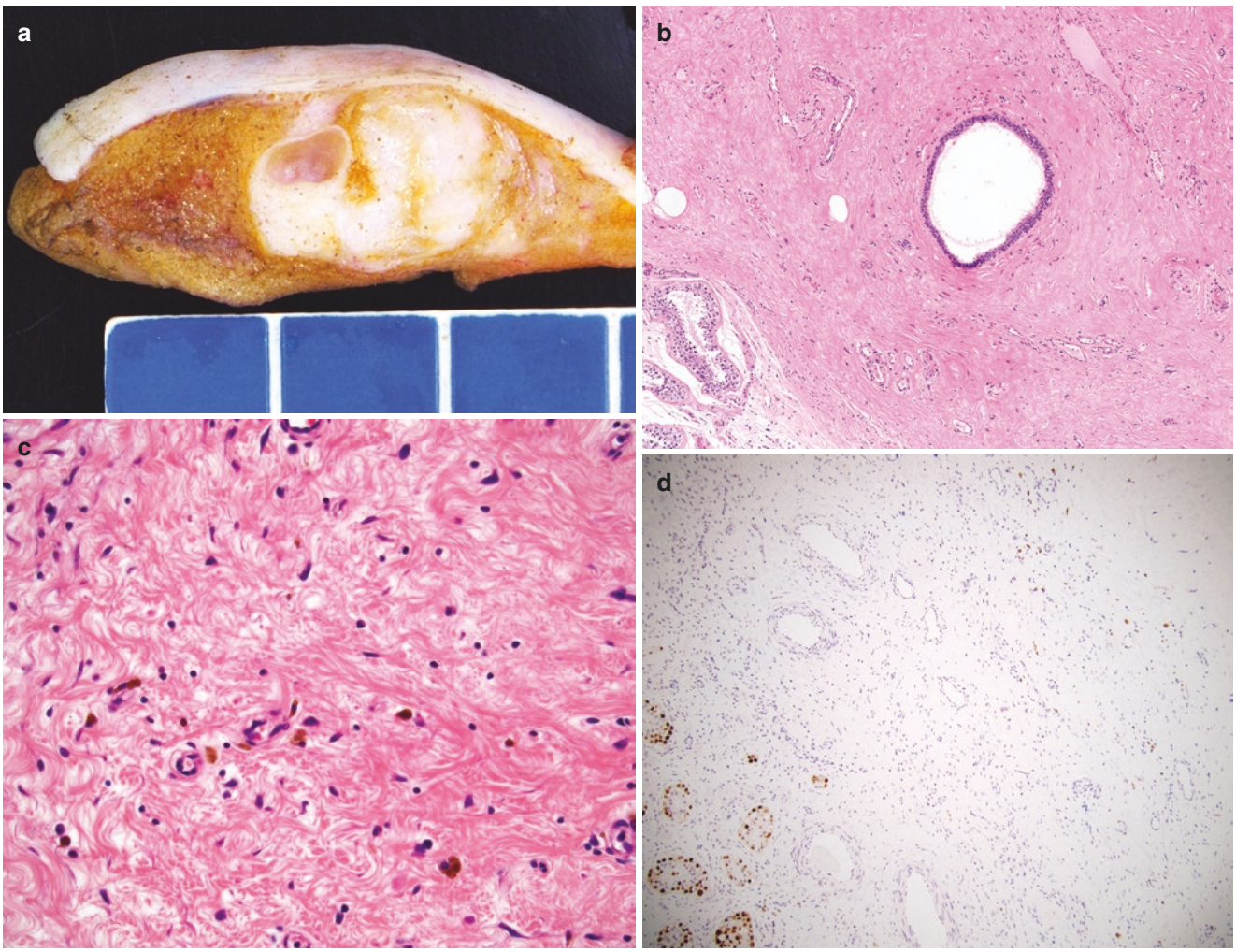

Fig. 6.15 Regressed germ cell tumor with minimal viable teratoma. (**a**) Grossly, a white scar is seen. (**b**) Teratoma (cyst) is seen within a well-demarcated scar. (**c**) Most of the lesion is fibrotic, paucicellular, with hemosiderin, small vessels, and scattered lymphocytes. (**d**) OCT3/4 highlights GCNIS in the tubules adjacent to the scar

What Are Post-chemotherapy Findings of a Germ Cell Tumor and how Is This Different Than a Regressed Germ Cell Tumor?

Chemotherapeutic changes are seen most frequently in retroperitoneal lymph node dissections or in other distant metastases but can be given neoadjuvantly prior to orchiectomy. Pseudocysts filled with necrosis and histiocytic inflammation are the most common findings, which are not seen in regressed tumors (Fig. 6.16). Ghosts of tumor cells can often be seen. Fibrotic scars are not present. Residual teratoma can display an increased degree of atypia and this does not have prognostic significance.

References: [43, 58]

What Are the Most Common Histologic Mimics Misdiagnosed as Testicular Germ Cell Tumors?

The following are critical nongerm cell lesions that mimic germ cell tumors (Table 6.7).

Sertoli cell tumor versus seminoma:

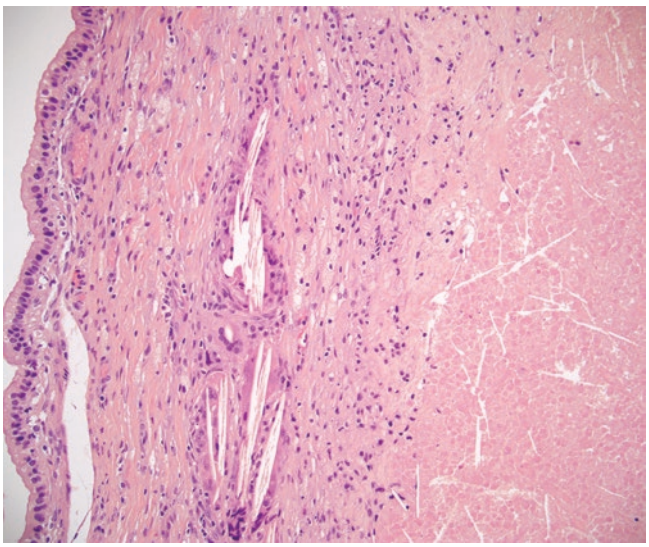

Fig. 6.16 Post-chemotherapy lung metastasis with residual teratoma (far left), histocytes, and necrosis containing ghost cells of nonviable tumor (right)

- Both have sheet-like growth and can have pale cytoplasm.
- The nuclei of Sertoli tumor are blander and mitotic rate is much lower and GCNIS will not be present.
- Sertoli cell tumor is negative for PLAP and OCT 3/4 and is usually positive for inhibin.

Granulomatous orchitis versus seminoma:

- Both can have granulomatous inflammation.
- GCNIS will not be present in granulomatous orchitis.
- OCT3/4 is negative in granulomatous orchitis.

Spermatocytic tumor versus seminoma:

- Both have sheet-like growth.
- Spermatocytic tumor lacks fibrous septae with lymphocytes, lacks GCNIS, have variable cell size, and patients are a mean age of 55, older that seminoma.
- Spermatocytic tumor is negative for PLAP and OCT3/4.

Lymphoma versus embryonal carcinoma or seminoma:

- All can have sheet-like growth of aggressive appearing cells.
- Lymphoma has rounded, more uniform nuclei and more dispersed chromatin and lacks GCNIS. Patients are also typically older.
- Lymphoma is usually positive for CD45 and negative for SALL4 and OCT3/4.

Dermoid cyst versus teratoma:

- Both have squamous cysts.
- Dermoid cysts have adjacent lipogranulomatous reaction and retained spermatogenesis but lack cytologic atypia or GCNIS.

Scar versus regressed germ cell tumor:

- Most importantly, a scar not derived from a regressed germ cell tumor will not have evidence of metastases.
- Additionally, there will not be residual viable tumor identified and GCNIS will be absent.

Table 6.7 Immunohistochemical expression of nonchoriocarcinoma gestational trophoblastic tumors

	PLAP	Glypican 3	CK7	HCG	GATA3	inhibin	p63	HPL
Placental site trophoblastic tumor	–			+	+		–	+
Epithelioid trophoblastic tumor	+		+	Variable	+	+	+	–
Cystic trophoblastic tumor		+		Variable	+	+ (focal)	Variable	–

Table 6.8 Common mimics of testicular germ cell tumors

Nongerm cell tumor mimicked	Germ cell tumor mimicked
Sertoli cell tumor	Seminoma
Granulomatous orchitis	Seminoma
Spermatocytic tumor	Seminoma
Lymphoma	Embryonal carcinoma or seminoma
Dermoid cyst	Teratoma
Carcinoma	Embryonal carcinoma or choriocarcinoma

Carcinoma of nongerm cell origin versus embryonal carcinoma or choriocarcinoma:

- Outside of the testicle, carcinoma is a critical consideration, especially years after treatment of a germ cell tumor.
- Carcinoma will be negative for SALL4, OCT3/4, and HCG and will express site specific markers (Table 6.8).

References: [34, 35, 46]

Which Immunostains Can Help Identify a Testicular Germ Cell Tumor in the Metastatic Setting?

SALL4 has reliable nuclear expression in all germ cell tumor types with the exception of variable reactivity in teratoma (Fig. 6.17a, b). It is thus an ideal marker in the metastatic setting. The inclusion of OCT3/4 adds a marker with strong nuclear expression of seminoma and embryonal carcinoma. Further immunostains can be used based on the histologic impression.

Reference: [59]

Which Florescent In Situ Hybridization (FISH) Test Can Help Identify a Testicular Germ Cell Tumor in the Metastatic Setting?

Testicular germ cell tumor has a high frequency of chromosomal 12p abnormalities including i(12p) and copy number increase of 12p. FISH testing for 12p can identify these aberrations corroborating the diagnosis of a germ cell tumor. Specifically, in the metastatic setting it sometimes difficult to determine if a tumor is a de novo sarcoma or a somatic-type malignancy derived from teratoma. Somatic-type malignancies demonstrated abnormalities for 12p in 78% of cases that were tested.

References: [60, 61]

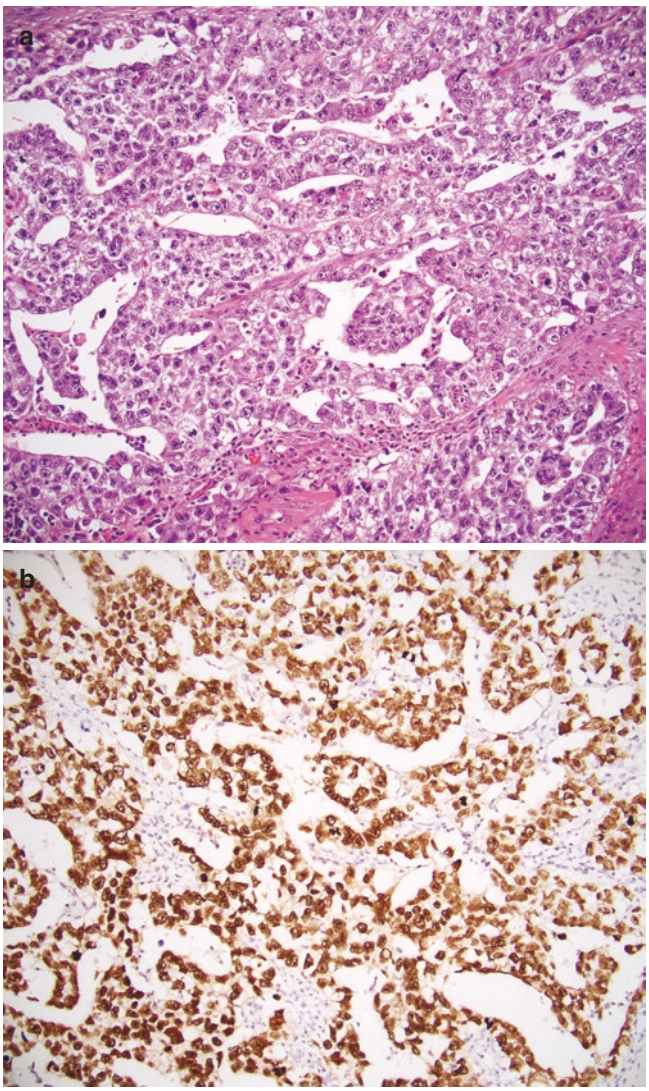

Fig. 6.17 Embryonal carcinoma with SAPPl4 expression. (**a**) Embryonal carcinoma with pseudoglandular spaces. (**b**) SALL4, with strong nuclear expression confirms a germ cell origin of the tumor and can be helpful in the metastatic setting

How Is the PT Classification for Seminoma Different Than a Mixed Germ Cell Tumor?

For tumors confined to the testis and that lack lymphovascular invasion, seminoma has a dichotomized pT1 category based on size (pT1a <3 cm, pT1b ≥3 cm) based on the AJCC Cancer Staging Manual eighth edition, while mixed germ cell tumors are not dichotomized (pT1) (Table 6.9). The rationale for this split is that size is a prognostic parameter of pure seminoma (Table 6.10). Because size is a prognostic parameter, it is imperative that multinodular tumors be measured in largest aggregate single dimension and that this is used for the pT category rather than listing the sizes of indi-

Table 6.9 pT category based on AJCC Cancer Staging Manual 8th edition

Primary tumor (pT)	
pTX	Cannot be assessed
pT0	No evidence of primary tumor
pTis	Germ cell neoplasia in situ
pT1	Germ cell tumor other than pure seminoma confined to testis/tunica albuginea/rete and no lymphovascular invasion
pT1a	Seminoma <3 cm confined to testis/tunica albuginea/rete and no lymphovascular invasion
pT1b	Seminoma ≥3 cm confined to testis/tunica albuginea/rete and no lymphovascular invasion
pT2	Lymphovascular, hilar fat, epididymal or tunica vaginalis invasion
pT3	Direct spermatic cord soft tissue invasion
pT4	Direct scrotum invasion

Table 6.10 Pathologic parameters predictive of aggressive germ cell tumor clinical course on multivariable analysis

Nonseminomatous tumor	Seminoma
Lymphovascular invasion	Size
Hilar soft tissue invasion	Rete testis invasion
Higher percentage embryonal carcinoma	Lymphovascular invasion
Higher percentage/pure choriocarcinoma	Pathologic stage

vidual adjacent nodules. Sectioning intervening tissue between nodules can demonstrate that the nodules are a single primary rather than multiple primary tumors.

References: [2, 7, 13, 62]

What Is the Relevance of Rete Testis Stromal Invasion and Is There Any Clinical Relevance of Pagetoid Extension of Germ Cell Tumor into the Rete Testis?

Rete testis stromal invasion is defined as tumor in the stroma on both sides of a rete testis duct (Fig. 6.18a). This contrasts pagetoid spread of tumor within the confined of the rete testis ducts (Fig. 6.18b).

Within nonseminomatous tumors:

- Rete testis stromal invasion is present in 25% of cases and there have been conflicting results regarding association with metastasis at initial diagnosis and relapse.
- Pagetoid extension is described in 17% of cases but is not associated with higher clinical stage or relapse.

Within pure seminoma tumors:

- Rete testis stromal invasion is seen in 47–58% of cases and pagetoid extension in 19%.

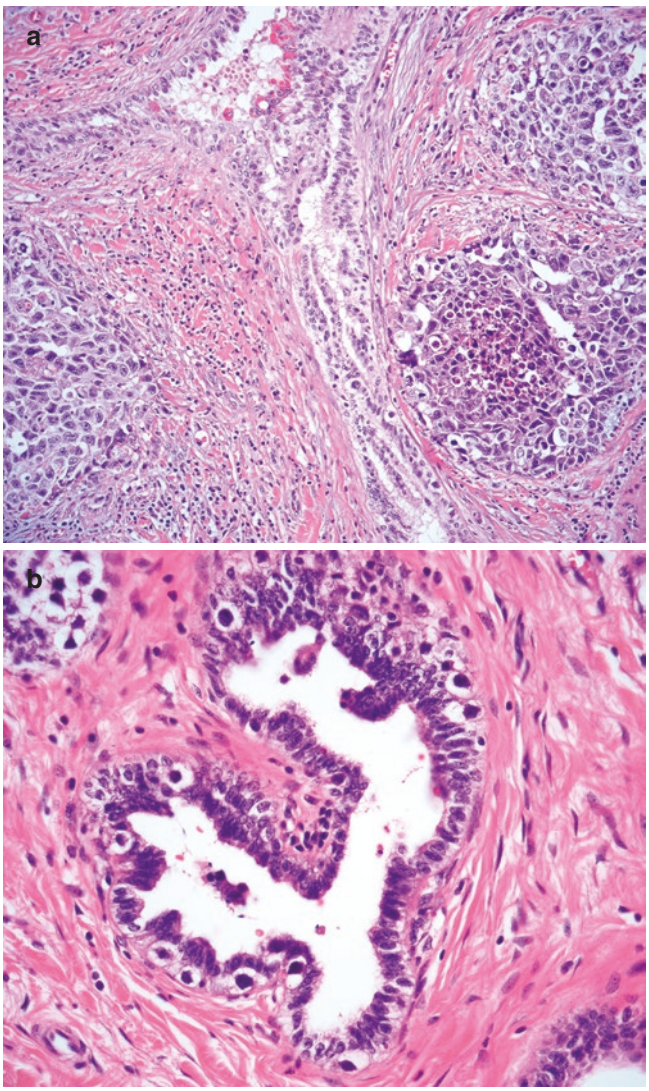

Fig. 6.18 Rete testis involvement. (**a**) Rete testis stromal invasion by embryonal carcinoma. Tumor is on either side of the rete testis duct (center). (**b**) Pagetoid involvement of the rete testis by GCNIS with enlarged atypica cells along the basement membrane of the rete duct. This currently does not need to be reported

- Recent data suggests that neither pattern of rete testis involvement is associated with advanced stage at presentation or of future relapse.
- However, these findings are controversial and a recent study has utilized the presence of rete testis invasion as the sole factor to stratify patients for adjuvant chemotherapy.

Rete testis stromal invasion should be documented in a pathology report while it is optional to report pagetoid extension. Neither impact pT category. If rete testis involvement by pagetoid extension is reported, it is important that the mode of extension be explicitly stated due to the lack of clinical significance.

References: [25, 27, 36, 63–66]

How Does Lymphovascular Invasion Impact PT Category for Germ Cell Tumors?

Testicular germ cell tumors with lymphovascular invasion are categorized as pT2 (Fig. 6.19; Table 6.9).

Within nonseminomatous tumors:

- Lymphovascular invasion is present in 41–43% of cases and is significantly associated with metastasis at initial diagnosis on multivariable analysis (Table 6.10).

Within pure seminoma tumors:

- Lymphovascular invasion is present in 15–18% of cases and was significantly associated metastasis at initial diagnosis in a recent, rigorous analysis. However, older literature has not identified this association.

Lymphovascular invasion should be documented in a pathology report. Lymphovascular invasion is a relative contraindication to surveillance in nonseminomatous tumors and patients are offered adjuvant chemotherapy. Lymphovascular invasion typically does not impact therapy of pure seminoma.

References: [2, 10, 25–27]

Which Histologic Findings Support the Diagnosis of Lymphovascular Invasion Over Pseudoinvasion in Germ Cell Tumor?

The following features of an emboli support a diagnosis of true lymphovascular invasion (Fig. 6.19; Table 6.11):

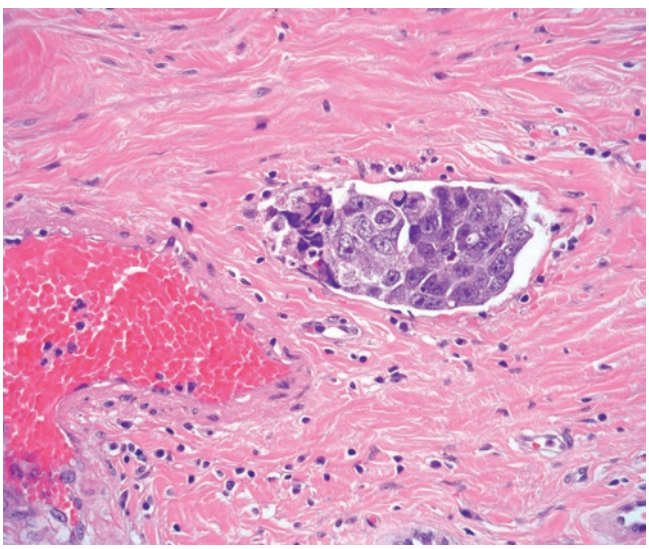

Fig. 6.19 Lymphovascular invasion by embryonal carcinoma. The embolus has characteristics including cohesion, smooth contours and adherence to the vessel wall that support true invasion

Table 6.11 Features to differentiate true lymphovascular invasion from pseudoinvasion

	True lymphovascular invasion	Pseudoinvasion
Cohesion	Yes	No
Smooth contours	Yes	No
Adherence to adjacent vessel wall	Yes	No
Tissue displacement artifact in other areas	No	Yes
Emboli predominately blood, fibrin, or inflammatory cells	No	Yes
Additional sectioning post-fixation lacks emboli	No	Yes

- Tumor cohesiveness.
- Smooth contours.
- Adherence to adjacent vessel wall.

The following are suggestive of pseudoinvasion (Fig. 6.20a, b; Table 6.11):

- Tissue displacement artifact in other areas of the tissue section.
- Discohesive tumor cells admixed with predominately blood, fibrin, and inflammatory cells.
- Additional tissue sectioning post-fixation fails to demonstrate tumor within lymphovascular spaces.

References: [10, 67]

How Can Tissue Carryover Artifact Impact the PT Category for Germ Cell Tumor and How Can This Be Pitfall Be Avoided?

Most notably, tumor displacement artifact occurs during gross prosection in which tumor is smeared on the surface and throughout the tissue sections. Tissue displacement artifact occurs in 60% of seminomas and 38% of nonseminomas. This "butter" artifact can increase discordance in the reporting of lymphovascular invasion (utilized in determining if the tumor is pT2) as it yields pseudolymphovascular tumor deposits. This is especially true for seminomas that are very friable. On secondary review, there is 6–22% discordance in interpretation of lymphovascular invasion, with overcalls more frequent. Overcalling lymphovascular invasion is the most common error identified upon review of referred testicular germ cell tumor cases.

The following are recommendations to decrease tissue displacement artifact (Table 6.12):

- Bivalve the tumor and fix the specimen overnight.

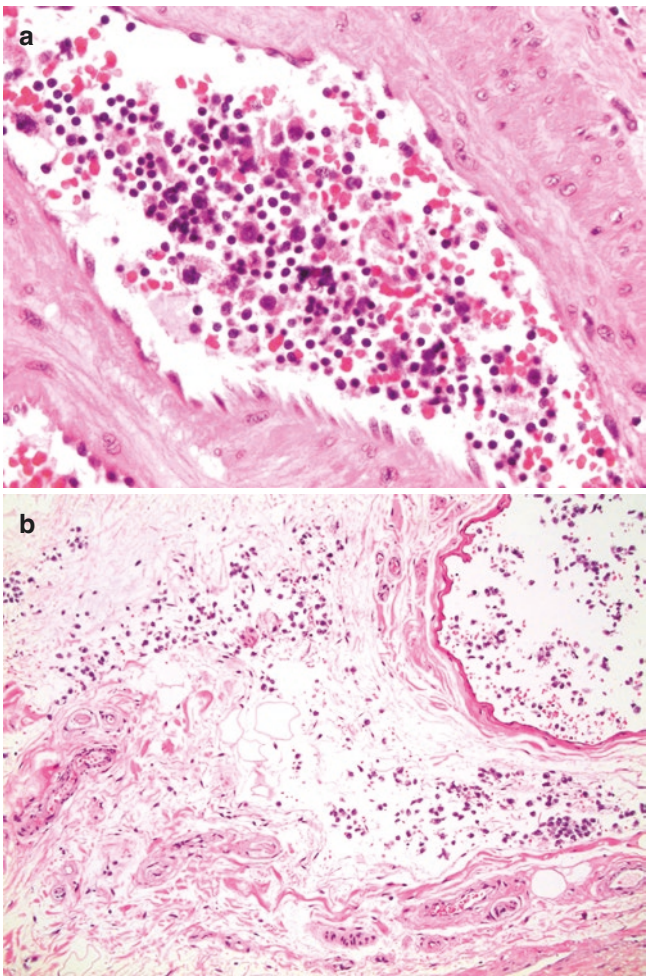

Fig. 6.20 Pseudolymphovascular invasion in seminoma. (**a**) Tumor cells are discohesive and cells within the vessel are predominately red blood cells and inflammatory cells, consistent with pseudoinvasion. (**b**) Tumor cells are scattered in a vessel but tumor displaced throughout the tissue does not support true invasion

Table 6.12 Recommendations to decrease pseudolymphovascular invasion

Gross protocol	Rationale
Bivalve the tumor and fix the specimen overnight	Fresh tumors and even tumors with a few hours of fixation are quite friable
Section the testicle from the tunica albuginea inward	Avoid central tumor displacement into peripheral lymphovascular spaces
Meticulously wipe and wash the knife blade between sectioning the tumor	Avoid tumor smeared on the surface and throughout the tissue sections

- Section the testicle from the tunica albuginea inward, so that tumor is not displaced into the peripheral lymphovascular spaces.
- Meticulously wipe and wash the knife blade between sectioning the tumor.

References: [10, 34, 65, 68]

What Is the PT Category of Lymphovascular Invasion of the Spermatic Cord? Is Lymphovascular Invasion in the Spermatic Cord Shave Margin Considered a Positive Margin?

Lymphovascular invasion of the spermatic cord is classified as pT2 as is lymphovascular invasion within the testicle (Table 6.9). However, nonseminomatous tumors with lymphovascular invasion of the spermatic cord may have a more aggressive disease course. Lymphovascular invasion in the spermatic cord shave margin is not considered a positive margin.

References: [67–71]

What Is the Significance of Tumor in the Tunica Albuginea Versus Tunica Vaginalis for Germ Cell Tumors?

Tumor in the tunica albuginea has no impact on pT classification while tumor involving the tunica vaginalis is classified as pT2 (Fig. 6.21a; Table 6.9). Tunica vaginalis invasion is extremely rare (Fig. 6.21b). Out of 148 nonseminomatous tumors, none invaded the tunica vaginalis and only 2% of seminomas had tunica vaginalis invasion.

References: [25, 27, 62]

Does Epididymal Invasion Impact PT Category for Germ Cell Tumor?

Epididymal invasion is classified as pT2 (Fig. 6.22; (Table 6.9). It is uncommon (8% of nonseminomatous tumor, 6% of seminoma). Epididymal invasion is not a predictor of higher clinical stage using multivariable analysis in either nonseminoma or seminoma.

References: [25, 27, 62]

How Is Hilar Soft Tissue Invasion Diagnosed Versus Direct Spermatic Cord Invasion and How Does It Impact the PT Category of Germ Cell Tumor?

Hilar soft tissue is defined as the stroma below the level of the epididymal head. Invasion of this stroma is classified as pT2 (Fig. 6.23; Table 6.9). Direct invasion of the soft tissue above the level of the epididymal head is considered spermatic cord invasion and is classified as pT3.

Within nonseminomatous tumors:

- Hilar soft tissue is present in 28% of cases and is significantly associated with metastasis at initial diagnosis on multivariable analysis (Table 6.10).

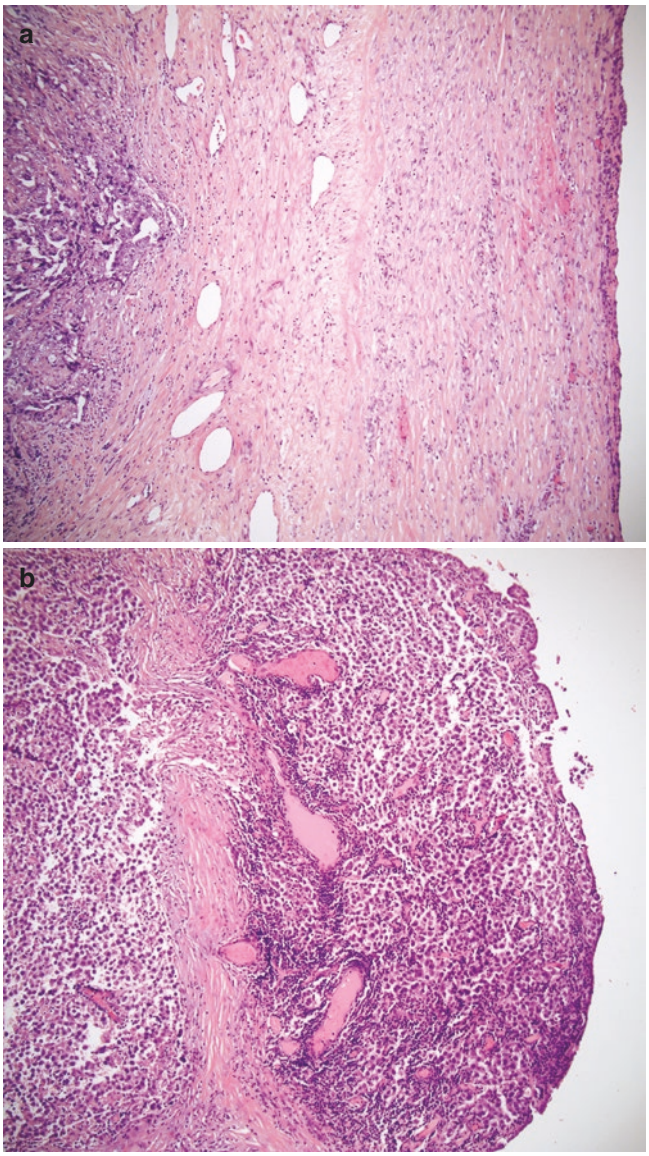

Fig. 6.21 Involvement of tunica. (**a**) The fibrous tunica albuginea is involved by embryonal carcinoma but the tunica vaginalis (flat lining far right) is not involved. This has no impact to pT category. (**b**) The tunica vaginalis (right) is eroded and ruptured by underlying seminoma. This is categorized as pT2

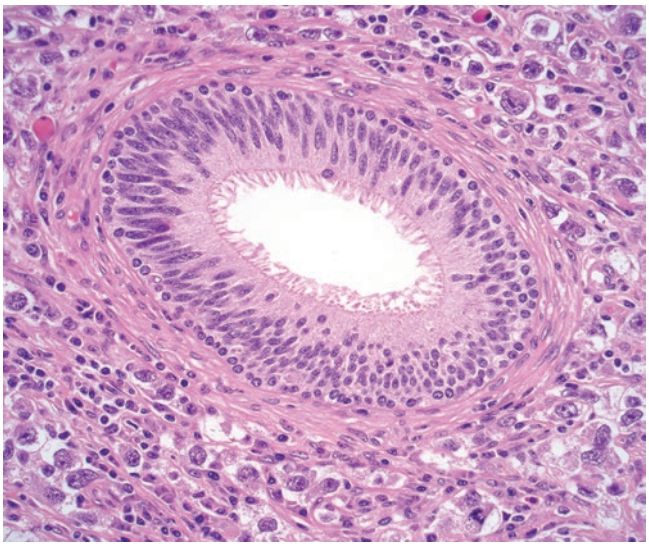

Fig. 6.22 Epididymal invasion. Seminoma surround a duct of the epididymis (center). This is categorized as pT2

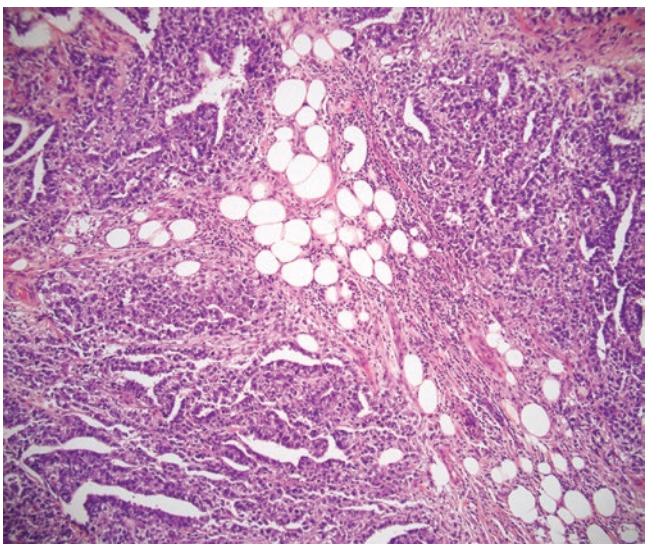

Fig. 6.23 Direct hilar soft tissue invasion by embryonal carcinoma. Below the level of the epididymal head as was present in this case is categorized as pT2 while above the epididymal head is pT3

- Direct spermatic cord invasion is present in 8% of cases and is not significantly associated with metastasis at initial diagnosis on multivariable analysis.

Within pure seminoma tumors:

- Hilar soft tissue is present in 19–22% of cases and is not significantly associated with metastasis at initial diagnosis on multivariable analysis.
- Direct spermatic cord invasion is present in 3% of cases and is not significantly associated with metastasis at initial diagnosis on multivariable analysis.

References: [25–27, 62, 69]

How Is Discontinuous Spermatic Cord Invasion Categorized for Germ Cell Tumor?

Discontinuous invasion of the spermatic cord arises through extension from lymphovascular spaces and is classified as pM1 rather than pT3 (Fig. 6.24a, b). This method of involvement of the spermatic cord is less common than direct invasion. Of tumors with spermatic cord invasion, 81% are via direct extension, 19% are due to discontinuous invasion from lymphovascular spaces, and 4% have both patterns. A non-statistically significant trend has been demonstrated for a more aggressive course for spermatic cord involvement (pM1) compared to direct invasion (pT3).

References: [62, 67, 69]

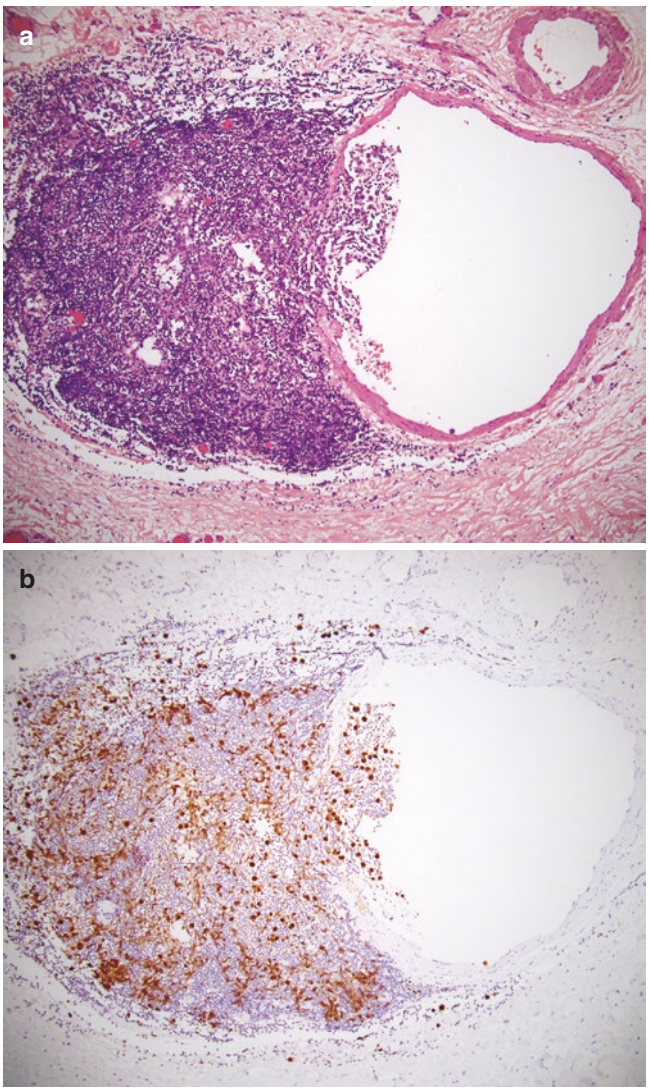

Fig. 6.24 Discontinuous invasion of the spermatic cord (pM1). (**a**) Seminoma is seen dispersed within lymphocytes in the spermatic cord soft tissue and within a ruptured vessel. (**b**) OCT3/4 highlights the tumor cells

Which Lymph Nodes Are Considered Regional for Germ Cell Tumor? How Does Prior Testicular Surgery Impact the Definition of Regional Lymph Nodes?

Regional lymph nodes that impact the pN category include interaortocaval, para/periaortic, paracaval, preaortic, precaval, retroaortic, and retrocaval nodes. Prior inguinal or scrotal surgery disrupts the lymphatic drainage after which intrapelvic and inguinal nodes are considered regional.

Reference: [62]

Table 6.13 pN category based on AJCC Cancer Staging Manual 8th edition

pNX	Cannot be assessed
pN0	No regional lymph node metastasis
pN1	1–5 involved nodes with node size ≤2 cm
pN2	>5 involved nodes OR extranodal extension OR involved nodes >2 cm and ≤5 cm
pN3	Lymph node mass >5 cm

Which Variables Impact PN Categorization of Germ Cell Tumor?

Number of involved lymph nodes, size of involved lymph node (rather than size of metastatic tumor deposit), and presence of extranodal extension are factors that impact the pN category based on the AJCC Cancer Staging Manual 8th edition (Table 6.13). As such, documenting the maximum dimension of a lymph node suspected to be involved by tumor, in addition to the size of metastatic deposit is required.

Reference: [62]

What Are the Likely Findings in a Retroperitoneal Dissection for Germ Cell Tumor?

Retroperitoneal lymph node dissection can be performed in high-risk nonseminoma in absence of imaging findings for patients that do not want or are not eligible for adjuvant chemotherapy. In nonseminoma with imaging consistent with retroperitoneal node involvement, retroperitoneal lymph node dissection is performed after chemotherapy. In seminoma with prior retroperitoneal lymph node disease and residual tumor detected postchemotherapy, a resection may be indicated. Therefore, a variety of pathologic findings should be anticipated in a retroperitoneal dissection ranging from all negative nodes to residual post-chemotherapy tumor.

The most frequent findings in a post-chemotherapy retroperitoneal lymph node dissection are necrosis and histocytic inflammation, indicative of pathologic response by the tumor to the chemotherapy. Teratoma is the most common residual germ cell tumor type. The most frequent tumor type in a retroperitoneal lymph node dissection without treatment is embryonal carcinoma, likely reflecting the higher risk nature of patients selected for this procedure.

It is critical for the pathologist to report the presence of viable germ cell tumor and their components in a retroperitoneal lymph node dissection or other sites of metastasis. In general, the presence of residual teratoma and cystic tropho-

blastic tumor does not warrant the use of additional chemotherapy while the presence of other tumor types does.

References: [2, 58, 72, 73]

What Are the PM Subcategories for Germ Cell Tumor?

Per the AJCC Cancer Staging Manual 8th edition, nonregional lymph node (e.g., iliac, inguinal, pelvic NOS) or lung metastasis are categorized as pM1a while pM1b consists of all distant metastatic sites other than lymph node/lungs, including discontinuous invasion of the spermatic cord (Table 6.14).

Reference: [62]

What Are the Unique Features of Spermatocytic Tumor?

- Spermatocytic tumor, previously named spermatocytic seminoma (not recommended in the current WHO classification), is a rare tumor accounting for about 1% of all testicular germ cell tumors (GCT).
- It is seen only in the testis and not associated with cryptorchism.
- Patients have a mean age of 55 years, much older than those of other GCTs.
- It is always pure and not associated with other GCT components.
- It shows the hallmark tripartite feature with 3 distinct cell groups (Fig. 6.25a):
  - Small cells with round dark nuclei and scant cytoplasm.
  - Intermediate cells with finely granular to filamentous (or spireme) chromatin and eosinophilic cytoplasm.
  - Multinuclear giant cells with similar nuclear features to the intermediate cells.
- It has frequent mitotic figures and apoptotic bodies but no necrosis.

Table 6.14 pM category based on AJCC Cancer Staging Manual 8th edition

pM1a	Non-regional lymph node (e.g., iliac, inguinal, pelvic NOS) or lung metastasis
pM1b	Distant metastasis (includes discontinuous spermatic cord, not lymph node/lungs)

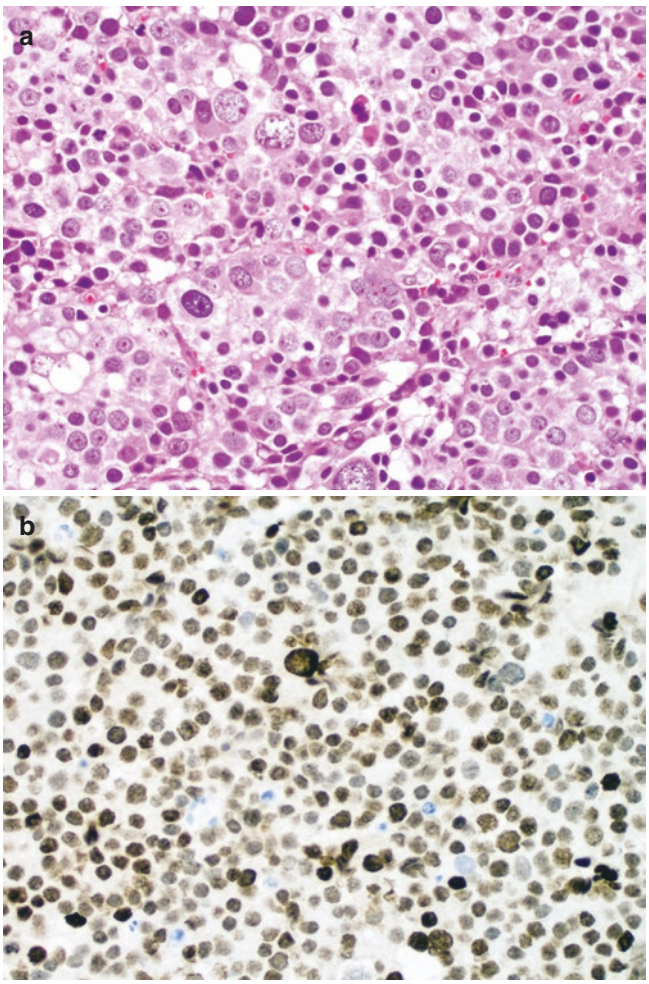

Fig. 6.25 Spermatocytic tumor. (**a**) Tumor is composed of three distinct cell types, large, intermediate, and small cells. (**b**) Tumor cells are positive for SALL4

- Lymphocytic infiltrates and granulomatous inflammation are generally absent.
- It is not associated with GCNIS.
- It shows frequent gains of chromosome 9 but lacks of isochromosome 12p.
- It is generally positive for SALL4 (Fig. 6.25b) and KIT but negative for OCT3/4, PLAP, AFP, and CD30.
- It may develop sarcomatous components sometimes, such as rhabdomyosarcoma and pleomorphic sarcoma.
- It generally has a benign clinical course, unless complicated by sarcoma.

References: [74–76]

How Is Sex Cord-Stromal Tumor Differentiated from Germ Cell Tumor?

See Table 6.15 for the differences between sex cord-stromal tumor and germ cell tumor.

References: [29, 31, 68, 77–79]

How Is a Sex Cord-Stromal Tumor Worked Up?

Sex cord-stromal tumors (SCSTs) demonstrate a number of distinct morphologies (Table 6.16). Over 90% of SCSTs are pure, but a small subset may contain more than one SCST component or even a GCT component, such as in gonadoblastoma. Among the pure SCSTs, Leydig cell tumors are the most common, followed by Sertoli cell tumors and granulosa cell tumors. In well-differentiated SCSTs, the tumor cells usually resemble the non-neoplastic Leydig cells, Sertoli cells, and stromal cells to various degrees. In poorly differentiated tumors, the resemblance is generally lost but may be present in focal areas.

Table 6.15 Comparison of clinicopathologic features between sex cord-stromal tumors and germ cell tumors

	Sex cord-stromal tumor	Germ cell tumors
Incidence	4% in adults and 25% in children	>90% in adults
Patient's age	A wide range from children to elderly	Young patients with a mean of 30 years
Common types	Leydig cell tumor	Seminoma
	Sertoli cell tumor	Embryonal carcinoma
	Granulosa cell tumor	Yolk sac tumor
		Teratoma
Growth pattern	Relatively uniform	Often heterogeneous
Cytologic atypia	Mild to moderate	Severe
Mitotic activity	Low	High
Necrosis	Uncommon	Common
Lymphovascular invasion	Uncommon	Common
Hemorrhage	Uncommon	Common
GCNIS	Absence	Often present
Iso12p	Absence	Often present
Elevated serum markers (LDH, AFP, βHCG)	Uncommon	Common
Positive IHC markers	SF1, inhibin, calretinin	Sall4, OCT3/4, and PLAP
Negative IHC markers	OCT3/4, Sall4, and PLAP	SF1, inhibin, calretinin
Metastasis	Uncommon	Common
Clinical course	5% are malignant	Most are malignant

Table 6.16 Classification of sex cord-stromal tumors of the testis

Pure tumors
Leydig cell tumor
Malignant Leydig cell tumor
Sertoli cell tumor
Malignant Sertoli cell tumor
Large cell calcifying Sertoli cell tumor
Intratubular large cell hyalinizing Sertoli cell neoplasia
Granulosa cell tumor
Juvenile-type granulosa cell tumor
Adult-type granulosa cell tumor
Tumors of fibroma/thecoma group
Thecoma
Fibroma
Mixed and unclassified tumors
Mixed sex cord-gonadal stromal tumor
Unclassified sex cord-gonadal stromal tumor
Tumor containing both germ cell and sex cord-stromal elements
Gonadoblastoma

Immunohistochemistry is an important tool in the diagnosis of SCST. Several markers, including α-inhibin, calretinin, WT-1, and Melan-A, are commonly expressed in SCSTs but not expressed in GCTs. Steroidogenic factor 1 (SF-1) is an emerging marker for SCST with a robust nuclear staining pattern. In contrast, GCT markers, such as SALL4, OCT3/4, and PLAP, are generally not expressed in SCSTs.

The main differential diagnosis of SCST is GCT in the testis (Table 6.15). Several other entities, such as metastatic carcinoma and lymphoma, also need to be distinguished from SCSTs. Metastatic carcinomas are usually seen in old patients with a clinical history of nontesticular malignancy. Metastasis typically shows intestinal growth pattern in the testis with wide-spread lymphovascular invasion. Tumor cells show greater cytologic atypia and pleomorphism than SCST. They are negative for SCST markers and positive for other tissue-specific markers. Lymphoma shows both diffuse and interstitial growth patterns. The lymphoma cells are negative for SCST markers and positive for LCA and other B-cell or T-cell markers (Table 6.16).

References: [29, 34, 77, 79]

What Are the Testicular Tumors with Both Germ Cell and Sex Cord-Stromal Elements?

- The majority of testicular tumors with mixed GCT and SCST are gonadoblastoma.
  - It is usually diagnosed in the neonates because of gonadal dysgenesis.
  - About 40% of cases are bilateral.
  - It is characterized by discrete round nests of germ cells and sex cord cells mixed with eosinophilic basement membrane material (Fig. 6.26a).

The germ cells usually resemble GCNIS and seminoma cells.
The sex cord cells simulate the Sertoli cells of the fetal testis, with angulated nuclei and little cytoplasm.
The basement membrane materials form round deposits and often develop calcified psammomatous bodies, which may coalesce to form mulberry-like aggregates (Fig. 6.26b).
Occasionally the cellular elements regress, leaving only the calcifications, diagnostic of a regressed (so-called burnt out) gonadoblastoma.

– The germ cells are positive for SALL4, OCT3/4, C-KIT, and PLAP; the sex cord cells are positive for SF1, inhibin, calretinin, and WT1.
– At the time of diagnosis, about half of cases have developed invasive seminoma and 8% to other non-seminomatous GCTs.

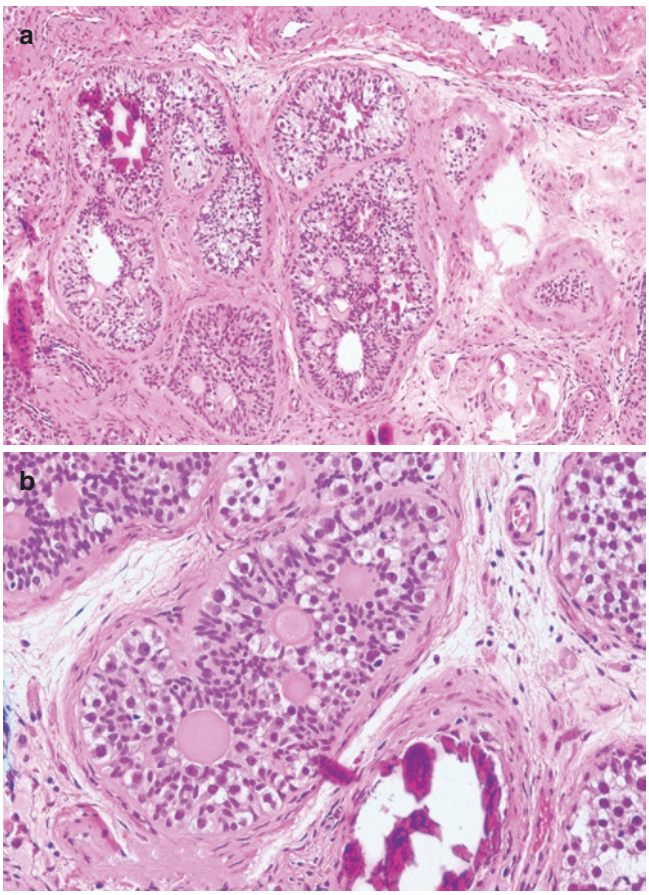

Fig. 6.26 Gonadoblastoma. (**a**) Tumor shows enlarged seminiferous tubules with round deposits of dense basement membrane materials and calcification. (**b**) The germ cells resemble GCNIS or seminoma cells, and the sex cord cells simulate the fetal Sertoli cells with angulated nuclei and scant cytoplasm, forming follicular and Call-Exner-like patterns

– The usual treatment is bilateral orchiectomy.

- Rare cases of testicular tumors with mixed GCT and SCST are unclassified type.
  – It shows large, infiltrating nodules of germ cells and sex cord stroma cells.
  – It is a benign tumor.
  – Orchiectomy is standard therapy.

References: [80–82]

How Is Sertoli Cell Nodule Differentiated from Sertoli Cell Tumor?

See Table 6.17 for the differences between Sertoli cell nodule and Sertoli cell tumor (Figs. 6.27 and 6.28).

References: [80, 83, 84]

Table 6.17 Comparison of clinicopathologic features between Sertoli cell nodule and Sertoli cell tumor

	Sertoli cell nodule	Sertoli cell tumor
Pathology	Usually cannot be identified on gross. Sometimes may appear as small white nodules (<1 cm) Small clusters of immature tubules that often contain hyaline luminal deposits with microcalcification (Fig. 6.27a) Immature Sertoli cells lack cytologic atypia or lipid-vacuoles in cytoplasm (Fig. 6.27b). No bands of dense collagen Spermatogonia could be interspersed in some immature tubules, mimicking GCNIS and even gonadoblastoma	Usually well-circumscribed, tan-white mass (2–5 cm). Cystic changes may be present in 1/3 of cases Typically a nodular growth of tubules in scant stroma (Fig. 6.28a) Tubules may be round or elongated. Lumens may not be apparent (Fig. 6.28b) Sometimes a diffuse growth pattern with nests, cords, and clusters separated by dense collagens (Fig. 6.28c) Tumor cells have pale to eosinophilic cytoplasm that may contain lipid vacuoles (Fig. 6.28d) Cytologic atypia is usually minimal and mitotic activity is low
Clinical features	Can occur in any age Usually an incidental finding associated with testicular tumors or cryptorchidism Non-neoplastic lesion Does not need additional treatment	Usually occur in adults Asymptomatic testicular swelling with no endocrine symptoms. Most are benign, but 5% are malignant. Treated with radical orchiectomy

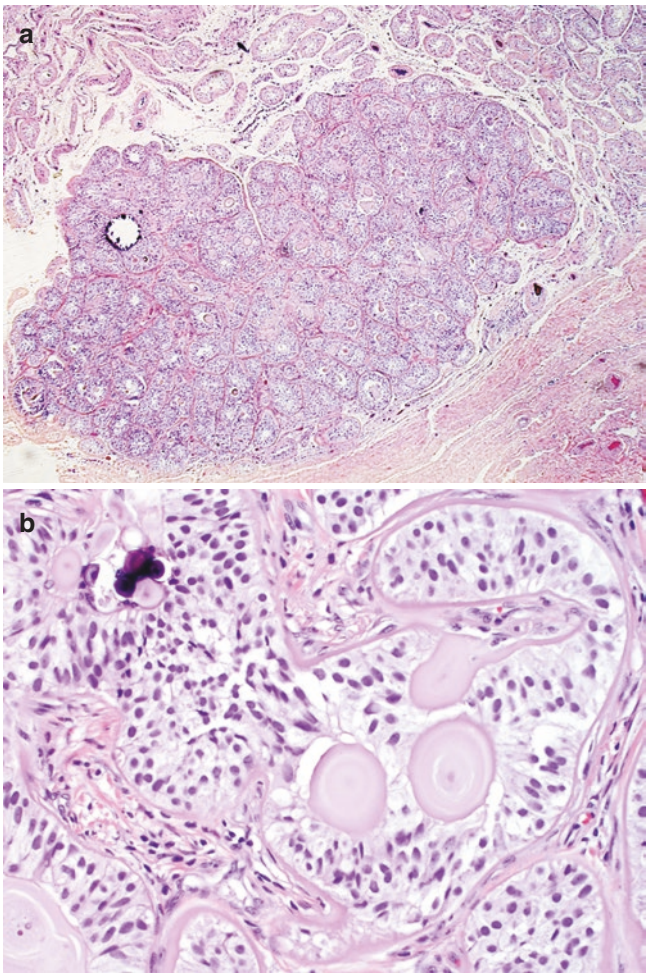

Fig. 6.27 Sertoli cell nodule. (**a**) A small nodular tumor is composed of immature tubules with focal calcification. (**b**) The tubules are lined immature Sertoli cells with minimal atypia and contain hyaline luminal deposits

What Are the Morphologic Features Are Associated with Malignancy in Sertoli Cell Tumor?

A small subset of Sertoli cell tumors (5%) are malignant and typically show two or more of the following morphologic features:

- Large size (>5 cm in largest dimension)
- Tumor necrosis
- Infiltrative border (Fig. 6.29a, b)
- Moderate-to-severe cytological atypia (Fig. 6.29c)
- Active proliferation (more than 5 mitotic figures per 10 high-power fields)
- Lymphovascular invasion (Fig. 6.29d)

If a tumor exhibits only one of the above features, it may be classified as a Sertoli cell tumor with uncertain malignant potential. Even in the absence of all these features, benign Sertoli cell tumor should not be used, as those tumors may still metastasize, although the risk is very low.

References: [85–87]

How Is Large Cell Calcifying Sertoli Cell Tumor Differentiated from Sertoli Cell Tumor, NOS?

See Table 6.18 for the differences between large cell calcifying Sertoli cell tumor and Sertoli cell tumor, NOS (Figs. 6.28 and 6.30).

References: [84, 87–90]

How Is Large Cell Calcifying Sertoli Cell Tumor Differentiated from Intratubular Large Cell Hyalinizing Sertoli Cell Neoplasia?

See Table 6.19 for the differences between large cell calcifying Sertoli cell tumor and intratubular large cell hyalinizing Sertoli cell neoplasia (Figs. 6.30 and 6.31).

References: [87, 88, 91, 92]

How Is Leydig Cell Hyperplasia Differentiated from Leydig Cell Tumor?

See Table 6.20 for the differences between Leydig cell hyperplasia and Leydig cell tumor (Figs. 6.32 and 6.33).

References: [93–95]

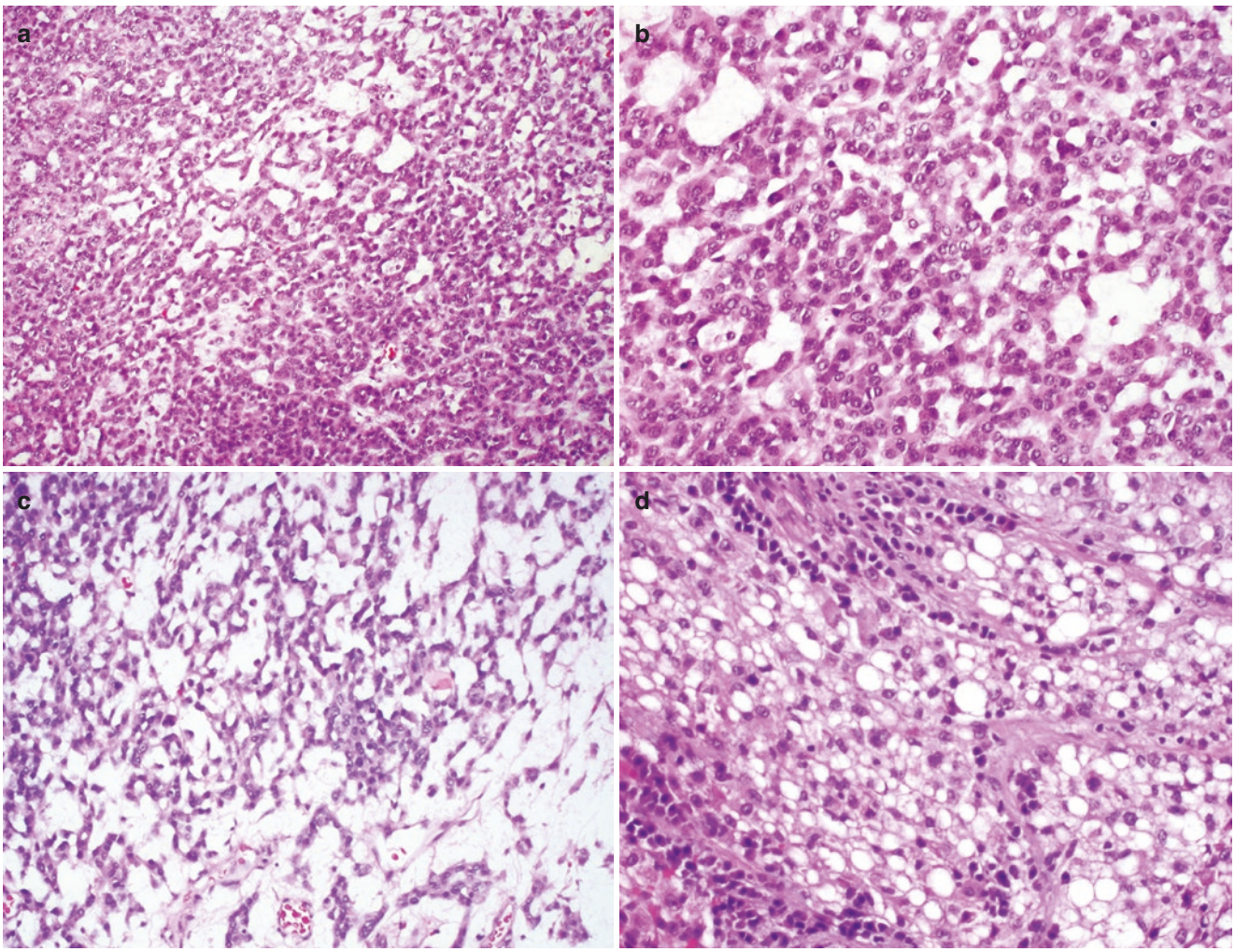

Fig. 6.28 Sertoli cell tumor. (**a**) The tumor shows a diffuse growth of tubules in scant stroma. (**b**) Some tubules have round lumens, and cytologic atypia is minimal. (**c**) Tumor cells form cords and clusters in a myxoid stroma. (**d**) Tumor cells have lipid vacuoles in the cytoplasm

What Are the Morphologic Features Are Associated with Malignancy in Leydig Cell Tumor?

Most Leydig cell tumors are benign, but approximately 5% are malignant. The average age of patients with malignant tumors is 62.5 years, in contrast to the late thirties for those with benign Leydig cell tumors. Malignant Leydig cell tumors usually demonstrate two or more of the following features: larger than 5 cm in diameter, infiltrative borders, prominent cytological atypia, >3 mitotic figures per 10 high-power fields, lymphovascular invasion, and tumor necrosis. Ancillary studies may have some value in predicting the clinical behavior of Leydig cell tumor. Aneuploidy is usually observed in metastatic Leydig cell tumors. MIB-1 staining indices show a significant increase in the malignant tumors. Staining for p53 protein may highlights

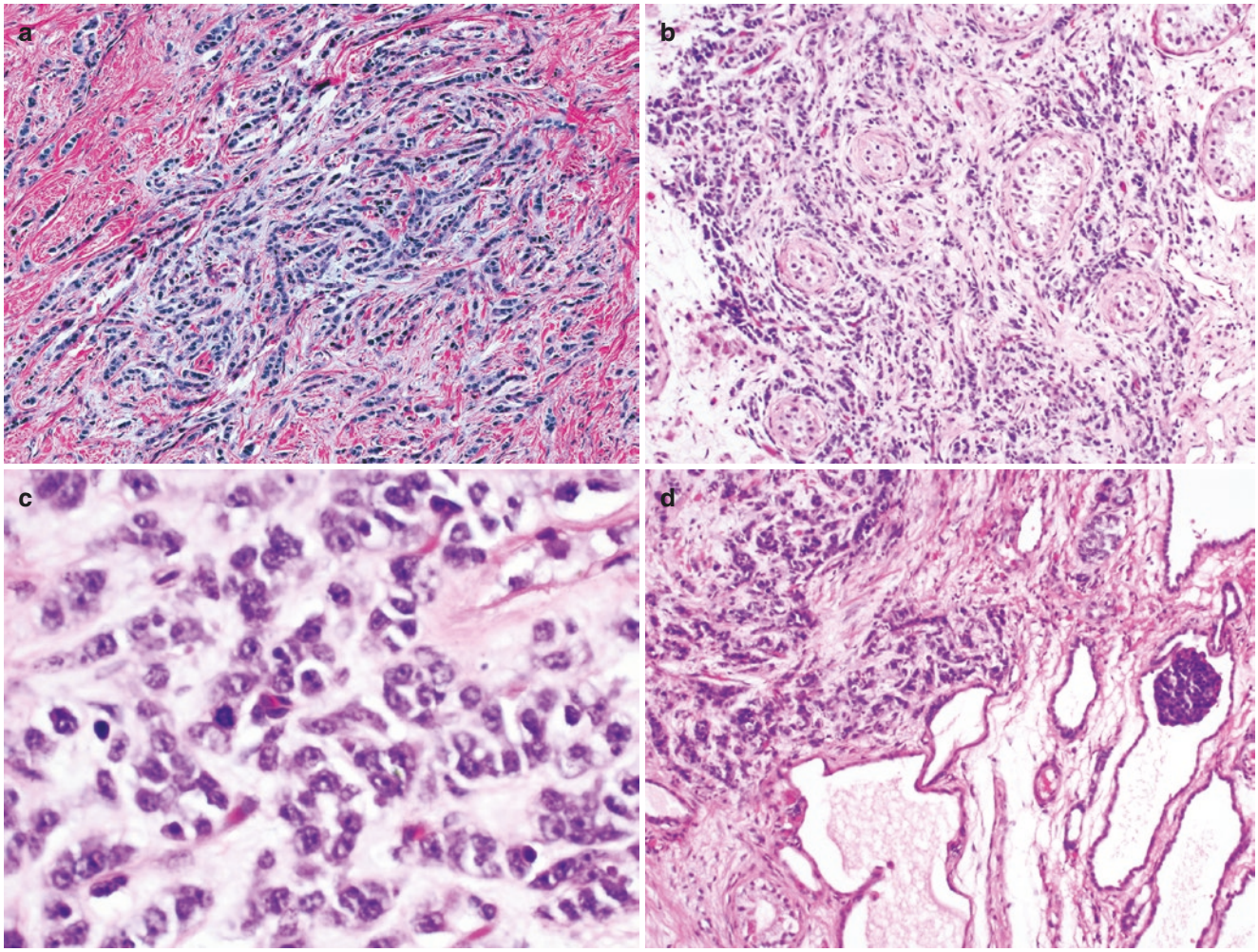

Fig. 6.29 Malignant Sertoli cell tumor. (**a**) Tumor diffusely invades the spermatic cord. (**b**) Tumor shows infiltrative growth in the testis. (**c**) Tumor cells show high-grade nuclear atypia and mitoses. (**d**) Tumor invades vascular spaces

>50% of nuclei in some malignant tumors. Malignant Leydig cell tumors usually spread to the regional lymph nodes (Fig. 6.34a, b), lungs, liver, and bones. The treatment is inguinal orchiectomy. If a tumor spread to regional lymph nodes, retroperitoneal lymph node dissection may be considered. The treatment of metastatic Leydig cell tumor has been generally unsatisfactory. Most patients die within 5 years.

References: [94, 96, 97]

How Is Adult Granulosa Cell Tumor Differentiated from Juvenile Granulosa Cell Tumor?

See Table 6.21 for the differences between adult granulosa cell tumor and juvenile granulosa cell tumor (Figs. 6.35 and 6.36).

References: [98–101]

What Are the Salient Features of Fibrothecoma?

Testicular fibrothecoma is a rare tumor that occurs in patients with a wide range of age (mean 45 years).

- It is usually a well-circumscribed, tan, and firm tumor (0.5–8 cm).
- It is characterized by spindle-shaped fibroblasts that usually shows fascicular or storiform patterns in scant stroma, resembling its ovarian counterpart (Fig. 6.37a).
- The tumor cells usually appear bland with elongated nuclei and scant cytoplasm.
- It is variably positive for inhibin (Fig. 6.37b), calretinin, cytokeratin, actin, desmin, S100, and CD34.
- All tumors follow a benign clinical course.

Table 6.18 Comparison of clinicopathologic features between large cell calcifying Sertoli cell tumor and conventional Sertoli cell tumor

	Large cell calcifying Sertoli cell tumor	Sertoli cell tumors
Pathology	Usually a well-circumscribed unilateral mass in sporadic cases Scattered small and bilateral tumors in Carney complex-related cases Tumors may show growth patterns of solid, tubules, nests, or cords in a myxoid stroma. Tumor cells are usually round to oval with abundant granular eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli (Fig. 6.30a). Calcifications vary from small psammomas to massive areas, sometimes with ossification (Fig. 6.30b) Intratubular hyalinizing Sertoli cell nodule may be seen in 40% of cases, particularly those associated with Carney complex Negative for nuclear β-catenin Malignancy is associated with the presence of two or more the following features: size >4 cm, marked nuclear atypia, >3 mitotic figures per 10 HPF, extratesticular spread, tumor necrosis, and lymphovascular invasion	Usually a well-circumscribed tan-white unilateral mass (2–5 cm). Cystic changes may be present in 1/3 of cases Typically a nodular growth of tubules in scant stroma Tubules may be round or elongated. Sometimes lumens may not be apparent Sometimes a diffuse growth pattern with nests, cords, clusters of cells separated by dense collagens Tumor cells show pale to eosinophilic cytoplasm that may become lipid vacuoles No calcifications are seen Cytologic atypia is minimal and mitotic activity is low Positive for nuclear β-catenin Malignancy is associated with the presence of two or more the following features: size >5 cm, significant nuclear atypia, >5 mitotic figures per 10 HPF, tumor necrosis, infiltrative borders, and lymphovascular invasion
Clinical features	Younger patients with a mean age of 21 years Testicular swelling in sporadic cases Patients with Carney complex may have skin myxomas, pigmented nodular adrenocortical disease, psammomatous melanotic schwannomas, etc. 60–70% of cases associated with Carney complex show germline mutations in PRKAR1A, a tumor suppressor gene Radical orchiectomy is usually performed for sporadic cases. In cases associated with Carney complex, conservative approach may be considered Most are benign, but 15% of cases are malignant	Older patients with a mean age of 46 years Asymptomatic testicular swelling with no endocrine symptoms Not asscoaited with Carney complex. Radical orchiectomy Most are benign, but 5% of cases are malignant

- It can be differentiated from fibromatous tumor of the testicular tunics because of their different cellularity and location.
- It can be differentiated from unclassified SCST, as the latter have at least focal SCST differentiation by morphology or immunohistochemistry.
- It can be differentiated from leiomyoma, as it lacks abundant eosinophilic cytoplasm and blunt-ended nuclei of the smooth muscle tumors.
- It can be differentiated from testicular fibrosarcoma, as it generally lacks nuclear atypia, mitosis and necrosis.

References: [102–104]

How Is Mesothelial Hyperplasia Is Differentiated from Malignant Mesothelioma?

See Table 6.22 for the differences between mesothelial hyperplasia and malignant mesothelioma (Figs. 6.38 and 6.39).

References: [105–108]

How Is Metastatic Adenocarcinoma Differentiated from Adenomatoid Tumor?

See Table 6.23 for the differences between adenomatoid tumor and metastatic adenocarcinoma (Figs. 6.40, 6.41, and 6.42).

References: [106–113]

What Are the Salient Features of Epididymal Adenocarcinoma?

It is a rare epithelial tumor that arises in the epididymis but commonly involves other structures, such as tunica vaginalis, testis and spermatic cord.

- The tumors may show cystic, papillary, and tubular growth pattern (Fig. 6.43a).
- Some papillary structures are lined by cuboidal and columnar cells with clear cytoplasm (Fig. 6.43b).
- Focal calcification may be present (Fig. 6.43c).
- Mitotic figures, tumor necrosis, and cytologic atypia are common.

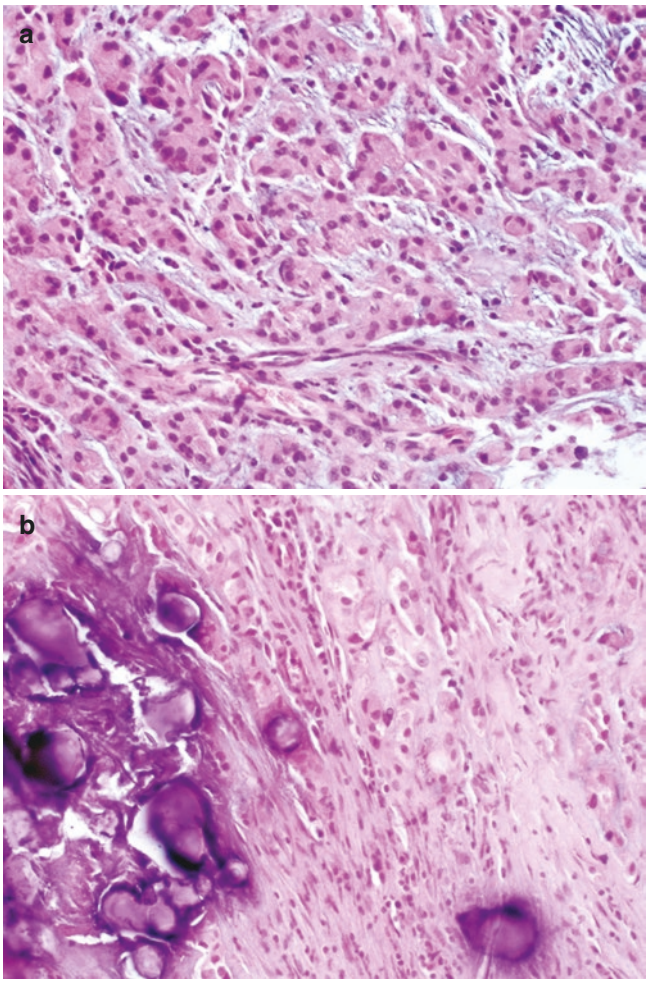

Fig. 6.30 Large cell calcifying Sertoli cell tumor. (**a**) Tumor cells have abundant granular eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli. (**b**) Tumor shows prominent microcalcification with psammoma bodies

- It is positive for CK7, carbonic anhydrase IX, and PAX8 (Fig. 6.43d), mimicking metastatic renal cell carcinoma, but it is negative for RCC antigen and AMACR.
- It is a malignant lesion that may cause death.
- It is differentiated from epididymal papillary adenoma, as the latter lacks an invasive growth pattern, tumor necrosis, and cytologic atypia.
- Other malignancies, such as metastatic carcinomas and mesothelioma, need to be differentiated, and immunohistochemistry is helpful (linage-specific markers for metastatic carcinomas and mesothelial markers for mesothelioma).

References: [114, 115]

How Is Testicular Germ Cell Tumor Differentiated from Metastatic Adenocarcinoma to the Testis?

See Table 6.24 for the differences between germ cell tumor and metastatic adenocarcinoma (Figs. 6.41 and 6.42).

References: [31, 68, 112, 113, 116]

How Is Paratesticular Lipoma Differentiated from Liposarcoma?

See Table 6.25 for the differences between paratesticular lipoma and well-differentiated liposarcoma (Fig. 6.44).

References: [117–120]

How Is Leiomyoma of the Spermatic Cord Differentiated from Leiomyosarcoma?

Leiomyoma is the second most common benign mesenchymal tumor in the paratesticular region after lipoma. It often occurs in the epididymis. The tumor shows pure smooth muscle differentiation, which is characterized by fascicles of spindle cells with brightly eosinophilic cytoplasm and cigar-shaped nuclei. However, it lacks of malignant features, such as nuclear atypia, mitotic activity, and necrosis. Leiomyomas are benign and do not recur. Leiomyosarcoma is the second most common malignant mesenchymal tumor in the paratesticular region after liposarcoma. It often involves the spermatic cord or tunics. Although the tumor is often well differentiated, malignant features, including mitotic activity, necrosis, and nuclear atypia, are present at least focally (Fig. 6.45a–d). The tumors cover the entire spectrum of smooth muscle differentiation from low to high grade. Rare paratesticular leiomyosarcoma are of pleomorphic, myxoid, epithelioid, inflammatory, and dedifferentiated types. The prognosis of leiomyosarcoma is associated with histologic grade. Low grade may develop local recurrence but no

Table 6.19 Comparison of clinicopathologic features between large cell calcifying Sertoli cell and intratubular large cell hyalinizing Sertoli cell neoplasia

	Large cell calcifying Sertoli cell tumor	Intratubular large cell hyalinizing Sertoli cell neoplasia
Pathology	Unilateral in sporadic cases and bilateral in cases associated with Carney complex Usually a well-circumscribed mass (range, 1–15 cm) in sporadic cases Scattered small and bilateral tumors are characteristic of Carney complex-related cases. Tumors may show growth patterns of solid tubules, nests, clusters, or cords in a myxoid stroma Tumor cells are usually round to oval with abundant granular eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli Calcifications vary from small psammomas to massive areas, sometimes with ossification Intratubular hyalinizing Sertoli cell nodule may be seen in 40% of cases, particularly those associated with Carney complex Negative for nuclear β-catenin	Usually bilateral Multiple, small, white-light pink nodules (1–3 mm) Typically lobular clusters of expanded seminiferous tubules are scattered in the testis (Fig. 6.31a) The tubules are lined mostly by Sertoli cells, which have oval nuclei, inconspicuous nucleoli, and pale to eosinophilic cytoplasm with vacuoles The tubules are surrounded by a thickened basement membrane, which may invigilate into the tubular lumens, mimicking intraluminal globoid deposits (Fig. 6.31b) Calcification is not prominent. Cytologic atypia is minimal and mitotic activity is low Positive for aromatase
Clinical features	Young adults with a mean age of 21 years 60–70% of cases associated with Carney complex show germline mutations in PRKAR1A, a tumor suppressor gene Patients usually have testicular swelling in sporadic cases Patients with Carney complex may have skin myxomas, pigmented nodular adrenocortical disease, psammomatous melanotic schwannomas, etc. Most are benign, but 15% of cases are malignant. All malignant tumors are unilateral and unifocal and are usually not associated with Carney complex Radical orchiectomy is usually performed for sporadic cases. In cases associated with Carney complex, conservative approach may be considered	Children with a mean age of 7 years Occurs almost exclusively in patients with Peutz-Jeghers syndrome Usually shows germline mutations in the STK11 gene Patients often have gynecomastia, because of estrogen overproduction Patients with Peutz-Jeghers syndrome may have benign hamartomatous polyps in the gastrointestinal tract and hyperpigmented macules on the lips and oral mucosa (melanosis) All are benign Conservative treatment with aromatase inhibitors is recommended

metastasis, while high grade is associated with frequent metastases and mortality. The presence of mitotic activity in conjunction with nuclear atypia, infiltrative margins, or necrosis distinguishes leiomyosarcoma from leiomyoma.

References: [121–125]

How Is Paratesticular Rhabdomyosarcoma Differentiated from Leiomyosarcoma?

See Table 6.26 for the differences between leiomyosarcoma and rhabdomyosarcoma (Figs. 6.45 and 6.46).

References: [126–130]

What Types of Ovarian-Type Epithelial Tumor May Be Encountered in the Testis and Paratestis?

- A variety of ovarian surface epithelial tumors have been reported in the testis and paratestis, although they are extremely rare.
- They may arise by Müllerian metaplasia of the peritoneal lining of the tunica vaginalis or Müllerian remnants in the paratesticular connective tissue.
- Serous and mucinous tumors account for the majority, and others include endometrioid, clear cell, and Brenner tumors.
- The microscopic features are identical to their ovarian counterparts.

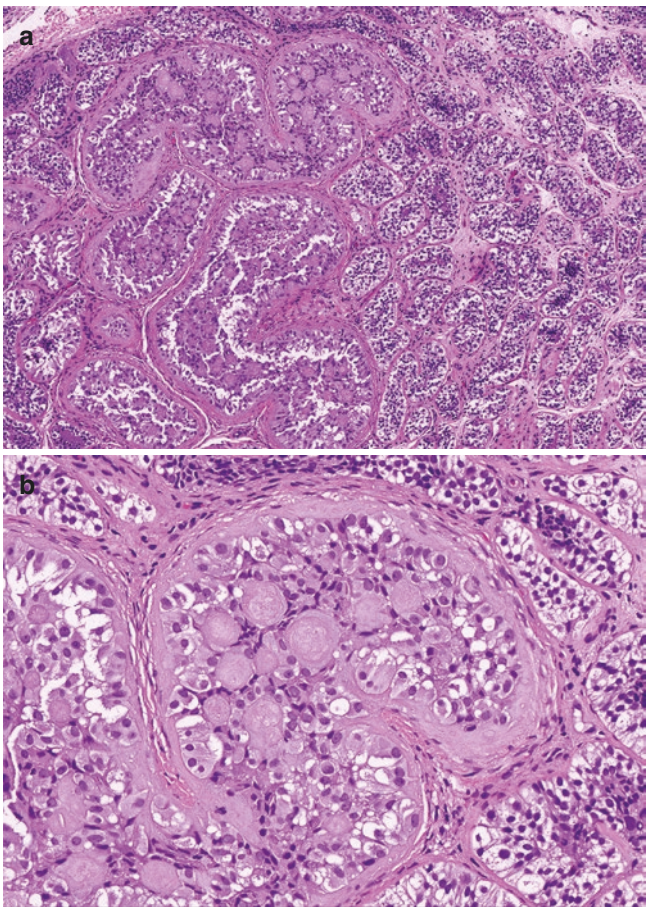

Fig. 6.31 Intratubular large cell hyalinizing Sertoli cell neoplasia. (**a**) The lesion is characterized by lobular clusters of expanded seminiferous tubules lined by mostly Sertoli cells. (**b**) The tubules are surrounded by a thickened basement membrane, which invigilates into the tubular lumens, mimicking intraluminal globoid deposits

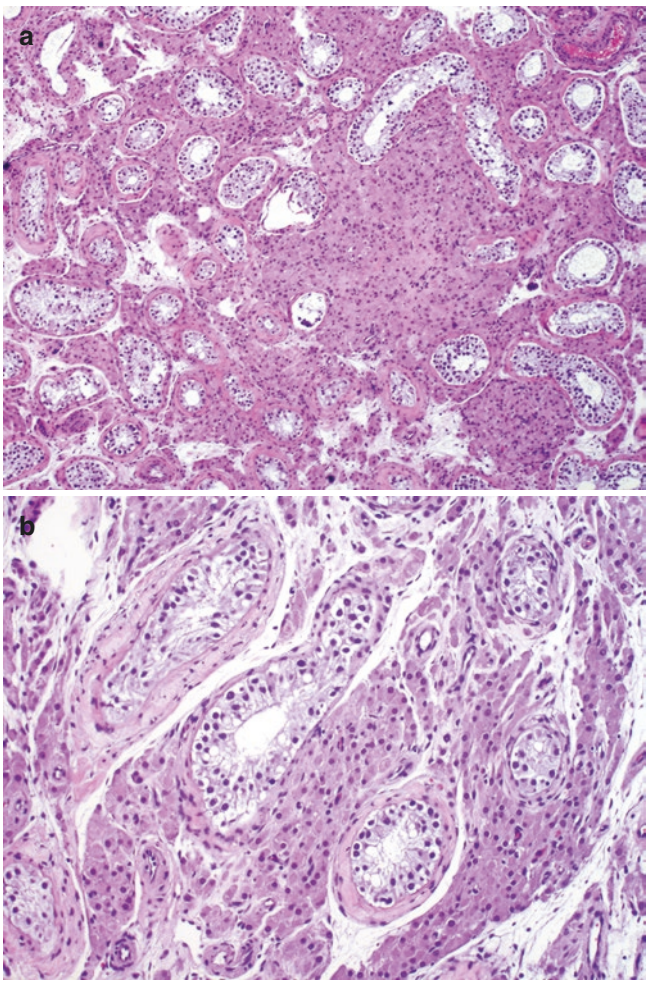

Fig. 6.32 Leydig cell hyperplasia. (**a**) It shows small clusters of Leydig cells interspersed among atrophic seminiferous tubules. (**b**) Cells show minimal cytologic atypia

Table 6.20 Comparison of clinicopathologic features between Leydig cell hyperplasia and Leydig cell tumor

	Leydig cell hyperplasia	Leydig cell tumor
Pathology	Usually bilateral Often grossly invisible but sometimes can produce multiple, small, yellow-brown nodules (<0.5 cm) Multiple small clusters of Leydig cells interspersed among preexisting, frequently atrophic seminiferous tubules (Fig. 6.32a). Leydig cells may be present in the tunica albuginea and beyond Leydig cells frequently involve nerves, which should not be misinterpreted as indicating they are neoplastic Similar cytology to normal Leydig cells (Fig. 6.32b)	Usually unilateral A well-circumscribed, homogenous, tan-yellow tumors (range, 0.5–5 cm) Diffuse growth pattern is the most common (Fig. 6.33a) Other patterns include nested (Fig. 6.33b), insular, trabecular, spindle cell, and microcystic Tumor cells are typically uniform and round with abundant granular eosinophilic cytoplasm The nuclei are round with minimal atypia and low mitotic activity Lipofuscin pigment and Reinke crystals may be present in up to 30% of cases
Clinical features	Any age Usually an incident finding Sometimes associated with infertility, precocity, undescended testis, and Klinefelter syndrome. Non-neoplastic No treatment is needed	Two incidence peaks – children (5–10 years) and adults (30–60 years) Testicular swelling. Gynecomastia may be seen in one-third of patients Most are benign but 5% are malignant Ususally treated with radical orchiectomy

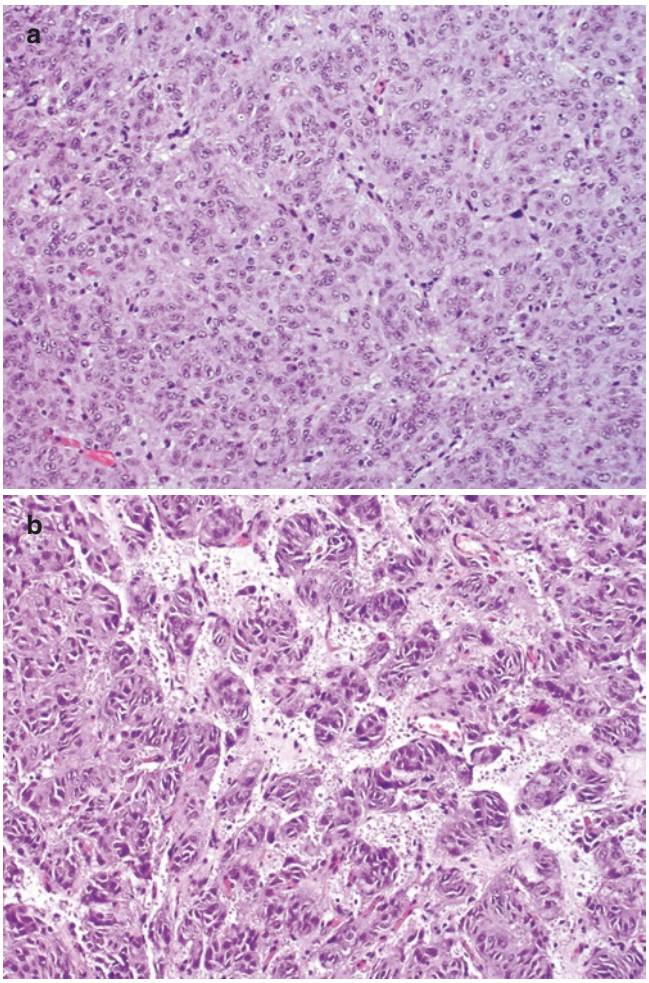

Fig. 6.33 Leydig cell tumor. (**a**) Tumor shows a diffuse growth pattern and tumor cells show minimal cytologic atypia. (**b**) Tumor shows a nested growth pattern with focal spindle cell features

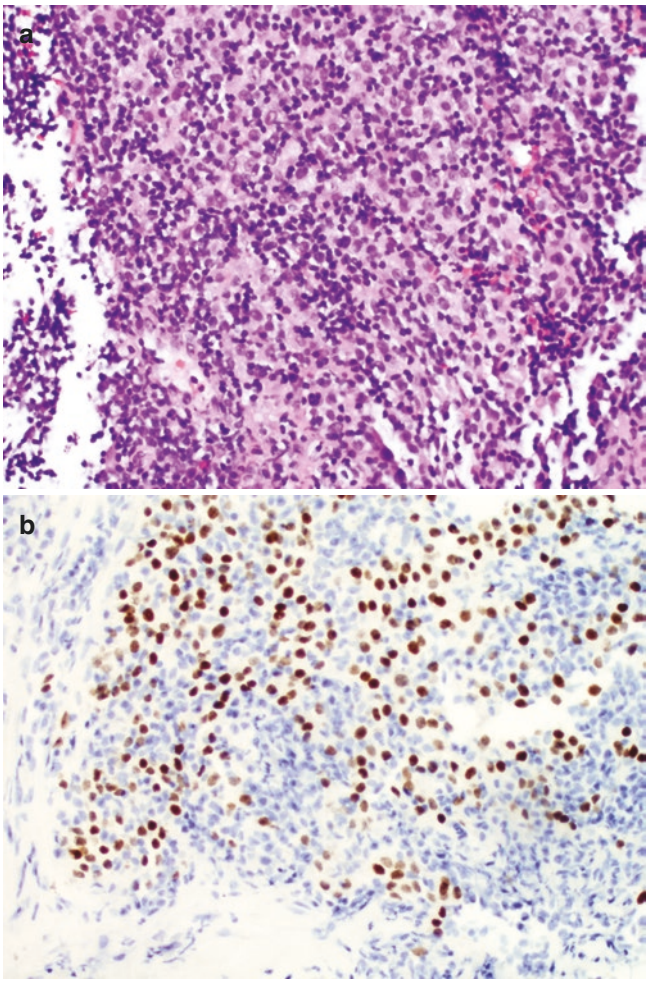

Fig. 6.34 Metastatic Leydig cell tumor. (**a**) Tumor cells with high-grade nuclear atypia and abundant eosinophilic cytoplasm involve lymphoid tissue. (**b**) Tumor cells are positive for SF-1

- The criteria for benign, borderline, and malignant tumors are similar to those for their ovarian counterparts.
- Benign and borderline tumors do not recur or metastasize, whereas carcinomas have the potential for both.

References: [131–134]

What Are the Salient Features of Myoid Gonadal Stromal Tumor?

- A spindle cell neoplasm shows features of both smooth muscle and gonadal stromal differentiation.
- It occurs over a wide age range (4–59 years).
- A small, well-circumscribed tumor (1.2–3.5 cm) but not encapsulated (Fig. 6.47a).
- It is characterized by densely packed, uniform spindle cells arranged in short fascicles with variably prominent intervening collagen deposits (Fig. 6.47b).
- Tumor cells show spindle nuclei, inconspicuous nucleoli, and scant cytoplasm (Fig. 6.47c).
- Mitotic figures are uncommon.
- The tumor cells are positive for smooth muscle actin, S100 protein (Fig. 6.47d), FOXL2, and SF1, but negative for SOX9, calretinin, and inhibin.
- The tumor is differentiated from fibroma (positive for SOX9, inhibin, and calretinin; and negative for S100) and leiomyoma (negative for S100).
- All the reported tumors have exhibited benign clinical behaviors.

References: [135–138]

Table 6.21 Comparison of clinicopathologic features between adult and juvenile granuloma cell tumors

	Adult granulosa cell tumor	Juvenile granulosa cell tumor
Pathology	A well-circumscribed, predominantly solid tumor It typically shows a nodular growth pattern (Fig. 6.35a) Within nodules, diffuse, microfollicular, trabecular, nest, cord, or spindle cell (Fig. 6.35b) patterns may be present Tumor cells have elongated nuclei and scant cytoplasm Nuclear grooves are common Mitotic figures are rare Tumor cells may be luteinized	A well-circumscribed predominantly cystic tumor It typically shows cysts of various sizes with eosinophilic or basophilic fluid (Fig. 6.36a) Cysts are lined by multilayered cells. The inner cells resemble granulosa cells with round nuclei, small nucleoli, and scant cytoplasm. The outer cells resemble theca cells with elongated nuclei and scant cytoplasm (Fig. 6.36b) Tumor cells lack nuclear grooves Mitotic activity is brisk
Clinical features	Patients may be any age with a mean of 40 years Testicular swelling Gynecomastia in 25% if cases Acquired FOXL2 mutations in some cases Most are benign, but 20% are malignant Malignancy is associated with >4 cm, infiltrative borders, tumor necrosis, and lymphovascular invasion. Orchiectomy for local disease Retroperitoneal lymph node dissection may be considered for metastatic disease	Almost all patients in the first decade of life and 90% in the first 6 months Testicular swelling Cryptorchism in 30% cases Some cases show abnormal karyotypes including mosaics 45,X/47,XYY or 45,X/46,Xr(Y) All are benign Orchiectomy is curative Testis-sparing enucleation may be considered in some cases

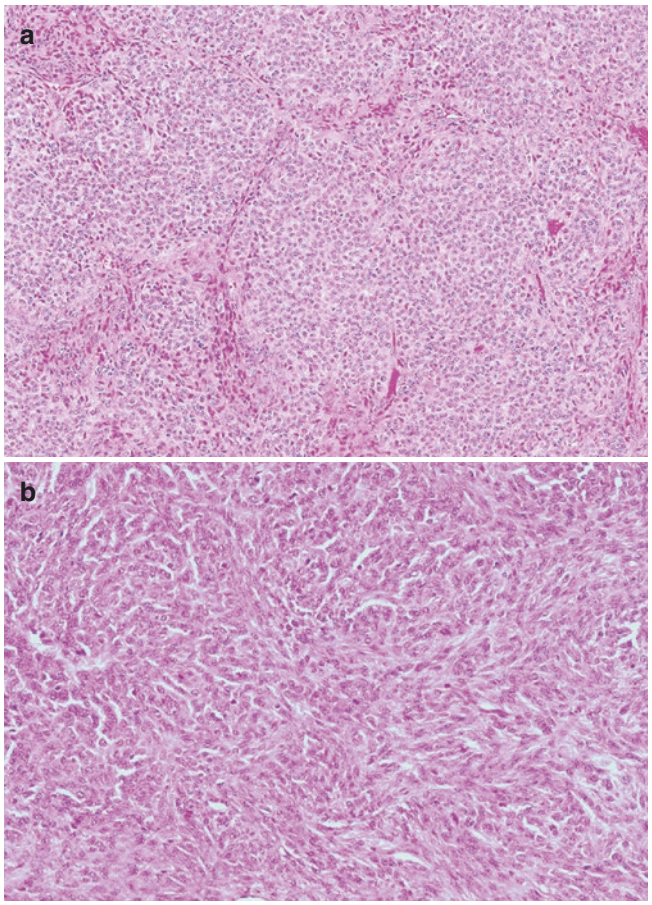

Fig. 6.35 Adult granulosa cell tumor. (**a**) Tumor usually shows nodular growth pattern. (**b**) Tumor shows focal spindle cell features

How Is Testicular Lymphoma Differentiated from Seminoma?

See Table 6.27 for the differences between seminoma and diffuse large B-cell lymphoma (Figs. 6.2 and 6.48).

References: [35, 79, 139–144]

How Is Adenomatoid Tumor Differentiated from Malignant Mesothelioma?

See Table 6.28 for the differences between malignant mesothelioma and adenomatoid tumor (Figs. 6.39 and 6.40).

References: [105–107, 109–111, 145]

How Is Rete Testis Adenocarcinoma Diagnosed?

It is a malignant glandular neoplasm arising from the rete epithelium. The tumor shows various growth patterns, such as tubuloglandular, retiform, Sertoliform, kaposiform, and spindle cell features (Fig. 6.49a). The tumor cells are cuboidal to columnar with moderate-to-eosinophilic cytoplasm and moderate-to-severe atypia (Fig. 6.49b). Necrosis, infiltrative growth, and desmoplasia are common (Fig. 6.49c). There are no specific linages associated immunohistochemical markers for rete testis. It must be differentiated from other glands-forming malignancies that occur at this site, such as malignant

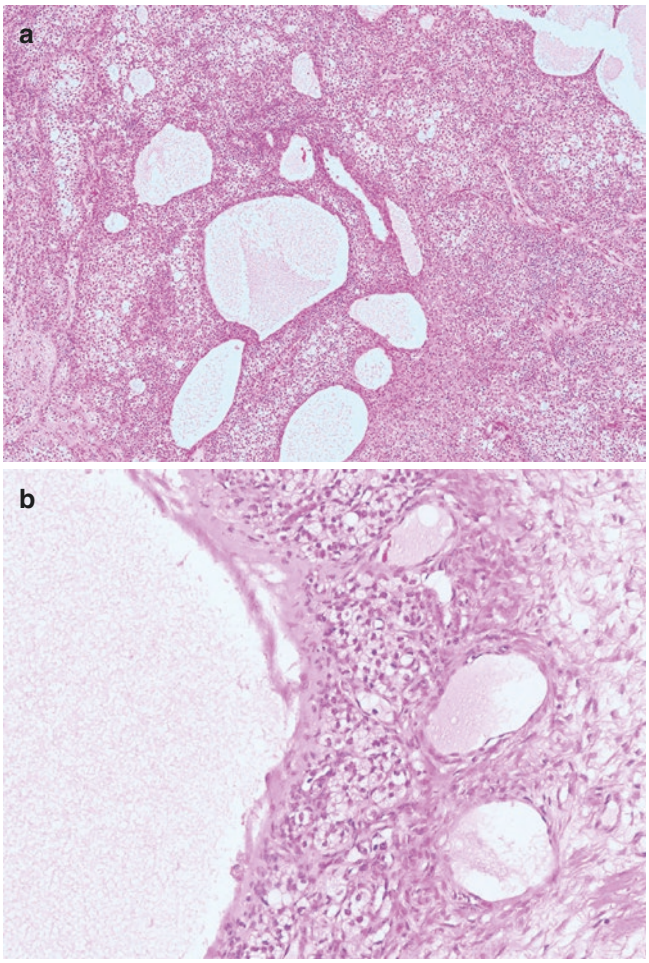

Fig. 6.36 Juvenile granulosa cell tumor. (**a**) Tumor shows cysts of various sizes with eosinophilic fluid. (**b**) Cysts are lined by multilayered cells. The inner cells resemble granulosa cells with round nuclei and scant cytoplasm. The outer cells resemble theca cells with elongated nuclei and scant cytoplasm

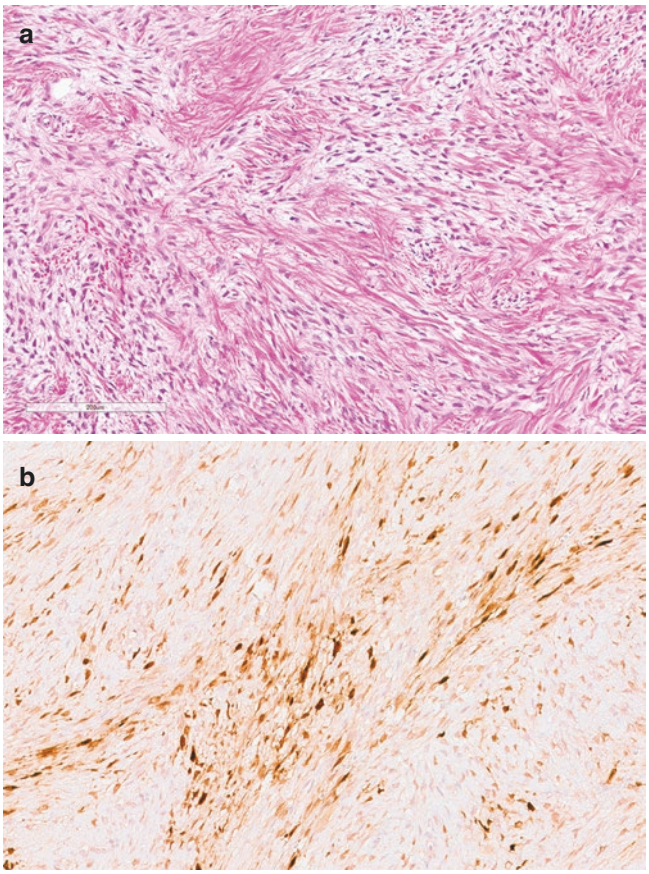

Fig. 6.37 Fibrothecoma. (**a**) Tumor is characterized by spindle-shaped fibroblasts with minimal cytologic atypia that usually shows fascicular or storiform patterns in scant stroma. (**b**) Tumor is positive for inhibin

mesothelioma, metastatic adenocarcinoma, and malignant Sertoli cell tumor. These malignancies often express lineage-associated immunohistochemical markers. The following diagnostic criteria are recommended: the tumor is grossly centered in the hilum of the testis; absence of a neoplasm elsewhere that resembles rete adenocarcinoma; morphologic and immunohistochemical features incompatible with other forms of primary testicular and paratesticular neoplasms; and at least partial tumor growth within channels of the rete testis (Fig. 6.49d). A transition from benign to malignant epithelium within the rete testis may help the diagnosis but not required, as advanced tumors may obliterate the non-neoplastic rete epithelium. Furthermore, metastatic carcinoma may grow within the rete and replace its epithelium, thereby mimicking the transition from benign to malignant.

References: [107, 146–148]

Case Presentation

Case 1

Learning Objectives

1. To become familiar with the gross and histologic features of the tumor
2. To learn the immunohistochemical features of this tumor
3. To provide the accurate pT category

Case History

A 37-year-old male with left testicular mass and elevated LDH.

Gross

Radical orchiectomy specimen with diffuse testicular involvement by a fleshy, partially nodular tumor measuring 5.8 cm with areas suspicious for epididymal invasion and hilar fat invasion (Fig. 6.50a).

Table 6.22 Comparison of clinicopathologic features between mesothelial hyperplasia and malignant mesothelioma

	Mesothelial hyperplasia	Malignant mesothelioma
Pathology	Fibrotic thickening of the walls of tunica vaginalis with no gross mass Epithelial proliferation shows simple papillary structures, tubules, and nests (Fig. 6.38). Reactive mesothelial cells have abundant cytoplasm and may contain enlarged vesicular nuclei Brisk mitotic activity may be seen in inflamed areas Lack solid and arborizing complex papillary growth patterns Lack the biphasic spindle cell pattern Often associated with inflammation An infiltrative growth pattern is absent Postive for WT-1	Usually multiple friable masses on the thickened tunica vaginalis. Sometimes tumors may invade the testicular parenchyma 75% of cases are epithelial type with broad arborizing complex papillary and tubular structures (Fig. 6.39a) 25% of cases are biphasic type with epithelial and sarcomatoid (or spindle cell) components An infiltrative component is present at least focally (Fig. 6.39b) Tumor cells may show prominent cytologic atypia with pleomorphism, mitoses, and prominent nucleoli (Fig. 6.39c) Tumor may invade the testis and paratesticular tissues Postive for WT-1 (Fig. 6.39d)
Clinical features	Any age Inflammatory irritation causes reactive hyperplasia of the mesothelial lining Scrotal swelling Sometimes inflammatory signs Hydrocele repair or needle aspiration May spontaneously regress Non-neoplastic and reactive disease	Old patients (mean age 65 years) Asbestos exposure in 40% of cases Scrotal swelling Sometimes palpable ill-defined intrascrotal firm mass Radical orchiectomy for local disease Retroperitoneal lymph node dissection, radiation and chemotherapy for metastatic disease Aggressive malignant disease with a median survival of 24 months and recurrence in 60% of patients in 2 years

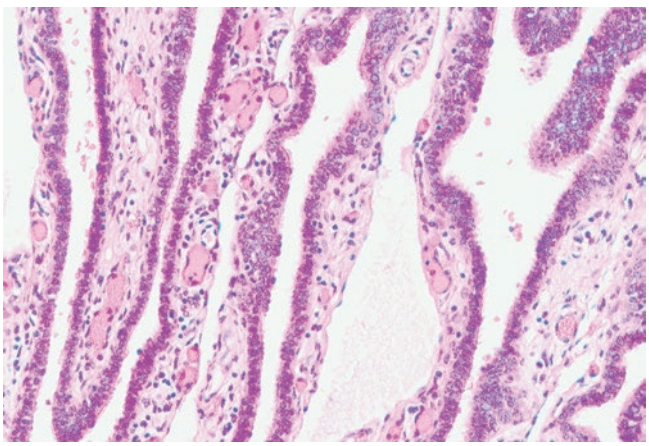

Fig. 6.38 Mesothelial hyperplasia. The epithelial proliferation is characterized by simple papillary structures lined by cells with vesicular nuclei and abundant cytoplasm

Histologic Findings

- Solid sheets with fibrous bands containing lymphocytes (Fig. 6.50b)
- Polygonal cells with distinct cell borders
- Pale eosinophilic cytoplasm
- Seminiferous tubules with atypical cells present against the basement membrane
- Invasion into the rete testis stroma, epididymal stroma and hilar soft tissue (Fig. 6.50c, d)

Differential Diagnosis

- Seminoma
- Embryonal carcinoma
- Sertoli cell tumor
- Spermatocytic tumor
- Lymphoma

IHC and Other Ancillary Studies

- Positive for PLAP, CD117/c-kit, D2-40/podoplanin, and OCT3/4
- Negative for CD30 and inhibin

Final Diagnosis

Seminoma, pT2

Take-Home Messages

1. Seminoma is a tumor with sheet-like growth and fibrous bands with lymphocytes.
2. Immunostains and the presence of GCNIS corroborate the diagnosis.
3. Hilar soft tissue invasion and epididymal invasion are a part of the pT2 category.

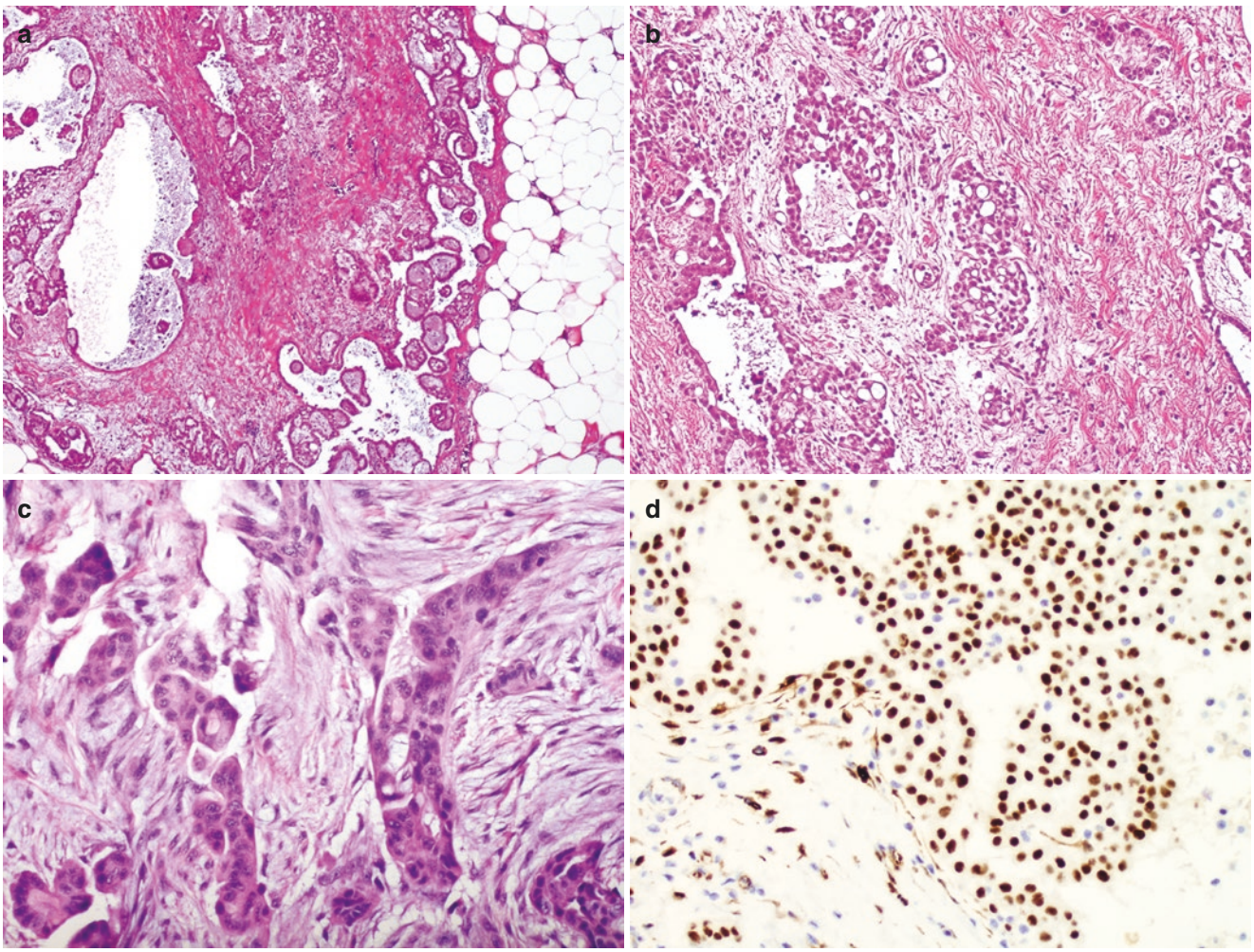

Fig. 6.39 Malignant mesothelioma. (**a**) Tumor shows complex papillary and tubular structures. (**b**) Tumor invades the fibrous stroma. (**c**) Tumor cells show prominent cytologic atypia with pleomorphism and prominent nucleoli. (**d**) Tumor is positive for WT-1

Case 2

Learning Objectives

1. To become familiar with the gross and histologic features of the tumor
2. To learn the immunohistochemical features of this tumor
3. To provide the accurate pT category

Case History

A 34-year-old male with left testicular mass with minor elevations of LDH, AFP, and HCG.

Gross

Radical orchiectomy specimen with diffuse testicular involvement by a hemorrhagic, yellow, focally cystic, and necrotic tumor measuring 7.4 cm (Fig. 6.51a)

Histologic Findings

- Predominantly tumor with sheets, papillary formation, and pseudoglandular spaces (utilized for IHC)
- Large, polygonal, pleomorphic cells with abundant mitotic figures (Fig. 6.51b)
- Amphophilic cytoplasm
- Seminiferous tubules with atypical cells present against the basement membrane
- Lymphovascular invasion (Fig. 6.51c, d)

Differential Diagnosis

- Embryonal carcinoma
- Seminoma
- Yolk sac tumor
- Choriocarcinoma
- Lymphoma
- Malignant melanoma

Table 6.23 Comparison of clinicopathologic features between adenomatoid tumor and metastatic adenocarcinoma to the testis

	Adenomatoid tumor	Metastatic adenocarcinoma
Pathology	Usually a unilateral, well-circumscribed, tan-white, small tumor (typically <2 cm) in the epididymis. Occasionally it may involve the testis It is characterized by gland-like or vascular-like spaces lined by an attenuated layer of neoplastic cells that often form thin, bridging strands across the lumen (Fig. 6.40a) Cytologic atypia is minimal (Fig. 6.40b) Prominent intracytoplasmic vacuolization component may be present (Fig. 6.40c) Necrosis, perineural invasion and lymphovascular invasion are uncommon May be positive for mesothelial markers, such as calretinin, WT1 (Fig. 6.40d), HBME1, and podoplanin	Mostly solitary nodules (62%) Sometimes multiple nodules (17%) and diffuse involvement (21%) and bilateral in 20% of cases Carcinomas of the prostate (Fig. 6.41a–d), GI tract (Fig. 6.42a–d), kidney, and lung are among the most common primary Metastases show morphologic features similar to the primary tumors Significant cytologic atypia is typical Necrosis, perineural and intravascular invasion are common Usually negative for mesothelial markers Express the lineage-specific markers of the primary tumors – NKX3.1 and Prostein, PSA for prostate cancer; TTF-1 for lung cancer; CDX-2 for colon cancer; PAX8 for kidney cancer
Clinical features	A wide age range with a mean of 36 years Usually scrotal mass, sometimes with pain May involve the scrotal skin The most common tumor in the paratesticular region Benign tumor Usually radical orchiectomy Sometimes partial orchiectomy upon confirming the diagnosis on frozen section	Usually old patients with a mean age of 60 years. Testicular or paratesticular mass Symptoms associated with the primary tumor Systemic therapy directed to primary tumor Generally poor

IHC and Other Ancillary Studies

- Positive for OCT3/4 and CD30
- Negative for glypican 3, AFP, GATA3, CK7, and HCG

Final Diagnosis

Mixed germ cell tumor, embryonal carcinoma (80%), teratoma (10%), yolk sac tumor (5%), and choriocarcinoma (5%) types, pT2

Take-Home Messages

1. Embryonal carcinoma is a pleomorphic, high-grade tumor.
2. Immunostains corroborate the diagnosis.
3. In tumors with predominant embryonal carcinoma, lymphovascular invasion is frequent yielding a pT2 categorization.

Case 3

Learning Objectives

1. To learn the gross and histologic features of this tumor
2. To learn the immunohistochemical features of this tumor
3. To distinguish this tumor from its mimics

Case History

A 68-year-old man was present with a hydrocele in the right scrotum. Image study revealed a large mass involved the testis and scrotum. His serum markers, AFP, HCG, and LDH, were within the normal ranges. He underwent an en bloc resection of the involved scrotum, testis, spermatic cord, and inguinal lymph nodes. The patient, otherwise healthy, did not have any previous cancer history.

Gross

Sections of the testis revealed a poorly defined, tan-white, solid mass (7.5 × 3.6 × 2.8 cm) with focal areas of necrosis and hemorrhage (Fig. 6.52a). The mass was centered at the rete testis and wrapped around the upper and posterior surface of the testis. The tumor also extended to the epididymis and spermatic cord.

Histologic Findings

- Tumor shows a pushing border growth with a thick fibrous capsule but does not invade the testicular parenchyma (Fig. 6.52b).
- Tumor exhibits papillary and tubulocystic structures are lined by cuboidal and flat cells and occasionally hobnail cells (Fig. 6.52c).
- The tumor cells show clear cytoplasm and high nuclear grade associated with a delicate fibrovascular vascular stroma (Fig. 6.52d).

Differential Diagnosis

- Metastatic renal cell carcinoma
- Ovarian type epithelial tumor of the paratestis
- Malignant mesothelioma
- Germ cell tumor (or yolk sac tumor)

IHC and Other Ancillary Studies (Fig. 6.52e, f)

- Positive for PAX2, PAX8, HNF-1B, and p504S
- Negative for SALL4, OCT3/4, calretinin, inhibin, and WT-1

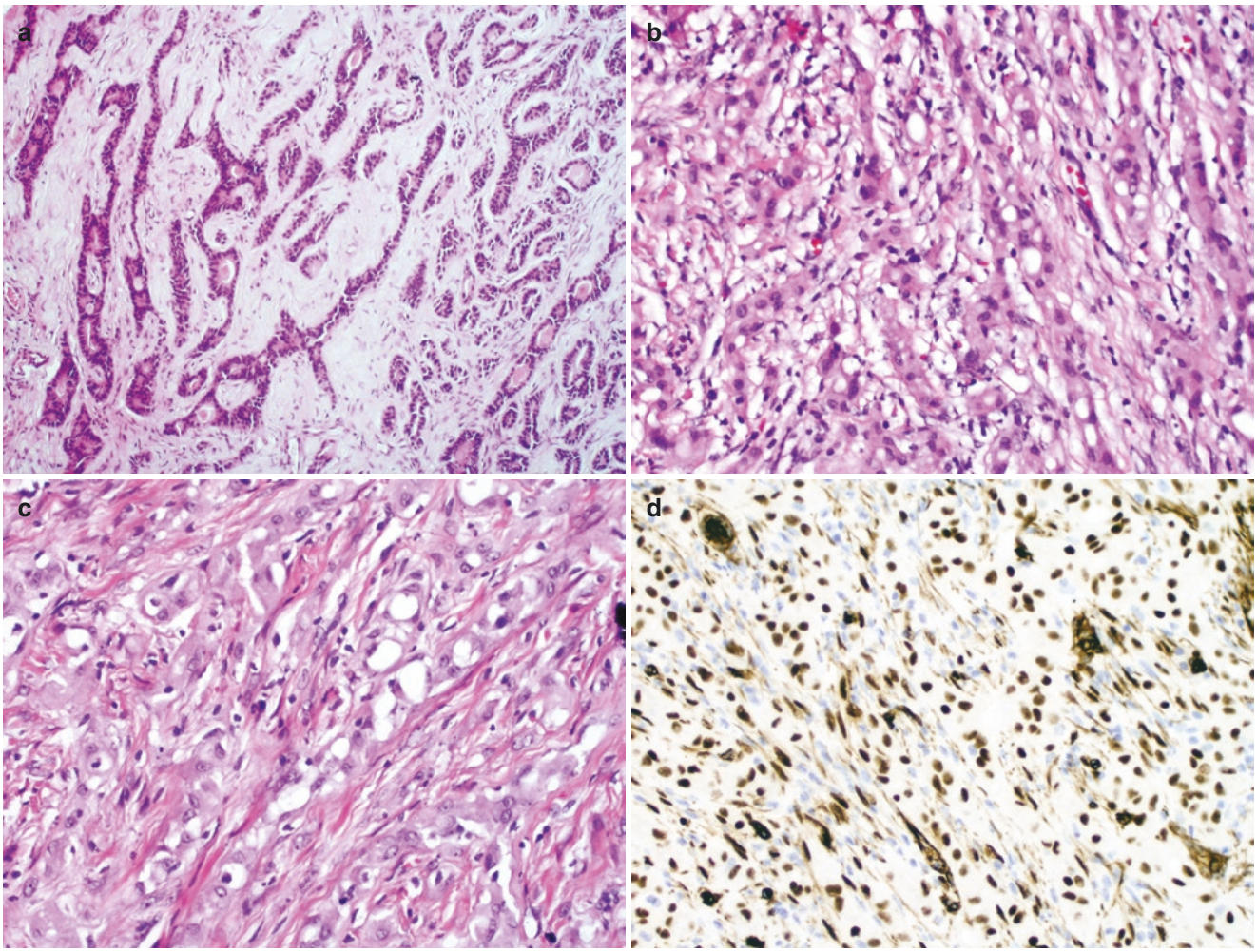

Fig. 6.40 Adenomatoid tumor. (**a**) Tumor is characterized by gland-like spaces with thin, bridging strands across the lumen. (**b**) Tumor cells have round nuclei with minimal atypia. (**c**) Intracytoplasmic vacuolization is present. (**d**) Tumor is positive for WT-1

- Ki-67 index ~30%.

Final Diagnosis

Ovarian-type epithelial tumor of the paratestis- Clear cell adenocarcinoma

Take-Home Messages

1. Clear cell adenocarcinoma may arise from the tunica vaginalis and shows microscopic and immunohistochemical features similar to its ovarian counterpart.
2. It is positive for PAX2, PAX8, HNF-1B, and p504S; and negative for germ cell tumor and mesothelial markers.
3. Clear cell adenocarcinoma cells have clear cytoplasm and form papillary structures, mimicking renal cell carcinoma, but patients do not have a previous history of RCC or renal mass.

References: [134, 149, 150]

Case 4

Learning Objectives

1. To learn the gross and histologic features of metastatic carcinoma to the testis
2. To learn how to differentiate metastatic carcinoma from other testicular malignancies
3. To learn how to use immunohistochemistry in the differential diagnosis and identifying the origin of metastatic carcinoma

Case History

A 32-year-old man presented to an emergency room with headache. He underwent evaluation that revealed a brain lesion as well as a large left lung mass. Ultrasound of the scrotum revealed bilateral testicular tumors. Interestingly, his markers were completely normal. He underwent bilateral radical inguinal orchiectomy for his presumptive diagnosis of metastatic testicular cancer.

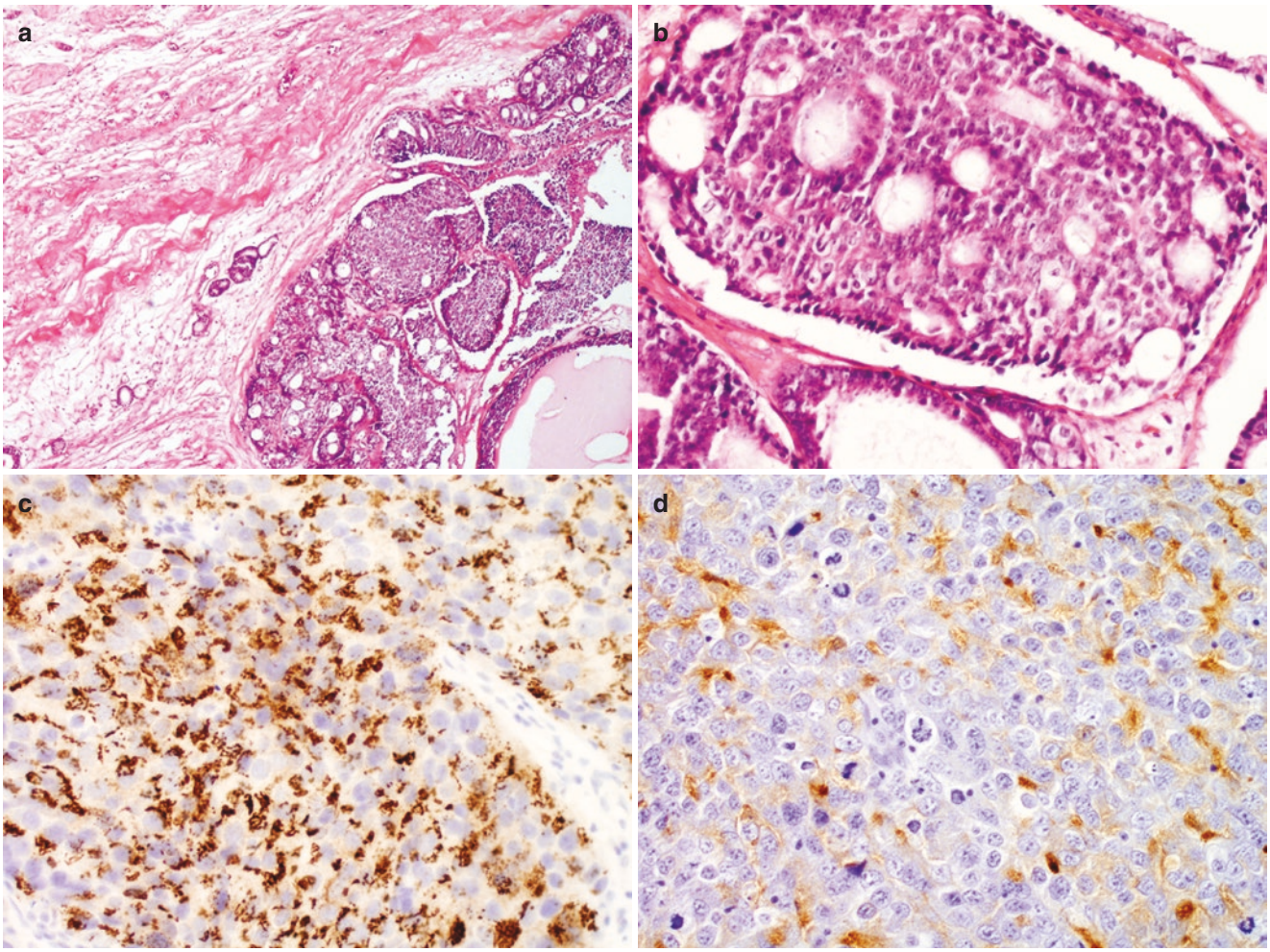

Fig. 6.41 Metastatic prostatic adenocarcinoma. (**a**) Poorly differentiated adenocarcinoma involves the testicular parenchyma. (**b**) Tumor cells form cribriform glands with prominent nucleoli. (**c**) Tumor is positive for prostein. (**d**) Tumor is positive for PSA

Gross

The right testis shows a white-tan, firm, multinodular mass (2.5 × 2.0 × 1.5 cm) with multiple miniscule satellite nodules. The left testis shows four discrete white-tan, firm nodules (0.6–2.2 cm). There was no apparent necrosis or hemorrhage on the glistening cutting surfaces. All the nodules were confined to the testis. The epididymis and spermatic cord were grossly free of tumor.

Histologic Findings

- Tumor shows large solid nodules involving the bilateral testis (Fig. 6.53a).
- Tumor cells show high-grade nuclear atypia and mitoses (Fig. 6.53b).
- The tumor involves the rete testis with lymphovascular invasion (Fig. 6.53c).
- Tumor shows an infiltrative growth pattern involving seminiferous tubules (Fig. 6.53d).

Differential Diagnosis

- Germ cell tumor (or embryonic carcinoma)
- Malignant mesothelioma
- Malignant sex cord-stromal tumor
- Diffuse large B-cell lymphoma

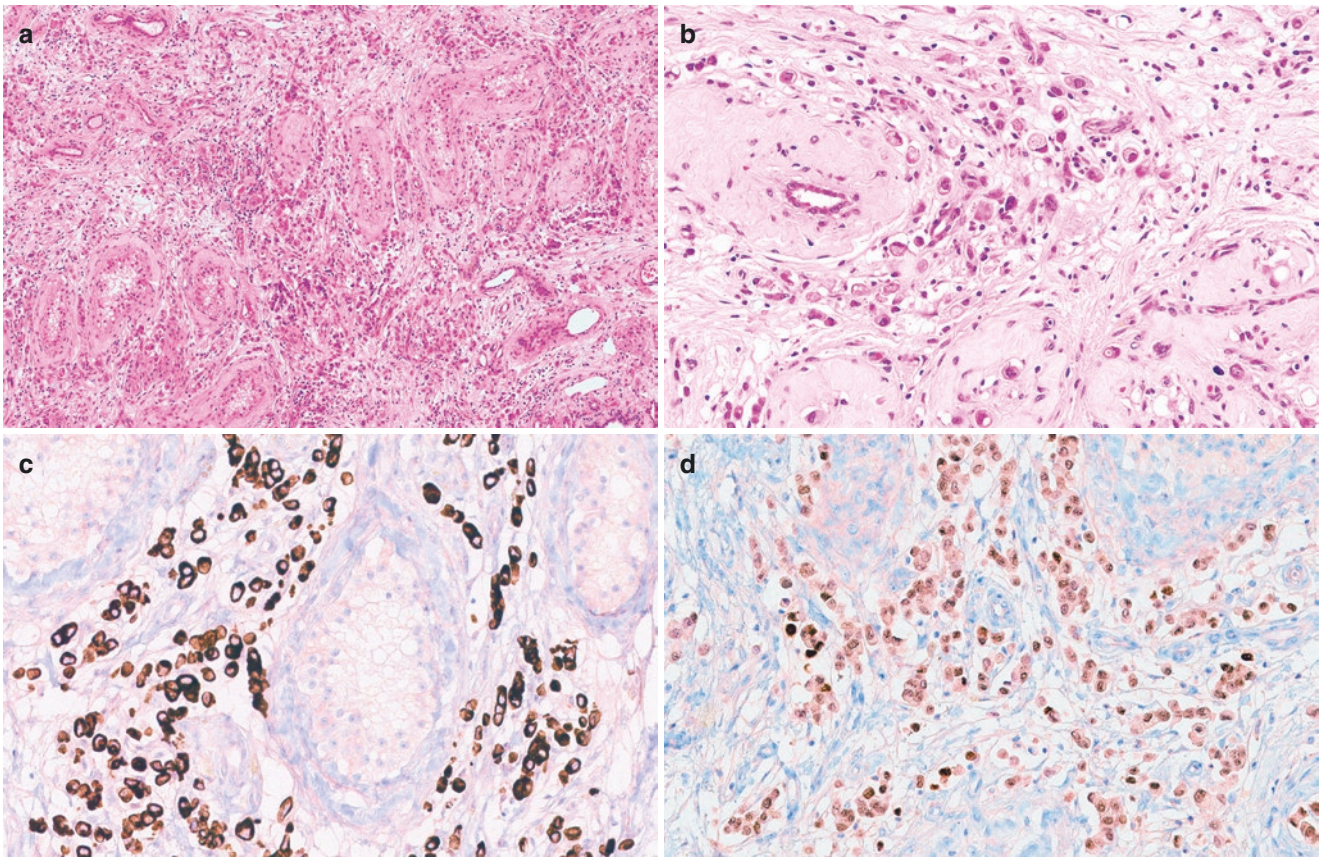

Fig. 6.42 Metastatic gastric adenocarcinoma. (**a**) Tumor diffusely invades the stroma around seminiferous tubules. (**b**) Tumor cells are poor differentiated with focal signet-ring cell features. (**c**) Tumor is positive for CK 7. (**d**) Tumor is positive for CDX2

- Metastatic lung carcinoma

IHC and Other Ancillary Studies (Fig. 6.53e–h)

- Tumor is positive for TTF-1, CK7, and Napsin
- Negative for SALL-4, OCT3/4, WT-1, SF-1, inhibin, and CD45
- DNA sequencing test shows mutations in BRAF, EGFR, and KRAS genes
- FISH test shows rearrangement of ALK gene

Final Diagnosis

Metastatic poorly differentiated lung adenocarcinoma to the testes

Take-Home Messages

1. Metastatic carcinoma often shows multiple lesions in bilateral testes.
2. Tumor may diffusely invade the testis as well as paratesticular structures with extensive lymphovascular invasion.
3. Tumor infiltrates the stroma around seminiferous tubules.
4. Immunohistochemistry is extremely valuable in the differential diagnosis and determining the origin of metastatic carcinoma.

References: [112, 151–153]

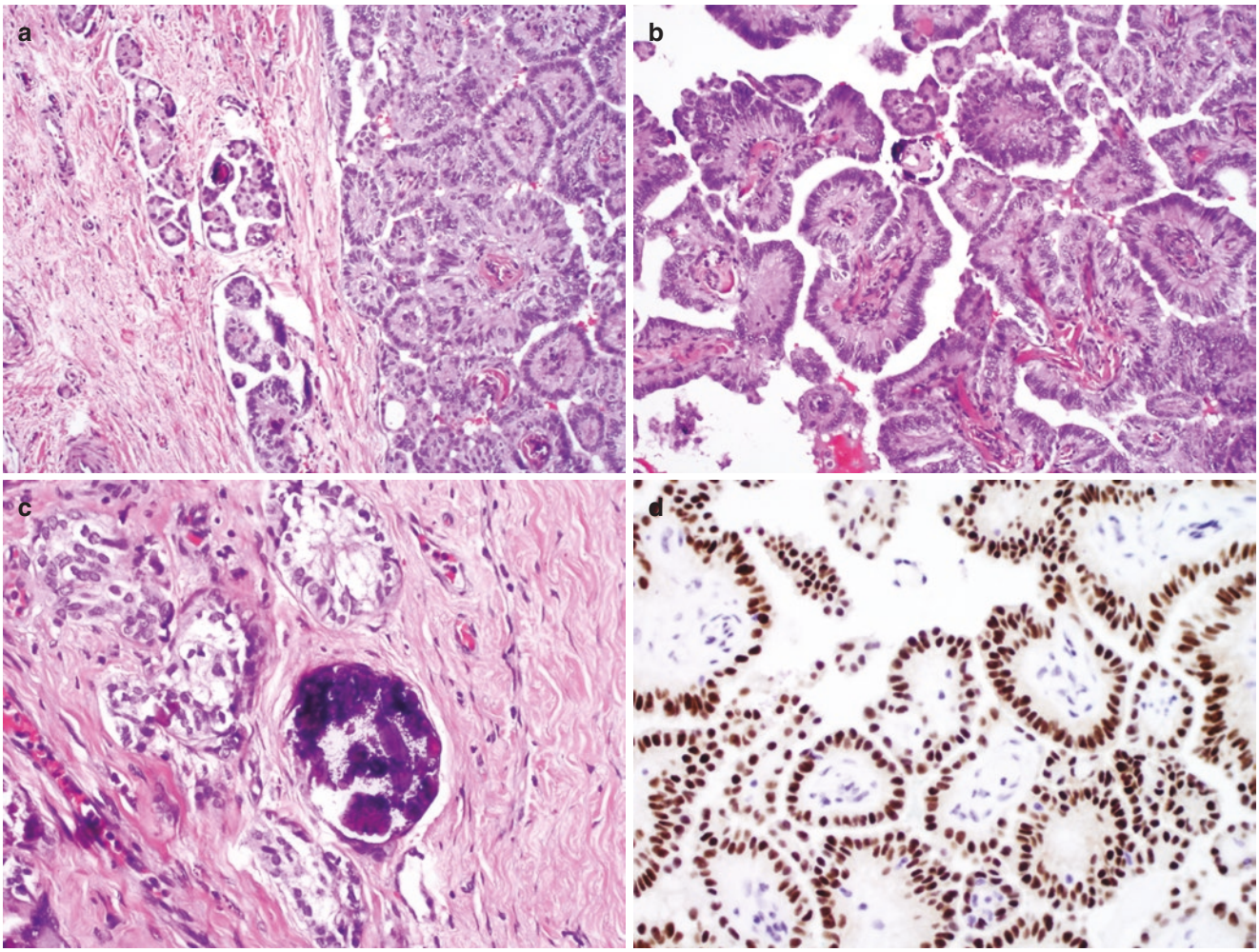

Fig. 6.43 Epididymal adenocarcinoma. (**a**) Tumor may show papillary and tubular features. (**b**) Papillary structures are lined by cuboidal cells with clear cytoplasm. (**c**) Focal calcification is present. (**d**) Tumor is positive for PAX8

Table 6.24 Comparison of clinicopathologic features between testicular germ cell tumor and metastatic adenocarcinoma to the testis

	Germ cell tumors	Metastatic adenocarcinoma
Pathology	Usually unilateral and bilateral in 5% of cases Seminoma, embryonal carcinoma, yolk sac tumor, and teratoma are among the most common types Each type shows distinct morphologic features and growth patterns GCNIS is present iso12p is present Positive for GCT markers, including OCT3/4, Sall4, and PLAP	Mostly unilateral and bilateral in 20% of cases Carcinomas of the prostate, GI tract, kidney and lung are among the most common primary Metastases show morphologic features similar to the primary tumors Lack iso12p Negative for GCTmarkers Positive for the lineage-specific markers of the primary tumors – NKX3.1 for prostate cancer; TTF-1 for lung cancer; CDX-2 for colon cancer; PAX8 for kidney cancer
Clinical features	Account for >90% of testicular tumros Young patient with a mean age of 30 years Testicular mass, sometimes with pain Elevated serum markers (LDH, AFP and βHCG) Orchiectomy, chemotherapy, or radiation therapy Most are malignant with frequent metastasis but prognosis is excellent Cure rates are close to 100% for local disease and 80% for metastasis	Account for <5% of tesituclar tumors Usually old patients with a mean age of 60 years. Testicular or paratesticular mass. Symptoms associated with the primary tumors Normal serum markers Systemic therapy directed to primary tumor Generally poor

Table 6.25 Comparison of clinicopathologic features between paratesticular lipoma and liposarcoma

	Lipoma	Liposarcoma
Pathology	A soft lobulated, well-defined mass lacking areas of hemorrhage or necrosis Mature adipocytes separated by thin fibrous septae No nuclear hyperchromasia, irregularity, or brisk mitotic activity Some lipomas may result from lipomatous hyperplasia of paratesticular soft tissue or extension of fat in an inguinal hernia rather than true neoplasms No MDM2 amplification No chromosomal abnormalities.	Well-differentiated liposarcoma appears as a soft lobulated, variably well-defined large fatty mass (3–30 cm) Dedifferentiated and pleomorphic liposarcomas may appear fleshy and often have necrosis, hemorrhage 50–60% of cases are well-differentiated type, which usually shows mature adipose tissue and a few lipoblasts characterized by nuclear indentation by intracytoplasmic lipid vacuoles (Fig. 6.44a, b). The stromal cells may have enlarged hyperchromatic nuclei Dedifferentiated type consists of an undifferentiated pleomorphic sarcoma, usually arising from a pre-existing well-differentiated liposarcoma Myxoid and pleomorphic types may also be seen and identical to those in other soft tissues locations. MDM2 amplification Giant marker/ring chromosomes in well-differentiated and dedifferentiated liposarcomas
Clinical features	A wide age range The most common paratesticular mesenchymal tumor Intrascrotal soft mass typically located in the upper portion of the spermatic cord Benign Local excision	Old patients with a mean age of 56 years Account for 20–56% of all paratesticular sarcomas Scrotal swelling near the base of the spermatic cord. Well-differentiated type often recurs but does not metastasize Dedifferentiated liposarcomas have a 5-year mortality rate of 10–30%. Conservative complete excision Radical orchiectomy, if the testis is involved

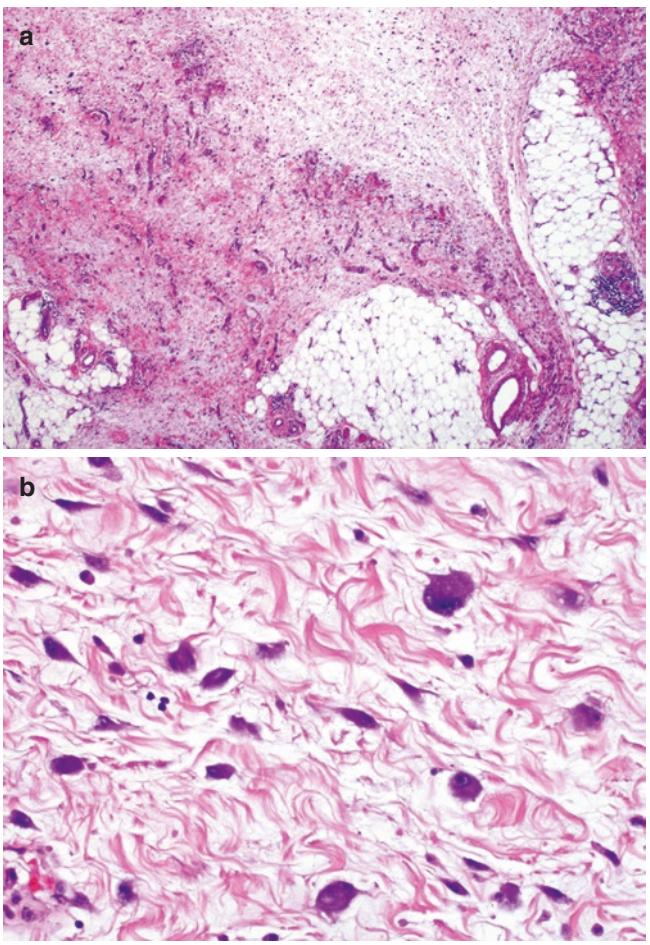

Fig. 6.44 Well-differentiated liposarcoma of the spermatic cord. (**a**) Tumor shows mature adipose tissue with bands of fibrotic stroma. (**b**) There are atypical stromal cells with enlarged hyperchromatic nuclei

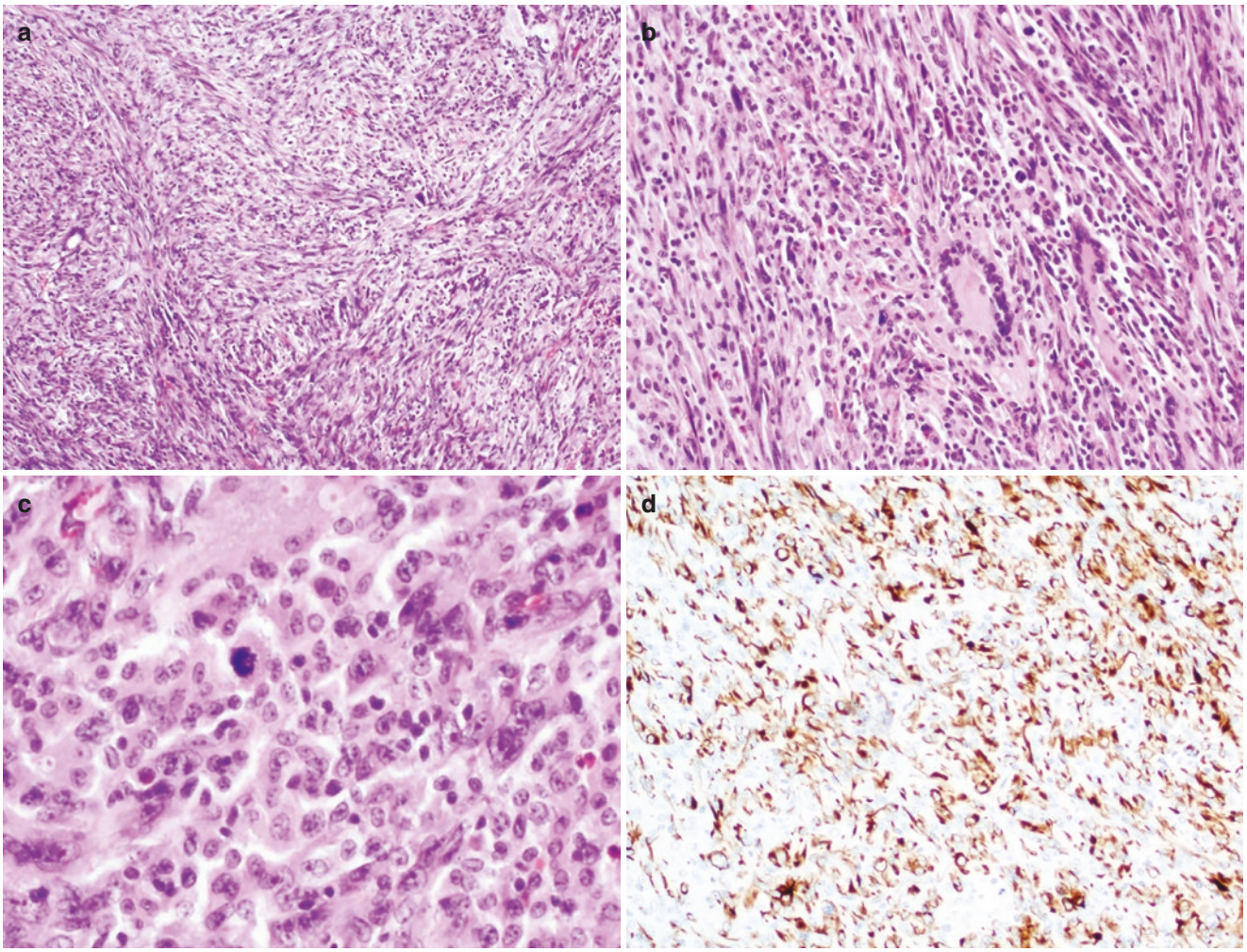

Fig. 6.45 Leiomyosarcoma of the spermatic cord. (**a**) Tumor is characterized by fascicles of atypical spindle cell proliferation. (**b**) Tumor cells show high-grade nuclear atypia. (**c**) Atypical mitosis is present. (**d**) Tumor is positive for desmin

Table 6.26 Comparison of clinicopathologic features between paratesticular rhabdomyosarcoma and leiomyosarcoma

	Rhabdomyosarcoma	Leiomyosarcoma
Pathology	Usually a lobulated, tan-white, glistening, soft tumor with focal hemorrhage and necrosis Most are embryonal type, consisting of primitive small round or spindle cells with hyperchromatic nuclei (Fig. 6.46a) Often show variable numbers of differentiated rhabdomyoblasts with distinct eosinophilic cytoplasm and discernible cross striation (Fig. 6.46b) Spindle cell type is characterized by fusiform cells arranged in a fascicle or storiform pattern. Alveolar and pleomorphic types are rare. Positive for desmin (Fig. 6.46c), muscle specific actin, myogenin (Fig. 6.46d), and MyoD1	Usually a solid, tan-white, well-circumscribed tumor with a whorled cut surface Characterized by fascicles of spindle cells with eosinophilic cytoplasm and cigar-shaped nuclei Tumor cells show variable degree (grade 1–3) of pleomorphism, tumor necrosis, and mitotic activity Tumor covers the entire spectrum of smooth muscle differentiation Other variants, such as myxoid and epithelioid, may be occasionally seen Positive for desmin and muscle specific actin Negative for myogenin and MyoD1
Clinical features	Usually occurs in children with a mean age of 6.6 years (range, 5–40 years). Painless paratesticular mass Orchiectomy for localized disease Systemic therapy for metastasis Excellent with a 5-year overall survival rate of about 90%	Usually occurs in old men with a mean age of 64 years (range, 17–92 years) Painless paratesticular mass Orchiectomy for localized disease Systemic therapy for metastasis Low grade may recur but not metastasize High grade often metastasizes and cause patient death

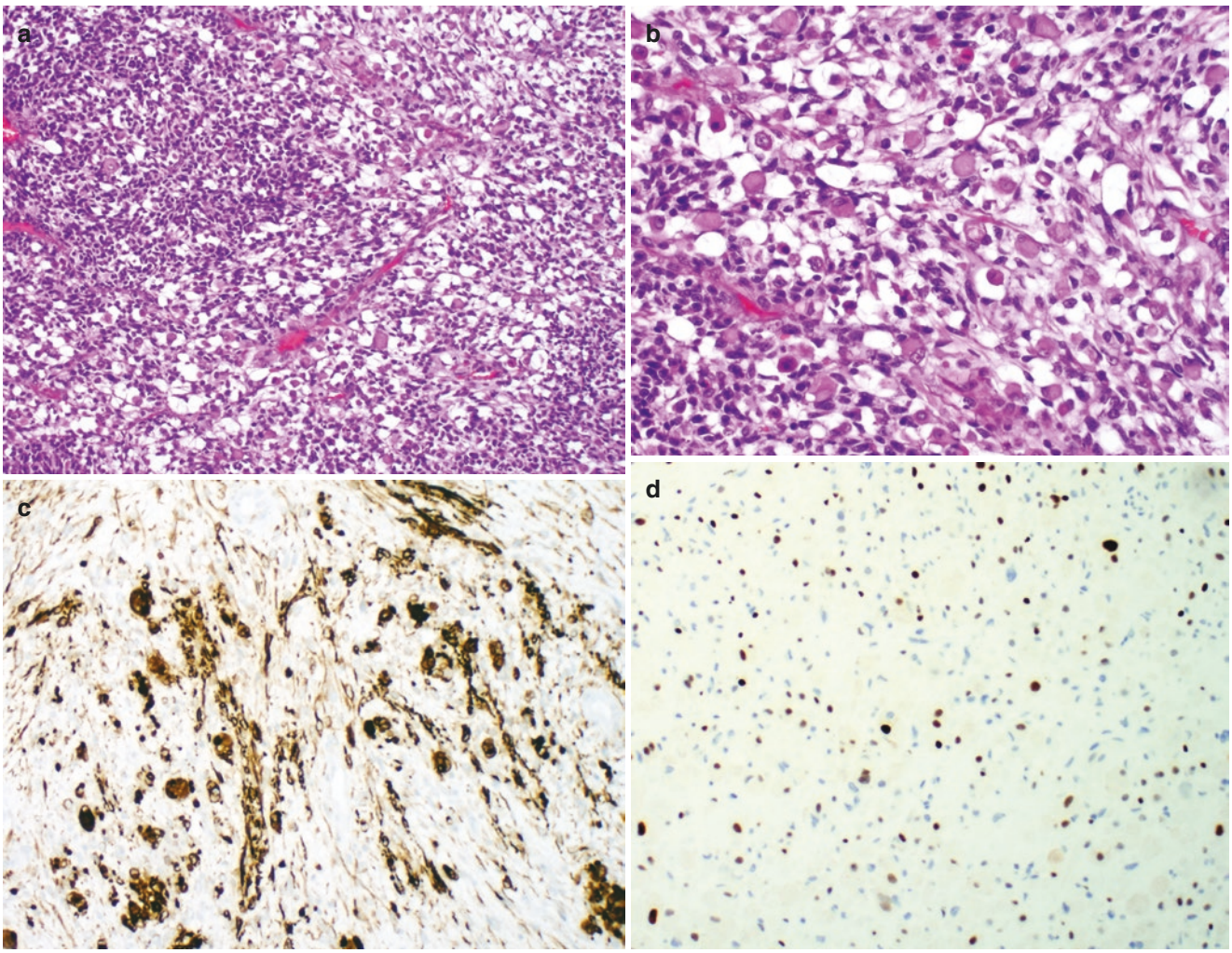

Fig. 6.46 Embryonal-type rhabdomyosarcoma. (**a**) Tumor consists of primitive small round and spindle cells with hyperchromatic nuclei. (**b**) Tumor shows a large number of differentiated rhabdomyoblasts with distinct eosinophilic cytoplasm. (**c**) Tumor is positive for desmin. (**d**) Tumor is positive for myogenin

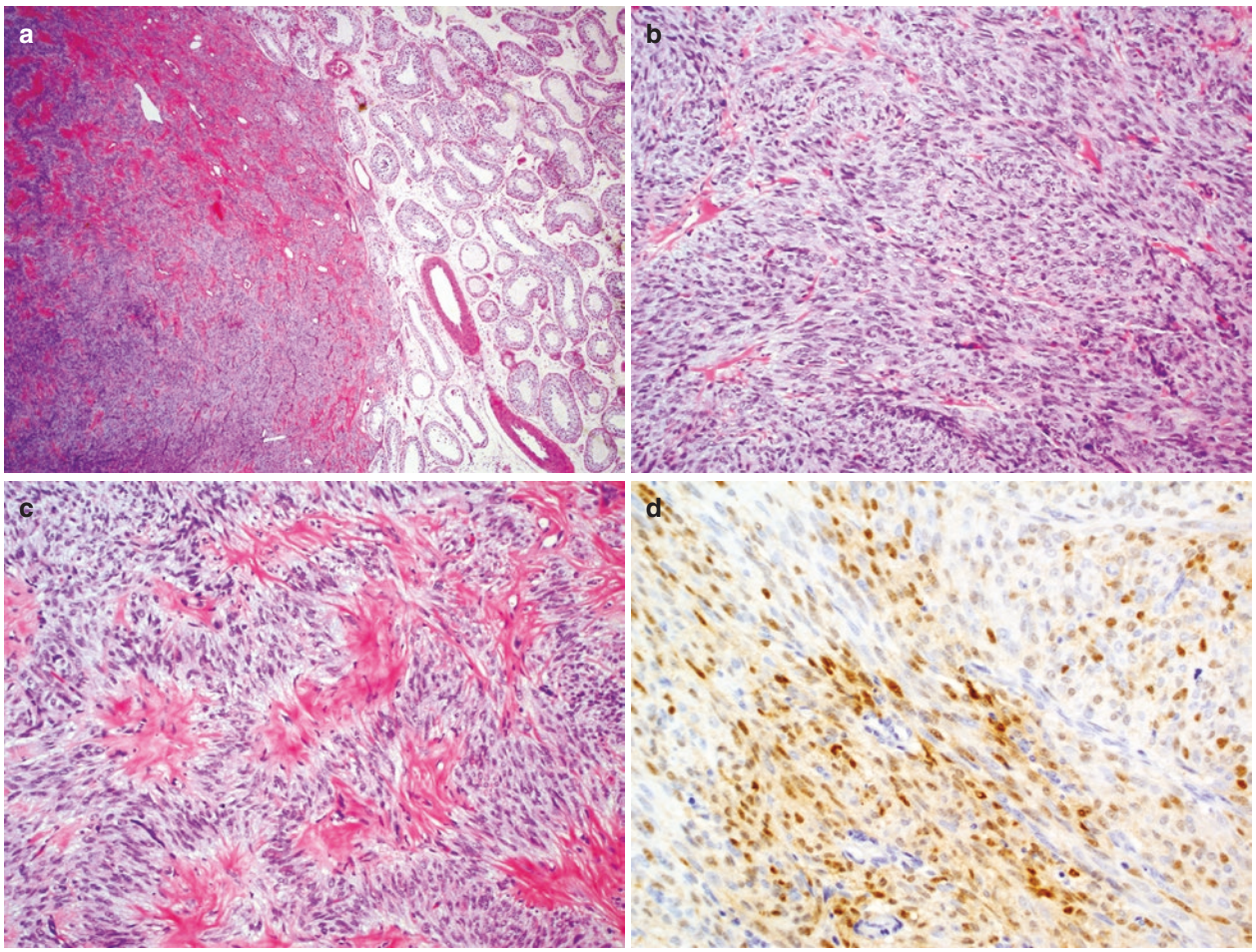

Fig. 6.47 Myoid gonadal cell tumor. (**a**) Tumor is well-circumscribed but not encapsulated. (**b**) Tumor shows densely packed, uniform spindle cells arranged in short fascicles. (**c**) Tumor cells show spindle nuclei and scant cytoplasm with prominent intervening collagen deposits. (**d**) Tumor is positive for S100

Table 6.27 Comparison of clinicopathologic features between testicular lymphoma and seminoma

	Seminoma	Testicular lymphoma
Pathology	Usually unilateral Usually a well-demarcated, tan-white multinodular mass with a mean size of 4 cm Typically shows diffuse growth pattern with solid sheets of tumor cells separated by fibrous septa. Sometimes focal cord or tubular patterns. Tumor cells show uniform and round nuclei with prominent nucleoli, distinctive cell borders, and abundant clear cytoplasm Septa usually contains abundant lymphocytes and chronic granulomatous inflammation Syncytiotrophoblasts present in 20% of cases GCNIS is present Positive for SALL4, OCT3/4, C-KIT, and PLAP Negative for CD45, CD20, and BCL2 Positive for Iso12p	Most are unilateral, but 15% of cases are bilateral A discrete fleshy, tan-white tumor with a mean of 6 cm Typically shows an interstitial growth pattern, with tumor cells surrounding but not replacing the seminiferous tubules About 80–90% of cases are diffuse large B-cell lymphomas, which are composed of atypical cells with large nuclei, prominent nucleoli, brisk mitotic activity, and scant cytoplasm (Fig. 6.48a, b). Follicular lymphoma, plasmacytoma, and other lymphomas are rare It may also involve the epididymis (60%) and spermatic cord (40%) GCNIS is absent Positive for CD45, CD20, and BCL-2 (Fig. 6.48c) Negative for SALL4, OCT3/4, C-KIT, and PLAP Negative for iso12p
Clinical features	Young patients with a mean age of 40 years The most common testicular tumor Painless scrotal swelling Orchiectomy followed by radiation and/or chemotherapy 30% of patients may have metastasis at presentation but prognosis is excellent Overall survival rate is 95%	Old patients with a mean age of 60 years The most common testicular tumor in men older than 50 years Painless testicular mass Orchiectomy followed by chemotherapy Recurrence in up to 80% of cases The 5-year survival is 60% for early stage and 20% for advanced stage

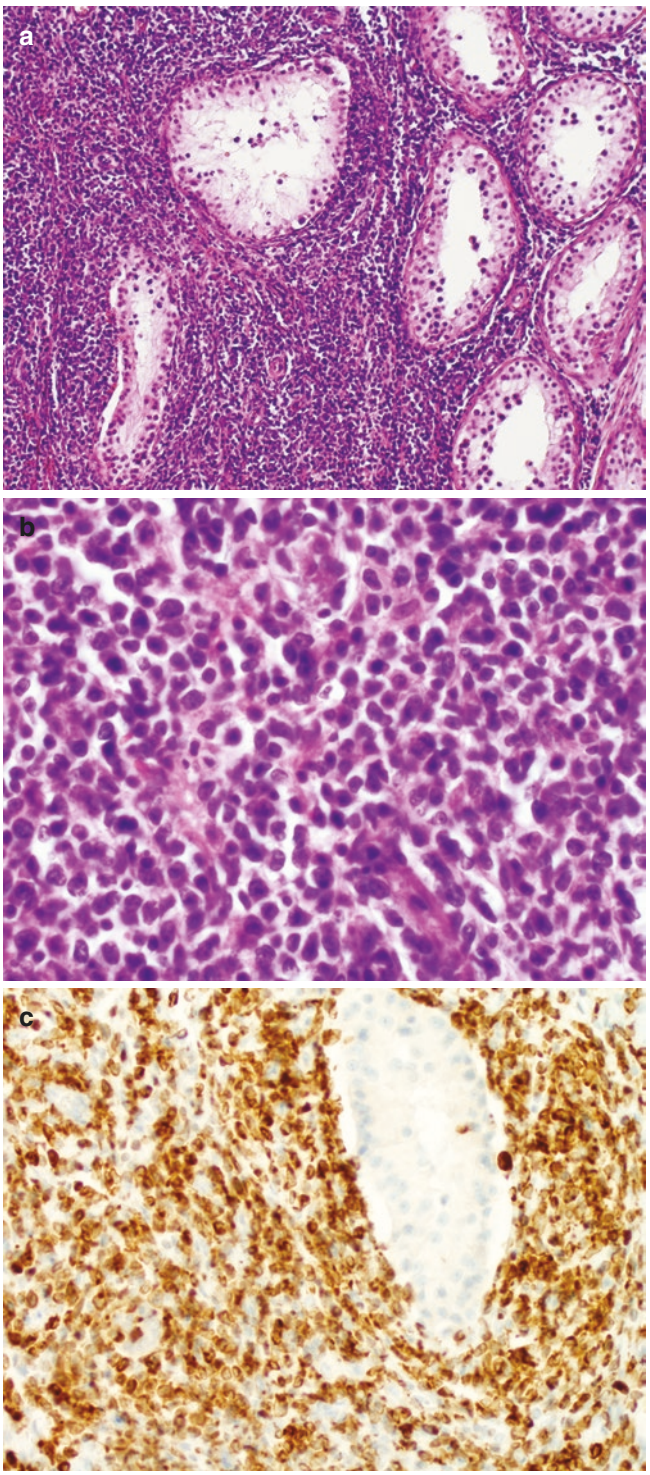

Fig. 6.48 Diffuse large B-cell lymphoma. (**a**) It shows an infiltrative growth pattern in the stroma around seminiferous tubules. (**b**) It is composed of large atypical cells with round to oval nuclei and scant cytoplasm. (**c**) It is positive for BCL-2

Table 6.28 Comparison of clinicopathologic features between adenomatoid tumor and malignant mesothelioma

	Adenomatoid tumor	Malignant mesothelioma
Pathology	Usually arise from the epididymis, sometimes from the spermatic cord and tunica Usually a unilateral, well-circumscribed, homogenous tan-white, small tumor (typically <2 cm) in the epididymis It is characterized by gland-like or vascular-like spaces lined by an attenuated layer of neoplastic cells that often form thin, bridging strands across the lumen Prominent intracytoplasmic vacuolization component may be present Cytologic atypia is minimal Necrosis, perineural invasion and lymphovascular invasion are uncommon	Usually arise from the tunica vaginalis, sometimes wrap around the testicular parenchyma The tumor coats the thickened tunica vaginalis with tan-white, solid or papillary friable nodules with focal hemorrhage and necrosis Tumor usually shows an invasive growth pattern with complex papillary or tubular architectures Tumor cells may show striking pleomorphism, with mitoses and prominent nucleoli 25% are biphasic with both epithelial and sarcomatoid components Some may have squamous, bone and cartilage differentiation
Clinical features	Younger adults with a mean age of 36 years No known risk factor The most common neoplasm in the paratesticular region. Scrotal mass Usually radical orchiectomy Sometimes partial orchiectomy upon confirming the diagnosis on frozen section Benign tumor with no metastatic potential	Old patients with a mean age of 60 years Asbestos exposure is a risking factor Scrotal mass, sometimes hydrocele Radical orchiectomy for local disease Retroperitoneal lymph node dissection, radiation and chemotherapy for metastatic disease. Aggressive malignant disease with a median survival of 24 months and recurrence in 60% of patients in 2 years

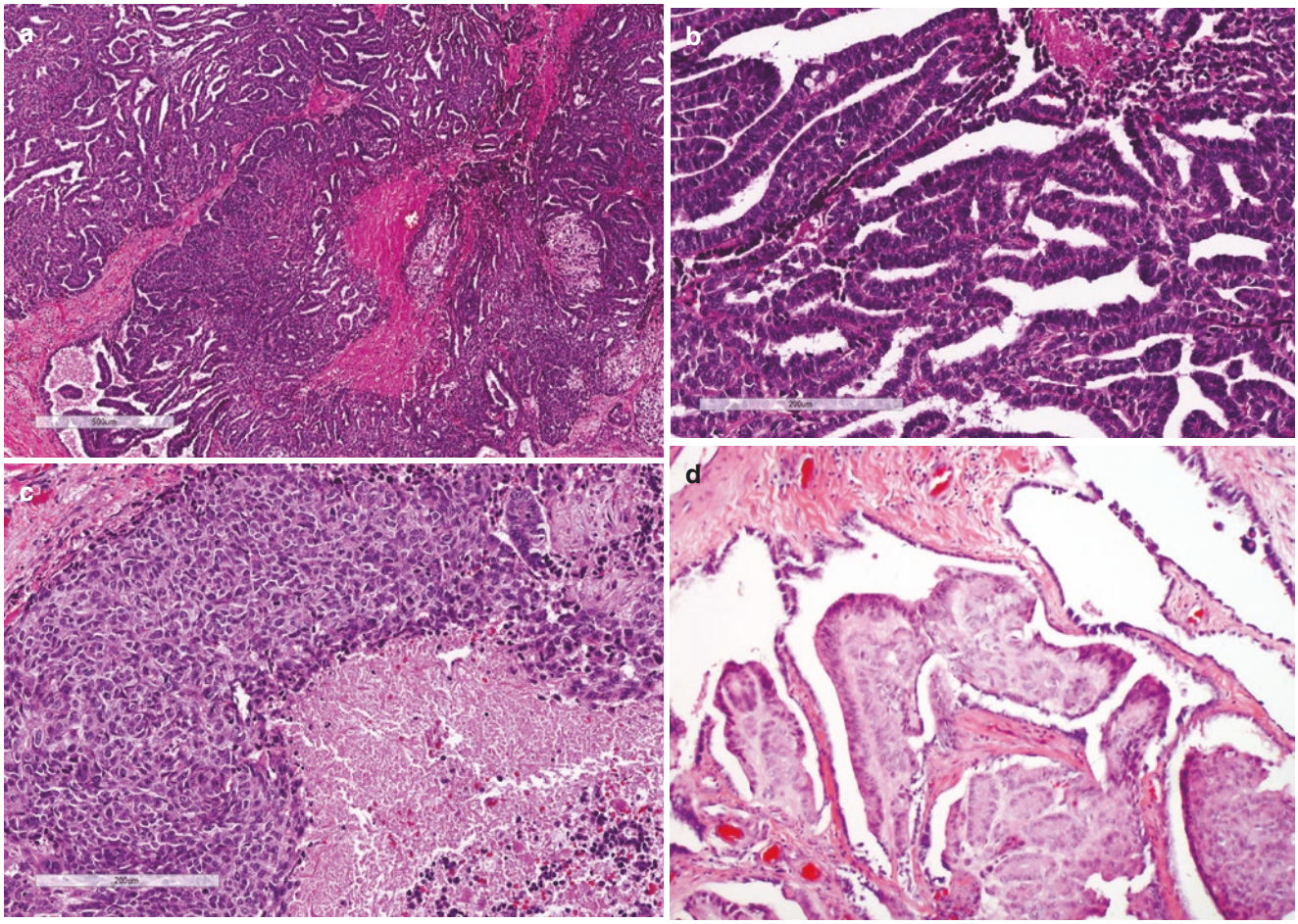

Fig. 6.49 Rete testis adenocarcinoma. (**a**) Tumor shows papillary and tubuloglandular growth patterns. (**b**) Tumor cells are cuboidal to columnar with marked nuclear atypia. (**c**) Tumor necrosis is present. (**d**) Tumor grows within channels of the rete testis

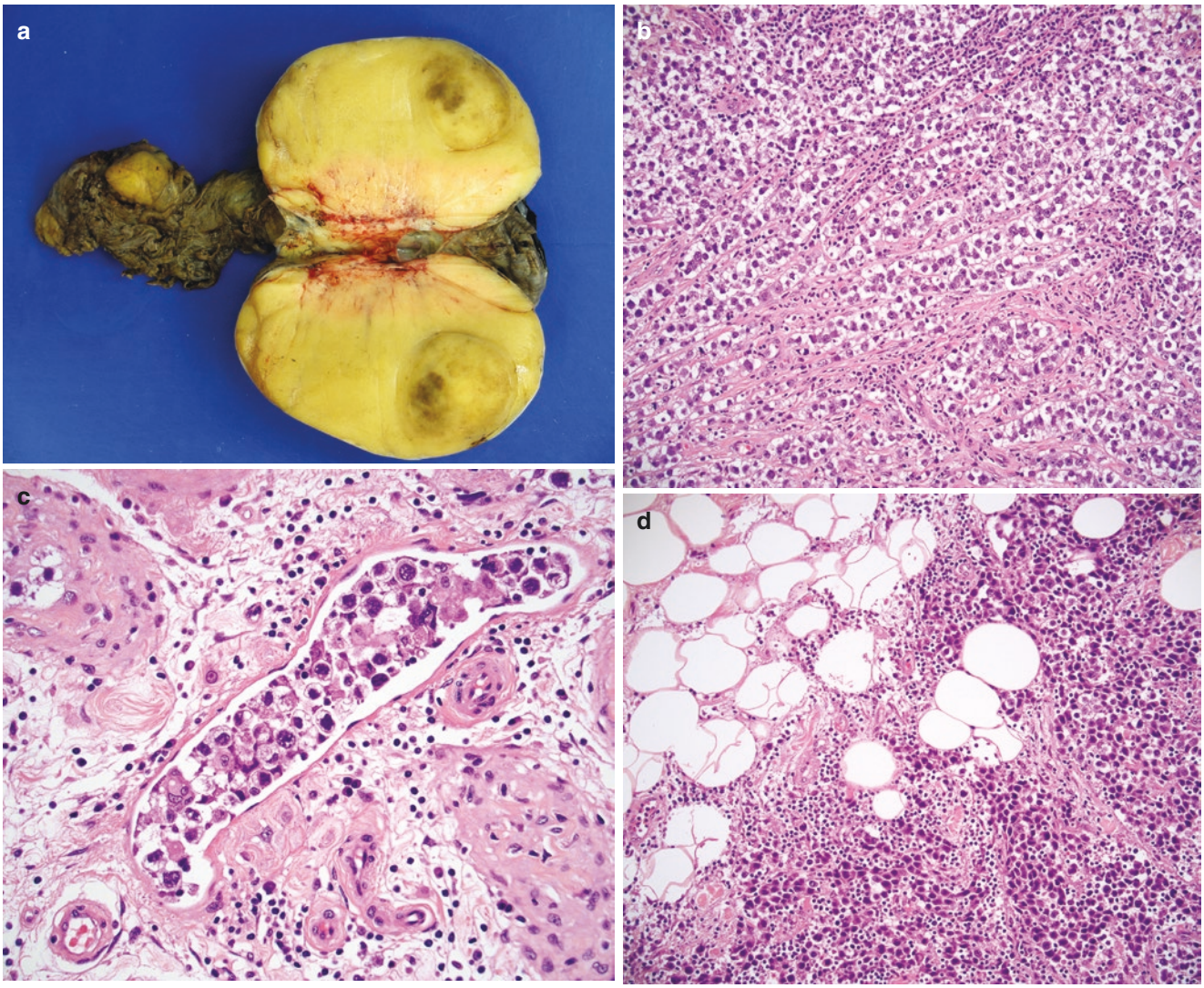

Fig. 6.50 Case 1. (**a**) Gross showing tan tumor occupying entire enlarged testis and invading surrounding hilar fat. (**b**) Tumor is separated by thin fibrous bands containing lymphocytes. Tumor cells are nonoverlapping with cleared-out cytoplasm and prominent nuclei. (**c**) Tumor is within lymphovascular spaces. This embolus is cohesive with smooth contours and is focally against the vessel wall. (**d**) Direct invasion of the hilar fat is seen

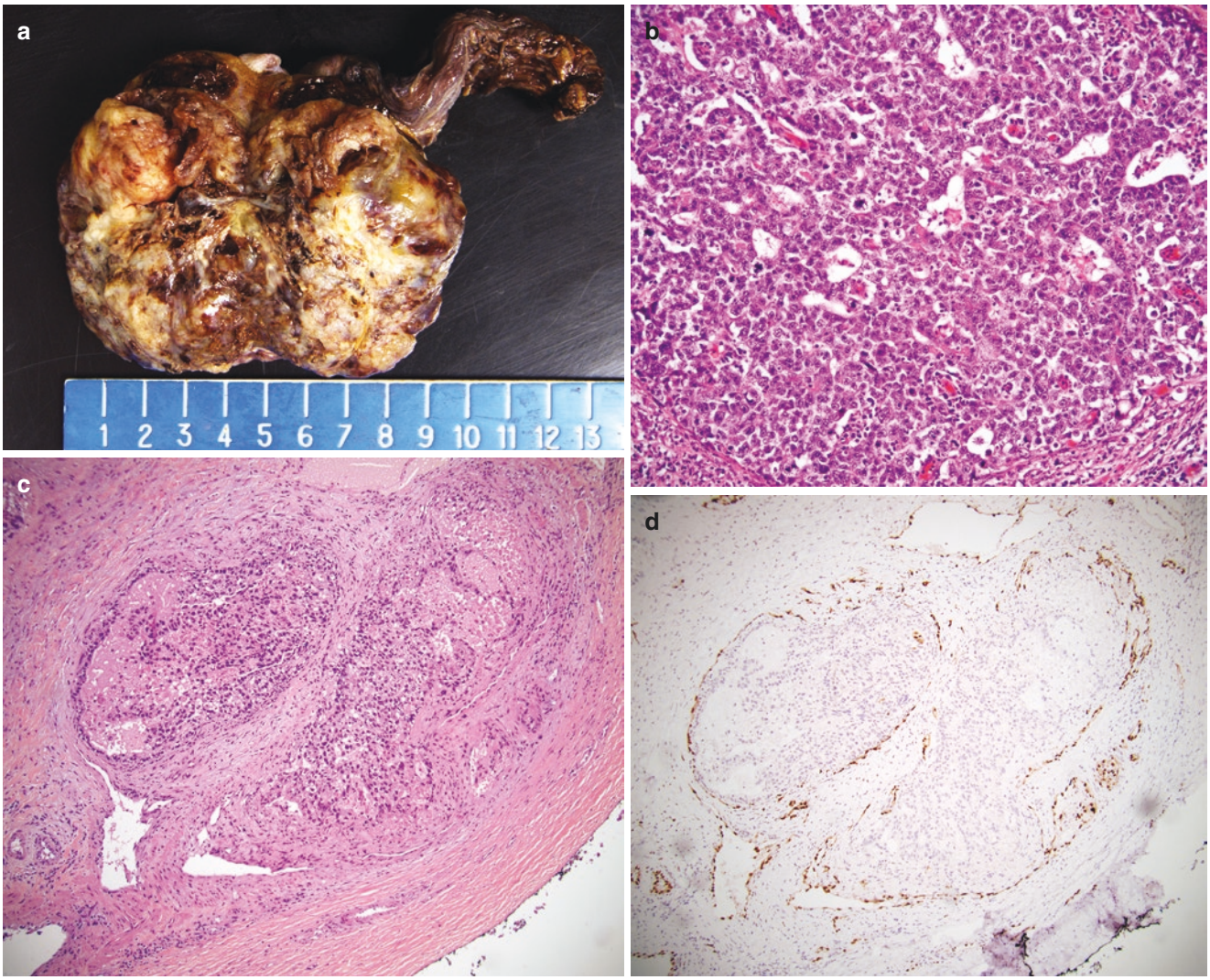

Fig. 6.51 Case 2. (**a**) Variegated, large tumor with hemorrhage and focal cyst formation. (**b**) Tumor cells are pleomorphic and overlapping and have prominent nucleoli. (**c**) Vascular emboli are difficult to appreciate as the tumor completely fills the vessels. (**d**) ERG immunostain confirms that the tumor is within vessels

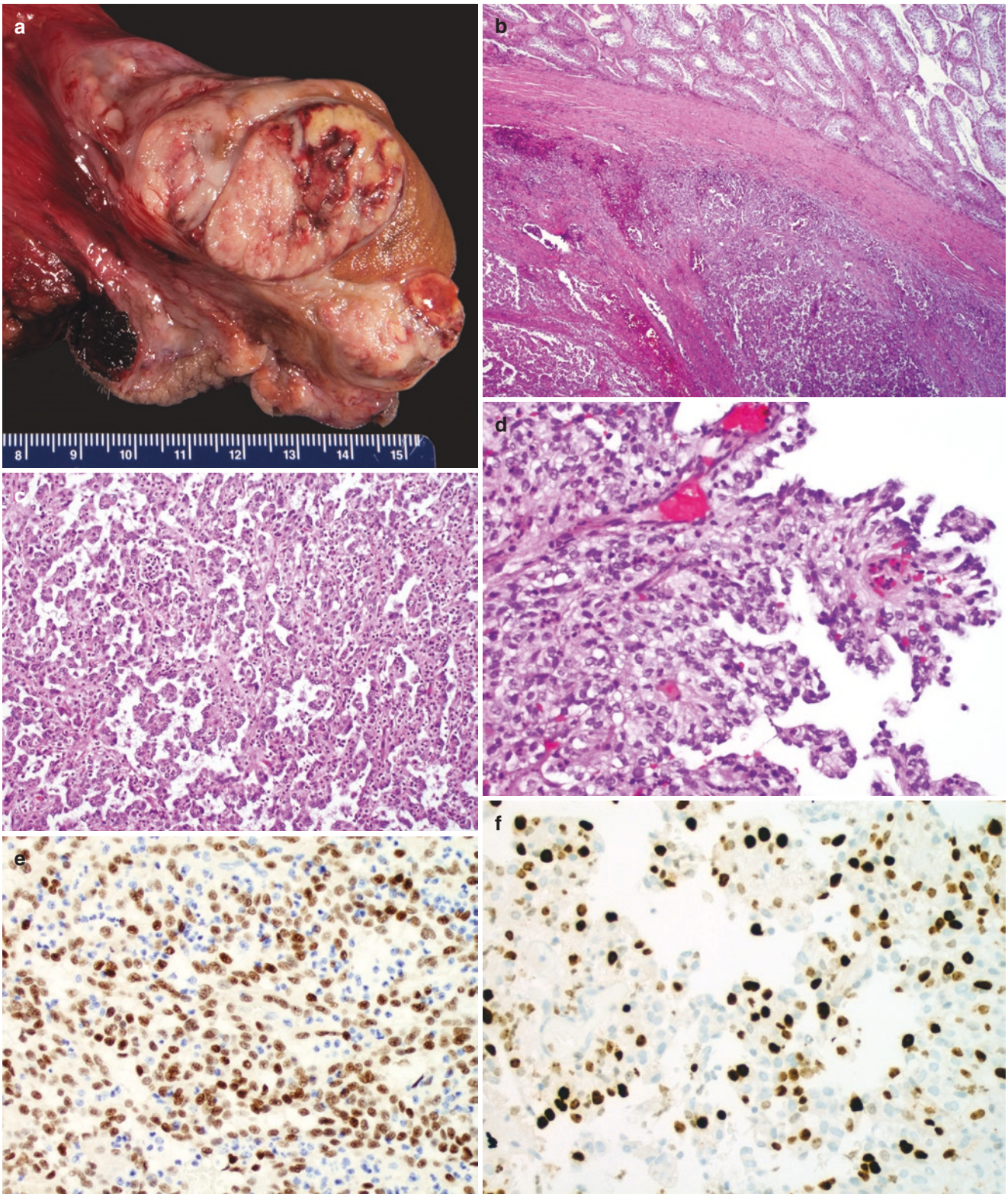

Fig. 6.52 Clear cell carcinoma of the rete testis. (**a**) Resection shows a poorly defined, tan-white mass centered at the rete testis with focal areas of necrosis and hemorrhage. (**b**) Tumor has a thick fibrous capsule and does not invade into the testicular parenchyma. (**c**) Tumor shows extensive papillary features with high nuclear grade. (**d**) Papillary structures are lined by tumor cells with clear cytoplasm. (**e**) Tumor is positive for PAX-8. (**f**) Tumor shows a Ki-67-staining index of approximately 30%

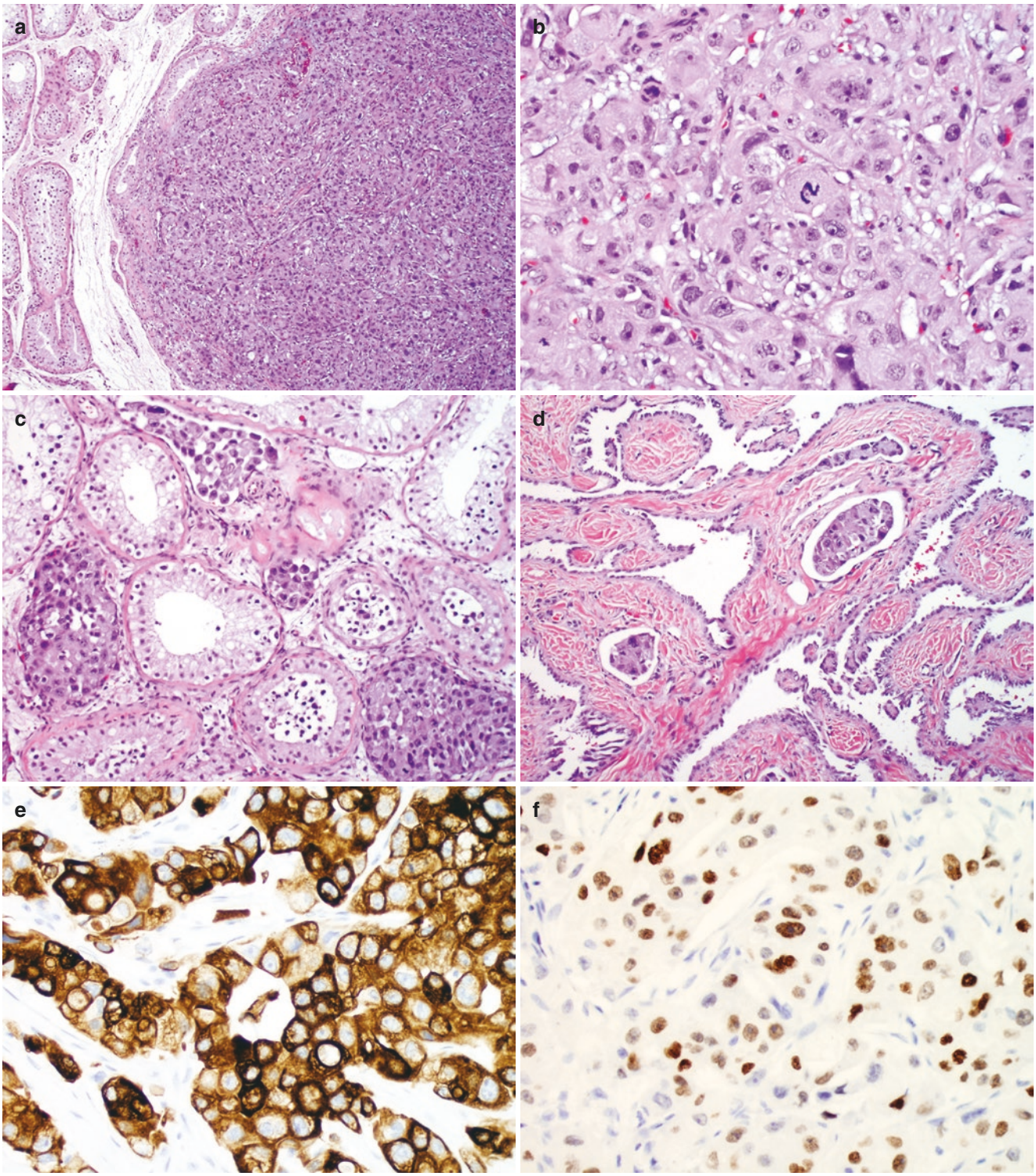

Fig. 6.53 Metastatic lung adenocarcinoma. (**a**) Tumor forms a large solid nodular involving the testicular parenchyma. (**b**) Tumor cells show high-grade nuclear atypia and mitoses. (**c**) Tumor infiltrates the stroma around seminiferous tubules. (**d**) Tumor involves the rete testis with lymphovascular invasion. (**e**) Tumor is positive for CK7 (**e**), TTF-1 (**f**), and Napsin (**g**) and negative for SALL-4 (**h**)

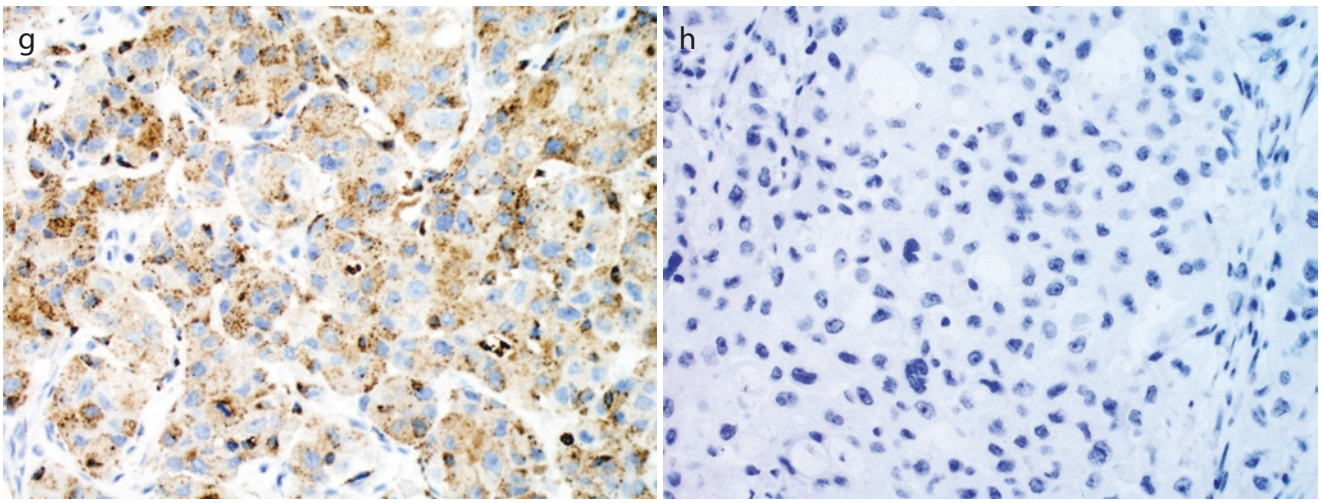

Fig. 6.53 (continued)

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