# Tumors of the Testis

6

Gregor Mikuz and Maurizio Colecchia

## Introduction

The clinical term "testicular tumor" is an umbrella term for all intrascrotal masses regardless of their actual anatomic location. In fact, some 90 % of tumors in the scrotum arise in the testis [1], and at least 90 % of them belong to the group of germ cell tumors (GCTs), the incidence of which is continuously increasing in western industrialized countries, especially in central and northern Europe. Although rare, GCTs have been of great interest to the pathologist because of their peculiar biology and morphology and also to the clinician, as they used to be deadly tumors, but nowadays can be cured in more than 90 % of cases. It took a long time before a comprehensive, histogenetically based classification was available, the classification proposed by Mostofi and Sobin in 1977 [2]. The discovery of a precursor lesion [3], originally called "carcinoma in situ of the testis", supported the theoretical background of this classification.

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## Classification

According to the WHO classification of 2004 [4], testicular tumors are grouped into tumors of germ cell origin and those arising from specialized testicular stroma (sex cord/stromal tumors) and tumors containing both germ cell and sex cord/gonadal stromal elements. Furthermore, the classification includes tumors of the collecting ducts, paratesticular tumors (epididymis and tunics), miscellaneous neoplasms mostly of unclear origin, tumors of nonspecialized stroma (soft tissue tumors), metastases, and hematopoietic tumors, which are rather frequent in older men. In the revised WHO classification of 2016 [5], the names of the precursor lesion and of spermatocytic seminoma were changed, while yolk sac tumor (YST) and teratoma were divided into a prepubertal and postpubertal type because of the different histogenesis and prognosis of these tumors in childhood.

## Germ Cell Tumors

As already mentioned, GCTs account for 90 % of all intratesticular tumors. The 2004 WHO classification [4] (modified in Table 6.1) distinguish between GCTs of one histologic type (pure forms) and those with a mixture of two or more different histologic patterns (mixed forms) (Table 6.1). Almost half (40–50 %) of all GCTs


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**Table 6.1** Classification of testicular tumors (only tumors arising in the testis are listed) (modified from [4])

| |
|---|
| **Germ cell tumors** |
| Germ cell neoplasia in situ |
| *Tumors of one histologic type (pure forms)* |
| Seminoma |
| Seminoma with syncytiotrophoblastic cells |
| Spermatocytic tumor |
| Spermatocytic tumor with sarcoma* |
| Embryonal carcinoma |
| Yolk sac tumor |
| Prepubertal |
| Postpubertal |
| Trophoblastic tumors |
| Choriocarcinoma |
| Non-choriocarcinomatous trophoblastic tumors |
| Epithelioid trophoblastic tumor |
| Placental site trophoblastic tumor |
| Cystic trophoblastic tumor |
| Teratoma |
| Prepubertal |
| Postpubertal |
| Dermoid cyst |
| Well-differentiated neuroendocrine tumour (monodermal teratoma) |
| Teratoma with somatic-type malignancies |
| Germ cell tumors of unknown type |
| Regressed germ cell tumors |
| *Tumors of more than one histologic type (mixed forms)* |
| Mixed embryonal carcinoma and teratoma* |
| Mixed teratoma and seminoma* |
| Choriocarcinoma and teratoma/embryonal carcinoma* |
| Mixed teratoma and yolk-sac tumor, pre-pubertal-type |
| **Sex cord/gonadal stromal tumors** |
| *Pure forms* |
| Leydig cell tumor |
| Malignant Leydig cell tumor |
| Sertoli cell tumor |
| Intratubular large cell hyalizing Sertoli cell neoplasia |
| Large-cell calcifying Sertoli cell tumor |
| Malignant Sertoli cell tumor |
| Granulosa cell tumor |
| Adult-type granulosa cell tumor |
| Juvenile-type granulosa cell tumor |
| Tumors of the thecoma/fibroma group |
| Unclassified sex cord-stromal tumor |
| Sex cord/gonadal stromal tumor, mixed forms |
| Malignant sex cord/gonadal stromal tumor |
| Myoid gonadal stromal tumor* |
| *Tumors containing both germ cell and sex cord/gonadal stromal element* |
| Gonadoblastoma |
| Germ cell-sex cord/gonadal stromal tumor, unclassified |
| **Miscellaneous** |
| Wilms' tumor |
| **Hematopoietic tumors** |
| **Metastases** |

*Not included in the WHO 2016 classification as a distinct tumor

are pure seminomas; a third are mixed forms of nonseminomatous germ cell tumors (NSGCTs) including combinations with seminomas; and only 14–16 % are pure NSGCTs [6–9].

## Germ Cell Neoplasia in Situ

In 1972 Skakkebaek [3] described the forerunner of all GCTs in biopsies of infertile men and called it "carcinoma in situ." The name was subsequently changed to "intratubular germ cell neoplasia, unclassified" (IGCNU) [4]. The adjective *unclassified* was used to emphasize that the morphology of the tumor cells does not permit the assignment to a definite type of GCT. In analogy to other intraepithelial neoplasia types, in German-speaking countries, the term "testicular intratubular neoplasia" (TIN) is still the most used. The new WHO classification of 2016 returns more or less to Skakkebaek's original phrasing and names the lesion "germ cell neoplasia in situ" (GCNIS). In this chapter, we adopt the term CIS to remember the first proposed terminology [3].

### Epidemiology

The prevalence of these lesions can be roughly estimated to account for 0.4–0.8 % of healthy men and approximately 1 % of the infertile male population [10]. The frequency in cryptorchid testes of adults is 2–4 %, while in those of children, it is significantly lower (0.5 %). However, the identification of atypical germ cells in prepubertal testis is rather difficult because these cells

are morphologically and immunophenotypically very similar to prepubertal gonocytes [11]. Maturation delay of germ cells and their progression to CIS frequently occurs in intersex patients (about 10 %). A developmentally delayed germ cell resembles a CIS cell and displays prolonged expression of immunohistochemical markers used for the diagnosis of CIS [11].

In patients with unilateral GCTs in situ, neoplasia is encountered in 4–6 % of contralateral testes [12], while in tissue surrounding GCT, it appears in more than 90 % of cases [13]. In retroperitoneal "extragonadal" GCTs, atypical germ cells can be found in the testes of about half of all cases, whereas in mediastinal GCTs, the testes only rarely show such cells [14] (Table 6.2).

**Table 6.2** Prevalence of germ cell neoplasia in situ

| Prevalence of germ cell neoplasia in situ | |
|---|---|
| Healthy men | 0.4–0.8 % |
| Infertile men | 1.0 % |
| Cryptorchid testis of adults | 2–4 % |
| Intersex | 20 % |
| Contralateral testis of patients with GCT | 4–6 % |
| Retroperitoneal "extragonadal" GCT | 50 % |

## Morphology

Macroscopically, the affected testes can be normal or atrophic. They have a firm consistency as a result of atrophy and fibrosis. Microscopically, the atypical germ cells are not uniformly distributed in the parenchyma but show focal or segmental accumulation. The seminiferous tubules containing these cells are narrowed and have a thickened, hyalinized wall. The atypical germ cells are attached to the usually thickened basement membrane and push the Sertoli cells toward the lumen of the seminiferous tubules (Fig. 6.1). The cytoplasm is clear because of the large amount of glycogen, which stains purple with PAS. The nuclei are larger ($Ø \approx 9.7$ µm) than those of spermatogonia ($Ø \approx 6.5$ µm) and contain 1 or more nucleoli. Mitoses (including abnormal ones) are abundant. The interstitium surrounding the affected tubules is frequently infiltrated by lymphocytes, and microcalcifications are frequent (40 %). These cells can spread with a "pagetoid" pattern to the epithelia of the rete testis or infiltrate the interstitium already in the

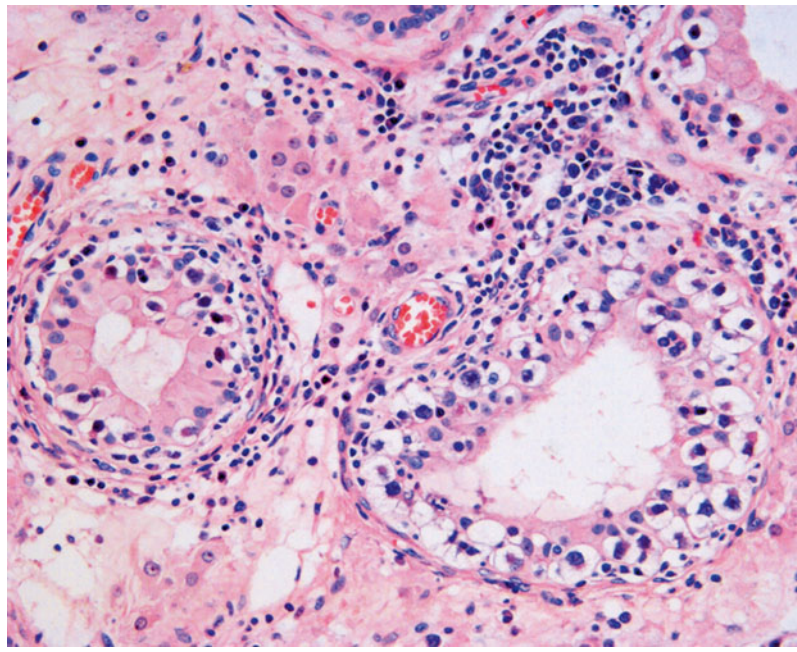

**Fig. 6.1** Germ cell neoplasia. Narrowed seminiferous tubules lined with atypical germ cells with clear cytoplasm. The atypical cells push the Sertoli cells toward the lumen. Lymphocytic infiltrates are common in the interstitium

undifferentiated stage. Intratubularly growing GCTs (mostly seminomas or embryonal carcinomas [ECs]) should not be mistaken for CIS.

### Immunohistochemistry

Atypical germ cells commonly react with PLAP (Fig. 6.2), CD117 (c-kit), OCT3/4, NANOG, AP-2γ, SALL4, and SOX17, but not with SOX2 [15, 16]. OCT3/4, NANOG, and AP-2γ are the most sensitive markers and are detected also in cases in which PLAP and other markers are absent [17]. Some of these markers, especially CD117, are expressed also in normal spermatogenesis or in cases of delayed maturation.

### DNA Ploidy and Cytogenetic Analysis

Atypical germ cells are aneuploid [18] and the chromosomal aberrations correspond to those of invasive GCTs, with the typical differences between seminoma and NSGCTs [19]. The isochromosome i(12p) appears only shortly before CIS turns invasive [20].

### Differential Diagnosis

Intratubular seminoma, EC and especially spermatocytic tumors, which always show areas of intratubular growth, can be mistaken for CIS. By extensive sampling, invasive growth areas can be found almost in every such tumor, and in ambiguous cases, the use of immunohistochemical algorithms leads to the correct diagnosis.

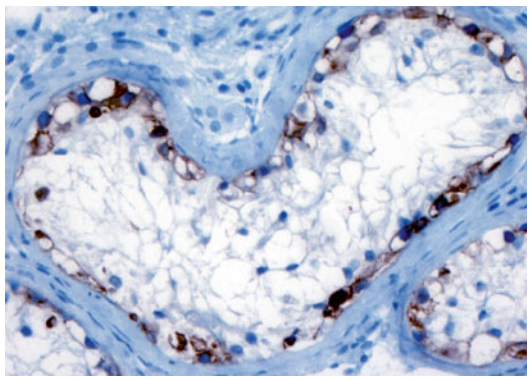

**Fig. 6.2** Intratubular germ cell neoplasia. Immunohistochemistry with antibody to PLAP shows strong reactivity of the neoplastic cells

In biopsies of infertile men, it was found that early maturation arrest of spermatogenesis can mimic CIS. The spermatogonia on the basement membrane are isolated from the other cells, and their nuclei have an atypical, worrisome appearance. Moreover, the basement membrane may be thickened and the cells are CD117 positive.

### Clinical Features

There is no doubt that with an interval of 5–7 years, 90 % of CIS will evolve into overt invasive GCT. For this reason, European urologists and oncologists advocate biopsy of the healthy contralateral testis in patients with GCTs [21–23]. In case such a biopsy is positive for CIS, the gonad will be treated with radiotherapy at a dose of 18–20 Gy (because with lower doses the lesion persists). Chemotherapy is completely useless to treat CIS [24]. Urologists in the USA are more skeptical about or even contrary to biopsy of the contralateral testis. They argue that a biopsy is positive in only about 5.5 % of cases, and bilateral GCTs are even rarer (3 %) and can be easily cured when they do occur [25].

## Seminoma

### Epidemiology

Seminoma comprises 40–50 % of all GCTs. In white American men, its incidence has increased over the last 20 years by more than 60 %, whereas the incidence of NSGCTs has risen only by 24 % [26]. It occurs commonly between the ages of 25–50, with a peak incidence at about 34 years [26] (Table 6.3). Seminoma is virtually nonexistent before puberty and it is rare in adolescence (1 %) [1, 27]. About 10 % of seminoma patients have a history of cryptorchidism [1].

### Morphology

Macroscopically, small seminomas are homogeneous, well-circumscribed tumors, whereas large seminomas cause marked testicular enlargement; the tunica albuginea is, however, mostly intact and the epididymis uninvolved. On section the tumor bulges above the testicular parenchyma and is lobulated and well circumscribed but without a

**Table 6.3** Typical ages of patients with various GCT

| Typical ages of patients with various GCT | |
|---|---|
| Seminoma | Average age 30–40<br>Extremely rare before puberty and after 70 |
| Spermatocytic tumor | >40 |
| Embryonal carcinoma | Average age 30<br>Rare before puberty and after 50 |
| Yolk sac tumor | |
| Prepubertal | 3–39 months |
| Postpubertal | 25–30 years |
| Choriocarcinoma | 20–30 years |
| Teratoma | |
| Prepubertal | 20 months |
| Postpubertal | 20–30 years |
| Mixed GCT | 28 years if NSGCT component prevails<br>33 years if SE prevails |

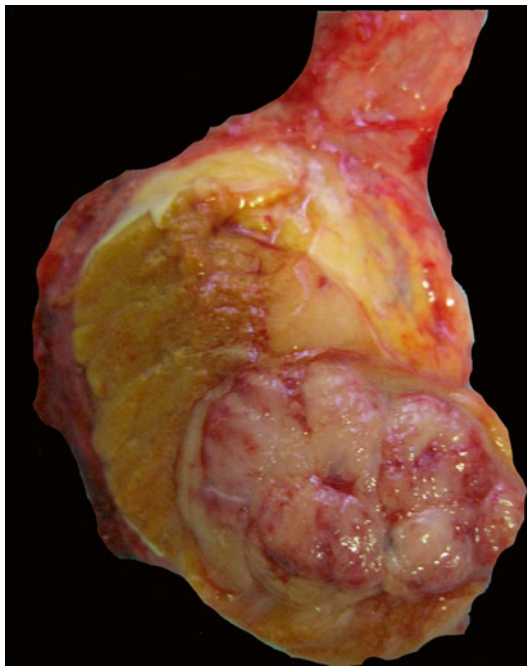

**Fig. 6.3** Seminoma. Macroscopic features with typical lobulated pinkish-white cut surface with punctate foci of hemorrhage

capsule (Fig. 6.3). The color is white to pinkish white or tan in cases with heavy lymphocytic infiltration. In large tumors, small necrotic areas and small dot-like hemorrhages are present, but large hemorrhagic, firm, or cystic areas are strongly suggestive of an NSGCT component. If the tumor shows these features or has a diameter >4 cm, extensive sampling is required.

The typical microscopic pattern of seminoma shows lobules composed of a few dozen to roughly 100 cells, which are separated by thin fibrous septa. The cells resemble immature spermatogonia and are rather monomorphous. The cytoplasm is rich in glycogen and fat and therefore appears water-clear in formalin-fixed material (Fig. 6.4). In well-fixed specimens, mitoses are abundant.

More than 80 % of seminomas show lymphocytic infiltration (CD8+ and CD4+ T lymphocytes and some NK cells) [1, 28] ranging in appearance from uniform peppering or clumps scattered in stroma to formation of lymphoid follicles in about 18 % of cases [1] (Fig. 6.5). Macrophages and (in lesser amount) B lymphocytes are also present. Some 10 % of seminomas develop a marked noncaseating granulomatous reaction with epithelioid cells and a few Langhans-type giant cells (granulomatous seminoma) [1] (Fig. 6.6). The reaction is usually patchy but may involve the entire tumor.

Beside this "classical" morphology, there are some variants (Table 6.4). Because they do not have any prognostic or therapeutic importance, these variants have not been listed in the WHO classification [4]. In pseudoglandular and tubular seminoma, tumor cells form small gland-like clefts (Fig. 6.7). Accumulation of edematous fluid in interstitial tissue gives the tumor a microcystic or cribriform appearance (Fig. 6.8). The name *intratubular* or *interstitial seminoma* derives from the predominant way the tumor cells spread (Figs. 6.9 and 6.10). Also seminomas with a high mitotic rate (formerly anaplastic or atypical seminomas) are not considered as an entity in their own right because the high mitotic count does not negatively influence the course of the disease.

Seminoma with syncytiotrophoblastic cells is a separate entity in the WHO classification [4]. On H&E-stained slides, multinucleated giant cells are detected in about 7 % of seminomas, mostly close to vessels (Fig. 6.11). With the use of antibodies against human chorionic gonadotropin (hCG), however, positive cells

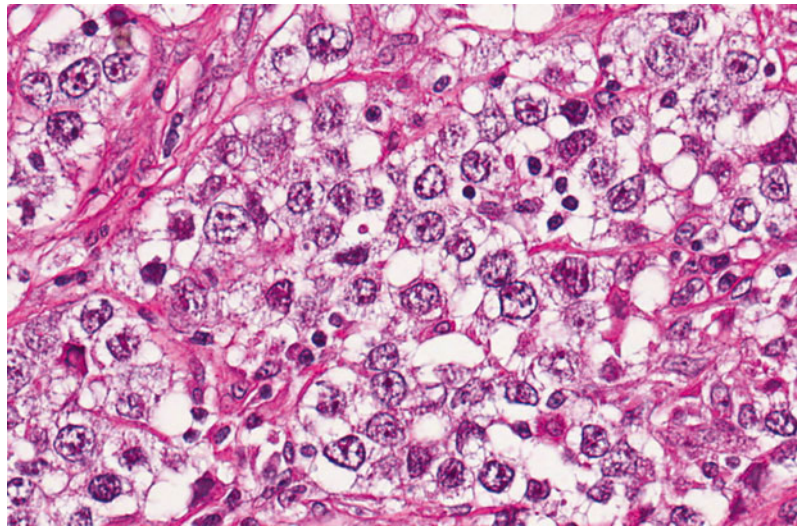

**Fig. 6.4** Seminoma. The tumor is composed of cells that have abundant clear cytoplasm and round nuclei with prominent central nucleoli

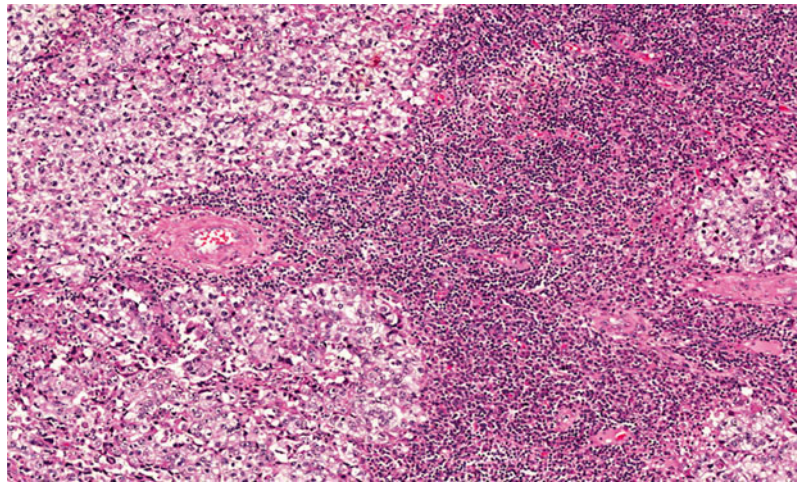

**Fig. 6.5** Seminoma. A dense lymphocytic infiltrate (right) is seen at low magnification

are detectable in about one-quarter of all cases [29]. In some cases also mononucleated cells are hCG positive. Syncytiotrophoblastic giant cells also appear in other NSGCTs, and such tumors must not be confused with true choriocarcinomas.

## Immunohistochemistry

Seminoma is positive for all markers of embryonic stem cells: PLAP, OCT3/4, NANOG, CD117 (c-kit), and AP-2γ as well as the transcription factor SALL4, which stains all GCTs

**Table 6.4** Morphological variants of seminoma non-listed in the WHO classification

| Morphological variants of seminoma non-listed in the WHO classification |
|---|
| Intratubular seminoma |
| Interstitial seminoma |
| Tubular seminoma |
| Pseudoglandular seminoma |
| Microcystic/cribriform seminoma |
| Granulomatous seminoma |
| Seminoma with high mitotic rate (“anaplastic seminoma”) |

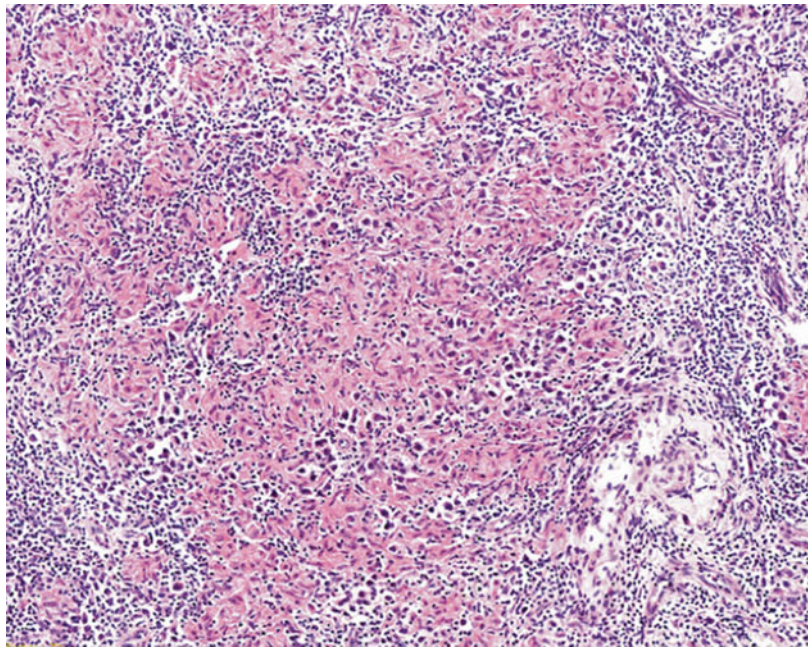

**Fig. 6.6** Seminoma. Epitheloid-cell reaction in a so-called granulomatous seminoma

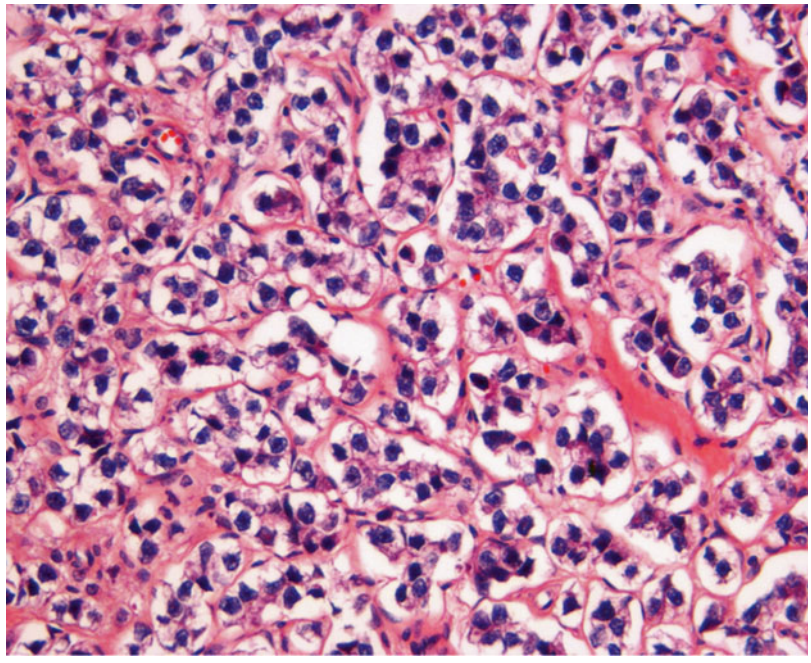

**Fig. 6.7** Seminoma. This "tubular" seminoma is composed of tumor cells forming tubular or gland-like structures (With permission of the editor from Gregor Mikuz, Peter Mazal "Hoden und Infertilität beim Mann" Springer-Verlag Berlin Heidelberg, 2016)

[30]. Novel markers are the membrane glycoprotein of podocytes podoplanin (D2-40) and SOX17, an essential factor for inducing the primordial germ cell lineage in humans [30, 31] (Table 6.5). In some seminomas, single tumor cells are positive for cytokeratin and CD30, perhaps as a sign of beginning transition from seminoma to EC [32].

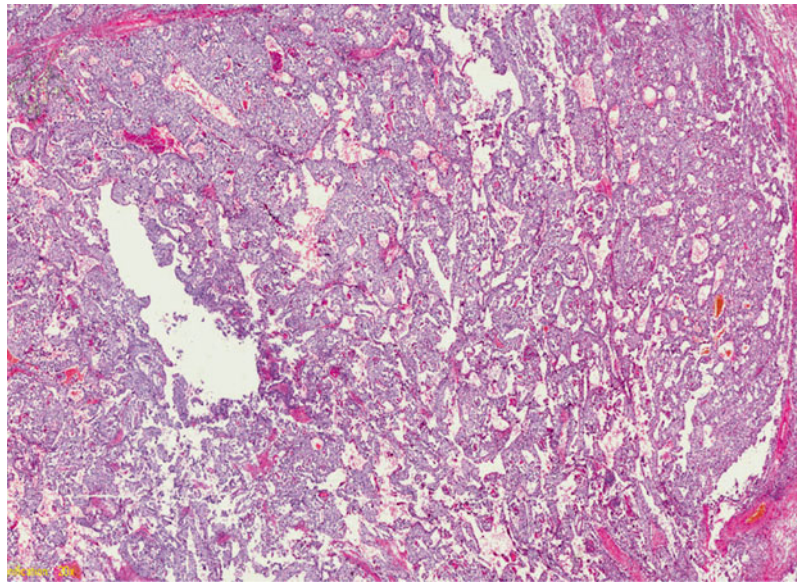

**Fig. 6.8** Interstitial edema gives a cribriform, microcystic appearance to seminoma

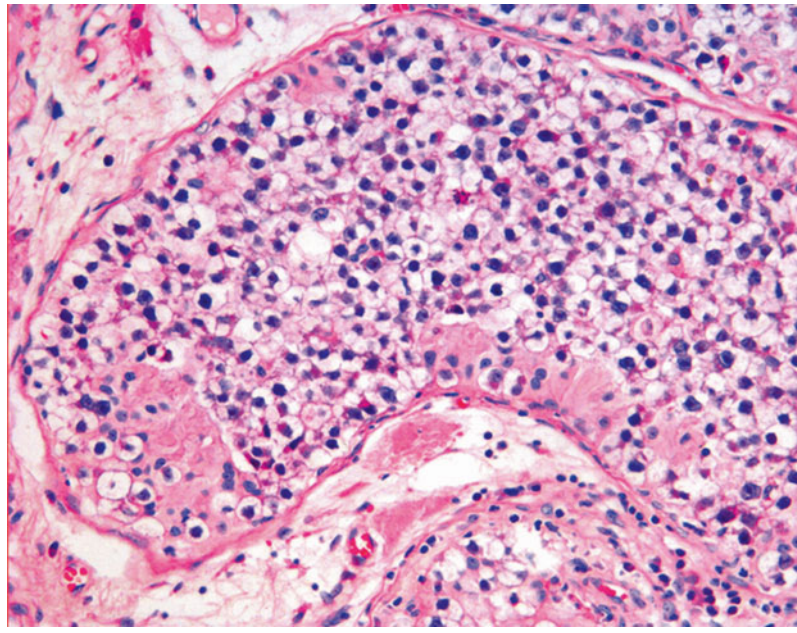

**Fig. 6.9** Intratubular seminoma. Tumoral cells fill the seminiferous tubules

### DNA Ploidy and Cytogenetic Analysis

All seminomas are aneuploid, mostly with a hypertetraploid stem line [33, 34]. Sporadic reports on diploid seminomas are the result of measurement errors. In flow cytometric measurements, the diploid stem line is not derived from the tumor cells but from the many lymphocytes present in the tumor [33].

Like all GCTs, also seminomas show gain of isochromosome i(12p); the number of copies is, however, lower than in NSGCTs [35]. Gain of chromosomes 1, 2, 7, 8, 20, and X and loss of chromosomes 4, 5, 9, 11q, 13, and 18 are typical of seminoma and NSGCT. Additionally, seminomas can show gain of chromosomes 3p, 6p, 10, and 22 and loss of 1q, 9p, 11p, 16p, and 17p [34].

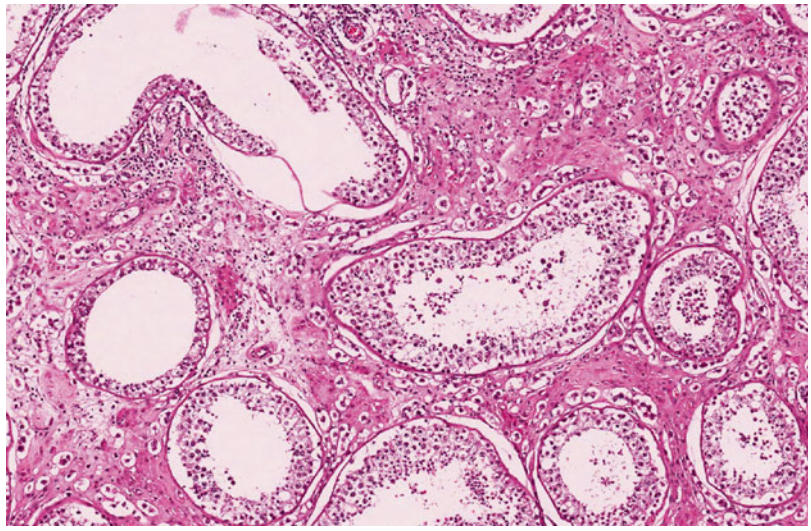

**Fig. 6.10** Intertubular seminoma. Tumors with exclusively intertubular growth are susceptible to being overlooked. Sometimes it is a component of a typical seminoma

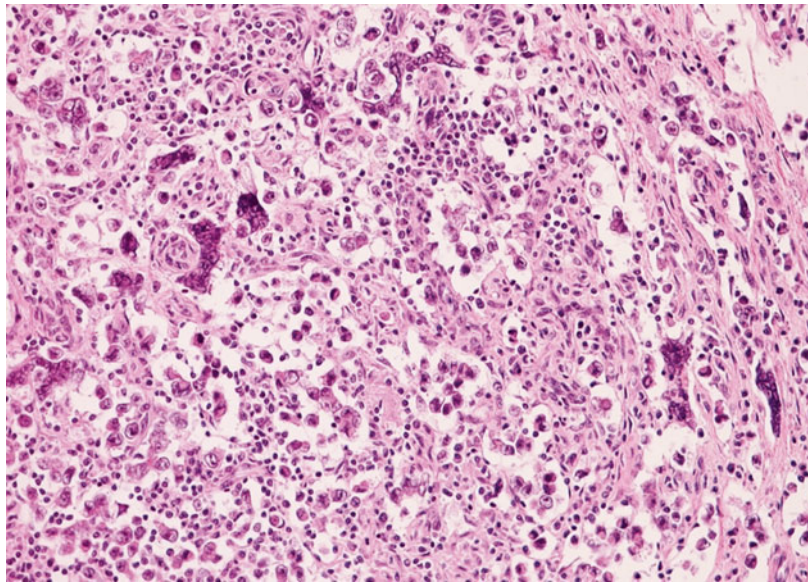

**Fig. 6.11** Seminoma with syncytiophoblastic giant cells. This tumor shows edema separating the tumor cells and multinucleated cells

## Differential Diagnosis

The cytomorphology of seminoma cells strongly depends on the proper fixation of the surgical specimen. In insufficiently fixed autolytic tissue, the cytoplasm of the tumor cells turns dark and eosinophilic, and the nuclei may swell or shrink. This leads to diagnostic difficulties; in the worst case, the tumor is mistaken for an EC, and as a consequence, the patient will receive totally different and inadequate therapy. If marked lymphocytic infiltration or a granulomatous reaction is present, the tumor is probably a seminoma. By contrast, glandular and papillary structures are highly suggestive of an EC. PLAP stains seminoma cells delicately and perimembranously, while it stains EC cells diffusely and very strongly. To avoid errors, the use of immunohistochemistry is mandatory: seminomas are CD117 and SOX17 positive and AE1/AE2, CD30, and SOX2 negative, whereas ECs are CD117 and

SOX17 negative and AE1/AE2, CD30, and SOX2 positive (Table 6.5) [30].

YSTs with a solid growth pattern can be mistaken for seminoma too (Fig. 6.12). YSTs are strongly pancytokeratin positive and OCT3/4 negative, but the most specific marker is glypican-3, which stains only YST cells [30]. Since alpha fetoprotein (AFP) expression in YST cells is not evenly distributed, absolutely negative areas can occur; therefore, the use of glypican-3 should be preferred. Seminoma cells do not produce AFP, so a high AFP level in serum means that the sampling was insufficient and NSGCT areas were missed; it can also result from an error in laboratory measurements.

Other possible pitfalls are caused by Sertoli cell tumors and malignant lymphomas, which are, however, tumors of aged men. With the use of SALL4 antibodies, which stain exclusively GCTs, such mistakes can be easily avoided [36].

**Table 6.5** Immunohistochemical reactions useful for the differential diagnosis of seminoma, embryonal carcinoma and spermatocytic tumor

| Antibody | Seminoma | Embryonal carcinoma | Spermatocytic tumor |
|---|---|---|---|
| PLAP | ++ | + | – |
| CD30 | – | ++ | – |
| AE1/AE3 | ± | ++ | *Dot-like* |
| CD117 | + | ± | ± |
| OCT3/4 | + | + | – |
| SALL4 | + | + | + |
| SOX2 | –- | + | – |
| SOX17 | + | – | – |

## Clinical Features

The presenting complaint associated with seminoma is mostly testicular swelling, while about 10 % of patients experience local discomfort and pain. Symptoms due to metastases include supraclavicular lymph node swelling and abdominal pain due to enlarged retroperitoneal lymph nodes, which can also obstruct the ureters and cause hydronephrosis. Gynecomastia can be a symptom in patients affected by seminoma with syncytiotrophoblastic giant cells.

The main unfavorable morphologic prognostic factors are a tumor diameter >4 cm and tumor pagetoid infiltration of the epithelium of the rete testis (Fig. 6.13) or the rete testis stromal infiltration, whereas vascular invasion is prognostically not as important as in NSGCTs [37]. In a recent publication, it was reported that the risk of tumor relapse was directly proportional to the tumor

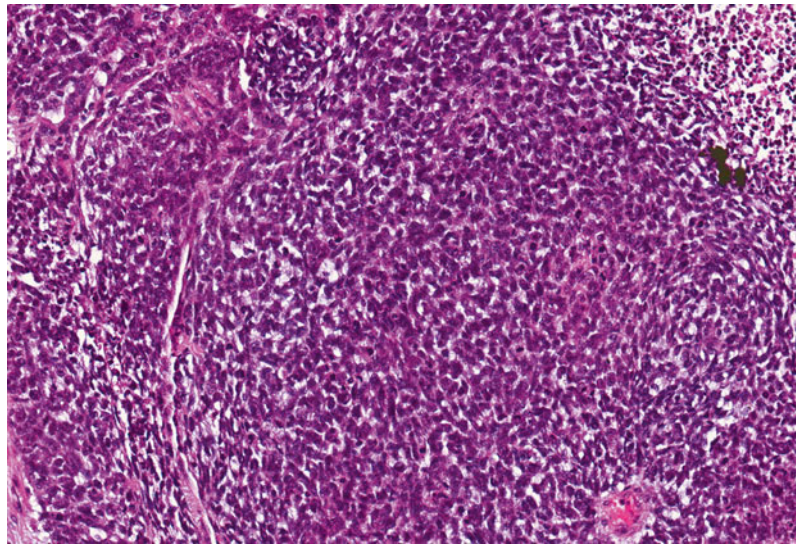

**Fig. 6.12** Solid yolk sac tumor resembling seminomatous proliferation

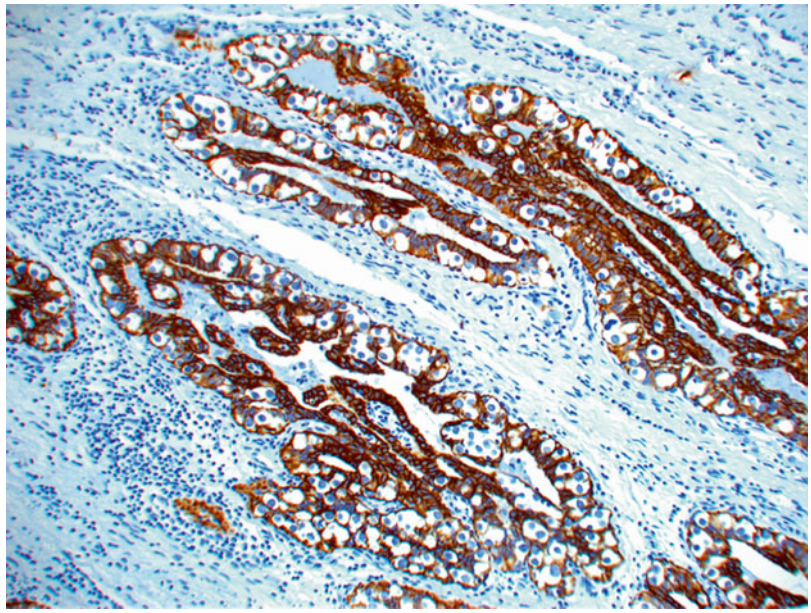

**Fig. 6.13** Pagetoid invasion of unstained seminoma cells in the epithelium of the rete testis immunohistochemically positive for cytokeratin antibodies

diameter; this can be used in therapeutic decision-making, i.e., in the choice between surveillance and adjuvant radio- or chemotherapy [38]. Following inguinal orchiectomy, the management options for patients with stage I seminoma are initial surveillance or adjuvant treatment. The recommendation for patients with two risk factors (tumor size and rete testis invasion) is treatment with carboplatin, while for patients with 0–1 risk factor, surveillance is recommended [39]. It should be mentioned that patients treated with chemotherapy often experience late complications such as metabolic syndrome, myocardial infarction, and secondary neoplasms [37].

## Spermatocytic Tumor

In 1946 the renowned French-Canadian pathologist Pierre Masson described a novel GCT composed of tumor cells with filamentous nuclear chromatin resembling spermatocytes and therefore named it "spermatocytic seminoma" [40]. In the 2016 WHO classification, the name has been changed to "spermatocytic tumor" (ST) to stress the fact that this tumor is not a variant of seminoma [5]. However, it does not originate from spermatocytes but from spermatogonia [41]. The pathogenesis seems to be quite different from that of the other GCTs because ST does not develop from the CIS precursor and the common chromosomal aberration i(12p) is missing. Moreover, it is the only GCT that does not occur in the ovary [42] (Table 6.6).

ST is an extremely rare tumor and accounts for only 0.61 % of all GCTs. The incidence is 0.3/1 million in men younger than 55 years of age and 0.8/1 million in older men [43]. With an average age of 55 years, patients are older than those with seminoma; nevertheless, in one-quarter of reported cases, patients were younger than 40 years. Young age, even under 30 years, is therefore not an exclusion criterion for this diagnosis.

There are no known risk factors for ST, not even cryptorchidism. There are also no differences in incidence between races.

### Morphology

Because of the gelatinous and mucinous cut surface and/or the presence of small mucoid

**Table 6.6** The main differences between seminoma and spermatocytic tumor

| Characteristics | Spermatocytic tumor | Seminoma |
|---|---|---|
| Site of primary | Only testis | Testis, ovary, mediastinum, retroperitoneum, CNS |
| Cryptorchidism | No | 10 % |
| Mean age | 53 (19–92)[a] | 36 (8–82) |
| Genetic predisposition | Unknown | Unknown |
| Incidence | 0.4/1 million | 2–5/100,000 |
| Metastases | Extremely rare | Frequent |
| Combined with other GCT | Never | ≈15 % |
| Combined with GCNIS | Never | >90 % |
| Combined with sarcoma | Occasionally | Never |
| Cytoplasmic glycogen | Missed | Abundant |
| Chromosome | +9 | i(p12) |

[a]Caveat, young age does not exclude the diagnosis of spermatocytic tumor

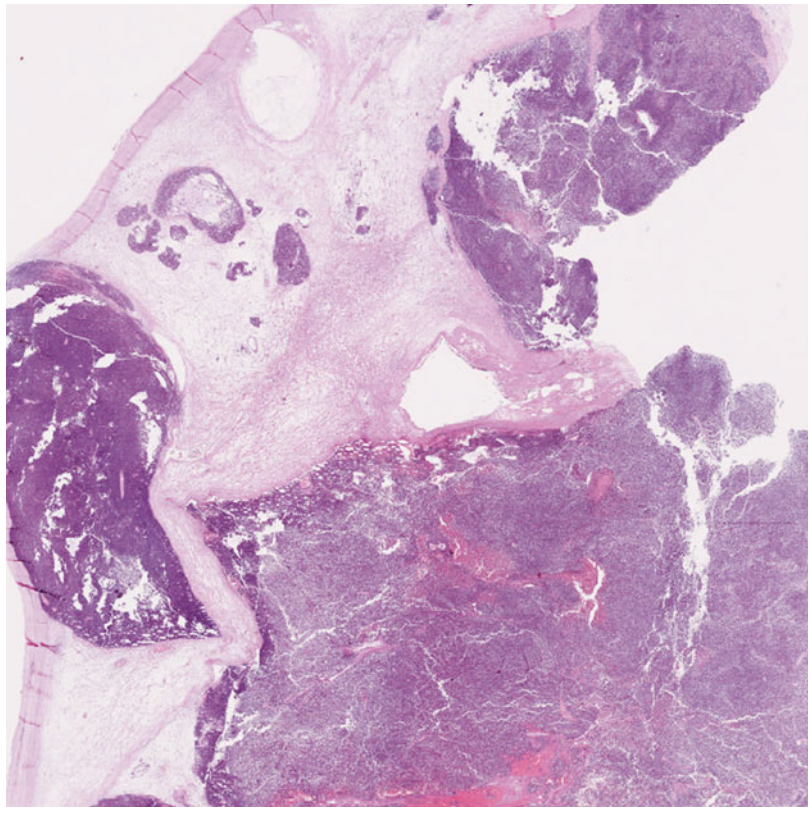

**Fig. 6.14** Spermatocytic tumor. A multinodular pattern is apparent on scanning magnification

cysts, the macroscopic appearance of ST is unique and would permit a diagnosis "at first glance." The tumors are usually rather large with a mean diameter of 4–5 cm, but sizes up to 15 cm have been reported. The outline of the tumor is well delineated, the color grayish white, and the consistency soft with typical multinodular pattern of growth (Fig. 6.14).

ST is microscopically composed of three distinct cell types: medium-sized cells (diameter,

15–20 μm) with a rather regular, round nucleus; small cells (diameter, 6–8 μm) resembling lymphocytes; and scattered single mono- or multinucleated giant cells (diameter, 50–150 μm) whose nuclei have coarse chromatin similar to the spireme of spermatocytes in meiotic division (Fig. 6.15) [44]. The main part of the tumor shows an expansive growth pattern, and the surrounding tubules are greatly extended and filled with neoplastic cells (Fig. 6.16). Tubular rupture in more than one area explains the occurrence of multiple distinct tumor nodules in one testis. In contrast to other GCTs, no CIS can be detected in the adjacent tubules; they may show completely normal spermatogenesis with mature spermatozoa. The stroma is inconspicuous and there are no lymphocytic infiltrates. Large edematous areas similar to those of microcystic seminomas are also often observed.

So far 18 cases of ST combined with sarcoma have been described [42, 45]. Eight of these sarcomas were rhabdomyosarcomas, and the others

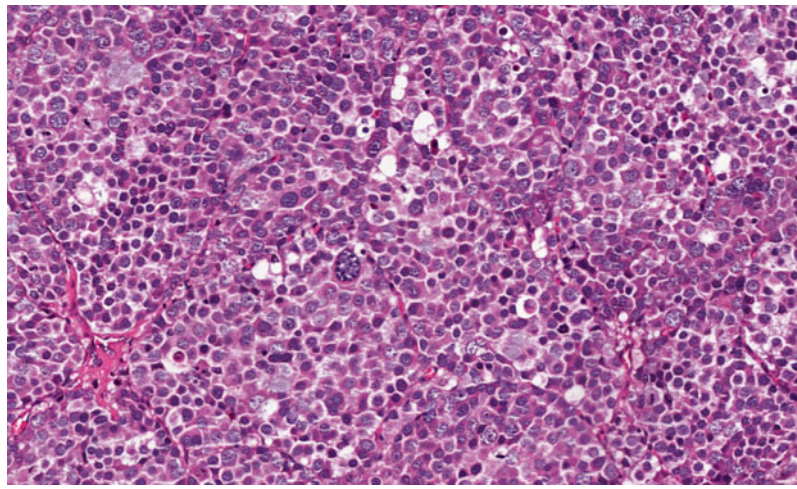

**Fig. 6.15** Spermatocytic tumor composed of three distinct cell types: predominant large cells, scattered small, lymphocyte-like cells, and a single giant cell

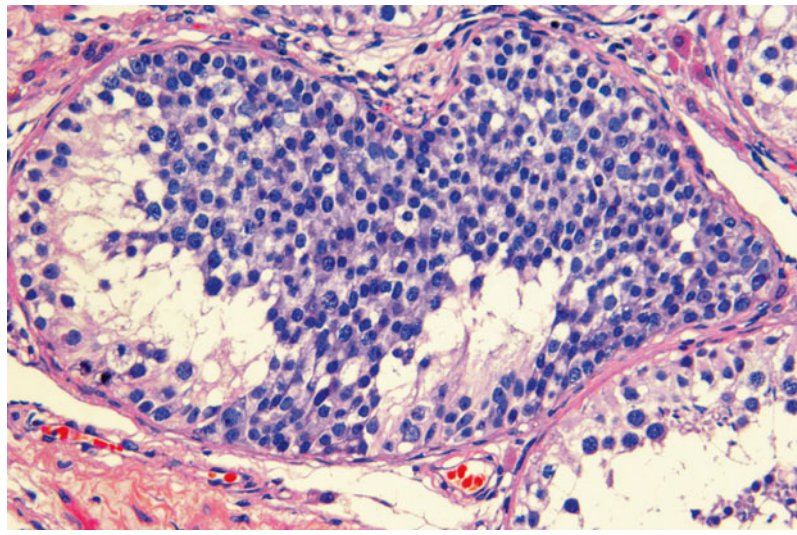

**Fig. 6.16** Intratubular growth of spermatocytic tumor. The adjacent tubules shows almost normal spermatogenesis

were defined as undifferentiated spindled or epithelioid.

In 1996 Albores Saavedra et al. [46] described four cases of a variant of ST named "anaplastic spermatocytic seminoma" (ASS). More recently, four additional cases were described [47]. In contrast to ST, ASS contains only the medium-sized cell type characterized by large nucleoli, causing the cells to resemble those of an EC. Moreover, mitotic activity is brisk and areas of necrosis are frequently observed, and there are usually many apoptotic tumor cells (Figs. 6.17 and 6.18).

### Immunohistochemistry

STs are negative for the classical markers of GCT: PLAP and OCT3/4. They stain positively for SALL4 and CD117, but not in all cases [47], and the cytoplasm of single cells shows a dot-like reaction for pancytokeratin (AE1/AE3; CAM5.2) (Fig. 6.19). The novel markers NUT, GAGE7, and NY-ESO-1 are variably sensitive to ST, and

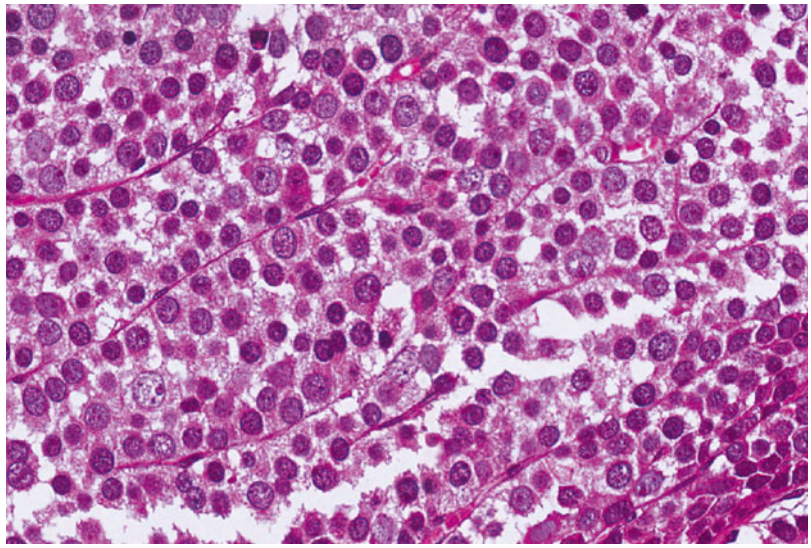

**Fig. 6.17** Spermatocytic tumor with many apoptotic tumor cells

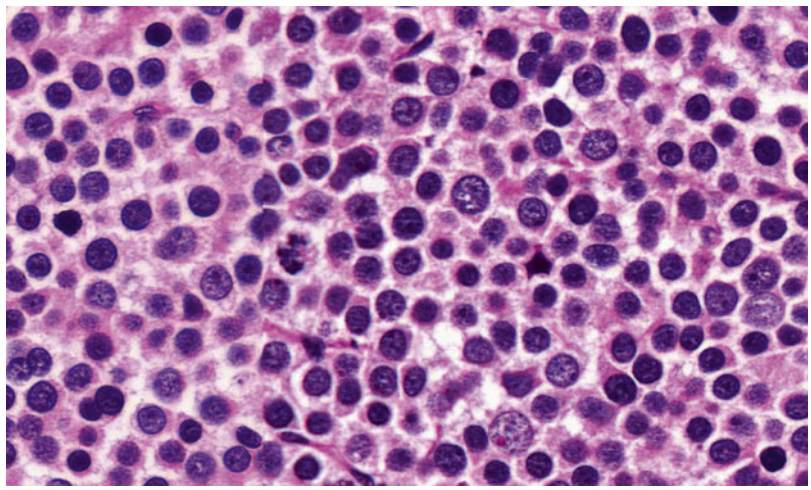

**Fig. 6.18** Anaplastic spermatocytic tumor composed only of large cells undergoing mitosis and apoptosis

high specificity is attained when there is multifocal and strong nuclear staining [48].

### DNA Ploidy and Cytogenetic Analysis

The ploidy of ST depends on the cell type: the small lymphocyte-like tumor cells are diploid, while the other types are hyperploid with single values up to 42c [49–51].

Gain of chromosome 9 and the absence of the i(12q) isochromosome are almost specific for ST. However, in one "hybrid" case, the isochromosome and gain of chromosome 7, which are characteristic of the other GCTs, were observed [47].

### Differential Diagnosis

In our experience, ST is one of the most frequently misdiagnosed tumors due to its rarity. The polymorphous and harmful-looking tumor cells and the lack of stroma make the tumor similar to malignant lymphomas. "Anaplastic seminoma" and even YST are other "popular" misdiagnoses. Immunohistochemistry is not very helpful unless a lymphoma should be confirmed or excluded. The macroscopic features of the tumor and recognition of the three cell types as well as the spireme-like structure of the nuclear chromatin will guide the pathologist to the correct diagnosis.

### Clinical Features

Like in other GCTs, the main symptom is painless swelling of the testicle. Serum markers are negative. Pure STs do not need any therapy after orchiectomy. Most cases of metastasizing ST diagnosed in the pre-immunohistochemistry era turned out to be malignant lymphomas [45]. After critical reevaluation, only six cases could be confirmed as metastasizing ST; five of these patients died and one is alive without disease after chemotherapy [42]. The patient with the hybrid tumor died of widespread organ metastases [47]. Metastasizing STs are therefore chemotherapy resistant. All patients with ST combined with sarcoma died of sarcoma metastases.

## Embryonal Carcinoma

EC is a highly malignant tumor composed of primitive cells that retain the ability to differentiate toward somatic or extraembryonic structures.

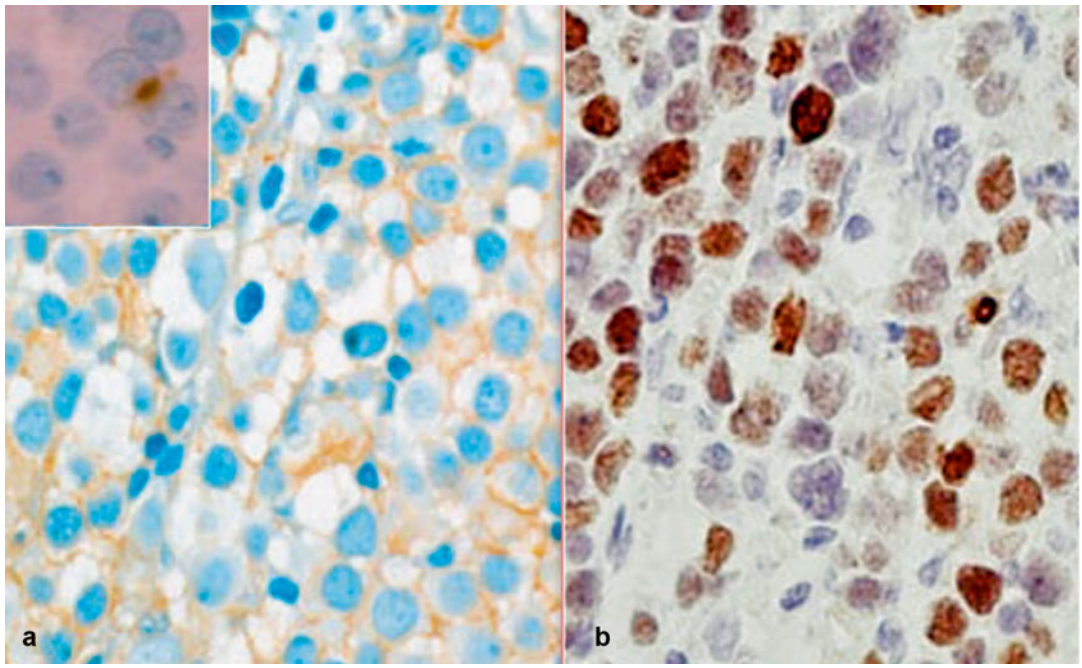


**Fig. 6.19** Spermatocytic tumor immunohistochemistry: (**a**) CD117 (c-kit). (**b**) SALL4. Insert: dot-like positivity for CAM5.2

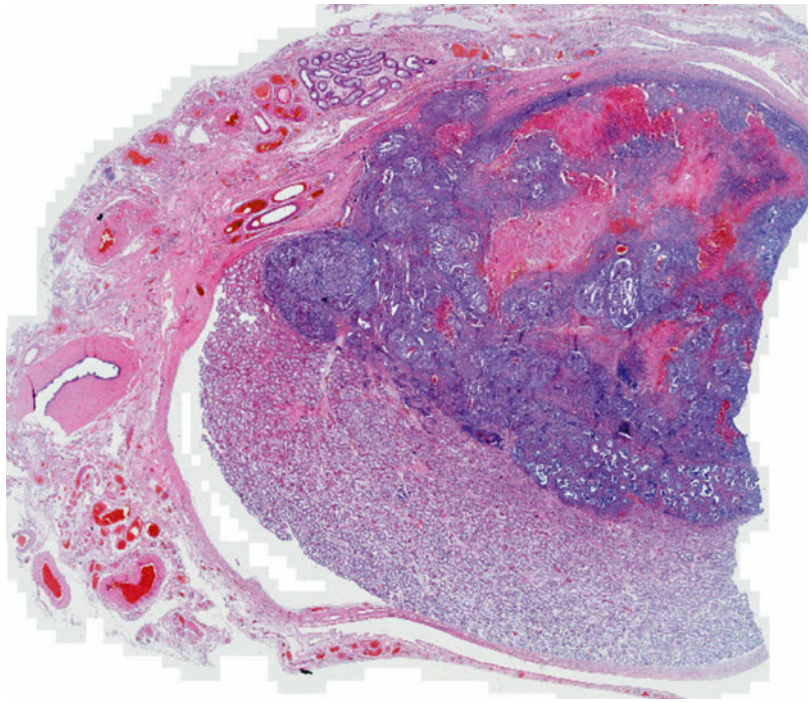

**Fig. 6.20** Overview of embryonal carcinoma with a large area of hemorrhage and necrosis

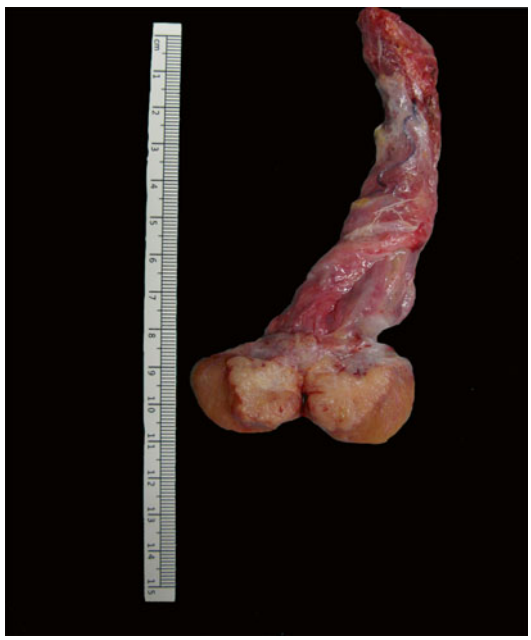

**Fig. 6.21** Embryonal carcinoma. A solid yellow-tan tumor occurring in an atrophic adult testis

## Epidemiology

The pure form of EC accounts for only 2–10 % of all testicular GCTs, but is very frequent (80 %) in mixed neoplasms with more than one germ cell component. Patients are on average 30 years of age, which is nearly as old as those with seminoma; around 5 % have a history of cryptorchidism [1]. EC in childhood and after age 50 is rare.

## Morphology

Macroscopically, ECs are mostly smaller and not as well circumscribed as seminomas. The cut surface is soft, grayish, and focally hemorrhagic or necrotic (Figs. 6.20 and 6.21). Microscopically, EC grows as a true epithelial neoplasm in solid sheets with or without clefting (Fig. 6.22) or in a papillary (Fig. 6.23) or adenomatous formation resembling an adenocarcinoma. It is frequent in the solid sheets to find darkly staining, degenerate-appearing cells that show the tendency to "apply" themselves to adjacent cells ("appliqué pattern of

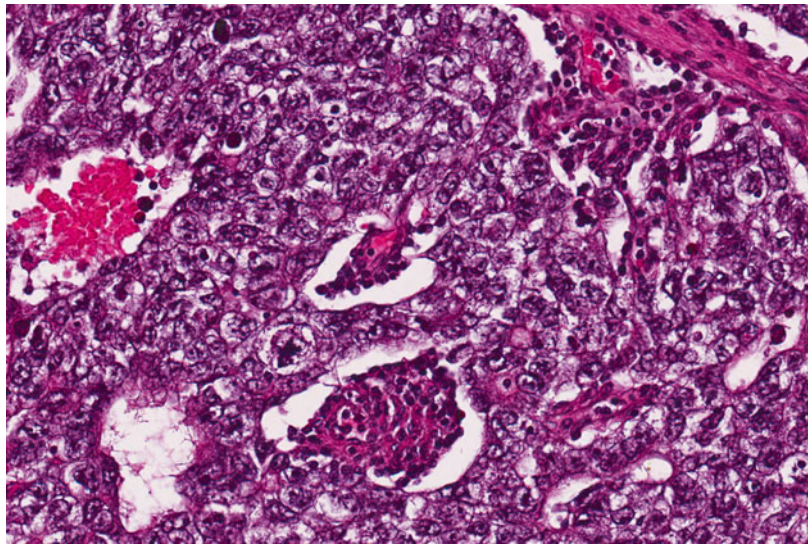

**Fig. 6.22** Embryonal carcinoma. The tumor is composed of undifferentiated cells that have overlapping nuclei and scant cytoplasm. Tumor cells form solid nests with some slit spaces

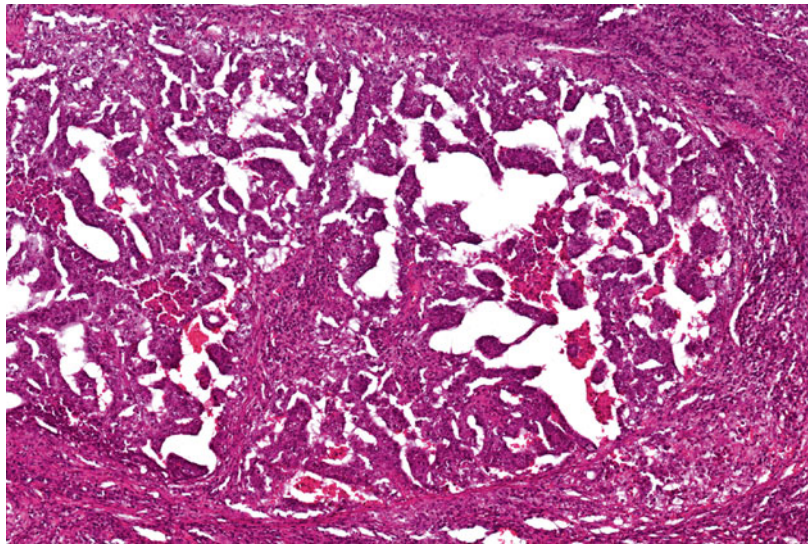

**Fig. 6.23** Embryonal carcinoma. This tumor has a papillary pattern lacking fibrovascular cores

embryonal carcinoma") (Fig. 6.24). Intratubular ECs form comedo structures with central necrosis as in breast cancer (Fig. 6.25). Lymphocytes are mostly absent. The tumor cells are very polymorphous and can have a polygonal, cuboid, or columnar shape. The color of the cytoplasm changes from clear to eosinophilic, amphiphilic, or basophilic. The nuclei have coarse chromatin and large single or multiple nucleoli. The mitotic activity is brisk, and vascular invasion is easily detected (Fig. 6.26). As in seminoma also in EC syncytiotrophoblastic giant cells can be scattered all over the tumor (Fig. 6.27). Rete testis involvement is of unclear prognostic significance (Fig. 6.28).

### Immunohistochemistry

In contrast to seminoma cells, the cells of EC show a strongly positive reaction to various

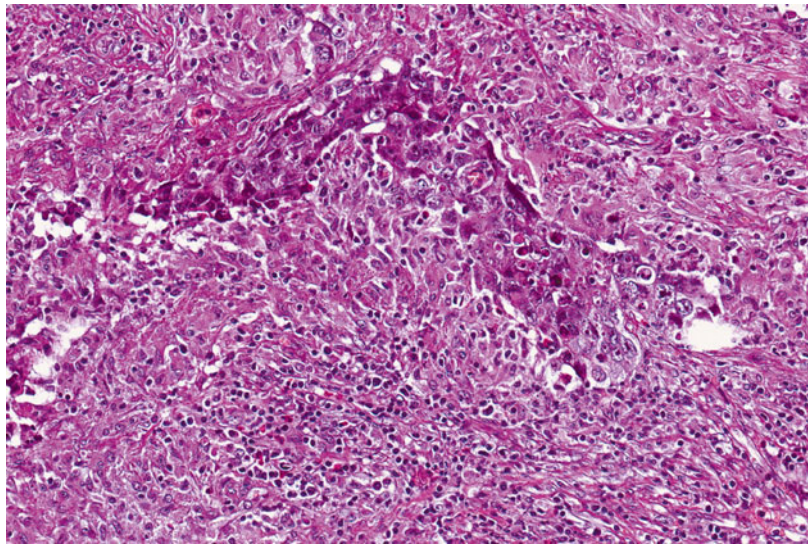

**Fig. 6.24** Embryonal carcinoma. Smudged cells "apply" themselves to adjacent cells in this so-called appliqué pattern (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

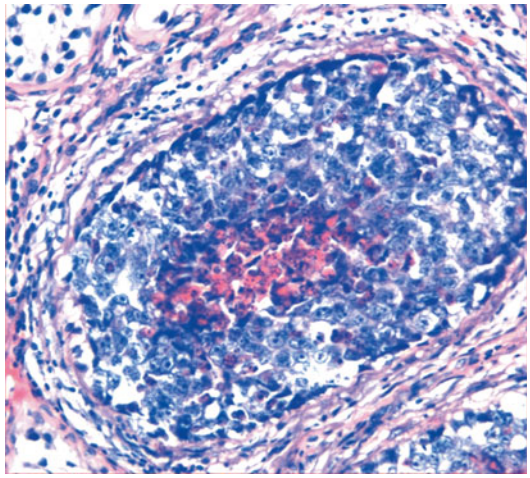

**Fig. 6.25** Intratubular embryonal carcinoma. The tubules are expanded by viable tumor cells with central comedo necrosis

cytokeratins (AE1/AE3, CAM5.2, CK7), CD30, SOX2, and OCT3/4, and are negative for CD117, SOX17, and D2-40. PLAP occurs only focally not only as a membranous but also cytoplasmic stain. AFP may be present in scattered cells, and hCG obviously stains the syncytiotrophoblastic giant cells [4, 15, 16, 30, 52].

**Caveat:** In multiple-relapse/chemoresistant cases, the persistence of CD30 expression is associated with a significantly poorer prognosis and is an independent prognostic factor for survival [53] (Fig. 6.29).

### DNA Ploidy and Cytogenetic Analysis

ECs are triploid or hypotriploid tumors [34]. Cytogenetic analysis shows unspecific anomalies, and only i(12p) is present in most cases. There is a correlation between the aggressiveness of the tumor and the number of isochromosome copies [54].

### Differential Diagnosis

EC should be differentiated from seminoma (see section on seminoma) because of the therapeutic consequences; any confusion with YST is, however, absolutely unimportant. The diagnosis of YST is based on its peculiar morphology and not on AFP positivity. EC may be confounded with large-cell B-cell lymphoma, especially if it is CD30 positive. In such cases, the use of PLAP and/or cytokeratin antibodies is recommended.

### Clinical Features

The main symptom is a testicular mass that causes pain and discomfort. Ten percent of patients suffer from systemic symptoms such as weight loss, fever, night sweats, and headaches

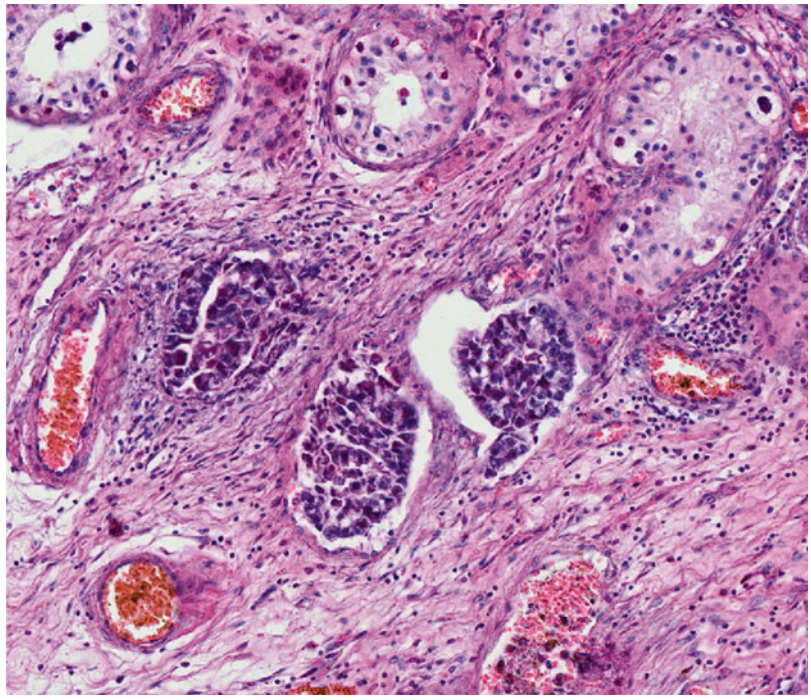

**Fig. 6.26** Vascular invasion is a frequent event in embryonal carcinoma with tumor cells conformed to the shape of the vessels

or have brain or lung metastases. AFP in serum may be elevated even in histologically pure EC, and hCG is detectable in cases with syncytiotrophoblastic giant cells. Less than half of the patients have localized disease at presentation, 40 % have retroperitoneal lymph node involvement, and 20 % have supradiaphragmatic lymph node and/or visceral metastases [55]. Even though pure EC is an extremely aggressive tumor, it can be cured with modern chemotherapy.

## Yolk Sac Tumor

YST is a tumor composed of structures resembling the embryonal yolk sac, allantois, and embryonal mesenchyme. Teilum first described this entity in 1959 and named it "endodermal sinus tumor" [56], while in the so-called British classification, the name was "orchioblastoma" [1].

Since with few exceptions the pure form occurs only in children and the oncogenesis in childhood and adults seems to be quite different, in the new WHO classification, a prepubertal and a postpubertal type are distinguished [5].

### Epidemiolology

According to the Prepubertal Testis Tumor Registry of the Urologic Section of the American Academy of Pediatrics, YST accounts for 62 % of all testicular GCTs and 70 % of all GCTs [57]. The median age of affected children is about 19 months (range, 3–39) [58]. The incidence is the same in Afro-American and Caucasian children [59]. In almost 40 % of adult cases, YST is a component of a mixed GCT [4].

### Morphology

YST's gross and microscopic appearance is identical in children and adults. Macroscopically, the tumor is grayish white and soft, with a mucoid surface and hemorrhagic and necrotic areas. The microscopic impression is that of a confusing variety of cells and patterns, but in sporadic cases, the tumor is composed of a single cell type or only one histologic pattern. The microcystic (reticular) and solid patterns are the

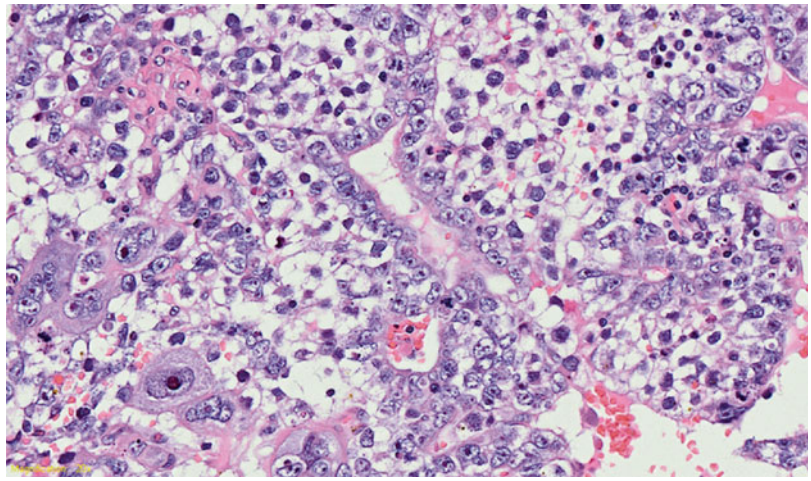

**Fig. 6.27** Mixed germ cells tumor. Seminoma with a rim of cuboidal embryonal carcinoma cells and scattered syncytiotrophoblastic giant cells

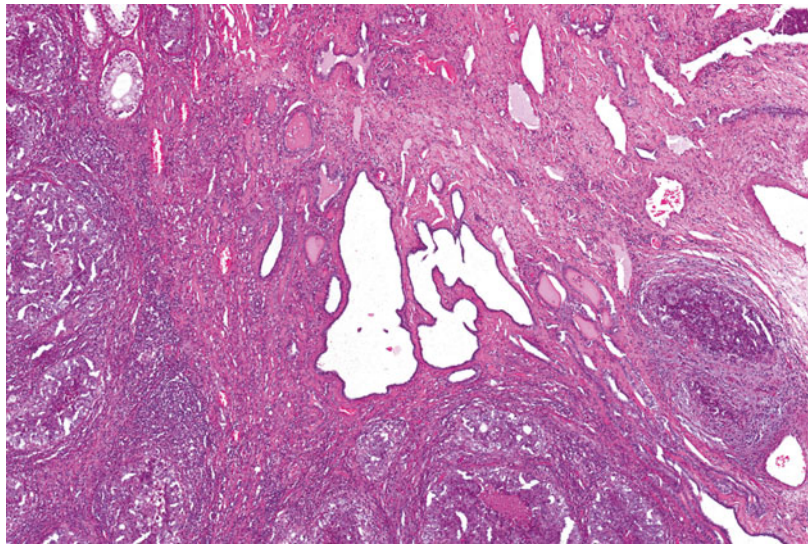

**Fig. 6.28** Embryonal carcinoma. The tumor infiltrates the rete testis

most common and are present in more than 80 % of cases (Fig. 6.30) [4]. The solid pattern has intercellular basement membrane deposits. The papillary and even the eponymous polyvesicular vitelline pattern as well as many others are not so frequently encountered (Table 6.7). Such patterns can blend into enteric-type glands, which focally show hepatic-like differentiation or the unusual endometrioid pattern (Fig. 6.31). Also the diagnostic Schiller-Duval bodies (Fig. 6.32), perivascular structures resembling the endodermal sinus of rat placenta, are scarce in most cases. Tumor cells can contain hyaline globules ($\varnothing \leq 1$ μm) staining positively with diastase-resistant PAS, which are absent in other GCTs (Fig. 6.33). Longitudinally and transversely sectioned endodermal sinus-like structures could be difficult to recognize to correctly identify yolk sac tumor subtype (Fig. 6.34). Rare cases occur with solid pattern yolk sac tumor with a blastema-like appearance (Fig. 6.35).

### Immunohistochemistry

The most reliable markers of YST are AE1/AE3 cytokeratin and glypican-3 (Fig. 6.36), whereas AFP is negative in about one-third of cases [60]. PLAP and OCT3/4 are always negative, but CD117 is positive in almost half of cases and therefore cannot be used as a discriminator between seminoma and YST (Table 6.8).

### DNA Ploidy and Cytogenetic Analysis

The DNA stem line of YST is peritetraploid and occasionally even diploid [18, 61]. Anomalies of chromosomes 1p, 6q, and 13q are common in pediatric tumors, whereas i(12p) is missing [62].

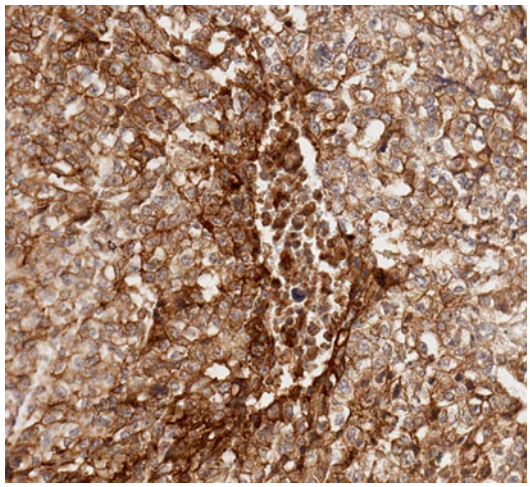

**Fig. 6.29** CD 30 immunoreactivity observed in this chemoresistant embryonal carcinoma

### Differential Diagnosis

As already mentioned, YST with a solid pattern can be mistaken for seminoma, but thorough analysis of the slides will reveal papillary or microcystic structures or hyaline globules in many cases, which will lead to the correct diagnosis [60]. The diagnosis of YST should be based on morphology and not on AFP positivity. In adults confusion with other NSGCTs is unimportant because the therapy is the same.

### Clinical Features

A painless testicular tumor and high AFP in serum are the main features of YST in childhood. Eighty percent of prepubertal patients present with stage I disease. Following surgical resection, they can be safely monitored, and chemotherapy is necessary only when the tumor recurs [57]. Retroperitoneal lymph node dissection (RPLND) is no longer performed in children [57].

## Polyembryoma

This tumor never occurs in a pure form and is only microscopically detectable in NSGCTs, mostly YSTs and teratomas. The characteristic embryoid

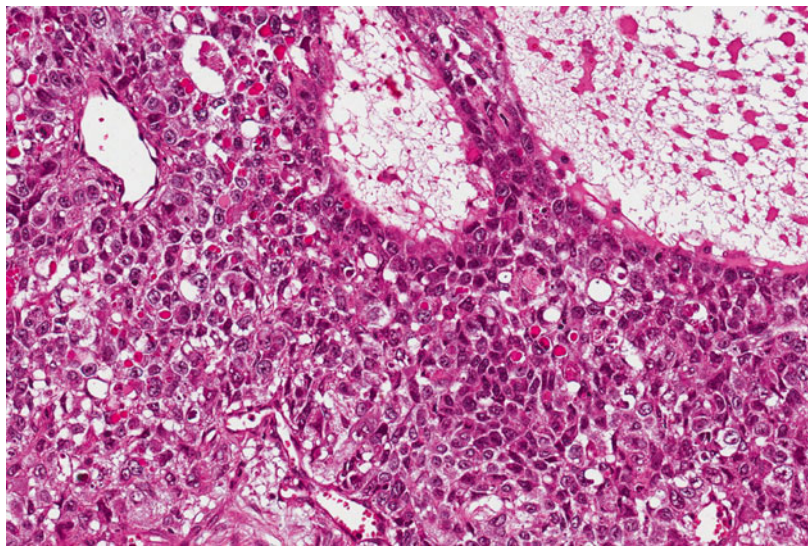

**Fig. 6.30** Yolk sac tumor. Microcystic and solid patterns are admixed in this area

bodies are composed of two or three layers of primitive embryonal cells with an amnion-like cyst on the convex side and a yolk saclike vesicle on the concave side (Fig. 6.37). These structures surrounded by a myxomatous stroma do not have any prognostic or therapeutic importance.

## Choriocarcinoma

Choriocarcinoma is composed of syncytiotrophoblasts, cytotrophoblasts, and intermediate trophoblasts.

### Epidemiology

Pure choriocarcinoma is an extremely rare tumor with an incidence of 0.8/100,000 in countries with a high incidence of GCTs. Even in mixed GCTs, choriocarcinoma elements can be found only in 8 % of cases [4].

**Table 6.7** Histologic pattern of yolk sac tumors

| |
|---|
| Endodermal sinus |
| Endometrioid |
| Glandular-alveolar |
| Hepatoid |
| Macrocystic |
| Microcystic-reticular |
| Myxomatous |
| Papillary |
| Parietal |
| Sarcomatoid-spindle cell |
| Solid pattern |
| Vitelline |

### Morphology

Macroscopically, these mostly small-sized tumors present as a hemorrhagic nodule surrounded by a whitish rim. Also in mixed GCTs, hemorrhagic nodules are highly suspicious for choriocarcinoma. Microscopically, syncytiotrophoblast and cytotrophoblast cells grow in solid sheets and are intermixed in a random fashion (Fig. 6.38). Occasionally syncytiotrophoblastic giant cells cover the proliferated cytotrophoblast like a cap, giving the impression of a placenta villus (Fig. 6.39). The cytotrophoblast cells have a distinct cell membrane, clear cytoplasm, and a vesicular nucleus. Similar cells with eosinophilic cytoplasm represent the intermediate trophoblast. Since the tumor does not have its own stroma, the syncytiotrophoblastic giant cells directly invade the local vessels.

## Other Trophoblastic Tumors

Tumors exclusively composed of cytotrophoblast are called “epithelioid choriocarcinoma” (formerly monophasic choriocarcinoma). The pure proliferation of intermediate trophoblast cells is called “placental site trophoblastic tumor”,

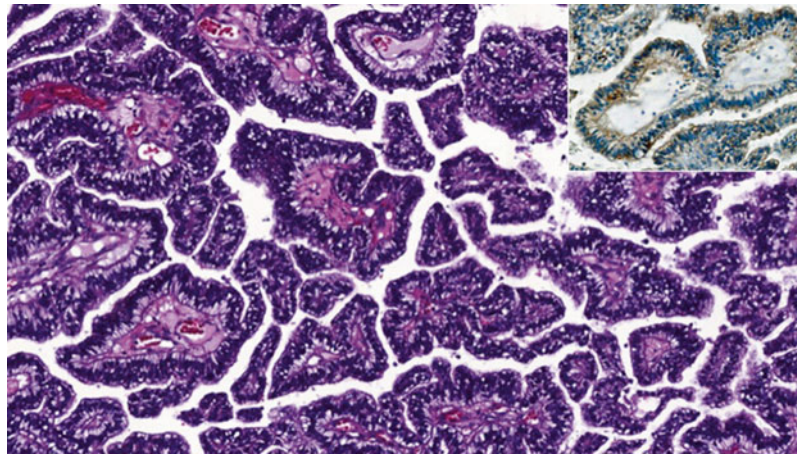

**Fig. 6.31** Yolk sac tumor with endometrioid pattern. This pattern is extremely rare in the testis. Insert: AFP positive tumor cells (Courtesy of Prof. Wittekind, Leipzig)

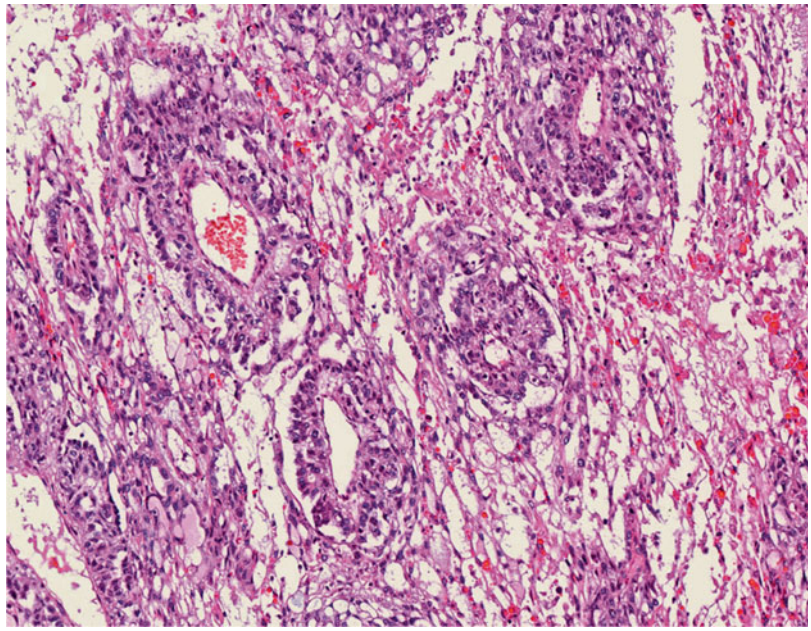

**Fig. 6.32** Yolk sac tumor. Typical Schiller-Duval bodies

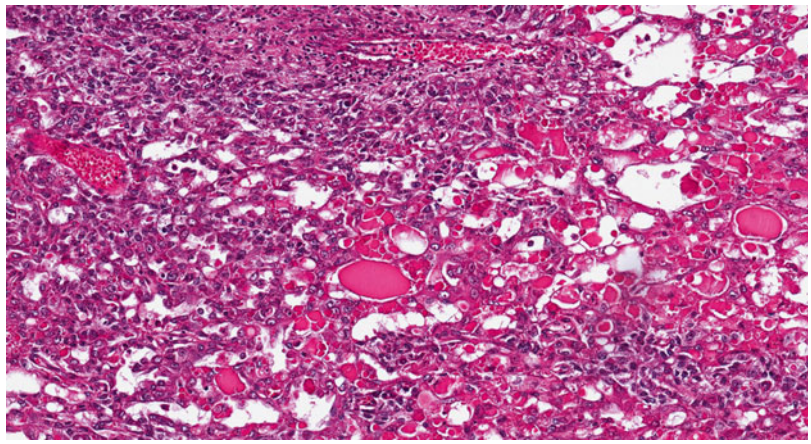

**Fig. 6.33** Yolk sac tumor. Mostly macrocystic pattern with intracytoplasmic hyaline globules

because it is morphologically identical to its counterpart in the uterus (Fig. 6.40) [63].

### Immunohistochemistry

All three cell types are strongly reactive for cytokeratin antibodies (CK7, 8, 18, 19, CAM5.2, AE1/AE3) and α-inhibin. hCG and EMA stain the syncytiotrophoblastic giant cells [4, 64–66]. Human placental lactogen and pregnancy-specific β1-glycoprotein are reactive to syncytiotrophoblastic giant cells and intermediate trophoblast but not cytotrophoblast. SALL4 reacts only with mononuclear tumor cells [36]. Cytotrophoblast cells proliferate, whereas syncytiotrophoblast giant cells do not [67]. Proliferation markers (MIB-1) can therefore be used to distinguish the two cell types.

### DNA Ploidy and Cytogenetic Analysis

Due to the rarity of these tumors, ploidy studies and cytogenetic analysis have rarely been carried out, but i(12p) has been detected also in choriocarcinoma [68].

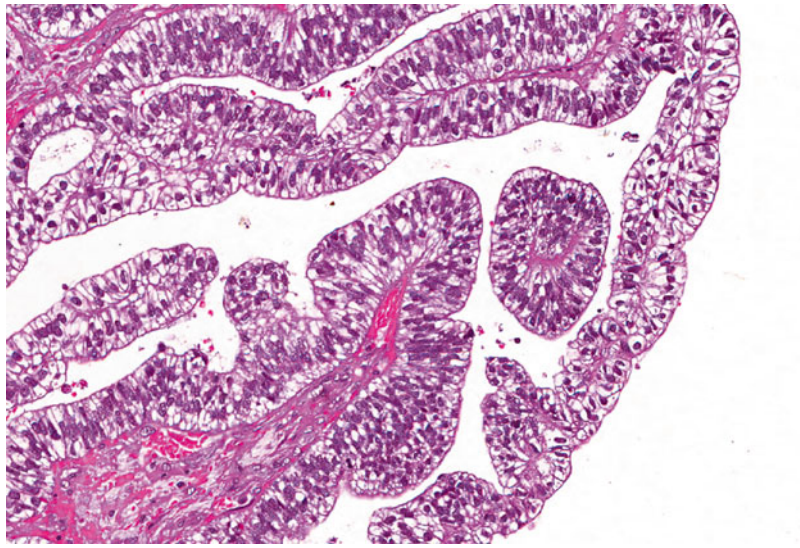

**Fig. 6.34** Yolk sac tumor. Endodermal sinus-like structures longitudinally and transversely sectioned

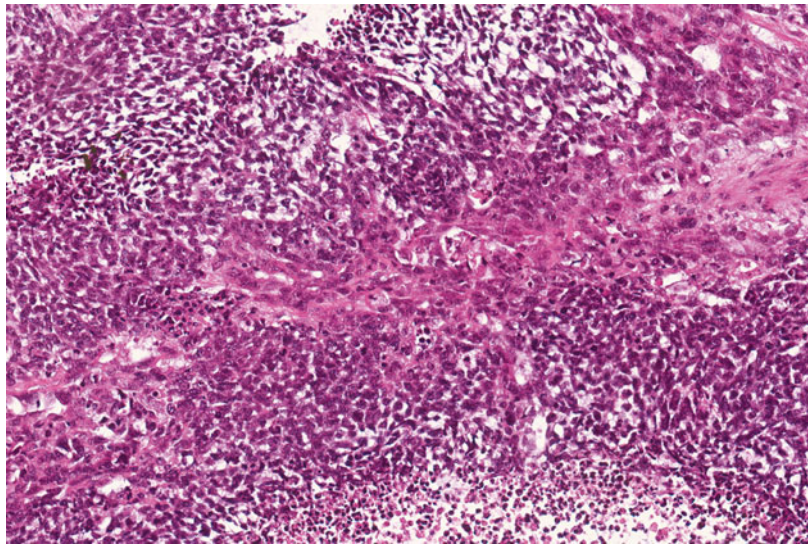

**Fig. 6.35** Yolk sac tumor. Solid pattern of blastema-like cells with oval to fusiform nuclei and scant cytoplasm (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

## Differential Diagnosis

Choriocarcinoma should not be confused with hemorrhagic necrosis of another origin (torsion, trauma, coagulopathy). In such conditions, testicular swelling is sudden and painful.

The main source of misdiagnosis is EC with syncytiotrophoblastic giant cells. For a correct choriocarcinoma diagnosis, cytotrophoblast cells have to be detected, which can, however, be similar to EC cells. The hemorrhagic background and lack of stroma are features not seen in EC. The diagnosis can be difficult in intratubular EC with comedo necrosis, where the necrotic cells squeezed against the tubule wall can mimic syncytiotrophoblastic giant cells. In doubtful cases, the use of hCG immunohistochemistry is mandatory.

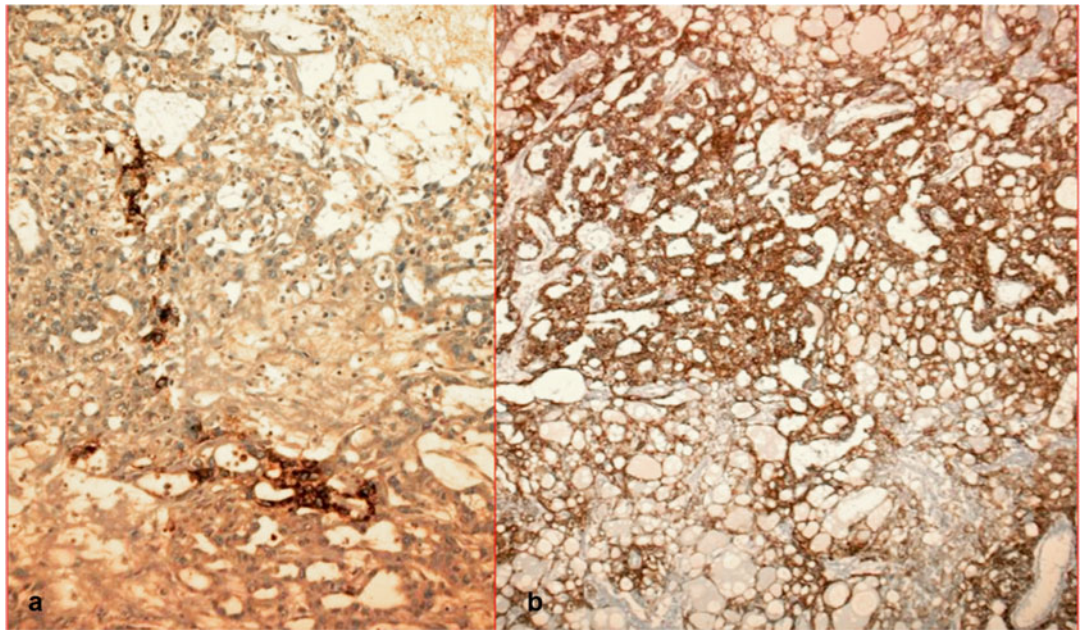


**Fig. 6.36** Yolk sac tumor immunohistochemistry. (**a**) Patchy positivity for AFP. (**b**) Marked reactivity with pancytokeratin

## Clinical Features

The first symptoms of the disease are mainly caused by organ metastases. Due to the hematogenous spread, the retroperitoneal lymph nodes are not involved. Metastases arise in the lung (100 %), liver (86 %), brain (56 %), and gastrointestinal tract (70 %) [69]. The high serum hCG levels (often >100,000 IU/L) cause gynecomastia.

Choriocarcinoma is a very aggressive tumor: up to the late 1970s, 90 % of patients died within a year. Nowadays it can be cured with energetic chemotherapy, but compared with the other GCTs, the mortality is still high [69]. Profuse intestinal and intracranial bleeding is referred to as "choriocarcinoma syndrome."

**Table 6.8** Immunohistochemical reactions useful for the differential diagnosis seminoma vs. yolk sac tumor

| Antibody | Seminoma | Yolk sac tumor |
|---|---|---|
| AFP | – | + |
| AE1/AE3 | ± | + |
| OCT3/4 | + | – |
| SALL4 | + | + |
| Glypican 3 | – | + |

## Teratoma

Teratoma is composed of tissue components deriving from all three germinal layers: endoderm, ectoderm, and mesoderm. The name, given by Virchow [70], derives from *teras* (τερασ), which in ancient Greek means marvel or monster. Because of the different histogenesis and prognosis, the new WHO classification distinguishes a pre- and a postpubertal form [5]. The use of the old denomination "mature" and "immature" teratoma should be avoided because clinicians understand these adjectives as synonyms for "benign" and "malignant."

## Epidemiology

After YSTs, teratomas are the second most frequent testicular tumors (14–20 %) in childhood [27]; about two-thirds of teratomas occur before the age of 2 years (mean age at onset, 20 months). In adults pure teratomas account for only 3–7 % of GCTs. Teratoma is, however, present as a tumor component in nearly half of all mixed GCTs [4, 34] (Figs. 6.41 and 6.42).

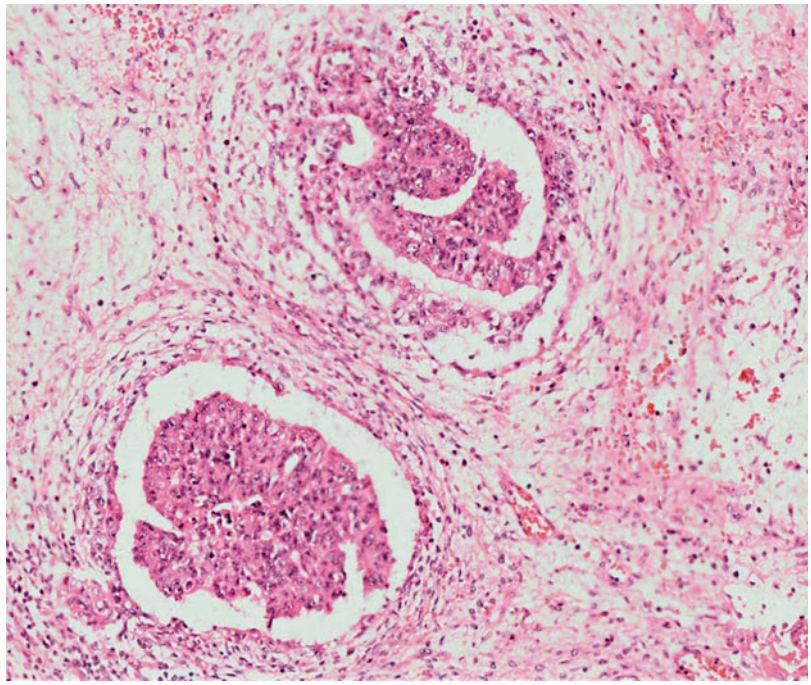

**Fig. 6.37** Polyembryoma with "embryoid bodies" resembling a 14-day-old presomite embryo

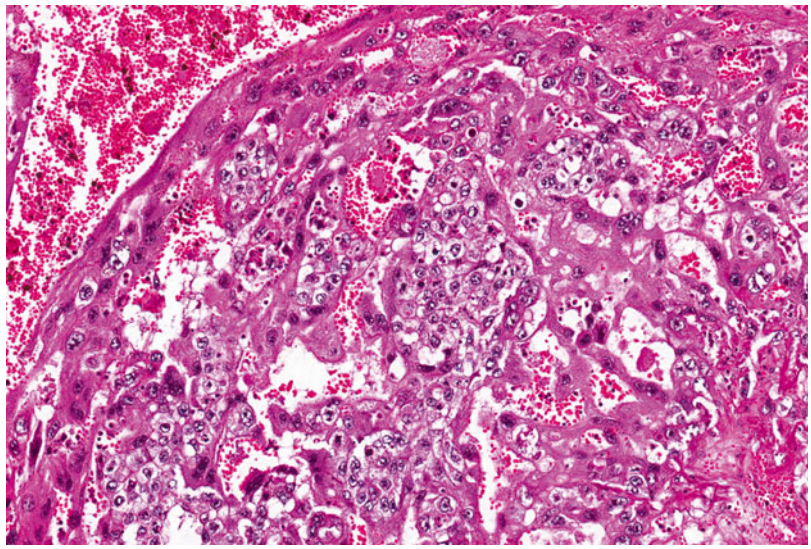

**Fig. 6.38** Choriocarcinoma. Pale mononucleated trophoblast cells are surrounded by multinucleated syncytiotrophoblasts with eosinophilic cytoplasm

## Morphology

The macroscopic and microscopic appearance depend on the amounts of different tissues present in the tumor. The cut surface has a variegated appearance with cysts filled with hair, mucus, or sebaceous material. Cartilage takes the shape of a glassy nodule. Pigmented areas derive from tissue simulating the retina.

Microscopically, the well-differentiated "mature" areas contain cysts lined with squamous

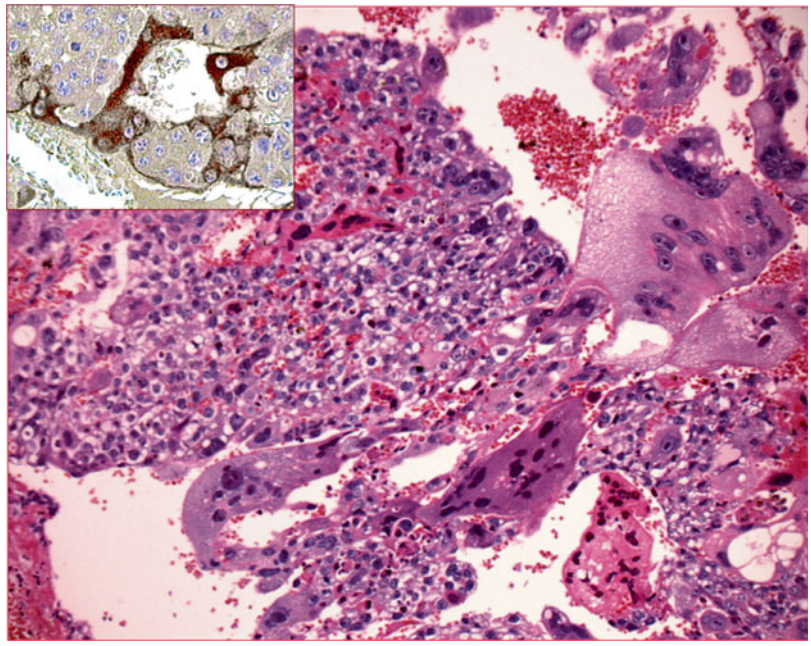

**Fig. 6.39** Choriocarcinoma. This tumor is composed of cytotrophoblastic clear cells covered with syncytiotrophoblastic giant cells. Insert: hCG positive giant cells

or glandular epithelium of the enteric-type or ciliated respiratory-type epithelium (Fig. 6.43). The cysts can be filled with mucus or keratin. Organoid structures mimicking gut or bronchus are composed of the corresponding epithelium encircled by smooth muscle. In these organoid structures, neuroendocrine cells producing all kinds of hormones (gastrin, bombesin, somatostatin, etc.) are scattered among the columnar epithelia [71]. Mesodermal tissue is always represented by smooth muscle and sometimes by cartilage; bone with or without hematopoietic marrow is less common. Neuroglia with ependymal differentiation is also a rather common component. Pigmented retinal epithelium can occasionally be present. Differentiated liver, prostate, pancreas, and thyroid are rare (Fig. 6.44).

Less differentiated "immature" tissues are represented by a mesenchymal stroma composed of undifferentiated spindle cells and small immature glands. Also the squamous epithelium is arranged in solid nests without keratinization. Other components are primitive neuroepithelium, renal blastema, rhabdomyoblasts, and fetal adipose tissue with lipoblasts (Fig. 6.45). Interestingly, "immature" tissue is more often encountered in adult patients than in children.

In the 2004 WHO classification, the rare "dermoid cyst" of the testis was listed as a separate category, because this tumor never metastasizes [4]. As in the ovary, the cyst is lined with epidermis, skin, hair follicles, and sebaceous glands.

In monodermal teratomas, a tissue component deriving from one germinal layer overgrows the other components present in the teratoma. The most frequent type is primitive neuroectodermal tumor (PNET), but also chondroma, nephroblastoma, and carcinoid have been described.

The epidermoid cyst, which accounts for 1 % of all intrascrotal tumors and can arise at any age, is the most common monodermal differentiated teratoma [72]. These tumors are easily recognizable with ultrasound and by the naked eye because they have a thin whitish wall and are filled with horny material arranged in a laminated layer similar to onion skin. An epidermis-like layer of squamous epithelium without skin

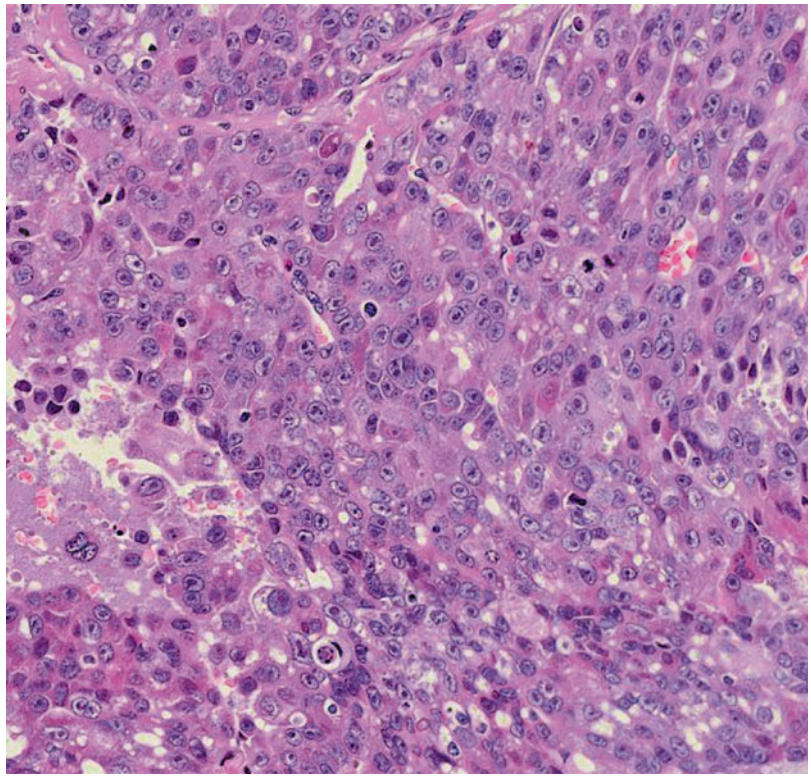

**Fig. 6.40** Epitheloid trophoblast in a choriocarcinoma metastasis (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

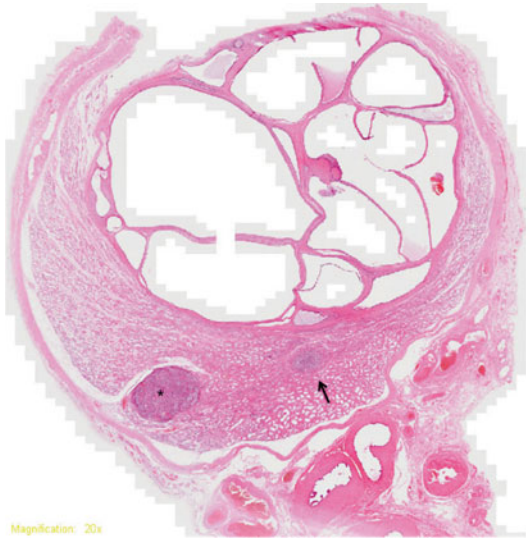

**Fig. 6.41** Cystic teratoma with a small embryonal carcinoma (*) and seminoma component (*arrow*)

appendages lines the cyst (Fig. 6.46). It has been discussed for many years whether this tumor is really a teratoma or only an inclusion cyst. Since this tumor is perfectly benign, in the new WHO classification, it will be classified as prepubertal teratoma, even when it arises in adults.

## Teratoma with Somatic-Type Malignancy

Transformation of a GCT into a somatic malignancy is uncommon. Its presentation differs from series to series, with almost half of adult cases identified within the primary tumor and the remainder in recurrences or metastases [73]. The most frequent somatic malignancies are sarcomas, especially rhabdomyosarcomas (Figs. 6.47 and 6.48). Among the epithelial

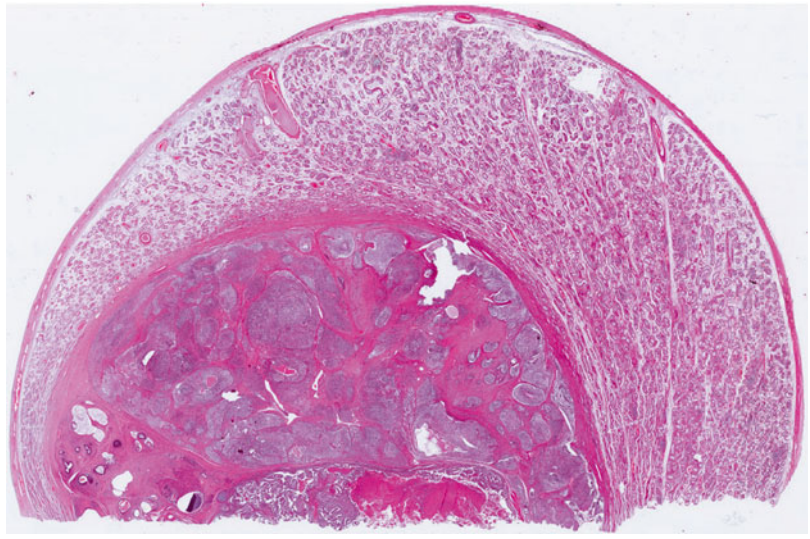

**Fig. 6.42** Mixed germ cell tumor. Small mature teratoma and a prevalent component of embryonal carcinoma

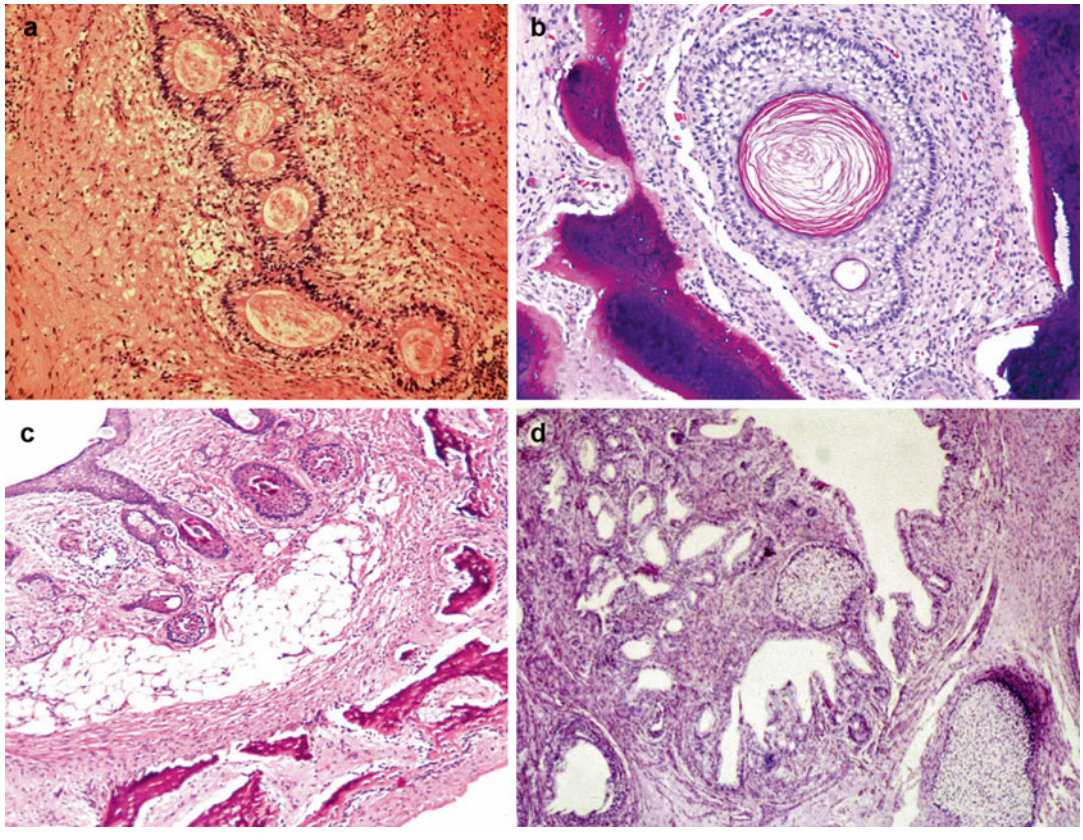


**Fig. 6.43** Teratoma. (**a**) Small glands lined with cylindrical intestinal epithelium. (**b**) Squamous epithelium and mature bone. (**c**) Cyst lined with dermis with hair follicle and sebaceous glands. (**d**) Cysts lined with respiratory epithelium and immature cartilage

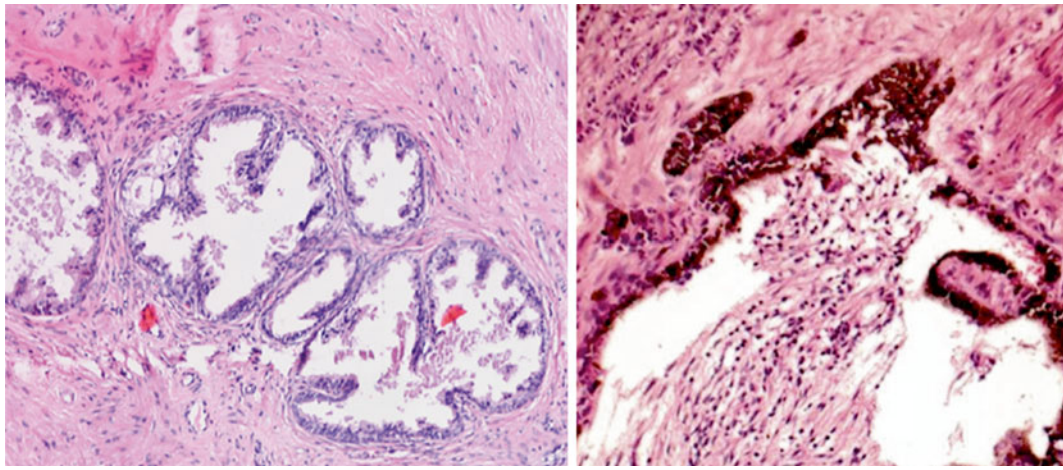

**Fig. 6.44** Teratoma containing prostate gland tissue (*left*) and retinal pigment epithelium (*right*)

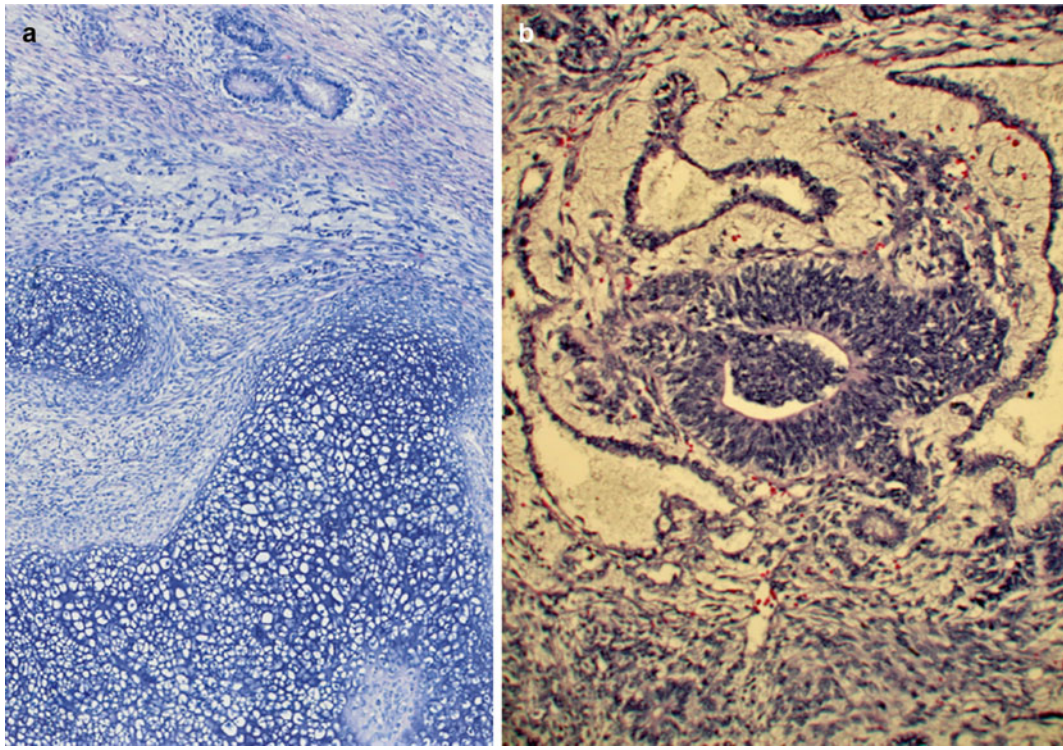


**Fig. 6.45** Teratoma with immature tissue. (**a**) Immature cartilage and some immature cysts. (**b**) Neural tubelike structure

neoplasms, adenocarcinomas and squamous cell carcinomas predominate. Such malignancies are clinically important only if the somatic malignancy fills a field of view at low magnification (×4) (Fig. 6.49) [74], although this criterion is still under debate.

## Immunohistochemistry

The different tissues in the tumor react with the same antibodies as their normal counterparts. SALL4 is positive in the epithelia of enteric-type glands [36] and is sometimes observed in a few tumor cells in PNET.

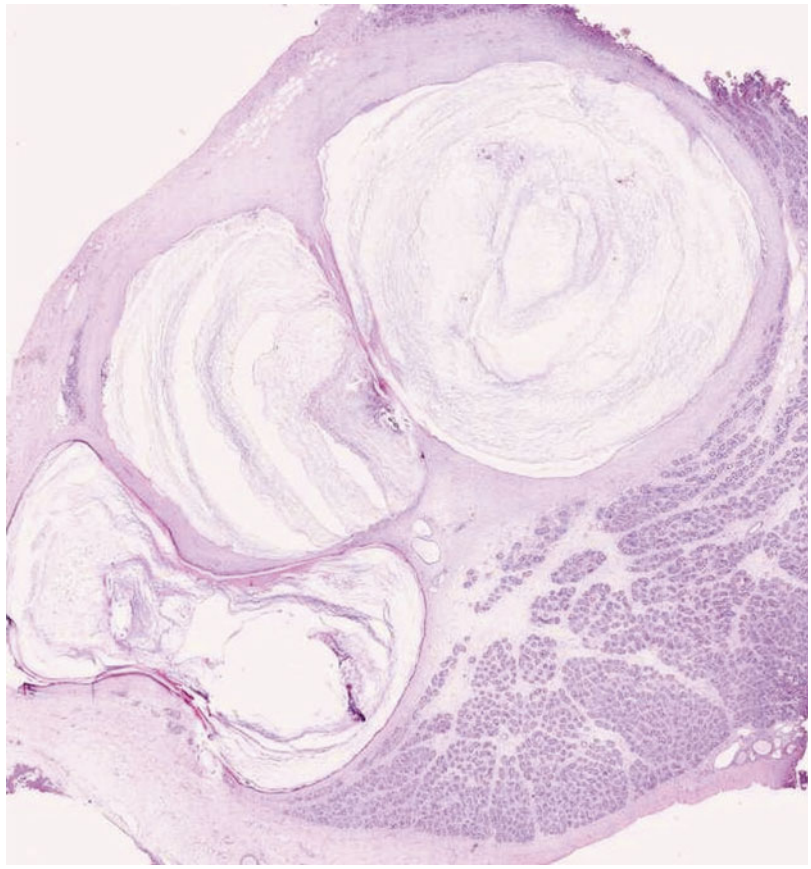

**Fig. 6.46** Epidermoid cyst lined with squamous epithelium and filled with abundant amounts of keratin. No teratomatous or adnexal structures are present

### DNA Ploidy and Cytogenetic Analysis

Teratomas are diploid in prepubertal and hypotriploid in postpubertal patients [75]. The i(12p) isochromosome is present in adults. Somatic-type malignancies can show aberrations typical of the respective somatic tumor (mostly translocations) as well as the i(12p) isochromosome that is specific for GCTs [76].

### Differential Diagnosis

The histology of teratoma is characteristic insofar as the tumor cannot be mistaken for any other GCT. It is important, however, that in epidermoid and dermoid cysts with accurate sampling, other tissue components can be excluded. Moreover, there are several other, also benign cystic testicular lesions in childhood, which should be ruled out (Table 6.9).

### Clinical Features

Painless testicular swelling is the main symptom. Since prepubertal teratoma does not metastasize, surgery, and for small tumors even parenchyma-sparing surgery, is the only necessary treatment [77]. Postpubertal teratomas metastasize first to the retroperitoneal lymph nodes and are resistant to chemotherapy and radiotherapy. Surgical removal of the lymph node and organ metastases is the only therapeutic option.

If in a somatic-type malignancy arising within a teratoma the tumor is limited to the testis, the prognosis is not negatively affected. In metastatic sites, somatic-type malignancies have a dismal prognosis. Colecchia et al. [78] reported a stage-specific survival of 100 % for patients with stage I tumors, 87.5 % for stage II, and 53 % for stage III.

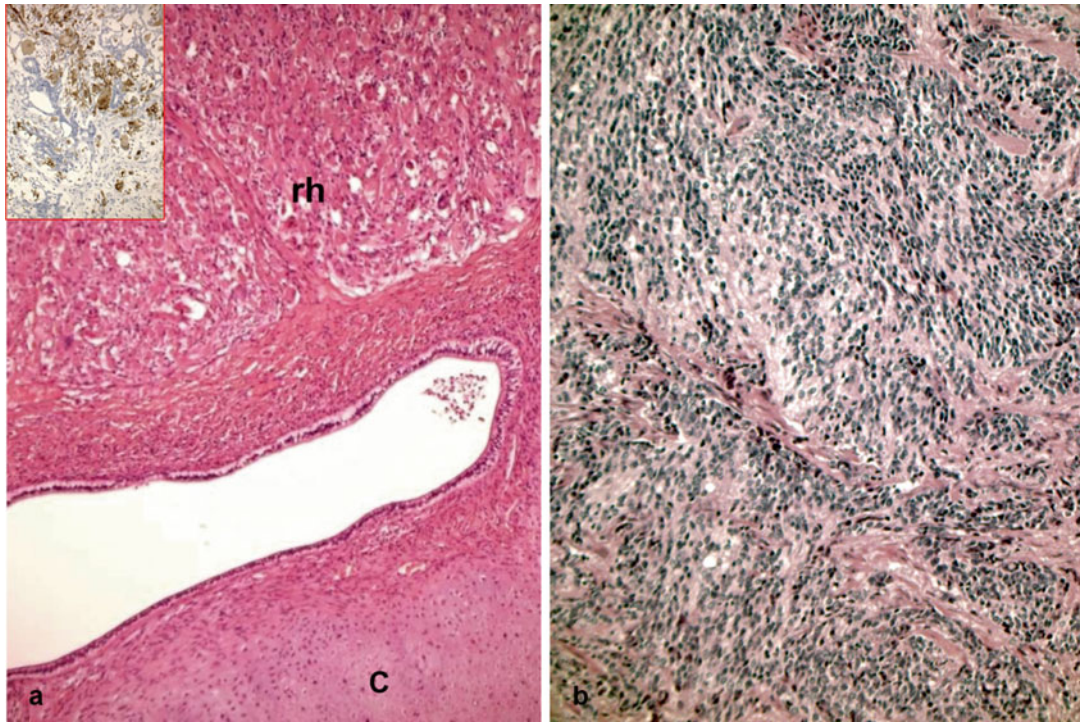


**Fig. 6.47** Teratoma with somatic-type malignancy. (**a**) Differentiated cyst with rhabdomyosarcoma and a small cartilage component (*c*). Insert: Desmin-stained rhabdomyoblasts. (**b**) Primitive neuroectodermal tumor

## Tumors of More Than One Histologic Type: Mixed Forms

Mixed forms account for 30–54 % of all GCTs and are about as frequent as seminomas. The macro- and micromorphology are dependent on the amount of the different components. Although the various types are randomly mixed, certain combinations are more frequent than others (Table 6.10) [79]. EC is with 80 % the most frequent component, and seminoma is present in about 15 % of mixed GCTs.

For the choice of treatment, it is important that seminomas are extensively sampled to rule out a nonseminomatous component (Fig. 6.50). High AFP in seminoma means that a nonseminomatous component has been overlooked. Unfortunately, serum AFP is meaningless for the pathologist because 15 % of NSGCTs are AFP negative.

The invasion of lymph or blood vessels is the most powerful predictor of relapse or metastases. A large EC component also negatively influences prognosis, whereas the presence of teratoma is a marker of favorable prognosis [80, 81]. The combination of percentage EC and vascular invasion allows correct prediction of the final pathologic stage in 88 % of patients [80].

## Burned-Out Germ Cell Tumors (pT0)

Many old reports suggested that GCTs could regress spontaneously. Conclusive evidence for spontaneous GCT regression was established by Azzopardi et al. who examined autopsy material from patients who died of metastatic GCT but lacked testicular masses [82]. Retroperitoneal so-called extragonadal GCTs are almost always associated with a burned-out tumor in the testis, whereas GCT located in the mediastinum only rarely shows such an association. Intracranial GCTs growing in the pineal region do not have any relationship with testicular tumors. Our experience but also other studies [83] show that regression of testicular GCT is mostly associated with seminoma.

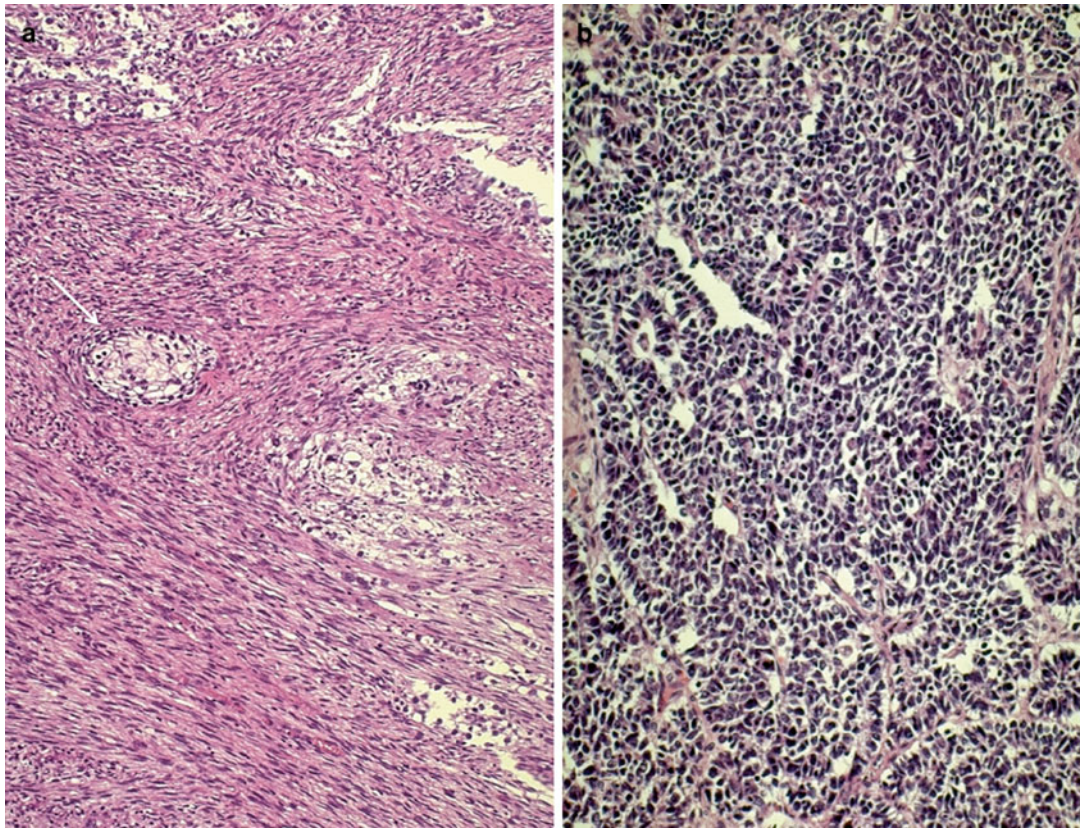


**Fig. 6.48** Teratoma with somatic-type malignancy. (**a**) Leiomyosarcoma with entrapped immature squamous epithelium and scattered seminoma cells. (**b**) Nephroblastoma (Wilms' tumor) with immature blastematous cells and tubule formations

## Morphology

Macroscopically, burned-out tumors consist of single or multiple scars (Fig. 6.51), and sometimes of cysts or cartilaginous areas. A well-demarcated, nodular scar with aggregates of proliferated Leydig cells in the surrounding atrophic testis is the main microscopic feature. The scar can show coarse calcification and scattered siderophages or foamy cells. The tubules of the surrounding parenchyma are atrophic with hyalinized or completely collapsed walls or may contain microliths (Fig. 6.52). In many cases, CIS can be detected [84].

## Differential Diagnosis

One should keep in mind that also trauma or vascular disease may cause a testicular scar. Scars in a testicular biopsy without a retroperitoneal tumor are not a priori burned-out tumors, unless the scar is associated with CIS in the surrounding tubules.

## Clinical Features

The prognosis and treatment of regressed GCT depend on the morphology of the primary tumor. Retroperitoneal metastases in young men are always suspicious for a primary tumor in the testis. A biopsy or surgical exploration with intraoperative frozen section is helpful for reaching a correct diagnosis. The detection of the tumor in the testis can be difficult even with ultrasound.

The pseudotubular pattern observed in Leydig tumor could represent in the intraoperative examination a pitfall about the stromal origin of the tumor (Fig. 6.53)

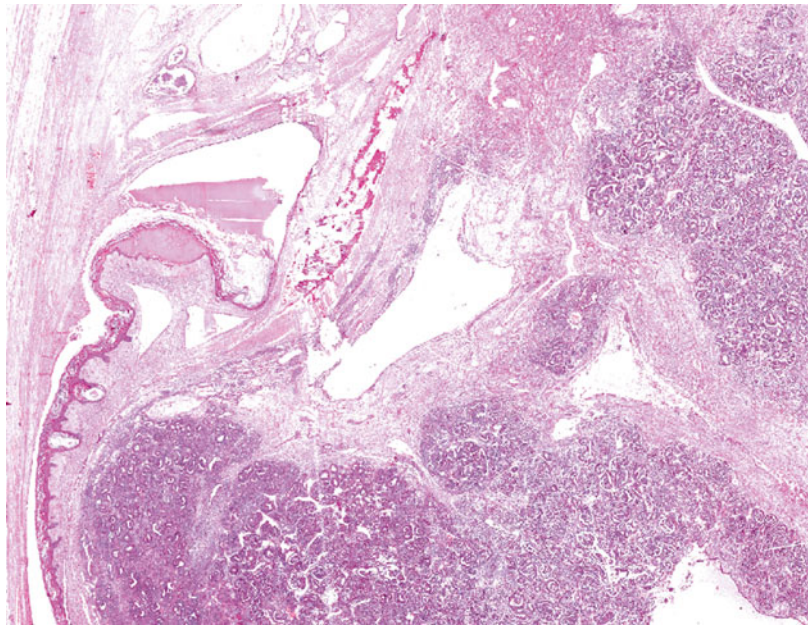

**Fig. 6.49** The low-power field (x4) is entirely occupied by Wilms' tumor in an otherwise mature teratoma (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

**Table 6.9** Cystic lesions occurring in the testis in childhood

| |
|---|
| Teratoma |
| Epidermoid cyst |
| Dermoid cyst |
| Yolk sac tumor |
| Cystadenoma of ovarian type |
| Granulosa cell tumor-juvenile type |
| Cystic lymphangioma |
| Cystic dysplasia of rete testis |
| Simple cyst |

**Table 6.10** Mixed germ cell tumors: some preferred combinations

| Combination | | OR | P value |
|---|---|---|---|
| Teratoma | Embryonal Ca | 0.48 | 0.001 |
| Teratoma | Chorioca | 1.47 | 0.002 |
| Teratoma | Yolk sac tumor | 2.58 | 0.001 |
| Teratoma | Seminoma | 0.71 | 0.001 |
| Embryonal Ca | Chorioca | 1.23 | 0.149 |
| Embryonal Ca | Yolk sac tumor | 1.42 | 0.001 |
| Embryonal Ca | Seminoma | 0.55 | 0.001 |
| Chorioca | Yolk sac tumor | 1.38 | 0.007 |
| Chorioca | Seminoma | 0.65 | 0.002 |
| Yolk sac tumor | Seminoma | 0.95 | 0.552 |

Modified after Mosharafa et al. [79]

### Retroperitoneal Lymph Node Dissection

RPLND is a standard procedure in the treatment of GCT. Because of the prognostic and therapeutic importance of retroperitoneal metastases, clinicians prefer to use staging systems (Table 6.11) and not the TNM algorithm (Table 6.12).

For adequate management of the disease, thorough sampling and histologic workup of the dissected lymph nodes is mandatory. Overlooked residual tumor can severely reduce the survival chances of the patient. Markers of unfavorable prognosis after chemotherapy include viable residual tumor, teratoma remnants, and the development of a somatic-type neoplasm.

## Sex Cord/Gonadal Stromal Tumors

The name was chosen in analogy to the name given by Teilum [85] to the same type of tumors of the ovaries. These tumors arise in the gonads of both genders and only differ in the frequency of the individual subtypes. In the testis, Leydig and Sertoli cell tumors predominate, whereas in

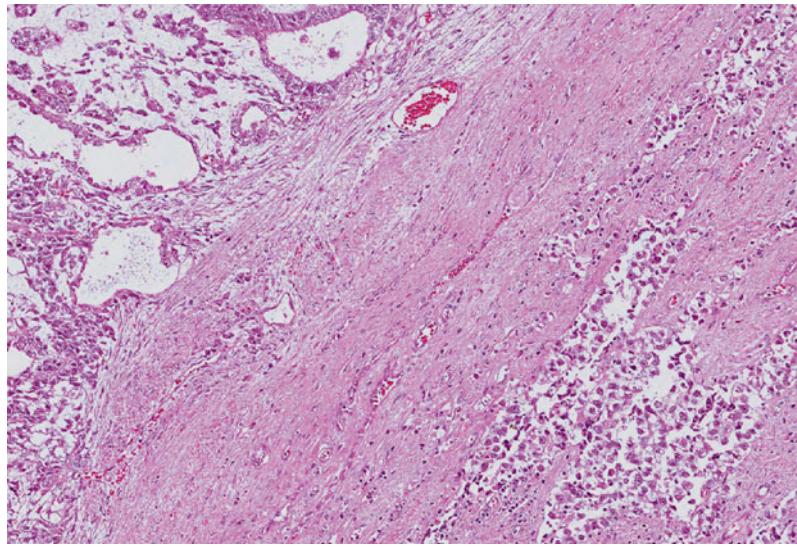

**Fig. 6.50** Mixed germ cell tumor. Seminoma (*lower right*) and yolk sac tumor (*left*)

the ovary, granulosa cell and theca-fibroma-type tumors are the most frequent. In addition to differentiated, "pure-form" tumors, also mixed types and poorly differentiated or completely undifferentiated tumors exist.

In large series, these tumors account for only 3–6 % of adult testicular tumors but over 30 % of infant and childhood tumors. About 10 % of sex cord tumors metastasize and do so predominantly in adults. Nothing is known about the causes and pathohistogenesis of these tumors [4].

## Leydig Cell Tumor

Leydig cell tumors (LCTs) are composed of more or less well-differentiated Leydig cells.

### Epidemiology

LCT is the most frequent sex cord tumor, accounting for up to 3 % of testicular tumors. The average age at diagnosis is between 30 and 50 years; in 20 % of cases, patients are younger than 10 years of age, and in 25 %, they are older than 50 (range, 2–90 years) [4]. Three percent of LCTs are bilateral, and 5–10 % of patients have a history of cryptorchidism [86]. In a few cases, LCT was found to be associated with Klinefelter syndrome [87].

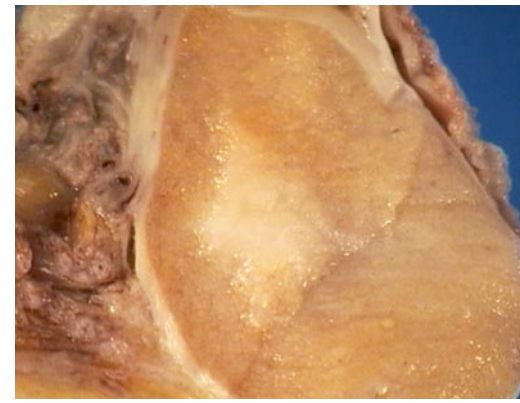

**Fig. 6.51** Burned-out germ cell tumor. A whitish scar with the irregular contour in the testicular parenchyma

### Morphology

On gross examination, LCTs are on average 2–3 cm in diameter (range, 0.5–10 cm). They have a thin fibrous capsule and a brown color of different shades (yellowish, reddish, and dark brown) as observed in metastatic localization too (Fig. 6.54). Tumors with a diameter ≥5 cm are almost without exception malignant.

Microscopically, the tumor is composed of nests or sheets of polyhedral cells with eosinophilic cytoplasm and big round to oval nuclei with prominent nucleoli (Fig. 6.55). Multinucleated nuclei may occur. Reinke

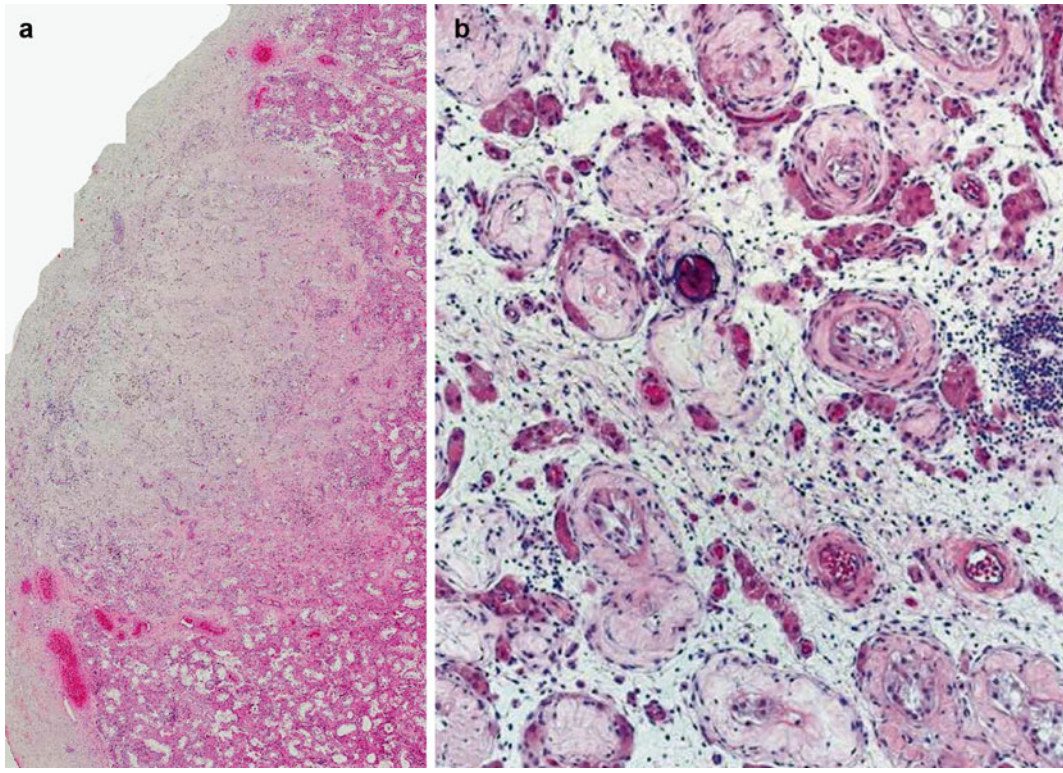


**Fig. 6.52** Burned-out germ cell tumor. (**a**) Large scar surrounded by atrophic testicular parenchyma. (**b**) Atrophic tissue surrounding the scar with hyalinized tubules, lymphocytic infiltration, and intratubular calcification (microlithiasis)

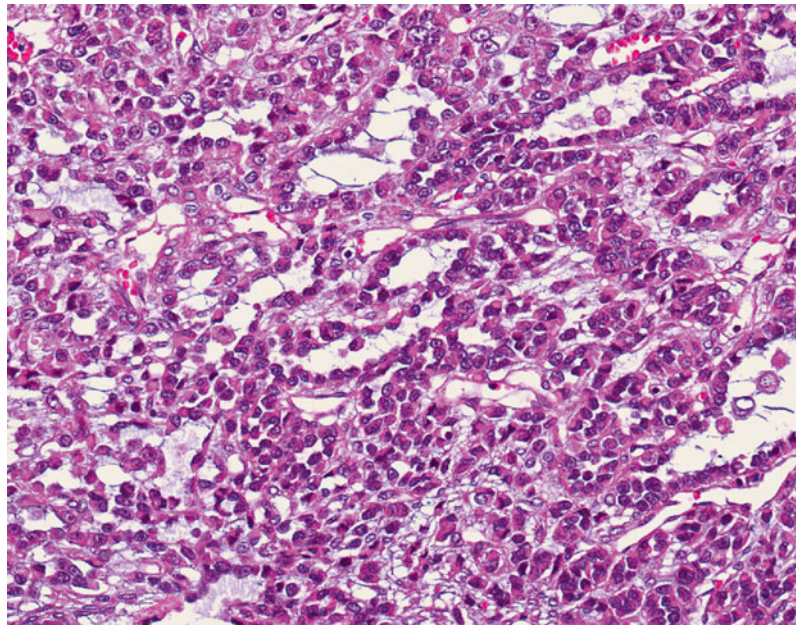

**Fig. 6.53** Leydig cell tumor showing pseudotubular structures (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

**Table 6.11** Prognostic factors of seminoma and non-seminomatous germ cell tumors

| Features | Seminoma | Nonseminomatous GCT |
|---|---|---|
| Size | >4 cm *unfavorable* | Insignificant |
| Rete testis invasion | *Unfavorable* | Insignificant |
| Vascular invasion | Insignificant | *Unfavorable* |
| High amount (%) of EC | | *Unfavorable* |
| In absence of EC S-phase fraction >29 % | Insignificant | *Unfavorable* |
| Presence of teratoma | | Favorable |

**Table 6.12** Clinical tumor stages and corresponding TNM stages

| Clinical staging AJCC | TNM |
|---|---|
| Stage 0 Tis | N0, M0, S0 |
| Stage IA | T1, N0, M0, S0 |
| Stage IB | T2–T4, N0, M0, S0 |
| Stage IC | Any T, N0, M0, S1–S3 |
| Stage IIA | Any T, N1, M0, S0–S1 |
| Stage IIB | Any T, N2, M0, S0–S1 |
| Stage IIC | Any T, N2, M0, S0–S1 |
| Stage IIIA | Any T, any N, M1a, S0–S1 |
| Stage IIIB | Any T, any N, M0–M1a, S2 |
| Stage IIIC | Any T, any N, M0–M1a, S3 or any T, any N,M1b, any S |

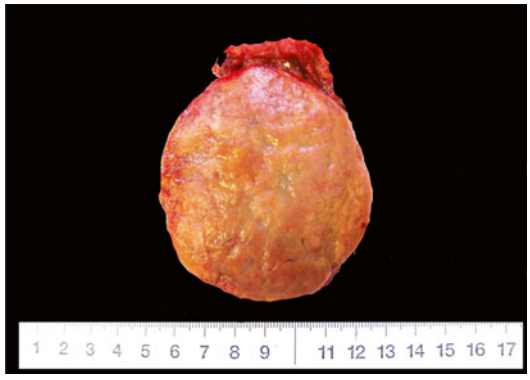


**Fig. 6.54** Metastatic Leydig cell tumor. A para-aortic nodule with brownish color and small necrotic areas (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

crystalloids are visible in about one-third and lipofuscin in 15 % of cases. The stroma is scanty with a network of capillaries typical of endocrine tumors. Some tumors are composed of spindle cells (sarcoma-like) or cells with a large quantity of intracytoplasmic lipids (Fig. 6.56). Even psammoma bodies and calcifications have been described [88].

The most important feature of malignant LCT is its size, which on average is about 7 cm versus <3 cm in benign LCT. Mitoses are obviously also more frequent in malignant than benign tumors 13.9/HPF vs. 1.9/HPF. Further microscopic indicators of malignancy are a spindled cell shape, nuclear atypia and polymorphism (Fig. 6.57), necrosis (Fig. 6.58), vascular invasion, and invasion of surrounding tissue [86, 89]. The number of proliferating cells (Ki67/MIB-1) is also greater in malignant LCT [89]. However, to predict a malignant course, at least two of these features should be present. In fact, only metastases provide the conclusive evidence of malignancy; one should therefore be somewhat restrictive in the histopathologic diagnosis of malignancy (Table 6.13).

## Immunohistochemistry

There are a number of antibodies that react more or less with all sex cord tumors (see Table 6.14); however, only rarely are 100 % of the cells of a given tumor type positive, and a negative result therefore does not exclude such a tumor [90].

Over 90 % of LCTs are positive for calretinin, $\alpha$-inhibin, melan-A, and steroidogenic factor 1 (SF1). But they also stain with $\beta$-catenin, CD99, FOXL2, and synaptophysin and in 20 % of cases with CK and S100. In some cases, the use of androgen receptor antibodies can be helpful. The only antibody that does not react with this tumor is WT1 [90].

## DNA Ploidy and Cytogenetic Analysis

As is well known, also benign endocrine tumors can have an aneuploid stem line [91]. It is therefore not surprising that all metastasizing LCTs but also 30 % of benign LCTs are aneuploid. For this reason, ploidy cannot be used as an absolute marker of malignancy.

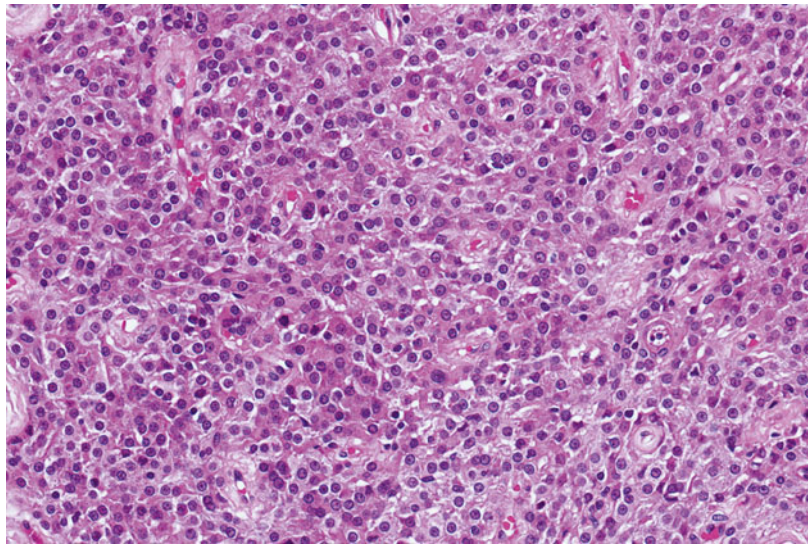

**Fig. 6.55** Leydig cell tumor. The tumor cells have abundant eosinophilic cytoplasm and regular round nuclei with inconspicuous nucleoli

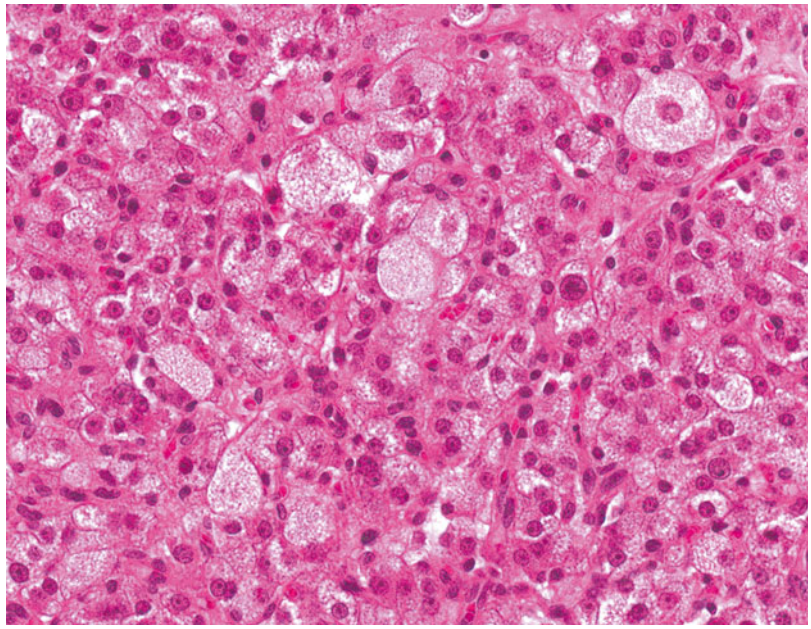

**Fig. 6.56** Leydig cell tumor. The cytoplasm is extensively vacuolated or spongy due to abundant lipid

The genetic features of the uncommon sex cord tumors are largely unknown. FISH analysis showed in 21/25 (84 %) of LCTs gain of chromosome X (Fig. 6.59), 19 or 19p, and loss of chromosomes 8 and 16 [92]. In two boys with LCT, LH-receptor gene mutations were detected [93].

## Differential Diagnosis

Three benign diseases can be mistaken for LCT. The most common is Leydig cell hyperplasia, which is commonly detected in cryptorchid testes and in Klinefelter syndrome. Unlike LCT, the hyperplasia is nodular and multifocal. Among

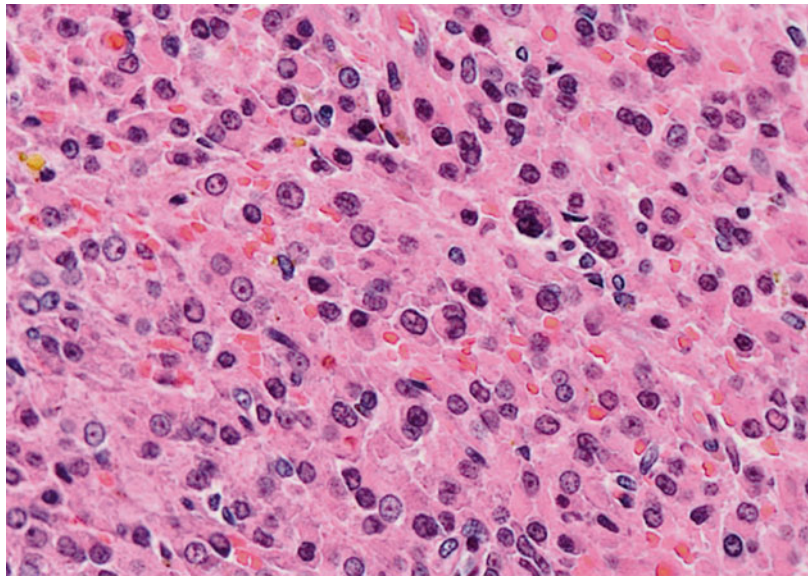

**Fig. 6.57** Malignant Leydig cell tumor. Slight cellular and nuclear polymorphism

the hyperplastic nodules, well-preserved or atrophic tubules can be observed, a feature which excludes a tumor diagnosis.

On the inner surface of the nuclear membrane, one Barr body (sex chromatin) is visible at higher magnification in Klinefelter syndrome. In humans with more than one X chromosome, the number of visible Barr bodies is always one less than the total number of X chromosomes.

In rare malacoplakia of the testis, large macrophages with eosinophilic granular cytoplasm show some similarity to Leydig cells. These inflammatory cells contain basophilic inclusions called Michaelis-Gutmann bodies and are strongly reactive for the macrophage marker CD68 and negative for α-inhibin.

Testicular tumor of adrenogenital syndrome (TTAGS) is a rare, mostly bilateral neoplasm, the cells of which resemble Leydig cells. Misdiagnosis of this tumor may have as its consequence an absolutely unnecessary bilateral orchiectomy. TTAGS regresses "spontaneously" under steroid therapy. Like in hyperplasia, tubules are entrapped among the proliferated tumor cells. The tumor cells are larger than those of LCT and are filled with dark-brown lipochrome pigment. Immunohistochemically, TTAGS shows diffuse and strong positivity for CD56 (NCAM) and negative reactivity for androgen receptor. In contrast, LCT displays focal weak to moderate (or negative) reactivity for CD56 and positive reactivity for androgen receptor [94].

Even melanoma metastases can mimic an LCT and, like LCT, they are melan-A positive [95].

## Clinical Features

In about half of the patients, unilateral testicular swelling is the presenting symptom; another frequent symptom is gynecomastia, which may also precede the swelling. Twenty-five percent of adults suffer from loss of libido and impotence because the tumor produces estrogen [86]. Prepubertal LCT produces testosterone and can cause pubertas praecox, in which case penile growth and pubic hair growth are the most common symptoms, followed by facial acne and a deep voice. Precocious closure of the growth plates arrests the longitudinal growth of the bones. Boys affected by LCT are aggressive and withdrawn. Twenty percent of malignant LCTs have already metastasized at the time of diagnosis. The average age at diagnosis is 67 years, which is significantly older than in benign tumors [41]. Prepubertal malignancy is rare.

Metastases first appear in the retroperitoneal lymph nodes (72 %); the tumor then spreads by

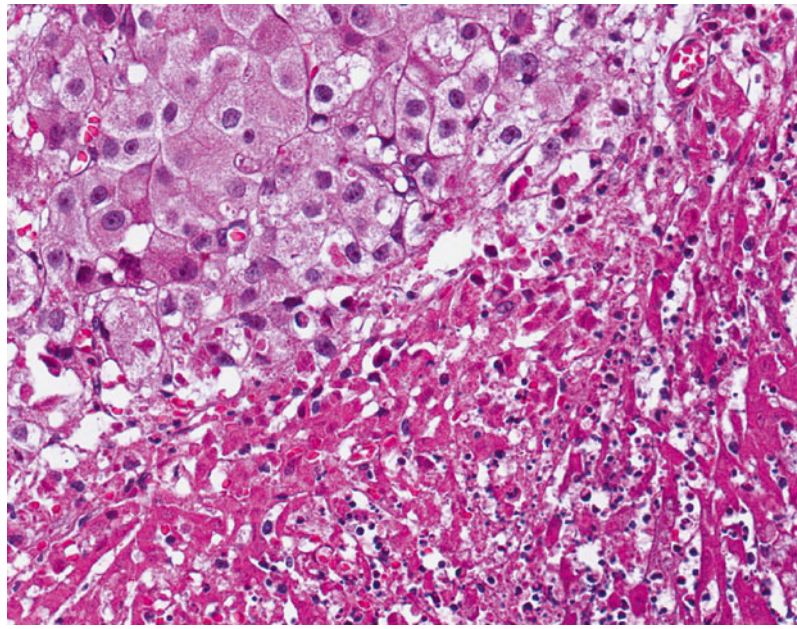

**Fig. 6.58** Malignant Leydig cell tumor. Microscopic findings in a necrotic area of the metastatic tumor reported in Fig. 6.53 (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

**Table 6.13** Malignancy criteria of Leydig- and Sertoli-cell tumors

| Leydig cell tumor | | Sertoli cell tumor |
|---|---|---|
| Only adults; never in infants | | At any age; >30 % gynecomastia |
| | *Diameter >5 cm* | |
| | High mitotic count (normal average 1.9/HPF) | |
| | Spindled cell shape | |
| | Nuclear atypia and polymorphism | |
| | Necrosis | |
| | Vascular invasion | |
| | Invasion of surrounding tissue | |

Only the diameter is a very reliable single prognostic factor. The other listed features are as a single criterion unreliable. For the prediction of malignancy, more of them must be present

the hematogenous route to the lungs (43 %), liver (38 %), and bones (28 %) [96]. Since LCTs are resistant to chemotherapy, orchiectomy with RPLND and radiotherapy is the only therapeutic option. The prognosis is dismal, and on average, patients do not survive more than 5 years.

## Sertoli Cell Tumor

Sertoli cell tumor (SCT) is a tumor of the gonadal stroma; it is composed of cells resembling embryonal, prepubertal, and adult Sertoli cells.

### Epidemiology

SCTs are rare and account for only 1 % of testicular tumors. The average age at diagnosis is 45 years. Before the age of 20, SCT is even rarer, unless it is associated with Peutz-Jeghers syndrome or Carney's complex. The occurrence of bilateral tumors is also extremely rare.

### Morphology

The tumor is encapsulated and rather small (average, 3.5 cm). The color of the cut surface may contain various shades of yellowish (yellowish white, gray, or tan). The tumor cells form well or poorly shaped tubular structures

**Table 6.14** Immunohistochemistry useful for the diagnostic of sex cord/gonadal stroma tumors [90]

| Antibody | LCT | SCT | USCST | GCT | LCCST | TTAG |
|---|---|---|---|---|---|---|
| SF-1 | 92 | 75 | 57 | 50 | 50 | 100 |
| FOXL2 | 21 | 83 | 67 | 100 | – | – |
| B-catenin | 50 | 83 | 60 | 100 | 50 | 100 |
| Inhibin | 97 | 67 | 38 | 67 | 75 | 100 |
| Melan-A | 94 | 67 | 75 | 50 | 50 | 100 |
| Calretinin | 97 | 56 | 75 | 44 | 75 | 100 |
| WT1 | 0 | 82 | 57 | 50 | 75 | 50 |
| CD99 | 74 | 56 | 25 | 86 | 0 | 0 |
| Synaptophysin | 65 | 24 | 29 | 0 | 0 | 50 |
| CK | 22 | 78 | 17 | 43 | 67 | – |
| S100 | 28 | 28 | 43 | 38 | 75 | 0 |

*LCT* Leydig CT, *SCT* Sertoli CT, *USCST* unclassified CST, *GCT* granulosa CT, *LCCST* large-cell calcifying SCT, *TTAG* testicular tumor of adrenogenital syndrome

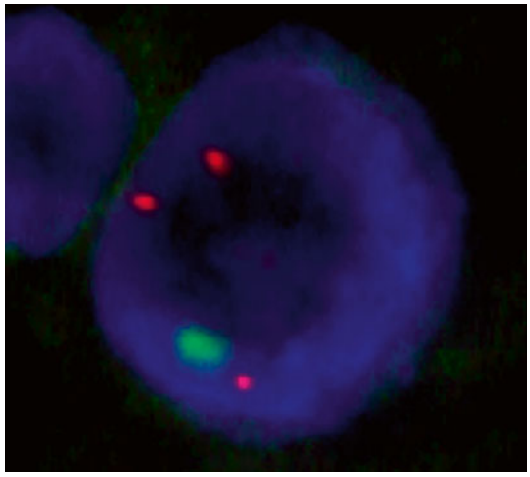

**Fig. 6.59** Interphase FISH of Leydig cell tumor: three signals (*red*) for chromosome X

(Fig. 6.60). The cytoplasm is usually eosinophilic but sometimes contains a large amount of lipids (the lipid-rich variant listed in the WHO classification of 2004 [4], though not as an entity of its own). The tubules can be highly differentiated with a clearly visible basement membrane lined with rather well-differentiated Sertoli cells having oval vesicular nuclei and prominent reddish nucleoli. Less differentiated tumors are composed of spindle-shaped cells growing in solid sheets, which are barely recognizable as Sertoli cells. Between the well- and less differentiated tumors, all possible transitional forms are possible. Heterologous carcinosarcomatous components were observed in one case [97].

Among the tumor cell formations, bands of fibrous tissue can be present in various amounts. The exuberant sclerotic stroma is the hallmark of sclerosing SCT [98] (Fig. 6.61).

Like other malignant sex cord tumors, malignant SCTs are quite large (7–15 cm) and show nuclear pleomorphism and occasionally invasion of the lymph vessels.

### Immunohistochemistry

The best markers are β-catenin, FOXL2, and WT1, although they stain no more than 80 % of SCTs. The reactivity of all other markers ranges between 28 and 75 % [90]. In many cases, immunohistochemistry is not very helpful for reaching a correct diagnosis.

### DNA Ploidy and Cytogenetic Analysis

The genetic features of these uncommon tumors are largely unknown. In a small series, five of 11 patients showed gain of chromosome X, and two patients showed complete loss of chromosome 2 [99]. The importance of these findings for tumor pathohistogenesis is unclear. Mutations of the *CTNNB1* (cadherin-associated protein β1) gene were reported in a recent study, and the authors argued that this mutation was likely to be involved in the pathogenesis of SCT, causing nuclear accumulation of β-catenin and affecting the expression of cyclin D1 (Fig. 6.62) [100].

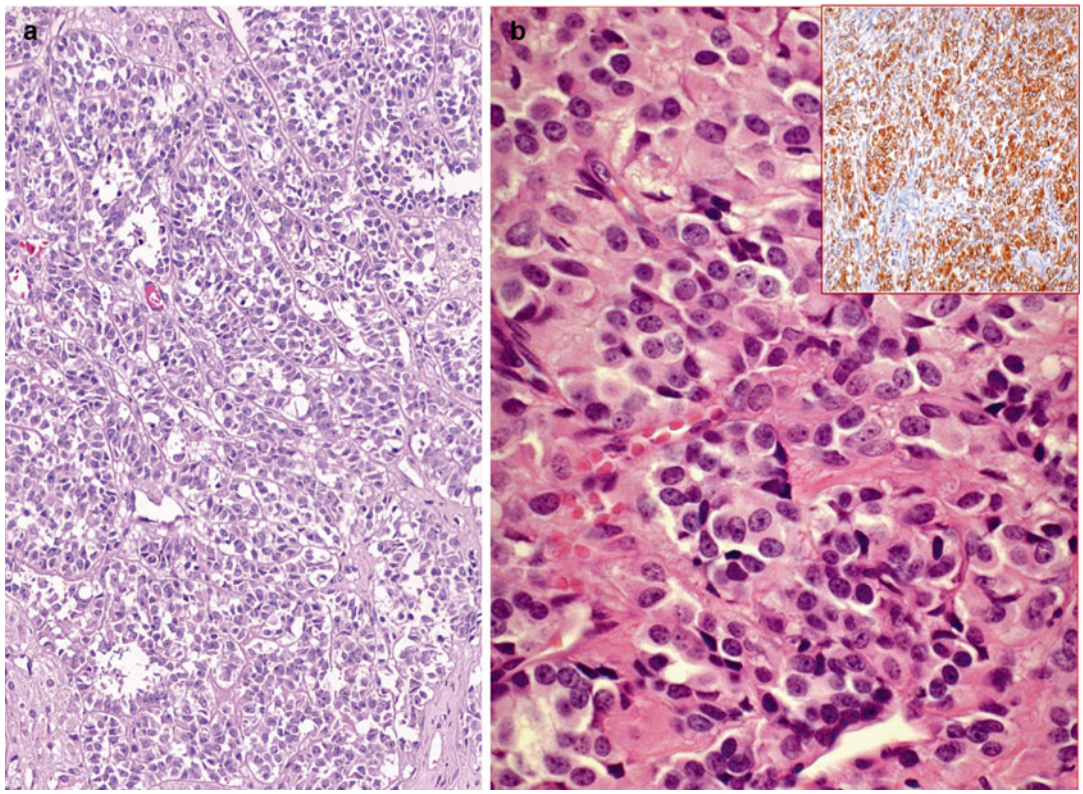


**Fig. 6.60** Sertoli cell tumor. (**a**) Sertoli cell tumor with tubular structures lined with well-differentiated Sertoli cells; (**b**) Solid-growing less differentiated Sertoli cell tumor. Insert: $\alpha$-inhibin positive tumor cells

### Differential Diagnosis

Hypoplastic zones (Sertoli cell nodules), a very common feature of cryptorchid testes, should not be mistaken for SCT. Such nodules are well circumscribed and are composed of prepubertal seminiferous tubules with a prominent basement membrane and lined with immature Sertoli cells. In testicular feminization, Sertoli "microadenomas" are a characteristic feature; it is, however, not clear whether these are true neoplasms or reactive hyperplastic nodules.

The tubular variant of seminoma can easily be mistaken for SCT, but in the surrounding tubules, CIS is present. If necessary, PLAP immunohistochemistry will bring clarity.

Adenomatoid tumors (which are positive for calretinin, CK, and vimentin and negative for α-inhibin) are rarely located in the testis. Intracytoplasmic vacuoles and the spindle shape of the tumor cells distinguish adenomatoid tumor from SCT.

### Clinical Features

The main symptom is testicular swelling. If the tumor produces estrogen, gynecomastia, loss of libido, and impotence are likely to occur. Gynecomastia seems to be more frequent in malignant cases.

About 12 % of SCTs are malignant; malignant cases have also been reported in children [101, 102]. The distribution of organ metastases is very similar to that of LCT. Orchiectomy is the only therapeutic option, because radiotherapy and chemotherapy have been unsuccessful to date.

## Large-Cell Calcifying Sertoli Cell Tumor (LCCSCT)

LCCSCT is a morphologic but also nosologic variant of SCT, morphologically characterized by coarse calcifications and clinically by its possible

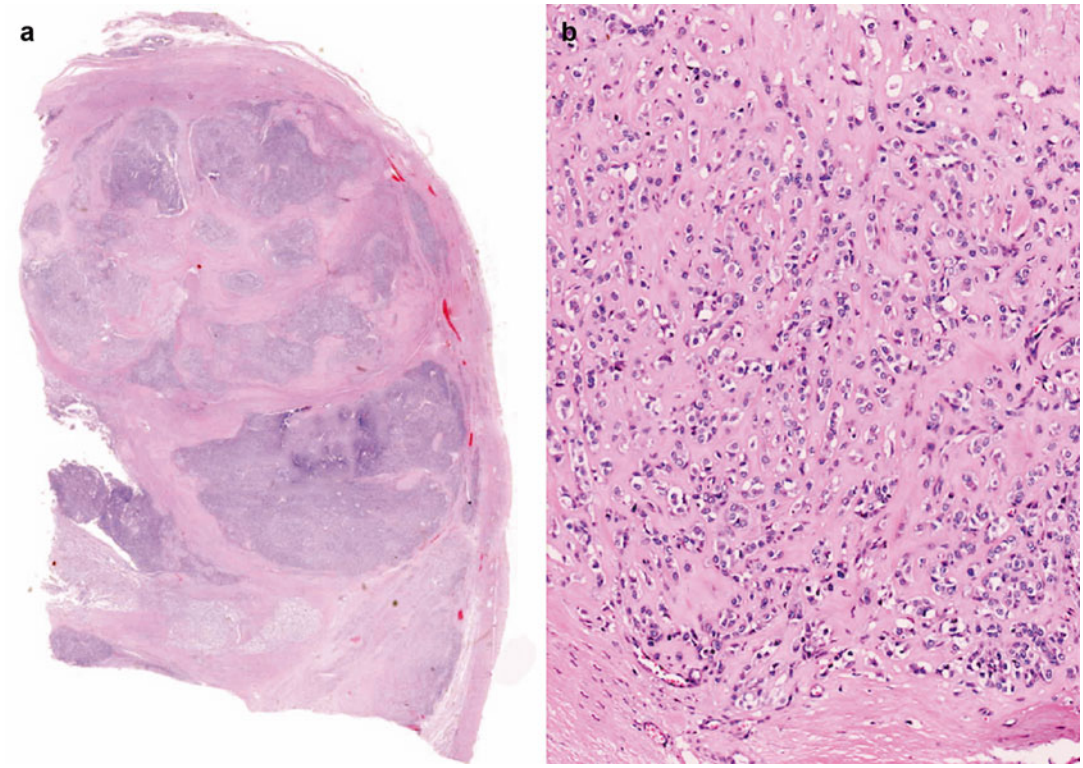


**Fig. 6.61** Sclerosing Sertoli cell tumor. (**a**) Overview shows broad hyaline bands dissecting the tumor. (**b**) Tumor cells entrapped in an abundant hyaline stroma

association with Peutz-Jeghers syndrome and Carney's complex (syndromic LCCSCT).

## Epidemiology

LCCSCT was first described in adolescents and later also in adult and aged men. In young men (mean age, 17 years; range, 2–38 years), the tumor is mostly benign, bilateral, and multifocal. Thirty-six of benign tumors in adolescents are associated with other endocrine disorders (mostly Carney's complex) [103]. Malignant LCCSCT occurs in adults (mean age, 39 years; range, 28–73 years), is unilateral and solitary, and is usually not associated with endocrine syndromes, although an exception has been described in the literature [104, 105] (Table 6.15).

## Morphology

LCCSCT is typically yellow or tan white on section (Fig. 6.63). Due to calcifications, the surface is gritty. Benign tumors are confined to the testis, while malignant tumors can extend to the neighboring organs. Benign LCCSCTs are smaller (range, 0.8–2.3 cm) than malignant ones (range, 2–15 cm), which can replace the entire testicular parenchyma. Foci of necrosis and hemorrhage are typical for malignant LCCSCTs [104, 105].

Large, irregular, and confluent calcifications are the microscopic hallmark and the namegiver of these tumors, regardless of the tumor's biologic behavior. The tumor cells are large with eosinophilic, finely granular cytoplasm and oval nuclei with one or two small to occasionally prominent nucleoli (Fig. 6.64). The tumor cells resemble Leydig cells more than Sertoli cells; in fact, their true origin was revealed by electron microscopy [106]. They are growing in tubules, cords, or trabeculae embedded in a myxoid (Fig. 6.65) or fibrous stroma with lymphocytic infiltrates. Intratubular growth is not rare.

Except for the cellular polymorphism, the cytomorphology of malignant LCCSCT is not

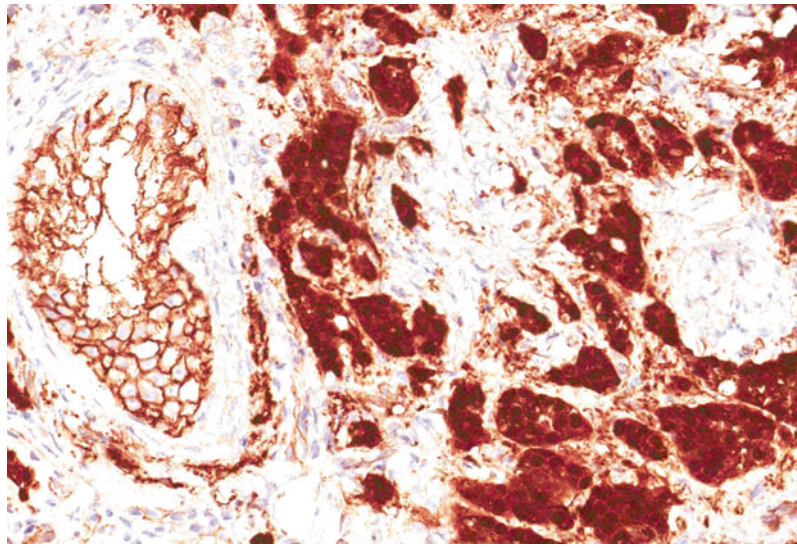

**Fig. 6.62** Sertoli cell tumor. Immunoreactivity with β-catenin antibody. The nuclear and cytoplasmic reaction is diffuse in the tumor cells

different from that of the benign variant, but the mitotic activity is brisk (4–14/HPF) compared with the benign counterpart in which mitoses are lacking . Thus, metastases are the only true evidence of malignancy.

Immunohistochemically these tumors behave like the other SCTs. Cytogenetic investigations do not exist.

## Differential Diagnosis

Even though the tumor cells microscopically resemble Leydig cells, the lack of a capsule, calcifications, and intratubular growth are features not found in LCT. Moreover, the gross morphology is completely different.

## Clinical Features

Painless testicular swelling is the only symptom in sporadic, nonsyndromic cases. Forty percent of cases in adolescent or young men are, however, associated with Carney's complex, which is an autosomal dominant condition. The main symptoms are spotty skin pigmentation, lentigines, and cardiac myxomas, which may lead to embolic stroke and heart failure and even to sudden death [107]. Myxomas may also occur outside the heart, usually in the skin and breast. Endocrine tumors may manifest as disorders such as Cushing's syndrome. The most common endocrine gland manifestation is an ACTH-independent Cushing's syndrome due to primary pigmented adrenocortical microadenomas. STH-producing pituitary microadenoma with acromegaly has also been reported [108].

**Table 6.15** Main clinical differences between benign and malignant large-cell calcifying Sertoli cell tumor

| Features | Benign LCCSCT | Malignant LCCSCT |
|---|---|---|
| Age | Average 17 (range 2–38) | Average 39 (range 28–73) |
| Location | 28 % bilateral and multifocal | Unilateral and unifocal |
| Association with Carney complex or other endocrine disease | 36 % | Almost never |

## Granulosa Cell Tumor

Granulosa cell tumors of the testis are macro- and microscopically equal to those arising in the ovaries. Because of the different morphology and clinical behavior, two types are distinguished: an adult and a juvenile type.

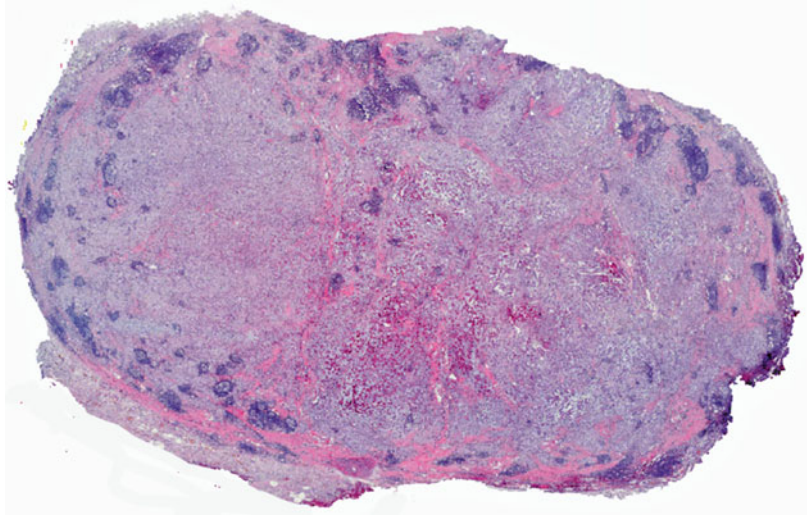

**Fig. 6.63** Overview of a large-cell calcifying Sertoli cell tumor which replaces the entire testicular parenchyma. Irregular calcifications are easily visible in the center. The blue areas randomly dispersed in the tumor are lymphocytic infiltrations

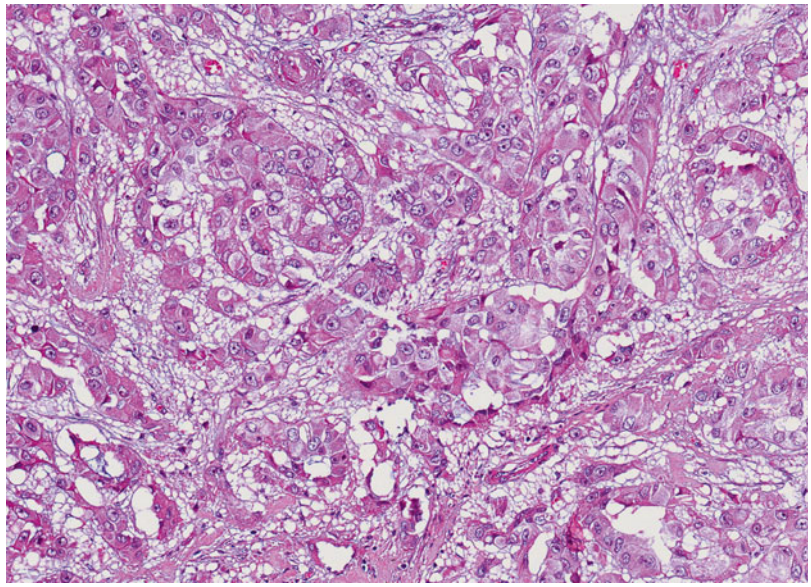

**Fig. 6.64** Large-cell calcifying Sertoli cell tumor. The tumor cells have abundant eosinophilic cytoplasm (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

## Adult Type Granulosa Cell Tumor

### Epidemiology

Adult type granulosa cell tumor is believed to be one of the most infrequent testicular tumors. In a recent publication [109], 43 cases were reviewed, but two additional cases were reported shortly after [110, 111]. The tumor arises predominantly between the ages of 40 and 60 (median, 45 years; range, 12–83 years), and only one case has occurred in an adolescent. About 10 % of the reported cases had a malignant course [109].

### Morphology

The cut surface has a lobulated appearance; its color is yellow and small cysts can be present.

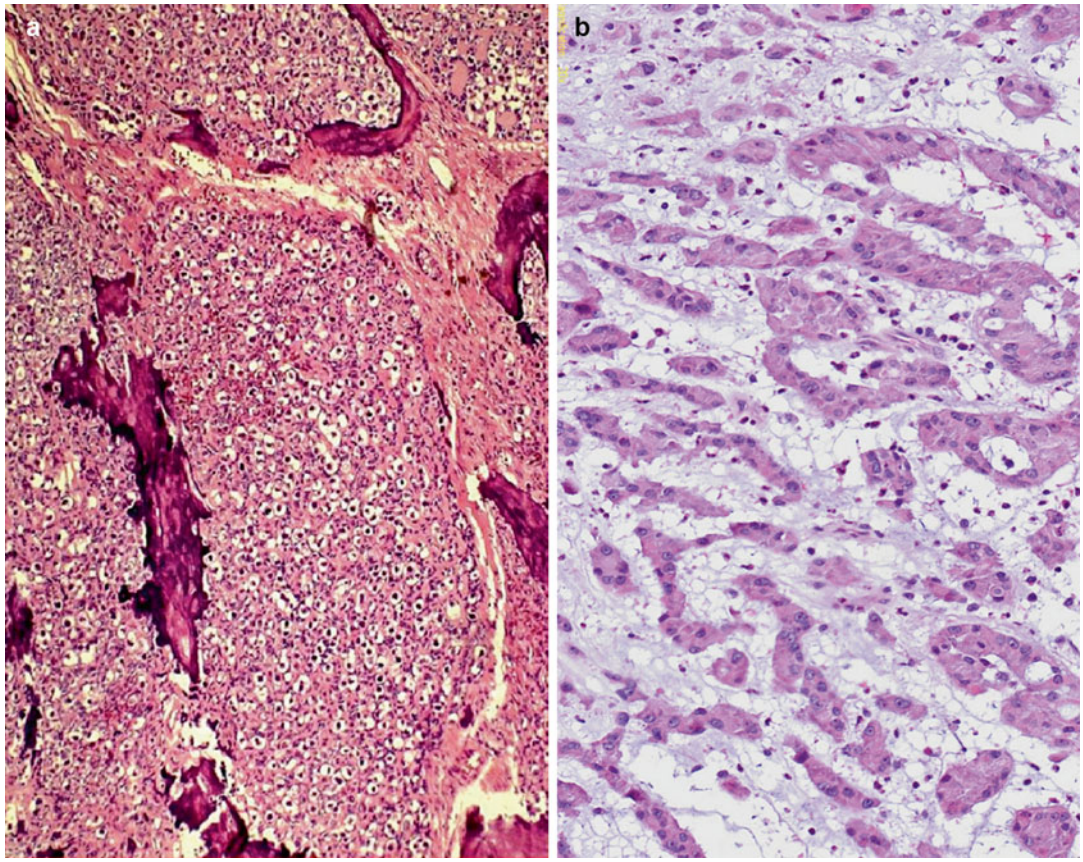


**Fig. 6.65** Large-cell calcifying Sertoli cell tumor with irregularly shaped calcifications (**a**) and tumor cells resembling Leydig cells more than Sertoli cells (**b**) embedded in a mucoid stroma

The tumor diameter ranges from 0.7 to 13 cm. Microscopically, the cells have scant cytoplasm, and the nuclei are typically grooved like coffee beans (Fig. 6.66). Many microscopic patterns have been recognized including trabecular, insular, gyriform, macrofollicular, and microfollicular patterns. Call-Exner bodies are usually present though not always. A sarcomatous "heterologous" pattern was observed in one case [109]. Mitoses are rare and there are no microscopically identifiable indicators of malignancy.

### Immunohistochemistry

The best immunohistochemical markers of granulosa cell tumor are $\beta$-catenin and FOXL2, which are reactive in 100 % of cases (Table 6.14). Other antibodies used in stromal tumors are positive in 50 % of cases at the most [90].

### DNA Ploidy and Cytogenetic Analysis

Cytogenetic studies have been performed only in ovarian granulosa cell tumor. The few pertinent studies do not show uniform results. Eighty percent of these tumors are diploid [112]. The main chromosomal aberrations are trisomy 12, monosomy 22 and X, and loss of chromosome 22 [112]. A somatic mutation of the *FOXL2* gene has been reported in virtually all adult type granulosa cell tumors in women. In men the mutation has been found in a smaller proportion than in women [109, 113].

### Clinical Features

Apart from testicular swelling, 25 % of men with adult type granulosa cell tumors suffer from gynecomastia. Serum inhibin and antimüllerian hormone (AMH) are elevated. About 10 % of reported cases were malignant. Reliable

morphologic features predictive of malignancy do not exist; hence, the histopathology report should be signed off with the comment that malignancy cannot be excluded. Many of these tumors have been observed to metastasize after years.

## Juvenile Type Granulosa Cell Tumor

### Epidemiology

Juvenile type granulosa cell tumor is the most common testicular tumor in the perinatal period; it is typically detected before the sixth month of life [114]. It may develop in the gonad of a patient with an abnormal karyotype and ambiguous genitalia and also in infants with true hermaphroditism [115, 116].

### Morphology

Given the age of the patients, juvenile type granulosa cell tumors are mostly small and do not exceed a diameter of 2 cm. The cut surface is yellow and shows small cysts. Microscopically, the cysts are lined with cells resembling granulosa cells (Figs. 6.67 and 6.68). Among the cysts, tubules with proliferated Sertoli cells form bizarre structures. The high mitotic count can erroneously suggest malignancy.

### Immunohistochemistry

The epithelium lining the cysts stains with different CK antibodies (CK8, CK18, CK19, CAM5.2), α-inhibin, vimentin, and very strongly with AMH [114, 117]. A positive reaction with S100 protein, smooth muscle actin (SMA), and desmin has been observed occasionally.

### DNA Ploidy and Cytogenetic Analysis

The number of cytogenetic studies is very limited. In one report, the tumor cells had an aneuploid DNA stem line in the majority of cases. Aneuploid tumors manifested polysomy 12 and monosomy X [118].

### Differential Diagnosis

Because of the age of the patients and to a lesser degree the presence of certain similarities, this tumor may be confused with YST, which can be a tragic mistake inasmuch as juvenile type granulosa cell tumor is totally benign and does not require any treatment other than simple surgical enucleation. Compared to YST, the morphology of juvenile granulosa cell tumor is very monotonous. Furthermore, YSTs do not have follicular structures and are positive for AFP. Mistaking a juvenile granulosa cell tumor for a teratoma is less harmful because the therapeutic approach is the same for both tumors.

### Clinical Features

Unilateral swelling, predominantly of the left testis, is the only symptom. As already mentioned, these tumors tend to arise in cryptorchid testes (30 %) and in children with dysgenetic gonads and ambiguous genital organs. If possible, simple enucleation of the tumor is the preferred treatment [119].

## Thecoma-Fibroma-Type Tumors

The 25 cases known so far [4, 120] were observed in men in their fourth to fifth decade. These tumors are firm, white, and well circumscribed.

### Morphology and Immunohistochemistry

The solid, encapsulated, grayish-white testicular mass displays the characteristics of testicular fibroma. The tumor is composed of cellular collagenized plaques and hypercellular areas of fibroblastic spindle cells (Fig. 6.69). Immunohistochemically, the neoplastic cells are reactive to vimentin and SMA.

### Differential Diagnosis

Similar tumors arising in the testicular tunics or spermatic cord can invade the testis. Macroscopic inspection will reveal the true location.

### Clinical Features

A painful palpable lump is the main symptom of these innocuous tumors.

## Mixed Forms and Incompletely Differentiated Gonadal Stromal Tumors

These tumors are composed of randomly mixed Leydig, Sertoli, and granulosa cells as well as

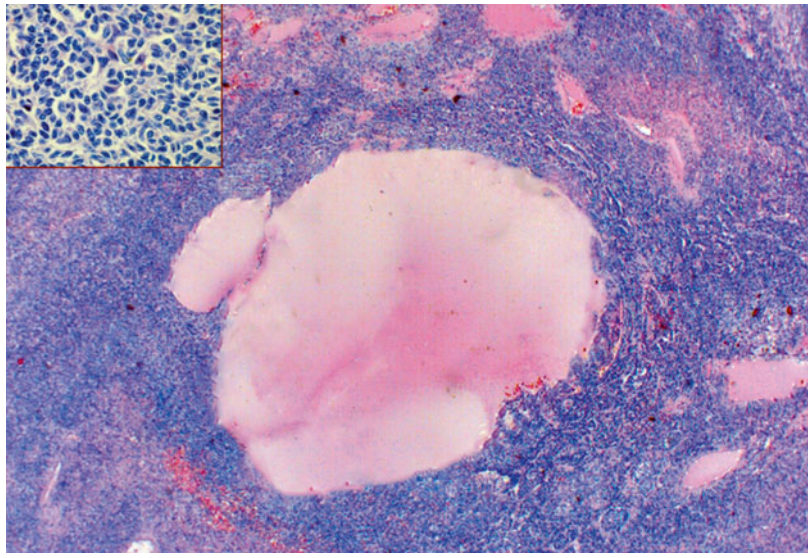

**Fig. 6.66** Adult type granulosa cell tumor, with colloid-filled cyst simulating ovarian follicles. Insert: Tumor cells with typical grooved, coffee-bean-like nuclei

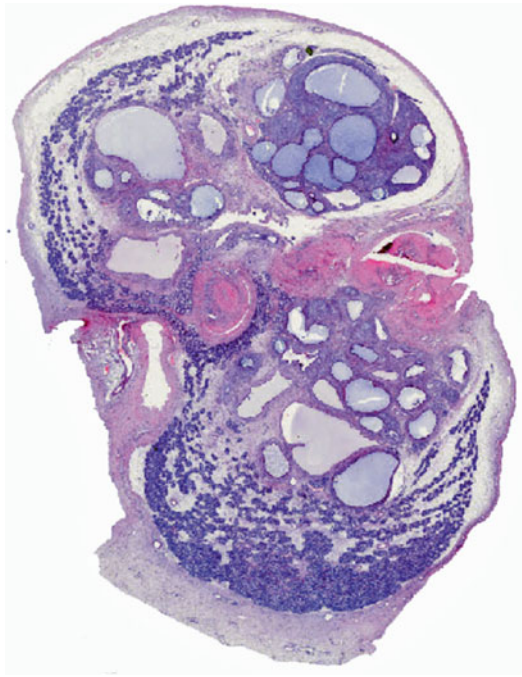

**Fig. 6.67** Overview of a juvenile type granulosa cell tumor. Multiple cyst resembling ovarian follicles are the morphological hallmark of the tumor (Copyright Springer Damjanov and Mikuz [149])

less differentiated or undifferentiated cells in which, however, some recognizable cells of specialized gonadal stroma can be detected (Fig. 6.70). Although these tumors are listed separately in the WHO 2004 classification [4], many experts argue that they can hardly be distinguished from each other.

## Morphology

Macroscopically, the tumors are nodular and yellow. Microscopically, they usually contain well-differentiated Leydig cells and less differentiated Sertoli cells, but combinations with granulosa cells also occur. The incompletely differentiated cells consist of spindled or more epithelioid cells and may contain differentiated elements. The sarcomatous tumors show brisk mitotic activity, necrotic areas, vascular invasion, and spread to the surrounding structures. Although no cytopathologic hallmarks of malignancy have been identified even in metastasizing cases, large tumor size seems to be an important indicator of malignancy.

## Immunohistochemistry and Cytogenetic Analysis

The differentiated cells react with the known antibodies (Table 6.14), while the undifferentiated cells are reactive for S100 protein, SMA, and rarely desmin [121]. In the only cytogenetically analyzed case, gain of many chromosomes was observed (+3, +7, +9, +12, +13, +18, +19, +20) [122].

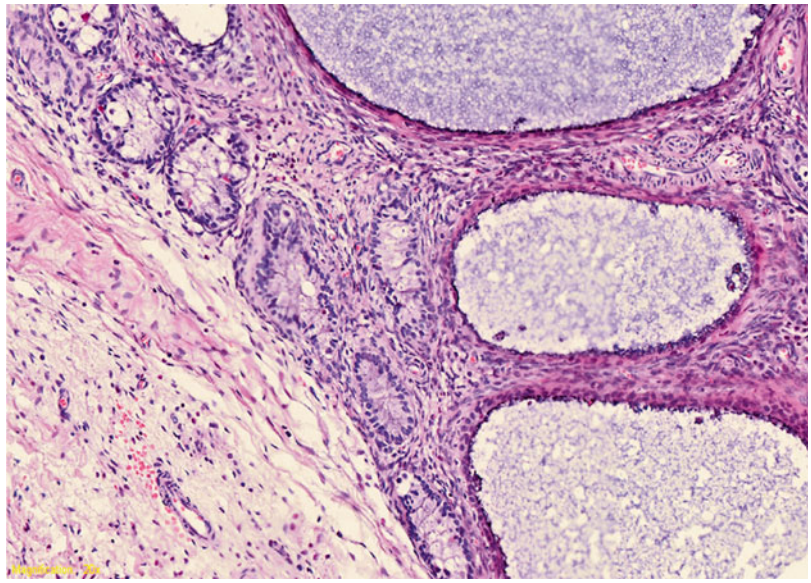

**Fig. 6.68** Juvenile type granulosa cell tumor, with follicle-like cysts lined with cuboidal or flattened cylindrical epithelium

### Differential Diagnosis

It is very difficult to distinguish between poorly differentiated and undifferentiated tumors. Some authors take the view that when tubular structures can be detected, the tumor should be classified as SCT [123].

### Clinical Features

Patient age ranges from 6 months to 60 years. A few cases have presented with gynecomastia. In childhood the tumors are perfectly benign, whereas one-quarter of tumors in adults metastasize to the retroperitoneal lymph nodes and/or abdominal organs. In adults the histopathology report should be signed off with the comment that, although malignancy is unlikely, it cannot be ruled out.

## Myoid Gonadal Stromal Tumor

The recently described myoid gonadal stromal tumor is a small (<4 cm) firm nodule composed of spindle cells arranged in fascicles. The nuclei are elongated and the nucleoli scanty. The tumor is strongly positive for SMA, S100 protein, SF1, and FOXL2, focally positive for $\alpha$-inhibin and calponin, and negative for h-caldesmon, calretinin, and SOX9 [124].

## Mixed Germ Cell/Sex Cord/Stromal Tumors

## Gonadoblastoma

Gonadoblastoma was first described by Scully [125, 126] and affects only dysgenetic gonads.

### Epidemiology

Gonadoblastoma arises more commonly in individuals who are phenotypically female (80 %) than in those who are phenotypically male [127]. The tumor is rare before the age of 12. More than 90 % of these tumors are diagnosed in the first 3 decades of life. Involvement of both gonads is common (30–40 %) [4].

### Morphology

Macroscopically, the gonadal surface is lobulated and yellow brown, but in a fair number of cases (25 %), the tumors are only microscopically visible (Fig. 6.71). Prominent calcifications may be present focally. Microscopically, the tumor shows a nesting pattern. Small nests of seminoma cells (and rarely EC cells) are surrounded by Sertoli or granulosa cells in a wreath-like manner (Fig. 6.72), whereas Leydig cells are rather

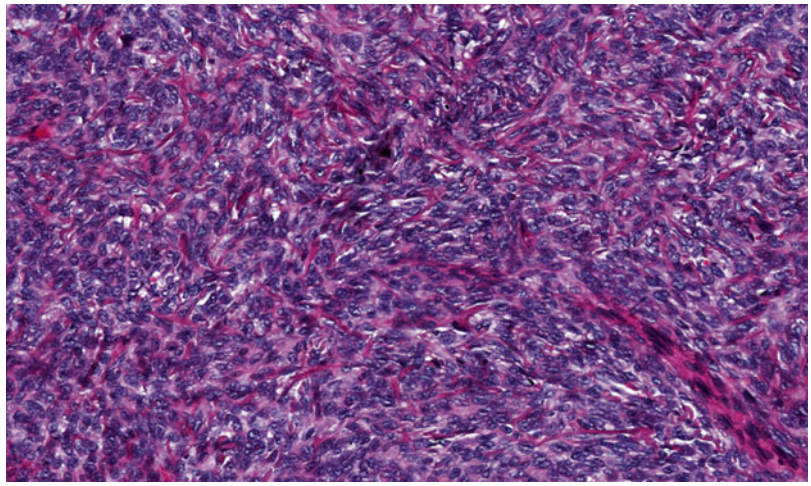

**Fig. 6.69** Fibroma-thecoma type of sex cord/stromal tumor composed of fibroblasts-like tumor cells (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

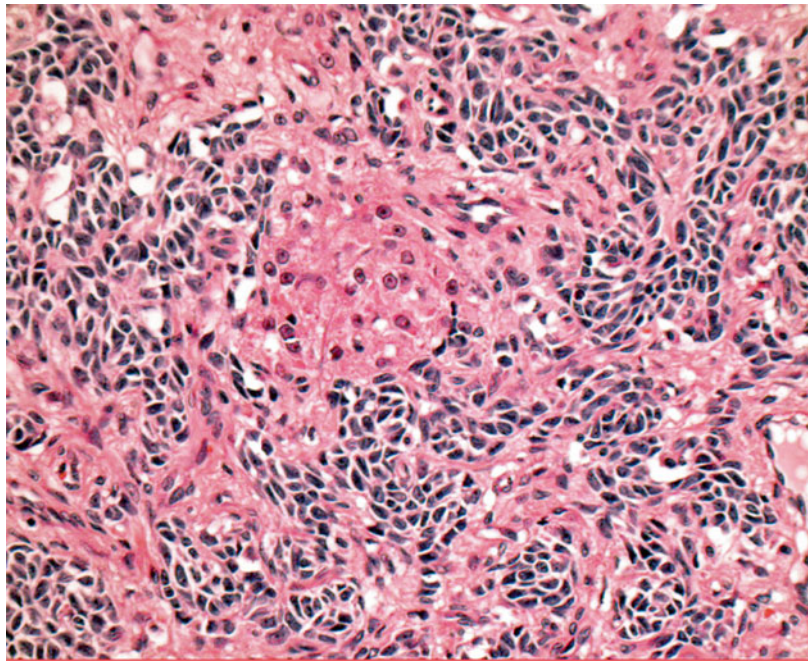

**Fig. 6.70** Mixed sex cord/stromal tumor with well-differentiated large Leydig cells with eosinophilic cytoplasm and less differentiated, spindle-shaped Sertoli cells

uncommon. In the center of the nests, the basement membranes are condensed to hyaline nodules, which can calcify to psammoma bodies. If the tumor is not removed early, the germ cells overgrow the stromal cells and in most cases a pure seminoma develops. The development of NSGCT is rather rare (8 %) [4].

### Immunohistochemistry

The germ cell component is reactive for PLAP and CD117 (c-kit) as well as for a protein encoded by the Y chromosome (TSPY) [128]. Sertoli or granulosa cells stain clearly with the specific antibodies including AMH. The hyaline nodules react positively with laminin.

### DNA Ploidy and Cytogenetic Analysis

Using the FISH technique, a Y chromosome or part of it can be detected in all gonadoblastomas. On the Y chromosome, the candidate gene *TSPY* is responsible for the origin of gonadoblastoma [127, 128]. The germ cell component is aneuploid.

### Differential Diagnosis

Sertoli cell nodules show some similarities to gonadoblastoma, but patients with Sertoli cell nodules do not have dysgenetic gonads.

### Clinical Features

Patients with dysgenetic gonads often show a chromosomal 45,X/46,XY mosaicism. Patients affected by partial androgen insensitivity syndrome with nonscrotal testes and those with Fraiser and Denys-Drash syndrome also belong to the high-risk group for developing malignancy. These syndromes are characterized by gonadal dysgenesis and glomerular diseases of the kidney because of mutations of the WT1 (Wilms'tumor) suppressor gene. Due to the lack of AMH, the internal genital organs are feminine. In case the neoplastic germ cells have already overgrown the gonadal stroma components, therapy follows the standard protocols for GCTs.

## Germ Cell Sex Cord/Gonadal Stromal Tumor, Unclassified

This is the name in the 2004 WHO classification [4] for mixed germ cell and gonadal stromal tumors arising in genotypically and phenotypically normal adult men. Since only a few cases in the testis and in the ovary have been reported to date [129], our knowledge is limited. The tumors consist of germ cells with clear cytoplasm, which are dissimilar from those of seminomas or ECs. The cells are arranged in small clusters surrounded by the predominant stromal component with inhibin-positive, small, often spindled cells (Fig. 6.73). The germ cells do not react with the classical markers PLAP and c-kit and also do not contain i(12p). For this reason, this tumor has been questioned by some authors, who considered the germ cells to be entrapped in a stromal tumor and not be a genuine part of it [130].

## Miscellaneous Tumors

Tumors having neither a germ cell nor sex cord/stromal origin are listed in the 2004 WHO classification [4] under this heading.

## Malignant Lymphoma and Plasmocytoma

Primary malignant non-Hodgkin lymphomas (NHL) of the testis are defined as isolated manifestations of lymphatic malignancies in the testis without generalized nodal manifestation.

### Epidemiology

In different series, 1–7 % of testicular tumors are NHL; nevertheless, they are the most frequent tumors after the age of 50 and also the most frequent bilateral tumors (20–30 %). Testicular NHL accounts for 1–2 % of all lymphomas and has an incidence of 0.26/100,000 [131]. Patients are mostly older than 60 years; in children NHL is less frequent [131].

Solitary extramedullary plasmocytoma of the testis is, with some 60 reported cases, much less frequent than other testicular NHL. The age at diagnosis ranges from 26 to 83 years, although the mean age at diagnosis is 60 years (Fig. 6.74) [132, 133].

In several large case series (Armed Forces Institute of Pathology, British Testicular Tumor Registry, Extranodal Lymphoma Study Group), not a single case of Hodgkin's lymphoma was observed [1, 4, 74, 131].

### Morphology

Macroscopically the entire organ is mostly involved. The parenchyma is replaced by a sometimes nodular, cream-pink, or yellowish-brown fish-flesh tumor. Necrosis and hemorrhagic areas are occasionally present. Plasmocytomas are softer, reddish in color, and hemorrhagic.

Microscopically, lymphoma cells diffusely infiltrate the interstitium, narrowing and rarely

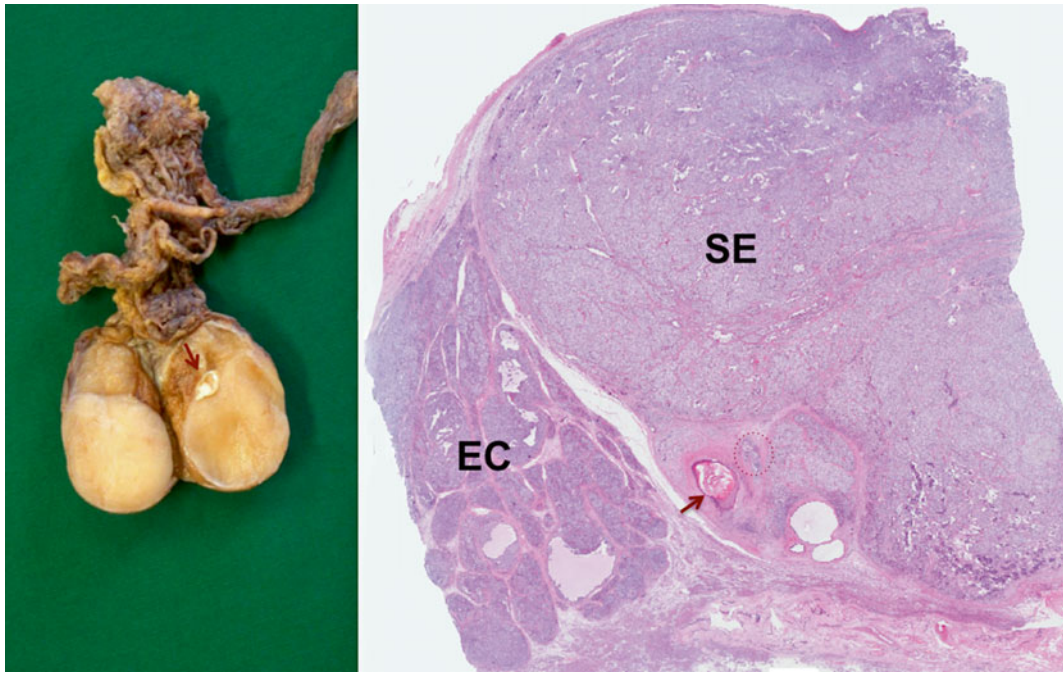


**Fig. 6.71** Gonadoblastoma overgrown by a mixed germ cell tumor. Gross morphology (*left*) shows a seminoma-like cut surface with a small teratoma cyst (*arrow*). In the microscopic overview (*right*), only the small encircled area corresponds to the gonadoblastoma. *SE* seminoma, *EC* embryonal carcinoma, *arrow* teratoma cyst lined with squamous epithelium

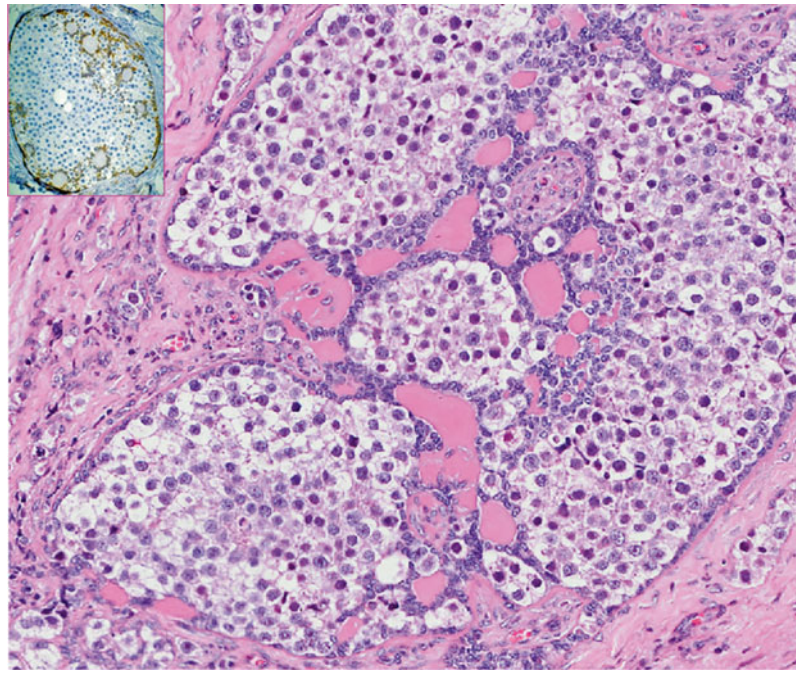

**Fig. 6.72** The unique morphology of gonadoblastoma composed of seminoma cells that are surrounded by Sertoli cells in a wreath-like manner. Insert: $\alpha$-inhibin positive Sertoli cells (With permission of the editor from Gregor Mikuz, Peter Mazal "Hoden und Infertilität beim Mann" Springer-Verlag Berlin Heidelberg, 2016)

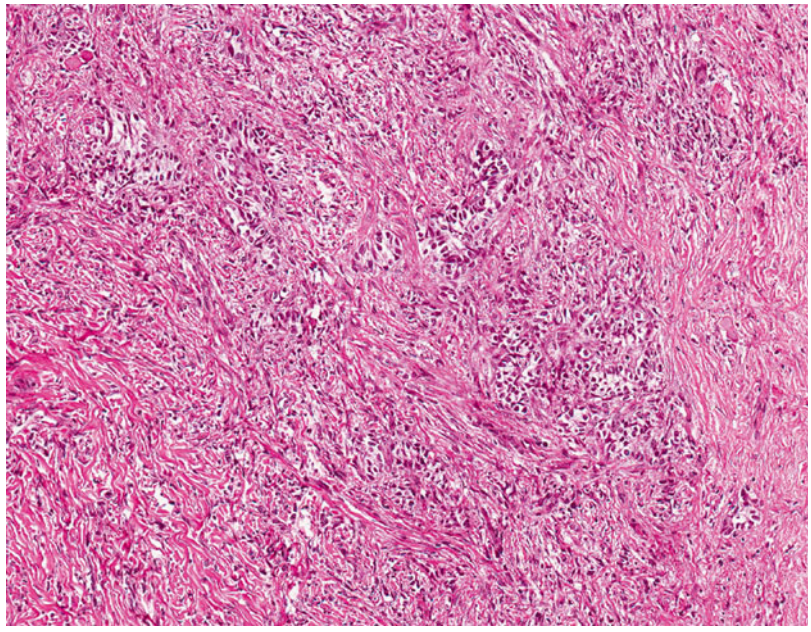

**Fig. 6.73** Sex cord/stromal tumor, unclassified. Small foci of sex cord cells are admixed with a more prominent stromal proliferation (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

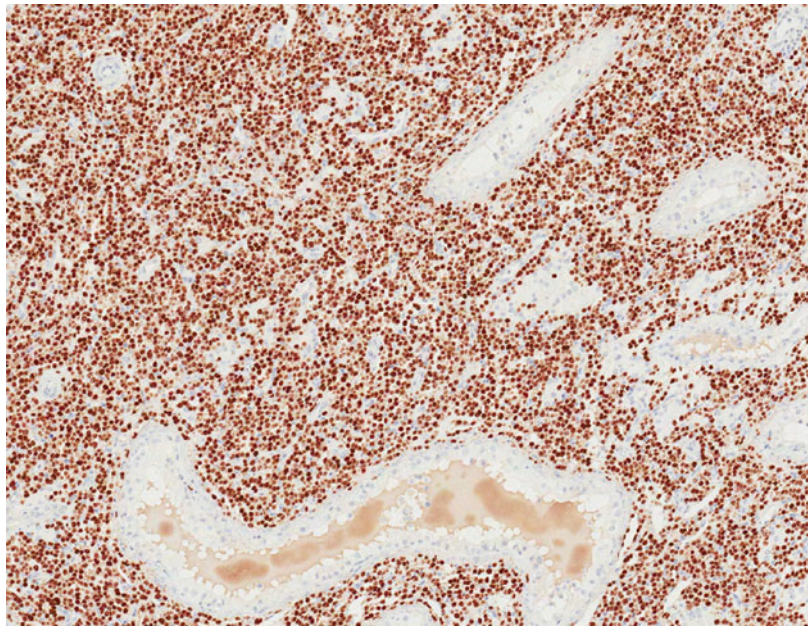

**Fig. 6.74** Plasmacytoma of testis. The plasmacytoid nature of the tumor cells is highlighted by the MUM-1 positive reaction (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

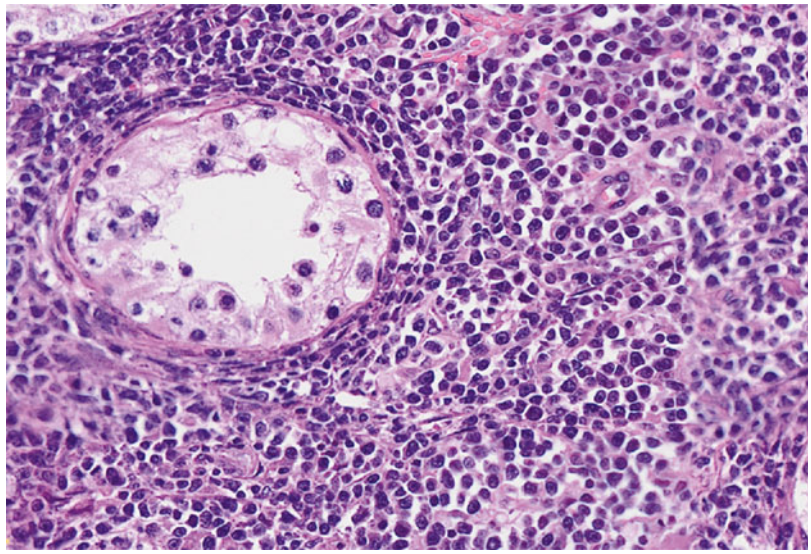

**Fig. 6.75** Intratubular infiltration by diffuse large B-cell lymphoma

involving the seminiferous tubules (Fig. 6.75), but intratubular spread may be observed. Interstitial sclerosis, vascular invasion, and spread to the epididymis are frequent.

Plasmocytomas show a similar histologic pattern, but intratubular growth is more frequent than in other NHLs.

Eighty to ninety percent of primary testicular NHLs are large-cell diffuse B-cell lymphomas with or without sclerosis. Other observed lymphomas are mantle cell lymphoma, Burkitt lymphoma, and single cases of T-cell lymphomas [131].

### Differential Diagnosis

Seminomas and even more often STs are mistaken for NHL or vice versa. Lymphoma patients are significantly older than GCT patients. Testicular GCTs only rarely invade the epididymis or other paratesticular structures. The use of lymphoma immunohistochemistry (CD45) is helpful, because PLAP is negative not only in lymphomas but also in ST.

Anaplastic large-cell lymphoma can also mimic an EC, but the epithelial nature of the EC cells is unmistakable. Immunohistochemistry (CD45, CAM5.2) can solve the diagnostic dilemma.

### Clinical Features

Unilateral or bilateral testicular swelling without B symptoms is the main feature of testicular NHL. In accordance with the definition of testicular NHL, patients are initially at Ann Arbor stage I. Later on the disease generalizes and has a predilection for the CNS: even after therapy, 15 % of recurrences affect the brain. The standard therapy is orchiectomy followed by chemotherapy and/or radiotherapy. In spite of this aggressive regime, the prognosis is poor: the median relapse-free time is 4 years and the survival time 5 years [131]. The prognosis of testicular plasmocytoma is even worse [131].

## Leukemia

In postmortem studies, 64 % of patients with acute leukemia and 22 % of those with chronic leukemia showed involvement of the testes [134]. Clinically this was mostly symptomless, because only 5 % of patients had swollen testicles. Best known is testicular involvement in children with acute myelocytic or lymphatic leukemia. Since recurrences were found to develop in the testis in 36 % of cases, it was common practice in the past

to carry out testicular biopsies for diagnosis of relapse [135, 136]. However, given that an early diagnosis does not improve the prognosis, testicular biopsy is no longer recommended [137]. All these diseases tend to rapidly generalize and recur and therefore have a poor prognosis.

Recently also extramedullary testicular involvement in myelodysplastic and myeloproliferative diseases has been described [138, 139]. Among these diseases, myelosarcomas (granulocytic sarcoma, chloroma) seem to be the most frequent.

Macroscopically and microscopically, it is difficult to distinguish leukemia from lymphomas. The presence of eosinophilic granulocytes is highly suggestive of a myeloid tumor. A diagnosis can only be reached with the naphthol AS-D chloroacetate esterase reaction or with immunohistochemical proof of lysozymes or myeloperoxidases.

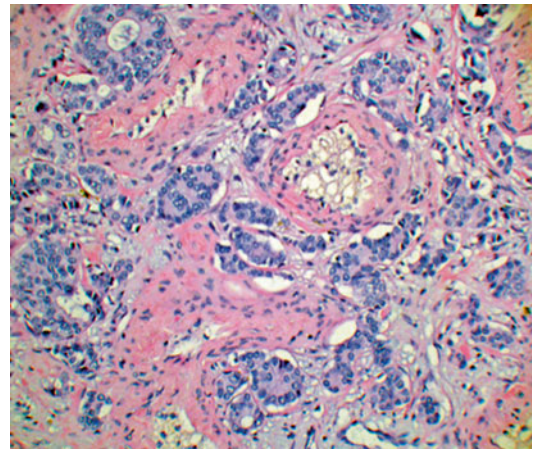

**Fig. 6.76** Testicular metastasis. Intratubular spread of prostate cancer glands

## Primary Testicular Carcinoid and Nephroblastoma (Wilms' Tumor)

Usually these tumors arise in teratomas as a somatic-type malignancy. However, some of the reported cases did not originate in such a tumor. The histogenesis of primary carcinoids is mysterious, because the normal testicular parenchyma does not harbor neuroendocrine cells, which in contrast are abundant in teratomas [71]. One may argue that so-called primary testicular carcinoids also arise from neuroendocrine cells in teratoma, which slowly overgrow the other tissue components.

Carcinoids account for 0.2–1 % of all tumors of the testis in various statistics. Patients' age ranged from 19 to 83 years. Sixty-one of the 80 (76 %) well-documented cases of testicular carcinoids were not associated with teratoma [140]. Obviously, for a correct diagnosis, a metastasis of a carcinoid located in the gut or elsewhere must be clinically ruled out. After surgery the prognosis is excellent. The few patients with metastatic disease died of their tumors.

Primary nephroblastomas (Wilms'tumor) can arise in heterotopic renal anlage. Clinically they behave like kidney tumors and require the same treatment.

## Metastases

Metastases of solid neoplasia are surprisingly very rare in the testis. In postmortem studies, their incidence oscillates between 0 and 3.6 % [141–143]. Patients with secondary testicular neoplasms are generally older than those with GCTs. The tumors most commonly reported to metastasize to the testis are in decreasing order of frequency: prostate (Fig. 6.76), lung, melanoma, colon, kidney, stomach, and pancreas carcinoma. Neuroblastoma, retinoblastoma, carcinoid tumor (Fig. 6.77), Merkel carcinoma (Fig. 6.78), and cancers of the bile duct, ureter, bladder, salivary gland, and thyroid have also involved the testis secondarily (Table 6.16).

Macroscopically, metastases are recognizable as small, single, or multiple nodules. Histologically, the presence of extensive lymphatic and vascular invasion and an interstitial pattern in which the seminiferous tubules are spared is typical. Although metastases can easily be distinguished from testicular GCTs, confusion of melanoma metastases with seminoma has been reported [144].

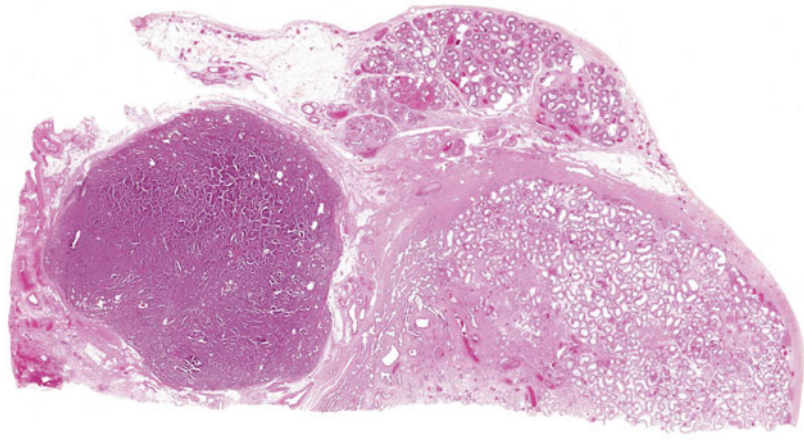

**Fig. 6.77** Neuroendocrine carcinoma metastatic to fat tissue adjacent to the testicular parenchyma

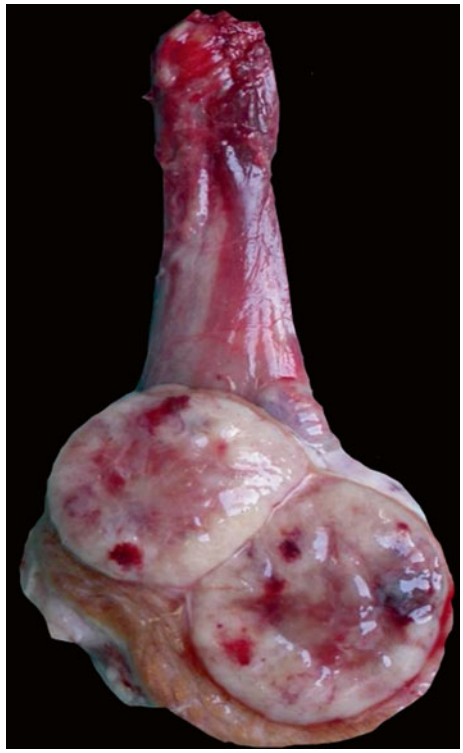

**Fig. 6.78** Unusual presentation of Merkel cell carcinoma metastatic to the testis (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

**Table 6.16** Most frequent sites of primary tumors metastasizing to the testis (range from different studies)

| | |
|---|---|
| Prostate | 35–60 % |
| Lung | 5–15 % |
| Melanoma | 9–15 % |
| Colon | 5–9 % |
| Kidney | 5–9 % |
| Stomach | 4 % |
| Miscellaneous | 1–10 % |

## Tumorlike Lesions

Some nonneoplastic lesions can cause a mass in the scrotum or a testicular swelling and have mainly the gross appearance of tumors. Most of such lesions are located in the testicular appendages or tunics and only few in the testis.

Testotoxicosis is an active Leydig cell differentiation associated with premature onset of spermatogenesis in children in the absence of pituitary gonadotropin stimulation. The testis enlargement is due to diffuse or nodular proliferation of mature Leydig cells [145].

The granulomatous forms of orchitis with slow onset, like syphilis or leprosy, which lead to fibrosis and induration of the gonad, might be mistaken for neoplasia. In particular the so-called idiopathic or pseudogranulomatous orchitis is clinically indistinguishable from a testicular tumor. It affects men in the fifth and sixth decades with a history of urinary tract infection. The testicular parenchyma is replaced by a tan-yellow mass resembling a seminoma (Fig. 6.79). Microscopically, the more or less destroyed tubules are filled with macrophages, which give the lesion the appearance of a granuloma [146].

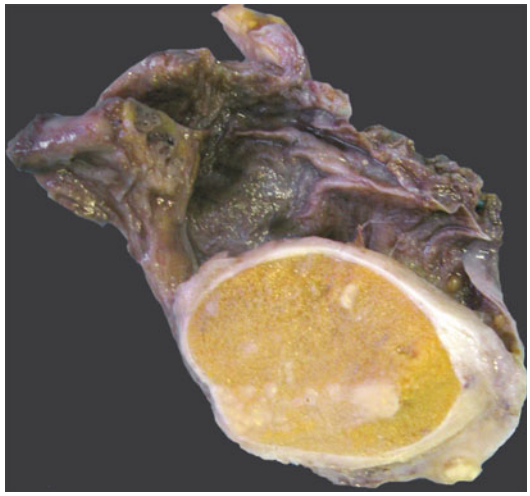

**Fig. 6.79** Multiple white nodules involve the testicular parenchyma resembling a germ cell tumor (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

A special form is malacoplakia, which is grossly not very different from pseudogranulomatous orchitis. Microscopically, the tissue is replaced by large epithelioid cells with eosinophilic cytoplasm sometimes containing targetoid basophilic inclusions called Michaelis-Gutmann bodies.

Infarcts and hemorrhage can lead to sudden testicular swelling. Hemorrhagic infarction in young men is commonly caused by testicular torsion. Hematomas are the result of trauma or vasculitis, which is either localized or a manifestation of generalized disease. The most common type of vasculitis in the testis is due to Henoch-Schönlein purpura [147]. Less frequent are polyarteritis nodosa and Wegener's granulomatosis.

Testicular lipomatosis in Cowden syndrome is histologically characterized by multiple foci of fat tissue in the testicular interstitium. On ultrasound imaging, these areas appear as diffuse bilateral hyperechoic lesions. Cowden syndrome is a rare autosomal dominant disorder characterized by multiple tumorlike growths called hamartomas and an increased risk of certain forms of cancer. The *PTEN/MMAC1/TEP1* tumor suppressor gene on chromosome 10q23.3 has proven to contain a germline mutation predisposing to uncontrolled cell growth [148].

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