Testicular Germ Cell Tumors

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7.1 General Concepts

Aside from benign teratomas of the ovary, germ cell tumors of the testis are the most common germ cell tumors (GCT). They also correspond to the vast majority of testicular tumors, encompassing about 98 % of the neoplasms arising in the male gonad [1–3].

Testicular GCT share the basic characteristics with GCT at other sites, but possess several unique features. Contrary to the ovarian counterpart, most are malignant. This is particularly the case in testicular teratomas, specifically the postpubertal type, which is malignant independently of the degree of maturation of its components. While for the most part, the histologic spectrum is similar to other sites, a specific type, spermatocytic tumor (ST), is unique to the male gonad. Most testicular GCT are characterized by the existence of an in situ lesion, germ cell neoplasia in situ (GCNIS), which is pivotal in their histogenesis. Finally, the phenomenon of regression, in which primary GCT may involute and frequently disappear, is characteristic of the testis.

This chapter deals preferentially with postpubertal testicular GCT; while on occasion pediatric tumors will be mentioned, detailed discussion of these may be found in Chap. 6.

7.2 Epidemiology

Testicular cancers correspond to approximately 1–2 % of tumors in men; however, they are the most common malignancy in men between the ages of 15 and 34 [1–3]. Approximately 95 % of testicular tumors correspond to GCT, with the majority of non-GCT histologies occurring in men over 50 years of age [4]. There is an increasing incidence of testicular GCT, particularly in those countries with an already high incidence [5]. Marked variations among countries and geographical regions have been described, with a higher incidence in Scandinavian and northern European countries and lowest in Middle Eastern and Asian countries [5]. Racial differences have also been widely reported within racially diverse countries. In the USA, the incidence per 100,000 varies from 1.1 in African-Americans to 6.3 cases in whites [3]. A more extensive review of GCT epidemiology can be found in Chap. 2.

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Statistical studies have suggested several risk factors that may increase the risk of developing testicular cancer. These include higher economic status, professional workers, technicians, and other occupational categories [6–9], immunodeficiency [10], history of sexually transmitted disease [11], past mumps orchitis [12], in utero exposure to estrogen [13], cannabis use [14, 15], testicular trauma [11], Down syndrome [16], Marfan syndrome [17], and Klinefelter syndrome [18]. Early male patterned baldness and severe acne have a negative association [19]. Most of these associations are weak, or are not demonstrated consistently in different studies. However, the following risk factors have been repeatedly linked with an increased risk for the development of testicular GCT:

1. *Cryptorchidism*: A maldescended or undescended testis is the most consistently associated risk factor for testicular cancer, conferring 3.7–7.5 times higher risk of developing this malignancy [20]. Conversely, 5–10 % of patients with testicular cancer have a history of cryptorchidism [21]. The mechanism is unclear; their association could be the result of a common cause for both pathologies, but, alternatively, it is more likely that it is related to the adverse environmental conditions to which the undescended testis is subjected. The varying relative risks depending on the location of the testis (abdominal vs. inguinal), and the impact early orchidopexy has in reducing the risk, would favor the latter possibility. Orchidopexy before age 13 is associated with a 2.23-fold relative risk, compared to 5.4 for patients who had orchidopexy after that age [22]. However, not all series have demonstrated a risk reduction dependent on the age at orchidopexy [23]. The GCT most commonly observed in patients with cryptorchidism is seminoma. Cryptorchidic patients have a higher proportion of seminoma vs. non-seminomatous GCT, compared to the general population [24].
2. *Contralateral GCT*: A previous history of testicular GCT in the contralateral testis confers approximately a 24.5–27.5-fold relative risk of developing testicular cancer [25, 26]. The metachronous tumor has a highest risk of developing in the first 5 years after the initial diagnosis [27]. The risk is higher if the testis is or was cryptorchidic or atrophic.
3. *Family history of testicular cancer*: Sons of fathers with testicular cancer have approximately 4 times the risk of the general population of developing a testicular tumor. This risk is almost doubled if the affected first-degree relative is a brother [28–30]. Migration studies have demonstrated that immigrants to a region with lower or higher incidence of testicular cancer carry the risk of the region from where they originate. Familial testicular cancer has been associated with several candidate genes, which include among others *TGCT1* – which may also predispose to cryptorchidism – located in chromosome Xq27 [31], *KITLG* in 12q22 [32, 33], *SPRY4* in 5q31.3 [34], *BAK1* in 6p21.3 [35], *DMRT1* in 9p24.3 [36, 37], *TERT* in 5p15.33, and *ATF7IP* in 2p13.1 [37]. Most of these genes have been associated to the KITLG-KIT pathway, implicated in primordial germ cell development [38].
4. *Disorders of sex development (DSD)*: Abnormally differentiated or maldeveloped gonads, with our without maldeveloped sex organs, are linked to a higher risk of development of testicular cancer [21]. DSD include gonadal dysgenesis with a Y chromosome, true hermaphroditism, and pseudohermaphroditism due to androgen insensitivity syndrome [39]. Approximately 25 to 30 % of patients with gonadal dysgenesis and a Y chromosome develop a GCT [40], usually gonadoblastoma, while those with an abnormal androgen function have a risk of around 5–10% [39]. This association is discussed at length in Chap. 10 and further below in the section on gonadoblastoma.
5. *Male infertility*: An increase in testicular cancer rates has paralleled a decrease in fertility and semen quality [41]. It is unclear if there is a causal relationship between both conditions or the association is a manifestation of a com-

mon cause [42–44]. Given the connection of both infertility and testicular cancer with cryptorchidism, the latter is not an unlikely possibility [38]. Similarly, gonadal dysgenesis, or other DSD, account for a significant portion of cases of infertility [38]. Patients with infertility have a higher incidence of testicular cancer than those that have undergone vasectomy [45].

It has been proposed that patients with an identified risk of developing GCT may benefit from a testicular biopsy. The two best scenarios in which this potential benefit has been studied are in the setting of cryptorchidism, and contralateral GCT. Patients with a history of cryptorchidism have a 2–8 percent risk of having GCNIS, the precursor lesion of GCT [26]. Of 1500 cryptorchidic patients whose biopsies did not reveal GCNIS and were followed for up to 8 years, none developed an invasive GCT [46]. Conversely, 50 % of patients with a positive biopsy for GCNIS will develop an invasive GCT in the same timeframe [47]. Timing, frequency, location, and management of a positive biopsy are still debated in the literature [46, 48–50]. Similarly, testicular biopsy of the contralateral testis on patients with a GCT may identify a second primary in earlier stages. In this setting, approximately 5 % of contralateral testis biopsies will be positive for GCNIS. Of these, approximately 30 % will have an invasive tumor upon orchiectomy, and 50 % more will develop an invasive tumor within 5 years [47]. As in the cryptorchidism scenario, patients with a negative biopsy rarely develop a second GCT [51]. Radiation therapy can then be offered to these patients to reduce the risk of a second neoplasm [52, 53]. Arguments against the widespread use of contralateral biopsy include the need for close follow-up on patients with negative biopsy (given the rate of approximately 1 % false positive), the need of radiation therapy resulting in irreversible infertility and impairment of endocrine Leydig cell function, a questionable outcome advantage over patients handled with only surveillance, and the availability of local resection as therapy for small tumors [54].

7.3 Histogenesis

A detailed explanation of the histogenesis of germ cell tumors has already been presented in Chap. 3. Herein we will summarize those aspects specific to testicular GCT. Testicular tumors fall mainly within three of the types of the Oosterhuis and Looijenga classification [55], described in Chap. 3 . They include prepubertal-type tumors (type I GCT), including teratomas and yolk sac tumors (YST), postpubertal tumors (type II GCT, seminomatous and non-seminomatous GCT), by far the most common ones, and ST (type III GCT) [55, 56]. Each of these categories has a characteristic epidemiological, biological, and clinical profile, as summarized in Table 7.1. While our understanding of the molecular pathology of types I and III is limited, most of the current knowledge is related to the most common form, type II or postpubertal GCT.

The different histologic types of type II GCT are intimately related. The precursor lesion of GCT, GCNIS, shares many phenotypical and morphologic features with seminoma, suggesting a precursor relationship [57–59]. However, molecular abnormalities more characteristic of other forms of invasive GCT, such as embryonal carcinoma (EC) or YST, can also be seen in GCNIS, suggesting that the in situ lesion may also play a role of precursor to other forms of GCT as well [57]. Further, the existence of "specialized" forms of intratubular tumors such as intratubular EC or seminoma suggests that transformation to other subtypes can occur within the tubular compartment [60–62], at least in a subset of cases, with later events inducing an invasive counterpart. Plasticity among different forms of invasive GCT subtypes has been documented experimentally and clinically and is likely more common than intratubular transformation. Patients with testicular seminomas can present with non-seminomatous metastases [63], and it is not uncommon that seminomas show isolated syncytiotrophoblastic giant cells, "early" epithelial differentiation [64], and expression of markers associated with other histologies, such as alpha-fetoprotein, CD30, or cytokeratin [65–67]. Similarly, patients with

Table 7.1 Pathogenetic types of GCT in the testis

Type	Histologic spectrum	Association with GCNIS	Other anatomical sites	Age of presentation	Incidence (per 100,000)	Originating cell	Cytogenetic abnormality	Ploidy
I	Prepubertal-type teratoma Dermoid cysts Possibly epidermoid cysts Prepubertal yolk sac tumor	No	Ovary Sacrum Retroperitoneum Mediastinum Neck Midline brain	Neonates Children Occasionally postpubertal	0.12	Early primordial germ cell/ gonocyte	Gains: 1q, 12(p13), 20q Losses: 1p, 4, 6q	Teratoma: Diploid Yolk sac tumor: Aneuploid
II	Seminoma Embryonal carcinoma Yolk sac tumor Choriocarcinoma and other trophoblastic tumors Postpubertal teratoma Mixed germ cell tumor	Yes	Ovary Dysgenetic gonad Mediastinum Midline brain	Postpubertal Median age: Seminoma 35 years Non-seminoma: 25 years	6.0	Primordial germ cell/gonocyte	Gains: X, 7, 8, *12p*, 21 Losses: Y, 1p, 11, 13, 18	Aneuploid (± triploid)
III	Spermatocytic tumor	No	None	>45	0.2	Spermatogonium/spermatocyte	Gains: 9	Aneuploid

Modified from Oosterhuis and Looijenga [55] and Reuter [56]

pure EC of the testis may present with teratomatous metastases [68, 69], and EC cells transplanted into peritoneal cavity of mice can differentiate into teratoma [70, 71]. YST may differentiate into mesenchymal tissues and may even show malignant somatic transformation (see Chap. 12), blurring the line between this histologic type and teratomas.

A common cytogenetic abnormality found in invasive types of type II GCT is the presence of isochromosome 12p (i12p) [56, 72, 73]. The isochromosome results in an overrepresentation of genes from the short arm of chromosome 12. Even cases lacking i12p have other forms of overrepresentation of these genes, such as duplication of the 12p11.21 region. Polysomy 12, while also seen in GCT, is less specific (Fig. 7.1) [73]. The i12p thus serves as a "common denominator" for the different subtypes of invasive type II GCT, providing further evidence of their intimate relationship at the molecular level. Interestingly, i12p is not found in GCNIS [74, 75], suggesting that its role is more important in the development of invasive capabilities, rather than in the original malignant transformation of germ cells.

In summary, these observations suggest a close association between the different histologies of GCT and suggest that different molecular events translate into morphologic transitions. Further analysis of the relationships between the subtypes of type II GCT is presented in Chap. 3.

In contrast with these suggested pathways, type I (pediatric GCT) and type III GCT (i.e., ST) have different histogeneses. Pediatric or prepubertal-type teratomas and YST are not associated with GCNIS and lack association with i12p. As explained in Chap. 3, it has been theorized that the cell of origin for this type of GCT is an earlier form of germ cell, such as a primordial

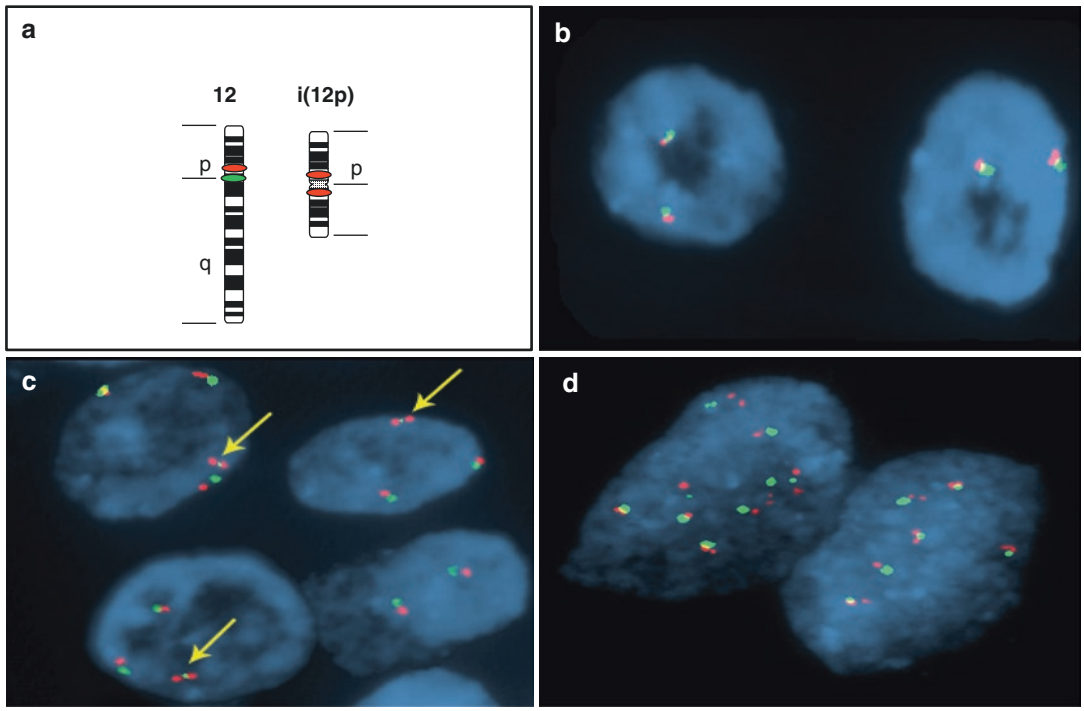


Fig. 7.1 Cytogenetic abnormalities of chromosome 12. The short arm of chromosome 12 is consistently abnormal in type II testicular GCT and can be detected with fluorescent in situ hybridization. Schematic representation of probes used to detect isochromosome 12p are shown in (**a**) when compared to normal hybridization pattern (**b**), abnormalities include isochromosome 12p (**c**), and gain of 12p (**d**)

or embryonic stem cell, compared to that of type II tumors. Similarly, ST lacks association with GCNIS and i12p and shows frequent cytogenetic abnormalities at the level of chromosome 9. Based on genomic imprinting analysis, the cell of origin for ST is believed to be a more mature germ cell than the one that gives rise to type II or type I tumors [55].

7.4 Classification of GCT

The pathogenetic mechanisms described above are relevant to the classification of GCT. Type II tumors, which constitute the majority of testicular GCT, are histologically characterized by their association with GCNIS. In fact, since GCNIS is an excellent surrogate for the molecular and biologic events in the pathogenesis of type II tumors, testicular GCT may be divided according to the presence or absence of GCNIS. Thus, tumors associated with GCNIS would correspond to type II GCT, while those not associated with GCNIS would encompass both type I and III neoplasms. The WHO classification of testicular neoplasms has incorporated this approach in its 2016 edition (see Table 7.2) [76].

For management purposes, testicular GCT are usually classified into seminomatous and non-seminomatous tumors. Seminomatous tumors include only pure seminomas. Non-seminomatous tumors encompass all mixed germ cell tumors (including those with seminoma as one of the components, even if predominant), as well as the less common pure forms of the other type II histologic types. The rationale for this classification resides in the completely different therapeutic approach for both categories, largely explained by the high radioensitivity of seminoma. However, the categorization into seminomatous and non-seminomatous tumors is overly simplistic and carries the risk of overlooking important features associated with specific histologic types. Additionally, it should be applied exclusively to type II tumors, and attention should be paid at not including within the non-seminomatous categories tumors with unique behavior and prognosis, such as ST or prepubertal-type teratomas.

Table 7.2 2016 WHO classification of GCT of the testis

Germ cell tumors derived from germ cell neoplasia in situ
Noninvasive germ cell neoplasia
Germ cell neoplasia in situ
Specific forms of intratubular germ cell neoplasia
Tumors of a single histological type (pure tumors)
Seminoma
Seminoma with syncytiotrophoblast cells
Non-seminomatous germ cell tumors
Embryonal carcinoma
Yolk sac tumor, postpubertal type
Trophoblastic tumors
Choriocarcinoma
Non-choriocarcinomatous trophoblastic tumors
Placental site trophoblastic tumor
Epitheliod trophoblastic tumor
Cystic trophoblastic tumor
Teratoma, postpubertal type
Teratoma with somatic-type malignancy
Non-seminomatous germ cell tumors of more than one histological type
Mixed germ cell tumors
Germ cell tumors of unknown type
Regressed germ cell tumors
Germ cell tumors unrelated to germ cell neoplasia in situ
Spermatocytic tumor
Teratoma, prepubertal type
Dermoid cyst
Epidermoid cyst
Well-differentiated neuroendocrine tumor
(Monodermal teratoma, carcinoid tumor)
Mixed teratoma and yolk sac tumor, prepubertal type
Yolk sac tumor, prepubertal type
Tumors containing both germ cell and sex cord-stromal elements
Gonadoblastoma

7.5 Tumors Associated with Germ Cell Neoplasia In Situ

7.5.1 Germ Cell Neoplasia In Situ

7.5.1.1 General Aspects

GCNIS is defined as the presence of malignant germ cells within the seminiferous tubules of the testis. Classically, these neoplastic germ cells are

characterized by having abundant clear cytoplasm and a prominent enlarged nucleus, and they are usually located in the basal layers of the tubule (Fig. 7.2). It was originally described by Skakkebaek in 1972 [77]. Because of its undifferentiated nature, the term *intratubular germ cell neoplasia unclassified type* has been historically preferred in the USA over the term carcinoma in situ, more popular in European countries, as the neoplastic cells do not show epithelial differentiation nor necessarily give rise to invasive carcinomas. Recently, the term germ cell neoplasia in situ has been proposed for this lesion and was incorporated in the 2016 WHO classification [76]. This terminology will be used throughout this chapter.

7.5.1.2 Incidence and GCT Risk

The neoplastic nature of GCNIS has been demonstrated by epidemiological, morphological, and biological studies. Fifty percent of patients with GCNIS will develop an invasive form of germ cell tumor within 5 years [47]. Similarly, more than 90 % of patients with an invasive form of GCT show GCNIS in the adjacent testicular parenchyma [78–80]. GCNIS is found in patients with a high risk of developing invasive GCT, including patients with cryptorchidism, gonadal dysgenesis, contralateral GCT, infertility, and androgen insensitivity syndrome [46, 48, 49]. Morphologically, the cells of GCNIS are markedly similar to the individual cells of seminoma and share a similar immunophenotype, including the expression of c-KIT, OCT4, SALL4, and placental-like alkaline phosphatase (PLAP) [81–83]. Molecularly, they are aneuploid and share allelic losses with invasive GCT [57].

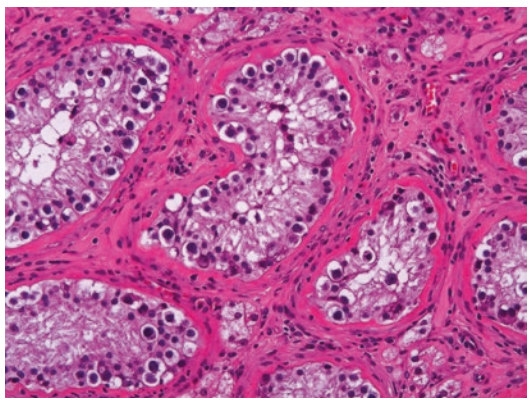


Fig. 7.2 GCNIS. Large cells with clear cytoplasm, conspicuous cell membranes, and enlarged and hyperchromatic nuclei, interspersed within seminiferous tubules with thickened basement membranes. Note the absence of active spermatogenesis

7.5.1.3 Morphology

No specific findings are grossly detected in cases of GCNIS that are associated with an invasive tumor. Given that it is commonly associated with infertility, changes of atrophy are not uncommon. Microscopically, GCNIS is characterized by the presence of large cells with clear cytoplasm, conspicuous cell membranes, enlarged and hyperchromatic nuclei, and prominent nucleoli (Fig. 7.2) [58]. These cells stand out in low power and are usually found in the basal layer of seminiferous tubules with atrophic features. In fact, it is extremely rare to find it in tubules with ongoing spermatogenesis. The involved tubules tend to be small and have a thickened basement membrane. Aside from the GCNIS cells, they usually contain only Sertoli cells. The distribution of GCNIS is usually patchy, and affected tubules may be located immediately adjacent to completely unremarkable ones. Peritubular lymphoid and granulomatous inflammation may also be present. GCNIS may show pagetoid spread into the rete testis (Fig. 7.3) [84] and less frequently into the epididymis and vas deferens [85].

PAS stains demonstrate abundant intracytoplasmic glycogen and may be useful as a screening stain. GCNIS is almost always positive for PLAP with a membranous/cytoplasmic pattern

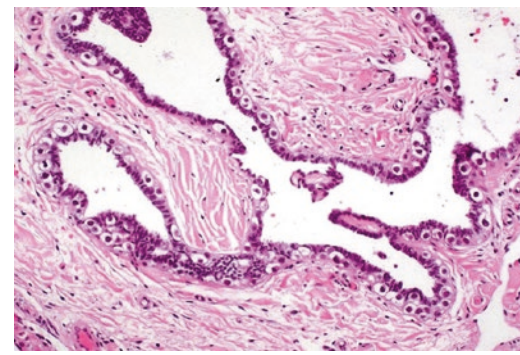


Fig. 7.3 GCNIS. GCNIS with pagetoid involvement of the rete testis

(Fig. 7.4a) and is quite useful, as normal spermatogonia are rarely positive for this marker. OCT4 is also highly specific, displaying nuclear staining only in neoplastic germ cells (Fig. 7.4b). c-KIT is highly sensitive, but its specificity is rather low, as nonneoplastic germ cells may react with this marker. The same can be said for SALL4 [82].

While GCNIS shares most of its molecular profile with invasive GCT, particularly seminoma, 12p amplification, usually in the form of i(12p), is rarely present in GCNIS, contrary to the case in invasive GCT. It is thus believed that the presence of i(12p) is probably involved in the ability of GCNIS to invade the stroma (see below) [82].

7.5.1.4 Differential Diagnosis

GCNIS must be distinguished from other intratubular forms of GCT, such as intratubular seminoma (Fig. 7.5a). These result for the most part from intratubular spread of invasive GCT, as they are rarely seen in the absence of an invasive component. Intratubular seminomas share many of the features of GCNIS; however, they fill and distend the involved tubules. They may be seen without an invasive seminoma counterpart, but usually they are accompanied by some kind of invasive GCT [61, 62]. Whether they represent an exaggerated form of GCNIS or an intratubular spread of an invasive seminoma is unresolved. Intratubular EC shows the epithelial differentiation and high-grade cytologic features of its invasive counterpart, including necrosis (Fig. 7.5b) [60]. Intratubular teratoma [86] and YST [87] have also been reported. Intratubular ST shows the three characteristic types of cells of the invasive counterpart (see below) and is always associated with an invasive component [58]. Metastatic carcinomas to the testis may show involvement of seminiferous tubules resembling GCNIS [88].

Prepubertal testes tend to show enlarged, slightly atypical germ cells with abnormal chromatin. In this setting, particularly in young

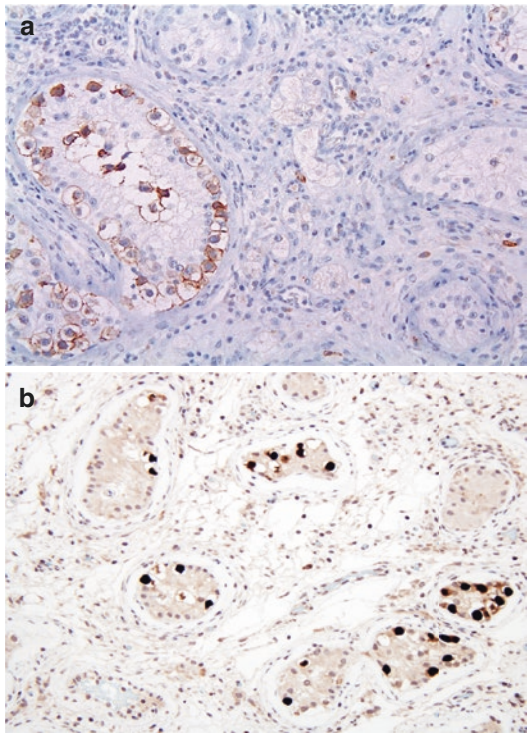


Fig. 7.4 (**a**, **b**) *GCNIS*, immunohistochemistry. GCNIS with characteristic membranous expression of PLAP (**a**) and nuclear expression of OCT4 (**b**)

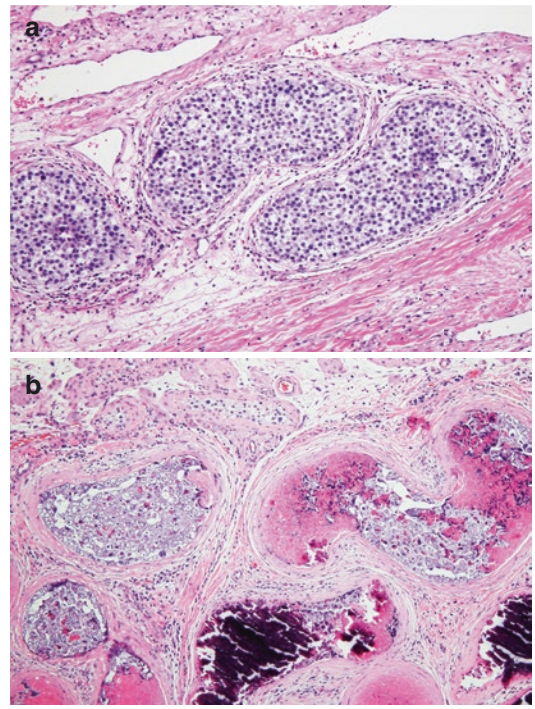


Fig. 7.5 (**a**, **b**) *GCNIS*, differential diagnostic considerations. (**a**) Intratubular seminoma filling and distending seminiferous tubules (**b**) Intratubular embryonal carcinoma, with intraluminal pleomorphic cells, necrosis, and calcifications

patients (less than 2 years), the atypical cells may share an immunophenotype with GCNIS. They are thought to represent delayed maturation of germ cells, frequently associated with DSD [89]. However, they are likely to be present diffusely throughout the parenchyma and are not limited to the basal layer within the tubules. Distinction between these two settings is clinically relevant, as these abnormal germ cells in prepubertal patients do not convey a high risk to progression to an invasive neoplasm. OCT4 is the preferred marker to use in the workup of this differential diagnosis [82].

Adult testis may also harbor occasional atypical germ cells, which usually show hyperchromatic nuclei, multinucleation, or enlarged size [90]. They lack the classic prominent nucleoli and typical distribution of GCNIS and do not share their immunophenotype (Table 7.3). While they may represent a manifestation of testicular dysgenesis, and thus may be present in the background of GCT, by themselves, they do not convey the high-risk implications of GCNIS.

7.5.1.5 Pathogenesis

During embryological development, germ cells, once located in the gonadal ridges where they are surrounded by mesenchymal cells, are termed gonocytes and are characterized by the expression of stem cell markers, including PLAP, NANOG, c-KIT, SOX2, and OCT4. Gonadal stromal cells express transcription factor SRY, which results in early development of Sertoli cells through the activation of SOX9 [58]. Sertoli cells create a microenvironment that allows differentiation of gonocytes into spermatogonia. This process marked by the gradual loss of expression of the stem markers mentioned above, the acquisition of expression of germ cell-specific proteins MAGE4A, VASA, TSPY, OCT2, and SSX2, and the migration toward the basement membrane of the seminiferous tubule. Disturbances of the microenvironment result in arrest of fetal germ cell differentiation. It is in this arrested stage that mutations in oncogenes or tumor-suppressing genes are believed to occur, resulting in transformation into a neoplastic cell [58]. In fact, GCNIS widely shares the immunophenotype of gonocytes, suggesting an arrest at this stage [91, 92].

With the acquisition of additional mutational events, likely potentiated by the changes in hormonal milieu at puberty, the neoplastic cells eventually acquire the capacity to invade through the basement membrane. The 12p abnormalities are consistently present in invasive tumors and are absent in GCNIS [74, 75]. It is thus likely that the abnormal region on 12p harbors genes that enable the tumor cells to survive, proliferate, and develop invasive growth independent of signals from the intratubular Sertoli cells and the adjacent Leydig cells. Candidate genes include KITLG, NANOG, BCAT1, and CCND2, but

Table 7.3 Differential diagnosis of GCNIS and atypical germ cells in postpubertal patients

	GCNIS	Atypical germ cells
Morphologic features:		
Involved tubules	Atrophic, absent spermatogenesis	Atrophic and normal with ongoing spermatogenesis
Distribution	Segmental	Diffuse and scattered
Location	Exclusively basal	Basal or luminal
Nuclear features	"Squared off," regular	Irregular, polylobated, or multinucleation
Immunohistochemistry:		
OCT4	+	–
PLAP	+	–
Podoplanin	+	–
SALL4	+	+
SOX17	+	+
CD117	+	+

their exact definition remains elusive [58, 93]. The pathway to this may include intratubular transformation to either intratubular seminoma or intratubular EC (nonlinear progression) [94] or development first of an invasive seminoma and then transformation into EC (linear progression) [57]. YST, teratoma, and choriocarcinoma (CC) appear to evolve by differentiation from EC (Fig. 7.6).

7.5.2 Seminoma

7.5.2.1 General Aspects

Seminoma is the most common GCT comprising approximately 50 % of these tumors in the postpubertal setting. The average age at presentation is 40 years with most patients presenting between 35 and 45 years of age. Seminoma is unusual in childhood, and after the fifth decade [95], however, in a study by Berney et al. [96], seminoma accounted for 82 % of cases of GCT in the elderly. Bilateral involvement is seen in up to 5 % of cases. Seminoma has shown the highest incidence of bilaterality among GCT in several studies [97, 98]. Patients with seminoma often present with a painless testicular mass or dull aching sensation. Up to 2–3 % of patients present with symptoms related to metastatic disease in the retroperitoneum. Typically serum levels of AFP are normal; however mild elevations have been described in pure seminomas [99]. Significant elevations are regarded as evidence of nonseminomatous elements and should prompt a careful search for these components. Liver disease including metastasis of pure seminoma may explain the presence of mild to moderate elevations of AFP. Mild serum β-hCG elevation is

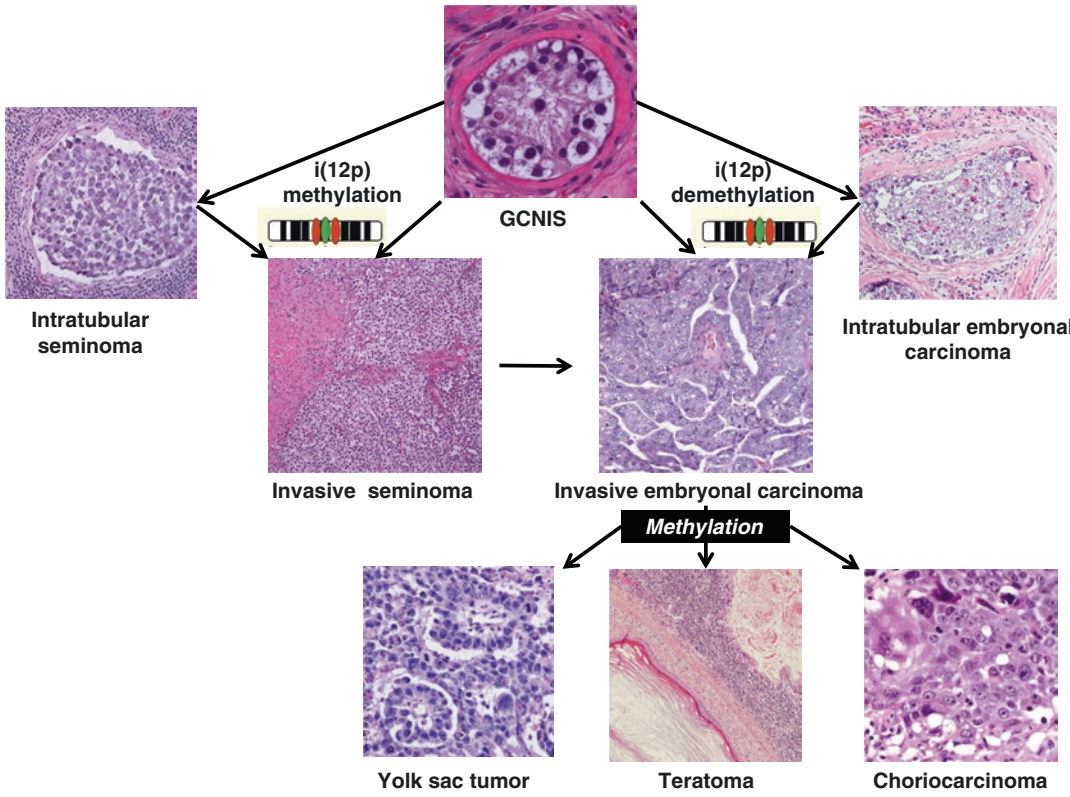


Fig. 7.6 Pathogenesis of germ cell neoplasia. Most forms of invasive GCT arise from GCNI, usually after the development of 12p abnormalities. GCNIS advances to seminoma or embryonal carcinoma, and from the latter, other forms arise, usually in association with DNA methylation

observed in seminomas with syncytiotrophoblasts and can be associated with the development of gynecomastia [100, 101].

7.5.2.2 Macroscopy

Grossly seminoma usually has a nodular configuration with well-circumscribed borders. The cut surface is lobulated, cream, tan, or white gray and shows variable consistency, reflecting the amount of fibrous tissue within the tumor (Fig. 7.7). Punctate foci of hemorrhage are often associated with the microscopic presence of syncytiotrophoblasts. Larger foci of hemorrhage and necrosis can be seen in tumors of large size. Invasion into the testis mediastinum and spermatic cord are uncommon with a reported frequency of 5–8 % [95].

7.5.2.3 Microscopy

Seminoma often has a diffuse sheetlike, nested, or trabecular growth. Characteristically the tumor is traversed by bands of connective tissue of variable thickness containing mature lymphocytes, predominantly of T cell type (Fig. 7.8a). These lymphocytes are also seen interspersed among tumor cells, but can be very prominent, occasionally obscuring the tumor cells. Cytologically the tumor cells show a uniform appearance with polygonal to round configuration and moderate amounts of clear, amphophilic, or eosinophilic cytoplasm with fairly distinct cell membranes (Fig. 7.8b). The latter attribute helps differentiate this tumor from EC, which exhibits a syncytial growth pattern. The nucleus is usually centrally placed and shows an evenly distributed chromatin with prominent nucleoli. The nuclear membrane is not perfectly round, with tendency to show angulated or flat contours, a term described by some as "squared-off" nuclei [102]. Some seminoma cells may have an eccentrically placed nucleus resulting in a plasmacytoid appearance. In contrast to plasma cells, a perinuclear hof is not observed. Mitotic activity is variable and may be quite brisk. Importantly, the degree of mitotic activity does not appear to correlate with tumor behavior. The term "anaplastic seminoma" was used in the past to designate seminomas with a mitotic rate equal or greater than three mitoses per high-power field and increased pleomorphism. This terminology has been discouraged due to insufficient data supporting a worsened prognosis in this subset of tumors [103, 104]. Similarly, necrosis, even when extensive, does not suggest a more aggressive behavior (Fig. 7.9). Prominent cytological atypia and pleomorphism, suggestive of early transition to EC, can be seen in seminoma [105]. In general most authors advice against designating these foci as EC, unless clear epithelial features such as glands or papillae are observed [106]. Up to 50 % of seminomas show granulomatous inflammation (Fig. 7.10a) [107]. This may range from scattered clusters of epithelioid histiocytes to an exuberant and diffuse reaction that may masquerade the tumor cells mimicking granulomatous orchitis. A subset of seminomas may exhibit ossification and calcification.

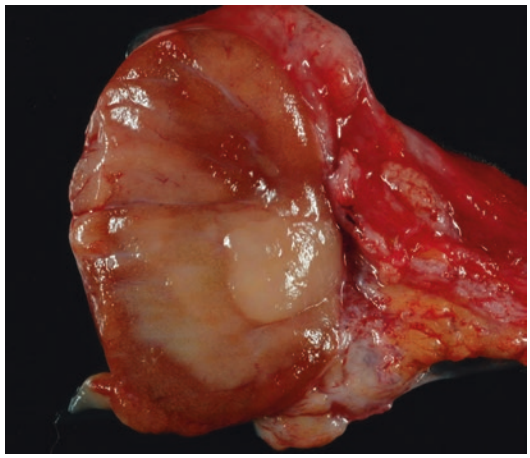
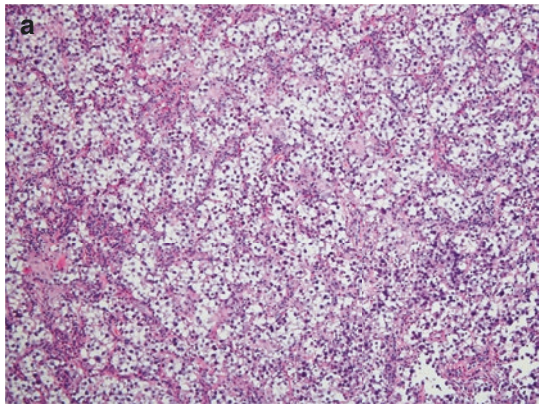


Fig. 7.7 Seminoma. Gross image of a seminoma showing a relatively well-circumscribed, lobulated, tan-white-colored bulging mass with a smooth surface

Scattered syncytiotrophoblasts can be seen in up to 20 % of seminomas (Fig. 7.10b) [108]. These are characterized by multinucleation, large size, and usually denser cytoplasm than the adjacent seminoma cells. Some may show prominent vacuolization of the cytoplasm. As mentioned above, these may be associated with small foci of hemorrhage. A distinction should be made with CC, which will require the presence of both syncytiotrophoblasts and cytotrophoblasts. The presence of syncytiotrophoblasts should thus be documented in the pathology report as it may explain the presence of mild elevations of β-hCG [109].



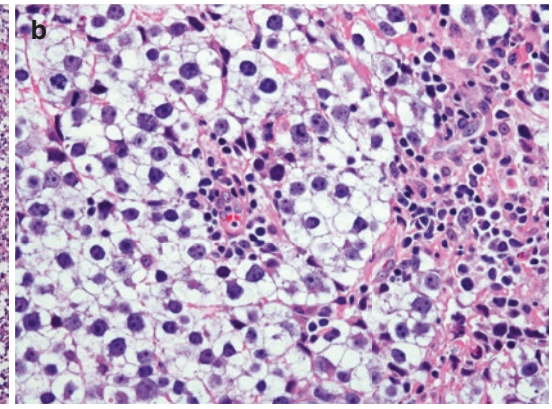


Fig. 7.8 (**a**, **b**) Seminoma. At low magnification a sheet-like pattern of growth with interspersed bands of connective tissue containing lymphocytes is seen (**a**). Higher magnification demonstrates uniform polygonal cells with clear cytoplasm, angulated or "squared-off" nuclei and distinct cell membranes (**b**)

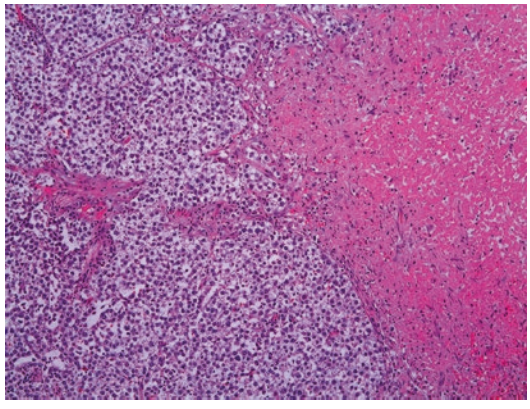
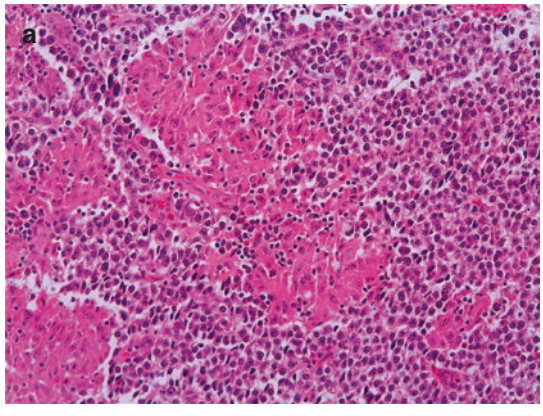


Fig. 7.9 Seminoma. Seminoma with prominent areas of necrosis



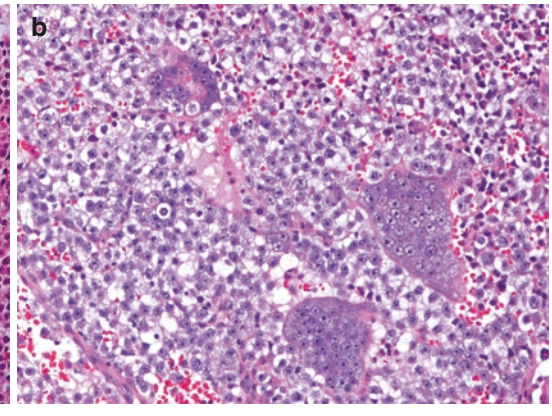


Fig. 7.10 (**a**, **b**) Seminoma. Seminomas are frequently associated with foci of granulomatous inflammation (**a**) and syncytiotrophoblastic giant cells (**b**)

Some seminomas show a tendency to form tubular, cribriform, or microcystic structures (Fig. 7.11), by virtue of developing spaces in between the solid growth of tumor cells [110–114]. These spaces are often associated with prominent intratumoral edema, but in other cases it may be artifactually induced by poor fixation or tumor degeneration. The result is a neoplasm that deviates from the classical appearance of seminoma and introduces the possibility of other diagnosis, such as YST or Sertoli cell tumor [112]. Usually typical areas of solid growth can be seen nearby. Difficult cases may require immunohistochemistry to resolve this differential diagnosis. Occasionally, seminomas may have prominent signet-ring cell change, a finding that may elicit the differential diagnosis with metastatic carcinoma (Fig. 7.11) [115]. Some seminomas may show exclusively or predominantly an intertubular growth pattern, without forming a discrete mass or nodule [116]. Intratubular seminoma was discussed in the section of GCNIS. It is not infrequently seen in association with invasive seminoma. Finally, some seminomas may have a very prominent lymphoid infiltrate that not only obscures the neoplastic cells but may even simulate a lymphoma involving the testis [117, 118]. Awareness of this phenomenon should prompt the careful search of typical seminoma cells and the use of appropriate immunohistochemical markers.

7.5.2.4 Immunohistochemistry

Seminoma is typically positive for OCT4, PLAP, c-KIT, podoplanin, SOX17, and SALL4 (Table 7.4). Keratin A1/AE3 expression is usually focal and weak, although, in our institutional experience, we have come across rare cases with diffuse reactivity. Seminoma lacks expression of CD30, SOX2, AFP, glypican-3, and ß-hCG [82].

7.5.2.5 Differential Diagnosis

The differential diagnosis of seminoma includes other forms of GCT, Sertoli cell tumors, and lymphoma. Solid variants of EC and YST are the most common types of GCT confused with seminomas. EC displays more pleomorphism than seminoma, and typically there is at least focal glandular differentiation. When both types of tumors are present, comparison of the nuclear characteristics may help in classifying an area of solid growth. Additionally, nuclei of EC frequently overlap, and cell borders are difficult to differentiate, imparting a "syncytium" appear-

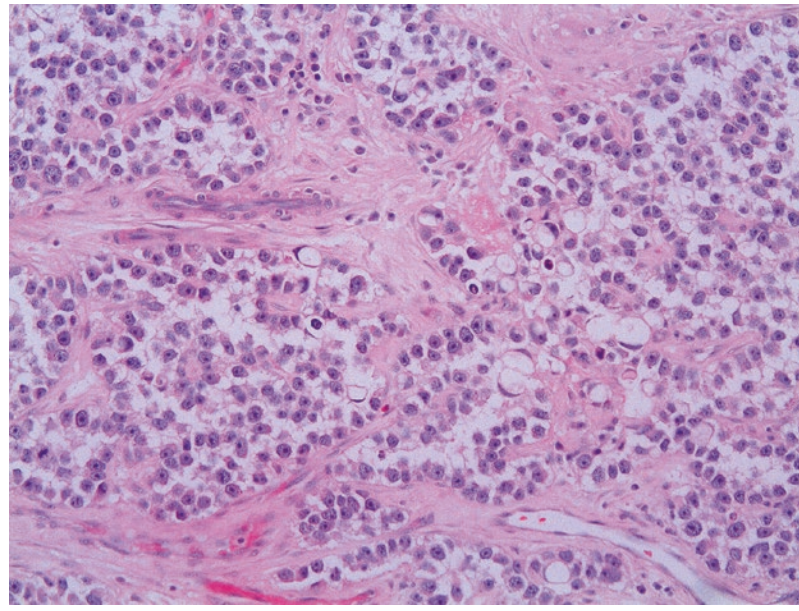


Fig. 7.11 Seminoma. Seminoma with tubular pattern of growth. Note also the focal signet-ring cell change

Table 7.4 Immunophenotype of GCT of the testis and their most common differential diagnosis considerations

	Seminoma	Embryonal carcinoma	Yolk sac tumor	Choriocarcinoma	Spermatocytic tumor	Sertoli cell tumor	Leydig cell tumor	Lymphoma	Adenomatoid tumor	Mesothelioma	Rete testis adenocarcinoma	Metastasis
SALL4	+	+	+/−	+	+	−	−	−	−	−	−	−
OCT4	+	+	−	−	−	−	−	−	−	−	−	−
PLAP	+	+	+	+	−	−	−	−	−	−	−	−
CD117	+	−	−	−	+/−	−	−	−/+	−	−	−	−/+
CD30	−	+	−	−	−	−	−	−/+	−	−	−	−
Pankeratin AE1/AE3	−	+	+	+	−	+/−	−/+	−	+	+	+	+/−
AFP	−	−	+	−	−	−	−	−	−	−	+	−
hCG	−	−	−	+	−	−	−	−	−	−	−	−
Glypican-3	−	−	+	+	−	−	−	−	−	−	−	−
Inhibin	− [a]	− [a]	− [a]	−	−	+	+	−	−	−	−	−
Melan-A	−	−	−	−	−	+	+	−	−	−	−	−/+
LCA/ CD20	−	−	−	−	−	−	−	+	−	−	−	−
Calretinin	−	−	−	−	−	−	+	−	+	+	+	−
WT1	−	−	−	−	−	+	+	−	+	+	−	−
Somatic markers (e.g., PSA, RCC, HMB45, CDX2, etc.)	−	−	−	−	−	−	−	−	−	−	−	Variable, depending on primary

Note: immunophenotype of teratoma is variable, depending on the somatic components present

[a]May be positive in scattered syncytiotrophoblastic giant cells

ance. Cytoplasm in EC tends to be more amphophilic and dense. Differential expression of cytokeratin, CD30, c-KIT, and SOX17 may help in difficult cases. YST may be confused with seminoma, specially its solid and microcystic growth patterns. Solid YST lacks the fibrous septae and lymphocytic infiltrate of seminoma and is rarely unaccompanied by more classical patterns, except in biopsy specimens. Cytologically, they show more variation in size and shape of the nuclei and are accompanied by hyaline globules and basement membrane material deposition. In tumors with microcystic architecture, attention should be paid to the cells lining the microcysts. In seminoma, they maintain their size and shape, while in YST they tend to be flattened, forming a lining [112]. A potentially critical misdiagnosis occurs when Sertoli cell tumors grow with a solid growth pattern mimicking seminomas, sometimes even with an associated lymphocytic infiltrate. Attention should be paid to the much lower nuclear grade of Sertoli cell tumors. The absence of associated GCNIS is an important diagnostic clue that should prompt appropriate immunohistochemical stains [119]. As stated above, some lymphoid stroma-rich seminomas may mimic lymphomas, while those associated with a prominent granulomatous reaction may lead to a misdiagnosis of granulomatous orchitis. Seminomas are the prototype of testicular neoplasms with a solid growth pattern. The differential diagnosis of this morphologic category is presented in Table 7.5.

7.5.2.6 Prognosis

Clinical stage I seminoma has a cure rate of 99 %. Relapse rates at this stage are 15–19 % [120], with most posttreatment relapses occurring within 3 years post-orchiectomy [121]. Metastases typically occur first in the retroperitoneal lymph nodes and subsequently at supradiaphragmatic sites. Metastatic seminoma within the good prognosis group as determined by the International Germ Cell Cancer Collaborative Group has an overall 95 % survival rate. Intermediate prognosis seminoma is rare; therefore survival rates reported are limited by low patient numbers [120]. There is contradictory data with regard to prognostic value of rete testis invasion, tumor size, and invasion into the tunica albuginea in stage I seminoma [122–126].

7.5.3 Embryonal Carcinoma

7.5.3.1 General Aspects

In its pure form, EC represents 3 % of testicular neoplasms, but nearly 40 % of testicular GCT have a component of EC. The peak incidence of this tumor is in the second to third decade with an average of 32 years, about a decade earlier than seminomas. EC is rare in the prepubertal setting and appears to be associated with DSD [102]. The most common presentation is that of a palpable testicular mass (80 %) followed by hormonal-related symptoms, such as gynecomastia (10 %) and symptomatic metastatic disease (10 %) [127]. Metastases occur via hematogenous and lymphatic pathways and primarily affect the periaortic lymph nodes, lung, and liver [63]. Although older reports have noted serum AFP elevations in patients with pure EC, current literature suggests this may be the result of unrecognized YST elements [128]. ß-hCG elevation is commonly seen in EC and reflects the presence of syncytiotrophoblasts.

7.5.3.2 Macroscopy

EC has a bulging soft, pale tan, pink, or dark-brown cut surface with areas of hemorrhage and necrosis (Fig. 7.12). The tumor borders are often ill defined. Tumor extension into the mediastinum testis and testicular adnexa is observed in up to 25 % of cases [106]. Compared to seminoma, EC are smaller at presentation, with average tumor size of 2.5 cm in diameter.

7.5.3.3 Microscopy

EC is composed of large pleomorphic cells with indistinct borders and nuclear crowding or overlap. Most tumor cells show vesicular chromatin and macronucleoli. The cytoplasm is predominantly basophilic although foci of amphophilic or clear cytoplasm are not unusual.

Table 7.5 Differential diagnosis of testicular tumors with a solid growth pattern

	Key features	Pearls for differential diagnosis
Seminoma	Solid sheets or nests Interstitial, tubular, trabecular, or sclerotic variants Fibrous septae dividing sheets of tumor cells Tumor cells evenly spread, no overlap Open chromatin with prominent nucleoli Squared-off nuclei	Clear to pale cytoplasm Variable lymphoplasmacytic infiltrate Granulomatous inflammation (30 % of cases) Fibrosis and sclerosis may be prominent Scattered syncytiotrophoblastic giant cells frequently present GCNIS in surrounding tubules
Sertoli cell tumor	At least focal tubular differentiation Uniform cuboidal or columnar cells Light eosinophilic to pale cytoplasm with vacuoles Round-ovoid nuclei, inconspicuous nucleoli, rare mitosis Fibrous septae and lymphoid infiltrates may be present	Tumors with solid growth, fibrous septae, and lymphoid infiltrates may strongly resemble seminoma Absence of GCNIS Smaller, more irregular nuclei, with less prominent nucleoli and less mitoses than seminoma
Yolk sac tumor (solid pattern)	Usually associated with other patterns of YST Solid sheets of polygonal cells with pale eosinophilic or clear cytoplasm Variable nuclear shape and size Hyaline globules Basement membrane deposition GCNIS present	More pleomorphism than what is seen in seminoma, but less than embryonal carcinoma Absence of fibrous septae and lymphocytic infiltrate
Embryonal carcinoma (solid pattern)	Areas of papillary and glandular pattern Large polygonal, highly pleomorphic cells with amphophilic or clear cytoplasm Necrosis and hemorrhage Frequent mitoses and apoptosis GCNIS present	Highest degree of pleomorphism Additional sampling may reveal areas more typical for embryonal carcinoma
Spermatocytic tumor	Solid growth pattern uninterrupted by fibrous septae Scant fibrous or edematous stroma Three distinct cell types: Small lymphocyte-like: 6–8 μm Intermediate cells: 15–20 μm Giant cells: 50–100 μm May have intratubular growth No GCNIS	Cells with pale cytoplasm, more pleomorphic on medium power than seminoma Lack of GCNIS, fibrous septae, lymphocytic infiltrate, or granulomatous inflammation differentiates it from classic seminoma Tends to occur in older patients, although age ranges may overlap
Leydig cell tumor	Solid sheets of oxyphilic cells Abundant eosinophilic cytoplasm, round nuclei, prominent nucleoli Cytoplasmic lipofuscin or Reinke crystals Fibrous, hyalinized, edematous, or myxoid stroma May show fatty metaplasia, spindle, clear cell, or microcystic changes	Dense eosinophilic cytoplasm separates them from the other entities; however, some may have cytoplasmic clearing Absence of GCNIS separates them from GCT
Lymphoma	More likely in older patients and bilateral Generally diffuse large B cell type Intertubular (interstitial) growth pattern Intratubular growth may be seen Variable sclerosis Large atypical cells with angulated nuclei and eosinophilic cytoplasm	Seminoma rarely shows a prominent interstitial growth pattern Cells in seminoma tend to have clearer and more abundant cytoplasm Absent GCNIS in lymphoma may aid in distinction
Metastasis	Metastatic clear cell renal cell carcinoma, prostatic adenocarcinoma, and melanoma may grow in sheets of clear/pale cells Morphologic features variable depending on primary origin of tumor	Usually known history of malignancy Metastases tend to occur in older patients, compared to germ cell tumors High level of suspicion in morphologic features that do not fit working diagnosis May require IHC to establish primary

YST yolk sac tumor, *GCNIS* germ cell neoplasia in situ, *GCT* germ cell tumors, *IHC* immunohistochemistry

Single-cell necrosis with frequent apoptotic bodies and mitosis are also readily encountered. Architecturally solid, papillary, and glandular patterns are the most common (Figs. 7.13, 7.14, and 7.15). The majority of EC show coexistence of two or more of the abovementioned patterns. Syncytiotrophoblasts are common in EC with a reported frequency of 46 % [129]. They are typically not associated with hemorrhage, in contrast with CC. Small amounts of undifferentiated spindled cellular stroma are accepted by some authors as part of EC, while others regard this as immature teratomatous mesenchyme [102, 127]. A granulomatous response of varied severity may be seen in EC [129]. Angiolymphatic invasion is commonly encountered at the periphery of the tumor. In fact, EC is the most common tumor identified in foci of lymphovascular invasion in mixed GCT. Intratubular EC is also similarly found at the edge of the tumor and is characterized by smudged hyperchromatic tumor cells admixed with abundant eosinophilic necrotic debris. Recognition of a thickened tubular basement membrane and residual Sertoli cells is helpful in avoiding misdiagnosis of intratubular EC as angiolymphatic invasion. Coarse calcifications are often seen in intratubular EC (Fig. 7.5b).

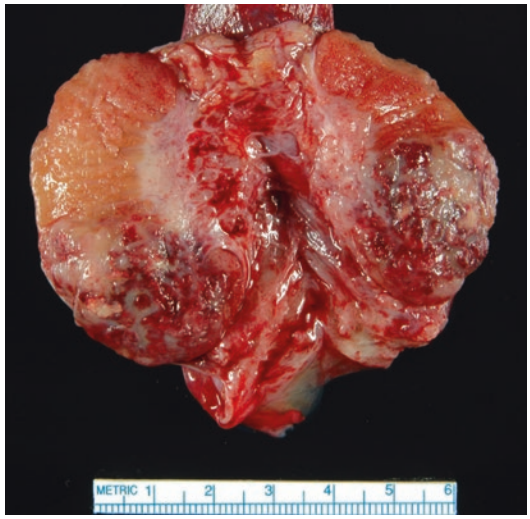


Fig. 7.12 Embryonal carcinoma. Gross image shows an ill-defined mass with a bulging, soft, pale-tan cut surface and prominent areas of hemorrhage and necrosis

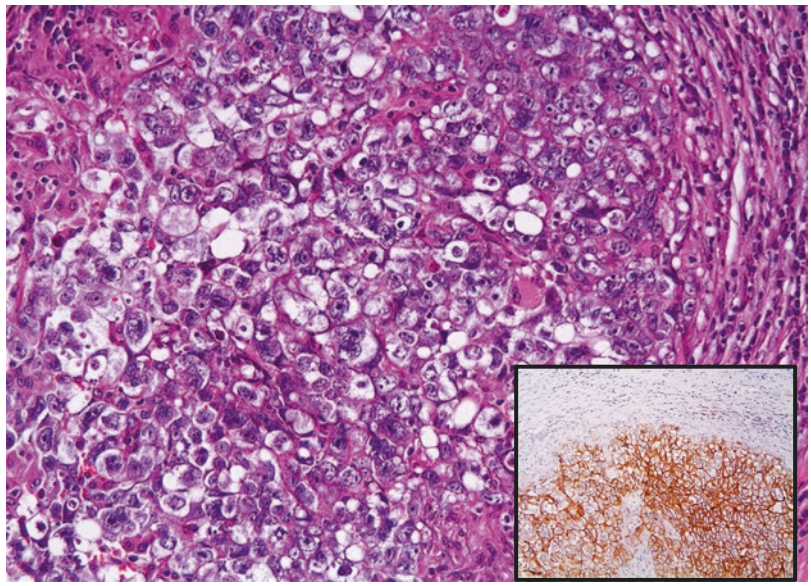


Fig. 7.13 *Embryonal carcinoma*, solid architectural pattern. These neoplasms show high-grade nuclear features, characterized by large pleomorphic cells with nuclear crowding and basophilic to clear cytoplasm. Foci of single-cell necrosis and apoptosis are easily appreciated. *Inset* shows strong membranous expression of CD30 by immunohistochemistry

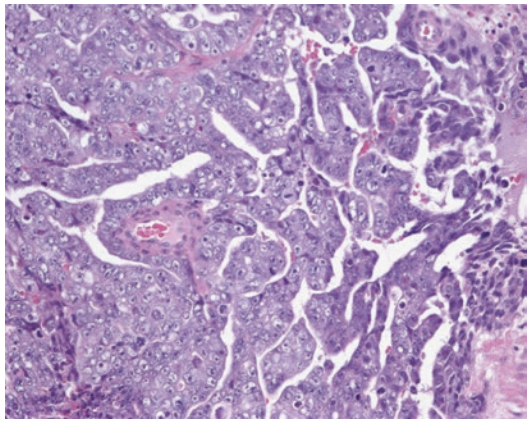


Fig. 7.14 Embryonal carcinoma. Glandular architectural pattern

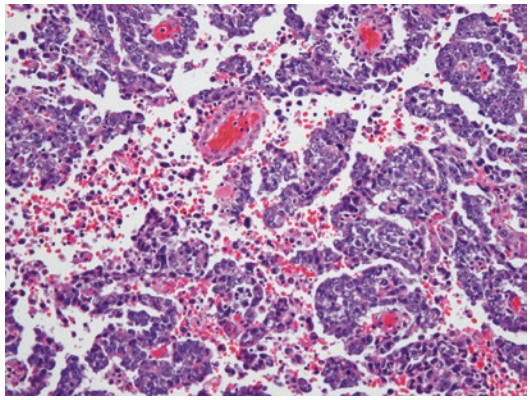


Fig. 7.15 Embryonal carcinoma. Papillary architectural pattern with prominent fibrovascular cores

The morphologic spectrum of EC is relatively broad [129]. It includes patterns commonly associated with YST (see below) or that may mimic seminoma or other neoplasms. An important pattern to recognize is the so-called appliqué pattern. This results in smudged degenerated cells located at the periphery of tumor nests. These cells closely resemble syncytiotrophoblasts and may lead to confusion with CC. Secretory-type change is characterized by subnuclear vacuoles similar to secretory endometrium. The pseudo-endodermal sinus pattern includes the presence of structures similar to the Schiller-Duval bodies of YST [130]. Sievelike pattern is reminiscent of the microcystic pattern of YST. In these patterns, differentiation from YST is based on the degree of pleomorphism of the tumor cells. In cases difficult to categorize, immunohistochemical staining with CD30 and OCT4 would favor EC. Solid forms may show tumor cells with prominent cell membranes and even mild lymphocytic infiltrate, resembling seminoma. Again, these EC variants will present higher degrees of pleomorphism than seminoma, and in difficult cases keratin and CD30 staining should resolve the problem. Other less common patterns include nested pattern, micropapillary pattern, anastomosing glands, necklace pattern, and a blastocyst-like pattern, characterized by large vesicles with edema fluid. Given the importance of reporting the percentage of EC in a mixed GCT (see below), accurate recognition of these patterns is mandatory to not under or overestimate the proportion of EC.

7.5.3.4 Immunohistochemistry

EC is positive for cytokeratin cocktails, OCT4, CD30 (Fig. 7.13, inset), SALL4, SOX2, and PLAP. The latter is usually weaker than that observed in seminoma. AFP may be focally positive. CD30 may be negative in metastatic EC [99]. In this setting coexpression of OCT4, SALL4, and strong and diffuse expression of cytokeratins may help support the diagnosis [131]. hCG expression is limited to syncytiotrophoblasts [97].

7.5.3.5 Differential Diagnosis

The solid pattern of EC may be confused with seminoma, lymphoma, ST, or solid YST (Table 7.5). YST is also a differential diagnosis in papillary and glandular patterns of EC (Table 7.6). The cytological features of EC may be sufficient to discriminate against other germ cell tumors in most cases; however, difficult cases can be easily resolved with the aid of immunohistochemical studies. Diffuse reactivity for OCT4, CD30, and cytokeratin is usually diagnostic (Table 7.4). Metastatic carcinomas to the testis may pose difficulty in distinguishing them from EC, but the absence of GCNIS, the usually older age of the patients, and commonly an intertubular growth pattern can raise the suspicion of a metastatic process [88].

Table 7.6 Differential diagnosis of testicular tumors with non-somatic glandular and/or microcystic growth pattern

	Key features	Pearls for differential diagnosis
Yolk sac tumor	Most morphologically versatile tumor YST patterns with glandular morphology include the microcystic/reticular, endodermal sinus, papillary and tubulopapillary, polyvesicular vitelline, glandular-alveolar, enteric/endometrioid, macrocystic patterns	Relatively uniform cells with clear or vacuolated to eosinophilic cytoplasm Bland cuboidal, columnar, flattened, or spindle cells Hyaline globules Basement membrane deposition GCNIS present
Embryonal carcinoma	Large infiltrative glands Areas of papillary and glandular pattern Large polygonal, highly pleomorphic cells with amphophilic or clear cytoplasm Necrosis and hemorrhage common Frequent mitoses and apoptosis GCNIS present	Pleomorphism is much more severe in embryonal carcinoma than in YST YST tend to have more variation in the morphologic patterns within one tumor Hyaline globules and basement membrane material suggest YST Frequently both tumors intermingled and closely associated
Rete testis/ epididymal adenocarcinoma	Invasive growth with prominent desmoplasia Centered in the rete testis or epididymis, where transition to malignancy may be seen Solid, papillary, tubulopapillary growth Marked nuclear atypia, mitoses, apoptosis, necrosis Intracytoplasmic or extracellular mucin	Higher grade and desmoplasia should differentiate it from YST Absence of GCNIS separates it from all GCT Location and transition to their benign counterparts helps in its separation from mesothelioma Metastatic process needs to be excluded with clinicopathologic correlation and IHC
Malignant mesothelioma	Epicenter in tunica vaginalis Histologic transition from mesothelial lining Majority pure epithelial or biphasic Papillary, tubulopapillary, glandular, or solid growth patterns Invasion beyond tunica	Tumor epicenter is different from testicular neoplasms GCT occur in younger patients May require IHC to separate from other entities in the differential diagnosis
Metastatic adenocarcinoma	Morphologic features variable depending on primary origin of tumor Tend to show a prominent intertubular and intravascular growth pattern Most common sites: prostate, lung, kidney, GI tract	Usually known history of malignancy Metastases tend to occur in older patients, compared to germ cell tumors High level of suspicion in morphologic features that do not fit working diagnosis May require IHC to establish primary
Leydig cell tumor	Oxyphilic cells, with abundant eosinophilic cytoplasm, round nuclei, prominent nucleoli Cytoplasmic lipofuscin or Reinke crystals may be seen Fibrous, hyalinized edematous, or myxoid stroma Fatty metaplasia, spindle, clear cell, or microcystic changes	Dense eosinophilic cytoplasm separates them from the other entities; however, they may have cytoplasmic clearing Absence of GCNIS separates them from GCT
Sertoli cell tumor	Uniform cuboidal or columnar cells Light eosinophilic to pale cytoplasm with vacuoles Round-ovoid nuclei, inconspicuous nucleoli, rare mitosis Tubular growth is the norm, whether hollow or solid Microcystic pattern not uncommon	Combination of tubular growth and relatively low nuclear grade should differentiate from germ cell tumors Relative monotony of seminomas may be more difficult to differentiate Absence of GCNIS is strong clue

(continued)

Table 7.6 (continued)

	Key features	Pearls for differential diagnosis
Seminoma with tubular pattern	Tubular or microcystic patterns may be seen Fibrous septae dividing sheets of tumor cells Tumor cells evenly spread, no overlap Open chromatin with prominent nucleoli Prominent lymphoid infiltrate and occasional granulomas	Seminomas more monotonous than YST Hyaline globules, papillary formation, basement membrane material suggest YST YST have flattened cells surrounding the cysts; in seminomas cells surrounding the cysts are identical to the rest
Adenomatoid tumor	Well-circumscribed mass, formed by tubules, gland-like irregular spaces, retiform architecture Cells may be cuboidal, flat, ovoid Round nuclei; dense cytoplasm with large vacuoles May show infarction	YST more intraparenchymal, while AT more peripheral YST has obvious malignant cytologic features GCNIS would suggest a germ cell tumor over AT Differentiated from mesothelioma on degree of infiltration and pleomorphism

YST yolk sac tumor, *GCNIS* germ cell neoplasia in situ, *GCT* germ cell tumors, *IHC* immunohistochemistry, *AT* adenomatoid tumor

7.5.3.6 Prognosis

EC is considered an aggressive form of GCT. In fact, the percentage of EC in mixed germ cell tumors has been regarded as a risk factor for metastatic spread [132, 133] (see "Mixed GCT" below).

7.5.4 Yolk Sac Tumor

7.5.4.1 General Aspects

YST is a malignant germ cell tumor that recapitulates the primitive endodermal structures, including embryonic yolk sac, allantois, and extraembryonic mesenchyme. A detailed review of the nomenclature, histogenesis, and histologic types is included in Chap. 6. In the testis, pure YST has a bimodal distribution with most cases occurring in the prepubertal period, while it is uncommon in the postpubertal period. Most reported cases of adult YST have occurred in the third and fourth decade. Elements of YST are present in up to half of mixed germ cell tumors. Clinically, YST presents as a painless palpable testicular mass. Elevation of serum AFP is noted in 95–100 % of cases [134].

7.5.4.2 Macroscopy

YST appears poorly circumscribed and nonencapsulated and has a homogenous gray to white to tan gelatinous cut surface. Hemorrhage, necrosis, and cystic degeneration may be seen.

7.5.4.3 Microscopy

YST shows the most diverse histology among GCT with a multiplicity of architectural patterns, including microcystic (reticular), macrocystic, endodermal sinus, papillary, solid, glandular/alveolar (including so-called endometrioid and enteric), polyvesicular vitelline, myxomatous, sarcomatoid, hepatoid, and parietal. A more detailed description of the histologic types is presented in Chap. 6.

The microcystic or reticular pattern is the most common and consists of anastomosing cords of vacuolated to spindled cells resulting in a meshwork or spider web like appearance (Fig. 7.16). The cystic spaces often show basophilic secretions. Coalescence of the small cysts gives rise to the macrocystic pattern. The endodermal sinus pattern is characterized by the presence of Schiller-Duval bodies, which consist of papillary structures lined by a cuboidal to columnar malignant-appearing epithelium with a distinct central vessel (Fig. 7.17). The papillae are recessed in a cystic space lined by flattened epithelium. Papillary formations with or without fibrovascular cores that project into cysts are the hallmark of the papillary pattern. The lining cells often exhibit a hobnail appearance with high

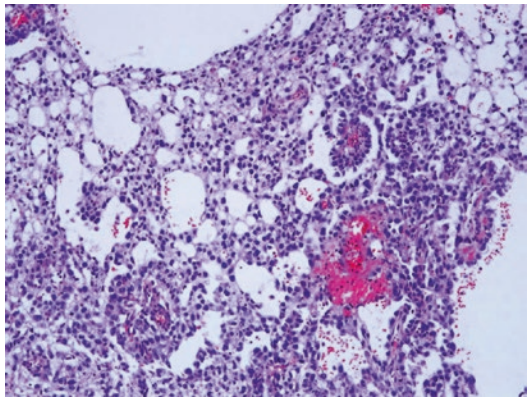


Fig. 7.16 Yolk sac tumor. Yolk sac tumor exhibiting the common microcystic or reticular architectural pattern

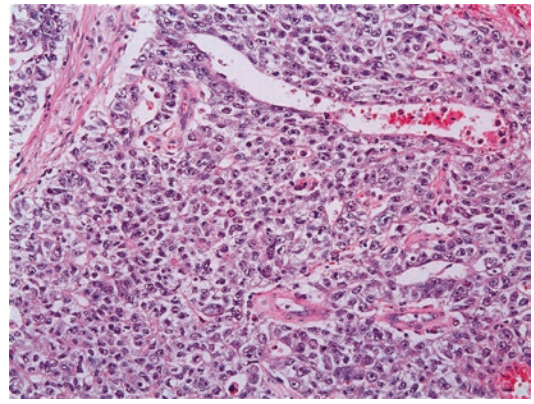


Fig. 7.18 Yolk sac tumor. Yolk sac tumor showing a solid pattern of growth. While exhibiting some degree of pleomorphism, it is considerably less atypical than embryonal carcinoma

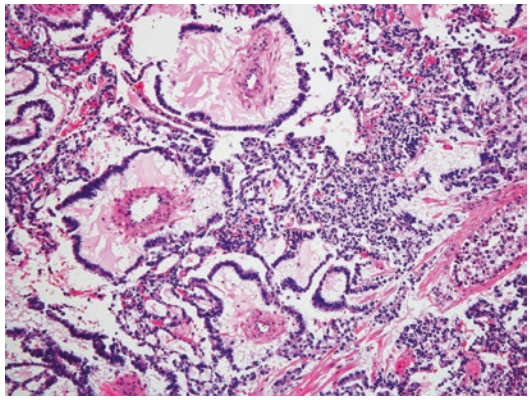


Fig. 7.17 Yolk sac tumor. Yolk sac tumor with an endodermal sinus pattern, characterized by papillary structures lined by a cuboidal to columnar epithelium with a distinct central vessel (Schiller-Duval bodies)

nuclear to cytoplasmic ratios. Exfoliated cells forming cell clusters can be seen in proximity of these papillae. The solid pattern consists of sheets of polygonal cells with variable nuclear yet with well-defined borders and moderate amounts of clear to amphophilic cytoplasm (Fig. 7.18). A variant form of solid YST with scant cytoplasm may have a blastema-like appearance. Glands lined by columnar epithelium with intestinal and secretory-phase endometrium-like features comprise the glandular pattern. These glands may be simple or branching and often present in a background of other YST patterns including microcystic, macrocystic, solid, or polyvesicular vitelline. The lining epithelium usually lacks cytological atypia and therefore it could be easily mistaken as teratomatous epithelium. Glandular branching and absence of an encircling smooth muscle layer are features that help differentiate YST from teratoma. The polyvesicular vitelline pattern is exceptional in the testis. It consists of vesicles/cysts lined by a bland epithelium present in an edematous to fibrous stroma. The vesicles may show an area of constriction which gives rise to an eight-shaped structure. The epithelium lining the vesicles often transitions from flat to cuboidal to columnar at the site of constriction. The myxomatous pattern consists of scattered innocuous spindle or stellate cells in a loose, myxoid stroma, which often features a rich capillary network (also called angioblastic pattern). Focal differentiation into skeletal muscle and cartilaginous elements is allowed in YST and should not prompt a diagnosis of teratoma [106]. The term sarcomatoid YST has been used to describe tumors with spindled cellular stroma that retains cytokeratin reactivity. A recent study [135] has proposed that some somatic sarcomatoid malignancies may actually represent sarcomatoid YST. Hepatoid YST consists of cells with abundant eosinophilic cytoplasm, large central nucleus, and prominent nucleolus arranged in nests, cords, or trabeculae. Bile secretion and

canaliculi have been observed in these tumors. Parietal YST is characterized by bland neoplastic cells embedded in dense eosinophilic basement membrane material that recapitulates the parietal layer of the murine yolk sac (Reichert's membrane). As noted above, cytological features of YST may vary across histological patterns. Significant nuclear atypia may be seen in solid, glandular, and sarcomatoid patterns of YST. Mitotic activity and single-cell necrosis can also be noted but are typically less prominent than in EC. A characteristic yet not pathognomonic feature of YST cells is the presence of intracytoplasmic eosinophilic globules, which are PAS-positive (Fig. 7.19).

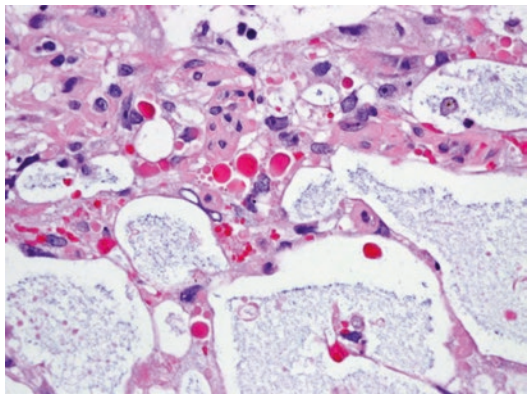


Fig. 7.19 Yolk sac tumor. Characteristic eosinophilic globules

7.5.4.4 Immunohistochemistry

Expression of AFP is variable and in many cases entirely absent. Intense staining for AFP is often seen in hepatoid pattern and in intracytoplasmic eosinophilic globules. Villin, glypican-3, SALL4, and low-molecular-weight keratins are often positive (Fig. 7.20) [82, 136, 137]. Rarely, c-KIT, SOX2, PLAP, and podoplanin positivity may be seen in YST [138]. This could represent a pitfall in the differentiation of the solid variant from seminoma. OCT4 and CD30 are negative. Hep-Par-1 reactivity has been documented in areas with or without hepatoid differentiation [136].

7.5.4.5 Differential Diagnosis

YST is the prototypic testicular neoplasm with glandular differentiation, a differential that is

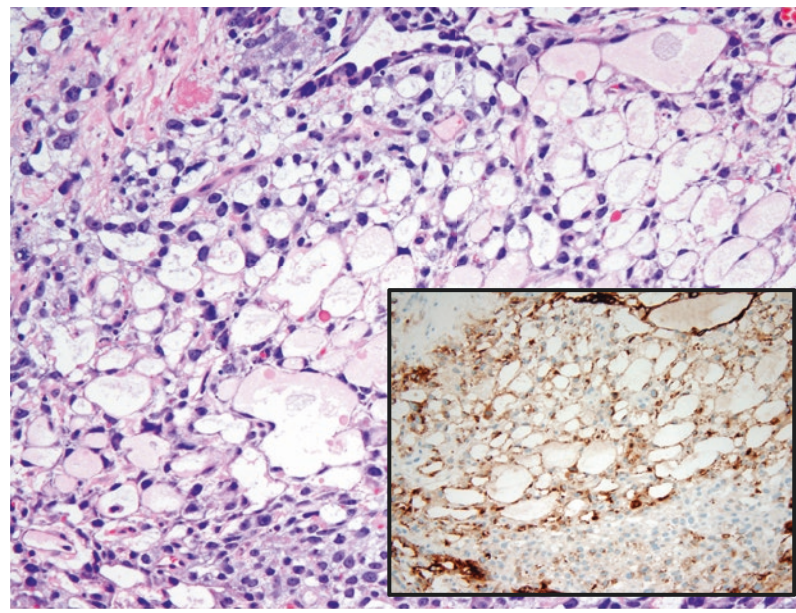


Fig. 7.20 Yolk sac tumor. Microcystic architectural growth pattern of yolk sac tumor, with the *inset* showing characteristic expression of glypican-3 by immunohistochemistry

summarized in Table 7.6. Glandular YST may be confused with immature teratoma, as previously discussed. Solid YST may resemble seminoma. The lack of fibrous septa with lymphocytic infiltration may help in their differentiation. Immunohistochemical reactivity for OCT4 excludes YST and therefore is useful in their distinction. OCT4 may prove useful when glands or papillary structures show cytological atypia that overlaps with EC.

7.5.4.6 Prognosis

Prognostic data for adult pure YST is limited due to the rarity of this entity. A series of 12 patients with stage I and II adult pure YST revealed a similar clinical behavior with respect to other non-seminomatous testicular GCT [139].

7.5.5 Postpubertal-Type Teratoma

7.5.5.1 General Aspects

Teratomas are GCT that display differentiation into somatic elements, including components of variable proportions from the ectoderm, mesoderm, and endoderm layers of the developing embryo. In the testis, they occur in two settings, based on the developmental stage of the surrounding testis: prepubertal or postpubertal. Contrary to their ovarian counterpart, the vast majority of postpubertal testicular teratomas are malignant, independent of the degree of maturity of its constituent elements. This is explained by the different histogenesis in both neoplasms. While in the ovary, teratomatous transformation of the germ cell occurs via parthenogenesis, in the testis it is most often an event that takes place after malignant transformation of a germ cell. As most other GCT in the male gonad, teratoma arises in association with GCNIS and, as explained before, likely corresponds to a terminally differentiated invasive component derived from more primitive forms, such as EC. Thus, postpubertal teratoma in the testis represents a form of differentiation of an already malignant neoplasm with a type II histogenesis. This explains its metastatic potential, independent of its degree of immaturity, and the fact that it is most frequently seen in association with other forms of GCT. Pediatric teratomas are reviewed in Chap. 10. However, occasionally, some teratomas in the postpubertal testis have a histogenesis and morphology comparable to those of the prepubertal gonad (type I) and thus behave in a benign fashion [140]. They are currently classified as prepubertal-type teratomas by the WHO [76] and will be considered separately (see below).

7.5.5.2 Macroscopy

Gross features of teratomas reflect their more prevalent somatic components (Fig. 7.21). Cysts filled with mucinous material or keratinaceous laminated debris are common. However, testicular teratomas tend to be more solid than the ovarian counterpart. More fleshy solid areas usually represent less differentiated components and may be associated with hemorrhage or necrosis. Bone, fat, cartilage, or even teeth material may be seen. Hair is rarely seen, and its presence should suggest a prepubertal-type teratoma.

7.5.5.3 Microscopy

In contrast to mature ovarian teratomas and prepubertal teratomas, postpubertal teratomas lack a well-organized organoid distribution of the different elements and display significant cytologic atypia and mitotic activity. Because of the lack of organoid arrangement, the exact somatic structure being replicated is sometimes difficult to determine. Representation from all three embryological layers is usually, but not always, present (Fig. 7.22). Glandular elements often include enteric-type epithelium, with variable amount of goblet cells, or mucinous glands (Fig. 7.23). Ciliated respiratory-type epithelium is also common. Frequently, glands with cylindrical cells with no particular differentiation are seen. Specialized glandular elements such as the liver, thyroid, or pancreas are rare [141]. Squamous nests are frequently present, displaying varying degrees of keratinization (Fig. 7.24). Commonly

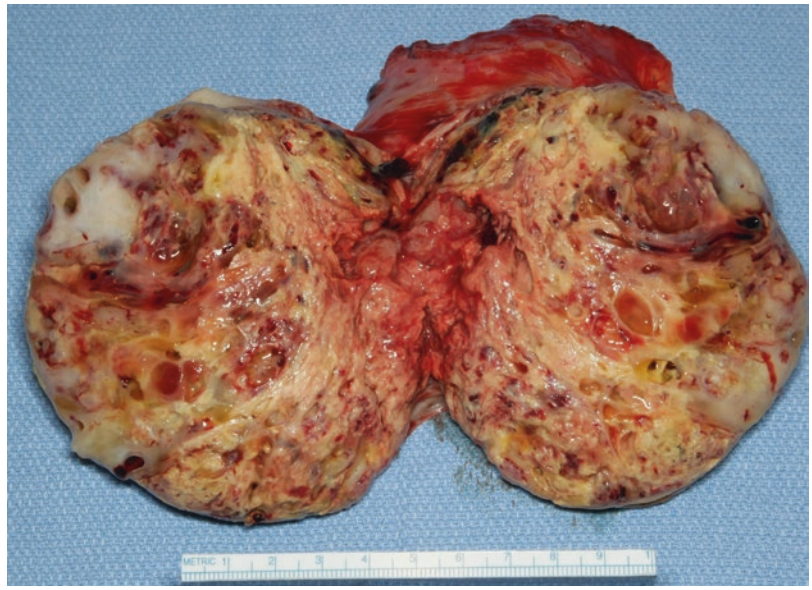


Fig. 7.21 Postpubertal teratoma. Gross image of a mixed germ cell tumor with prominent teratomatous elements characterized by cartilaginous (*upper left*) and numerous cystic areas

encountered mesenchymal elements include the cartilage, skeletal and smooth muscle, and rarely fat. Some of these elements may not be fully mature and may resemble mesenchymal tissue of the fetus and embryo.

More primitive, embryonic-type tissues, such as neuroepithelium and nephroblastic-type tissue, are commonly seen (Fig. 7.25). The presence of these elements does not impact prognosis or diagnostic terminology, unless frank overgrowth is present, in which case one must consider the possibility of a secondary malignancy [135] (see Chap. 12). Neuroectodermal tissue usually includes formation of neural-type tubules, rosettes, or sheets of undifferentiated primitive neuroectodermal small cells. Transition to better-differentiated glial type tissue may be seen. Other neural related tissues include meninges and retina-type pigmented epithelium. Nephroblastoma-type elements include primitive tubules, primitive spindle cells, and blastema elements. As in other types of postpubertal germ cell neoplasia in the testis, GCNIS is seen in adjacent tubules.

Another feature in testicular teratomas that differs from the ovarian counterpart is that all elements, including those with complete maturity, show some degree of cytologic dysplasia. This is easily seen in the epithelial elements, which frequently show nuclear hyperchromasia, irregular chromatin, and mitotic features, and can also be seen in the chondrocytes of the cartilage islands and other mesenchymal elements (Figs. 7.22 and 7.23).

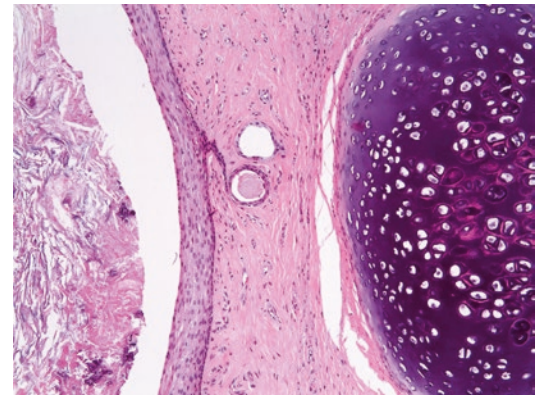


Fig. 7.22 Postpubertal teratoma. Squamous epithelium-lined cystic space is seen adjacent to cartilage

7.5.5.4 Immunohistochemistry

The immunophenotype of teratoma components recapitulates that of the somatic elements that are being reproduced. Pluripotentiality markers are expressed less consistently than in other types of GCT. SALL4 marks up to 80 % of elements within the teratoma. Glypican-3 is seen usually in more immature elements. PLAP and

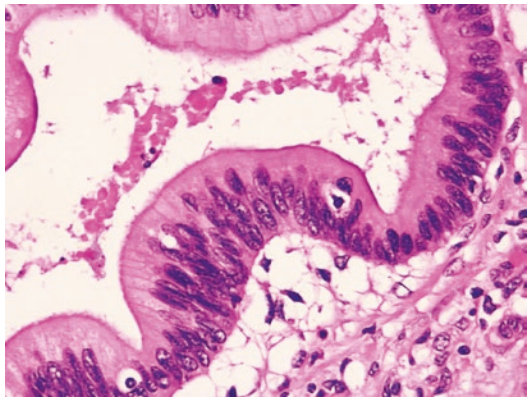


Fig. 7.23 Postpubertal teratoma. Glandular, enteric-type epithelium exhibiting prominent cytologic atypia

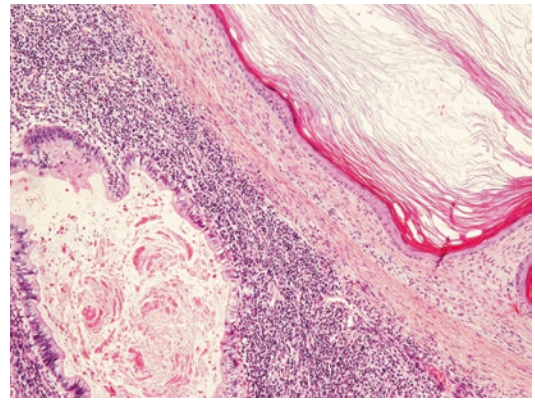


Fig. 7.24 Postpubertal teratoma. Keratinizing squamous epithelium is seen adjacent to glandular elements with nondescript histologic differentiation

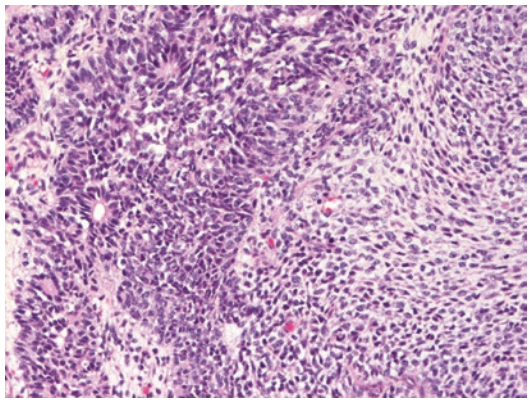


Fig. 7.25 Postpubertal teratoma. Primitive, embryonic-type tissues, such as neuroepithelium, in this case with prominent rosetting, is frequently seen

AFP are usually seen in only a subset of epithelial elements, while OCT4 is usually negative [82]. IMP3, an oncofetal protein that plays an important role in embryogenesis and carcinogenesis, is selectively expressed in postpubertal male teratomas and is negative in the female counterpart [142].

7.5.5.5 Differential Diagnosis

Teratoma needs to be differentiated from other GCT, particularly in the setting of a mixed GCT. While a large component of teratoma is hardly underrecognized, small amounts of somatic glands within extensive areas of EC or YST may be overlooked. Attention should be paid to the organization of the cells within the gland, which contrasts with the disorganized and primitive look of YST and EC elements. Some patterns of YST may be misinterpreted as teratoma, particularly the glandular, alveolar patterns, or the hepatoid patterns. Teratoma admixed with YST usually have abrupt transitions between both elements, while these YST patterns usually merge imperceptibly with more classical patterns. Also, teratomas will usually display other more easily recognizable components, such as cartilage or squamous epithelium. Regardless, misinterpretation of small amounts of teratoma as other GCT or vice versa, in the setting of a mixed GCT, would rarely have a significant clinical impact. Distinction from prepubertal-type teratomas, including dermoid cysts, which carry a markedly different prognosis, is explained below.

7.5.5.6 Prognosis

Postpubertal teratomas are rarely pure, and thus its behavior is usually compounded by that of the other elements associated with it. Cases of pure teratomas have been shown to present with metastases, and metastases from mixed GCT frequently contain teratoma components. Whether this represents and inherent metastatic potential of the teratoma elements or the teratoma represents a maturation process occurring in a metastasis from another GCT (particularly EC), is difficult to determine. Nevertheless, the associa-

tion of teratoma with metastases and potential death due to disease in patients with GCT is well established. Up to 37 % of pure teratomas present with metastases [143]. Pure teratoma metastases are frequently found in patients that have undergone chemotherapy for metastatic mixed GCT, presumably because other GCT components have a better response to chemotherapy, or, alternatively, because chemotherapy induces other components to differentiate into teratoma. Regardless, outcome is generally favorable. Exceptions include the occurrence of secondary malignancy [135] (see Chap. 12) or cases where complete surgical removal is not possible. In this setting, progressive growth of the teratomatous metastases may result in lethal compression of vital structures with ultimate demise of the patient [144–146].

7.5.6 Choriocarcinoma

7.5.6.1 General Aspects

Choriocarcinoma (CC) is a GCT that shows trophoblastic differentiation and is composed of a variable mixture of mononucleated cytotrophoblastic and multinucleated syncytiotrophoblastic cells. A pure form of the former may be seen, more commonly in the metastatic setting, and occasionally in primary tumors [147]. In the testis, CC is usually a component of a mixed GCT, with pure forms corresponding to less than 1 % of all GCT [148]. Other variants of less common trophoblastic tumors, such as epithelioid trophoblastic tumor and placental site trophoblastic tumor, will be discussed separately.

7.5.6.2 Clinical Presentation

As part of a mixed GCT, they usually present as a painless testicular mass. However, occasionally in this context or more frequently when extensive, predominant, or pure, CC presents as metastatic disease, with symptoms related to hemorrhagic metastasis (hemoptysis, melena, intracranial hemorrhage, etc.) [149–152]. In these cases, a clinically evident primary may not be readily apparent. Serum β-hCG levels are typically high (usually >100,000 mIU/mL). Gynecomastia and hyperthyroidism have been described, and this is secondary to structural and functional similarities between the alpha chain of hCG and TSH and FSH [153–157].

7.5.6.3 Macroscopy

CC are frequently diagnosed while they are still small primary lesions in the testis, given their propensity to present clinically with symptoms of metastatic disease before a testicular mass is discovered. Even at this small size, tumors tend to be extensively necrotic and hemorrhagic, with usually solid residual tumor in the periphery. Larger tumors tend to be extensively cystic.

7.5.6.4 Microscopy

Histologically, classic CC shows a mixture of cyto- and syncytiotrophoblasts (Figs. 7.26 and 7.27). The latter is characterized by multinucleated giant cells with abundant eosinophilic cytoplasm. They may show vacuolated cytoplasm and other degenerative changes. Nuclei within them tend to have dense chromatin and occasional nucleoli. Cytotrophoblasts are polygonal or round cells with well-demarcated cell borders. They are usually small to medium sized, with irregular nuclei, vesicular chromatin, and visible nucleoli. Mitotic activity is easily seen. They usually cluster, forming tight aggregates. Some tumors contain cells of intermediate size, with more abundant and eosinophilic cytoplasm. Because these cells appear to morphologically and immunophenotypically imitate intermediate trophoblasts [158], some authors prefer to refer to all non-syncytiotrophoblast cells as “mononucleated trophoblast cells” to encompass both lines of differentiation (i.e., cytotrophoblast and intermediate trophoblast) [86]. Both mononuclear and multinucleated components are intimately associated, with syncytiotrophoblast cells frequently wrapping or capping aggregates of cytotrophoblast cells. Some cases have a relative paucity of syncytiotrophoblast cells and may appear monophasic, particularly when composed predominantly of the larger mononucleated cells. Extensive areas of necrosis and hemorrhage are frequently seen. Tumor cells tend to project into

hemorrhagic areas with columns recapitulating the extravillous growth of trophoblast in the placenta. Vascular invasion is almost invariably seen in tumors with large components of CC. As with most of the other germ cell tumor types, GCNIS is seen in the adjacent seminiferous tubules.

7.5.6.5 Immunohistochemistry

By immunohistochemistry, CC is negative for OCT4 [82]. Syncytiotrophoblastic giant cells are usually positive for β-hCG and glypican-3, while both components tend to show expression of EMA, MUC1, CEA, SALL4, GATA3, and α-inhibin [159]. Contrary to other epithelial GCT, CK7 is expressed in a subset of trophoblasts [160]. p63 is preferentially expressed in cytotrophoblastic cells [161]. hPL is expressed strongly in syncytiotrophoblastic giant cells, but may stain some of the larger mononucleated trophoblasts [158].

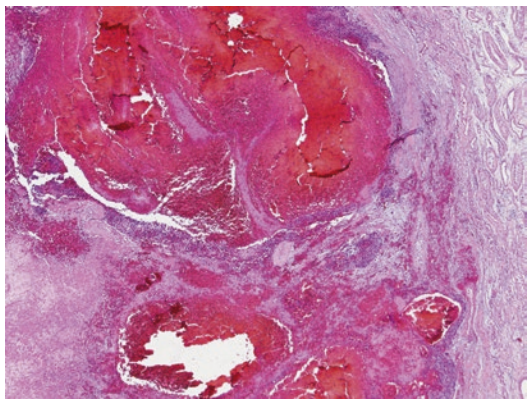


Fig. 7.26 Choriocarcinoma. Choriocarcinoma associated with extensive hemorrhage

7.5.6.6 Differential Diagnosis

The main differential diagnosis is another GCT type associated with syncytiotrophoblastic giant cells. As explained before, it is not uncommon for other types of GCT to be associated with occasional syncytiotrophoblastic giant cells. Since these are not associated with cytotrophoblast, they do not represent a component of CC. This is particularly significant in seminoma, where a misinterpretation of isolated syncytiotrophoblastic cells as CC may exclude a patient from the treatment arm of seminoma. In other GCT types, an overdiagnosis of CC may incorrectly assign a patient an adverse prognosis. Attention should be paid to the morphologic features of the other components and the absence of cytotrophoblasts. The pleomorphism of this component is usually higher than what is seen in YST but less severe than what is seen in EC. Seminoma would present with typical uniformity throughout the tumor mass, with intervening fibrous septa and lymphocytic aggregates. Neither would show the classic wrapping or capping of syncytiotrophoblasts over the cytotrophoblast component. In difficult cases, immu-

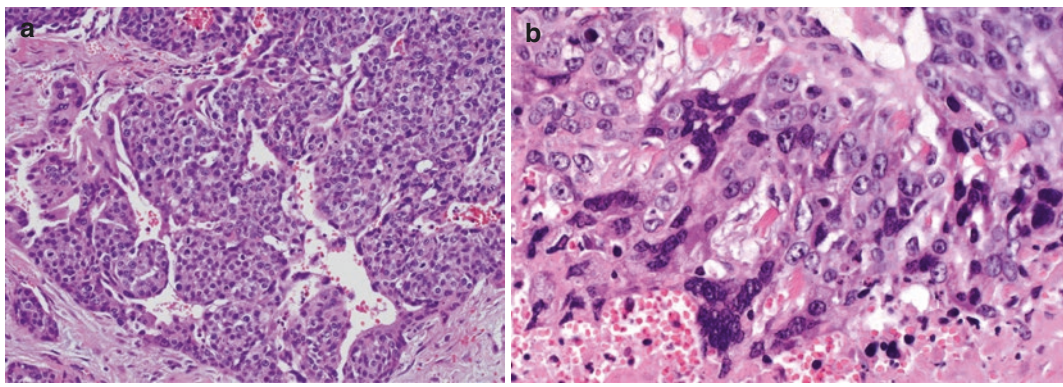


Fig. 7.27 (**a**, **b**) Choriocarcinoma. (**a**) At intermediate magnification, syncytiotrophoblasts characterized by multinucleated giant cells, with abundant eosinophilic cytoplasm, are seen interspersed among polygonal to round cytotrophoblasts with well-demarcated cell borders. (**b**) Higher magnification

nohistochemical stains may be used to correctly identify each component.

7.5.6.7 Prognosis

A CC component within a mixed GCT is usually associated with more aggressive behavior. However, when predominant or exclusive, CC is associated with a particularly ominous prognosis. In a recent study, 15 cases of pure or predominant CC component presented with metastases to distant sites, including the lungs, liver, and brain. About 79 % of these patients died of disease-related complications, with a median survival of 13 months, despite current regimes of chemotherapy [148]. Pulmonary metastases have a better prognosis than other visceral metastases. In the above-referenced study, two patients with exclusive pulmonary metastases were disease-free after 60 and 72 months of follow-up, respectively [148].

7.5.7 Other Trophoblastic Neoplasms

7.5.7.1 Placental Site Trophoblastic Tumor

Contrary to what occurs in the female genital tract, only a handful of cases of testicular placental site trophoblastic tumor have been described, three of them in a metastatic setting [147, 162–166]. The tumors are characterized by the presence of intermediate trophoblast cells exhibiting moderate amounts of dense eosinophilic cytoplasm with occasional vacuolization. The nuclei are smudged, and the majority of cells are mononuclear, with only occasional multinucleation of up to four nuclei per cell. Vessel wall invasion and small areas of hemorrhage are seen. The stroma is myxoid, and Alcian Blue positive. The tumor cells express HPL, and only focal β-hCG. Of the three primary tumors described, one was pure (in a 16-month old boy) [147], while the others were associated with a teratomatous component [163, 166]. Of the three tumors in the metastatic setting, one was chemotherapy naive and occurred in a pulmonary metastasis of a primary mixed GCT [162]. The other presented as a post-chemotherapy retroperitoneal recurrence 4 years after resection of a mixed GCT that included chorciocarcinomatous elements [164]. The third was also a retroperitoneal, post-chemotherapy recurrence of a mixed GCT in a 39-year-old man [165]. In this setting, the main differential diagnosis is a partially regressed CC, as treated CC may show numerous mononuclear intermediate trophoblastic cells. A hemorrhagic background with necrosis would favor the latter (Table 7.7).

7.5.7.2 Epithelioid Trophoblastic Tumor

Originally described in the uterus, epithelioid trophoblastic tumor (ETT) is a rare neoplasm of mononuclear cells that shows differentiation toward the chorionic-type intermediate trophoblast found in the *chorion laeve*. In the testis it was initially described as a component of a metastatic GCT [167], but five recently reported cases included this component in primary tumors [165]. They are characterized by nests of cells with squamoid appearance, with well-defined cytoplasmic membranes and intracytoplasmic vacuoles containing fibrinoid debris. Nuclei are mostly single, with occasional multinucleation. The tumor cells are positive for inhibin, GATA3, p63, PLAP, and variably for β-hCG while negative for SALL4, glypican-3, and OCT4. Serum β-hCG levels were normal or mildly elevated. Most tumors have been part of a mixed GCT with other components, although two cases corresponded to 95 % and 100 % of a recurrence, respectively. The ETT component did not appear to confer a different prognosis to the GCT [165].

7.5.8 Mixed Germ Cell Tumors

With the exception of seminoma, all invasive histologic types described above present more frequently as part of a mixed GCT than as pure forms. Mixed GCT are the most common non-seminomatous GCT. By definition, they contain various combinations of GCNIS-associated tumors and exclude non-GCNIS-associated components such as ST, pediatric YST, and prepubertal-type

Table 7.7 Differential diagnosis of trophoblastic tumors

	Choriocarcinoma	Placental site trophoblastic tumor	Epithelioid trophoblastic tumor	Cystic trophoblastic tumor
Clinicopathologic setting	Primary or metastatic Pre- or post-chemotherapy	Primary or metastatic Pre- or post-chemotherapy	Primary or metastatic Pre- or post-chemotherapy	Metastatic Post-chemotherapy
Neoplastic cell	Cytotrophoblast (CT) and syncytiotrophoblast (SCT)	Implantation site intermediate trophoblast (IT)	Chorionic laeve IT	Likely treated CT and SCT cells, or other GCT cells with induced trophoblastic differentiation
Main morphologic features	Biphasic pattern, with SCT cells wrapping aggregates of CT cells	Large discohesive cells with moderate amount of dense eosinophilic cytoplasm, large nuclei, prominent nucleoli. Infiltrative	Squamoid mononuclear cells with abundant cytoplasm and prominent cell membranes. Fibrinoid material	Mono- or multinucleated cells with abundant eosinophilic cytoplasm, lining cystic cavities, usually associated with teratoma (Fig. 7.46)
Necrosis	+++	++	+/−	−
Hemorrhage	+++	++	+/−	−
Vascular invasion	+++	+++	+/−	−
Immunohistochemistry				
hCG	+	+	+/−	+
hPL	+/−	+	−	+/−
p63	+	−	+	−
Inhibin	+/−	+	+	+
GATA3	+	+	+	+
Proliferative index (MIB1)	>10 %	>10 %	>10 %	<5 %

teratomas. Pure histologic types, including seminoma, associated only with syncytiotrophoblastic giant cells are also not considered mixed GCT.

The most common histologic type present in mixed GCT is EC, which is present in up to 84 % of cases, followed by teratoma (69 %), YST (60 %), and seminoma (39 %). CC is the least frequently present element, with only 17 % of cases containing this element [168]. The most frequent combinations of histologic type are summarized in Table 7.8. EC with teratoma is often cited as the most combination in mixed GCT, followed by EC with seminoma, and EC + YST + teratoma [168] [95, 169, 170]. However, Mosharafa et al. determined that the highest concordance and strongest correlation between histologic types were between teratoma and YST [168].

Grossly, mixed GCT reflect the features of their components. Tumors containing seminoma elements may show solid, tan, lobulated areas, while those containing EC are frequently necrotic and hemorrhagic (Fig. 7.28). Similarly teratoma elements usually confer a multicystic appearance, with mucinous contents. The distribution of elements histologically tends to be rather unpredictable (Fig. 7.29). Seminoma elements tend to concentrate in a specific area, while the other elements are frequently interspersed among each other. EC and YST tend to be spatially close to one another, sometimes intimately admixed. When

Table 7.8 Most common association patterns of elements in mixed germ cell tumors

Incidence of mixed germ cell tumor combinations (adults)	Jacobsen et al. [95] (%)	Mosharafa et al. [168] (%)
T + EC	60	56
T + CC	11	12
T + YST	21	43
T + S	19	22
EC + CC	22	15
EC + YST	29	50
EC + S	33	31
CC + YST	8	9
CC + S	6	4
YST + S	8	19

T teratoma, *EC* embryonal carcinoma, *CC* choriocarcinoma, *YST* yolk sac tumor, *S* seminoma

distributed in a fashion reminiscent of an embryoid body, the terms polyembryoma and diffuse embryoma may be used (see below).

While mixed GCT are usually grouped together under the category of "non-seminomatous GCT," prognostic differences between the different components which are clinically relevant have been identified. Thus, reporting of mixed GCT should include a detail of the different components present and their relative extent, usually expressed as a subjective percentage of the tumor comprised of each component. Of particular importance is the relative amount of EC. Tumors with high percentages of EC are associated with worse prognosis and thus may be ineligible for surveillance [171–173]. This is also true for cases with high percentages of CC [174, 175]. On the other hand, large proportions of YST in the primary tumor are associated with a lower probability of relapse [171]. The presence of teratomatous elements in the primary tumor predicts the presence of residual teratoma metastases in the post-chemotherapy setting [168]. Thus, accurate identification of the different elements in mixed GCT is of utmost importance, as it conveys significant prognostic information. Judicious use of immunohistochemistry panels may help in achieving this objective [82, 176]; however, in our opinion, their use should be reserved for particularly difficult cases and where the results would make clinically significant differences, as most cases can be accurately classified based on their morphology.

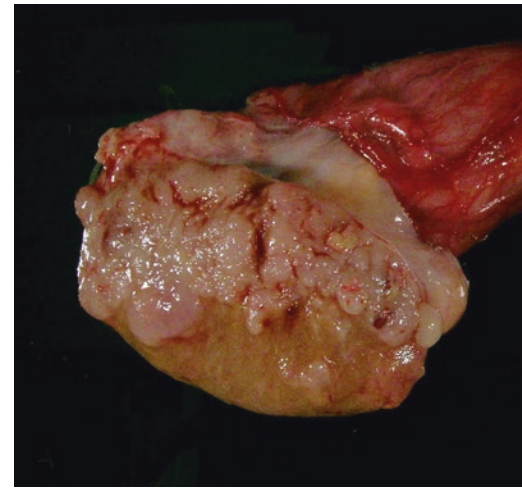


Fig. 7.28 Mixed germ cell tumor. Gross image shows a relatively well-circumscribed mass, with varied features. The smooth, pink-tan cut surface corresponds to an underlying seminoma. Focal hemorrhagic areas represent an embryonal carcinoma component

7.5.9 Polyembryoma and Diffuse Embryoma

Polyembryomas and diffuse embryomas are GCT that are composed of an EC and a YST component, organized in distinct architectural patterns.

Polyembryomas, specifically, recapitulate day 12 to day 18 embryonic structures by forming "embryoid bodies." Similar to a developing embryo, embryoid bodies have a central plate, which is comprised of an EC component. At the dorsal pole, this structure is surrounded by an empty space limited by a lining of flattened cells, recapitulating the amniotic sac and amnion. The ventral pole has a YST component in a reticular to microcystic architectural pattern, recapitulating the primary embryonic yolk sac. These embryoid bodies are embedded in a loose mesenchymal matrix, such that on low magnification the matrix is usually the predominant component, and often these neoplasms demonstrate a cystic pattern of growth [177]. Non-embryoid elements, if present, constitute less than 10 % of these tumors and range from mature teratomatous elements to trophoblastic cells [178].

Conceptually, polyembryomas may be regarded as a distinct architectural subtype of mixed GCT comprised of an EC and YST com-

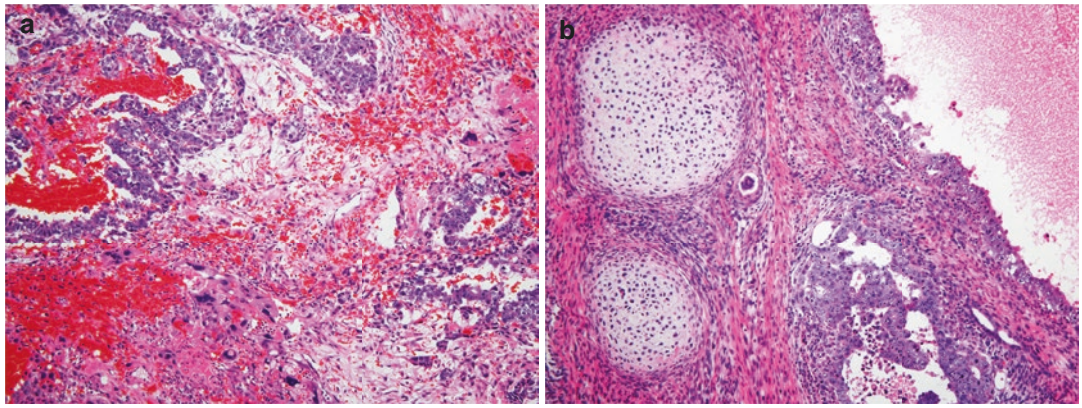


Fig. 7.29 (**a**, **b**) Mixed germ cell tumor. (**a**) Areas with high-grade cytology, corresponding to embryonal carcinoma (*upper left*), are seen juxtaposed adjacent to choriocarcinoma with prominent hemorrhage (*bottom left*). (**b**) Areas of cartilage corresponding to a teratoma are seen adjacent to embryonal carcinoma

ponent (Fig. 7.30). Conversely, they may also be regarded as a form of immature teratomas as the embryoid bodies represent a primitive stage of development [177, 178].

An area of debate is whether the presence of focal microscopic aggregates of an EC or YST element adjacent to an embryoid body is part of the spectrum of polyembryoma or needs to be classified as a mixed GCT. A size cutoff of 3 mm has been arbitrarily proposed, and, as the literature is limited, further studies are required to resolve this question [177, 178].

Diffuse embryomas were first reported by Cardozo de Almeida and Sculley in 1983 [179]. They differ from polyembryomas in that these tumors are comprised of roughly equivalent proportions of YST and EC components and do not form embryoid bodies. Herein, typically, the YST component encircles and often invaginates EC elements, with the latter being arranged in solid, gland-like, and tubulopapillary patterns (Fig. 7.31) [179, 180]. Recent studies have demonstrated the presence of GCNIS component in these tumors suggesting that the latter is the precursor lesion. These studies have therefore made a strong case for classifying diffuse embryomas as postpubertal mixed GCT [181, 182].

Pure forms of both polyembryomas and diffuse embryomas are rare, and these elements are more commonly found as components of mixed GCT [178].

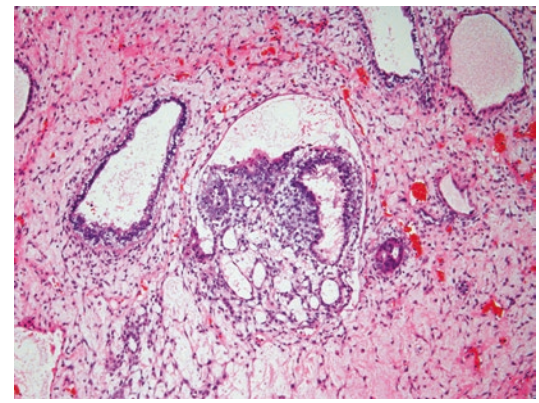


Fig. 7.30 Polyembryoma. A characteristic embryoid body is seen in the center, constituted by a central embryonal carcinoma component, limited by a lining of flattened cells at one pole and a yolk sac tumor component arranged in a microcystic pattern at the opposite pole. The embryoid body is embedded in a loose mesenchymal matrix

7.6 Tumors Not Associated with Germ Cell Neoplasia In Situ

7.6.1 Spermatocytic Tumor (Spermatocytic Seminoma)

7.6.1.1 General Aspects

Spermatocytic tumor (ST) is a rare germ cell tumor that occurs exclusively in the testis. It accounts for 1–2 % of testicular neoplasms [183, 184]. Previously referred to as spermatocytic

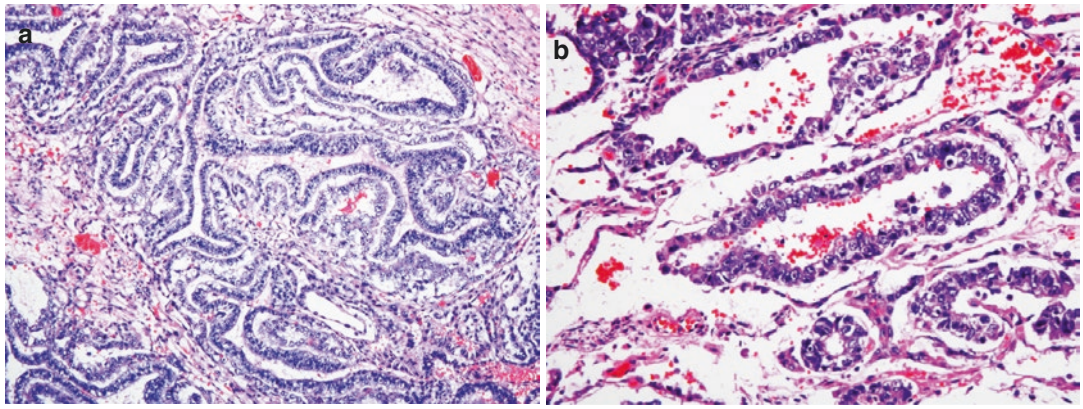


Fig. 7.31 (**a**, **b**) Diffuse embryoma. (**a**) Higher-grade embryonal carcinomatous components are shown organized in gland-like and tubular patterns and are encircled by a yolk sac tumor component. (**b**) Higher power

seminoma, the current terminology of ST has been recently adopted to avoid confusion with the much more common (classic) seminoma, which would carry prognostic and therapeutic implications. Age at presentation ranges from 25 to 87 years; however its peak incidence is in the fifth–sixth decade [185, 186]. ST is not associated with GCNIS, cryptorchidism, or gonadal dysgenesis and is not observed in association with other GCT. Bilaterality is rare with less than ten cases reported in the literature [187] and may be synchronous or sequential in occurrence. Serum markers are not characteristically elevated in ST.

7.6.1.2 Macroscopy

ST is well circumscribed and multilobulated. The cut surface is pale gray or pink tan and shows friable, mucoid, or gelatinous consistency (Fig. 7.32). Cystic change may be noted. Hemorrhage and necrosis may occur in larger tumors. The tumors are limited to the testis with rare exceptions of extratesticular extension reported in tumors with sarcomatous transformation [188, 189].

7.6.1.3 Microscopy

The tumor is arranged in sheets or solid nests (Fig. 7.33a). The stroma is usually scant and may be fibrous or edematous. The tumor cells may show discohesion and intercellular edema which results in a cystic or pseudoglandular appearance. In contrast with seminoma, a granulomatous reaction is extremely rare; nonetheless a discrete lymphocytic infiltrate may be present.

ST is characterized by a polymorphous population of cells composed of three distinct types: small cells with dense chromatin and scant cytoplasm that resemble lymphocytes; intermediate cells with round nucleus, finely granular chromatin and moderate amounts of eosinophilic cytoplasm; and a smaller population of large cells which may be multinucleated (Fig. 7.33b). Medium and large cells may exhibit spireme chromatin distribution, characterized by visible filamentous or cord-like strands of chromatin. Mitotic activity is brisk and atypical forms may be encountered. Rare cases of sarcomatous transformation have been documented in the form of undifferentiated, rhabdomyoblastic, or fibrosarcomatous lesions (see also Chap. 12) [186, 188–192].

7.6.1.4 Immunohistochemistry

ST shows reactivity for SALL4 and c-KIT. OCT4, CD30, keratin, PLAP, and podoplanin are negative [82, 193].

7.6.1.5 Differential Diagnosis

The differential diagnosis of ST includes seminoma, EC, and lymphoma. The presence of GCNIS

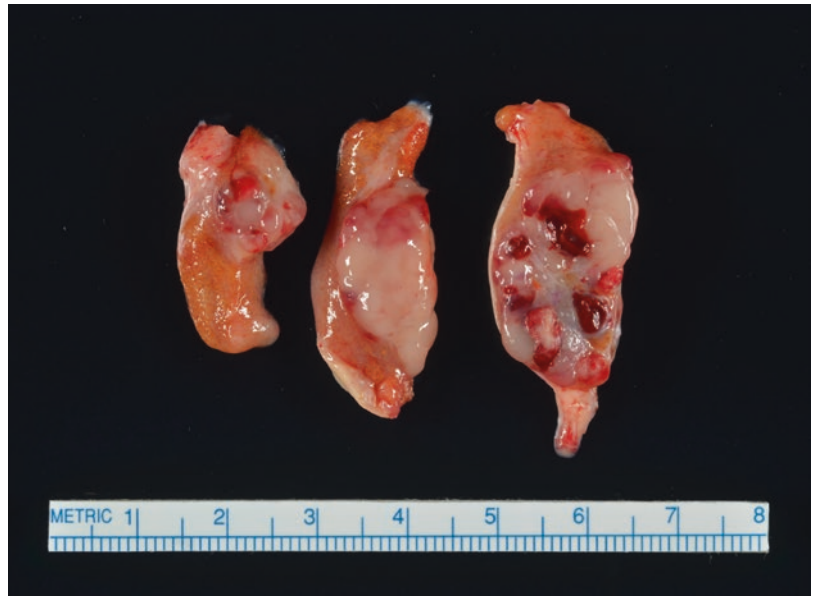


Fig. 7.32 Spermatocytic tumor. Gross image of a spermatocytic tumor showing a tan-pink mass with a mucoid to gelatinous consistency and focal hemorrhagic areas

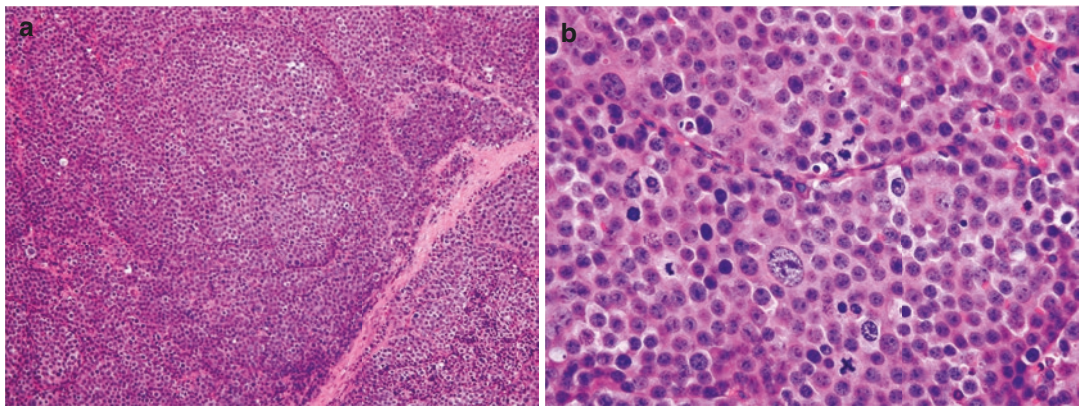


Fig. 7.33 (**a**, **b**) Spermatocytic tumor. Spermatocytic tumor showing a sheetlike growth pattern, in a background of fibrous stroma with minimal lymphocytic infiltration (**a**). Higher magnification reveals three distinct cell populations: lymphocyte-like small cells, intermediate cells, and a population of large cells (**b**)

can help exclude seminoma and EC. The latter should be distinguished from intratubular growth of spermatocytic seminoma which may be noted in few cases of ST. In general a lymphocytic infiltrate is not prominent in ST (see Table 7.5). Difficult cases may require immunohistochemical studies with OCT4 and lymphoid lineage markers.

7.6.1.6 Prognosis

Most ST follows an indolent behavior. Metastases are rare and almost exclusively seen when sarcomatous transformation is present (see Chap. 12) [185]. The metastatic foci are typically composed of sarcomatous elements. Exceedingly rare cases of metastatic spermatocytic seminoma without sarcomatous transformation have been reported [194, 195].

7.6.2 Prepubertal-Type Teratoma in the Postpubertal Testis

Pathologists have for a long time recognized that a subset of testicular teratomas appear different from the classic postpubertal teratomas [196, 197].

These are usually referred to as dermoid cysts [198–200], as their most prevalent component include squamous epithelium and cutaneous adnexae. These tumors are not associated with any other type of GCT, including GNCIS, with the possible exception of carcinoid tumor. Their teratomatous elements are much better organized and reproduce the relationships between elements seen in normal somatic tissues. They also do not display cytologic atypia in the cells of these elements.

Dermoid cysts are grossly usually filled with sebum-type material, admixed with hair and fatty fluid. Microscopically they consist of one or more cavities lined by squamous epithelium with granular layer and abundant keratinization (Fig. 7.34). Every so often, adnexal structures, such as pilosebaceous units or sudoriparous glands, are seen, draining in the cavity through the squamous epithelium. A series of reactive changes can be seen, such as histiocytic aggregates interrupting the squamous lining, or foreign body granulomatous reaction in cases of rupture. Lipogranulomatous reactions are also common. The adjacent seminiferous tubules show normal spermatogenesis, and GCNIS is remarkably absent.

Most published cases of dermoid cyst of the testis include examples that do not have exclusively cutaneous elements [199, 200]. Ciliated epithelium, mucinous epithelium, smooth muscle, fat, glia, bone, meninges, and cartilage have been reported in varying proportions. Recently, Zhang et al. [140] published a series of 25 cases of mature teratomas of the testis; ten of them corresponded to dermoid cysts. However, 15 contained predominantly non-cutaneous elements, including glandular cysts lined by ciliated/respiratory epithelium with goblet cells, surrounded by the smooth muscle, cartilage, and seromucinous glands, resembling a somatic bronchus. Others displayed intestinal-type epithelium surrounded by lamina propria and smooth muscle, recapitulating gut (Fig. 7.35). Fat and meningeal tissue were also present. Interestingly, none of the cases with available follow-up had recurrence or progression of the disease. Finally, in 18 cases tested, no cytogenetic abnormalities of 12p were identified. These data suggest that: (1) These teratomas show a spectrum of conforming elements that goes beyond what's conveyed by the narrowly descriptive term of "dermoid cyst" and may have a wider variety of tissues present. (2) They are benign neoplasms. (3) They are pathogenetically and biologically distinct from classic postpubertal (type II) testicular teratomas, being more likely analogous to prepubertal (type I) teratomas. Recently, the 2016 WHO classification of testicular tumors has included them under the category of prepubertal-type teratomas [76].

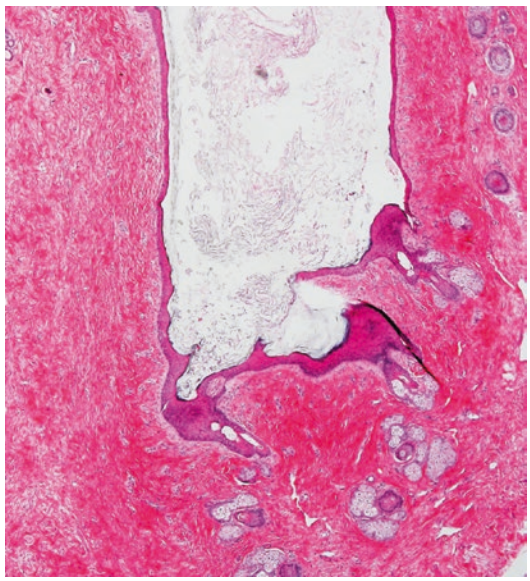


Fig. 7.34 Prepubertal teratoma. A dermoid cyst with prominent adnexal structures which distinguish it from epidermoid cysts. Note the organization of the elements recapitulating the normal skin

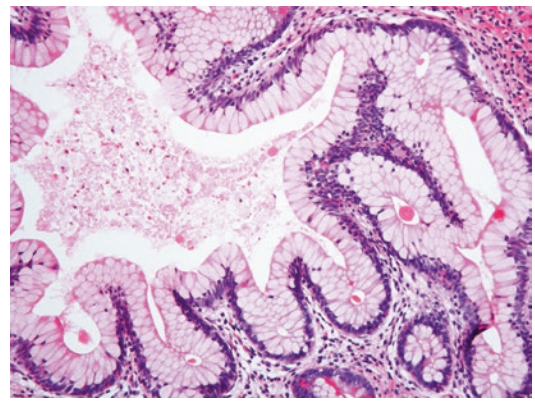


Fig. 7.35 Prepubertal teratoma. Glandular, enteric-type epithelium lacking discernible cytologic atypia. Compare with the cytologic atypia of postpubertal-type teratomas in Fig. 7.23

These mature benign teratomas need to be accurately distinguished from classic (type II) teratomas of the testis, as the former would not need additional therapy and the patient can be reassured of their benign nature. Also, if diagnosed preoperatively, they may be amenable to conservative surgical excision. Attention should be paid to: (1) The more cystic gross pathology of benign mature teratomas, with evidence of hair and sebum, similar to ovarian mature cystic teratoma. (2) The presence of a "polarity of growth," i.e., a structured architecture that recapitulates the microscopic anatomy of skin and sometimes bronchial or enteric elements. (3) The absence of cytologic atypia in the conforming elements, easily seen in classic type II teratomas, in both epithelial and mesenchymal elements (Figs. 7.23 and 7.35). (4) The absence of GCNIS or evidence of testicular dysgenesis in the background seminiferous tubules, with the presence of ongoing spermatogenesis. (5) The lack of association with any other form of GCT

As one can quickly surmise, however, these distinctions can still be challenging on a case-by-case basis and requires a thorough microscopic evaluation of the testicular tumor (Table 7.9). We agree with Zheng et al. [140] when they recommend a conservative approach to diagnosing this entity, since an overdiagnosis of classic (type II) teratoma is probably a more acceptable error than a missed diagnosis. In cases with less than definitive morphology, FISH studies for 12p abnormalities may be valuable in this differential diagnosis.

Another possible variant of mature benign testicular teratomas is *epidermoid cyst* (EpC). As its name implies, EpC is characterized by a keratinizing squamous epithelium-lined cavity, filled with keratinaceous debris (Fig. 7.36a). It is distinguished from dermoid cysts by the absence of adnexal structures and other teratomatous ele-

Table 7.9 Differential diagnosis of prepubertal- and postpubertal-type teratomas

Feature	Prepubertal-type teratoma	Postpubertal-type teratoma
Gross features	Cystic, hair, and keratinaceous debris common	Multicystic alternating with solid. Cysts contain a variety of mucinous, serous, or keratinaceous material. Hair unusual
Background parenchyma	Normal postpubertal, with active spermatogenesis. No significant atrophy beyond area adjacent to tumor	Postpubertal. Scarring, microlithiasis, extensive atrophy
Distribution of elements	Organoid distribution (elements recapitulate architecture of organ that it is trying to emulate – bronchus, skin, or gut)	Random
Teratomatous elements	Predominantly squamous epithelium and cutaneous adnexae, or respiratory-type epithelium, seromucinous glands, cartilage, and muscle recapitulating a bronchus. Intestinal epithelium uncommon	Random, heterogeneous elements Epithelium frequently nondescript. Intestinal epithelium common
Stroma	Normal or reactive. Lipogranulomatous reaction may be present	Primitive, nondescript. May be neoplastic in nature
Other types of GCT present	Usually none. Carcinoid tumors may be present. Rarely associated with prepubertal-type YST	Usually part of a mixed GCT, with EC, YST, seminoma, or choriocarcinoma. Less frequently pure
Cytologic atypia	Absent	Present in epithelial and mesenchymal elements
Mitotic activity	Absent to low	High
GCNIS	Absent	Present
12p abnormalities	Absent	Present

ments (Fig. 7.36b) [201–204]. A teratomatous origin of these cysts cannot be completely excluded, as they could represent a simplified version of a dermoid cyst. Favoring this possibility is the age of presentation, which overlaps with other germ cell tumors, the occasional occurrence of epidermoid cyst with carcinoid tumor [205], and the presence of morphologically indistinguishable cysts within mature teratomas. Their lack of association with GCNIS [206] and 12p abnormalities [207] and their uniformly benign behavior would suggest, similarly to dermoid cysts, a teratomatous process more akin to type I GCT. However, their occurrence in other organs and their occasional location immediately underneath the tunica albuginea and even in the paratesticular region [208] suggest a nonneoplastic origin, probably related to squamous metaplasia of the mesothelium, rete testis, or epididymal epithelium, for at least a subset of these tumors. Indeed, a metaplastic origin for their ovarian equivalent has been suggested [209].

Grossly, EpC are unilocular, well-circumscribed cystic cavity filled and distended by white, doughy laminated contents. Mean size has been reported as 2.0 cm [203]. Microscopically they consist of a fibrous wall internally lined by benign keratinizing squamous epithelium with a granular layer and, as stated, absent skin appendages. Granulomatous reaction to rupture and keratin debris may be seen. On occasion EpC can exhibit stromal osseocalcific metaplasia, which should not be confused with other teratomatous elements. As stated, some testicular carcinoid tumors may be associated with an adjacent EpC [205].

DC and EpC can present as paratesticular masses without connection to the testis proper [208]. This is especially true with EpC that was derived from the scrotal skin. The main issue is whether the DC/EpC resides in a location well beyond the paratesticular soft tissues and spermatic cord, such that a metastasis from a mature teratoma in a postpubertal patient has to be considered in the differential diagnosis.

7.6.3 Carcinoid Tumor

Carcinoid tumor in the testis can occur in one of the following settings:

1. As a pure primary carcinoid
2. As part of a prepubertal-type teratoma (including dermoid and epidermoid cysts)
3. As part postpubertal-type teratoma
4. As a metastatic lesion

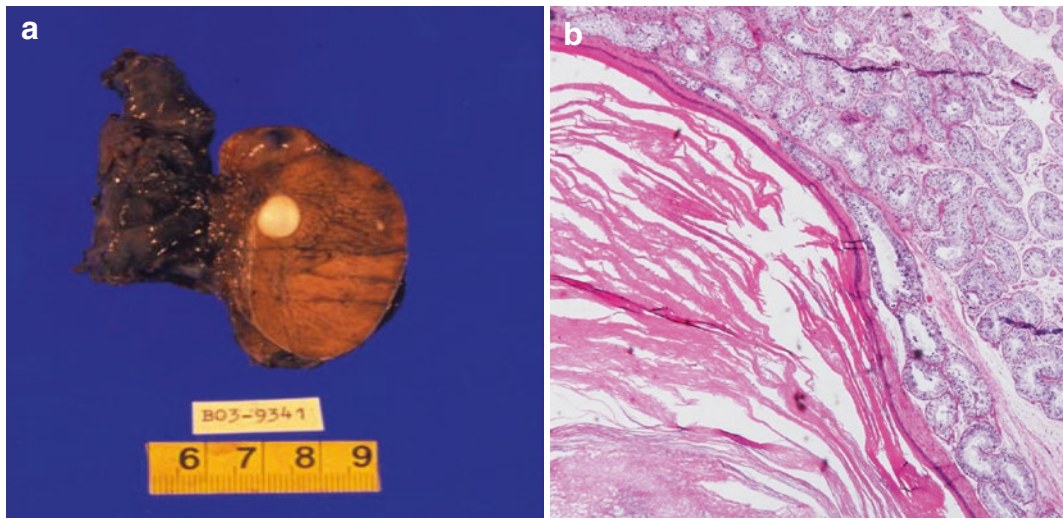


Fig. 7.36 (**a**, **b**) Epidermoid cyst. (**a**) An epidermoid cyst showing a well-circumscribed cystic cavity, filled with keratinaceous debris. (**b**) An epidermoid cyst showing a keratinizing squamous epithelium-lined cavity, filled with keratinaceous debris, adjacent to seminiferous tubules

In published series, pure primary carcinoid corresponds to approximately two-thirds of cases [205, 210–212]. In these cases, evidence to support a germ cell origin is scant, as there is lack of other teratomatous elements or GCNIS. A common origin with Leydig cell tumors has been suggested [213]. When associated teratomatous elements are identified, they are exclusively mature and frequently consist exclusively of an epidermoid or dermoid cyst. These suggest that when teratomatous in origin, carcinoid tumors are most often part of a prepubertal-type teratoma (type I GCT). However, it must be borne in mind that association with GCNIS and 12p abnormalities have been infrequently reported [214, 215]. Furthermore, in Wang et al.'s series, one case associated with a dermoid cyst had subsequent metastasis of YST and EC [205]. These data suggest that a subset of testicular carcinoids may arise in the setting of type II GCT.

Tumors tend to present as unilateral painless masses. Carcinoid syndrome is relatively rare and usually associated with large tumors or metastatic disease [205, 212, 214, 216, 217].

Pathologically, carcinoid tumors of the testis share similar features with those of other sites. Grossly, they are generally solid neoplasms when pure, and solid and cystic when associated with teratoma. They are usually well circumscribed. Mean size in one review of 57 published cases was 3.5 cm; however, pure tumors were larger than those associated with teratoma (4.2 vs. 1.5 cm, respectively) [212]. Histologically, the majority grow with a mixture of an insular or nested pattern, with trabecular pattern (Fig. 7.37). The nests or trabeculae are separated by fibrous septae. Follicular patterns can also be seen, as well as spindle cell differentiation. Cytologically the tumors show characteristic features for neuroendocrine neoplasms, with generally regular round nuclei with salt and pepper chromatin. Abundant eosinophilic cytoplasm is a characteristic. Mitotic activity is usually low. In a recent series, 4 of 29 cases were classified as "atypical carcinoids," based on mitotic activity in 3 cases, and the presence of necrosis in the fourth [205]. Cytologic atypia tends to be focal.

Tumors are consistently positive for one or more neuroendocrine markers, including chromogranin, synaptophysin, neuron-specific enolase, serotonin, gastrin, neurofilament proteins, substance P, and vasoactive intestinal polypeptide. Argentaffin pos-

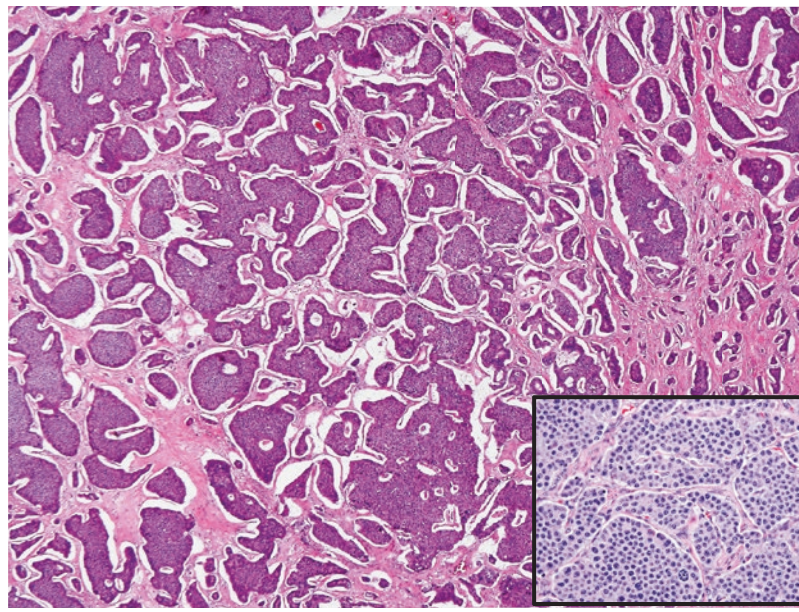


Fig. 7.37 Pure primary carcinoid. Carcinoid tumor with an insular architectural pattern is seen at low magnification. *Inset* shows neuroendocrine features characterized by round nuclei with salt and pepper chromatin, abundant eosinophilic cytoplasm, and occasional mitotic activity

itivity and argyrophillia are present in most cases [210–212, 218, 219].

The main differential diagnosis is metastatic carcinoid tumor, which is usually of gastrointestinal origin. While bilaterality favors metastases, bilateral primary tumors have been described [212]. Sertoli and Leydig cell tumors, adult-type granulosa cell tumors, and paraganglioma may be confused with carcinoid tumors. In cases of morphological ambiguity, a battery of immunostains including cytokeratins, α-inhibin, and neuroendocrine markers is useful in separating these entities. Sertoli and Leydig cell tumors may express neuroendocrine markers, but would be positive for α-inhibin in the vast majority of cases.

Carcinoid tumors tend to have a favorable outcome. Metastases have been reported, sometimes after a prolonged follow-up, and usually to regional lymph nodes, but also to the lung, bone, soft tissue, and liver [212]. Histologic findings cannot predict metastatic behavior, although it is likely that this is more frequent, if not restricted, to "atypical carcinoid" histology [205, 211].

7.6.4 Prepubertal-Type Yolk Sac Tumor

Contrary to prepubertal-type teratoma, prepubertal-type YST occurs almost exclusively in the pediatric testis and thus is reviewed in Chap. 10. However, a recent paper suggests its occurrence in the postpubertal testis, whether pure or in combination with prepubertal-type teratoma [220]. In its most usual setting, it comprises 75–80 % of testicular neoplasms in childhood with half to a third of cases taking place within the first and second year of life. Recent studies have challenged the reported prevalence of pediatric YST, suggesting a reporting bias may have underrepresented cases of teratoma and epidermoid cysts [221]. In contrast to postpubertal cases, prepubertal YST are not associated with GCNIS or isochromosome 12p gains, supporting a type I histogenesis. An association with cryptorchidism and white race is also lacking in prepubertal YST. Histologic features are similar to postpubertal YST, and these are extensively reviewed in Chaps. 6 and 10.

7.7 Tumors with Germ Cell and Sex Cord Stromal Elements

Gonadoblastoma (GB) is the only histologic type in this category in the current WHO classification. Previous editions contained a category of unclassified mixed germ cell-sex cord-stromal tumors, which, unlike gonadoblastomas, were reported in genotypically and phenotypically normal males [222–224]. However, recent literature has demonstrated the lack of staining for PLAP and CD117 in the germ cells, contrary to what would be expected in GCNIS and seminoma, suggesting that these tumors are comprised primarily of neoplastic sex cord-stromal elements, with entrapped nonneoplastic germ cells [177, 225]. Thus, the current WHO classification no longer includes this category. Rare reports of tumors with an architectural pattern of two distinct neoplasms, as would be seen in a collision tumor, have been reported, and it is unclear if these truly represent mixed germ cell-sex cord-stromal tumors [225, 226].

7.7.1 Gonadoblastoma

7.7.1.1 General Concepts

Gonadoblastoma (GB) is a tumor of young patients with gonadal dysgenesis and other DSD, characterized by the presence of neoplastic germ cell and sex cord-stromal elements [227]. To better understand GB, it is important to appreciate some basic concepts of gonadal dysgenesis (GD).

GD is the improper development of the gonad, which, importantly, includes both germ cell and sex cord components [228]. Full understanding of GD is impaired by a complex pathogenesis involving mutations in multiple genes that can manifest in a variety of clinical pictures [229–231] [232–240]. Following the developmental migration of the gonad, a dysgenetic testis can present within the abdomen, inguinal canal, or scrotum. As might be anticipated, a dysgenetic testis will be smaller than normal and is often less white to the naked eye due to the lack of a thick, fibrous tunic. Some represent "streak" gonads in which identification as testis or ovary may only be inferred [241].

Within the dysgenetic testis, there are a plethora of microscopic findings. These include tubules, typically closely positioned to one another and uniformly rounded in appearance, comprised mainly of immature Sertoli cells with varying numbers of germ cells, which often resemble embryonic germ cells (spermatogonia) [39, 241, 242]. Between the tubules reside Leydig cells with scant cytoplasm.

GB might be expected to present in the very young. While it is true that the majority present prior to the age of 20 years, there is as rather wide range of ages from 1 to almost 40 years with a case report described in a 46XY fetus [227, 243]. The most common occurrence of GB is in phenotypical females, who, however, almost invariably have a Y chromosome. GB occurrence in 45X0 Turner syndrome likely represents undetected mosaicisms [244]. Twenty percent of GB occurs in phenotypic males. An infantile uterus is typically present as are fallopian tubes; if bilateral tubes are identified, the patient is likely a phenotypic female, while a male phenotype is more likely if unilateral [227]. Phenotypic male patients commonly have other abnormalities of the genitourinary system, such as cryptorchidism, hypospadias, and gynecomastia.

For GB to develop, the presence of a Y chromosome is necessary, in particular the GBY region, which harbors the *TSPY* gene [245, 246]. Mutations of the sex-determining gene Y (SRY) are also associated with high incidence of GB [244].

When present exclusively in the gonad and treated appropriately, GB has an excellent prognosis. However, at the time of diagnosis, about 50 % have progressed to an invasive germinoma (seminoma or dysgerminoma) and 8 % to other types of GCT [227]. Due to this, GB is considered a precursor for GCT in the setting of GD, specifically in the prepubertal patient.

7.7.1.2 Macroscopy

In the vast majority of reported GB, the tumor develops in an "undeclared" gonad with about one in five developing in either a testis or a streak gonad [227]. The reason for this is due to effacement of the gonad (streak or otherwise) by tumor. If the tumor is pure GB, it displays a tan-yellow or gray and firm appearance that can have a gritty cut surface due to the presence of calcifications. If it is admixed with other GCT, it will exhibit other findings that reflect the type of GCT present (usually seminoma/germinoma) [228].

7.7.1.3 Microscopy

The typical histologic appearance of GB makes the pathologist quickly recognize that the neoplasm is quite unusual, but if the clinical presentation is well understood, the diagnosis can quickly distil into either pure GB or a mix of GB with a more common type of GCT. GB is characterized by round nests of both germ cells and sex cord cells. The germ cells of GB resemble seminoma or GCNIS, but may include a population of less mature looking cells, resembling spermatogonia. They are intermixed with sex cord cells, which resemble Sertoli cells, and are arranged in three patterns, which are usually admixed. In the coronal pattern, the sex cord cells are mostly at the periphery of the nests; in the follicular pattern, they surround individual or small groups of germ cell; and in the Call-Exner-like pattern, they surround globoid basement membrane deposits (Fig. 7.38). The nests are arranged in relatively large lobules surrounded by a fibroinflammatory stroma, peppered with Leydig cells and calcifications, some of which have replaced "regressed" or "burned-out" lobules of GB [228]. The morphology of the invasive GCT, if present, is the usual for each type of invasive GCT. An invasive seminoma/dysgerminoma may be quite subtle and easily overlooked.

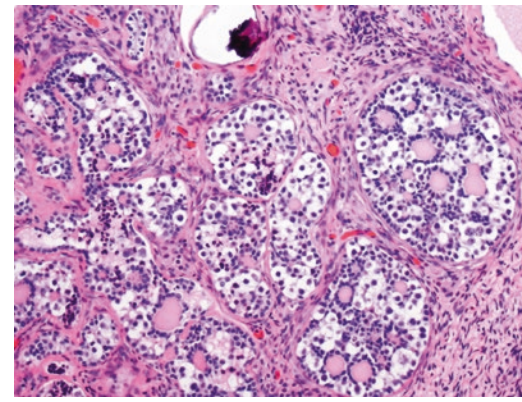


Fig. 7.38 Gonadoblastoma. Nests of germ cells resembling seminoma or GCNIS are surrounded by a fibrous stroma. Focal calcifications likely represent "regressed" lobules of gonadoblastoma. The germ cells surround globoid basement membrane deposits, reminiscent of Call-Exner bodies (Image courtesy of Gary Keeney, MD, Mayo Clinic, Rochester, MN)

7.7.1.4 Immunohistochemistry

Germ cells within GB that resemble germinoma or GCNIS will react with PLAP, OCT4, podoplanin, and CD117 [247]. The smaller ones resembling spermatogonia are usually positive for TSPY and negative for OCT4, while another subpopulation may have an inverse immunophenotype [246]. The sex cord cells are positive for inhibin, vimentin, and WT1 [248].

7.7.1.5 Differential Diagnosis

Sertoli cell nodules resemble GB, particularly if colonized by GCNIS. While they frequently occur in cryptorchidic testes, these are usually nondysgenetic and occur in phenotypically normal males. Sex cord-stromal tumors with entrapped germ cells are also in the differential diagnosis, particularly granulosa cell tumor, whose Call-Exner bodies may be mistaken for GB.

7.7.1.6 Prognosis

Untreated GB carries a high risk of progression to an invasive GCT. In the seminal work by Scully [227], the majority (almost 60 %) of GB were also associated with germinoma with a smattering of EC, YST, and teratoma. Thus, the postulation is that all GB would likely progress to invasive tumors if not removed. As such, if identified on biopsy, gonadectomy may play an important role in the management of patients with possible gonadal dysgenesis. Due to the relatively young age at presentation, and even when mixed with more typical GCT elements, outcomes for gonadoblastomas are excellent [249, 250].

7.8 Germ Cell Tumor Regression

The phenomenon of GCT regression, was initially reported in 1961 by Azzopardi et al., in a series of 17 patients that presented with metastatic germ cell tumors, where sampling of the testicular tissue revealed either the presence of minute foci (<5 mm) of viable neoplasm or complete absence thereof [251]. Subsequent studies by the same group laid the groundwork for defining the histopathologic features of this phenomenon, and its incidence was independently estimated from a series of 61 autopsy cases to comprise about 10 % of cases with metastatic GCT [252, 253].

At present, identification of GCT regression has important clinical implications. Following orchiectomy for metastatic disease, if residual disease or diagnostic evidence of GCT regression is not identified, orchiectomy for presumed contralateral disease must be considered, to prevent the development of recurrences. It may also influence the selection of therapeutic modalities. For instance, in patients with a seminomatous tumor component with a regressed non-seminomatous GCT, the use of radiotherapy alone may be suboptimal [254].

Commonly identified features include the presence of well- to poorly defined scars in a background of testicular atrophy, where the seminiferous tubules are often hyalinized or show a Sertoli cell-only pattern (Fig. 7.39a–e). Scarring by itself is relatively nonspecific as it can be seen secondary to vascular lesions, trauma, or infection. The most specific feature, in this context, is the presence of a residual GCNIS component, which is only seen in approximately half the cases [178, 254–256]. Other features that have been reported include microlithiasis, persistent neovascularization, Leydig cell hyperplasia, and the presence of lymphocytic infiltrates. Microlithiasis must be distinguished from the presence of coarse intratubular calcifications, which is thought to correlate with regressed EC. It is not entirely clear if Leydig cell hyperplasia is a true hyperplasia or a misleading visual impression as a consequence of the atrophy of the surrounding testicular parenchyma. Finally, the presence of lymphocytic infiltrates have been hypothesized to contribute to immune-mediated tumor regression, based on studies that correlate the presence of lymphocytic infiltrates with outcomes in seminomas which were managed with surveillance [254, 257].

Though it appears that seminomas have a greater tendency to undergo spontaneous regression than other GCT, this may be more of a reflection of their higher overall incidence among GCT. Recent studies indicate that CC is not prone to regression [254]. This, on the other hand, may reflect a selection bias as most of these patients likely present with advanced, disseminated disease and receive chemotherapy prior to orchiectomy making it difficult

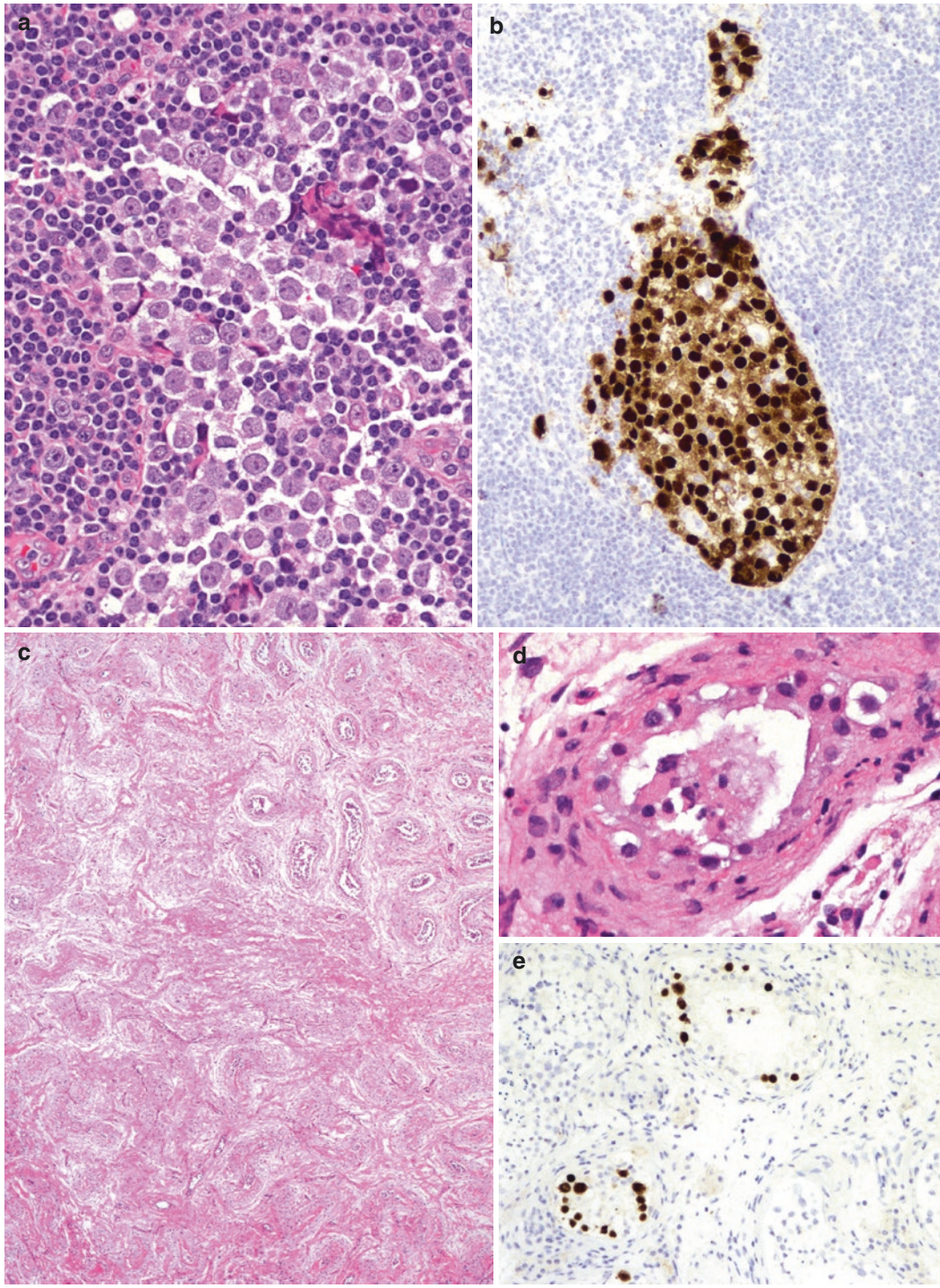


Fig. 7.39 (**a**–**e**) Germ cell tumor regression. Cervical lymph node with a metastatic seminoma (**a**), which showed strong nuclear expression of OCT4 (**b**). Orchiectomy revealed scarring and a background of testicular atrophy (**c**), with hyalinized seminiferous tubules. Focal GCNIS was identified (**d**), which was confirmed by positive OCT4 expression (**e**)

to differentiate therapy-induced regression from spontaneous regression. Finally, no GCT subtype, including teratoma, shows resistance to regression based on a comparison of reported overall incidences and incidences of regression.

7.9 Clinical Presentation

The vast majority of testicular neoplasms present as painless, self-detected masses, while a minority presents with scrotal pain [258]. Aggressive variants of GCT, such as CC, may present with symptoms related to metastatic disease [157], such as hemoptysis or neurological manifestations, before a testicular mass is detected. Some tumors may be detected incidentally, during workup for other symptoms, such as infertility [258].

Additionally, as stated before, a subset of tumors may present with endocrine manifestations, the most common being gynecomastia [100, 101, 259]. This symptom is usually associated with high serum hCG levels, and thus it is more common in tumors containing trophoblastic components, particularly CC, but also other forms containing syncytiotrophoblastic giant cells. Rarely, high β-hCG levels may produce thyrotoxicosis due to TSH-like activity of the hCG [153, 154, 260, 261]. Carcinoid syndrome is unusual in cases of testicular carcinoid [205, 212].

A variety of neurological paraneoplastic syndromes have been described in patients with testicular GCT, the most common one being Ma2 antibody-mediated limbic encephalitis [262–266]. Patients develop a constellation of symptoms that include short-term memory disturbance, epileptic seizures, acute confusional syndrome, personality change, hallucinations, depression, and cognition disturbances. Others present with symptoms more oriented to brainstem, cerebellar, or peripheral nerve dysfunction. The process is believed to be immune-mediated secondary to cytotoxic T cells attacking the neurons. Patients present with elevated levels of Ma antibodies directed against PNMA-2 proteins (also referred to as anti-Ta or anti-Ma2), which play an important role in apoptosis [262]. Neurological symptoms precede the detection of the tumor in the majority of patients, and about a third of them respond to appropriate treatment of the tumor [264]. Frequently, tumors associated with anti-Ma2 antibodies are small, or have undergone regression, as it is believe that the antibodies are a reflection of an effective immune response to the tumor [265–267]. It is still debated whether blind orchiectomy should be performed in symptomatic patients with no clinically documented tumor, as frequently an occult neoplasm may be found [264–266]. Before orchiectomy, clinical exclusion of an extragonadal tumor needs to be performed [268].

Other reported paraneoplastic manifestations of testicular GCT include dermatomyositis [269], polycythemia [270], hypercalcemia [271], membranous glomerulonephritis [272], and Raynaud's phenomenon [273].

7.10 Staging

The American Joint Committee on Cancer and the International Union Against Cancer staging for testicular neoplasms, widely known as the TNM staging system, is the most accepted staging system [274]. T categories are defined by the presence of the following parameters: the presence of invasive vs. in situ tumor, extent of invasive disease (whether tumor invades the spermatic cord, tunica vaginalis, or scrotum), and presence of lymphovascular invasion. Lymphovascular invasion has been extensively demonstrated as a significant prognostic factor, particularly in nonseminomatous GCT (Fig. 7.40) [127, 275–277].

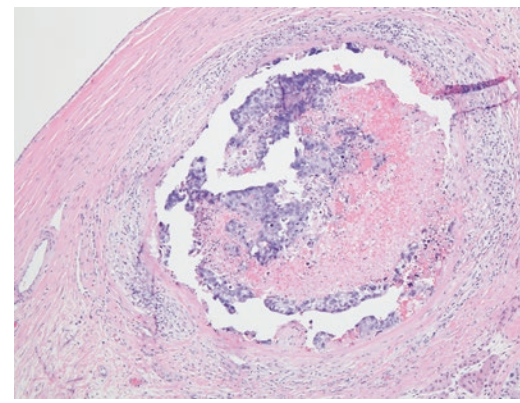


Fig. 7.40 Staging. pT2 disease, characterized by lymphovascular invasion by embryonal carcinoma

In pure seminomas, the association of lymphovascular invasion with relapse is less clear [122, 123, 126, 278] N categories are based on the number of nodes involved and size of metastatic deposits, and M categories depend on whether there is metastatic deposits and, if so, if these involve nonregional nodes, lung, or any other site. The TNM staging for testicular tumors is unique among other organs in that it incorporates serologic marker levels, establishing an additional category labeled S. The S category may thus place two tumors with identical T, N, or M categories into different stage groupings (Table 7.10).

Several shortcomings of the current TNM have been identified and are likely to be

Table 7.10 AJCC/ICCC TNM staging system (7th edition) for testicular GCT

Primary tumor (T):	
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor (regressed GCT)
pTis	Germ cell neoplasia in situ
pT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion. Tumor may invade into the tunica albuginea, but not tunica vaginalis
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea into the tunica vaginalis
pT3	Tumor invades the spermatic cord
pT4	Tumor invades the scrotum
Regional lymph nodes (N)	
Clinical	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm, but not more than 5 cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2 cm, but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
Pathologic	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and less than or equal to five nodes positive, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm, but not more than 5 cm in greatest dimension; or more than five nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
Serum tumor markers (S)	
SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH <1.5x normal *and* hCG <5000 mlu/ml *and* AFP <1000 ng/ml
S2	LDH 1.5 -10x normal *or* hCG 5000–50,000 mlu/ml *or* AFP 1000–10,000 ng/ml
S3	LDH >10x normal *or* hCG >50,000 ml/ml *or* AFP >10,000 ng/ml
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional nodal or pulmonary metastasis
M1b	Distant metastasis other than to nonregional lymph nodes and lung

Table 7.10 (continued)

AJCC/ICCC anatomic stage/prognostic groups

Group	T	N	M	S
Stage 0	pTis	N0	M0	S0
Stage I	pT1–4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2–4	N0	M0	S0
Stage IS	Any pT	N0	M0	S1–3[a]
Stage II	Any pT	N1–3	M0	SX
Stage IIA	Any pT	N1	M0	S0–1
Stage IIB	Any pT	N2	M0	S0–1
Stage IIC	Any pT	N3	M0	S0–1
Stage III	Any pT	Any N	M1	SX
Stage IIIA	Any pT	Any N	M1a	S0–1
Stage IIIB	Any pT	N1–3	M0	S2
	Any pT	Any N	M1a	S2
Stage IIIC	Any pT	N1–3	M0	S3
	Any pT	Any N	M1a	S3
	Any pT	Any N	M1b	Any S

[a]Measured post-orchiectomy

addressed in future updates of the system[1]. The size of the tumor is not currently included as a staging parameter. However, a review determined that seminomas larger than 4 cm were twice more likely to recur than smaller tumors [123]. Similarly, von der Maase et al. found a significantly higher relapse 4-year relapse rate in patients with tumors larger than 6 cm [279]. The rete testis invasion has also been associated with higher odds of recurrence (Fig. 7.41) [123, 277, 278]. In the same study by Warde et al., patients with tumor invading into the rete testis had a 1.7 higher risk of relapse. Other studies have not found significant differences in survival between tumors with and without the rete testis involvement [126, 280]. Attention should be paid to not equate pagetoid spread of GCNIS to the rete testis epithelium with direct invasion of the rete testis by invasive tumor (Figs. 7.2 and 7.41) [281]. Similarly, there is controversy regarding the adequate stage for a tumor that involves the hilar fat of the testis, but not the spermatic cord. Currently, this tumor should be staged as pT1 or pT2 (depending on the absence or presence of lymphovascular invasion). However, it clearly represents extratesticular extension of the tumor and likely a higher risk of recurrence [281, 282]. Other criticisms to the system include the disproportionate weight conferred to the invasion of the tunica vaginalis and the scrotum, which are relatively rare phenomena [282], and the lack of differentiation of the pattern of involvement of the spermatic cord, which may be involved by direct extension (Fig. 7.42) or lymphovascular invasion [281]. Given the different impact that some features have on seminoma and non-seminomatous germ cell tumors, it may be reasonable to question if the same staging system should be used for both types of tumors.

[1] Since the submission of this manuscript the 8th edition of the AJCC Cancer Staging Manual has been published, addressing some of the issues mentioned in this section. For more information please refer to AJCC Cancer Staging Manual, 8th edition. Amin M et al (ed). Springer 2017.

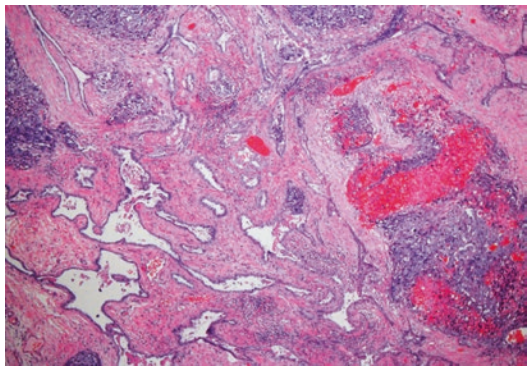


Fig. 7.41 Staging. Embryonal carcinoma demonstrating infiltration into the rete testis

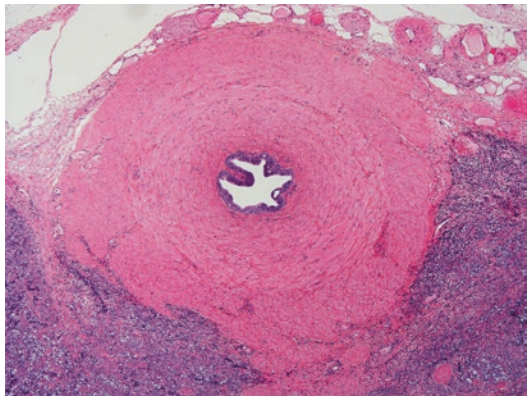


Fig. 7.42 Staging. Seminoma involving the spermatic cord represents pT3 disease

7.11 Handling of Orchiectomy Specimens

Radical orchiectomy specimens usually include the distal segment of the spermatic cord, with attached soft tissue, and the testis and epididymis covered by the parietal layer of the tunica vaginalis. Preferably, orchiectomy specimens should be inspected and at least initially handled in their fresh state. Measurements of the spermatic cord should be obtained. Attention should be paid to the external surface of the tunica vaginalis, to check for tumor invasion. Before opening the tunica vaginalis, the proximal end of the spermatic cord should be transversely sectioned and placed in a separate cassette, to avoid contamination with tumor cells once the tumor is cut [283]. The remaining spermatic cord should be serially sectioned, and any area suspicious for tumor should be submitted. If no gross abnormality is detected, representative sections of the mid and distal portion of the cord should be taken and separately submitted. The parietal layer should then be incised, and the inner lining of the visceral and parietal layers of the tunica vaginalis should be inspected. Any fluid should be noted and described, and measured and collected when appropriate. Attention should be paid to any nodules in the tunica, or evidence of tumor invasion. After recording the three measurements of the testis, this one should be bivalved by longitudinally sectioning from the outer surface toward the hilum. Any tumor should be measured and multifocality or extension to the hilum or rete testis, epididymis, tunica albuginea, or extratesticular soft tissues documented. Larger tumors may require parallel sections to assess for these changes. The cut surface of the tumor should be described, including features such as circumscription and lobulation and the presence of hemorrhage, necrosis, fleshy solid surfaces, cysts and their contents, or cartilaginous material. Sections for histologic examination should include all grossly different areas, including all hemorrhagic and necrotic ones. Because of the importance of finding even a small non-seminomatous component, tumors with the gross appearance of seminoma should be sampled extensively. While small tumors can be easily submitted entirely, larger tumors should be sampled at a minimum of one section per centimeter, usually erring on the side of generous sampling [281]. Additional sections should include those of non-neoplastic parenchyma, including close to and away from the tumor, and the relationship of the tumor with the rete testis, tunica albuginea, and extratesticular structures should be demonstrated in representative sections.

7.12 Pathology of Retroperitoneal Lymph Node Dissection

Retroperitoneal lymph node dissection (RPLND) is the most common surgical procedure for staging of testicular GCT. The rationale behind this is the

predictable pattern of spread of testicular tumors, following the lymphatic drainage of the testis. This pattern is identical to all forms of GCT, with the possible exception of CC, which has a propensity to disseminate hematogenously. The primary "landing site" for right testicular tumors is the interaortocaval lymph nodes, followed by the precaval and paracaval nodes, while left testicular tumors tend to drain first into the preaortic and para-aortic lymph nodes, followed by the interaortocaval nodes. Contralateral spread is common in right testicular tumors, while rare in left-sided tumors, except in the setting of bulky disease [284, 285].

In general, RPLND is performed in one of the following settings [286]:

1. Primary RPLND in patients with clinical stage 1 or clinical stage 2 disease non-seminomatous GCT
2. Post-chemotherapy RPLND (PC-RPLND) in patients with a clinical stage 2 or higher non-seminomatous GCT
3. Post-chemotherapy RPLND in patients with seminoma with residual masses
4. Salvage RPLND in the setting of recurrences after any modality of management of non-seminomatous GCT

The above settings are derived from the different management approaches to GCT at different stages, which are extensively discussed in Chap. 5.

7.12.1 Pathologic Findings in Primary RPLND Specimens

The surgical pathologist plays a significant role in defining the staging and management of GCT. Approximately 30 % of clinical stage I testicular GCT will have metastatic disease detected after histopathologic examination of an RPLND specimen [287, 288], or upon recurrence at this site during surveillance [276, 289, 290]. Because of this, management approach of clinical stage I non-seminomatous GCT is still controversial, with primary RPLND being one of the three options available, the other two being active surveillance and one adjuvant cycle of BEP chemotherapy. Advantages of the adjuvant RPLND approach include an accurate staging of the retroperitoneum, marked reduction in the number of cycles and amount of chemotherapy needed long term, the use of chemotherapy exclusively on patients with documented metastatic disease, decrease need of imaging studies for follow-up, and removal of teratoma elements from the retroperitoneum. Disadvantages include exposure to surgery for a large proportion of patients that will not have metastatic disease, risk of retrograde ejaculation and other less common morbidities, need of expert surgeons, and slightly higher levels of relapse compared to BEP (8 % vs. 3 %) [291].

In a recent series [292], the most common histology found in the setting of positive primary RPLND was EC. Out of 183 patients with pathologically positive RPLND, 160 contained this element, and in 99 of those EC was the only element found. YST was present in 50 cases, while seminoma was present in 11 (8 of which had a pure seminoma component). Teratoma was present in 44 cases, but was pure only in 12.

Tumor histologic type does not appear to predict which patients are going to relapse [292, 293]. Other histologic findings, such as extra nodal extension, have been suggested as predictive of higher rates of relapse by some series [294, 295], but not by others [292, 293]. While number of lymph nodes involved and metastatic tumor size define stage and thus impact prognosis and therapy, within the category of pN1 a number or ratio of positive lymph nodes do not appear to confer significant prognostic information [296].

7.12.2 Pathologic Findings in Post-chemotherapy RPLND Specimens

RPLND may be performed in patients that have had previous chemotherapy, usually patients with high-stage clinical disease (N2 or N3). Most RPLND are performed after two cycles of chemotherapy, although it is not uncommon to have it done after three or four cycles [297]. In the post-chemotherapy setting, the histologic findings are not only useful in the staging of the disease but also provide an idea of the response of the tumor to therapy (Table 7.11). Therapy

response and volume of residual disease may impact incidence of relapse in these patients.

Three basic histologic patterns may be seen in PC-RPLND specimens:

1. Evidence of tumor response: Usually in the form of necrosis, but also as granulomatous inflammation or fibrosis (Fig. 7.43). However, recent data revealing similar molecular changes between fibrosis and adjacent mature teratoma suggests that fibrosis may actually correspond to residual teratoma and thus should not be considered evidence of tumor response [298].
2. Residual GCT, non-teratomatous types: These include the presence of histologically viable tumor, with EC, seminoma, YST, or CC morphology (Fig. 7.44).
3. Residual teratomatous elements, histologically viable (Fig. 7.45). The rationale for separating teratomatous and non-teratomatous elements resides in the fact that teratoma response to chemotherapy is not expected, and thus, the presence of teratoma does not imply ineffective or insufficient chemotherapy. Surgical removal of teratoma elements is required, as teratomas may grow and impinge on vital structures ("growing teratoma syndrome") [145, 146] or may undergo development of somatic malignancy [135]. The presence of teratoma and YST in the primary tumor is a predictor of teratoma in PC-RPLND specimen [168].

Table 7.11 Pathologic findings in post-chemotherapy RPLND specimens

Evidence of tumor regression:
Fibrosis
Necrosis
Granulomatous inflammation
Residual viable non-teratomatous tumor:
Embryonal carcinoma
Yolk sac tumor
Seminoma
Choriocarcinoma
Mixed GCT
Residual teratoma
Residual special histologies
Somatic-type malignancy
Rhabdomyomatous differentiated tumor
Cystic trophoblastic tumor

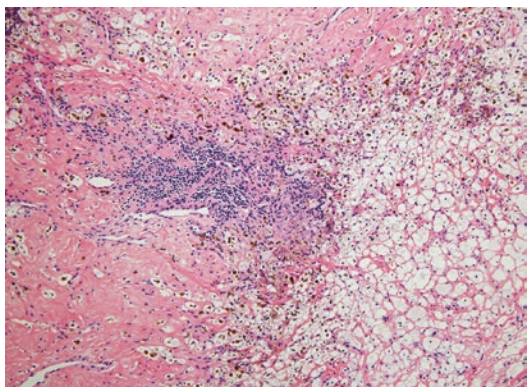


Fig. 7.43 Retroperitoneal lymph node dissection (RPLND). RPLND shows a lymph node with extensive treatment effect characterized by the presence of fibrosis, diffuse histiocytic infiltrates, and focal hemosiderin deposition

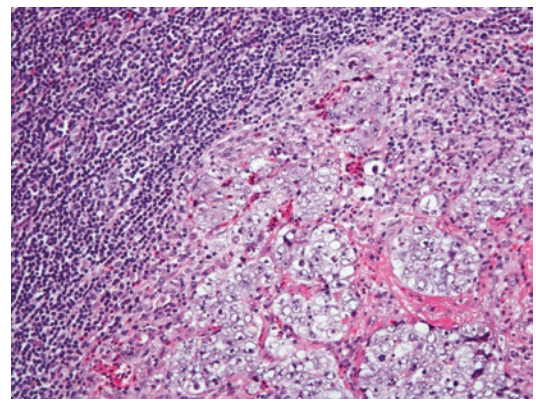


Fig. 7.44 Retroperitoneal lymph node dissection (RPLND). RPLND shows a lymph node with residual embryonal carcinoma

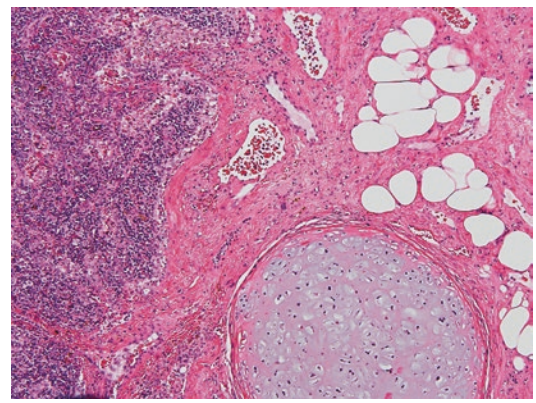


Fig. 7.45 Retroperitoneal lymph node dissection (RPLND). RPLND shows a lymph node with only histologically viable teratoma within a lymph node

In a series from Indiana University of 71 patients that underwent PC-RPLND, fibrosis was found in 51 % of cases, teratoma-only was found in 21 % of cases, and residual viable non-teratoma GCT in 28 % of cases. A 5-year survival for both the fibrosis and teratoma categories was 87 %, compared to 47 % 5-year survival for those with residual viable non-teratoma GCT [297]. In another series of PC-RPLND, this time in patients with pure seminoma associated with elevated levels of AFP, Peterson et al. found viable non-teratoma GCT in 37.5 %, teratoma only in 12 (30 %), and necrosis/fibrosis only in 13 (32.5 %). The histologies of the cases with residual viable non-teratoma GCT included seminoma, EC, YST, sarcoma, and mixed GCT [63].

Post-chemotherapy specimens also may harbor unusual GCT histologies, which the surgical pathologist needs to recognize for appropriate diagnosis and management. These include histologic entities whose development is likely induced or at least potentiated by chemotherapy:

1. *Somatic-type malignancy*: While the development of somatic-type malignancy is not a phenomenon exclusively found in post-chemotherapy specimens, it is more commonly seen in this setting [135]. The most common histologies are peripheral neuroectodermal tumors, rhabdomyosarcoma and other sarcomas, and adenocarcinomas; however, a wide spectrum of somatic histologic types has been described. Development of somatic-type malignancy confers a poor prognosis, particularly in the post-chemotherapy setting. A thorough review of this phenomenon is presented in Chap. 12.
2. *Rhabdomyomatous differentiated tumor*: These unusual tumors, which are explained in larger detailed in Chap. 12, correspond to aggregates of benign terminally differentiated rhabdomyoblasts, in the setting of teratomatous elements, and found in post-chemotherapy RPLND specimens [299]. Its recognition is important to differentiate it from rhabdomyosarcoma arising in teratoma as a somatic-type malignancy.
3. *Cystic trophoblastic tumor (CTT)*: These tumors are characterized by cysts of variable sizes, lined by cells with abundant cytoplasm, smudged nuclei, occasional multinucleation, and cytoplasmic lacunae (Fig. 7.46) [300] (see also Table 7.7). None to minimal mitotic activity is usually seen. The cells are arranged in one or several layers of flattened epithelium, with occasional tufting or micropapillae. Fibrinous material is present in the lumen of the cysts. Immunohistochemical studies show focal β-hCG reactivity. CTT is usually associated only with teratoma elements. Follow-up reveals a relapse rate comparable to that of RPLND specimens with only teratoma elements, in contrast with residual CC, which is associated with high relapse rate and requires additional chemotherapy. Serum β-hCG is only mildly elevated in a few cases. It is thought that CTT represents another form of cytodifferentiation induced by chemotherapy, in this case from original trophoblastic elements. Accurate recognition of this type of tumor is important to avoid overtreatment given to PC-RPLND specimens that show residual CC. Attention should be paid to the lack of biphasic pattern characteristic of CC and the lack of mitotic activity, necrosis, and hemorrhagic background.

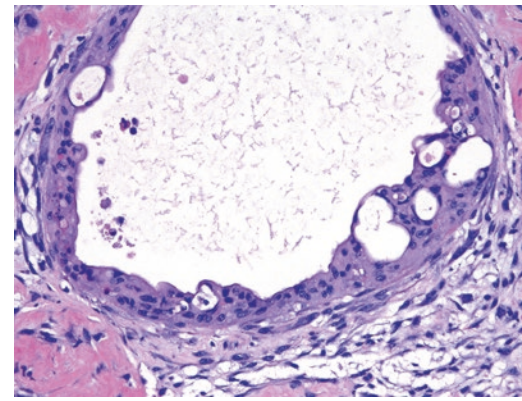


Fig. 7.46 Cystic trophoblastic tumor (CTT). Cystic lesion lined by several layers of flattened epithelium with scant fibrinous material in the lumen. Individual cells have abundant cytoplasm, lack mitotic activity, and show occasional cytoplasmic lacunae (Image courtesy of Gladell Paner, MD, University of Chicago, Chicago, IL)

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