# Somatic-Type Malignancy in Germ Cell Tumors

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## 12.1 Introduction

The presence of somatic-type malignancy (STM) within a preexisting germ cell tumor (GCT) is defined as a GCT that "develops a distinct secondary component that resembles a somatic-type malignant neoplasm, as seen in other organs and tissues (e.g., sarcomas and carcinomas)" [1]. In the literature it is also referred to as "teratoma with secondary malignant component," [2] "non-germ cell malignancy," or more recently and appropriately "STM arising from GCT" (STM-GCT) [3]. The term "teratoma with malignant transformation" is discouraged, particularly in the setting of testicular GCT, as it would imply a benign nature of the background teratoma. The phenomenon of STM-GCT impacts both the prognosis and the management of patients with germ cell neoplasms, and its recognition is of utmost importance.

STM has been described in a wide spectrum of GCT. Its occurrence in benign mature cystic teratomas of the ovary (type IV GCT of the Oosterhuis and Looijenga classification [4]) has been long recognized. It is also a known complication of mixed GCT (type II GCT) of the testis, where it is most frequently associated with a postpubertal-type teratoma component. The development of a high-grade sarcoma is a well-known albeit infrequent complication of spermatocytic tumor (type III GCT). Finally, its occurrence in type I (prepubertal type teratomas) has been reported, and it may be actually more common than thought, as the recognition of this type of GCT in postpubertal patients is rather recent. STM may occur at the primary site, at metastatic sites, or at both sites, and it has been reported both in gonadal and extragonadal GCT. The frequency, pathogenesis, clinical presentation, and prognostic and therapeutic implications of STM-GCT vary depending on the abovementioned scenarios (Table 12.1).

## 12.2 Pathogenesis

The pathogenesis of STM is a matter of debate. The most accepted theory is that STM arises from corresponding somatic elements in teratomas, given that in this GCT type, somatic differentiation has already occurred, independently of whether it is originally benign (as in ovarian or prepubertal testicular teratomas) or already

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**Table 12.1** Comparison of somatic-type malignancies arising in different settings across the spectrum of germ cell neoplasia

| | Type I GCT | Type II GCT | Type III GCT | Type IV GCT |
|---|---|---|---|---|
| Frequency | Rare | Uncommon | Rare | Common |
| Location | Testis<br>Ovary<br>Extragonadal | Testis<br>Ovary<br>Extragonadal | Testis | Ovary |
| Preexisting GCT | Prepubertal type teratoma<br>Yolk sac tumor | Postpubertal type teratoma<br>Seminoma/dysgerminoma/germinoma<br>Mixed GCT | Spermatocytic tumor | Mature cystic teratoma<br>Immature teratoma |
| Most frequent STM histologies | Adenocarcinoma<br>Sarcomas | Rhabdomyosarcoma and other sarcomas<br>PNET<br>Adenocarcinoma | Undifferentiated sarcoma<br>Rhabdomyosarcoma | Squamous cell carcinoma (overwhelming majority)<br>Adenocarcinoma<br>Sarcomas<br>Melanoma |
| Molecular signature | Unknown | 12p abnormalities | Unknown | Isodisomy (homozygosity) |

*GCT* germ cell tumor, *STM* somatic-type malignancy, *PNET* primitive neuroectodermal tumor

malignant (as in postpubertal testicular teratomas) [1, 5]. Coexistence of teratoma and STM in the majority of reported cases supports this hypothesis. Anomalies of chromosome 12, notably duplication of the short arm of chromosome 12 (isochromosome 12p), a hallmark of invasive type II GCT, have been documented in somatic malignancies arising from teratoma, either at the primary site or metastatic location (Fig. 12.1) [6–8], and in gonadal and extragonadal tumors [9]. This finding is also well documented in hematologic malignancies derived from mediastinal GCT [10–14]. Similarly, the classical finding of homozygosity (isodisomy) of mature cystic ovarian teratomas has been demonstrated in somatic adenocarcinomas arising within them [15]. This evidence supports the notion of a metachronous origin of STM from an already neoplastic germ cell. The somatic malignancy thus likely arises from the activation of oncogenes that normally play a role in the development of these tumors at their normal sites. For example, rearrangements of chromosome 2, region 2q34–37, present in rhabdomyosarcomas [16], have been also identified in the rhabdomyosarcoma component of STM [17]. Similarly, genetic alterations in 11q24, which have been frequently reported in Ewing's sarcoma and PNET, were found in a case of PNET arising from a GCT [17]. Chromosome 5 abnormalities such as del(5q), classically associated with hematologic malignancies, have been identified in leukemias originating from GCT [11, 17]. Finally, loss of heterozygosity reported at 11p13 locus in Wilms' tumor has been identified in a nephroblastoma arising from testicular GCT [18]. Thus, it appears that the molecular mechanisms associated with neoplastic progression of usual somatic malignancies are also common in those arising from germ cell neoplasia. It is not clear whether the triggers of these mechanisms are the same ones as in regular sites or whether they differ among the different cells of origin and locations of teratomas. Senescence of tissues may explain the development of STM in certain cases, particularly those associated with benign GCT. STM in benign cystic teratomas of the ovary, for example, is more often diagnosed in the fifth to sixth decade of life [19], which contrasts with the usual presentations of these tumors in adolescence and early adulthood, suggesting that a certain elapsing time is necessary for the activation of these oncogenetic mechanisms.

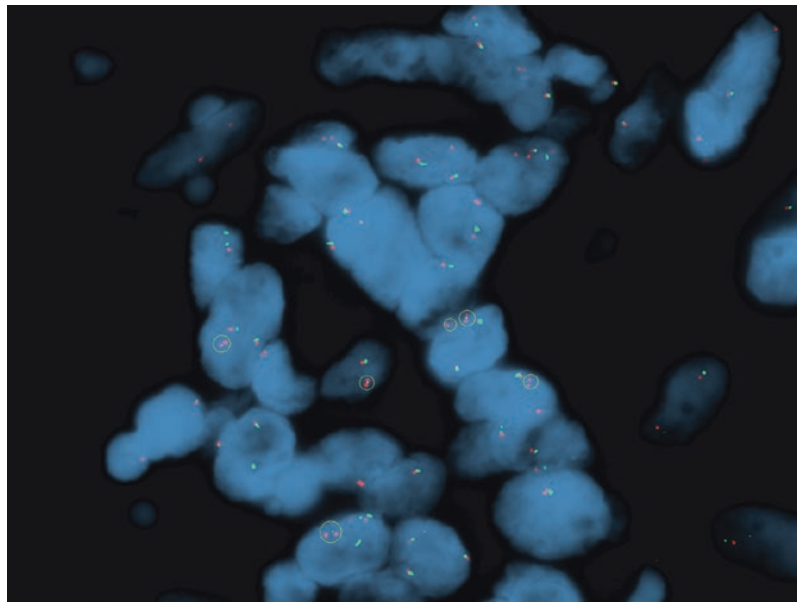

**Fig. 12.1** Isochromosome 12p in metastatic adenocarcinoma (same patient as Fig. 12.3). The tumor cells had two copies of 12p (*red dots*) attached to the centromere (*green dot*), as identified with fluorescent in situ hybridization

Another mechanism of development of STM-GCT is the overgrowth of immature elements. While the presence of immature tissue elements is relatively common, particularly in type II GCT, an expansile growth of these primitive tissues is associated with more aggressive behavior and metastases from the overgrown component. Examples of primitive tissues that may show overgrowth include neuroepithelium, rhabdomyoblasts, and nephrogenic blastema, and thus, when present, a diagnosis of primitive neuroectodermal tumor (PNET), rhabdomyosarcoma, or nephroblastoma, respectively, is considered. The definition of "overgrowth" is arbitrary and has been traditionally defined in type II testicular tumors as a low-power field (40x) of pure immature elements [1]. However, while this definition appears necessary in type II tumors where immature elements are frequently part of the spectrum of tissues present in these teratomas, the presence of any amount of developmentally immature tissue, in particular neuroepithelium, is considered an adverse finding in ovarian teratomas [20, 21]. Interestingly, the presence of these immature elements, even if extensive, has not been historically considered STM at these sites but rather evidence of "immaturity." Regardless, the finding is frequently associated with a far more aggressive clinical behavior than the original teratoma.

The occurrence of STM in patients that lacked teratomatous component in their primary or metastatic GCT has prompted other histogenetic theories [17, 22–28]. Some studies have suggested yolk sac tumor (YST) origin as an alternative in these cases [3, 23, 29–31]. Spindle cell sarcomas may arise from sarcomatoid YST by a process of epithelial to mesenchymal metaplasia. Similarly, some intestinal-type adenocarcinomas may arise of progressive differentiation of glandular YST [3]. The development of a high-grade sarcoma component is also a rare complication of spermatocytic tumors, an uncommon scenario where this tumor is associated with malignant clinical behavior (see also Chap. 7) [32]. The mechanism by which these GCT develop a somatic phenotype is unknown but is likely related to the pluripotential nature of germ cells and the activation of differentiation pathways.

The role of chemotherapy in the pathogenesis of STM-GCT, specifically in patients with type II GCT, is not clear. The majority of cases of STM occur in the metastatic and post-chemotherapy setting [3]. However, the extended use of chemotherapy in current management of GCT increases the number of patients with STM who have previously received chemotherapy. Additionally, STM occurs also in patients that did not receive chemotherapy [3, 17, 22, 33]. The presence of STM in metastatic sites without a corresponding counterpart in the primary site has led authors to propose the development of STM from totipotential germ cells at the metastatic site [25, 34]. By destroying the more aggressive tumor components, chemotherapy may select the more indolent slow-growing elements, which after further genetic changes may be responsible for the formation of biologically aggressive STM and late recurrence of GCT [3, 35]. Hematologic malignancies arising from mediastinal GCT were thought to be due to chemotherapy or radiation for a long time. Occurrence of hematologic malignancies in patients that did not receive irradiation or chemotherapy argues against this statement [11, 13, 36]. Further, in contrast to treatment-related leukemia, these GCT-derived somatic-type hematologic malignancies develop earlier [37]. Similarly, STM associated with intracranial GCT was thought to be treatment related. Documented STM in treatment-naïve GCT and the relatively brief interval between initial diagnosis and transformation supports an origin independent of therapy. Despite theories such as partial differentiation of totipotential germ cells with concomitant malignant transformation, tumor arising from differentiated teratomatous elements [23], or dedifferentiation similar to the phenomenon that occurs in liposarcoma and chondrosarcoma [32], the transformation mechanism remains unsettled.

## 12.3 Histologic Diagnosis

Recognition of a malignant somatic component in GCT depends on the type of malignant component. In general, carcinomatous malignancies are recognized by usual morphologic criteria applied to carcinomas in other locations. Overt cytological atypia, brisk mitotic activity, infiltrative and confluent growth, desmoplastic reaction, and invasive borders are part of such criteria. These criteria are more easily recognizable when the background GCT is benign. However, recognizing these features may prove problematic in the background of a type II GCT, as some elements interpreted as somatic may actually correspond to variants of these GCT, particularly YST. Non-seminomatous GCT usually have a prominent, reactive stroma, which may be confused with desmoplasia. Additionally, the inherent cytologic atypia invariably present in teratomatous elements of type II tumors makes the recognition of a carcinomatous component more difficult [27]. Thus, the addition of a quantitative criterion in carcinomas may be useful to establish a diagnosis of STM in the setting of type II neoplasms [1, 3]. Similarly, because the morphologic features of some sarcomas overlap with normal embryonal or fetal tissue frequently present in teratomas, particularly in type II GCT, it is necessary to establish additional criteria for the diagnosis of a somatic mesenchymal or neuroectodermal malignancy arising in a GCT. As stated above, the most commonly used criterion is the presence of an expansile component exclusively filling at least one low-power microscopic field (40× magnification) [1, 3]. Thus, for example, a nodule composed of embryonal-appearing skeletal muscle would be considered part of a teratoma if it involves less than one low-power field, while it would be considered rhabdomyosarcomatous transformation if the nodule involves a larger area. Even in the setting of high-grade stromal atypia, most authors favor needing a quantitative criterion to diagnose a stromal somatic malignancy [3, 23]. Melanocytic and hematologic neoplasms are usually diagnosed by extrapolating diagnostic criteria applied elsewhere.

## 12.4 STM in Type I GCT

The occurrence of STM in pediatric teratomas is well documented. Biskup et al. reported on nine cases of STM associated with pure teratomas (two sacrococcygeal and seven ovarian tumors) [38]; eight of the nine were children and adolescents. Another series reported 14 cases of STM in children and adolescents [39]. While based on the age of the patients and described histology, some of their cases may correspond to type II and type IV tumors; at least some of them were likely type I. STM histologies reported in these series included adenocarcinomas, rhabdomyosarcoma, other sarcomas, neuroendocrine carcinoma, astrocytoma, and neuroblastoma. Sites included ovary, retroperitoneum, sacrococcygeal, and mediastinal. One interesting case of an adenocarcinoma arising in a testicular dermoid cyst in a 52-year-old patient was reported [40]. The patient had had the testicular mass since childhood and developed sudden enlargement of the mass and metastatic disease. The depicted pathology is classical of dermoid cyst and convincingly shows the adenocarcinoma arising from mucinous epithelium within the teratoma. The presence of the mass since childhood, aside from being consistent with a type I neoplasm, underscores the importance of senescence in the development of STM in this setting. A metastasizing PNET has been reported arising in an immature teratoma of a 20-month-old [41]. As stated, STM in type I GCT may occur more frequently than thought, as the occurrence of type I tumors in postpubertal patients has only been recently recognized [42], and reported series do not allow to confidently separate type II from type I teratomas. For example, in a series of GCT associated with sarcomatous STM, three patients with a sarcomatous

component had testicular tumors that encompassed exclusively teratomatous elements and thus could have represented type I neoplasms [34]. The overlapping morphology between type I and type IV tumors makes this issue even more likely when dealing with ovarian neoplasms [4].

## 12.5 STM in Type II GCT

### 12.5.1 Testicular Tumors

By far, the majority of cases of STM occurring in type II tumors correspond to testicular neoplasms and is in this setting where most of the experience with this phenomenon has been developed. The incidence is estimated to range from 3 to 6.6 % [17, 23, 43, 44]. In one of the earliest studies [43], 580 GCT were reviewed, and teratoma with "malignant transformation" was found in 17 cases, while in another study [23] teratoma with STM was identified in 11 cases of a total of 269 GCT reviewed. In a later series [24], of 607 GCT reviewed, 21 patients had teratoma with STM; 11 cases (54 %) of those had STM in the primary tumor. Thus, STM may develop either in the primary GCT or in a metastatic deposit and may develop in treatment-naïve tumors or in the post-chemotherapy setting.

The majority of cases of STM-GCTs have an associated teratoma component; however, up to 30 % may not have a recognizable teratoma neither in the primary nor in the metastatic tumor [3]. In a recent series, both glandular and spindle cell tumors had intermediate morphologic and immunophenotypic features between glandular and sarcomatoid YST and somatic adenocarcinomas and sarcomas, respectively [3]. This suggests that at least a proportion of STM-GCT cases may arise from YST. This would not be surprising, given the morphologic plasticity of YST.

Sarcomas, particularly rhabdomyosarcomas, are the most common STM to be reported in type II neoplasms (Fig. 12.2). In a recent series from five institutions, sarcomas represented 37 % of cases of STM, with rhabdomyosarcomas representing 13.5 % of the total [33]. Other sarcoma histologies reported include leiomyosarcoma, myxoid liposarcoma, chondrosarcoma, and malignant peripheral nerve sheath tumor. However, some of these sarcomas may actually correspond to sarcomatoid YST and thus do not represent true STM. In a recent study, of 68 sarcomas, 24 were reclassified as sarcomatoid YST and five as sarcomatoid carcinomas [3]. Adenocarcinomas (Fig. 12.3) are the most common epithelial neoplasms, representing 16 % of cases in the series mentioned above [33]. Other carcinomas include squamous cell carcinoma, neuroendocrine carcinomas, renal cell carcinoma, and hepatocellular carcinoma. While carcinoid tumors are currently classified as a type of monodermal teratoma [1], an alternative approach would be to consider them as a form of STM. PNET are also common, representing 31 % of cases in the abovementioned series (Fig. 12.4) [33]. Other primitive tumors include neuroblastoma and nephroblastoma (Fig. 12.5). Mixed histologies are also encountered. A detailed list of reported histologies in STM of the testis is presented in Table 12.2.

The type of histology impacts the prognosis. Rhabdomyosarcoma histology is associated with a better prognosis, while PNET is associated with the worst [33]. Elapsed time between diagnosis of the GCT and the diagnosis of STM appears to correlate with histology of STM. The vast majority of PNET and rhabdomyosarcoma are diagnosed concomitantly to or within two years of GCT diagnosis, while most adenocarcinomas are diagnosed after two years of diagnosis of the GCT [22, 33, 55]. This suggests that senescence and perhaps exposure to therapy may be more important risk factors in the development of epithelial STM and less important in the development of sarcomatous or primitive histologies. Correlation between grade of STM and aggressive behavior is controversial. One series did not find a correlation with prognosis according to the grade of glandular tumors but did find it with sarcomas [3], while another one did not find a difference in behavior between low- and high-grade sarcomas [34].

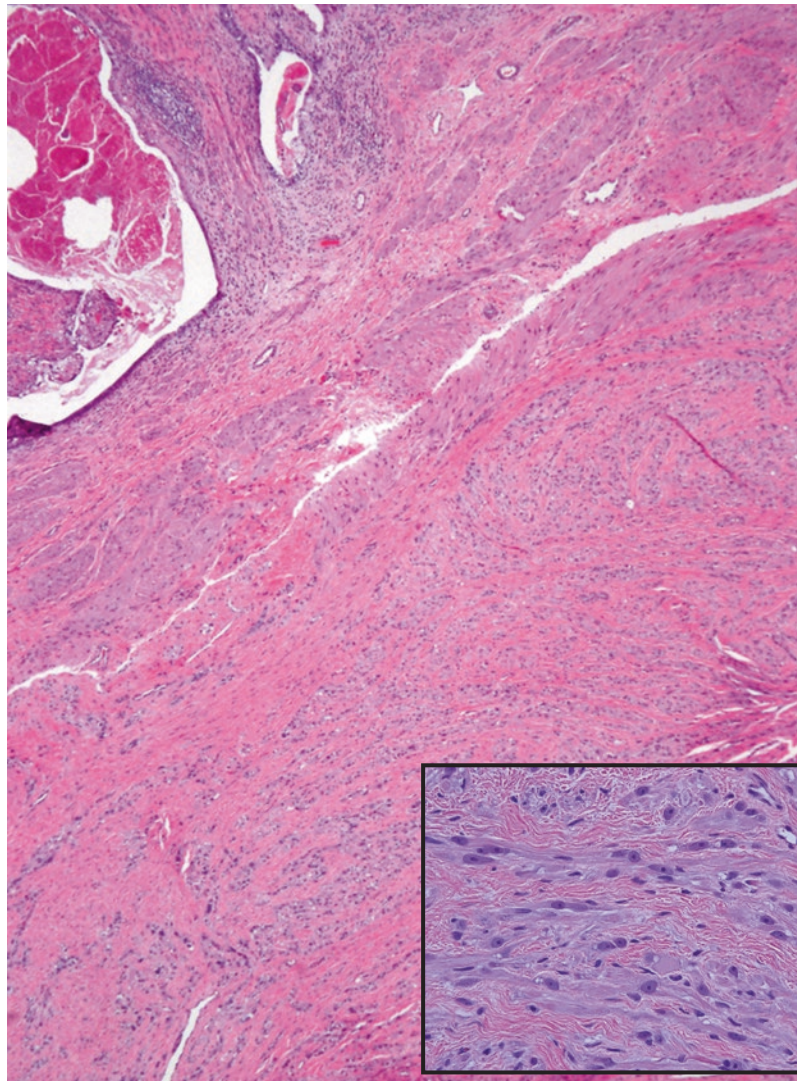

**Fig. 12.2** Rhabdomyosarcoma, occupying more than one low-power field of this teratoma. Inset: high-power view, revealing polygonal to *spindle-shaped* cells with hyperchromatic nuclei and cytoplasmic cross striations

Overall, the presence of STM confers patients with a detrimental impact on survival across all stages. Clinical stage I and metastatic good-risk patients with STM-GCT had approximately 10 % and 20 % reduction in overall survival, respectively, compared to patients with pure GCT [33]. However, the site where STM is present is also important. STM present in primary tumors is associated with better prognosis than STM developed in metastatic deposits [2, 56]. Partially reflecting this, elapsed time from diagnosis of GCT to diagnosis of STM also impacts prognosis, with the best prognosis associated with STM diagnosed at the same time as the GCT [33]. The presence of STM diagnosed after therapy for GCT is associated with dismal prognosis, particularly if developed more than two years after GCT diagnosis [3, 33]. This is particularly significant, since STM-GCT represent approximately 23 % of late recurrences (i.e., after two years) in patients with testicular GCT [35, 57]. Patients who do

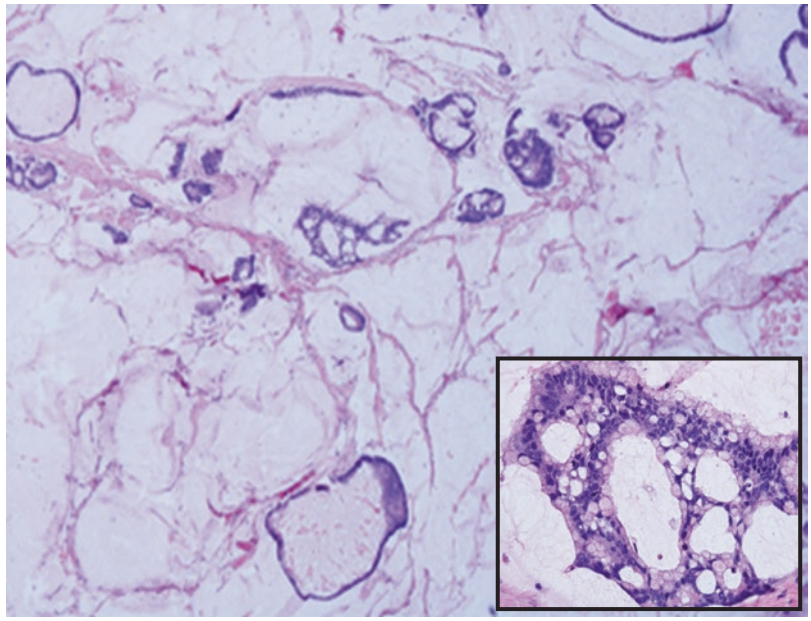

**Fig. 12.3** Adenocarcinoma in retroperitoneal lymph nodes, 23 years after a diagnosis of mixed germ cell tumor. Tumor associated with abundant extracellular mucin. Inset: high-power view showing intracellular apical mucin in the neoplastic cells. (Same patient as Fig. 12.1)

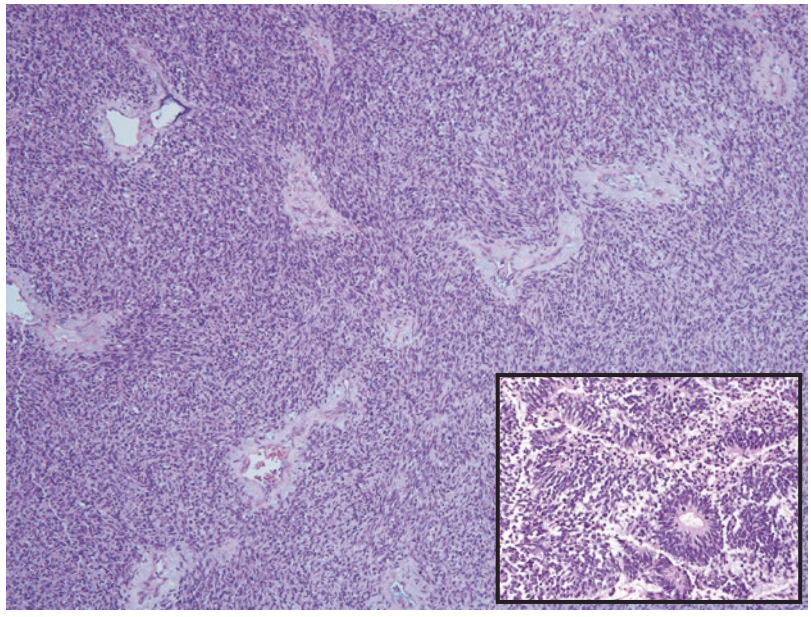

**Fig. 12.4** Primitive neuroectodermal tumor, *small round blue cells* in broad sheets, occupying more than one low-power field. Inset: higher-power view shows occasional rosette formation

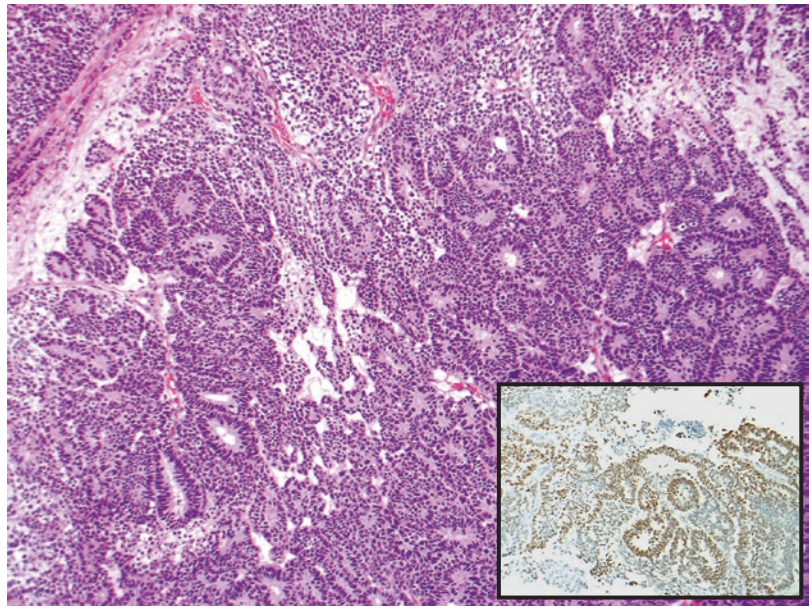

**Fig. 12.5** Wilms' tumor with undifferentiated blastema, fibroblast-like stroma, and epithelial elements including abortive tubules. Inset: WT stain showing nuclear positivity in the epithelial component

not respond to initial therapy, experience relapse, or have metastatic or disseminated disease have poor prognosis [2, 22, 58].

### 12.5.2 Ovarian Tumors

The published experience with STM in ovarian type II GCT is limited to occasional case reports. This, however, may be a reflection of the much more uncommon occurrence of these tumors in the ovary, compared to the testis. Type II GCT can usually be inferred if the STM arises in a background of a mixed GCT or associated with non-teratomatous elements, like dysgerminoma. Similarly to the testicular counterpart, the majority of the reported histologies correspond to sarcomas. These include a case of a 33-year-old with an ovarian dysgerminoma associated with a fibrosarcoma component [59], a case of dysgerminoma with a rhabdomyosarcoma in a 14-year-old girl [60], and another case of rhabdomyosarcoma in a 23-year-old associated with dysgerminoma and teratoma [61]. Additionally, in the series of sarcomatous STM-GCT mentioned above [34], two of the three ovarian GCT with STM contained mixed germ cell elements, including mature teratoma and embryonal carcinoma with leiomyosarcoma, and dysgerminoma and immature teratoma with rhabdomyosarcoma. Collective evidence on this particular setting is quite scarce to draw significant conclusions about prognosis and treatment. Further, published series not always include enough information to allow retrospective identification of a type II teratoma and differentiate it from a type I or type IV teratoma or to exclude the possibility of its occurrence in a phenotypic female with an underdiagnosed Y chromosome mosaicism (see Chap. 6).

## 12.6 STM in Type III GCT

Spermatocytic tumors (ST) are rare and the presence of an associated sarcomatous component is even rarer. ST is not associated with other GCT and usually has a favorable prognosis (see Chap. 7). In reported cases of ST with a sarcomatous component, undifferentiated spindle cell sarcoma and rhabdomyosarcomas have been mentioned (Fig. 12.6). The presence of a sarcomatous component is associated with poor prognosis and metastatic disease [32, 62, 63].

**Table 12.2** Reported STM histologies in primary or metastatic GCT of the testis

| STM histology | References |
|---|---|
| Rhabdomyosarcoma | Colecchia [2], Guo [25], Malagon [34], Motzer [17], Necchi [22], Donadio [45], Comiter [24] |
| Adenocarcinoma | Colecchia [2], Necchi [22], Motzer [17], Donadio [45], El Mesbahi [46] |
| Squamous cell carcinoma | Ahmed [43] |
| Neuroendocrine carcinomas | Colecchia [2], Wang [47], Reyes [48], Necchi [22] |
| PNET | Ganjoo [49], Necchi [22], Mohanty [50], Comiter [24], Motzer [17], Donadio [45], Colecchia [2] |
| Nephroblastoma | Necchi [22], Ulbright [23], Colecchia [2], Emerson [18] |
| Well-differentiated liposarcoma | Colecchia [2], Necchi [22] |
| Leiomyosarcoma | Colecchia [2], Ahmed [43], Necchi [22], Comiter [24] |
| Myxoid leiomyosarcoma | Malagon [34] |
| Chondrosarcoma | Colecchia [2], Necchi [22], Comiter [24] |
| Angiosarcoma | Ulbright [51], Malagon [34] |
| Neuroblastoma | Colecchia [2], Ulbright [23] |
| Malignant fibrous histiocytoma | Ahmed [43] |
| Glioma | Ahmed [43] |
| Malignant peripheral nerve sheath tumor | Colecchia [2], Comiter [24], Necchi [52] |
| Gemistocytic astrocytoma | Colecchia [2] |
| Choroid plexus tumor | Colecchia [2], Necchi [22] |
| Microcystic meningioma | Allen [53] |
| Sarcoma not otherwise specified | Colecchia [2], Malagon [34], Necchi [22] |
| Dendritic cell tumor | Necchi [22] |
| Hemangioendothelioma | Necchi [22] |
| Malignant giant cell tumor | Ulbright [23] |
| Hepatocellular carcinoma | Jain [54] |
| PNET and choroid plexus tumor | Colecchia [2] |
| Gemistocytic astrocytoma and choroid plexus teratoma | Colecchia [2] |
| Rhabdomyosarcoma and adenocarcinoma | Colecchia [2] |
| Nephroblastoma and rhabdomyosarcoma | Colecchia [2] |
| PNET and rhabdomyosarcoma | Colecchia [2] |
| Rhabdomyosarcoma and undifferentiated sarcoma | Ganjoo [49] |
| Rhabdomyosarcoma and Ewing's sarcoma/primitive neuroectodermal tumor | Ganjoo [49] |
| Rhabdomyosarcoma and small round blue cell tumor not otherwise characterized | Ganjoo [49] |
| Osteogenic sarcoma and rhabdomyosarcoma | Motzer [17] |
| Rhabdomyosarcoma and primitive neuroectodermal tumor | Motzer [17] |
| Rhabdomyosarcoma and chondrosarcoma | Motzer [17] |
| Rhabdomyosarcoma and squamous cell carcinoma | Motzer [17] |

*GCT* germ cell tumor, *STM* somatic-type malignancy, *PNET* primitive neuroectodermal tumor

Published experience with this phenomenon is limited to case reports and small series. The largest one reported five cases of ST with sarcomatous "transformation," four undifferentiated sarcomas and one rhabdomyosarcoma. Two (possibly three) of the patients died of metastatic disease [32]. Another series reported two cases of ST with sarcomatous component. The sarcomatous element in one case was rhabdomyosarcoma, while the other case had primitive mesenchymal spindle cell sarcoma. Both cases were older than 40 years; their sarcomatous component metastasized and had a poor outcome

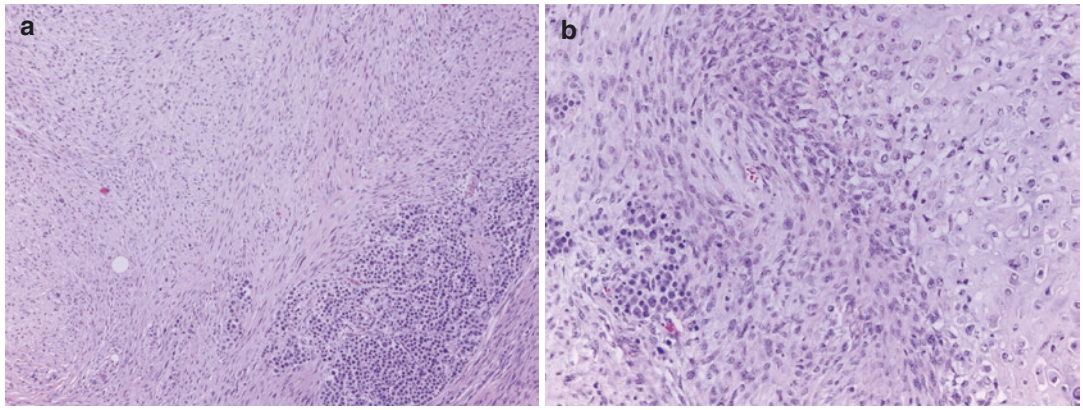


**Fig. 12.6** Spermatocytic tumor (type III GCT) with associated malignant spindle cell (**a**) and cartilaginous (**b**) components (Pictures courtesy of Dr. Thomas Ulbright, Indiana University)

despite aggressive treatment. In their description of the ST component, the authors point out slight differences with classic description, including high mitotic rate and atypical mitotic figures [64]. One case report presented an ST with undifferentiated sarcomatous component in a 43-year-old male. The tumor was resected but chemotherapy was not given. The patient developed a recurrent scrotal mass and multiple bilateral lung metastases 9 months later. A chemotherapy regimen of cisplatin, bleomycin, and etoposide was initiated, but the patient died after 1 month [65]. Similarly, another case report presented an ST in a 51-year-old male with rhabdomyosarcoma component, metastasis to the lungs, liver and retroperitoneal lymph nodes, and death 2 months after the diagnosis [62].

The exact mechanism explaining the origin of sarcomatous component is not clear. As expected, teratomatous elements were absent in all reported cases. True et al. suggested that the sarcomatous components are an expression of anaplastic transformation of the ST [32]. One could also theorize that the sarcomatous component is a result of the pluripotential features of the neoplastic germ cell, although it is not clear why only mesenchymal neoplasms arise in this setting. Due to aggressive behavior of ST with sarcomatous component, additional treatment is warranted, although no specific modality is favored based on the limited experience. These tumors are rare and the effectiveness of chemotherapy and/or radiotherapy is not clear [66, 67].

## 12.7 STM in Type IV GCT

Mature cystic teratomas of the ovary (type IV GCT) can also be complicated by STM, and this phenomenon is extensively reviewed in Chap. 6. A few salient aspects will be discussed here.

STM occurs in 1.5–3 % of mature cystic teratomas [19, 68]. Contrary to what occurs in type II GCT, the majority of STM arising in mature cystic teratomas of the ovary are squamous cell carcinomas (Fig. 12.7) [69]. They seem to affect elderly women in their fifth and sixth decade [19]. Other epithelial neoplasms that may be found within mature cystic teratomas include adenocarcinoma (Fig. 12.8) [70], neuroendocrine carcinoma, and transitional cell carcinoma [71]. Sarcomas are much less frequent and include osteosarcoma [71, 72], rhabdomyosarcoma, angiosarcoma (Fig. 12.9), malignant fibrous histiocytoma, chondrosarcoma, spindle cell sarcoma, and undifferentiated sarcoma [73, 74]. Malignant melanomas are much less common than metastatic melanomas to the ovary [75, 76]. A thorough list of histologies reported in STM in mature cystic ovarian teratomas is presented in Chap. 6 in Table 6.5.

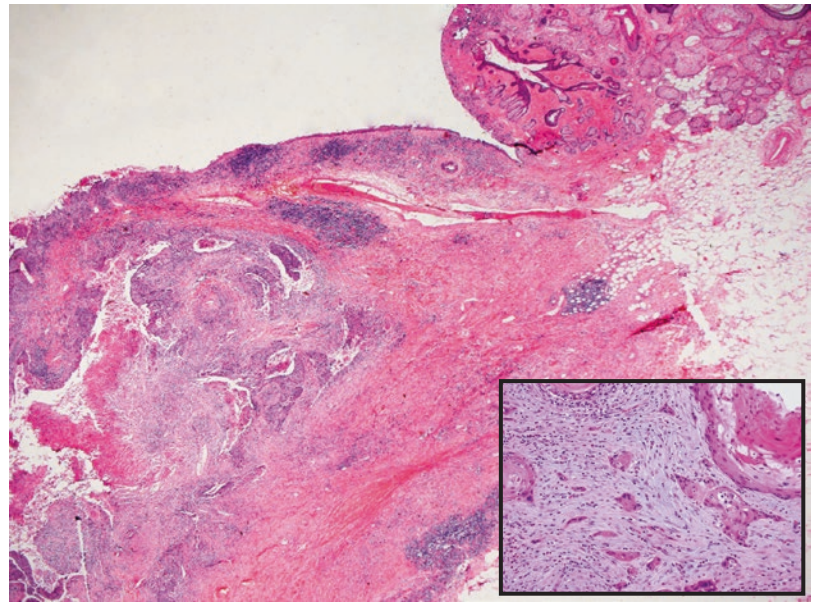

**Fig. 12.7** Well-differentiated squamous cell carcinoma arising in a mature cystic teratoma of the ovary. Inset: high-power view of invasive nests of squamous cells and keratin formation

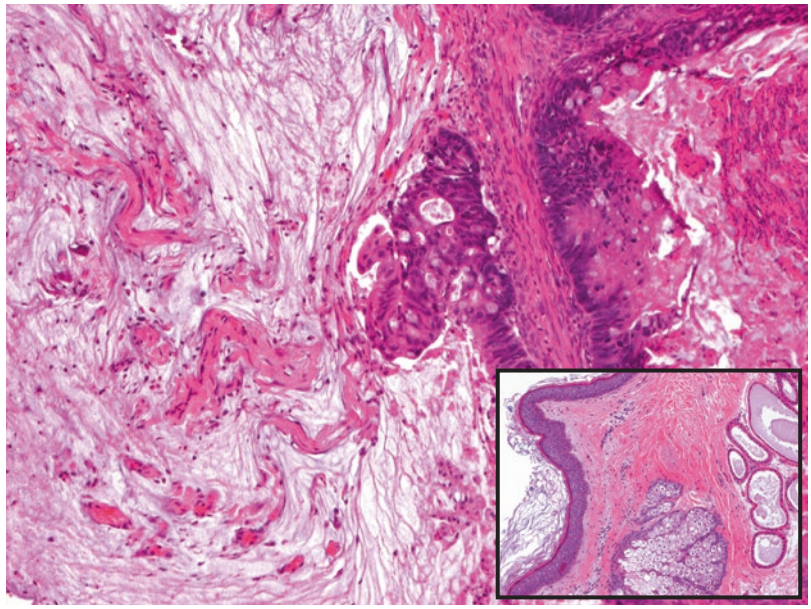

**Fig. 12.8** Mucinous adenocarcinoma arising in mature cystic teratoma of the ovary. Malignant mucinous epithelium with extravasated mucin. Inset: the tumor arose within a classic dermoid cyst

Some have proposed that the different histological spectrum between STM in ovarian and testicular teratomas reflects the differences in tissues present in the teratomas from both gonads [77]. While this may be the case, it is also likely that the inherent biological behavior of the background tumor impacts the type of STM that develops in both settings. Thus, tumors associated with tissue senescence, like squamous cell carcinomas and adenocarcinomas, are more likely to occur in benign tumors that can remain occult for prolonged periods of time (i.e., ovarian) and would be less likely to develop in a malignant

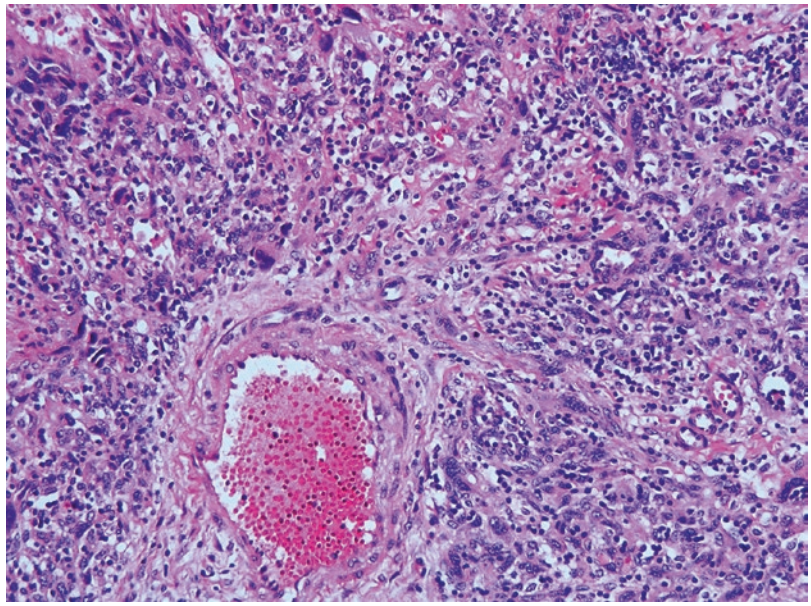

**Fig. 12.9** Angiosarcoma arising in a mature cystic teratoma of the ovary. Anastomosing vascular spaces lined by cytologically atypical endothelial cells

tumor that would manifest early or advance rapidly (i.e., testis).

As stated above, a different approach to the one in testicular tumors has been followed in ovaries, regarding the presence of immature elements in mature cystic teratomas. While in testicular tumors a small amount of immature neuroepithelium is irrelevant, a diagnosis of PNET is rendered when this reaches an expansile growth measuring at least one low-power field [1]. In ovarian tumors any amount of immature neuroepithelium is diagnostically relevant but is not considered STM even if expansile and occupying more than one low-power field, but rather is described as "immaturity" and renders a teratoma as an "immature teratoma" [20, 21]. This different approach is more based on historical and definitional reasons, but the difference in the biologic behavior of the background teratomas in both settings and their different pathogenesis may provide also biological fundament. Irrespective of terminology, larger amounts of immature elements are associated with more aggressive behavior, which constitutes the rationale for the "grading" of immature teratomas (see Chap. 6). STM has also been described in ovarian immature teratomas. Due to higher frequency of immature neural tissue in immature teratomas, secondary somatic malignancies are often neural in origin [78]. Sarcomas, particularly rhabdomyosarcomas, can also occur. Similar to testicular tumors, its diagnosis is based on the presence of "overgrowth," although a definitive criterion for its diagnosis has not been established [21].

## 12.8 STM in Extragonadal GCT

Extragonadal GCT in mediastinum, intracranial (pineal gland), retroperitoneum, and sacral region may undergo transformation to STM. Extragonadal GCTs most likely correspond to type I or type II GCT [4]. However, it is difficult to retrospectively determine in published reports the type of GCT described, although likely both types are represented in most series. Reports on STM in mediastinum are by far more prevalent, with retroperitoneum and intracranial (pineal gland) sites being far less common. Sarcomatous transformation is the most common encountered STM

in extragonadal GCT, and rhabdomyosarcoma is its most common subtype [9, 17, 34, 45].

In mediastinum, other reported histologies include PNET [45], adenocarcinoma [45, 79], squamous cell carcinoma [79], osteosarcoma [79], anaplastic small-cell cancer [45], angiosarcoma [34, 79, 80], MPNST [24, 34], leiomyosarcoma [34], epithelioid hemangioendothelioma [34], undifferentiated sarcoma [34], myxoid liposarcoma [34], malignant "triton" tumor [34], sarcoma accompanied by non-Hodgkin's lymphoma [17], sarcoma accompanied by acute nonlymphocytic leukemia [17], squamous cell carcinoma [79], liposarcoma [79, 80], osteosarcoma [79], malignant schwannoma [80], carcinoid tumor [80], glioblastoma multiforme (Fig. 12.10) [34], and hematologic malignancies. Hematologic malignancies seem to be quite specific to mediastinal GCT with no reported cases of transformation to hematologic malignancy in other locations [2, 11–13]. Additional information on mediastinal tumors with STM may be found in Chap. 8.

GCT of the retroperitoneum may show STM such as rhabdomyosarcoma [17, 34, 39], adenocarcinoma [17, 81], liposarcoma [39], chondrosarcoma [39], Wilms' tumor [82], and PNET [83].

Cases of intracranial (pineal gland) GCT with STM are rather sparse. Rhabdomyosarcoma [84–87] and adenocarcinoma [86] have been described. The majority of these cases were associated with teratoma. YST was the second most common intracranial GCT associated with STM [85, 87].

Similar to gonadal sites, poor prognosis has been observed in extragonadal STM-GCT [17, 24, 34]. Mediastinal STM-GCT are detected in more advanced stages with higher rates of progression, metastasis, and relapse. They are less amenable to complete resection with clean borders. They tend to be larger, bulkier, and poorly circumscribed, involving complex vital organs, making radical surgery difficult and inducing comorbidities such as cardiac tamponade and superior vena cava syndrome [17, 34, 79]. Similarly, intracranial GCT with STM tend to have metastases at the time of diagnosis, are less amenable to complete resection, and generally show very poor prognosis [86]. Extragonadal site was an adverse prognostic factor on multivariate analysis in a large series [33]. Extragonadal

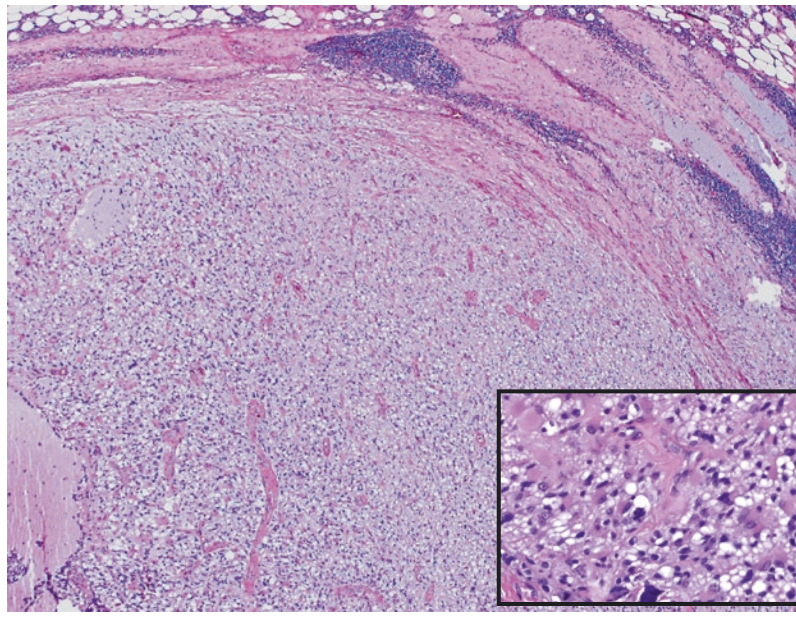

**Fig. 12.10** Glioblastoma multiforme arising in a teratoma of the mediastinum. Inset: high-power view showing the neoplastic glial cells with an atypical mitotic figure

STM-GCT should be distinguished from metastasis of a gonadal GCT. This is particularly troublesome when the gonadal primary has undergone regression.

## 12.9 Therapeutic Implications

Development of STM has major clinical implications. Despite excellent prognosis of GCT with surgery and chemotherapy, the presence of somatic malignant component is associated with dismal prognosis [17, 24, 34, 88]. Incomplete surgical removal is consistently shown as an adverse prognostic factor. In a recent series, 35 % of STM-GCT with clinical stage I that were treated with primary retroperitoneal lymph node dissection (RPLND) had viable STM in the lymph nodes [33]. Based on this finding, the authors advocate primary RPLND in cases with STM in the primary tumor. Overall, prompt surgical resection of the primary tumor, any metastasis, and residual post-chemotherapy tumor are the mainstay of treatment [52]. Surgery should be considered in all patients regardless of stage.

Even though investigators universally advocate timely radical surgery as the most important treatment step, the role and type of chemotherapy regimen is less clear. Conventional cisplatin-based chemotherapy has been shown to be ineffective in patients that develop STM associated with otherwise responsive GCT [2, 17, 22–24, 58, 88]. It is not clear if histology-driven chemotherapy provides benefit. In cases that are not amenable to surgery, higher doses of cisplatin-based chemotherapy will cause severe toxicity, and, considering the resistance of STM, it may not provide much therapeutic benefit [3]. Tailored chemotherapy may be considered in relatively chemosensitive histology such as rhabdomyosarcoma and PNET, but further studies are needed [17, 45, 46, 89]. STM with multiple histologic types poses another therapeutic challenge. Their treatment is more complicated and their prognosis is usually worse than single transformed histology [22]. Some authors recommend a cisplatin-based regimen as both initial and salvage therapy especially if there is still evidence of the presence of cisplatin-sensitive elements by biopsy or tumor marker levels. Rescue chemotherapy oriented to GCT may provide salvage in persisting disease cases [52, 55]. In the above-mentioned series, a definitive recommendation on the type of chemotherapy could not be rendered despite being the largest series published so far, given the multiple subgroups in the study with different histologies and treatment regiments [33].

Refractoriness to cisplatin-based chemotherapy or a mixed response, with regression in one site, and no change or progression in another site, should raise suspicion of STM transformation. Decrease or normalization of tumor biomarker levels, despite objective disease progression as evidenced clinically or by imaging, may be another telltale sign of transformation to STM. Suspicion should be high in such cases. Serum tumor markers are not optimal surrogates of treatment response, and close radiologic follow-up of tumor size is thus warranted.

No standardized treatment plan has been devised for STM arising from either immature or mature ovarian teratoma. Reported treatments for mature ovarian teratoma include surgical treatment [90], surgical treatment in combination with chemotherapy [91], external radiation, radionucleotide therapy, chemotherapy only, and both radiation and chemotherapy [19].

As in gonadal cases, surgery with chemotherapy remains the mainstay treatment in mediastinal and intracranial STM-GCT. Additional radiation therapy has been tried in some cases [34, 86].

## 12.10 Differential Diagnosis

### 12.10.1 GCT Elements

Atypia seen in teratoma can mimic STM. This is particularly problematic in type II teratomas, as teratomatous elements invariably display significant degrees of cytologic atypia [27, 77]. Atypical features may also be exacerbated by prior treatment [92]. The degree of atypia, expansile growth, and infiltrative borders are key features

in differentiating between microscopic foci of atypia and STM. Overgrowth and replacement of adjacent conventional germ cell elements should be taken into consideration.

Differentiating adenocarcinoma and glandular YST may be diagnostically challenging as well. Magers et al. excluded ten cases from their series initially diagnosed as somatic-type adenocarcinoma, as they represented glandular YST or indeterminate glandular tumors by morphology and immunohistochemistry [3]. Glandular YST tends to be positive for glypican 3 and/or AFP but not always [93, 94]. Unlike adenocarcinomas in STM, glandular YST usually lacks reaction to EMA or CK7. Both entities express CDX2 and both are often positive for SALL4. In cases that lack a clear-cut pattern of staining, the dominant combination of stains may be considered. Similarly, sarcomatoid YST may be misinterpreted as sarcomatoid tumors [3]. In the series mentioned above, of 68 cases originally classified as sarcoma, 24 were reclassified as sarcomatoid YST. A panel of stains would be helpful in ambiguous cases. Sarcomatoid YST shows positivity for both AE1/AE3 and glypican 3.

Hepatocellular carcinoma arising in a teratoma, while rare, may pose a difficult differential diagnosis [54]. First and foremost, it must be differentiated from benign hepatic tissue within a teratoma. Glypican 3 is considered helpful in differentiating benign hepatic cells from hepatocellular carcinoma, as its expression is associated with early events in hepatocarcinogenesis [95]. However, it may not be as useful in the setting of GCT, given its expression in hepatoid YST [96]. Conversely, SALL4 may be positive in hepatocellular carcinomas [97]. Serum tumor markers and the presence of multiple morphologic patterns of YST favor hepatoid YST, while infiltrative pattern in the stroma, nuclear atypia, trabecular, and acinar or pseudoglandular arrangement would favor hepatocellular carcinoma [54].

Embryonal carcinoma may sometimes mimic somatic carcinomas or vice versa. Attention to the distribution of the carcinoma elements (scattered, versus localized), and the classic immunophenotype of CD30-positive, EMA negative in embryonal carcinoma should resolve most of the difficult cases.

### 12.10.2 Post-therapy Changes

In 2009, Clevenger et al. reported seven cases of a highly differentiated rhabdomyomatous proliferation in the setting of post-chemotherapy RPLND [98]. Contrary to rhabdomyosarcomas arising in teratomas, these tumors were characterized by cells with abundant eosinophilic cytoplasm with occasional cross striations. They displayed mild cytologic atypia and no necrosis, mitotic activity or primitive appearing component. All but one was associated with typical teratoma. Of six patients with follow-up, none had evidence of progressive or recurrent sarcoma, although some had recurrence of teratomatous elements. The authors concluded that the phenomenon is that of cytodifferentiation induced by chemotherapy, a phenomenon that has been seen in treated somatic rhabdomyosarcomas, also associated with a good prognosis [99]. Recognition of this type of tumor is important to avoid confusion with rhabdomyosarcoma arising in teratoma, which would carry a significantly worse prognosis (Fig. 12.11).

### 12.10.3 Metastatic, Non-GCT-Related Neoplasms

When the teratomatous elements are relatively minor or completely effaced, the distinction between STM and metastatic non-GCT-related tumor is difficult. Thorough sampling to find the teratomatous elements is essential and should be undertaken in tumors with somatic histology at gonadal and extragonadal sites likely to harbor GCT. Late recurrence up to 30 years after the initial treatment has been reported in testicular tumors [100, 101]. The association of a new STM to a testicular GCT that was treated years prior may not be readily evident to the physician at the time of presentation. Differentiating STM derived from GCT and de novo somatic malignancies is challenging. Complete physical exam and imag-

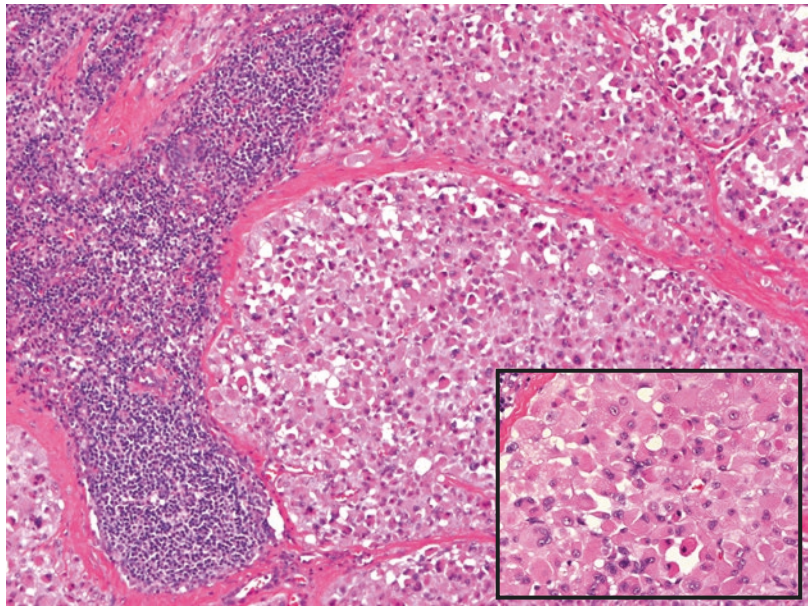

**Fig. 12.11** Differentiated rhabdomyomatous tumor. This patient had rhabdomyosarcoma arising in a testicular teratoma and underwent four cycles of chemotherapy before RPLND. Inset: notice the "maturation" of the tumor cells, with globoid appearance, lack of mitosis activity, and degenerative-type atypia

ing studies should be performed in search for possible germ cell primary. The i12p testing may shed light in this workup when a type II tumor is suspected [7]. Conversely, ample sampling of a teratoma is essential in making an accurate diagnosis as undersampling poses a pitfall of missing STM components. The differential diagnosis of ovarian melanoma arising in mature cystic ovarian teratoma and the much more common melanoma metastatic to the ovary usually relies on the unilaterality, presence of junctional change, and clinical exclusion of another primary in the former [75, 76, 102].

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