Pediatric Germ Cell Tumors

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Germ cell tumors (GCT) are relatively rare in the pediatric age group, representing only 1–3 % of childhood tumors [1]. Pediatric GCT comprise a remarkably diverse group, with significant variability in age and site of presentation, clinical behavior, and histology [2–4]. Although they share a common origin from progenitor germ cells, markedly different types of GCT may develop due to variations from normal differentiation (i.e., gonadal GCT) and/or aberrant migration (i.e., extragonadal GCT), most commonly occurring in midline locations (mediastinal, retroperitoneal, sacrococcygeal, genital, or cranial) [1, 5–7]. Most correspond to types 0 and I of Oosterhuis and Looijenga's classification (see Chap. 3).

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10.1 Epidemiology

GCT may occur at any age; however, a bimodal age distribution is more commonly observed, with a first peak between birth and 4 years of age (pediatric GCT proper), and a second one beginning with the onset of puberty and continuing through the third and fourth decades [2, 3, 6, 8]. In children, extragonadal sites predominate, accounting for 50 % of cases, compared with adults in whom only 10 % are extragonadal [1].

The majority of pediatric GCT (type I GCT) are benign, with mature teratomas being the most common [9–11]. Approximately 20 % of pediatric GCT are malignant, representing approximately 3 % of all pediatric cancers [3, 12], although the rate of malignancy varies by age of presentation and anatomical site [1, 12, 13]. The majority of malignant GCT in children are yolk sac tumors (YST) [4, 6].

GCT are the most common neoplasm in the newborn accounting for 35–40 % of all tumors in the first month of life [4, 6]. Most GCT in the fetal and neonatal periods are teratomas. Only approximately 5 % of neonatal GCT contain a malignant component, usually YST [6]. Overall, sacrococcygeal tumors are the most common perinatal GCT,

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Table 10.1 Most frequent GCT in the pediatric population by age group, anatomical site, and histologic type

Age group	Anatomical site	Usual histologic type	Comments
Newborn/infancy	Sacrococcygeal (40 %) Ovary mediastinal > abdominal (15–20 % vs. 5 %) Cervicofacial (rare <5 %)	Teratoma	GCT are the most common neoplasm in newborns (35–40 % of tumors during first of month of life); only 5 % are malignant (most commonly YST)
Childhood	Testes	Mostly YST with low (5 %) metastatic rate	Usually benign/indolent behaviors when presenting in gonadal sites Gonadal seminoma and dysgerminoma are rare and frequently associated with gonadal dysgenesis
	Ovary	Teratoma (40 %) Mature cystic teratoma	
	Mediastinal	Approximately 15 % are malignant. Most common malignant histology is YST in girls and younger boys and mixed histology in older boys	
Puberty/adolescence	Testes	Postpubertal teratomas have higher metastatic potential than prepubertal	GCT are the most common solid tumor in adolescent males
		Higher incidence of embryonal carcinoma and mixed non-seminomatous tumors	
	Ovary	Mature cystic teratoma	

GCT germ cell tumors, *YST* yolk sac tumor

accounting for 40 % of the total [4]. GCT rank as fourth or fifth most frequent malignant neoplasm in patients below 14 years of age, after neuroblastoma, rhabdomyosarcoma, Wilms tumor, and retinoblastoma [6, 14]. Table 10.1 presents a summary of the most common types of GCT affecting the pediatric population by age group and anatomical sites of involvement

10.1.1 Risk Factors for Developing GCT

GCT lack familial distribution and are thought to arise from sporadic genetic mutations [3]. Several common chromosomal mutations have been identified that may represent random occurrences although some common environmental risk factors have been reported. Maternal exposure to various chemicals and solvents may be associated with an elevated risk of GCT in the offspring; however, this has not been proven conclusively [3, 15].

Cryptorchidism is associated with 3- to 9-fold increased risk of GCT (most commonly seminoma) compared to the general male population [3, 16–18]. Early orchiopexy is associated with a lower incidence of developing a testicular germ cell tumor [3, 19].

There is an increased risk for development of gonadal GCT in certain disorders of sex development (DSD), with an incidence reported as high as 30 % in patients with gonadal dysgenesis, and 5–10 % for undervirilization syndromes [3, 20–24]. These risks are thought to increase significantly with age. Therefore, prophylactic gonadectomy during childhood is recommended [3, 25, 26].

10.1.1.1 Neoplastic Risk in Disorders of Sex Development

The risk in each group of DSD is difficult to evaluate, because the reported prevalence per diagnostic group varies considerably and also because statistical data from literature reviews are based on gonadectomies performed during the previous decades, mainly prophylactically in early childhood; therefore, the real incidence of GCT may be higher. In addition, an accurate risk for malignant transformation in DSD patients is hard to predict because of two major problems: first, the confusing terminology and classification systems referred to the different forms of DSD, in which several synonyms and eponyms are used in literature, and definitions for the terminology are often lacking from bibliographical sources; second, there are no well-established criteria for the identification of malignant germ cells, especially in young children. This is specifically due to the phenomenon of delay of germ cell maturation, which might result in overdiagnosis of germ cell neoplasia *in situ* (GCNIS) [20].

10.1.1.2 Gonadal Tumors in Patients with DSD

Seminoma (if the gonad is considered a testis)/dysgerminoma (if the gonad is considered an ovary) and the non-seminomatous germ cell tumors are by far the most frequently occurring tumors in patients with DSD [24, 25, 27–33]. However, other gonadal (benign and malignant) neoplasms have sporadically been reported in patients with DSD, often in combination with the above-mentioned GCT. The development of invasive GCT is always preceded by the presence of an *in situ* neoplastic lesion. In gonads of DSD patients, the precursor of cancer may be GCNIS in testicular tissue or gonadoblastoma (GB), in those without obvious testicular differentiation or in patients with testicular dysgenesis [26, 34, 35]. Because gonadectomies in patients with DSD have often been performed prophylactically, most of the encountered changes in germ cells are benign or *in situ* malignant conditions. Recently, detailed histologic investigation of gonads of DSD patients led to the identification of the putative precursor of GB, which was referred to as undifferentiated gonadal tissue [25].

10.1.1.3 The Prevalence of GCT in Patients with DSD

The prevalence of GCT is increased in patients with DSD containing Y chromosome material in their genome and especially the chromosome Y "GBY" region, which is related to the presence of the TSPY gene, the most likely candidate [36, 37]. The presence of SRY or other sex determining genes is irrelevant in this context. Specifically DSD patients with gonadal dysgenesis (DSD with maldeveloped gonads, including streak gonads and testicular dysgenesis) or undervirilization (DSD with abnormal androgen function) are at risk. Traditionally, the prevalence of GCT in patients with gonadal dysgenesis is estimated at around 30 % [25] and in patients with undervirilization syndromes at 5–10 % [22, 23]. However, reported prevalence numbers per diagnostic group may vary considerably.

A clear insight into the prevalence of GCT in patients with gonadal dysgenesis (either complete or partial) is hampered by confusing nomenclature, which is most pronounced for this patient category, as well as an overestimated incidence of GCNIS in some series, reported as high as 91 % [38] to 100 % [39] that probably corresponds to a state of arrested or delayed maturation of the germ cells. GCT in patients with gonadal dysgenesis are frequently found at a very young age, during the first year of life [25, 29, 33, 40] or may even at birth [41]. Nearly all the *in situ* neoplastic lesions in patients with gonadal dysgenesis are GB, leading to seminoma/dysgerminoma in 92 % of the cases. A high risk of GB exists when sex determination is disrupted at an early stage of Sertoli cell differentiation (due to abnormalities in SRY, SOX9, or WT1). It must be remembered that development of GB requires the GBY region of the Y chromosome, which is in and of itself sufficient to lead to this neoplasm. Early Sertoli cell development is also disturbed in patients with mixed gonadal dysgenesis, who

also carry a high risk of developing GB as precursor lesion. The same is true for patients with 9p deletions, likely related to the loss of DMRT1 [42]. Careful histological analysis of gonadal tissue of DSD patients revealed that undifferentiated gonadal tissue is the most likely precursor stage of GB [26]. The GCNIS lesion accounts for only 8 % of precursor lesions in patients with gonadal dysgenesis and is probably only encountered in the presence of testicular tissue [25].

In the group of undervirilized patients (DSD with abnormal androgen function), the overall prevalence of GCT approximates 2.3 % [25]. In the androgen insensitivity syndrome (AIS), the reported prevalence of GCT has varied from 5–10 % [22, 23] to 22 % [43], although in more recent series of prophylactic gonadectomies, the estimated prevalence is 5.5 % [28, 34, 44–51]. Tumor prevalence in AIS markedly increases after puberty and reaches 33 % by 50 years of age [28]. Although data are limited, the risk seems to be markedly higher in the partial form (PAIS) (15 %) [34, 44, 49] than in the complete variant (CAIS) (0.8 %) [28, 34, 44, 47–49]. This difference may be explained by the fact that there is a rapid and total loss of germ cells by apoptosis in CAIS patients, starting from the age of 1 year, whereas PAIS patients maintain their germ cell population at about two-thirds of the normal number at puberty [34]. The risk of cancer in the PAIS patients is influenced by the anatomical localization of the gonad, being the highest in abdominal sites and the lowest in scrotal localization [42, 52]. In contrast to patients with gonadal dysgenesis, nearly all the reported tumors in the group of patients with undervirilization syndromes are GCNIS lesions (81 %) or seminomas (19 %), probably because these defects have occurred in late gonadal development. For other causes of undervirilization, the development of GCT is exceptional: one tumor is reported in a series of six patients with 17β-hydroxysteroid dehydrogenase deficiency (17 %) [34]; no tumors were found in a series of three patients with 5α-reductase deficiency [47] and of two patients with Leydig cell hypoplasia [34].

The risk for GCT development in patients with DSD can be grouped into four categories: high, intermediate, low, and unknown. High-risk patients include those with gonadal dysgenesis (DSD with maldeveloped gonads) [20], intra-abdominal gonads and the GBY region in their genome, including Frasier [53] and Denys–Drash syndromes and also patients with PAIS and non-scrotal gonads. The percentages found in the literature vary from 15 to 60 %. At intermediate risk are patients with the Y+ (GBY+) Turner syndrome and those with 17β-hydroxysteroid dehydrogenase deficiency, gonadal dysgenesis (harboring the Y chromosome), or PAIS, the two latter categories with scrotal gonads. The low-risk group includes patients with CAIS as well as patients with ovotesticular DSD (in which the gonads mostly consist of well-differentiated ovarian and testicular tissue) [54] and those with Turner syndrome lacking an apparent Y chromosome. The unknown category includes 5α -reductase deficiency, Leydig cell hypoplasia and specific gene mutations for which there are insufficient or no data for proper analysis [52, 55].

An interesting question is why GB forms in some patients and GCNIS in others. Hersmus et al. [42] hypothesized that this is due to the specific microenvironment, especially the absence of functional Sertoli cells, leading to female development. In other words, GCNIS can only be formed at a certain level of testicular development. Thus, GB and GCNIS are simply two variants of the same defect, being in fact a continuum, of which the phenotypic presentation is determined by the microenvironment, the level of virilization [42].

10.2 Classification of Pediatric GCT by Histologic Type

The totipotential nature of germ cells allows a wide variety of tumors. Different histologic patterns are common in a single tumor, and 25 % of childhood tumors contain more than one histology, which is often a malignant histology with

coexisting teratoma [12]. Since many of the entities described below are illustrated in other chapters such as those dealing with the ovary and the testis, we have included only images relevant to the pediatric age group or with specific clinical relevance.

10.2.1 Teratomas

The most common GCT in the pediatric population, teratomas are often composed of multiple embryologic layers, arising from multipotent cells, containing one or more embryonic germ layers (ectoderm, mesoderm, endoderm) of tissue foreign to the anatomic site of origin [56]. In its usual definition, tissue elements of all three blastoderm layers (endoderm, mesoderm, and ectoderm) are present; however, teratomas also occur in which only one or two of the germ layers are present (referred to as monodermal or bidermal teratomas, respectively) [6]. They are divided into both mature and immature forms. Mature teratomas are benign; they are commonly cystic and may contain several well-differentiated cell types (i.e., skin, hair, teeth, thyroid, gastric mucosa, brain tissue). Immature teratomas are less differentiated and more reminiscent of embryonal tissue, frequently including neuroectoderm typically in the form of neuroepithelial rosettes and tubules and often mixed with mature tissue [3, 6, 57].

A grading system has been developed for immature teratomas, based on the amount of neuroepithelial tissue present. Mature teratomas containing only fully differentiated tissue are considered grade 0 and immature teratomas range from grade 1 (composed of <10 % immature neuroepithelium) to grade 3 (>50 % immature neuroepithelium present). In adult ovarian teratomas, the finding of grade 2 or 3 immature teratoma predicts the likelihood of metastasis and confers a worse prognosis [57]. In children, however, it is not clear that the same relationship of grade to outcome of immature teratomas applies. A Pediatric Oncology Group study concluded that surgery alone was curative in children and adolescents with stage I immature teratomas of any grade and that chemotherapy should be reserved for cases of relapse [58–60]. However, an association between grade 3 immature teratoma and microscopic foci of YST (83 %) has been demonstrated, emphasizing the need for thorough histologic evaluation of tumors [59].

10.2.2 Dysgerminomas and Seminomas

These GCT result from abnormal premeiotic differentiation [3]. Seminoma or dysgerminoma has a reduced ability for further differentiation and is rare before puberty but occurs at gonadal sites in adolescence [1]. Testicular seminoma and ovarian dysgerminomas are analogous malignant tumors that occur more commonly in young adults. When they occur in younger children, it is typically in association with gonadal dysgenesis [3].

10.2.3 Choriocarcinoma and Yolk Sac Tumors

Choriocarcinomas and YST result from abnormal postmeiotic extraembryonic differentiation [3].

YST is the most frequent malignant histological type in pediatric GCT and is common at the sacrococcygeal, retroperitoneal, mediastinal, and prepubertal testicular locations [1, 4, 6]. In neonatal GCT, YST most commonly occurs within a teratoma; about 5 % of neonatal teratomas have a yolk sac component [4]. In older infants and young children, YST more commonly occurs as a pure YST, not as a component of a teratoma [6]. AFP elevation is seen in the presence of YST and serves as a marker of persistent or recurrent disease, especially in infants between 6 months and 2 years of age, when the normally elevated newborn levels ranging from 41,000 to 160,000 ng/ml decrease. AFP levels are reported up to 87 ng/ml within 95.5 interval assuming a logarithmic

normal distribution, decreasing to a mean of 8 ng/ml at 2 years of age before finally reaching the normal adult serum level of 0–6 ng/ml (vide infra) [61].

Choriocarcinoma is rare in childhood. It is even rarer in the infant and is usually thought to originate from a focus of choriocarcinoma that has arisen in the placenta as a variant of gestational trophoblastic disease [1, 6]. Choriocarcinoma is composed of cytotrophoblast, syncytiotrophoblast, and extravillous trophoblast, often mixed in random fashion surrounding areas of hemorrhage and necrosis. Vascular invasion is a common feature of choriocarcinomas [6]. The disease is rapidly fatal if left untreated [62]. Given that placental choriocarcinoma can also metastasize to the mother (up to 60 % of cases), if an infantile choriocarcinoma is diagnosed, the mother should also be screened for the disease [6].

10.2.4 Embryonal Carcinoma

Embryonal carcinoma possesses the ability to differentiate into embryonic and extraembryonic tumors [1, 7]. It most frequently presents in postpubertal GCT [9].

10.2.5 Gonadoblastoma

GB are benign tumors that contain both germ cells and stromal cells. As mentioned above, neonates can also present with GB in patients with dysgenetic gonads.

10.3 Classification of Pediatric GCT by Anatomical Site

10.3.1 Extragonadal GCT

10.3.1.1 Sacrococcygeal Teratomas

Sacrococcygeal teratomas [63] (SCT) are the most common extragonadal GCT in the pediatric population. They are the most common GCT in newborns and infants, occurring in approximately 1:35,000 live births. Anatomically, they have been classified into four types according to the degree of their external vs. intrapelvic/intra-abdominal extension [3, 64]. Clinically, however, SCT usually fit one of two distinct scenarios: those presenting with large predominantly external and benign (>90 %) lesions in the neonatal period or those presenting between birth and 4 years that typically have more intrapelvic/intra-abdominal tumor involvement. The latter group of tumors is much more likely to be malignant (60–90 %). It has been theorized that the absence of visible external tumor leads to a delay in diagnosis and therefore a higher incidence of cancer due to malignant degeneration. Symptoms in these patients are often the result of pelvic enlargement with compression of the bladder or rectum [3].

Large SCT can cause symptoms in utero secondary to mass effect, fetal hydrops, maternal polyhydramnios, fetal dystocia, tumor rupture (Fig. 10.1) or shunting with high-output cardiac failure, and maternal polyhydramnios. Fetal resection or other fetal intervention (cyst drainage, laser ablation, alcohol sclerosis) may be necessary. Cesarean section delivery is recommended [1, 65, 66].

The association of presacral teratoma with anal stenosis/anorectal malformation and sacral defects is known as the Currarino triad, an autosomal dominant disorder [67], secondary to mutations in the HLXB9 homeobox gene [68, 69].

Factors that Predict Recurrence of SCT

Recurrence of disease post resection ranges from 2 to 35 %, averaging 12.5 % [70]. About 50 % of patients with immature or mature teratoma that recur have a malignant component at recurrence. Recurrence is more likely among patients with immature teratoma (33 % recurrence) than for patients with mature teratoma (10 % recurrence) [6]. In a retrospective review of all teratomas diagnosed during childhood, grade of immaturity correlated with risk of recurrence; higher grade of immature teratoma

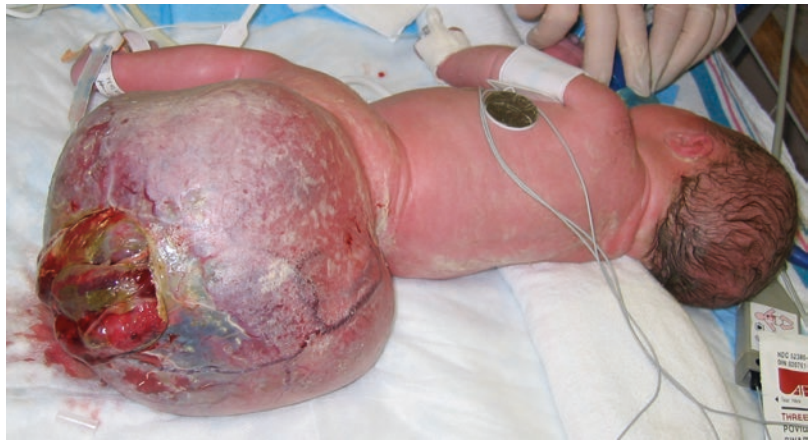

Fig. 10.1 Neonate with a giant sacrococcygeal teratoma that ruptured during delivery. Note the thin skin coverage with prominent vascular markings and the area of rupture showing solid and cystic components forming the tumor mass

was more likely to relapse than lower grade (grade 0, mature), 10 %; grade 1, 14 %; grade 2, 21 %; grade 3, 31 %) [6].

10.3.1.2 Thoracic and Mediastinal Germ Cell Tumors

Mediastinal pediatric GCT are extremely rare, representing 5 % of all GCT and 6–18 % of all pediatric mediastinal tumors [2, 3]. Thoracic GCT are more common than abdominal GCT in the newborn period (15–20 % vs. 5 %) [6, 71]. The majority of these tumors are located in the anterior mediastinum and originate in the thymus, though they can be found to rise from the posterior mediastinum, heart, or epicardial structures [6].

Older children typically present with chest pain, precocious puberty or facial fullness, and vascular congestion as a result of caval obstruction and superior vena cava syndrome. In younger children, respiratory distress is more common and often accompanied by fever [2, 3].

Approximately 15 % of pediatric mediastinal GCT are malignant and carry the worst prognosis of all germ cell tumors [6]. YST is the predominant histology in girls as well as younger boys, whereas older boys have mixed histology in over 50 % [1, 72]. An association with Klinefelter syndrome and certain hematologic disorders has been described [3, 73].

10.3.1.3 Abdominal and Retroperitoneal Germ Cell Tumors

Abdominal GCT (retroperitoneal, gastric, other abdominal viscera) account for only 5 % of all GCT [71]. They can be both intraperitoneal and retroperitoneal, and complete extirpation is the main treatment [6]. The vast majority present within the first 5 years of life, and especially the first year of life (one half of them occur during the first year of life and 73 % occur before 5 years of age) [6]. Most present during infancy with a mass and pain as the common symptoms; weight loss, constipation, and acute abdomen may also occur [1]. There is a 2:1 female predominance [3].

The majority of these tumors are benign: mature and immature teratomas predominate, with malignancy rates up to 15–24 % [70, 74, 75]. The most frequent malignant histology is YST (63 %), but choriocarcinoma and mixed tumors also occur [71].

Fetus In Fetu

The term *fetus in fetu* (FIF) is attributed to Meckel in 1800 and describes the inclusion of one fetus inside of another. Since then, around 100 cases have been reported. The embryologic origins of FIF are unclear, and it is not decided whether FIF is a monochorionic, monozygotic twin of the host

or rather a well- differentiated teratoma (fetiform teratoma) [6]. Differentiating between FIF and teratoma can be challenging; Spencer suggested that a FIF must have one or more of the following conditions: (1) be enclosed within a distinct sac, (2) be partially or completely covered by normal skin, (3) have grossly recognizable anatomic parts, (4) be attached to the host by only a few relatively large blood vessels, and (5) either be located immediately adjacent to one of the sites of attachment of conjoined twins or be associated with the neural tube or the gastrointestinal system [6, 76]. Most cases present as an asymptomatic abdominal mass during infancy. Although 80 % of FIF occurs in the upper retroperitoneum, FIF has also been reported in the liver, sacrum, pelvis, scrotum, external genitalia, mediastinum, and oropharynx. We have seen examples attaining a highly advanced degree of fetal development (Figs. 10.2 and 10.3) and even spontaneous limb movement (Fig. 10.4) [77]. The treatment is surgical resection [6, 78].

10.3.1.4 Cervicofacial Teratomas

GCT of the cervical and facial regions represent 5 % of all GCT during childhood, but GCT in this site most commonly present during the prenatal or perinatal period [79]. Nearly all are mature or immature teratomas. Approximately one-third presents with airway obstruction [80]. Giant fetal tumors have been noted with hydrops fetalis, which may lead to fetal demise [81].

10.3.2 Gonadal GCT

10.3.2.1 Testes

Pediatric testicular GCT are rare and occur in a bimodal distribution, with a small peak in the first 3 years of life and a larger peak in adolescence (Figs. 10.5 and 10.6) [1]. They are more frequently diagnosed in adolescents and young adults and are the most common solid tumor in adolescent males [9, 82]. They have distinct histologic and biologic differences associated with each age group (pre- and postpubertal) [1, 56, 83, 84].

In the prepubertal male, testicular GCT frequently present as a mass or testicular enlargement with approximately 10 % associated with a hydrocele [3, 85]. Postpubertal testicular GCT typically behave more aggressively than prepubertal GCT [9].

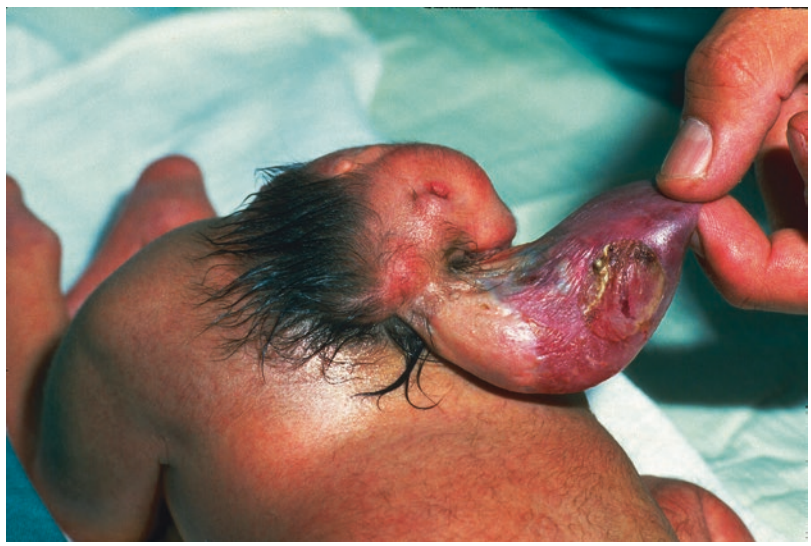

Fig. 10.2 Neonate with an example of *fetus in fetu* located in the lumbosacral area. The abnormal growth shows advanced fetiform development, featuring half of a face, with hair in a distribution similar to the scalp, forehead, the left eye, and partial development of the nose and ear. The right side of the face is continuous with a membranous sac containing neuroepithelial and other teratomatous elements

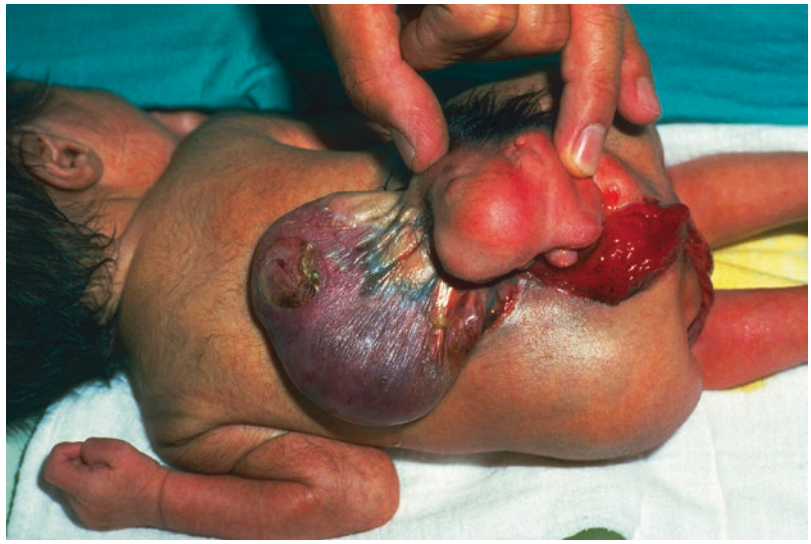

Fig. 10.3 Another view from the lesion shown in Fig. 10.2. The incomplete half of a face is flanked by a membranous sac on the left and a fleshy mass of teratomatous elements on the lower sacral area on the right

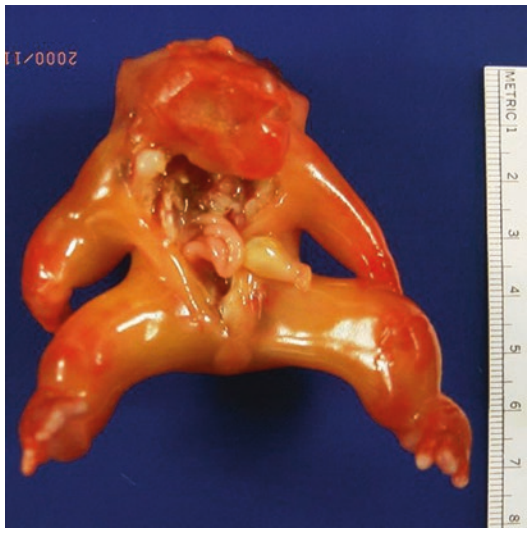

Fig. 10.4 *Fetus in fetu* with remarkably advanced fetiform anatomy showing a head with anencephalic features, a thorax and abdomen, four limbs, and digit formation. This case showed intrauterine movement of the limbs in ultrasound analysis [77]

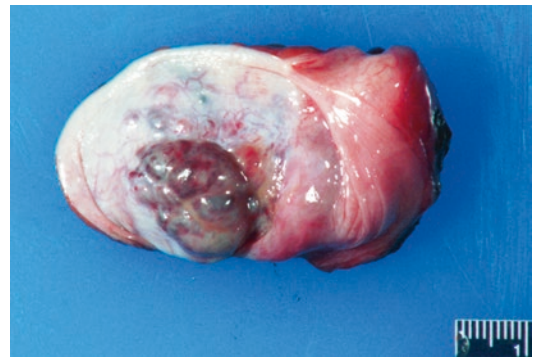

Fig. 10.5 Intratesticular mixed germ cell tumor in an adolescent. The tumor is located in the center of the testis showing a lobulated surface with hemorrhage and prominent vascularity

A review of recent pathology-based studies demonstrates that 70–75 % of prepubertal testicular tumors are benign [9–11]. Testicular GCT in prepubertal males are typically pure YST with a low incidence of metastasis (approximately 5 %) [9]. Pure teratoma is also common in children, accounting for about 40 % of such testicular tumors, but in the prepubertal patient uniformly exhibits a benign behavior [9, 86, 87]. In contrast, adolescents have a higher incidence of pure embryonal carcinoma and mixed GCT non-seminomatous, which behave more aggressively than their prepubertal counterparts, with 20–30 % presenting with metastatic disease at diagnosis [9, 11, 83]. Additionally, postpubertal teratomas are typically part of a mixed non-seminomatous GCT and have a higher potential for metastasis

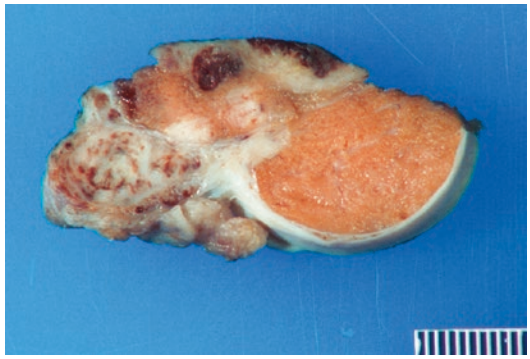

Fig. 10.6 Cross section of the tumor shown in Fig. 10.5. The mass is relatively well circumscribed, featuring several nodules of white neoplastic tissue with areas of prominent vascularity and focal infiltration into the testicular parenchyma. Hemorrhagic foci are evident on the upper portion of the lesion

and malignant degeneration than prepubertal teratomas [9, 10].

In a recent study comparing pediatric, adolescent, and adult testicular GCT, higher rates of pure seminomas were observed in adults, compared with children and adolescents; adolescents had higher proportion of mixed tumors, while younger pediatric patients were more likely to harbor pure YST or teratoma. In this study, adolescents had significantly more advanced AJCC Stage Group at presentation, and they also had lower event-free and overall survivals compared with pediatric or adult patients. As mentioned by the authors, the difference in histology may partially account for the higher stage at presentation observed in adolescents. However, adolescent patients were observed to suffer statistically significantly worse event-free survival than children or adults even when attempting to statistically account for stage and histology. A possible explanation for this difference may include the surge in hormonal stimulation occurring in adolescence, which leads to a deregulation of the complex mitosis–meiosis switch in pre-existing testicular carcinoma *in situ* [9].

In young patients other tumors, such as Sertoli cell tumors and paratesticular rhabdomyosarcomas, are more common than germ cell tumors. The exact incidence of malignancy in prepubertal testicular masses is not known, but in one series, 74 % were benign with 48 % teratomas and only 5 % YST [1, 84, 85].

10.3.2.2 Ovary

The ovary is the most common site for GCT after infancy. More than 80 % of all ovarian tumors are benign, with many of these having predominantly cystic components [1, 88]. Most ovarian GCT in children are teratomas, followed by dysgerminomas, YST, embryonal carcinomas, and mixed tumors [3, 89]. Presenting symptoms are pain, lower abdominal fullness, and less commonly an acute abdomen from torsion or tumor rupture [1].

10.3.2.3 Placenta

Primary GCT, although rarely, may also occur in the placenta [90] and even in the umbilical cord [91]. The most frequently reported type is teratoma [90], which should be distinguished from an "amorphous fetus." Other forms of nontrophoblastic primary placental neoplasia include YST [92, 93], chorangioma, and foci of hepatocellular (hepatocellular adenoma) [94] or adrenal parenchyma, which may represent a challenging differential diagnosis. Placental teratomas can be distinguished from the nonneoplastic fetus amorphus by the presence in the latter of an umbilical cord and skeletal organization [93]. YST in the placenta show the characteristic histological features seen in these tumors in other locations. Hepatocellular adenomas usually express a characteristic morphology and immunohistochemical markers, such as Hep Par1. The same is true for adrenal rests, which can be highlighted by alpha inhibin immunohistochemistry.

10.4 Interpretation of Serum Tumor Markers

Proteins secreted by certain subtypes of GCT may be used as tumor markers, and their pattern and degree of elevation can provide an indication of the likely tumor histology. AFP is generally elevated in patients with YST, although low levels of AFP (<100 mg/l) can be observed in immature teratomas (perhaps due to occult microscopic

foci of YST within the tumor) [6]. However, because AFP is also normally synthesized by fetal liver, yolk sac, and gastrointestinal tract, interpretation of AFP levels during the neonatal period must incorporate knowledge of age-related norms [6, 7, 61, 95]. AFP is elevated in all infants at birth but drops to normal levels over the course of the first 2 years of life, as its synthesis in the liver ceases. The half-life of AFP varies with age during the first months of life and stabilizes at 5–7 days by 9 months of life [95]. In adult men with metastatic testicular cancer, the degree of elevation of the tumor markers is of prognostic value, and the failure of tumor markers to decline appropriately when undergoing treatment indicates likely resistance to chemotherapy; however, neither of these factors has consistently been shown to be prognostic in children [6, 96].

When an elevated AFP level is detected, alternative possibilities should be considered including synthesis by liver tumors such as hepatoma, hepatoblastoma, and even mesenchymal hamartoma of the liver [97], or diseases such as hypothyroidism, folate deficiencies, autoimmune disorders, acquired immunodeficiency disorder, congenital heart defects, cystic fibrosis, and platelet aggregation disorders [6].

hCG is a peptide hormone produced in pregnancy, which is made by the embryo soon after conception and later by the placental syncytiotrophoblast [6]. The beta subunit of hCG serves as a marker of syncytiotrophoblasts when they are present in the tumor, typically a choriocarcinoma, where it can be significantly elevated. Its half-life is 16 h [7].

10.5 Molecular Genetics of Pediatric GCT

The genomic alterations seen in malignant GCT of infants and children are generally distinct from those occurring in tumors from postpubertal patients [4, 6, 76, 98]. In the prepubertal period, pure teratomas of the testis or of extragonadal sites nearly always exhibit normal genomic profiles, which contrasts sharply with the universally abnormal cytogenetic profile of postpubertal teratomas arising as a component of a mixed malignant GCT [6, 64, 86].

Adolescent and adult GCT tend to be aneuploid. The most consistent chromosomal aberration in adolescent/adult malignant GCT is the overrepresentation of chromosome 12p (80 %) [3, 99–101], which is found in all histologic subtypes and primary sites (ovarian, testicular, and extragonadal) [6]. Abnormalities of chromosomes 7 and 8 have also been found in up to 70 % of adolescent and adult testicular GCT [101].

Unlike teratomas, cytogenetic and other genomic aberrations are consistently reported in YST on infants and children. Array CGH profiles on patients aged <5 years have shown that most teratomas have normal profiles, with occasional loss of chromosome 20p as the only recurrent change. In contrast, YST show abnormal profiles, including gains of chromosomes 1q, 3p, and 20q, and loss of chromosomes 1p, 6q, and 18q [102].

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