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Seminar article

Current urologic care for testicular germ cell tumors in pediatric and adolescent patients

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Abstract

Testicular germ cell tumors make up 0.5% of pediatric malignancies, and 14% of adolescent malignancies. Young boys have primarily pure teratoma and pure yolk sac histologies; however, adolescent histology is mostly mixed nonseminomatous germ cell tumor. Surgical excision of the primary tumor is the crux of treatment. Chemotherapy, retroperitoneal lymph node dissection, and targeted treatment of distant metastases make even widely disseminated disease treatable. Since the discovery of platinum-based chemotherapy, testicular germ cell tumors are a highly curable disease. However, adolescents remain the group with the highest mortality. Focus has expanded beyond survival to emphasize quality of life issues when optimizing treatment algorithms.

Keywords: Testicular cancer; Germ cell tumor; Pediatric; Adolescent; Oncology

Introduction

Testicular germ cell tumors (TGCTs) are a rare but highly benign malignancies in pediatric and adolescent boys comprising 0.5% of malignant tumors in children younger than 15 years of age, with an incidence of 1.6 cases per million [1,2]. TGCTs are diagnosed in a bimodal distribution, with peak incidences below the age of 1 year and over the age of 15 years. Although the diagnosis of TGCT is rare between the ages of 4 and 11 years [3], in adolescents aged 15 to 19 years, the incidence increases to 32.6 cases per million, and represents 14% of all cancer diagnoses in this population [4].

Racial and ethnic variations are observed in both prepubertal and postpubertal TGCTs. Prepubertal TGCTs are most common in children of Asian-Pacific Island background, followed by white children. Postpubertal TGCTs are most common in whites, followed by Asian-Pacific Islanders, and then blacks [5]. Additionally, testis cancer incidence in adolescents and young men has been increasing over the last decades, with the largest increases observed in hispanic nonwhite and nonhispanic white populations [6].

Although thought to be sporadic, there are established TGCT risk factors. Men with undescended testes who undergo a prepubertal orchiopexy have a lifetime risk of TGCT 2.23 times that of men with bilaterally descended testes; this risk increases to 5.40 times if orchiopexy is performed after puberty [7]. A very recent study examined whether undergoing orchiopexies within the first 2 years of life further decreases the TGCT rate [8]. Notably, cryptorchidism has not been reported as a risk factor for prepubertal TGCTs. A family history of TGCTs in a first-degree relative confers a 3.1-fold increased risk [9]. Additionally, intratubular germ cell neoplasia (ITGCN) is a known precursor to TGCTs in adults and is associated with a 50% development of a TGCT within 5 years of diagnosis of ITCGN [8]. ITGCN and TGCTs share many immunohistochemical staining patterns and characteristic genetic mutations in chromosome 12p in adult men. However, prepubertal TGCTs do not show histologic or genetic similarities to ITCGN [10].

In contrast with established risk factors, there are conflicting data regarding the risk of testicular microlithiasis (TM). TM has been observed to coexist with TGCT and is associated with the finding of ITGCN on biopsy in adult men. However, TM has not been associated with children and adolescents with ITGCN, and the relationship between

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TM and TGCTs is unclear [11]. Therefore, TM should be considered as a possible but not definite risk factor for the development of TGCTs.

Differential diagnosis and presentation

Most of the (85%–90%) TGCTs present as a painless testicular mass detected by the patient, parent, or clinical examination. Trauma, persistent swelling, bruising, and hernia/hydrocele account for most other presentations [12]. Approximately 15% to 20% of patients with a testicular tumor have a concomitant hydrocele, possibly delaying timely diagnosis. TGCT must also be suspected and differentiated from other scrotal pathology, including testicular torsion, rupture, epididymitis, and paratesticular masses. Paratesticular rhabdomyosarcoma should be high on the differential diagnosis in this age group, as it represents 5% of all testicular and paratesticular malignancies [13]. Other non-GCTs of the testis such as gonadal stromal tumors (leydig cell, sertoli cell, granulosa cell, and mixed stromal tumors) also present with asymptomatic testicular masses. The notable exception is the potential for precocious puberty in virilizing or feminizing stromal tumors [14]. Additionally, metastatic TGCTs may present with symptoms from metastatic disease such as hemoptysis, cough, hematochezia, and back pain.

Regarding early detection, testicular self-examination (TSE) has been advocated to improve identification of TGCT while still at a low stage. Although the United States Preventive Task Force assigned TSE a "D—the harms outweigh the benefits" rating [15], their analysis did not consider the difference in treatment cost and morbidity between low-stage and high-stage testicular cancers. Instead, they considered the workup cost of benign lesions and patient anxiety compared to the overall survival rates. A more nuanced cost evaluation [16] published subsequently showed that detection, treatment, and surveillance in advanced testicular cancer costs 2.4 times more than that of early stage detection, with the cost of 322 false positive TSEs resulting in office visits equaling that of a single advanced TGCT. Additionally, the United States Preventive Task Force focuses heavily on overall survival, which is too blunt a metric when assessing a disease that has a relatively high potential for cure, such as TGCT. The authors feel that considering the cost and morbidity from treatment of advanced metastatic TGCTs, adolescents would benefit from being educated about TGCTs and TSE.

Prepubertal vs. postpubertal tumors

Classically in cancer care, patients have been divided into pediatric and adult populations, leaving adolescents inconsistently assigned to one of these other age groups. However, there is increasing recognition that the 15- to 19-year-old age group has different outcomes than those of the 0- to 14-year-old group [17]. A recent institutional review of adolescent patients with TGCT suggesting a decreased event-free survival in adolescents when compared with either pediatric or adult patients demonstrates further support for adolescent disease being considered distinctly [18].

Despite significant improvements in pediatric oncology outcomes, success has not been enjoyed equivalently in the adolescent age group. Lack of progress can be attributed to numerous challenges. Adolescence is a difficult, dynamic psychological and emotional period, which contributes to delays in presentation and diagnosis [19], and transition between pediatric and adult providers can limit access to appropriate care [20]. Furthermore, in contrast with the very high clinical trial participation of the pediatric age group leading to advances in the treatment of many other malignancies such as Wilms tumor and rhabdomyosarcoma [17], there is a paucity of trials focused on the adolescent population.

Largely because of the benign nature of prepubertal tumors, adolescents with TGCT have traditionally been included with the adult population. In recent studies, prepubertal testis tumors are typically demonstrated to be of benign pathology (70%–75%) [14,21], with malignant yolk sac tumor (YST) accounting for only 14% of cases. Teratoma comprises the largest proportion of prepubertal testicular tumors, accounting for 48% [14]. Additionally, even in the malignant prepubertal tumors only 5% of the prepubertal YSTs are metastatic at presentation, compared with 20% to 30% of postpubertal GCTs [22]. Further evidence of the aggressive and unique nature of adolescent patients with TGCTs is that although 85% of prepubertal patients present with Stage I disease only 33% of postpubertal adolescents present with localized disease [18,23].

The underlying biology of testicular tumors varies between prepubertal and postpubertal cases. In the adult and postpubertal patients, testicular tumors invariably develop from ITGCN. Puberty likely plays an important role, with increased testosterone stimulating the dormant germ cells to divide along 2 malignant pathways. One distinct pathway leads to seminoma, the other leads to nonseminomatous histology: relatively undifferentiated embryonal carcinoma (EC), more differentiated teratoma, trophoblastic choriocarcinoma, and YST [24]. Presumably, this second pathway contributes to the clinically noted increase in tumors with mixed cell lines after puberty.

Prepubertal tumors are not thought to develop from ITGCN, and thus do not follow the same differentiation pathway as adult and adolescent tumors [25]. Virtually all adult and postpubertal TGCTs have a gain of genetic material on chromosome 12p. Conversely, alteration of chromosome 12p is not seen in prepubertal patients; instead, characteristic changes to chromosomes 1, 6, and 20 have been noted [26]. These data fit with the prepubertal clinical presentation of predominantly benign testicular tumors such as pure teratoma, with pure YST as the primary malignant histology [14].