Testis Tumor

22

Jonathan Ross

Introduction

Pediatric testis tumors are relatively rare compared with testis tumors occurring postpubertally and with other pediatric urologic tumors, such as Wilms' tumor. The incidence of testis tumors in children is 0.5–2.0 per 100,000 children, accounting for only 1–2 % of all pediatric tumors. Testis tumors are classified by the putative cell of origin. Those arising from germ cells include yolk sac tumors (YSTs), teratomas, and epidermoid cysts. Stromal tumors include juvenile granulosa cell tumors, Leydig cell tumors, Sertoli cell tumors, and mixed or undifferentiated stromal tumors. Gonadoblastomas contain both germ cell and stromal elements. Secondary tumors rarely affect the testis, although testicular involvement with acute lymphoblastic/lymphocytic leukemia (ALL) is an important exception. By far the most common testis tumors in children are teratomas which are benign and YSTs which are malignant.

Until recently, because of their rarity, most information on prepubertal testis tumors was obtained from small series and case reports. The appropriate management of YSTs in children has been clarified by recent multicenter trials, including those by the Children's Oncology Group. There is little data regarding the behavior and management of testis tumors occurring in adolescents. The majority of testis tumors in the teen years are malignant mixed germ cell tumors, the same as seen in adults. These tumors have been extensively studied in the adult population, and it is assumed that the adolescent tumors are equivalent.

Presentation and Evaluation

While testis tumors in children are rare, a prompt diagnosis is obviously important when they do occur, and primary care physicians will often be the first to see these patients. Testis tumors most commonly present as a testicular mass. The mass may be noted by the patient or detected on a routine physical examination. Approximately 10 % of patients have a hydrocele at presentation, which may be secondary to the tumor or coincidental. The presence of a hydrocele may delay the diagnosis of a testis tumor, and an ultrasonogram should be considered for any boy with a hydrocele in whom the testis cannot be palpated. Occasionally, patients will present with pain—presumably from an acute bleed into the tumor. Physical examination will usually reveal a hard mass in the testicular parenchyma. These masses must be distinguished from extratesticular lesions such as epididymal cysts (see Table 22.1).

J. Ross, M.D. (✉)
Department of Pediatric Urology, University Hospitals Rainbow Babies and Children's Hospital, 11100 Euclid Avenue RBC 2311, Cleveland, OH 44106, USA
e-mail: jonathan.ross@uhhospitals.org

R. Rabinowitz et al. (eds.), *Pediatric Urology for the Primary Care Physician*, Current Clinical Urology,
DOI 10.1007/978-1-60327-243-8_22, © Springer Science+Business Media New York 2014

Table 22.1 Differential diagnosis of a scrotal mass

Lesion	Physical exam	Typical lesion appearance
Testicular tumor	Hard mass within the testis	Heterogeneous mass within the testis
Paratesticular tumor (rhabdomyosarcoma)	Usually very large hard irregular scrotal mass	Heterogeneous mass encasing the testis
Epididymal cyst	Smooth round mass usually in the head of the epididymis and separate from the testis	Round fluid-filled cyst in the epididymis separate from the testis
Hydrocele	Round smooth transilluminating mass filling the scrotum	Fluid surrounding normal testis
Hernia	Soft irregular mass filling inguinoscrotal region—may feel gas—usually reducible	Bowel loops in the scrotum with normal testicle
Testicular torsion	Extremely tender swollen high-riding testis with erythema of scrotal wall—reactive hydrocele may be present	Swollen testis with lack of blood flow
Torsion of the appendix testis	Moderately tender nodule at upper pole of the testis with erythema of the scrotum—reactive hydrocele may obscure findings	Normal testicular blood flow with swollen appendix—may not be distinguishable from epididymitis
Epididymitis	Tender epididymis with normal testis—inflammation may include the testis	Swelling and increased blood flow to the epididymis—may not be distinguishable from appendiceal torsion

Once a testis tumor is suspected, a thorough physical examination is undertaken. Signs of androgenization or feminization should be sought. Metastatic disease is uncommon, and the primary sites—the retroperitoneum and lungs—are unlikely to result in symptoms or physical findings. In rare cases, metastases to the bone or central nervous system may occur. Symptoms or signs of involvement at these locations are important in guiding the radiographic evaluation.

The initial radiographic evaluation of children with a suspected testis tumor is limited. Because many prepubertal testis tumors are benign, any metastatic evaluation is usually deferred until tissue confirmation of the tumor's histology is obtained. However, when a malignancy is suspected (e.g., in children with an elevated alpha-fetoprotein (AFP) level or in adolescents), a computerized tomography scan (CT) of the abdomen may be obtained preoperatively. Imaging of the primary tumor is sometimes helpful. Ultrasonography is most often employed (see Fig. 22.1). It is able to distinguish testicular tumors from benign extratesticular lesions. The extent of testicular involvement can also be determined, which is helpful if testis-sparing surgery is being considered. The ultrasonographic appearance of specific testis tumors has been described. Unfortunately, ultrasound findings are too inconsistent to allow a definitive diagnosis of a specific tumor.

Tumor markers play an important role in the evaluation and follow-up of childhood testis tumors. AFP is the most important tumor marker. It is an albumin precursor synthesized by the yolk sac and fetal liver and gut. AFP is specific for YST. Levels are elevated in 80–90 % of children with a YST, and AFP has a biological half-life of approximately 5 days. An elevated level of AFP preoperatively in a child nearly always reflects the presence of a YST. An important caveat is that AFP levels are normally quite high in infancy (see Table 22.2). An "elevated" level in a boy less than 1 year of age does not rule out the possibility of a benign tumor, such as teratoma. The beta subunit of human chorionic gonadotropin (HCG) is an important marker in adolescent testis tumors, but this is rarely elevated in children because the histological types that lead to elevated HCG levels are rarely encountered in prepubertal testis tumors.

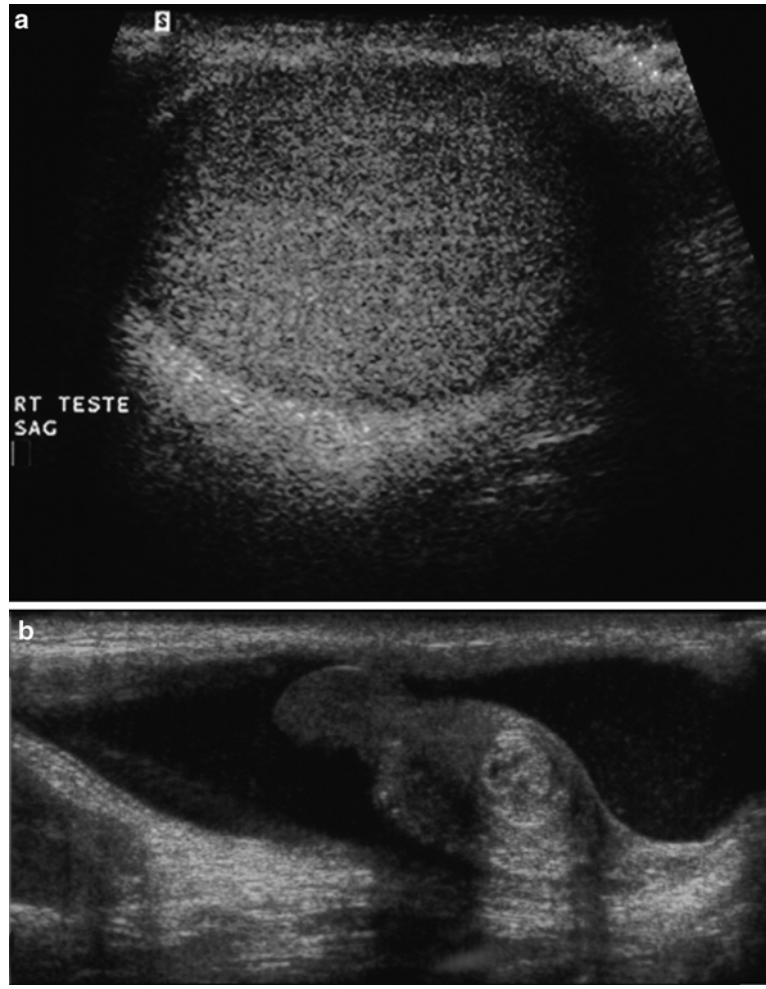

Fig. 22.1 Ultrasonic findings of a testicular tumor in a boy presenting with a hydrocele. (**a**) A normal testis which has an ovoid shape and homogenous texture. (**b**) The affected testicle. A round hyperechoic mass is seen within the normal parenchyma surrounded by the fluid of the hydrocele

Table 22.2 Alpha-fetoprotein (AFP) levels in normal infants (data from Wu JT, Book IL, Sudar K, Serum alpha-fetoprotein (AFP) levels in normal infants, Pediatr Res 1981; 15:50–52)

Age	AFP level (ng/mL)	Standard deviation
Newborn (term)	48,406	±34,718
1 month	9,452	±12,610
2 months	323	±278
3 months	88	±87
4 months	74	±56
5 months	46.5	±19
6 months	12.5	±9.8
7 months	9.7	±7.1

Management

Any child with an intratesticular mass should be referred promptly for surgical intervention. Testis tumors can be rapidly growing, and evaluation and treatment should be undertaken immediately. The standard approach to a testis tumor is an inguinal orchiectomy. Increasing consideration has been given to performing testis-sparing surgery for benign testicular tumors. This is particularly attractive in prepubertal patients because many, if not most, prepubertal tumors are benign.

The preoperative evaluation plays a significant role in patient selection for testis-sparing surgery. An elevated AFP level in a child over 1 year of age virtually always reflects the presence of a YST and precludes a testis-sparing approach. However, in older children with a normal AFP and in infants, the likelihood of a benign tumor is considerable. This is also true in boys presenting with androgenization. For these patients, if there is salvageable normal testicular parenchyma evident, an inguinal exploration with excisional biopsy of the lesion should be considered so that a testis-sparing approach may be performed if a benign histology is confirmed on frozen section analysis. This approach is rarely indicated in adolescents, for whom the majority of tumors are malignant. After orchiectomy, some children with testicular tumors require additional evaluation and therapy. The type of adjunctive management selected will depend on the histology of the primary tumor and the results of radiographic and biochemical studies. The intensity of follow-up also depends on the malignant potential of the primary tumor.

Germ Cell Tumors

Yolk Sac Tumor

YST accounts for nearly all malignant prepubertal testis tumors. The majority of patients with YST present under 2 years of age. Metastatic evaluation of YSTs includes a computed tomography (CT) scan of the abdomen and pelvis to rule out retroperitoneal lymph node or hepatic metastases and a chest X-ray or chest CT scan to rule out pulmonary metastases. Bone and brain metastases are rare. Therefore, bone scans and head CT scans are obtained only when there is clinical suspicion of metastases at these sites. Serum AFP level is also measured postoperatively. Its half-life is approximately 5 days, and a persistent elevation of AFP after orchiectomy suggests the presence of metastatic disease. However, AFP levels as high as 50,000 ng/mL can occur in normal infants, and levels greater than 50 ng/mL can occur in children up to 6 months of age. Therefore, serial measurements are particularly important in infants.

A tumor-node-metastasis (TNM) staging system exists for testis tumors, but its applicability to pediatric tumors is limited owing to the infrequent employment of retroperitoneal lymph node dissection (RPLND) in these patients. Several other systems have been proposed. The simplest system segregates patients into three stages. Stage I patients have tumor confined to the testis with a negative metastatic evaluation and a normalization of AFP postoperatively. Stage II patients have retroperitoneal disease detected by radiographic studies or RPLND and/or a persistent elevation of AFP postoperatively. Stage III patients have metastatic disease beyond the retroperitoneum. Approximately 80 % of children with YSTs have stage I tumors.

Historically, RPLND was the most common form of adjunctive therapy for the treatment of YSTs. With the widespread use of AFP to detect occult metastases and improvements in multiagent chemotherapy, the reliance on RPLND to diagnose and treat metastatic disease in prepubertal patients has waned. The operative morbidity of RPLND in children is significant, including wound complications, bowel obstruction, chylous ascites, and anejaculation as adults due to injury to the sympathetic nerves. Currently retroperitoneal surgery in prepubertal patients is limited to excisional biopsy of retroperitoneal masses in patients with a normal AFP and excisional biopsy of residual masses following chemotherapy—both rare events.

Chemotherapy is very effective in treating metastatic YST. The most commonly used regimens include cisplatin or carboplatin in combination with other agents such as etoposide and bleomycin. Because children with metastatic disease often have multiple sites of spread, chemotherapy is particularly appropriate for these patients. Radiation does not play a role in the standard treatment for metastatic YST. The selection of adjuvant therapy for YST depends on the stage of the tumor. The trend in managing stage I tumors is toward observation. The recurrence rate for patients with stage I tumor managed by observation is approximately 15 %, and virtually all of these patients can be salvaged with chemotherapy. Patients with stage I tumor are therefore generally observed closely without adjuvant therapy. Patients are evaluated on

a regular basis with serum AFP level, CT of the abdomen and pelvis, and chest X-ray. Recurrent disease is usually treated with chemotherapy. If the patient remains free of disease for 2 years, then he is almost certainly cured, though annual follow-up is continued.

Patients with a negative metastatic evaluation, but a failure of the AFP to normalize, are generally treated with chemotherapy. It must be remembered that a "normal" AFP in infants may be quite high. Patients with positive lymph nodes on CT scan are also usually treated with chemotherapy. An RPLND is considered when retroperitoneal disease is not responding to chemotherapy or for a persistent mass after chemotherapy when the AFP level has normalized. Some of these residual masses will contain only necrotic tumor and calcifications. Chemotherapy is also the mainstay of treatment for patients with hematogenous metastases. Chemotherapy with second-line agents is used for patients failing to respond to standard agents. Surgical excision and radiation should also be considered for those with limited sites of metastatic disease who fail to respond to chemotherapy. Even in the face of metastatic disease, the prognosis for children with YST is excellent.

Teratoma and Epidermoid Cyst

Teratoma is the most common benign prepubertal testis tumor. The median age of presentation is 13 months, with several patients presenting in the neonatal period. Histologically, teratomas consist of tissues representing the three germinal layers—endoderm, mesoderm, and ectoderm. The presence of cysts on ultrasonography suggests the diagnosis but is neither sensitive nor specific. Epidermoid cysts are benign tumors composed entirely of keratin-producing epithelium. They are distinguished from dermoid cysts, which contain skin and skin appendages, and from teratomas, which contain derivatives of other germ cell layers. On ultrasonography, most epidermoid cysts appear as discrete intratesticular masses with areas of increased echogenicity corresponding to the keratin debris or peripheral calcification. Other areas of decreased echogenicity may also be present corresponding to regions of the cyst not filled with debris. However, these findings are variable, and an epidermoid cyst may appear as a fairly homogeneous solid mass. The primary value of ultrasonography is in characterizing the mass as intratesticular and in excluding abnormalities elsewhere in the testis that would necessitate total orchiectomy. Teratomas and epidermoid cysts are universally benign in prepubertal children. Testis-sparing surgery is a reasonable consideration for these patients. In older children with teratoma, the normal testicular parenchyma must be carefully evaluated. If there is histological evidence of pubertal changes, then an orchiectomy is performed because teratomas are potentially malignant in postpubertal males. Epidermoid cysts are benign in children and adults and may be treated by simple tumor excision. For patients with epidermoid cyst and prepubertal patients with teratoma, no radiographic studies or follow-up for the development of metastatic disease is required. Because of the potential for malignancy, postpubertal patients with teratoma should be evaluated and followed on the same protocol as adults with other malignant germ cell tumors.

Adolescent Germ Cell Tumors

Adolescent testis tumors are usually malignant, the most common histologies being embryonal cell or mixed germ cell. RPLND plays a larger role in these patients than in younger children with YSTs. Depending on the specific histology and the philosophy of the treating physicians, stage I germ cell tumors in young adults may be treated with observation, a brief course of chemotherapy or an RPLND. Patients with metastatic disease are usually treated with chemotherapy, though RPLND may have a role in patients with minimal retroperitoneal disease.

Stromal Testis Tumors

Stromal testis tumors are rare in children, and there are no large series to guide their management. However, anecdotal reports and small series in the literature offer some experience on which to base therapy. Leydig cell tumors are universally benign in children. They usually present between 5 and 10 years of age with precocious puberty. Presenting symptoms include an

early growth spurt, prominent external genitalia, erections, pubic and axillary hair, facial hair, acne, and deepening of the voice. Other causes of precocious puberty include central nervous system lesions, adrenocortical carcinoma, and congenital adrenal hyperplasia (CAH). In the presence of a testicular mass, a Leydig cell tumor is the most likely diagnosis. An elevated testosterone level with low or normal follicle-stimulating hormone and luteinizing hormone levels is consistent with a Leydig cell tumor. Normal levels of 17-hydroxyprogesterone exclude the diagnosis of CAH. Because virilization may present before a tumor is palpable, all boys with precocious puberty and no obvious cause should undergo an ultrasonogram of the testicles to rule out a small tumor. Leydig cell tumors may be treated by orchiectomy or testis-sparing excision. Persistence of androgenic effects may be due to a contralateral tumor, but this is rare in children. However, even after successful removal of a solitary tumor, androgenic changes are not completely reversible, and some children may proceed through premature puberty.

Sertoli cell tumors account for only 2 % of primary prepubertal testis tumors. Sertoli cell tumors are usually hormonally inactive in children, although they may occasionally cause gynecomastia or isosexual precocious puberty. Whereas all reported cases to date have been benign in children under 5 years of age, there have been a few cases of malignant Sertoli cell tumors in older children. Orchiectomy is sufficient treatment in infants, although a metastatic evaluation could be considered in infants with worrisome histological findings. Older children should undergo an abdominal CT scan and chest x-ray to rule out metastases. When metastatic disease is present, aggressive combination treatment including RPLND, chemotherapy, and radiation therapy should be considered.

The large cell calcifying Sertoli cell tumor is a clinically and histologically distinct entity with a higher incidence of multifocality and hormonal activity. Whereas standard Sertoli cell tumors are more common in adults, large cell calcifying Sertoli cell tumors are found predominantly in children and adolescents. Most present with a testicular mass. Approximately one fourth of patients have bilateral and multifocal tumors. The presence of calcifications results in a characteristic ultrasonographic appearance including multiple hyperechoic areas. Approximately one third of patients with large cell calcifying Sertoli cell tumor have an associated genetic syndrome and/or endocrine abnormality. The two syndromes most commonly associated with large cell calcifying Sertoli cell tumor are Peutz-Jeghers syndrome and Carney's syndrome. Peutz-Jeghers syndrome is an autosomal dominant disorder consisting of mucocutaneous pigmentation and hamartomatous intestinal polyposis. Features of Carney's syndrome include myxomas of the skin, soft tissue, and heart; myxoid lesions of the breast; lentigines of the face and lips; cutaneous blue nevi; Cushing's syndrome; pituitary adenoma; and schwannoma. Awareness of this familial syndrome is important because patients and their first-degree relatives are at risk for the potentially lethal associated entities. Whereas they are occasionally malignant in adults, large cell calcifying Sertoli cell tumors have been universally benign in patients under 25 years of age. Orchiectomy is sufficient treatment for children.

Juvenile granulosa cell tumor is a stromal tumor bearing a light microscopic resemblance to ovarian juvenile granulosa cell tumor. Granulosa cell tumors occur almost exclusively in the first year of life, most in the first 6 months. Structural abnormalities of the Y chromosome and mosaicism are common in boys with juvenile granulosa cell tumor. Several cases have been described in association with ambiguous genitalia. These tumors are hormonally inactive and benign. Although these children should undergo chromosomal analysis, no treatment or metastatic evaluation is required beyond orchiectomy or tumor enucleation.

Gonadoblastoma

Gonadoblastomas contain both germ cells and stromal cells. Gonadoblastomas occur more frequently in postpubertal patients, but they may be seen in childhood. Gonadoblastoma occurs almost

exclusively in dysgenetic gonads, usually in association with an intersex disorder. Gonadoblastoma is more likely to occur in dysgenetic gonads occurring in patients with a Y chromosome or evidence of some Y chromatin. Gonadoblastomas occur in 3 % of patients with true hermaphroditism and 10–30 % of patients with mixed gonadal dysgenesis or pure gonadal dysgenesis and an XY karyotype. They also occur commonly in the dysgenetic testis syndrome.

Gonadoblastomas are usually asymptomatic—often detected incidentally when dysgenetic gonads are removed. However, virilization has been associated with some of these tumors. Forty percent of gonadoblastomas are bilateral. Whereas gonadoblastomas are benign, overgrowth of the germinal components leading to a dysgerminoma (also known as seminoma) occurs in as many as 50 % of cases. Approximately 10 % develop overtly malignant tumors. While most invasive tumors associated with intersex occur in young adulthood, there are several reports in children as well.

Gonadoblastomas are treated by orchiectomy. Indeed, any dysgenetic gonad in a child with a Y chromosome should be removed prophylactically in infancy or early childhood. Tumors are much less likely in patients who lack a Y chromosome such as those with Turner's syndrome or XX patients with pure gonadal dysgenesis. When malignant degeneration is present, a metastatic evaluation and appropriate follow-up are indicated. Fortunately, these tumors are radiosensitive and have a favorable prognosis.

Hyperplastic Nodules in Congenital Adrenal Hyperplasia

Adrenal rest tissue can be found along the spermatic cord and in the testicular hilum of newborns. This tissue generally regresses in infancy but may persist in boys with CAH. Stimulation of the tissue by high levels of adrenocorticotropic hormone can lead to multiple, usually bilateral nodular growths in the testes. Some patients with milder unrecognized forms of CAH may present with testicular masses. In such patients who present with precocious puberty, the testicular masses could be misinterpreted as Leydig cell tumors. The nodules of CAH are very similar histologically to Leydig cell tumors, potentially perpetuating the error even after excision. Therefore, any child presenting with precocious puberty and a testicular mass(es) should undergo an endocrinologic evaluation, including measurement of serum 17-hydroxyprogesterone, to distinguish these two entities.

The hyperplastic nodules of CAH are benign. Many, but not all of these nodules, will resolve or significantly reduce in size in response to steroid replacement or an increase in steroid therapy. If this occurs, the patient may safely be followed with serial examinations and/or ultrasonography. Because any testicle may develop a true testicular tumor, a biopsy should be performed on any nodules that fail to respond to adjustments in steroid replacement.

Leukemia

Secondary malignancies of the testicle are rare. The most important is ALL. Only 2 % of boys with ALL will have overt clinical evidence of testicular involvement at diagnosis. This is usually reflected in firm diffuse enlargement of one or both testicles and portends a poorer prognosis. Subclinical (i.e., microscopic) involvement of the testes is present in approximately 20 % of patients with ALL at the time of diagnosis. However, most patients with microscopic testicular involvement achieve a complete remission following modern standard chemotherapy. Conversely, some patients without microscopic evidence of testicular involvement at diagnosis will ultimately relapse in the testicles. Therefore, pretreatment testicular biopsy is unnecessary because it does not predict those patients who are prone to have persistent or relapsing disease at that site.

Relapse in the testicles after chemotherapy used to occur in approximately 10 % of patients. The testis may represent a protected site from chemotherapy, more prone to relapse. However, with modern ALL chemotherapy, testicular

relapse occurs in less than 1 % of cases. Postchemotherapy biopsy in the absence of physical findings (to rule out occult persistence of tumor in the testes) is therefore no longer routine. Those few patients with testicular enlargement persisting or occurring after chemotherapy should undergo biopsy to confirm testicular ALL. Most of these patients will be found to have relapsed at other sites as well and require additional intensive systemic chemotherapy to prevent ultimate clinical hematological relapse. Radiation to the testicles is also required. In the rare cases of unilateral testicular relapse, consideration is given to orchiectomy. This could allow lower doses of radiation to the remaining testicle and, ultimately, better endocrine function than would occur with higher doses of radiation to both testicles if the affected testicle were left in place. In any case, most patients with testicular relapse after chemotherapy can be salvaged and attain long-term survival. Relapse during chemotherapy portends a more dire outcome.

Recommended Reading

Coppes MJ, Rackley R, Kay R. Primary testicular and paratesticular tumors of childhood. Med Pediatr Oncol. 1994;22:329.

Cortez JC, Kaplan GW. Gonadal stromal tumors, gonadoblastomas, epidermoid cysts, and secondary tumors of the testis in children. Urol Clin North Am. 1993;20:15.

Ross JH, Rybicki L, Kay R. Clinical behavior and a contemporary management algorithm for prepubertal testis tumors: a summary of the Prepubertal Testis Tumor Registry. J Urol. 2002;168:1675.

Schlatter M, Rescorla F, Giller R, et al. Excellent outcome in patients with stage I germ cell tumors of the testes: a study of the Children's Cancer Group/Pediatric Oncology Group. J Pediatr Surg. 2003;38:319.