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Germ Cell Tumors of Gonadal/Sacrococcygeal Area

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Epidemiology

Germ cell tumors (GCTs) constitute 2%-3% of childhood malignancies.[1] GCTs occur in a bimodal distribution in infants and adolescents.[2,3] There are 4.9 cases of germ cell or other gonadal tumors per million children less than 15 years of age and 26 cases per million children age 15-19 years. The major risk factor for developing a gonadal GCT is gonadal dysgenesis, with incidence up to 30 percent in these patients. GCTs also occur in 5%-10% of patients with undervirilization syndromes. Risk is thought to increase with age, therefore a gonadectomy during early childhood is recommended.[3,4,5,6,7] In males with cryptorchidism, there is a 3-9 fold increase risk for GCTs compared to the normal male population.[3,8,9]

There are several subtypes of GCTs, but all are thought to have a common cell of origin, the primordial germ cell. Many of the tumor characteristics depend upon when in development the tumor occurs, the gender of the patient, and specific genetic aberrations. For a list of histologic subtypes see Table 1.

Pathology

Teratoma

Teratomas most commonly appear in children less than 4 years of age. Teratomas usually have a benign course even if they have poorly differentiated elements or if immature neuroectodermal components are present. In prepubertal patients only surgery is required for treatment.[10,11] Post-puberty these tumors are considered malignant irregardless of absence of poorly differentiated elements.

Mature Teratomas

Mature teratomas are the most common subtype of childhood GCTs, arising from ovary or extragonadal tissue. It is composed of all three germ cell layers: ectoderm, mesoderm and endoderm. Teratomas arising from the gonads are encapsulated and either multicystic or solid.

Immature Teratomas

Immature teratomas appear similar to mature teratomas, but have immature components such as neuroepithelium. They are almost universally benign in children unless they have foci of malignant germ cell elements or if there are specific clinical characteristics such as advanced stage.

Yolk Sac Tumor (Endodermal Sinus Tumor)

Yolk sac tumors are the most common pure malignant GCTs in young children and the most common GCTs in testes of infants and young boys.[12] There are four general patterns of tumor, which have no prognostic indication, but help for identification of the tumor.

Germinoma (dysgerminomas or seminomas)

Pure seminomas are the most common malignant GCTs in males older than 20 years of age, but are uncommon in younger patients. However, seminomas can appear in younger patients with sex chromosomal abnormalities or cryptorchidism. Strong staining for placental alkaline phosphates (PLAP) and c-kit is present. Testicular seminoma and ovarian dysgerminomas are analogous malignant tumors that occur more commonly in young adults.

Embryonal Carcinoma

This subtype rarely occurs in pure form in children. Embryonal carcinomas can be distinguished from yolk sac tumors because cells are alpha-fetal protein (AFP) negative and usually lack eosinophilic hyaline globules. These tumors are also positive for CD 30.

Choriocarcinoma

Rarely occurs in pure form, but can be seen as a foci in mixed, malignant germ cell tumors in adolescents.[1,12,13] There are two cell types present, cytotrophoblasts and syncytiotrophoblasts, which stain positive for beta-human chorionic gonadatropin (â-HCG).

Gonadoblastoma

This is a benign tumor found in dysgenetic gonads of phenotypic females who have a portion of the Y chromosome. Germinomas frequently develop with gonadoblastoma.[1]

Clinical Features/Presentation

The main presentation for a testicular tumor is as a testicular mass or swelling. Males can also present with back pain from retroperitoneal disease, but this is a rare presentation in children. In a collaborative study in the United States, the preoperative diagnosis at time of procedure was tumor in only 50% of the cases (8/16 patients). It was undescended testes in 1, acute scrotum in 1, torsion in 2 and hydrocele in 4 patients.[14] Approximately 20% of masses are associated with reactive hydrocele at time of diagnosis, thus an ultrasound can help distinguish an uncomplicated hydrocele from a secondary, reactive hydrocele. This is especially true in patients in which the testicle is not palpable.[1,15]

In females the presentation is fairly variable. Many patients have non-specific symptoms such as nausea/vomiting, subacute or chronic pain, abdominal distention, or change in weight. Some patients may present with a palpable abdominal mass. In the most recent collaborative study in the United States, data on clinical presentation was available for 82 patients. Most presented as per the previously described signs or symptoms, but 9 had acute abdomen, 3 had ovarian torsion, and 4 had signs of precocious puberty.[16]

Diagnosis

In making the diagnosis of testicular GCT, a thorough history for risk factors should be obtained. As discussed previously the major risk factor for developing testicular tumor in childhood is undescended testis, but other risk factors include contralateral testicular tumors, undescended testis/cryptorchidism, history of poor semen analysis, and testicular tumor among first degree relatives, particularly in a father or brother.[17]

As part of the laboratory evaluation for both testicular and ovarian GCTs, a serum lactate dehydrogenase (LDH), â-HCG and AFP should be obtained, since these markers can be used to monitor response to therapy as well as monitor for relapse. As discussed previously an ultrasound of the testis should be performed using a >7.5-MHz transducer.[17] In females ultrasound is useful in differentiating a cystic from solid mass. Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI) of the abdomen and pelvis can help evaluate the extent of the tumor, the retroperitoneal lymph nodes and other possibly involved structures. Metastatic evaluation should include a CT scan of the chest and a radionucleotide bone scan.[14,18]

Staging/Prognostic Factors

The staging system currently used in the United States is detailed in Table 2.[14,18] In children only the site of the primary tumor and elevation of AFP have been associated with worse event free survival (EFS) and overall survival (OS). In adults several other factors have been predictive of outcome.[19]

Treatment Options

Surgery

The overall goal in treating pediatric patients with malignant GCT is to cure the patient with preservation of the patient's fertility. Surgery, when feasible, is the frontline treatment for malignant GCT.

Testicular GCT

Orchiectomy is recommended to be performed prior to chemotherapy. Radical orchiectomy should be performed through an inguinal incision with high ligation of the spermatic cord. Vascular control of the spermatic cord is obtained prior to mobilization of the testicle into the field. Scrotal violation through biopsy or open surgery is to be avoided.[17,20] Giguere *et al*. reported recurrence of tumor associated with procedures that violate the scrotum, tunica vaginalis and tunica albuginea.[20] If there is a scrotal biopsy with delayed orchiectomy, then a hemiscrotectomy is recommended.

Ovarian GCT

For ovarian tumors it is recommended that patients undergo a complete surgical staging. During surgery, peritoneal fluid, if present, should be collected to send for cytology. If peritoneal fluid is not present, then peritoneal washes should be obtained. Surfaces of the pelvic viscera, lymph nodes, omentum, liver surface and peritoneal surfaces are to be inspected, and peritoneal nodules biopsied and/or removed when feasible. With regards to local control, the involved ovary/ies should be removed with preservation of the fallopian tubes and uterus whenever possible. A complete omentectomy should be performed if it is adherent or there are any nodules, though a partial can be performed if it includes all areas of suspicion. Surgeons should be familiar with the International Federation of Gyencology and Obstetrics (FIGO) staging system (Table 3) and how their findings will affect patient's staging.[21]

Gliomatosis Peritonei

Glomatosis peritonei are nodules that are implanted in the peritoneum or lymph nodes that are composed of mature glial tissue. If all the lesions are mature glial tissue, then these nodules have no impact on staging or diagnosis. If lesions reoccur, then surgical resection is the treatment of choice.

Lymph node sampling

In testicular tumors lymph node sampling is recommended only if retroperitoneal lymph nodes are greater than 2 cm on the staging CT scan studies. If lymph nodes are positive, then the patient is upstaged to stage III. If lymph nodes are greater than 4 cm, then sampling is unnecessary. For patients with ovarian tumors, lymph node sampling of internal iliac, common iliac, low para-aortic and peri-renal chains is recommended.[14,18]

Chemotherapy

In the most recently completed CCG/POG clinical trials, patients with GCTs (Ovarian stage I-IV and Testicular II-IV) were treated with PEB (etoposide 100mg/m2/day for 5 days, bleomycin 15 U/m2 on day 1, and cisplatin 20mg/m2/day for 5 days). Prior to treatment patients underwent initial resection of tumor. Those patients in the high risk group (stage III-IV ovarian/testicular or stage I-IV extragonadal) were randomized to either high dose (40 mg/m$^{2)}$ or standard dose of cisplatin. (20 mg/m^2). Patient response was evaluated after four cycles of chemotherapy.[14,18]

In the low/intermediate risk trial there were 74 patients enrolled and treated with PEB. Overall event free survival (EFS) at 6 years was 94.5% and overall survival (OS) was 95.7%. Enrolled on the trial were 17 stage II testicular malignant GCTS with EFS and OS of 100%. Of the 41 stage I ovarian tumors, EFS was 95% and OS 95.1% and of 16 stage II ovarian tumors EFS was 87.5% and OS was 93.8%.[14]

The high risk trial had a total 299 eligible patients enrolled. At the week 12 evaluation the complete response (CR) rate was 58% in the high dose group (HDPEB) and 51% in the PEB group (p=0.15). In the HDPEB group 6 year EFS was 89.6% $\pm$ 3.6% versus 80.5% $\pm$ 4.8% in the PEB group (p=0.03) The OS was not statistically different with HDPEB OS of 91.7% $\pm$ 3.3% and PEB OS of 86% $\pm$ 4.1%. With no statistical difference in the overall survival and presumed risk of more long term side effects from higher dose, the standard dose of cisplatin is recommended.[18]

Patients with immature teratoma or patients less than 10 years of age with stage I testicular malignant GCT received surgery alone followed by observation. Only 4/79 with teratoma had reoccurrence, and 3 of the 4 were successfully salvaged with PEB. Eleven of the 63 boys with stage I malignant GCT had recurrence, but all were successfully salvaged with PEB.[22,23]

The United Kingdom Children's Cancer Study Group (UKCCSG) used a JEB regimen (carboplatin, etoposide and bleomycin). The 5 year OS and EFS were 90.9% (83.9-95%) and 87.8%. The hematologic toxicity of carboplatin was more severe than seen with cisplatin.27 However, staging systems in the UKCCSG and CCG/POG protocols are different so the two studies cannot be directly compared.[18,24]

Genital region

In an analysis performed by Rescorali *et al*, 14 of 317 high risk patients had malignant genital tumors and 13 were evaluable. Presenting signs included bleeding in 9, mass in 2, and urinary obstruction in 1 patient. All 13 patients had pure yolk sac tumors. Five of the patients received high-dose cisplatin, and the other 8 received standard dose cisplatin. Four year EFS was 76.2% +/- 13.1% and OS was 91.7% +/-8.4%. Three of the 8 on standard dose arm had progressive disease or relapse whereas none on the high-dose arm had an event.[25]

Progressive Disease/Relapse Therapy

Salvage therapy for patients who fail initial therapy or relapse is surgical resection if feasible. Options for chemotherapy include vinblastine, ifosfamide and cisplatin (VeIP), which has been shown to work best in patients with primary gonadal tumors who relapse after complete remission (CR) post first–line therapy.[26] Another option is TIP (paclitaxel, ifosfamide and cisplatin). Kondagunta *et al*. reported on the experience of 46 patients who had favorable prognostic factors with progressive GCTs. These patients received four cycles of TIP, and durable CR after therapy was 63%. The use of high dose chemotherapy with autologous stem cell rescue is being investigated, and in one report of 37 patients with relapsed GCT who received autologous stem cell rescue after induction, there was a 3 year OS of 57%. [29,30,31]

Growing Teratoma Syndrome

This syndrome occurs in patients with non-seminomatous germ cell tumors (NSGCT). It is characterized by growing metastatic lesions despite normalization of tumor markers during systemic chemotherapy. On pathology there are benign mature teratomatous elements with no viable germ cell tumor. The treatment of choice is full surgical resection. If partially resected, lesions are likely to recur, and though pathologically benign they can lead to tissue damage including bowel necrosis or urinary fistulas. Chemotherapy and radiotherapy are generally not effective treatments, though there has been some success with interferon and humanized monoclonal antibody bevacizumab. These treatments may have a role in decreasing tumor burden prior to resection or in patients who cannot undergo full resection.[32]

Post-Therapy Monitoring

Post surgery serum tumor markers are followed at 3 week intervals until they have normalized.[3] After patients complete 3-4 cycles of platinum-based therapy, reevaluation with serum markers and scans will be important in determining if further treatment is necessary or if patients can be clinically observed. Once off therapy patients should initially have serum markers monitored monthly with imaging scans every 3 months for a period of 2 years.

Sacrococcygeal Germ Cell Tumors

Sacrococcygeal GCTs have two different clinical presentations. In neonates they are usually large, mostly external tumors with pathology consistent with mature or immature teratomas. In infants and children up to four years of age, they are primarily internal, presacral and abdominal tumors, which frequently are malignant. In newborns sacrococcygeal teratomas are the most common tumor, though still rare (1/40,000 births). They are more common in females and are associated with congenital anomalies, most commonly musculoskeletal and central nervous system anomalies. When sacrococcygeal teratomas occur prenatally, fetuses are at high risk for complications or even neonatal death. Complications include dystocia, tumor rupture, preterm labor from polyhydraminos, hydrops, and high-output cardiac failure due to the vascular/metabolic demands of a rapidly growing tumor. Post-natally most neonates do well.[33,34]

The initial treatment for neonates is early and complete surgical excision. If the fetus is at high risk and if the mother is in good health, prenatal surgeries can also be performed. Post-surgical resection patients need close monitoring because malignant GCTs can recur from residual malignant elements of original tumor or malignant transformation of residual disease. Patients need excision of these recurrent tumors with addition of platinum-containing regimens.[33,34,35]

The outcome of sacrococcygeal GCTs has greatly improved with the introduction of platinum-based regimens. In a German series 66 patients with sacrococcygeal GCT were treated with platinum-based regimen and had an EFS of 66%. The POG 9049/CCG 8882 clinical trial compared PEB to HDPEB with overall EFS of 84% and no significant difference between the two treatment groups. In these trials patients also underwent a full surgical

resection if feasible prior to chemotherapy. If a full surgical resection was not feasible, then patients received 3-4 cycles of cisplatin-based chemotherapy followed by a surgical resection.[36,37]

Patients who presented at 2 months or older have a higher rate of malignancy (48% of girls, 67% of boys) than patients less than 2 months of age (7% of females and 10% of males).[38] Thus, surgery with close post surgical monitoring is the treatment of choice for neonates. Possible prognostic indicators include AFP >10,000 ìg/L and extent of surgical resection.[30, 39]

Conclusion

Even though gonadal GCTs are rare in the pediatric population they are important to diagnose and fully stage. With the addition of platinum based therapy to surgical resection gonadal and sacrococcygeal GCTs, even at advanced stages, have a good outcome. Current trials are now evaluating if decreasing low risk patient's exposure to platinum based chemotherapy is feasible without compromising their outcome.

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