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Gonadal germ cell tumors in children

A retrospective review of a 10-year single-center experience

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Abstract

Background: The true incidence of gonadal germ cell tumors (GCTs) in children is unknown. Few studies have been published concerning about pediatric gonadal GCTs. The aim of this study is to review and analyze clinical data on the diagnosis and management of gonadal GCTs in children.

Methods: Between 2005 and 2015, 127 pediatric patients (<14 years old) with gonadal GCTs admitted to our institute were reviewed. Clinical features, imaging and laboratory studies, surgical approaches, as well as pathological diagnoses were recorded.

Results: The series comprised 53 males with testicular GCTs and 74 females with ovarian GCTs. Their median age was 5.8 years old. Palpable mass was the main clinical manifestation of testicular GCTs, while abdominal pain and abdominal distention were the most frequent presenting symptoms of ovarian GCTs. Both computed tomography and magnetic resonance imaging showed a high diagnostic yield. AFP levels were elevated in most malignant GCTs, markedly elevated in yolk sac tumors. All patients were treated surgically. Mature teratoma was the most common type of benign GCTs, while yolk sac tumor was the most common type of malignant GCTs.

Conclusion: Gonadal GCTs in children have various of pathological types, as well as clinical manifestations. Imaging and laboratory data could be useful for differentiation of malignant from benign tumors. Final diagnosis depends on pathology. Surgical excision of the gonadal GCTs is the prior option.

Abbreviations: AFP = alpha-fetoprotein, CA-125 = carbohydrate antigen-125, CT = computed tomography, GCT = germ cell tumor, βHCG = beta-human chorionic gonadotropin, MRI = magnetic resonance imaging, US = ultrasonography.

Keywords: children, germ cell tumor, gonadal, yolk sac tumor

1. Introduction

Germ cell tumors (GCTs) arise due to variation from normal differentiation of germ cells and include a heterogeneous group of neoplasms with remarkable variability concerning histology and site of presentation.[1] A total of 60% of pediatric GCTs come from the extragonadal sites, while the gonadal sites (ovary and testis) account for 40% of cases.[2,3] GCTs are the most common tumors of the gonads in children and adolescents.[4] But the true incidence of gonadal GCTs in children is unknown. Correctly diagnosed and properly treated in the early stage, most gonadal GCTs in children are curable; misdiagnosed or improperly managed, they can affect future fertility or even sterility, particularly malignant gonadal GCTs. Pediatric gonadal GCTs seem to have a consistent clinical and biologic course. However, few studies have been published concerning pediatric gonadal GCTs so far. In order to better understand the clinical characteristics and management of pediatric gonadal GCTs, we reviewed a series of 127 patients with gonadal GCTs treated at our institute over the last 10 years.

2. Patients and methods

From January 2005 to December 2015, a total of 127 patients (<14 years old) with gonadal GCTs were treated operatively in the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (Wenzhou, China). Only patients with primary tumor in the gonadal sites were considered. All the clinical details, radiologic, laboratory, and pathologic findings were collected from the department's data base.

3. Results

From 2005 to 2015, 53 males and 74 females pediatric patients were diagnosed with gonadal GCTs. The clinical features of our patients with gonadal GCTs were shown in the Table 1. Patients' ages ranged from 3 months to 14 years with a median age of 5.8 years old. The breakdown of cases included 41.7% ≦4 years of age, 26.8% between 5 and 9 years of age, and 31.5% between

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Table 1

Clinical features of 127 patients with gonadal germ cell tumors (GCTs).

	Testicular GCTs	Ovarian GCTs	Total
Number	53	74	127
Age, y			
0–4	43	10	53
5–9	7	27	34
10–14	3	37	40
Location			
Left	25	33	58
Right	28	41	69
Nature			
Benign	31	64	95
Malignant	22	10	32

10 and 14 years of age. As the growth of the age, the incidence of testicular GCTs decreased, while the incidence of ovarian GCTs increased. The primary lesions were in the right ovary in 41 (55.4%) patients and left ovary in 33 (44.6%) patients. Although the testicular GCTs were right-sided in 28 (52.8%) patients and left-sided in 25 (47.2%) patients. In the 127 patients, 95 patients were benign tumors (74.8%), and 32 patients were malignant tumors (25.2%).

As shown in the Table 2, the main symptoms of ovarian GCTs were abdominal pain or abdominal distension in 55 patients (74.3%). The duration of symptoms ranged from several hours to 10 months, with or without increasing severity. Of these patients, 26 (35.1%) were emergent admissions. There were 9 patients who had ovarian torsion, and 1 had an ovarian rupture. Eleven patients (14.8%) were identified by ultrasonography (US) in routine examinations. Other symptoms included enlarge abdominal perimeter, menstrual disorder, and precocious puberty. Palpable mass was the main clinical manifestation of testicular GCTs in 51 patients (96.2%). The other 2 patients of testicular pain were emergency admissions because they were suspected testicular torsion.

US was performed in all patients to measure the size of the lesion and the gross morphologic nature of the tumor. However, only 3 (30%) patients received a diagnosis of torsion or rupture based on US. Forty-eight (64.9%) patients of ovarian GCTs had computed tomography (CT) scan or enhanced CT scan, and 11 (14.9%) patients had abdominal magnetic resonance imaging (MRI), where further evaluation of the nature of the ovarian tumor and abdominal organs was necessary. Fifty-one (96.2%) patients of testicular GCTs had enhanced CT scan.

Tests for serum tumor markers including alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (βHCG) were routinely measured in most cases. Carbohydrate antigen-125 (CA-125) was performed in a part of ovarian GCTs. AFP levels were markedly elevated in 25 patients (2 with malignant mixed GCT, 2 patients with immature teratoma, and 21 patients with yolk sac tumor); slightly elevated in 3 patients (1 with a mature teratoma, 2 patients with immature teratoma). βHCG was elevated in 2 patients with malignant mixed GCT and 2 patients with dysgerminoma. CA-125 levels were elevated in 4 patients with immature teratomas and 1 patient with malignant mixed GCT.

Table 2

Presenting symptoms of ovarian germ cell tumors (GCTs).

Presenting symptom	Number	%
Abdominal pain	35	47.3
Abdominal distention	20	27.0
Routine examination	11	14.8
Enlarge abdominal perimeter	4	5.4
Menstrual disorder	3	4.1
Precocious puberty	1	1.4
Total	74	100

Table 3

Histopathological diagnosis of germ cell tumors (GCTs).

Histology	Testicular GCTs	Ovarian GCTs	Total
Mature teratoma	31	64	95
Immature teratoma	2	5	7
Yolk sac tumor	19	2	21
Dysgerminoma	0	2	2
Malignant mixed germ cell tumor	1	1	2

All patients received surgery. Intraoperative rapid frozen biopsy was applied to determine the nature of tumor in most patients. In the ovarian GCTs, the procedure performed was open ovarian cystectomy in 38 patients, laparoscopic cystectomy in 25 patients, laparoscopic oophorectomy in 2 patients, open oophorectomy in 9 patients with 1 requiring conversion from an initial laparoscopic approach. In the testicular GCTs, mass resection was performed in 31 patients, a radical orchidectomy in 22 patients. All of the masses were successfully resected with no common intraoperative complications such as incision infection, scrotal hematoma, abdominal infection, and abdominal bleeding. Some patients with malignant tumors were treated with postoperative chemotherapy in hematology department. Chemotherapy regimens such as PVB (cisplatin, vinblastine, and bleomycin) and PEB (cisplatin, etoposide, and bleomycin) were used in testicular GCTs, while VAC (vincristine, dactinomycin, and cyclophosphamide) and PEB were used in ovarian GCTs. The patients recovered well with no relapse for 3 to 6 months of follow-up.

Pathology of the excised tumors was shown in Table 3. Mature teratoma was the most common type of benign GCTs, reported in 95 (74.8%) patients, while yolk sac tumor was the most common type of malignant GCTs. Immature teratoma was the 2nd common type of malignant GCT, which was diagnosed in 7 patients. According to a grading system of immature teratoma introduced by Norris, modified by Gonzales-Crussi and others,[5] 4 were grade 1, 2 were grade 2, and 1 was grade 3. The pathology of malignant mixed GCT included dysgerminoma and yolk sac tumor. The most common pathological type of testicular GCTs was mature teratoma in 31 (58.5%) patients, and yolk sac tumor in 19 (35.8%) patients. The most common pathological type of ovarian GCTs was mature teratoma in 64 (86.5%) patients.

According to the staging system used was the Children's Oncology Group,[1] data of postsurgical staging were available for 98 cases (77.1%). Among these, 89 patients with benign tumors were stage I, 8 patients with malignant tumors were stage II, and 1 patient with malignant tumors was stages III. Of testicular tumors, 42 patients were stage I and 5 patients were stages II. Although in ovarian tumors, 47 patients were stage I, 3 patients were stages II, and 1 patient was stages III.

4. Discussion

Pediatric gonadal GCTs are rare tumors. The incidence of pediatric gonadal GCTs have increased in the past years.[6–9]

Gonadal GCTs can be observed in children with different rates, also according to age.[10] Ovarian GCTs account for about 30% of GCTs and 70% of all neoplastic ovarian masses, being the most common ovarian tumors in children.[1] The peak of incidence is in early adolescence. Testicular GCTs represent about 10% of all pediatric GCTs, but about 30% of malignant GCTs.[11] Testicular GCTs have 2 age peaks: children under 3 years may experience both mature teratoma and malignant GCTs, while adolescents may also have seminomas or other mixed tumors.[12,13] In our series, ovarian GCTs often occurred in the 10 to 14 year age group, while testicular GCTs mostly occurred in the age of less than 4 years.

Gonadal GCTs have many types of benign and malignant histologies, including some common types such as teratomas, endodermal sinus tumor or yolk sac tumors, dysgerminoma, and mixed malignant GCTs. Also, there are some rare types such as primary cell tumor, choriocarcinoma, and embryonal carcinoma. Teratomas are the most prevalent benign tumors of the gonads in children, while yolk sac tumors are the most prevalent malignant tumors of the gonads in children.[14,15] Benign and immature teratomas constitute about 80% of all ovarian GCTs and are bilateral in 5% of cases, whereas the incidence of malignant forms is reported in about 20% and increased during adolescence.[16] In our series, 95 (74.8%) patients with gonadal GCTs were benign tumors, whereas in Islam Nasir et al[17] study, malignant GCTs were more prevalent than benign GCTs. We also found that mature teratomas were the most prevalent benign tumors of the gonads, yolk sac tumors were the most prevalent malignant tumors, especially in testicular GCTs. Moreover, in our study the common stage of the tumors was stage I which was similar to Khaleghnejad-Tabari et al study.[18] However, only 8 patients with malignant GCTs were stage II and 1 was stage III. This may be related to the lack of the data about patients with malignant tumors. In addition, most patients with high-risk malignant tumors chose to go to well-known hospital for better treatment, especially in our city. In De Pasquale et al[19] study, 70% patients with malignant mediastinal GCTs had stage III, and the remaining patients had stage IV with distant metastases.

Clinical manifestations of gonadal GCTs are various, with no specificity. There are no differences between the benign and malignant GCTs. In general, abdominal pain and abdominal distention are the main symptoms of ovarian GCTs. Other rare symptoms include constipation, endocrine symptoms, nausea, and vomiting. The reported incidence of ovarian torsion in patients with ovarian neoplasms range from 17% to 33%.[20–22] In our series, 22 patients had acute symptomatology requiring urgent surgical exploration, and 10 patients were found to have ovarian torsion or rupture. Some patients were identified by US in routine examinations without any clinical signs or presentation. Palpable mass was the main clinical manifestation of testicular GCTs. Also some patients with testicular GCTs had testicular pain.

In our series, all of the masses could be detected by US. Because it is convenient and cheap, US is employed as a routine imaging tool and primary diagnostic method for the characterization of gonadal GCTs. However, its sensitivity and specificity are not as good as CT and MRI. The accuracy of US, CT, and MRI scans, in diagnosis of pelvic pathologies, were 77%, 87%, and 97%, respectively.[23] CT and MRI are not only useful in detection and localization of gonadal GCTs but also helpful in evaluating tumor characteristics.

The preoperative diagnostic work-up includes not only imaging data, but also blood samples for tumor markers such as AFP, βHCG, and CA-125. Evaluation of serum tumor markers could increase accuracy in the differential diagnosis of pediatric gonadal GCTs, especially in the malignant GCTs. AFP is also an early sign of relapse of malignant GCTs, and testing AFP levels may help to reduce the burden of follow-up.[5] In recent literature, the rate of benign lesions associate with the rise of tumor markers varies from 3.4% to 20.7%.[24,25] In our study, the patients with benign GCTs who had serum tumor markers detection had a normal level, except 1 patient with ovarian GCT had a slightly high level of AFP. AFP of all patients with yolk sac tumor and malignant mixed GCT were elevated obviously, with a maximum of 74,638.94 ng/mL in testicular yolk sac tumor. Some teratomas also presented a high level of AFP. The patients with malignant mixed GCT had a high level of βHCG and CA-125. CA-125 levels were increased in nearly half cases of immature teratoma. All of the auxiliary examinations were to identify the type of tumors before operation, but the final diagnosis depended on postoperative pathology.

Surgical resection has a central role in the management of gonadal GCTs. Intraoperative frozen-section biopsy may be determinant in the choice of the appropriate surgical procedure.[26] If the tumor is benign, we usually perform mass resection, because the preservation of gonad and function is very important for children. If the tumor is malignant, radical surgical excisions are recommended. In our study, laparoscopic or open cystectomy is performed for most benign ovarian GCTs. For malignant ovarian GCTs, a conservative surgical treatment approach with unilateral oophorectomy or salpingo-oophorectomy is appropriate.[27] Laparoscopic surgeries have been reported to show good results in children, expecially in benign GCTs,[28] although there are some risks including intraoperative spillage and potential loss of staging information. For benign testicular GCTs, mass resection or partial orchiectomy is an option for patients. Traditionally, high inguinal orchiectomy is recommended for testicular yolk sac tumor because of the cancer's aggressive nature.[29] Retroperitoneal lymph node dissection (RPLND) may prevent metastasis in patients with testicular yolk sac tumors. However, there is still controversy concerning the use of RPLND.[30] Adjuvant treatment in the form of chemotherapy is recommended for the treatment of malignant GCTs according to International Germ Cell Consensus Classification (IGCCC) prognostic criteria. The postoperative chemotherapy depends largely on the histology of the tumor and the stage of progression at the time of surgery. In our study, all of the masses were successfully resected with no intraoperative complications. Some patients with malignant tumors were treated with postoperative chemotherapy in hematology department. The patients recovered well with no relapse for 3 to 6 months of follow-up.

This study improves current knowledge of the diagnosis and management for gonadal GCTs. However, it is associated with some limitations. First, it is a retrospective review, and some patients' records are incomplete, including stages of tumors. Second, we have no data of patients' long-term follow-up results and the overall recurrence and survival rate are also not clear. Future studies with long-term follow-up are needed to fully assess the safe and effective management of gonadal GCTs as well as patients' future fertility.

5. Conclusion

Gonadal GCTs in children have various of pathological types, as well as clinical manifestations. Imaging and laboratory data

could be useful for the differentiation of malignant from benign tumor. Final diagnosis depends on pathology. Surgical excision of the gonadal GCTs is the prior option. A multidisciplinary approach with surgical, radiological, pathological, and oncological input is the cornerstone of management in order to achieve excellent outcomes.

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