Ovarian germ cell tumors in children: a 20-year retrospective study in a single institution

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Summary

Purpose: Ovarian germ cell tumors are rare in childhood. The goal of the study is to provide information that may help guide the evaluation and surgical management of future children with ovarian tumors. *Methods:* A retrospective review of patients with ovarian germ cell tumors between January 1990 and January 2010 was performed. *Results:* 137 patients were included with a median age of 9.5 years. Teratomas were found most frequently (mature: 78, immature: 6), followed by yolk sac tumors (n = 51), dysgerminoma (n = 1) and embryonal carcinoma (n = 1). Abdominal pain (81.8%) and abdominal distension (58.4%) were the most common symptoms. Twenty-six infants were found prenatally. Twenty-one patients presented torsion of the ovary. Alpha-feto-protein levels were elevated in all pure yolk sac tumors, two immature teratomas and one embryonal carcinoma. Most patients (84) were Stage I, 16 were Stage II, 23 Stage III, and four Stage IV. All patients with mature and immature teratomas (grade 1) underwent surgery alone. Surgery + chemotherapy were conducted in 55 other patients. The surgical procedures consisted of salpingo-oophorectomy (n = 68), oophorectomy (n = 21) and ovarian-sparing tumorectomy (n = 48). Sixteen patients gave up the treatment and died. Excluding this subset, 5-year relapse-free survival and overall survival was 93.4% and 98.3%, respectively. No recurrences were observed in any patients. *Conclusion:* Ovarian germ cell tumors have an excellent prognosis. With accurate staging, complete resection, and adjuvant chemotherapy, patients should be expected to have excellent survival rates. Preservation of ovarian tissue should be considered whenever safe and feasible, however, this needs to be confirmed by studies on larger numbers of patients.

Key words: Germ cell tumor; Ovary; Teratoma; Ovary; Yolk sac tumor; Dysgerminoma; Pediatric.

Introduction

Ovarian tumors, whether cystic, solid, or both, have been considered rare in the pediatric population. The incidence is estimated to be approximately 2.6 cases per 100,000 girls per year, with malignant ovarian neoplasms making up about 1% of all pediatric cancers [1]. Germ cell tumors are the most common type of ovarian tumors in children and adolescents, comprising 3% to 4% of all pediatric patients [2, 3]. About one-third of all childhood ovarian neoplasmas are reported to be malignant, therefore the possibility of malignancy should be considered in all cases. Pediatric ovarian germ cell tumors (GCTs) are highly chemosensitive with a high curability rate. Surgery with adjuvant chemotherapy is the mainstay of treatment. The aim of this study was to review the clinical presentation, management and outcome in a series from a single institution over a 20-year-period. The goal of this study is to provide information that may help guide the evaluation and surgical management of future children with ovarian tumors.

Patients and Methods

With approval from the hospital Human Research Ethics Committee, the medical records of 172 consecutive girls with ovarian problems treated surgically at Children's Hospital of Chongqing Medical University, Chongqing, China between January 1990 and January 2010 were studied. Our hospital provides secondary and tertiary pediatric care in Chongqing City and is also a major pediatrics referral center for southwest China. Every patient was diagnosed by surgery or puncture biopsy and pathology; ovarian cysts, follicular cysts of the ovary and granular cell tumors were excluded. At last, 137 records were included in the study. We recorded symptoms that led to further investigation and to diagnosis, age at diagnosis, the radiological and biochemical methods employed in the diagnosis, methods of treatment, and complications. Clinical staging was according to the Children's Oncology Group staging, a modification of the FIGO (International Federation of Gynecology and Obstetrics staging for ovarian tumors) classification [4]. This classification defines Stage I as a tumor limited to the ovary, Stage II as a tumor with pelvic extension, microscopic residual or positive lymph nodes < 2 cm, Stage III as a tumor with gross residual or biopsy only, contiguous visceral involvement, lymph nodes with malignant metastatic nodules > 2 cm, and Stage IV as a tumor with distant metastases, including the liver. Histological typing of tumors followed the WHO classification. Immature teratomas were graded according to the Norris classification.

Results

Patient characteristics

Median age at presentation was 9.5 years (range from neonatal to 15 years). Malignant tumors were diagnosed in girls at a median age of 8.5 years (range from 4 months to 14 years). Past medical histories and family histories were unremarkable. Ninety percent of the patients were from rural areas with most of them having upper lower or lower socioeconomic status. The parents of one-third of the patients were illiterate.

Revised manuscript accepted for publication August 26, 2010

Presenting signs and symptoms

The vast majority of patients presented with a combination of symptoms and signs; however the most frequent primary symptom was abdominal pain, either acute, chronic, or both and was reported for 112 patients (81.8%). The second most frequent symptom, major abdominal distension by the abdominal or pelvic mass, was noted in 80 patients (58.4%), associated with pain in 45 and painless in 35; however it was the primary sign in only seven. Other symptoms and signs included nausea and vomiting, constipation, urinary symptoms and fever. For 26 infants, the tumor was found prenatally, and surgery was performed within two months after their birth. Twenty-one patients presented torsion of the ovary, 20 of which were mature teratomas, and the rest were dysgerminoma. For two patients the ovarian tumor was an incidental finding during investigations for an unrelated pathology (both of them were consulted for pneumonia). The duration of symptoms ranged from six hours to two years.

Imaging

Various imaging studies were used for these patients over the years, except in those with an acute abdomen. Abdominal ultrasound was the most common investigation, performed in all patients. Plain abdominal films were used for 65 patients. Computed tomography was performed in 127 patients. Calcifications were observed in 40 patients. The space-occupying lesion was reported to be purely cystic in six, purely solid in 65, and mixed cystic-solid in 66 patients. Tumor dimensions ranged from 2.5×1.5×1.5 cm till 21 cm in diameter.

Tumor markers

Alpha-feto-protein (AFP) levels were elevated in 54 patients, 51 with pure yolk sac tumors, two with immature teratomas (Gr 2 and 3), one with an embryonal carcinoma, and were normal in all others. Beta human chorionic gonadotropin (β-HCG) and AFP levels were both elevated in the patients with embryonal carcinoma.

Staging

According to postsurgical staging all 84 patients with mature and immature teratomas and ten patients with a malignant tumor were Stage I. Sixteen patients with malignant tumors had Stage II, 23 had Stage III and four patients with lung metastases (2), liver metastasis (1), peritoneum metastasis (1) had Stage IV disease (Table 1).

Histology

The histologic diagnosis of the 137 tumors is summarized in Table 2. Mature teratomas were the commonest tumors (n = 78), followed by yolk sac tumors (n = 51), immature teratomas (n = 6), dysgerminoma (n = 1) and embryonal carcinoma (n = 1). The distribution of benign or malignant tumor by age groups is shown in Table 2.

Table 1. — *Distribution of benign/malignant GCTs by age groups*.

Age (years)	Total GCTs	Benign	Malignant (% of total)
0-3	57	16	41 (71.9%)
4-6	24	22	2 (9.1%)
7-10	26	21	5 (19.2%)
11-15	30	19	11 (36.7%)

Table 2. — *Histopathologic diagnosis in 137 patients with ovarian GCTs*.

Histology	Number of patients
Teratoma	84
Mature	78
Immature	6
Grade 1	4
Grade 2	1
Grade 3	1
Yolk sac tumor	51
Dysgerminoma	1
Embryonal carcinoma	1
Total	137

Table 3. — *Stage and outcome*.

Stage	N	DFS (%)	OS (%)
I	94	95.7%	96.8%
II	16	62.5%	75%
III	23	52.2%	78.2%
IV	4	25%	50%

DFS indicates disease free survival; OS, overall survival.

Treatment

For all patients with mature and immature teratomas (grade 1) treatment consisted of surgery alone. Surgery + chemotherapy were done in 55 other patients; no patient received radiotherapy.

Twenty-two patients with acute symptomatology had undergone emergency surgery: 21 for torsion of the tumor (16 right-sided) and one for apparent tumor rupture. The others had been operated upon selectively. Stage III and Stage IV patients had biopsy first, either puncture or surgery, when the diagnosis was confirmed. Neoadjuvant chemotherapy was given for three to six courses, then followed by surgery, and chemotherapy was also given after surgery. Sixteen patients with malignant tumors gave up treatment because of the poor economic conditions (including 3 Stage I, 4 Stage II, 7 Stage III and 2 Stage IV). The tumors were right-sided in 76 patients and left-sided in 61 patients. Tumor dimensions ranged from 2.5 × 1.5 × 1.5 cm to 21 × 18 × 15 cm. No bilateral tumors were found in surgery. The procedures consisted of salpingo-oophorectomy (n = 68), oophorectomy (n = 21) and ovarian-sparing tumorectomy (n = 48). The contralateral ovary was always inspected and palpated very carefully in every patient. Five patients were suspected of having malignant tumors and biopsy of the contralateral ovary was made; meanwhile, no one had tumor. The tumors themselves were not subjected to frozen section

histology. Ascites was sent for cytologic analysis when present, and revealed malignant cells in one patient with peritoneum metastasis.

Postoperatively, six patients developed a wound infection and 12 mechanical small intestinal obstructions by adhesions. In eight patients the obstruction subsided with conservative measures, while in the four others surgical adhesiolysis was necessary to relieve the obstruction.

Based on the disease stage, patients underwent protocol treatment with surgery and cisplatin-based chemotherapy (PEB). The chemotherapy regimen used was PEB which was administered once every three weeks for six to eight cycles. Bleomycin was given at a dose of 30 units D2, etoposide 120 mg/m^2/d D1-3, and cisplatin at a dose of 100 mg/m^2/in divided doses D1-3. All malignant patients received chemotherapy except with Stage I immature teratoma grade 1.

Outcome

There were no recurrences in patients with malignant tumors. The median duration of follow-up was 7.3 years (3 months to 15 years). Sixteen patients refused chemotherapy and died because of widely metastasized tumor. Excluding the 16 patients who gave up treatment, the 5-year relapse-free survival and overall survival was 93.4% and 98.3%, respectively. The 5-year disease-free survival and overall survival was 100% for patients with dysgerminoma. Patients with early-stage disease had an excellent survival (Table 3).

There were no recurrences in patients with malignant tumors. All patients are on long-term follow-up with monitoring of endocrine function and fertility. Seventy out of 78 patients in puberty had regular menstrual cycles. Six patients had menostaxis and two patients required psychological input during the follow-up period. None of these patients experienced pregnancy because none have married yet.

Discussion

GCTs are rare in childhood. In our hospital, which performs more than 8,000 general pediatric surgeries per year, there have been only 137 GCTs in the last 20 years. Over a 20-year-period 137 GCTs do not really constitute a large series, yet it is the largest of its kind reported in the past decade. The age distribution for malignant tumors varies in the literature. Malignant tumors have been reported to occur more frequently at lower ages [5], although it has also been reported that the risk of malignancy increases with age, especially around puberty [6]. The age distribution of our study showed that tumors were diagnosed at every age with the peak age 10-15 years and below three years. The proportion of malignant tumors was even higher in infants than teenagers. From our study, we might conclude that younger infants and teenagers are at higher risk for malignancy than other children are. We also noticed that most parents of the patients were illiterate (1/3 of the patients) and from rural areas (> 90%) with a low socioeconomic status. Late stage of presentation may be owing to late presentation to the doctor or delayed referral to the tertiary care center.

Patients with ovarian tumors seek medical attention in a variety of ways. Most patients present with acute abdominal pain and signs of peritonitis that can be difficult to distinguish from acute appendicitis. Patients may present with a large pelvic or abdominal mass. Some patients may refer with precocious puberty or other signs of endocrine disorder. Bowel obstruction, ureteral compression and hydronephrosis may be present in some patients with a mass effect from an enlarged ovary. Distinguishing patients with ovarian torsion, acute appendicitis or other surgical lesions may be challenging for a pediatric surgeon. In our experience, the presence of nausea, anorexia, and vomiting may favor appendicitis over ovarian pathology, however, these symptoms are not specific or reliable. Although ultrasound can be helpful in confirming a preoperative diagnosis of ovarian torsion and in differentiating nonoperative ovarian pathology from appendicitis and other acute surgical conditions, delays in obtaining the examination and false-negative results reinforce the role that operation (and perhaps laparoscopy) plays in evaluating these patients [7].

Tumor markers are a significant factor for management, prognosis and follow-up of germ cell tumors. AFP is the commonest one used in pediatric population. AFP may be elevated in patients with teratomas and it is invariably elevated in yolk sac tumors [8]. Germinoma may present with either positive β-HCG, a marker associated with choriocarcinoma, or CA-125, which is associated with epithelial tumors. In our study, all patients with malignant germ cell tumors had significantly elevated levels of AFP or AFP and β-HCG. Two patients with immature teratoma (grade 2/3) presented with elevated AFP, and all other patients had tumor markers within the normal range. The AFP levels were all within the normal range after treatment at follow-up.

Surgical excision has a central role in the management of GCTs, apart from being the only treatment required in many cases, surgery provides valuable information for staging. Because GCTs often occur in girls and young woman, preservation of ovarian function and fertility is an important goal of treatment. More recently, investigations have recommended detorsion and preservation of all ovaries (either open or laparoscopic), even of those that appear frankly necrotic [9]. Radical ovarian excision was performed if the mass proved to be malignant. However, for benign tumors, unilateral salpingo-oophorectomy or ovarian-sparing tumorectomy is often sufficient. Bilateral ovarian involvement is rare in children, and in our study none were found to have bilateral involvement. In our opinion, if the contralateral ovary appears normal, biopsy is not necessary and may contribute to adhesion formation. Although it is not clear to what extent oophorectomy affects the fertility of these patients, it is known that there is a dramatic increase in the incidence of women with a single ovary compared with the general population in infertility clinics. However, pregnancy rates appear to be the same as that of general population when patients

undergo follow-up longitudinally [10]; the fate of remaining with a single ovary does not imply a reduced fertility potential to conceive. Therefore, considering the risk of asynchronous torsion or other contralateral ovarian disorders, we suggest preserving ovarian tissue whenever safe and feasible. Howerer, more work is needed to shed more light on the fertiliy potential of patients with GCTs after surgery.

The rise of minimally invasive surgical procedures, such as the laparoscopic technique for ovarian tumors was developed in the past decades. The effectiveness of laparoscopic or open cystectomy for mature teratomas is well documented [11]. Skills in pediatric laparoscopic surgery have increased as well. However, GCTs in childhood are often very large, rendering laparoscopic removal less advantageous when compared with adults. Moreover, the reported spillage rates in laparoscopic excision of ovarian tumors range considerably, from 13% to 52% [12, 13]. In our opinion, laparoscopic excision should be considered when the tumor is small and more likely to be benign. If tumors are large and malignance cannot be excluded, open exploration should be a better approach. However, a laparoscopic procedure is helpful in tumor staging with minimal invasion.

Chemotherapy plays an important role in malignant tumor treatment and outcome. Immature teratomas, although not truly malignant, have been treated as malignant neoplasms in our department because of their potential to recur as malignant tumors. Chemotherapy based on cisplatin was given to patients with grade 2 or 3 immature teratomas. There has been no recurrence of immature teratomas in our study, and the overall survival rate was 100%. All patients are alive, aged 6-20 years now, and are between five months and 12 years post diagnosis.

Overall survival for GCTs was 86.9% in our study, which is lower than the literature reports ranging between 97-100% [6, 7]. Lower overall survival rate may be owing to 16 patients with malignant tumors who gave up chemotherapy. When excluding this subset, the 5-year relapse-free survival and overall survival was 93.4% and 98.3%, respectively. The application of platinum-based agents in pediatric chemotherapy regimens has improved survival significantly in children with malignant GCTs. The 6-year overall survival rate with the PEB protocol has been 95.1% for Stage I, 93.8% for Stage II, 97.35% for Stage III and 93.9% for Stage IV disease [14]. In our series, excluding the 16 patients who gave up therapy, the 5-year overall survival rate with the PEB protocol was 100% for Stage I, 100% for Stage II, 87.5% for Stage III and 100% for Stage IV disease.

Conclusion

Ovarian germ cell tumors are uncommon in children. Both benign and malignant tumors have an excellent prognosis. For benign ovarian neoplasms operation should be designed to optimize future fertility. Malignant tumors are highly chemosensitive with a high curability rate. With accurate staging, complete resection, and adjuvant chemotherapy, patients should be expected to have excellent survival rates. Preservation of ovarian tissue should be considered whenever safe and feasible, however, this needs to be confirmed by studies on larger numbers of patients in the future.

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