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Gynecological Conditions

Pediatric ovarian immature teratoma: Histological grading and clinical characteristics

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ABSTRACT

Background: Ovarian immature teratomas (ITs) are relatively rare among all pediatric ovarian tumors. The histological grading for ovarian ITs, which ranges from 1 to 3, is based on the proportion of immature neuroepithelial component. Higher-grade ITs in adults are treated as malignant neoplasms and require adjuvant chemotherapy. However, there is no consensus on the therapeutic management of pediatric ovarian ITs. The aim of our study was to analyze the histological grades and clinical characteristics of ovarian ITs in pediatric patients.
Methods: This retrospective chart review consisted of seven patients, including one, three, and three patients with histological grade 1, 2, and 3 pediatric ovarian ITs, respectively, who were treated at our institute between 2000 and 2016. Collected data comprised age, alpha-fetoprotein (AFP) level, clinical stage, tumor size, treatment, and prognosis.
Results: The median age and AFP levels of patients with grade 1, 2, and 3 ovarian ITs were 8, 7, and 10 years and 37, 112, and 221 ng/ml, respectively. All cases were Children Oncology Group (COG) stage I and International Federation of Gynecology and Obstetrics (FIGO) stage IA. All patients had unilateral tumors in the right ovary. The median tumor sizes of the grade 1, 2, and 3 IT patients were 104, 160, and 100 cm^2, respectively. All patients underwent primary open surgery alone. Two patients, including one patient each with grade 2 and 3 ITs, underwent tumor enucleation as ovary-sparing surgery, whereas the remaining five patients underwent unilateral salpingo-oophorectomy. The median follow-up was seven years, and all cases achieved event-free survival.
Conclusions: Clinical characteristics of patients with grade 3 ovarian ITs were relatively older and had higher AFP levels than those with lower-grade ITs. According to our patient's clinical course and prognosis, COG stage I pediatric ITs should be treated by surgery alone and that postoperative chemotherapy is unnecessary even for those with grade 3 ITs as well as patients with rather low AFP levels.
Level of evidence: IV

1. Introduction

Pediatric ovarian tumors are rare, with a reported incidence rate of 2.2/100,000 girls aged 0 to 15 years [1]. About 60–80% of all ovarian tumors in the pediatric age group are of germ cell origin [2–4]. While mature teratomas are the most common ovarian tumors, ovarian immature teratomas (ITs) are relatively rare among ovarian tumors in the pediatric population. The histological grading of all ovarian ITs, which ranges from 1 to 3, is based on the proportion of immature neuroepithelial component [5,6].

In adults, ITs are classified under malignant germ cell tumors, both the grade and stage of ITs correlate with prognosis, and higher-grade ITs in adults require adjuvant chemotherapy [7,8]. However, there is no consensus on the therapeutic management of pediatric patients with ovarian ITs. In addition, several recent reports recommended surgical treatment alone for patients with grade 1, stage I pediatric ovarian ITs [9,10] due to the excellent prognosis.

Examination of the relationship between the histological grade and the clinical characteristics of this rare tumor is necessary to better understand the available treatment strategies. The aim of this study was to analyze the relationship between the histological grade and the clinical characteristics of ovarian IT in pediatric patients.

2. Materials and methods

This retrospective chart review included pediatric patients with ovarian tumors who were treated at the Department of Pediatric

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Surgery of the University of Tsukuba Hospital between 2000 and 2016. Twenty-six cases of ovarian tumors were identified, consisting of twenty-five germ cell tumor cases and one sex-cord stromal tumor case. All patients were under the age of 16. There were 22 patients with teratomas, including 15 patients with mature teratomas and 7 patients with ITs. Cases involving three malignant germ cell tumors (yolk sac tumor) and one juvenile granulosa cell tumor were included (Fig. 1). All seven patients with ITs had pure histology without any foci of yolk sac tumor. The histological grades of ITs were 1, 2, and 3 in one, three, and three patients, respectively.

The demographic and clinical data, including age, symptoms, alpha-fetoprotein (AFP) level, clinical stage, tumor size, treatment, and prognosis, were collected for all patients with ITs. Although various histological grading systems have been reported for IT [11,12], the one developed by O'Connor[6] was used in the current study, which is summarized in Table 1. The Children's Oncology Group (COG) [13] and the International Federation of Gynecology and Obstetrics (FIGO) [14] systems were used to categorize the clinical stages of the patients. The tumor size was calculated by multiplying the long and short axes of the largest axial slice on abdominal computed tomography images.

Table 1
Histological grading of immature teratomas [5,6].

Grade	Quantity of immature neuroepithelial components
1	The amount of immature neuroepithelium present on any slide occupying up to low-power (×40) microscopic field but not exceeding one low-power field.
2	Immature neuroepithelium present on any one slide occupying more than one low-power but not exceeding three low-power microscopic fields.
3	Immature neuroepithelium present on any one slide exceeding three low-power microscopic fields.

3. Results

During the study period, the incidence of IT among all ovarian tumors was 26.9% (7/26), and ITs constituted 31.8% (7/22) of all teratoma cases. Of these, 42.9% (3/7) were histological grade 3 ITs. The clinical characteristics of the seven patients with ITs are presented in Table 2. The median age was 9 (range, 7–13) years for all cases. The median age of the grade 1, 2, and 3 IT patients were 8, 7, and 10 years, respectively. The initial symptoms included abdominal pain, abdominal mass, and nausea. The median duration of the symptoms was 2 weeks in patients with abdominal pain and 3 months in those with abdominal mass as the first initial symptom. Cases 4 (grade 2) and 7 (grade 3) were post-menarche.

The median AFP level of seven patients was 112 (range, 4–720) ng/ml, and the median AFP levels of patients with grade 1, 2, and 3 ITs were 37, 112, and 221 ng/ml, respectively. The median tumor size was 104 (range, 36–280) cm^2, and the median tumor sizes of the patients with grade 1, 2, and 3 ITs were 104, 160, and 100 cm^2, respectively.

Radiological findings revealed that all tumors had cystic and solid components with foci of calcification and fat. Preoperative diagnoses were IT, mature teratoma, and malignant germ cell tumor in four, two, and one patient, respectively.

All patients underwent open surgery, according to our department's treatment policy, in order to avoid tumor spillage. The surgical features and procedures as well as the prognosis of these seven patients are detailed in Table 3. All cases had unilateral tumors in the right ovary. None of the patients had lymph node or distant metastasis at the time of diagnosis. According to the intraoperative findings, all cases were COG stage I and FIGO stage IA, and all patients underwent primary surgery. Two patients (cases 4 and 5) among these seven IT cases underwent tumor enucleation as an ovary-sparing surgery, whereas the remaining five patients underwent unilateral salpingo-oophorectomy. Only case 5 experienced ovarian torsion in this study. The median tumor weight, including tumor fluid, in the study was 570 (range, 276–3,950) g in all cases, whereas the median tumor weight including the tumor fluid, in patients with grade 1, 2, and 3 ITs were 580, 500, and 570 g, respectively. Cytology of the ascites was negative in all cases except case 1 (data unavailable). In cases 4 and 5, no microscopic tumor residuals remained on the tumor beds after tumor enucleation.

None of the patients were treated with adjuvant chemotherapy postoperatively. The median follow-up of the study was 7 (range, 2-16) years, and all patients achieved event-free survival.

4. Discussion

Pediatric ovarian ITs are rare, with reported incidence rates ranging from 3% [2]–11.1% [1,2,15] of all ovarian tumors. Specifically, grade 3 ITs exhibit varied incidence rates from 6.5%–39% [5,9,10,12] among all pediatric ovarian ITs. Although Cushing et al. reported that mixed ovarian ITs with yolk sac tumors presented more frequently as grade 3 tumors than pure IT [9], all cases in the present study were pure-type IT, and the rate of grade 3 tumors was higher than previously reported (42.9%). Pashankar et al. [10] compared pediatric and adult patients with ITs and reported that grade 1 tumors were more frequent in the pediatric cohort and that grade 3 tumors were more common in the adult cohort. Due to rarity of ITs in pediatric population, the precise incidence rates of pediatric ovarian ITs and grade 3 ITs are not known.

In our study, the median age of the patients with grade 3 ITs was found to be relatively higher than that of patients with grade 1 or 2 ITs. The median AFP level was relatively higher in patients with grade 3 tumors than in those with lower-grade tumors. Several reports indicated that tumors with higher AFP levels exhibited additional foci of malignant germ cell components [9,11,16]. Therefore, adequate sampling of tumor, requiring one block of tissue for every centimeter of the maximum diameter of the tumor [5], is essential. In a 2005 report by the UK Children's Cancer Study Group, patients with ITs who had

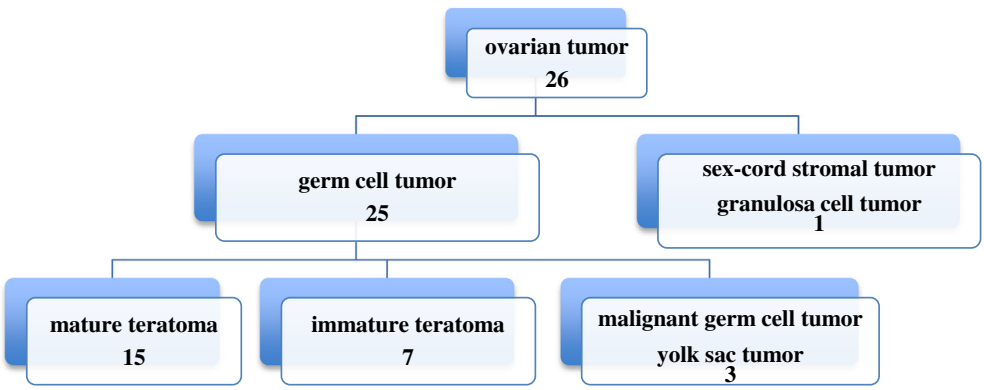

Fig. 1. Twenty-six cases of pediatric ovarian tumors treated at our institution between 2000 and 2016.

Table 2
Clinical characteristics of seven patients with immature teratomas.

Case	Grade	Age (years)	Symptom Duration	Menarche	AFP (ng/ml)	Tumor size (cm^2)	Radiological examination	Radiological Findings	Preoperative Diagnosis
1	1	8	Abdominal pain 1 day	pre	37	104 (13 × 8)	US CT	Multicystic tumor with solid components including calcification and fat	mature teratoma
2	2	6	Abdominal pain 2 weeks	pre	288	36 (6 × 6)	US CT	Solid and multicystic lesion with calcification and fat	IT
3	2	7	Abdominal mass 4 months	pre	112	159.5 (14.5 × 11)	US CT MRI	Multicystic tumor with solid components including calcification and fat	IT
4	2	13	Abdominal mass 2 months	post	8	176.7 (19 × 9.3)	US CT MRI	Multicystic tumor with solid components including calcification and fat	IT
5	3	9	Nausea -	pre	4	84 (12 × 7)	US CT	Cystic tumor with solid components including calcification and fat	mature teratoma
6	3	10	Abdominal pain 1 month	pre	720	100 (10 × 10)	US CT MRI	Solid tumor with multicystic lesion including calcification and fat	malignant GCT
7	3	12	Abdominal mass 3 months	post	221.3	280 (28 × 10)	US CT MRI	Multicystic tumor with solid component including calcification and fat	IT

Tumor size (cm^2) = long axis (cm) × short axis (cm) [largest sagittal slice on abdominal computed tomography].

AFP levels above 1,000 kU/l (conversion; 1 ng/ml = 0.84 kU/l) were managed as having malignant germ cell tumors [17]. Pashankar et al. [10] did not include the patients with AFP levels > 1,000 ng/ml in their study to exclude ITs with malignant germ cell comporments. Terenziani et al. [18] analyzed IT with elevated AFP without any optimal cutoff level. Regarding their report, an international agreement on the correct AFP cutoff level is sorely needed to avoid mismanagement of treatment in patients with ITs.

Norris et al. [5] reported that tumor size did not correlate with the tumor grade. Pediatric ovarian ITs can sometimes present as huge abdominal masses [4,5]. Therefore, the absence of correlation between the tumor sizes and tumor grades in the present study was not unexpected.

Radiological differential diagnosis of IT and mature teratoma is considered to be difficult. However, immature elements are usually seen as solid parts in CT and MRI images [19]. Therefore, radiological findings, such as solid components with small foci of fat and coarse calcification could help in making a better preoperative diagnosis.

Ovarian ITs are classified as malignant germ cell tumors in adult patients [7,8], whereas they are considered to have intermediate malignancy potential in pediatric cases [11], in whom grade 1 ovarian ITs are usually considered to be non-malignant. Given the controversy on the malignancy potential of ITs in pediatric age groups [11,16], the treatment strategies for ITs are different than those in adult patients [7–10]. Several recent studies reported that all patients with stage I, grade 1 ITs should be treated with surgery alone [8–10,16–18,20]. Moreover, postoperative chemotherapy was found not to decrease the relapse rates in pediatric cohorts [10,16,17]. Higher tumor grade and stage are the most important risk factors for tumor relapse [7,10]. Incomplete resection is also an important risk factor for tumor recurrence [10,21]. Thus, the recommended initial surgery is oophorectomy when complete resection is considered to be feasible [9,21]. In the current study, all patients were COG stage I and FIGO stage IA, independently of the tumor grade. In our study, all patients underwent surgery alone, and there were no relapses during the follow-up period. Based on the prognosis in the current study, we suggest that stage I ITs should be treated with surgery alone, and postoperative chemotherapy may not be necessary, even in grade 3 patients.

Ovary-sparing surgery is increasingly considered as the optimal surgical approach for benign pediatric ovarian tumors [22]. This approach preserves ovarian function and fertility potential. During ovary-sparing surgery, achieving a perfect dissection plane between the tumor margins and the healthy ovarian tissue is critical [22]. In the current study, we noted that cases 4 (grade 2) and 5 (grade 3) were treated by tumor enucleation alone as an ovary-sparing surgery, and both patients had good prognoses. Complete resection is a key factor in avoiding tumor relapse [16,21] however, preservation of ovarian function is also a very important issue in pediatric patients [17,22]. Our limited experience in such cases makes determining a clear indication for ovary-sparing surgery (tumor enucleation) in pediatric ovarian

Table 3
Operative findings and prognosis of seven patients with immature teratomas.

Case	Grade	Laterality	Stage		Surgery	Cytology of ascites (class)	Tumor weight (g) Tumor fluid (ml)	Prognosis
			COG	FIGO				
1	1	R	I	IA	USO	ND	280 300	EFS 7 years
2	2	R	I	IA	USO	2	310 -	EFS 13 years
3	2	R	I	IA	USO	2	500 -	EFS 7 years
4	2	R	I	IA	Tumor enucleation	2	405 2,200	EFS 3 years
5*	3	R	I	IA	Tumor enucleation	2	130 440	EFS 16 years
6	3	R	I	IA	USO	2	276 -	EFS 10 years
7	3	R	I	IA	USO	1	640 3,310	EFS 2 year

USO, unilateral salpingo-oophorectomy; R, right; EFS, event-free survival;
COG, the Children Oncology Group;
FIGO, the International Federation of Gynecology and Obstetrics
* : Case 5 was experienced with ovarian torsion.

ITs difficult. We decided tumor enucleation according to the intraoperative findings. Regarding the cases mentioned in this report, no microresidual tumor cells were detected in the patients who underwent tumor enucleation. However, if any postoperative microresiduals had remained, re-surgery by way of salpingo-oophorectomy would have been performed. Based on our data, ovary-sparing surgery has the potential to be an optional treatment approach for pediatric ovarian ITs with close postoperative active surveillance. We recommend a nation-wide discussion regarding indications and validity of ovary-sparing surgery in cases involving pediatric ovarian ITs, with consideration of the tumor grade [17].

Although there is little evidence regarding the adequate follow-up period after surgery, long-term follow-up is recommended so as to confirm that are no recurrences of ipsilateral lesions or contra-lateral tumor developments. Further investigation of the clinical characteristics and their association with tumor grades in pediatric ovarian ITs is also critical to elucidate surgical indications preoperatively.

5. Conclusions

We herein presented seven patients with ovarian ITs, including three patients with grade 3 tumors. All patients were COG stage I and FIGO stage IA. The patients with grade 3 tumors were relatively older and had higher AFP levels than those with lower-grade tumors. All cases were treated by surgery alone, including two cases that underwent ovary-sparing surgery, and none of the cases experienced relapse during the follow-up period. These findings suggest that patients with lower-stage ITs, including those with grade 3 tumors, have a good prognosis with surgery alone. The outcome of this study suggested that postoperative chemotherapy is unnecessary, even for patients with early-stage grade 3 tumors as well as patients with rather low AFP levels.

The authors have no competing interests to declare.

The Ethics Committee of University of Tsukuba Hospital approved this study (H30-315).

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