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Juvenile granulosa cell tumor: 20 years' experience of a Tertiary Center

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ABSTRACT

Objectives: The aim of this study is to share of the 20-year experience of a tertiary center about juvenile granulosa cell tumor (JGCT) and describe clinic manifestations, treatment, and outcome of patients who diagnosed JGCT.

Material and methods: Five patients who diagnosed juvenile granulosa cell tumor between 2000 and 2020 were included in the study. The demographics, clinical findings and outcomes were retrospectively evaluated. Of the 5 patients in our study, one was in the premenarcheal girl. The common complaint in all of our patients was abdominal swelling. In preoperative imaging methods, all patients had unilateral adnexal mass and no signs in favor of metastasis. All patients were staged according to FIGO classification for ovarian tumors; 3 of patients had stage IA disease, one of patients had stage IC1 and one of patients had stage IC2. All patients underwent different surgecal procedures which is appropriate for their clinical manifestations. In addition to surgery 2 patients received adjuvant chemotherapy.

Results: The median follow-up period of the patients was 60 mounts and recurrence was observed in two patients who were reoperated. We have no patients who died due to this disease.

Conclusions: Possible diagnosis of juvenile granulosa cell tumor should be kept in mind in a patient of young age with unilateral adnexal mass with benign features.

Key words: juvenile granulosa cell tumours; ovarian malignancy; sex cord–stromal tumours, pathology

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INTRODUCTION

Among the malignant sex cord-stromal tumors, the most common type is granulosa cell tumors (GCT) [1]. They are divided into two groups, juvenile and adult type, according to their clinicopathological features. Juvenile type constitutes five percent of all granulosa cell neoplasms [2]. It is generally seen in premenarchal girls and young women and is more aggressive than the adult type [3]. These tumors, which are usually unilateral, appear in the form of a large mass, smooth surface, solid and/or cystic components [4].

In a microscopic examination, granulosa cells can show several different characteristics. Call-exner body and coffee bean nuclei, which are mostly seen in the adult type, are not very common in the juvenile type. Inhibin as immune histochemical staining is the most specific and sensitive marker for the diagnosis [5].

This tumor is clinically coming up with many symptoms such as precocious puberty, early breast development, increased pubic hair, advanced bone age, palpable abdominal mass, nonspecific abdominal pain and abdominal swelling. In older patients, it manifests with signs of menstrual irregularity and virilization [4].

While the standard treatment in women completing childbearing is total hysterectomy and bilateral salpingo-oophorectomy including surgical staging, fertility-sparing surgery is performed in young women with appropriate staging [6]. In advanced stages or recurrent disease, platinum-based adjuvant chemotherapy treatment is recommended [7].

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Despite the high mitotic activity, juvenile granulosa cell tumors (JGCT) is almost always limited to one ovary. The most common prognostic factors are stage and residual disease after surgery [8]. In contrast to patients with advanced-stage disease which have a poor prognosis, the patients having tumors limited to one ovary have a good prognosis after unilateral salpingo-oophorectomy [9].

In this study, cases with a histopathological diagnosis of juvenile granulosa cell ovarian tumor who were followed between 2000–2020 in our clinic were presented and the literature on this rare disease was reviewed.

MATERIAL AND METHODS

Eight patients were included in this study. Patients who discontinued their follow-up and had missing medical records were not included in the study and the data of five patients were evaluated. The reason why three patients were lost from follow-up was that the patients had surgery in another center and applied to our clinic only for repeat histopathological evaluation. For this reason, follow-up of these patients was never performed in our clinic. The medical information of the patients was accessed retrospectively from their medical records. Patients' age, body mass index, clinical symptoms, laboratory findings, surgery, stage of the disease, histopathological features, follow-ups and outcomes were recorded. Pelvic ultrasound and contrast-enhanced MRI were performed before surgery. Tumor staging was performed according to FIGO classification for ovarian tumors. The research protocol of this study was approved by the ethics committee in our institution.

RESULTS

Clinical features of five patients were showed in Table 1. One patient who is 9-years-old was in the premenarcheal girl. The other patients were in the menstrual period. Three of them also had menstrual irregularities (Patients 2, 3, 4). In preoperative imaging methods, unilateral adnexal mass was discovered on the right side in three patients and on the left side in two patients. One patient had unilateral mass with intraabdominal free fluid as a sign of preoperative ovarian tumor rupture (Patient 5). None of the patients had signs in favour of metastasis or metastases. Three patients had high CA-125 levels; in one patient high AMH was detected. Other tumor markers and sex hormones were in the normal range in all patients.

Surgery was performed on four patients in our clinic. Of these, two patients underwent primary surgical staging (Patients 2 and 5). A patient who had undergone incomplete surgery in another clinic had referred to our clinic for staging surgery (Patient 1). A patient who had undergone complete surgical staging in another clinic applied to our clinic for follow-up (Patient no 4). A patient who underwent full staging in another clinic and had tumor recurrence a year later was referred to our clinic for secondary cytoreductive surgery (Patient 3). All patients underwent fertility-preserving staging surgery.

Right salpingo-oophorectomy, omentectomy and abdominal fluid aspiration were performed for Patient 1, who underwent incomplete surgery (only right cystectomy) in another clinic. This patient was classified as stage IA.

Patient 2 underwent laparoscopic resection to the right ovarian mass without ipsilateral salpingo-oophorectomy, because it was thought to be being as a result of preoperative examinations (Fig. 1–2). The patient was taken back to the surgical staging procedure and had ipsilateral salpingo-oophorectomy, partial omentectomy, a biopsy from the contralateral ovary and peritoneal biopsy, once the diagnosis of ovarian juvenile granulosa cell tumour was made (Fig. 3). This patient was classified as stage IA.

Patient 3 had right salpingo-oophorectomy, partial omentectomy, left ovarian wedge resection, abdominal fluid aspiration for complete staging at another clinic. This patient was classified as stage IA. One year later, the patient presented to our clinic for recurrence. This patient underwent left unilateral salpingo-oophorectomy, complementary omentectomy, left pelvic lymphadenectomy. But this time, the patient had the final histopathology gynandroblastoma. Following this, she received three courses of adjuvant chemotherapy which is paclitaxel+ carboplatin regimen.

Patient 4, who had undergone complete surgery involving left salpingo-oophorectomy, omentectomy, appendectomy, abdominal fluid aspiration in another clinic presented to our clinic for follow-up. Perop tumor rupture was written in the surgery report so this patient was classified as stage IC1. Adjuvant chemotherapy was recommended to the patient, but she refused treatment.

In Patient 5, a mass adhering to the anterior abdominal wall extending from the left salpinx to the bladder, and intraabdominal fluid, which is thought to be due to preop tumor rupture, was observed during surgery. This patient was classified as stage 1C2. The patient underwent tumorectomy and left salpingectomy. Suspected benign mesenchymal tumor result came up at intraoperative frozen section evaluation. After the final pathology resulted in juvenile granulosa cell tumor, the patient was given six cycles of chemotherapy consisting of cisplatin + etoposide regimen. Four years later the patient had a recurrence. Left oophorectomy was performed as secondary cytoreduction.

In all cases, the cut surfaces of tumors were multiloculated cystic with solid areas. In the microscopic examination, follicles of different sizes and shapes separated by cellular areas were seen. Pseudopapillary and trabecular patterns were also present in one case (Patient 2). Tumor cells were round to polygonal-shaped with hyperchromatic nuclei

Table 1. Five patients characteristic, outcome and pathological features of the five ovarian juvenile granulosa cell tumor patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	9	16	16	15	25
BMI [kg/m^2]	17.8	19	19.5	22.8	24
Clinic presentation	abdominal swelling	abdominal swelling + menstrual irregular cycles	abdominal swelling + menstrual irregular cycles	abdominal swelling + menstrual irregular cycles	abdominal swelling + urinary incontinence
Tumor markers	normal	normal	CA-125: 373 U/mL	CA-125: 44 U/mL	CA-125: 135 U/mL
Surgical type	1. Right cystectomy	1. Laparoscopic right cystectomy	1. Right USO+ Partial omm+ Left ovarian wedge resection+ Abdominal fluid aspiration	Left USO+ Omm+ App# + Abdominal fluid aspiration	1. Tumorectomy + Left salpingectomy
	2. Right USO* + Omm& + Abdominal fluid aspiration	2. Ipsilateral USO + Partial omm + Biopsy from the contralateral ovary + Peritoneal biopsy	2. Left USO+ Complementary omm+ Left pelvic lymphadenectomy		2. Left oophorectomy
Tumor laterality	right	right	right	left	left
Tumor size (cm)	14	11	24	30	19
Gross morphology	multiloculated cystic with solid areas	multiloculated cystic with solid areas	multiloculated cystic with solid areas	multiloculated cystic with solid areas	multiloculated cystic with solid areas
Capsul status	intact	intact	intact	defective	defective
Figo stage	1A	1A	1A	1C1	1C2
Mitotic index	35	7–30	unspecified	40–44	10–15
Call-exner body	no	no	no	no	no
Inhibin	positive	positive	positive	positive	positive
Nucleer groove	no	no	no	no	unspecified
Calretinin	positive	positive	positive	positive	positive
Pancytoceratine	unspecified	negative	unspecified	negative	in patch style positive
Chemotherapy	no	no	3 cycle paclitaxel+ carboplatin	no	6 cycle cisplatin+ etoposide
Follow-up [months]	96	12	84	24	60
Recurrence	no	no	(+)	no	(+)

BMI — body mass index; *USO — unilateral salpingo-oooferectomy; &Omm — omentectomy; #App — apendektomi

and abundant eosinophilic or vacuolated cytoplasm. In one case, striking cytologic atypia was observed in the focal area (Patient 4). Mitotic figures ranged 7–44 per 10 high-power fields.

The median follow-up period of the patients was 60 months (range: 12–96 months). Recurrence was observed in two patients. One of the patients with stage 1a recurred as 10 cm mass in the other ovary after 12 months (Patient 3). With the reoperation, the tumor was completely removed and chemotherapy was given. This patient had no evidence of disease at 49 months after secondary surgery. The other patient who has recurrence at 48 months after primary surgery had stage 1C2 disease (Patient 5). Isolated recurrent mass of 10 cm located left ovary of this patient was removed during the second surgery without residual disease and this patient had no evidence of disease at 12 months after the second surgery.

DISCUSSION

Ovarian cancers are the fourth most seen cancer in women after breast, lung and colorectal cancer [10]. Primary ovarian malignancies are originated in three subgroups according to cells they originate from: tumors of ovarian surface epithelium, germ cells, and sex cord cells [11]. GCT are the most common type of sex cord-stromal cell tumors (SCST) [1]. It is divided into two subgroups which are an adult and juvenile types and JGCT consist of 5% of GCTs. In this study, the 20-year experience of a tertiary center about JGCT was shared.

JGCT is generally seen in the first 30 years of life at median age of seven years [10]. The literature review revealed that more than 50% of patients are under 20 years old [12]. In the present study, the mean age of patients was 17 years

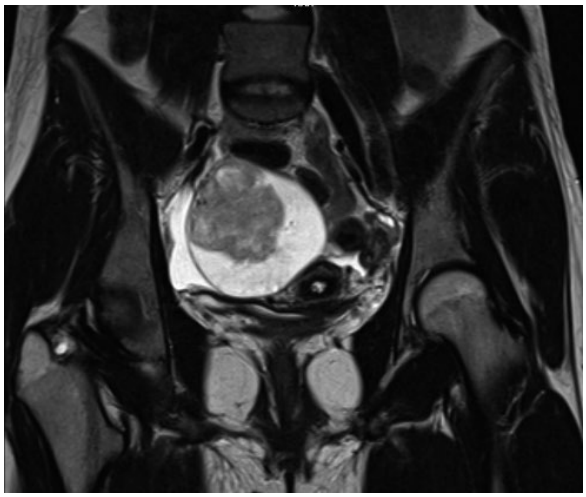

Figure 1. Pre-operative magnetic resonance imaging with contrast

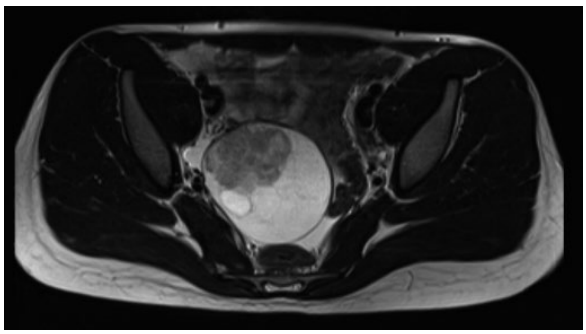

Figure 2. Pre-operative magnetic resonance imaging with contrast (Axiel plane)

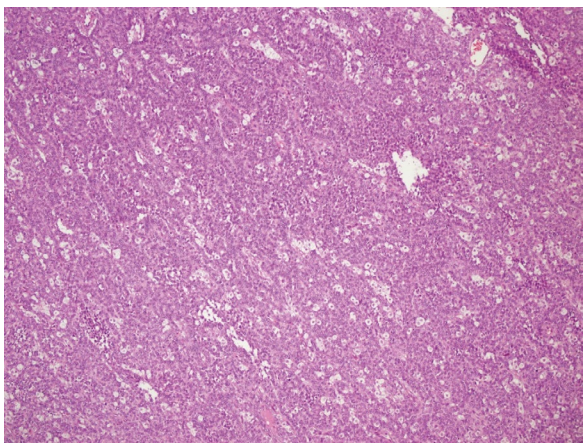

Figure 3. Pathologic image of juvenile granulosa cell tumors

and we had no patients older than 30 years old and we had only one patient over 20 years-age (20%).

A different study reported that there may be a relation between BMI and development of GCT [13]. In the meantime, van Meurs et al. [14] showed that high BMI was associated with shortened disease-free survival. However, the relationship between juvenile granulosa cell tumor and BMI has not been studied before in the literature. In the present group, the mean BMI was 20.6 and none of our patients were obese.

Because of the estrogen production from neoplastic cells, amenorrhea, isosexual precocious puberty, endometrial hyperplasia, endometrial neoplasm or even breast cancer can present in those patients who have JGCT. Serum estradiol concentrations increase in most patients; however precocious puberty can be seen even at normal or low plasma estradiol levels. It is thought that this situation may be based on the diurnal change in estradiol levels secreted from JGCT cells [15]. None of our patients had high levels of estradiol, three of them had an irregular menstrual cycle. In the present group, there is only one patient in the premenarchal period which did not have any findings related to isosexual precocious puberty. This neoplastic cell may sometimes present with masculinization and virilization. Increased androgen production from granulose cells or aromatase enzyme deficiency in those cells may be the reason for these hyperandrogenic findings [16]. Since none of our patients had evidence of masculinization or virilization, the androgen profiles were not evaluated.

The diagnosis of granulosa cell tumors is made by the clinical presentations of the patients and diagnostic imaging procedures must be used [10]. JGCT's are large in size. There is no difference at tumor size between premenarcheal or postmenarcheal period [4]. They may be solid (37%), cystic (14%), or solid component in dominant solid-cystic (45%) appearance [1]. The estrogenic effect may result in uterine enlargement or increased endometrial thickening. Four of our patients had solid and one had multicystic appearing tumors in preoperative imaging methods.

The only tumor markers used in monitoring the course of the disease is inhibin [17]. Inhibin is released from the granulosa cells for follicle development in women [18]. Serum FSH, LH, GnRH levels are very low due to increasing inhibin level in patients with JGCT. The value of serum estradiol and CA125 as a tumor marker for ovarian juvenile granulosa cell tumor remains uncertain [19]. In this study, serum CA-125 level was found to be significantly high in two recurrent cases.

In the pathological examination of the tumor, the surface is usually smooth and firm macroscopically. Because of immature granulosa cells with frequent mitoses; microscopically view has a macrofollicular or cystic pattern. Macrofollicles filled with mucinous fluid are typical sign for JGCT. The Call-Exner body is uncommon at JGCT [4]. In immunohistochemical analysis, all subgroups of GCT has expressed vimentin, cytokeratins [20]. Vimentin positivity has been shown to help differentiate well-differentiated

tumors from poorly differentiated ones [11]. Only one patient in this study had positive vimentin in the pathology report, and recurrence was observed in this patient. Some studies suggested that inhibin and tissue AMH levels can be used as histochemical markers [21]. Positive staining with inhibin is the most important diagnostic feature for GCTs [22]. Other important markers for ovarian juvenile granulosa cell tumor diagnosis are also CD99 and calretinin [23]. Anttonen et al. [24] showed that AMH decreases in reverse correlation with tumor size in GCTs, and transcription factor GATA-4 expression, which plays a role in the regulation of AMH, increases in correlation with tumor stage and recurrence. In our study, the positivity of inhibin and calretinin was detected in all patients, tissue AMH level was not measured in any patient, but serum AMH was high [(23 ng/mL) (normal range 0.05–11)] in one patient.

Treatment options for JGCT may vary based on the age of the patient and extend of the disease. The primary treatment of the disease is surgery which includes staging [25]. A standard surgical procedure is hysterectomy and bilateral salpingo-oophorectomy. However, fertility-sparing surgery which is consists of unilateral oophorectomy or unilateral salpingo-oophorectomy is an acceptable option for young women. Retrospective studies have suggested that there is a nearly similar cure rate for early-stage disease whether treated by unilateral salpingo-oophorectomy or bilateral salpingo-oophorectomy [26]. Systemic lymphadenectomy has no place in JGCT surgical staging [27].

According to FIGO stage, 88% of JGCT were stage IA, 2% of JGCT were stage IB, 8% of JGCT were IC, and 3% of JGCT were stage II. Three of our patients were stage 1a, one was stage 1c1, and one was stage 1c2. Previous studies showed that preoperative abdominal fluid was observed in 10% of JGCT patients. This fluid can be due to tumor rupture or acid accumulation due to metastasis [28]. We had only one patient having intraabdominal free fluid.

The benefit of postoperative adjuvant therapy is unclear. Postoperative chemotherapy is suggested for stage IC to IV disease of women had complementary surgery [29]. In some studies, the combination of a platinum agent with vinblastin and bleomycin, or adriamycin and cyclophosphamide, has been used as adjuvant therapy, while some studies have recommended the use of bleomycin, etoposide and platinum (BEP) [30]. The combination of paclitaxel with platinum, which are hormone-based therapies, is currently the adjuvant therapy suggested due to their lesser toxicity than BEP treatment [31]. In our general clinical approach, adjuvant chemotherapy is recommended in advanced or recurrent cases. Radiotherapy has not been shown to benefit survival at any stage of JGCT. Sunitinib and bevacizumab which are angiogenesis blockers are new agents for experimental treatment of this pathology [31].

The prognosis depends upon the stage of disease at diagnosis and the presence of residual disease after surgery. In stage 1 patients, 5-year survival with surgery alone has been shown to be between 90–100% [32]. Although they are malignant, their prognosis is good [33, 34]. Advanced stage (FIGO stage 2, 3, 4) JGCT is rare but has a poor prognosis with the 5-year survival rate of 25–50%. In these patients, most of the recurrences occur within 12 months after the initial treatment [35]. It is not reported that JGCT has recurrence after three years from primary treatment [5]. Although recurrent JGCT cases have a poor prognosis, long-term remission has been demonstrated with optimal resection of the recurrent tumor and appropriate postoperative treatment [36]. Recurrence was observed in two of our patients (40%) after 12 and 48 months from first line therapy. In some studies, it was highlighted that the mitotic index in tumor tissue has an important role in prognosis [3, 32]. From other side, although there was a relation of tumor size, mitotic activity, and nuclear atypia to the outcome when tumors of all stages were evaluated, no such relation was evident when only stage Ia and Ib tumors were considered [12]. Our four patients have mitotic index results with more then10 per 10 high-power fields in pathology, three of these cases have no recurrence, so there was no correlation between the relapse of the disease and the mitotic index. Currently, all our patients are in remission.

CONCLUSIONS

Possible diagnosis of juvenile granulosa cell tumor should be kept in mind in a patient of young age with unilateral adnexal mass with benign features. Most patients with JGCT present with early stage. Although it is a good prognostic tumor at stage Ia, the recurrence rate of JGCT is not uncommon.

Conflict of interest

The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

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