Clinicopathologic assessment of patients with ovarian granulosa cell tumor in a tertiary medical center

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Original Article

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ABSTRACT

Objectives: To evaluate the clinic-pathological characteristics and management of adult granulosa cell tumor in a university clinic.

Design: Retrospective study

Setting: Department of Obstetrics and Gynecology, Eskisehir Osmangazi University School of Medicine

Subjects: A total of 48 patients with diagnosis of adult granulosa cell tumors between 2005-2014.

Intervention: Clinicopathologic assessment of patients with adult granulosa cell tumors who underwent surgical treatment and had follow up visits at our institution

Main outcome measure: Patients' age, body mass index, menopausal status, presenting manifestation, tumor size, CA 125 level, stage of the disease, surgical treatment, recurrence, adjuvant therapy, endometrial sampling, pathology and operation records

Results: Abdominal pain and vaginal bleeding were common symptoms. The median tumor size was 8 cm (2-20cm). The majority of patients were FIGO stage I (87.5%). Four patients had well-differentiated endometrioid adenocarcinoma of the endometrium. Chemotherapy was administered as an adjuvant treatment to patients with stage IC, II, and IV disease. The recurrence of the disease was noted in five patients (10.4%). While three of them were FIGO stage IC, two of them were stage IVA. The median recurrence time was 50 months. The most common recurrence site was intraabdominal peritoneum. Surgery and chemotherapy were used in the treatment of recurrent disease.

Conclusion: Most of the patients with adult granulosa cell tumors are diagnosed in stage I. Although recurrence is rare, recurrence can be seen even in the early stage. Lifelong follow up should be recommended. The endometrium should be evaluated before or after the diagnose. Attention should be given to endometrial sampling.

KEY WORDS: Adult type, granulosa cell tumor, ovarian cancer, ovary, sex cord stromal tumor

INTRODUCTION

Granulosa cell tumors (GCT) derive from the gonadal stroma and it is the most common malignant sex cod stromal tumors [1]. They account for 2%-5% of all ovarian cancers [2]. GCT can occur in all age. However, perimenopausal women are mostly affected [3]. It is divided into two subtypes according to histological findings: adult type (AGCT) and juvenile type (JGCT). AGCTs are more common than JGCT [4]. As GCT produce estrogen, patients will refer to hospital with hyperestrogenic symptoms like menstrual irregularities and endometrial hyperplasia [5, 6]. Most of the patients present with stage I disease and it is usually unilateral [7]. Primer treatment of this tumor is surgery. The extensiveness of surgery will be decided according to the patient's fertility desire [3]. Complete surgical staging and adjuvant treatment are controversial because of the low recurrence rate and low incidence of lymph node metastasis [8]. As five-year overall survival is above 90%, AGCT has a good prognosis. Even though its good prognosis, late recurrences will cause morbidity and mortality, and it will be difficult to manage [9]. Most of the recurrences occur more than five years after primary treatment. Therefore, long term follows up requires [10]. The rarity of AGCTs makes it challenging to decide primary and recurrence disease treatment.

The objective of this study is to evaluate the clinic-pathological characteristics and management of these rare tumors in a university clinic.

SUBJECTS AND METHODS

Retrospectively, we reviewed a total of 48 patients with the diagnosis of adult granulosa cell tumors at Eskisehir Osmangazi University between 2005-2014. The study was approved by the ethics committee (2019-296).

Patients diagnosed with AGCT, underwent surgical treatment and had follow-up visits at our institution included the study. Ultrasound scan of pelvis was performed by a gynecologist oncologist before the surgery. Frozen section was used for intraoperative assessment of pelvic mass in all of the 48 patients. The extension of the surgery was decided according to the results of the frozen section and patient's fertility desire. Our exclusion criteria were; sex cord-stromal tumors other than granulosa type, having surgery out of our institution, no follow up visits, incomplete records and pathologic information. It was found that 82 patient had sex-cord stromal tumors, 32 of them had sex cord stromal tumor other than granulosa type, and 2 of them quitted their follow-up. 34 patients were excluded from the study and the records from 48 patients with diagnosis of granulosa cell tumors were included.

The data included age, body mass index (BMI), menopausal status, presenting manifestation, tumor size, CA 125 level, stage of disease according to International Federation of Gynecology and Obstetrics (FIGO), surgical treatment, recurrence, adjuvant therapy, endometrial sampling were obtained from hospital database system, pathology and operation records, and patients health records. BMI, a measure of body fat, was calculated by weight in kilograms divided by height in meters squared. Surgical treatment was defined as primary fertility-sparing staging, primary non-conservative staging, and not staged surgery, either total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO) or unilateral salpingo-oophorectomy (USO). For fertility sparing surgery, the uterus and at least one adnexa conserved. Unilateral salpingo-oophorectomy or unilateral salpingo-oophorectomy with staging surgery was performed to preserve the fertility. After treatment, patients were examined every three months in the first two years, every six months the consecutive three years and then annually.

Statistical analysis was performed by using SPSS 20.0 software.

RESULTS

Forty-eight women were identified with a diagnosis of AGCT between 2005-2014 in our institution. The median age and BMI of the patients were at the time of diagnosis were 50 years (range, 22-70 years), and 28. 5 kg/m^2 (range, 23-44 kg/m^2) respectively. Of the patients, 18 (37.5%) of them were premenopausal. Abdominal pain and vaginal bleeding were common symptoms causing the patient to come hospital. Most of our patients had a unilateral disease (95.8%). The median tumor size was 8 cm (2-20cm). When the preoperative CA125 values were evaluated, it was seen that only 14 patients (29.16%) had elevated CA125 level. The majority of patients were FIGO stage I (87.5%). The endometrial assessment was performed to 15 patients preoperatively. Four patients had well-differentiated endometrioid adenocarcinoma of the endometrium, three of them were known preoperatively. Other endometrial alterations were endometrial hyperplasia and polyp (Table 1). The majority of patients were treated by staging surgery (70.7%). Preserving of uterus was decided according to patient's age and fertility desire. Complete pelvic and paraaortic lymphadenectomy were performed to surgically staged patients. Except for four patients with stage IV disease, optimal cytoreduction was achieved. Two patients had disease of FIGO stage IB endometrial cancer

and FIGO stage other than I AGCT that they received chemotherapy and radiotherapy as adjuvant treatment. One patient had concomitant stage IB1 cervical cancer that was determined in pathology specimen and was referred to adjuvant radiotherapy. Chemotherapy was administered as adjuvant treatment to patients with stage IC, II, and IV disease (Table 2). One patient could not receive adjuvant chemotherapy because of her medical condition. While twenty-two patients received bleomycin, etoposide, and cisplatin (BEP) chemotherapy, five patients received paclitaxel and carboplatin chemotherapy.

Recurrence of disease was noted in five patients (10. 4%). While three of them were FIGO stage IC, two of them were stage IVA. The median recurrence time was 50 months. We diagnosed the recurrence with histologically by surgery in two patients and by radiologic guided biopsy in three patients. The most common recurrence site was intraabdominal peritoneum. Surgery and chemotherapy were used in the treatment of recurrent disease (Table 3).

Four patients died because of the disease. Three of them had recurrence disease. One of them had recurrence in the liver and chemotherapy was used for treatment. The other two of them had recurrence in the intraabdominal peritoneum. Chemotherapy was used for one of them for treatment of recurrence disease. Both surgery and chemotherapy were used for treatment of the other intraabdominal recurrence. Despite ongoing treatment, 3 had progressive disease and died because of recurrence. The last patient who died because of the disease had FIGO stage IVB disease. After surgery the patient was referred to chemotherapy as adjuvant treatment however she could not receive chemotherapy because of her medical condition and died because of the progression of liver parenchymal metastasis.

DISCUSSION

Our study showed that most of the patients with AGCT are diagnosed in stage I disease. Although recurrences are rare, even in the early stage recurrence can be seen, and patients should stay in follow up. Because of secreting estrogen, endometrium should be evaluated before or after the diagnose. CA125 value may not always rise like ovarian epithelial tumors.

Compatible with the literature, our study populations median age at the diagnose were 50 years (22-70 years), most of them were postmenopausal and median BMI was 28.5 kg/m² (23-44 kg/m²). As in our study, the most reported presenting symptoms are vaginal bleeding and abdominal mass in the literature [11, 12]. In a systemic review, Levin et al. reported that stage I disease ranges 74-95%, stage II disease ranges 5.1-11%, stage III disease ranges 0.8-10% and stage IV disease ranges 0.5-8.6%[1]. Our results showed that FIGO stage I disease was 87.5% among patients with AGCT.

Lee et al. analyzed 68 patients with AGCT and reported endometrial pathology was found in 26.4% of them, of which 2.9% were endometrial cancer [11]. Some studies informed higher rates of endometrial cancer (6.2%, 17%) [12, 13]. In our study population endometrial alterations were endometrial hyperplasia, polyp and endometrial cancer. We found that endometrial cancer was seen 8.3% of patients. All these findings highlight the importance of endometrial sampling in management of AGCT. Preoperative endometrial sampling can be used to guide patient management and to inform them.

We evaluated CA125 value as a tumor marker in AGCT and 29.1% of our patients showed elevated CA125 level (55± 78 IU/ml). In a case-control study, Yesilyurt *et al* stated that GCT patients had elevated CA125 level (64.5± 130 IU/ml) [14]. Another study evaluated patients with AGCT by Lee *et al* reported 13.1%

of patients had elevated levels [11]. It is not expected that the CA125 level to rise as in epithelial ovarian cancer, determining preoperative CA125 level will be important in following the patient postoperatively if she had high level of CA125.

The standard treatment of AGCT is surgery. Hysterectomy and bilateral salpingo-oophorectomy should be performed according to the patient's fertility desire [1]. Surgical resection with negative margins is considered as best treatment [15]. Performing lymphadenectomy is controversial. While some researchers mention lymph node status as a prognostic factor for survival and recommend complete surgical staging[16,17], some researchers are against lymph node dissection because of the low rate of lymph node metastasis[18,19]. We performed pelvic and paraaortic lymphadenectomy to most of our patients (70.7%). None of them had lymph node metastasis. We have been still performing surgical staging to patients with AGCT at our clinic; however we cannot claim the necessity of lymph node dissection.

The role of adjuvant chemotherapy and radiotherapy is controversial. In our study, half of our patients and all of the patients with recurrence received bleomycin, etoposide, and cisplatin (BEP) or paclitaxel and carboplatin as adjuvant chemotherapy. For patients with high-risk stage I tumors and higher stages, it can be acceptable to recommend adjuvant chemotherapy. Platinum-based chemotherapy is one of the recommended options [20]. Adjuvant radiotherapy is usually to palliate late-stage isolated recurrences [1]. None of our patients received adjuvant radiotherapy because of AGCT. Two patients with endometrial carcinoma and one patient with cervical cancer were referred to adjuvant radiotherapy.

Studies in the literature identified that stage of disease at diagnose, and size of the tumor were correlated with recurrence [11, 13, 21]. In our study, three of five patients with recurrence were stage IC and the median tumor size was 10 cm in recurrence disease. It can be said that small study population may contribute to this recurrence in patients with the early-stage. Even if this is the case, based on our findings, we argue that recurrence can be seen in stage I disease. As follow-up visits are important to detect the recurrence early, patients should stay in follow up.

There were some limitations to our study. First, the methodological design of the current study is retrospective; therefore it has got some inherent biases such as selection bias and information bias. First of all, the study group both included patients with fertility desire and patients underwent complete cytoreduction surgery. Therefore, there is not a single surgical procedure for this rare neoplasm. It may be better to perform a multicenter study to reach an adequate number of patients who underwent same surgical procedure to conclude a better result. Nevertheless, the extent of our study group may be accepted as adequate from a single center who underwent surgery with the same surgery and oncology team. Second, the other limitation is lack of long-term survival analysis of the patients. It is very difficult to make a study about a very rare ovarian neoplasm and its long-term survival comparing with different stages and types of ovarian cancer. Most of our patients were diagnosed mostly in stage IA and IC. Moreover, it is also difficult to comment on chemotherapy regimen in patients with stage IC. Lastly, during the time, paclitaxel carboplatin regimens were more preferable regimen than bleomycin, etoposide, cisplatin and our study group included patients who received both chemotherapy regimens. Therefore, again it is difficult to conclude a uniform result, but the main aim of our study is not to compare chemotherapy regimens directly. Moreover, single-center experience gives similar treatment protocols with similar surgery and oncology team.

CONCLUSION

In conclusion, most of the patients with AGCT are diagnosed in stage I. Although recurrences are rare, even in the early stage recurrence can be seen. Lifelong follow up should be recommended. Because of secreting estrogen, endometrium should be evaluated before or after the diagnosis. Attention should be given to endometrial sampling especially in patients with conservative surgery.

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Author contribution:

TO: Performed the operations, designed the study, wrote the article

DKC: Helped to perform operations, comment on and edited the article, statistical analyses

YC: Helped to perform operations, collected the data, comment on the article

IS: Collected the data, comment on the article, statistical analyses

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Table 1: Characteristics of patients with adult granulosa cell tumor

Patients Characteristics	n:48	%/ range
Age (years, median)	50	22-70
BMI (kg/m², median)	28.5	23-44
Menopausal status		
Premenopausal	18	37.5%
Postmenopausal	30	62.5%
Presenting manifestation, n (%)		
Vaginal bleeding	20	41.6%
Abdominal mass	6	12.5%
Abdominal pain	22	45.8%
Ovarian tumor		
Unilateral	46	95.8%
Bilateral	2	4.1%
Tumor size (cm, median)	8	2-20
CA 125 level		
Elevated (>35 IU/ml)	14	29.1%
Normal	34	70.8%
FIGO stage		
IA	20	41.6%
IB	0	0
IC	22	45.8%
II	2	4.1%
III	0	0
IV	4	8.3%
Endometrial pathology		
Normal	29	60.4%
Endometrial polyp	5	10.4%
Hyperplasia	10	20.8%
Carcinoma	4	8.3%
Follow up time (months, median)	83	22-155
Recurrence	5	10.4%
Recurrence time (months, median)	50	37-133
Died of disease	4	8.3%

BMI: body mass index; FIGO: International Federation of Gynecology and Obstetrics.

Table 2: Surgical procedure type and adjuvant treatment

Treatment	n:48	%
Surgical treatment		
Primary fertility sparing staging	2	4.1%
Primary non-conservative staging	32	66.6%
Not staged (TAH+BSO)	10	20.8%
Not staged (USO/cystectomy)	4	8.3%
Adjuvant chemotherapy	24	50%
Adjuvant radiotherapy	1	2%
Adjuvant radiotherapy+ chemotherapy	2	4.1%

TAH+BSO: total abdominal hysterectomy and bilateral salpingo-oophorectomy; USO: unilateral salpingo-oophorectomy.

Table 3: Characteristics of patients with recurrence

Case	Age (years)	FIGO stage	Tumor size(cm)	Initial treatment	Recurrence Time(months)	Site of recurrence	Treatment of recurrence	Outcome
1	30	IC	6	USO	37	Intraabdominal Peritoneum	Surgery+ Chemotherapy	DOD
2	45	IVA	8	Staging surgery	40	Liver	Chemotherapy	DOD
3	34	IC	10	Staging surgery	133	Vagen vault	Surgery+ Chemotherapy	NED
4	38	IC	10	TAH+BSO	50	Paraaortic Lymph node	Chemotherapy	NED
5	54	IVA	11	Staging surgery	97	Intraabdominal Peritoneum	Chemotherapy	DOD

FIGO: International Federation of Gynecology and Obstetrics; TAH+BSO: total abdominal hysterectomy and bilateral salpingo-oophorectomy; USO: unilateral salpingo-oophorectomy; DOD: die of disease; NED: no evidence of disease