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TOGETHER LET’S BEAT NCDs

Cancer

Diabetes

Cardiovascular Diseases

Chronic Respiratory Diseases

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Original Article

Clinicopathological outcome of ovarian granulosa cell tumors

Ehab Al-Rayyan¹, Maher Maaita¹, Omar Alelwan¹, Omar Taso¹, William Hadadin²

¹Department of Obstetrics and Gynecology King Hussein Medical Center, Amman, Jordan.
²Department of Pathology and Laboratory King Hussein Medical Center, Amman, Jordan.

Abstract

Objective: The aim of our study was to analyze the clinical and pathological characteristics of women who were diagnosed with malignant ovarian granulosa cell tumors and managed at single institution.

Materials and methods: A retrospective study was conducted regarding patients who were diagnosed with ovarian granulosa cell tumors and received treatment at King Hussein Medical Center. Data was extracted from the patient’s files and reports from the period 2007 to 2017 (over ten years period). The collected data included patient’s characteristics for age, parity, presenting symptoms, marital and menopausal status. Tumor characteristics included the site, size, mitotic index, type and associated uterine pathology. Other data included the type of surgery performed, adjuvant treatment provided, outcome data regarding tumor stage, recurrence and survival. Data was revised, arranged in tables and statically analyzed.

Results: Twenty-one cases of ovarian granulosa cell tumors were identified. The median age of cases was 45.5 years (range of 17–76). Abdominal pain was the most common presenting symptom11/21 (52.4%). Endometrial hyperplasia was associated with ovarian tumor in six patients (28.6%) and endometrial cancer in three cases (14.3%). The primary surgery ranged from unilateral cystectomy to hysterectomy, bilateral salpingo-oophorectomy, and debulking surgery. Stage I–II were recorded in 18/21 (85.7%) of the cases, while stage III–V were found in 3/21 (14.3%). No adjuvant treatment was required in 11 cases (52.4%). Less than five years survival was 19% (4/21). Over all recurrence rate was 23.8%.

Conclusion: Granulosa cell tumors is a rare ovarian malignancy. Surgery is the standard treatment with a role for fertility preservation. Most tumors are diagnosed at an early stage with very good outcomes. Recurrence and survival are related mainly to initial tumor stage, however, further studies are needed to study the effect of other factors on outcome.

Keywords: Granulosa cell tumor, pathological, ovary

Introduction

The somatic cells of the sex cord of the ovaries are called granulosa cells and they are associated with forming the oocytes. The main function of these cells is producing sex steroids and some peptides, which are important for ovulation and folliculogenesis.

Granulosa cell tumors developing from these cells usually are rare tumors of the ovaries, constituting about 2–5% of all ovarian tumors. The commonest is sex cord stromal malignancies (70%) (¹). Granulosa ovarian tumor has two types juvenile and adult type. The most common form is the adult type that forms 95% of granulosa cell tumors leaving the juvenile type with only 5%, which is usually seen in pre menarche or young patients (², ³). Furthermore, the adult type mostly presented at the peri and post–menopausal periods with peak age of 50–55 years (⁴). Granulosa cell tumors (GCT) mostly discovered at early stage with sometimes hyperestrogenism state, maybe, that is why they have better prognosis than the other types of the ovarian tumors. They have potential for late recurrence even after 30 years (⁵,⁶).

Similar to other ovarian cancers, the presenting symptoms are mostly nonspecific abdominal pains or abdominal distension. Due to increased vascularity, tumor rupture is seen in 10% of cases, which leads to hemoperitoneum. The tumor is bilateral in <10% of cases (⁶). These tumors are concurrent with endometrial hyperplasia in 25–50% of cases and in 3–27% of cases with endometrial cancer. Surgery alone usually is enough

Corresponding Author: Dr. Ehab Al–Rayyan, Department of Obstetrics and Gynecology King Hussein Medical Center, Amman, Jordan.
Email: erayyane@yahoo.com
for early stages but for the late stages, chemotherapy is recommended.

Materials and Methods

The database of the gynecologic oncology clinic at King Hussein Medical Center, Amman, Jordan was reviewed from 2007 to 2017. Patient’s records were reviewed and a systemic research was made through the pathology records of patients reported as having malignant ovarian granulosa cell tumors. The retrieved data included patient’s characteristics, tumor characteristics, modality of management performed and outcome regarding stage of tumor, recurrence and survival. Patient’s characteristics at the time of diagnosis included age, parity, marital status, menopausal status, and the presenting symptoms. Tumor characteristics included size, location, mitotic index, type of tumor and any other associated malignant or premalignant uterine pathology. Modality of treatment included primary and secondary surgery, adjuvant chemotherapy and radiotherapy. Patients were included in the study if complete data was available for analysis and at least part of their management was undertaken at King Hussein Medical Center as some patients were referred to us from other hospitals. A retrospective chart review and analyses of patient’s data were conducted. Ethical committee approval was obtained before commencing the study.

Results

Our data was recorded from 21 patients who had a confirmed diagnosis of malignant granulose cell tumors on histopathology and treated at our institution. The age group ranged from 16–76 years (mean age 45.5 years). Table 1 showed patients characteristics. About half of our patients were in the age group between 20–50 years. Only two cases were below the age of 20 years and 8 cases (38%) aged 50 years and more. 13 patients were grand multipara whom had two or more children. About one fifth (19.1%) of cases were nulliparous whom had never given birth before. Two cases (9.5%) had one or two previous pregnancies and another two cases of unknown parity. Our data showed that more patients were in the premenopausal status compared to the postmenopausal status (61.9% vs 38.1%) with a ratio equals 1:6. Most patients were married (85.7%) and only 3 patients were single at the time of diagnosis. Abdominal pain was the most common presenting symptom in slightly more than half of cases (52.4%), this was followed by feeling of abdominal distention or pelvic masses in 38.1% of cases. 28.6% and 4.8% of cases presented with abnormal vaginal bleeding and amenorrhea respectively.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (Total=21 patients)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>2</td>
<td>9.5%</td>
</tr>
<tr>
<td>20-50</td>
<td>11</td>
<td>52.4%</td>
</tr>
<tr>
<td>&gt;50</td>
<td>8</td>
<td>38.1%</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P 0</td>
<td>4</td>
<td>19.1%</td>
</tr>
<tr>
<td>≤2</td>
<td>2</td>
<td>9.5%</td>
</tr>
<tr>
<td>&gt;2</td>
<td>13</td>
<td>61.9%</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>9.5%</td>
</tr>
<tr>
<td>Menopause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>13</td>
<td>61.9%</td>
</tr>
<tr>
<td>Post</td>
<td>8</td>
<td>38.1%</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11</td>
<td>52.4%</td>
</tr>
<tr>
<td>Pelvic mass</td>
<td>8</td>
<td>38.1%</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>6</td>
<td>28.6%</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>1</td>
<td>4.8%</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>4.8%</td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>3</td>
<td>14.3%</td>
</tr>
<tr>
<td>Married</td>
<td>18</td>
<td>85.7%</td>
</tr>
</tbody>
</table>

Table 1: Patient characteristics

Six patients presented with more than one presenting symptom (28.6%).

Tumor characteristics were described in Table 2. Most tumors were unilateral with only one case detected as bilateral ovarian forming 4.8% of all cases recorded. Tumors recorded less than 10cm in size were double those of 10cm or more (47.6% vs 23.8%) while 6 cases had undocumented size of tumor at the time of diagnosis. Final histopathological reports failed to identify mitotic index in most cases (71.4%). Three cases were reported as low mitotic index compared to two cases with intermediate and one case of high mitotic index forming (14.3%, 9.5%, 4.8%) respectively. Two cases were of juvenile type (9.5%) and fourteen cases of adult type (66.7), while five other tumors showed no final histopathological type (23.8%). Associated endometrial pathology was diagnosed among 9 cases with ovarian granulosa cell tumors (42.9%). Six cases had endometrial hyperplasia (28.6%) and three cases had endometrial carcinoma (14.3%).
Table 2: Tumor characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (Total=21 patients)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>7</td>
<td>33.3%</td>
</tr>
<tr>
<td>Left</td>
<td>8</td>
<td>38.1%</td>
</tr>
<tr>
<td>Bilateral</td>
<td>1</td>
<td>4.8%</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
<td>23.8%</td>
</tr>
<tr>
<td>Size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>10</td>
<td>47.6%</td>
</tr>
<tr>
<td>≥10</td>
<td>5</td>
<td>23.8%</td>
</tr>
<tr>
<td>Mitotic index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>28.6%</td>
</tr>
<tr>
<td>Low (1-3)</td>
<td>3</td>
<td>14.3%</td>
</tr>
<tr>
<td>Intermediate (4-10)</td>
<td>2</td>
<td>9.5%</td>
</tr>
<tr>
<td>High (≥10)</td>
<td>1</td>
<td>4.8%</td>
</tr>
<tr>
<td>Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile</td>
<td>2</td>
<td>9.5%</td>
</tr>
<tr>
<td>Adult</td>
<td>14</td>
<td>66.7%</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
<td>23.8%</td>
</tr>
<tr>
<td>Associated pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial hyperplasia</td>
<td>6</td>
<td>28.6%</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>3</td>
<td>14.3%</td>
</tr>
</tbody>
</table>

Table 3 showed the type of primary surgery performed during the management of our patients. The majority of patients had total abdominal hysterectomy and bilateral salpingo-ooophorectomy plus infracolic omentectomy in 15 cases forming (71.4%); two cases of them underwent pelvic and para-aortic lymphadenectomy. Four cases (19.2%) had a more conservative management, one unilateral ovarian cystectomy and three unilateral oophorectomy plus infracolic omentectomy. Two advanced tumor cases had ovarian or omental biopsies for diagnosis (9.5%). More than half of cases 11/21 (52.4%) required no adjuvant therapy. Ten cases (47.6%) required chemotherapy. Four cases of them requiring both adjuvant chemotherapy and radiotherapy (19%). Secondary cytoreductive surgery was performed to two cases (9.5%) due to recurrence.

The stage of tumors and the recurrences were shown in Table 4. Nearly 90% of patients were stage I at the time of diagnosis (17/21). Fourteen of them were stage IA, three additional cases were stage IC. The rest of patients (10%) were diagnosed with stage II, III, IV forming (4.8%, 4.8%, 9.5%) respectively. Five cases showed recurrence of tumor. Stage I showed the least recurrence rate 2/17 (11.7%), one recurrence for each stage IA and IC. All patients with advanced tumor (Stage III and IV) showed recurrence. Over all recurrence rate was recorded at 23.8%. Nine cases showed five years and more survival (42.8%) compared to only five cases survived less than five years (19%). The rest of cases (7 cases), 5 years did not pass since they were diagnosed with the tumor. The
longest period until recurrence was seven years after being initially diagnosed with this tumor.

Discussion

Ovarian granulosa cell tumors considered one of the rare tumors constituting 2–5% of all ovarian tumors. Rokitansky first described it in 1855. Two types were recognized: The adult and the juvenile. The adult type forms about 95% of all granulosa cell tumors and mostly were discovered around the perimenopausal period with age ranged from 46–54 in different studies. However, other studies showed peak incidence at 50–55 years. The other less frequent form is the juvenile type. It forms about 5% of all granulosa cell tumors and mostly diagnosed before female puberty. Unfortunately, we failed to recognize the type of granulose tumor in five cases in our series. Nevertheless, our data regarding the adult type is similar to what is published in the literature. Our two cases of juvenile type were diagnosed at the age of sixteen.

Macroscopically Ranganth et al described granulosa cell tumors as unilateral tan yellow complex masses with wide range of size of 3–24cm, though; it is usually more than 10cm in size. Only one case reported by our study as bilateral tumor and about half of our cases showed a tumor more than 10 cm in size with a range of 5–20cm. Microscopically granulosa cells are tiny round to oval shape with nuclei looks like coffee bean. It is characterized by the presence of Call Exner Bodies, which are seen in 30% of cases. Other commonly used histopathological features are the presence of nuclear atypia, number of mitotic index, and serum markers. The presence of those features are considered as a bad prognostic factor, which has a bad impact on disease free survival.

The most common presenting symptom in our study was abdominal pain and was detected in half of our patients. This was followed by feeling of pelvic mass and menstrual cycle abnormalities which together formed about one third of all presenting symptoms. These numbers are so close to another study by Khosla et al that showed abdominal pain to form 57.7% of all symptoms. A recent study in Egypt on 17 patients showed abdominal pains as the presenting symptom in about 64.7% of cases. Other clinical manifestations can be related to excessive hormonal secretions specially estrogen. This explains the concomitant presence of endometrial hyperplasia in our cases (28.6%) and endometrial cancer in (14.3%). Many other studies confirm the incidence of associated hyperplasia between 25–50% and cancer between 5–10%. Data regarding performing routine endometrial sample for patients with ovarian granulosa cell tumors is controversial. Ottolina et al. recommended performing endometrial sampling to only symptomatic patients with ovarian granulosa cell tumors above the age of 40 years. In our patients routine endometrial sampling was not performed before surgery as most patients were diagnosed after hysterectomy. For patients who were diagnosed with the juvenile type, it is not acceptable culturally in Jordan to perform endometrial biopsy as all these patients are virgins.

The standard surgical staging for managing ovarian granulosa cell tumor is total hysterectomy and bilateral salpingo–oophorectomy with removal of all gross disease at the time of primary surgery. Our data regarding the primary surgery ranged from ovarian cystectomy to total abdominal hysterectomy with removal of omentum and lymph nodes. The only patient who underwent ovarian cystectomy in our study was a 16 years old. Her family refused any further surgery regarding removal of the whole ovary although she was counseled about the possibility of residual tumor. She has been followed closely at our outpatient department. A similar case was reported by a recent Turkish study for a juvenile type granulosa cell tumor treated by ovarian cystectomy and it showed no recurrence during the follow up period. Three other cases were treated with unilateral salpingo–oophorectomy and all showed no recurrence of tumor until the time of writing this paper. In patients where fertility preservation is an issue, unilateral salpingo–oophorectomy is an acceptable option. In one large study involving 376 patients, it has shown no significant survival between the group that was managed conservatively and the group that was managed with radical surgery. Although lymphadenectomy was performed in some of our patients whom pre–operative radiological imaging showed enlarged lymph nodes, no case of lymph node metastasis was detected among them. Several studies reported lymphadenectomy as an insignificant factor for survival and recommended against performing it in surgical staging. Performing a wedge biopsy of the opposite ovary is controversial due to very low incidence of occurrence (about 2%). One study recommended against it and it was reported to be performed only with caution if the contra lateral ovary looks suspicious. This procedure was not performed on any of our patients during the period of study.

Chemotherapy was given to 10 patients (47.6%) in our study. This high percentage is related to providing chemotherapy as adjuvant therapy for advanced stage tumor as well as to all recurrent cases. Due to the rarity of this type of cancer, until now there is no well—established standard chemotherapy protocol. The most frequently used multi agent chemotherapy regimens...
are BEP (bleomycin, etoposide, cisplatin) or BVP with the usage of vinblastine instead of etoposide (27). The first protocol was used in all our patients. Four cases required adjuvant pelvic radiotherapy. One of them after secondary cytoreductive surgery following recurrence. One study showed a prolonged clinical remission after both pelvic and whole abdominal radiotherapy for persistent or recurrent tumor (28). Due to high toxicity and morbidity rates, no case was treated with whole abdominal radiotherapy in our study. Granulosa cell ovarian tumors are characterized by its indolent growth and late recurrence (29).

A Japanese study reported multiple lung recurrence of a 72 years old lady 36 years after initial diagnosis with this tumor and proved by histopathology after surgical excision (30). Our study showed 5 cases of abdominal and pelvic recurrence. The latest recurrence discovered 7 years after initial diagnosis. Until today, the longest reported time of recurrence is 40 years (6). Therefore life—long follow up is recommended for this type of cancer. The effect of patient’s age on tumor recurrence is controversial. One study by Lee et al (7) showed a high recurrence rate in patients below the age of 40 years when comparing the survival of patients to those older than 40 years. However, other studies showed a better prognosis in young patients (29,30). We found no relation of age and the overall prognosis in our study. Nevertheless, the most important factor affecting the prognosis was the stage of tumor at primary surgery. The same was reported by many other studies (13,31,32).

Many retrospective studies reported the importance of several factors on survival which included age, size, intact tumor, mitotic activity, presence of nuclear atypia, and stage of the disease (14,33). One study reported 5 years disease free survival rate for stage I–II tumor between 89%–99% compared to 72%–80% for stage III–IV tumors (34). Zhang et al. reported the 5 and 10 years disease specific survival to be 97% and 94% respectively (23). The longest published study showed a 25–years overall survival rate to range from 40 to 60%. The complete surgical debulking of the disease without leaving a residual tumor is essential for better survival (14). Nine cases in our study showed five years and more disease free survival (42.8%) compared to only five cases who survived less than five years (19%). All of them were at advanced stage at the time of diagnosis and showed recurrences. No report on the 7 cases where 5 years did not pass since they were diagnosed with granulose cell tumor. The longest period until recurrence was seven years after being initially diagnosed with this tumor.

The weakness of our study is that it is a retrospective study and the number of patients treated were small. However due to the rarity of these tumors, it is very difficult to perform a prospective or randomized studies. The strengths of the current study included long follow up duration and patients were treated in a single centre with standard management by a gynecologic oncologist.

**Conclusion**

Granulosa cell tumors are very rare malignant ovarian tumors. The standard treatment is surgery with removal of uterus, both tube and ovaries, though there is a role for fertility preserving surgery without having a poor impact on outcome. Mostly, these types of tumors are diagnosed at an early stage with very good outcomes. Tumor stage at the time of diagnosis remain the most significant factor to predict recurrence and survival. Further studies are needed to study the effect of other factors on outcome.

**References**

Clinicopathological outcome of ovarian granulosa cell tumors, Ehab Al-Rayyan, et al.


