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GRANULOSA CELL TUMOR OVARY: REVIEW OF CASES AT A TERTIARY CARE CENTER

Oncology

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ABSTRACT

INTRODUCTION: Granulosa cell tumors constitute less than 5 % of all ovarian tumors. Unlike epithelial ovarian tumors, they occur in a younger age group, are usually detected in an early stage and often have features of hyperestrogenism. Diagnosed by pelvic examination which is subsequently confirmed by radiologic studies. Whereas surgery provides definitive tissue diagnosis and staging. Total abdominal hysterectomy, bilateral salpingo-oophorectomy and removal of all gross disease is treatment for those who have completed their family. Fertility preserving surgery with unilateral salpingooophorectomy is the treatment preferred for younger women with stage Ia disease. GCT has features of prolonged natural history, relatively favourable prognosis and a tendency to late recurrences.

METHODS: The study is performed period from July 2011 to June 2016 at Kidwai Memorial Institute of Oncology, a tertiary care center at Bangalore, Karnataka, India. The clinical data of patients who were treated in the institute for adult granulosa cell tumors of the ovary were collected retrospectively. Data for age, clinical manifestation, imaging, diagnosis and treatment of the patients were reviewed and analyzed. Post-operative histology was obtained for all patients.

RESULTS: 41 cases were retrieved. The median patient age was 42 years. The most common clinical manifestations at diagnosis were abdominal pain and vaginal bleeding. In 15 (36.6%) tumor size was less than 10 cm whereas in 26(63.4%) tumor size was more than 10 cm. The majority of patients were in stage IA (43.9%), followed by stage IIIB (26.82%). 12.19% patients were in stage IC, whereas 4.8% patients were in stage IV. In the follow-up period, 5 (12.1%) patients relapsed.

CONCLUSIONS: Granulosa cell tumor of the ovary is an uncommon neoplasm. The adult form progresses slowly and often is diagnosed in an early stage of disease. Surgery is indicated. A prolonged post-therapeutic follow-up is necessary because of the risk of late recurrences, exceptionally for the adult form.

KEYWORDS

Granulosa cell tumors, Outcomes, Ovary cancer

INTRODUCTION

Granulosa cells are the somatic cells of the sex cords of the ovary which are closely associated with the developing oocyte. Granulosa cells differentiate from either the coelomic epithelium or mesenchymal precursors (the embryological origin is still disputed). Granulosa cells are responsible for production of sex steroids and folliculogenesis and ovulation.

Granulosa cell tumors (GCT) comprises rare ovarian malignancies, and represents around 2 to 3% of all ovarian cancers. They originate from sex cord tumors and stroma. Unlike epithelial ovarian cancers, they have relatively good prognosis.[1]

Granulosa cell tumor represents two histological types. Adult GCT (AGCT) and Juvenile GCT (JGCT) which have characteristic different presentations, clinical and histopathological features.

AGCTs are commonly seen in postmenopausal or peri menopausal women, age ranges from 50–55 years. Whereas JGCTs are relatively uncommon tumors, representing 5 % of all GCTs. JGCT occurs at an early age in premenarchal girls and young women.[2,3]

The GCT represents age standardized incidence of 0.58 to 1.6/100,000 women per year . GCT is associated with various chromosomal abnormalities including trisomy at 12, monosomy at 22, and deletion of chromosome 6. GCTs are also associated with few predisposing syndromes, like Peutz Jeghers syndrome, Potters syndrome, Maffucci disease and Ollier disease. Other risk factors includes continuous exposure to ovulation induction drugs like clomiphene citrate, selective estrogen receptor modulators (SERM) and gonadotropins.[4]

FOXL2 gene is responsible for normal development of the granulosa cell. Shah et al. detected somatic mutation of FOXL2 in 86 of 89 (97 %) adult GCT and in 1 of 10 (10 %) juvenile GCT. Whereas and 3 of 14 (21 %) thecomas were associated with mutation in FOXL2 gene. [5]

Various signaling pathways associated with GCT include Adenyl cyclase/cAMP/protein kinase A (PKA) pathway, MAPK and phosphatidyl innositol 3-kinase- PI3K/AKT pathway , Vascular endothelial growth factor (VEGF) and its receptors mediated angiogenesis, Estrogen receptors activated tumorigenesis and Nuclear factor kB (NFkB) mediated increased cell proliferation and escape from apoptosis . Any alteration of these pathways results in uncontrolled proliferation and the formation of GCT. [6]

Recurrence of GCT may be variable. Early detection of recurrence can be easily diagnosed by tumor markers.17b- Estradiol (E2), Inhibin, Mullerian Inhibiting Substance (MIS)/ Anti Mullerian Hormone (AMH) and Follicle Regulatory Protein (FRP) are various tumor markers for GCT. [7,8]

Various factors associated with prognostic significance include age, tumor size, rupture of tumor, mitotic activity, nuclear atypia, aneuploidy (in 5–20 % GCT), p53 overexpression, high Ki-67 and stage of the disease.[9]

GCTs are diagnosed from the pathology specimen after surgery, although a preoperative diagnosis can be made based on presence of an adnexal mass associated with features of hyperestrogenism, thickened endometrium and elevated serum inhibin.

Surgical staging constitutes the initial management. The principles of surgery includes tumor debulking. Surgical staging includes exploration of peritoneal cavity, washings for cytology, multiple peritoneal biopsies and omentectomy. Whereas a secondary surgical staging may be required in unstaged cases of GCT.[10]

GCT may recur any time after treatment, however longest period of recurrence is noticed as up to 40 years after diagnosis. [11]

METHODOLOGY-

This is a retrospective study of patient data originally collected from

July 2011 to June 2016 at department of gynecology oncology at Kidwai Memorial Institute of Oncology, A tertiary care center at Bangalore, Karnataka, India. A total of 41 patients were diagnosed with granulosa cell tumors during that time. The recorded information includes, age, parity, menopausal status, symptoms, diameters of tumors, stage of disease, type of surgery, adjuvant treatment, survival in months, recurrence and mortality. Patients were treated as per hospital protocol.

The statistical analyses was done using SPSS 21 software

RESULT

Patient characteristics- Total 41 patients of GCT were included in our study. Age range was from 13 to 70 years with mean age of 42 years. 17 (41%) patients belonged to age less than 40 years where as 24 (59%) patients belonged to age equal to or more than 40 years.(Table 1)

Table 1

NO OF PATIENTS	AGE RANGE(YEAR)	MEAN
41	13 – 17	42
Patients < 40 years of age	17(41%)	
Patients ≥ 40 years of age	24(59%)	

Symptoms at diagnosis- Abdominal pain and distension were main presenting complaints in our study.Which included 63.4% and 58.5% patients respectively. irregular menstruation was seen in 29.2% patients whereas postmenopausal bleeding was found in 24.3% patients.(Table 2)

Table 2

SYMPTOMS	NO OF PATIENTS(PERCENTAGE)
Abdominal distension	24(58.5%)
Abdominal pain	26(63.4%)
Irregular menstruation	12(29.2%)
Postmenopausal bleeding	10(24.3%)

Tumor characteristics- Tumor size and stage were analyzed as parameters for tumor characteristics. In 15 (36.6%)patients, tumor was found to be less than 10 cm while in 26 (63.4%)patients, tumor was found to be more than 10 cm in maximum diameter (Table 3). Majority of tumors were found to be in stage 1A, in 18 patients(43.9%) followed by stage IIIB, in 11 patients (26.82%). 5 (12.19%) patients belonged to stage IC and only 2 (4.8%) patients belonged to stage IV. 5 (12.19%) patients were associated with recurrent disease (Table 4).'

Table 3

Tumor size	Number of patients(Percentage)
<10 cm	15(36.6%)
>10 cm	26(63.4%)

Table 4

Tumor stage	Number of patients(Percentage)
1A	18(43.9%)
Ic	5(12.19%)
IIIb	11(26.82%)
IV	2(4.8%)
Recurrent tumor	5(12.19%)

Treatment modalitity- All patients were managed by surgery with or without chemotherapy. 21 (51.21%) patients underwent Staging laparotomy with LN dissection, 13 (31.70%) patients underwent tumor debulking (TD) surgery whereas 7 (17.7%) patients underwent fertility preserving surgery. (Table 5)

Table 5

Type of surgery	Number of patients(Percentage)
Staging laparotomy with LN dissection	21(51.21%)
Debulking surgery	13(31.70%)
Fertility preserving surgery	7(17.07%)

Histopathology- All samples were send for histopathological examinations after surgery for confirmation and staging of disease. Features of Lymph node positivity, endometrial hyperplasia, and endometrial hyperplasia with atypia were noted. None of the sample showed lymph node positivity. 6 (14.63%)patients showed endometrial hyperplasia without atypia whereas 2 (4.87%) patients showed endometrial hyperplasia with atypia (Table6)

Table 6

Feature	Number of patients(Percentage)
Endometrial hyperplasia	6(14.63%)
Endometrial hyperplasia with atypia	2(4.87%)
LN positivity	0

Chemotherapy- chemotherapy was administered in 23 patients. 10 (24.39%) patients were given BEP regimen whereas 13 (31.70%) patients received Paclitaxel plus Carboplatin regimen (Table 7).

Table 7

Adjuvant Chemotherapy	Number of patients(Percentage)
BEP	10(24.39%)
Paclitaxel + Carboplatin	13(31.70%)

Outcome parameters Outcome parameters recurrence of tumour, survival and death were analyses as Outcome parameters. Total 5 patients showed recurrence, out of which 4 patients were primarily operated outside with inadequate staging and follow up. Maximum age at recurrence was 65 years while minimum age at recurrence was 18 years. First relapse occurred in a 46 year women, after 7 years of primary treatment. She was elsewhere operated primarily, and was inadequately staged. The recurrence was retroperitoneal and was managed by Tumor debulking (TD) plus omentectomy plus adjuvant CT (C+P) . Second relapse was noted in left adnexa, in a 41 year women, after 9 years of primary treatment. She was also operated elsewhere primarily, and was inadequately staged. The recurrence was managed by Lt oophorectomy+Lt pelvic lymph node dissection (PLND)+ Total omentectomy (TO) + Adjuvant CT(BEP regimen).

Third patient who showed relapse was a 32 year women of stage IA disease, operated outside by TAH +Lt oophorectomy. She developed two recurrences, first after 3 years in left adnexa and second, after 6 years in pelvis. First relapse was managed by TD + ICO + small bowel resection anastomosis (RA) + adjuvant CT(BEP). Patient did not complete CT and second relapse was treated be TD + appendectomy+ adjuvant CT(T+P).

Fourth relapse was noted in pelvis, in a 41 year women, after 2 years of primary treatment. She was operated primarily by TAH +BSO+IO . patient belonged to stage IA, and recurrent pelvic mass was seen in vicinity to major vessels. The recurrence was managed by CT alone (T+C regimen).

Fifth relapse was noted in a 18 year old patient, after 3 years of primary treatment. She was operated primarily elsewhere by RSO+PLND . She also belonged to stage IA, and recurrent pelvic mass was noted in right adnexa, liver and diaphragm. The recurrence was managed by TAH+TD+adjCT(T+C). (Table 8)

None of the patient died in our study while one patient lost the follow up during treatment

Table 8. Characteristics of patients with recurrent disease

S.N.	Age	Stage	Primary treatment	Time to relapse(Yr)	Site	treatment
1	46	unstaged	TAH+BSO (operated elsewhere)	7	Retroperitoneal	Tumor debulking + omentectomy + Adj CT(T+P)
2	41	unstaged	TAH+ Lt ovariotomy (operated elsewhere	9	Lt adnexa	Lt oophorectomy+Lt PLND+TO+AdjCT(BEP)
3	32	1A	TAH+Lt oophorectomy (operated elsewhere	1st relapse- 3 years 2nd relapse- 6 years	1st relapse-Lt adnexa 2nd- pelvis	1st relapse-TD+ICO+small bowel RA+ adjCT (BEP, defaulted)

4	65	1A	TAH+BSO+IO	2	Pelvic mass surrounding major vessels	Advised CT(T+C), defaulted
5	18	1A	RSO+PLND(operated elsewhere	3	Rt adnexa, liver and diaphragmatic deposits	TAH+TD+adjCT(T+C)

DISCUSSION

Granulosa cell tumors was first described by Rokitansky in 1855, it is a rare tumour. The tumour is named because of their appearance near the granulosa cells of ovarian follicles. Another characterstic feature of this tumour is bimodal age distribution. One peak occur in pre pubertal age group whereas another peak occur at peri- and postmenopausal women at the age of 50 to 55 years. [12]

The common presenting symptoms include abdominal pain (30 to 50%) and abdominal distension primarily caused by mass effect of the tumour. Features of hormonal disturbances include irregular menstruation, intermenstrual bleeding, postmenopausal bleeding or amenorrhea. Hormonal disturbances are usually as a result of altered estrogen secretion by tumour. Overproduction of estrogen is also responsible for its frequent association with endometrial hyperplasia (4 to 10%) or endometrial adenocarcinoma (5 to 35%) .Pseudopuberty is another presenting symptom associated with the juvenile form of GCT. [13,14]

Radiologic features of GCT includes presence of a solid component with multicystic appearance. Diameter is highly variable, ranging from 1to 30 cm (median diameter of 12 cm). The imaging appearances of the two forms of granulosa cells tumors are similar. The confirmatory diagnosis is done by histological analyses. The Microfollicular variety is the commonest form of adult GCT which is characterized by Call-Exner bodies and cores “coffee bean”. Whereas the juvenile form often show lobulated architecture and signs of luteinization and Call-Exner bodies are rarely seen. [15]

The immunohistochemical markers expressed by GCT are vimentin, CD 99 and alpha inhibin. estradiol, inhibin, and anti-Müllerian hormone are serum tumor markers associated with GCT. Cancer antigen 125 (CA-125) is not correlated to the tumor progression. Kalfa et al. [19] identified a mutation FOXL2 (transcription factor gene) which is seen in the majority of adult form of granulosa cell tumor. [16,17]

Prognosis is defined by various factors, the most important prognostic variable is the stage of the disease. Malmstrom et al. reported the survival rates at 5 years and 10 years as , 94% and 88%, respectively, for stage I, which decreases to 44% for stage II and III. [18]
The study of Wu et al. [22] also reported the survival rates at 5 years and 10 years as 98% and 96%, respectively, for stage I and 70% and 60%, respectively, for stage II. The recurrence rate is also related to the stage.[19]

An age younger than 40 years is associated with a better prognosis, but the opinions differ in various studies. In Ahyan's trial, patients aged below 60 years had better mean time of survival (154.6 versus 89.2 months, $P = 0.015$).[20]

In most of studies, larger tumor size was found to be associated with poor prognosis, particularly tumors that measured more than 10 cm.

Another prognostic factor is residual disease after surgery.In Sehouli's trial showed lower survival for patients with postoperative residual disease.[21]

Other prognostic factors include tumor rupture (Schumer trial) and expressions of P53 mutations.

Ala Fossi et al. noted 10 times higher survival of patients with no mutations of P53 as compared with tumor mutation. Increased level of inhibin is also correlated to the tumor mass and hence relapse. [22]

The mainstay of treatments are complete surgery (hysterectomy, bilateral salpingoopherectomy) with staging for early stage and debulking surgery for advanced stage or recurrent disease. Adjuvant treatment is recommended for the adult form of granulosa cell tumors and for high risk patients. Chemotherapy regimen which is commonly used is BVP (bleomycin, vinblastine, and cisplatin) or a BEP regimen, which substitutes etoposide for vinblastine.

REFERENCES

1. Malmstrom H, Hogberg T, Risberg B, Simonsen E: Granulosa cell tumors of the ovary: prognostic factors and outcome. Gynecol Oncol 1994, 52:50–55.
2. Young RH, Dickersin GR, Scully RE: Juvenile granulosa cell tumor of the ovary. A clinicopathological analysis of 125 cases. Am J Surg Pathol 1984, 8:575–596.
3. Pautier P, Lhommé C, Culine S, Duvillard P, Michel G, Bidart JM, Gerbaulet A, Droz JP: Adult granulosa-cell tumor of the ovary: a rétrospective study of 45 cases. Int J Gynecol Cancer 1997, 7:58–65.
4. Mehta H, Trivedi P, Parikh B, Shukla K (2005) Clinicopathological prognostic factors of adult granulosa cell tumors of the ovary—a study of 37 cases. Indian J Pathol Microbiol 48:439–443
5. Shah SP et al. Mutation of FOXL2 in granulosa-cell tumors of the ovary. N Engl J Med 360: 2719–2729
6. Jamieson S, Fuller PJ (2012) Molecular pathogenesis of granulosa cell tumors of the ovary. Endocr Rev 33:109–144
7. Petraglia F, Luisi S, Pautier P, Sabourin JC, Rey R, Lhomme C, Bidart JM (1998) Inhibin B is the major form of inhibin/activing family secreted by granulosa cell tumors. J Clin Endocrinol Metab 83:1029–1032
8. Geerts I, Vergote I, Neven P, Billen J (2009) The role of inhibins B and antimullerian hormone for diagnosis and follow-up of granulosa cell tumors. Int J Gynecol Cancer 19:847–855
9. Ayhan A, Salman MC, Velipasaoglu M, Sakinci M, Yuce K (2009) Prognostic factors in adult granulosa cell tumors of the ovary: a retrospective analysis of 80 cases. J Gynecol Oncol 20:158–163
10. Thrall MM, Paley P, Pizer E, Garcia R, Goff BA (2011) Patterns of spread and recurrence of sex cord—stromal tumors of the ovary. Gynecol Oncol 122:242–245
11. East N, Alobaid A, Goffin F, Ouallouche K, Gauthier P: Granulosa cell tumour: a recurrence 40 years after initial diagnosis. J Obstet Gynaecol Can 2005, 27:363–364.
12. Stenwig JT, Hazekamp JT, Beecham JB: Granulosa cell tumors of the ovary: clinicopathological study of 118 cases with long-term follow-up. Gynecol Oncol 1979, 7:136–152.
13. Bompas E, Freyer G, Vitrey D, Trillet-Lenoir V: Granulosa cell tumour: review of the literature. Bull Cancer 2000, 87:709–714.
14. Calaminus G, Wessalowski R, Harms GD, Öbel U: Juvenile granulosa cell tumors of the ovary in children and adolescents: results from 33 patients registered in a prospective cooperative study. Gynecol Oncol 1997, 65:447–452.
15. Stuart GC, Dawson LM: Update on granulosa cell tumours of the ovary. Curr Opin Obstet Gynecol 2003, 15:33–37.
16. Zhang M, Cheung MK, Shin JY, Kapp DS, Husain A, Teng NN, Berek JS, Osann K, Chan JK: Prognostic factors responsible for survival in sex cord stromal tumors of the ovary: an analysis of 376 women. Gynecol Oncol 2007, 104:396–400.
17. Kalfa N, Veitia RA, Benayoun BA, Boizet-Bonhoure B, Sultan C: The new molecular biology of granulosa cell tumors of the ovary. Genome Med 2009, 1:81.
18. Malmstrom H, Hogberg T, Risberg B, Simonsen E: Granulosa cell tumors of the ovary: prognostic factors and outcome. Gynecol Oncol 1994, 52:50–55.
19. Wu L, Zhang W, Li L: Prognostic factors in granulosa cell tumor of the ovary. Zhonghua Fu Chan Ke Za Zhi 2000, 35:673–676.
20. Ayhan A, Salman MC, Velipasaoglu M, Sakinci M, Yuce K: Prognostic factors in adult granulosa cell tumors of the ovary: a retrospective analysis of 80 cases. J Gynecol Oncol 2009, 20:158–163.
21. Miller BE, Barron BA, Wan JY, Delmore JE, Silva EG, Gershenson DM: Prognostic factors in adult granulosa cell tumor of the ovary. Cancer 1997, 79:1951–1955.
22. Lappöhn RE, Burger HG, Bouma J, Bangah M, Krans M, de Bruijn HW: Inhibin as a marker for granulosa-cell tumors. N Engl J Med 1989, 321:790–793.