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Granulosa Cell Tumors of Ovary – A Systematic Review

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Abstract **Review Article**

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. They follow an indolent course and are characterized by a long natural history. Stage of the disease is the only factor which affects survival of these patients. Fertility preserving surgery is an acceptable option in young women with stage I A disease. For whom fertility is not an issue, total abdominal hysterectomy, bilateral salpingo-oophorectomy and removal of all gross disease is recommended. Nodal dissection is not recommended in surgical staging of GCT. Patients with early stage disease (stage I and II) have a very good prognosis with 5 year DFS and OS of 89% and 99% respectively and usually don't require any postoperative treatment. Advanced stage disease (stage III and IV), the 5 year DFS and OS disease was 72% and 80 % respectively hence the option of postoperative treatment with BEP chemotherapy or taxane platinum based chemotherapy should be considered. Due to high chance of recurrence even years after apparent clinical cure of the primary tumor, lifelong follow up with clinical examination and tumor markers like inhibin B is recommended.

Keywords: Granulosa cell tumor, Ovarian malignanc.

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). The major functions of granulosa cells include the production of sex steroids and various peptides required for folliculogenesis and ovulation. Granulosa cell tumors (GCT) are derived from the granulosa cells. They constitute less than 5 % of the ovarian tumors and more than 70 % of the sex cord-stromal tumors. There are two distinct histological types—adult GCT (AGCT) and juvenile GCT (JGCT) which display different clinical and histopathological features. AGCTs are more common and are usually seen in perimenopausal and postmenopausal women, with a peak incidence at 50–55 years. JGCTs are rare tumors, representing 5 % of all GCTs and occurring in premenarchal girls and young women. What makes them different from the epithelial ovarian cancers is the nature of presentation and clinical behaviour. They occur in a younger age group, are usually detected in an early stage and often have features of hyperestrogenism. They are more readily cured by surgery alone. Generally they have a better prognosis than epithelial ovarian tumors and follow an indolent course [1]. The growth rate of JGCT is considered more slowly because it is borderline malignant tumor [2]. There has been a lot of interest in the molecular pathogenesis of these tumors and due to their origin from the granulosa cells, they are potential targets for hormonal and targeted therapy.

Etiology and Risk Factors

Chromosomal abnormalities have also been recently evaluated in granulosa cell tumors. Detected abnormalities include trisomy 12, monosomy 22, and deletion of chromosome 6. Among juvenile granulosa cell tumors, cytogenetic studies have identified trisomy 12 and a deletion in chromosome 6q [3]. BRCA1 and BRCA 2 mutations are not associated with an increased risk of GCT [4]. Few tumor predisposition syndromes associated with GCT are Peutz Jeghers syndrome and Potters syndrome. Ollier disease and Maffucci disease are associated with juvenile GCT. Continuous exposure to ovulation induction drugs like selective estrogen receptor modulators (SERM), clomiphene citrate, gonadotropins may increase the risk of GCT [1].

Imaging features

They are slow-growing, predominantly solid masses with variable amounts of cystic change and intratumoral hemorrhage. Bilaterality is rare. Oestrogenic effects on the uterus may manifest as uterine enlargement or as endometrial thickening or hemorrhage. In ultrasound, the appearance varies widely. It may appear anywhere from a solid mass to a multiloculated solid and cystic mass, to a purely cystic lesion, with varying degrees of hemorrhage or fibrosis and they are less likely to have intracystic papillary projections than epithelial ovarian tumors (Figure 1). The CT appearance of a granulosa cell tumor is usually that of a large, well-defined low-attenuation ovarian mass. (Figure 2)

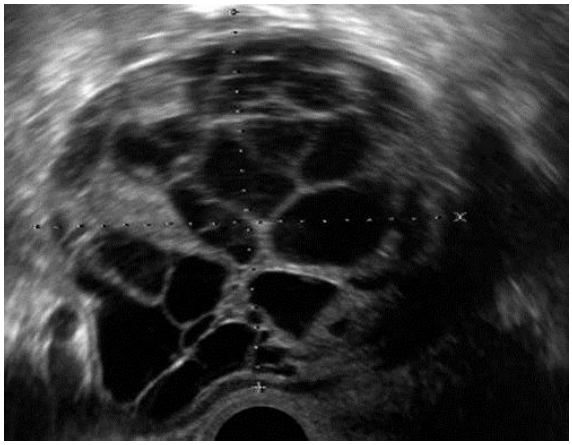

Fig-1: ultrasound image of GCT of ovary showing an multiloculated solid and cystic mass

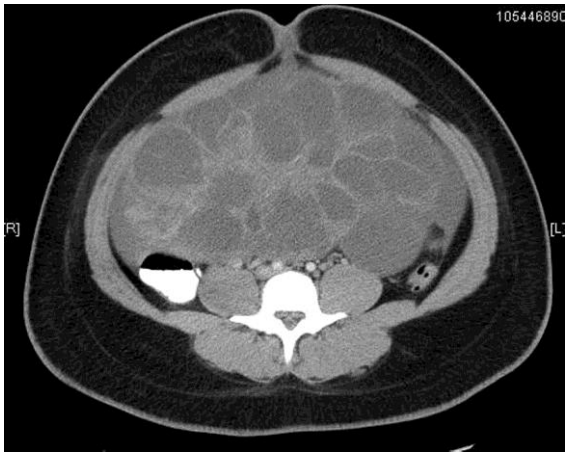

Fig-2: Contrast-enhanced coronal CT image demonstrating a large, multi-lobulated, low attenuation abdomino-pelvic mass.

The Molecular Genetics of GCT

FOXL2 gene encodes the transcription factor required for the normal development of the granulosa cell. Shah et al. detected a somatic missense mutation in FOXL2 (c.402C- > G; p.C134W) in GCT. This mutation was seen in 86 of 89 (97 %) adult GCT, 1 of 10 (10 %) juvenile GCT and 3 of 14 (21 %) thecomas. The high frequency of mutation suggests this mutation may be pathognomic for AGCT, and the absence of this mutation in JGCT shows that JGCT may be an entirely different tumor [6]. Granulosa cell proliferation is dependent on different signaling pathways and any alteration of these pathways leads to uncontrolled proliferation of these cells and the formation of GCT. Understanding the role of these pathways involved in the pathogenesis of GCT helps in the use of novel drugs to treat GCT especially in the recurrent scenario [7]. These pathways include 1. Adenyl cyclase/cAMP/protein kinase A (PKA) pathway [7], 2. MAPK and phosphatidyl innositol 3. Kinase-PI3K/AKT pathway, Vascular endothelial growth factor (VEGF) and its receptors [9–11], Estrogen receptors [12], Nuclear factor kB (NFkB) [13] and TNF-related apoptosis-inducing ligand (TRAIL; CD253) via its receptors TRAIL-R1/DR4 and TRAIL-R2/DR5 induce cell death.

Tumor Markers

Tumor markers are useful in early detection of recurrence. In GCT secreted hormones are used as tumor markers.

a) 17b- Estradiol (E2)

Due to unregulated aromatase action, high estrogen level is seen in GCT. But the role of E2 as a tumor marker is limited as no correlation was noted between E2 levels and disease progression or recurrence in most cases. This may be due to lack of theca cells seen in 30 % cases of GCT [11]. Thus E2 can be helpful in postoperative management of certain cases but is not sensitive enough to be used as a reliable tumor marker. In androgen secreting GCT, testosterone or its precursors can be used as tumor markers.

b) Inhibin

Inhibins are mainly formed in granulosa cells and are made of two subunits, an a subunit covalently bound to either bA or bB subunit forming inhibin A and inhibin B respectively. In the postmenopausal women, with depletion of ovarian follicles, inhibin levels become undetectable. But in GCT, inhibin levels are elevated, thus inhibin can be used as a marker for GCT in premenopausal and postmenopausal women. Newer studies using subunit specific ELISA showed inhibin B to be the major form secreted in GCT, and that inhibin B was more accurate than inhibin A in detecting GCT. Epithelial ovarian tumors especially the mucinous variety may also secrete inhibin (82 % cases); showing inhibin is not specific for GCT. Inhibin levels fall to normal range around 1 week after tumor removal, suggesting inhibin could be secreted either by the tumor tissue or surrounding normal ovarian tissue.

c) Mullerian Inhibiting Substance (MIS)/ Anti Mullerian Hormone (AMH)

MIS are formed in granulosa cells during reproductive life. MIS are cyclically elevated during the menstural cycle but are never more than 5 mcg/L. MIS becomes undetectable in postmenopausal women. An

elevated level of MIS is highly specific for GCT. MIS parallel changes in inhibin levels in GCT and predate clinical recurrence as early as 11 months. Several studies show MIS to be a reliable tumor marker with sensitivity between 76 % and 100 %.

d) Follicle Regulatory Protein (FRP)

FRP is secreted by granulosa cells and is detected in normally menstruating women. Regulation of secretion occurs with granulosa cell differentiation. Elevated levels of FRP have been noted in few cases of GCT but its clinical significance is yet to be confirmed.

Pathology

GCT usually appears as a large unilateral mass having a tan yellow color due to steroid production. It often has solid and cystic areas (Figure 3) (Pic courtesy Kristin R. Rusterholz, M.D). They are usually >10 cm in size (73.5 %) but can vary from a small nonpalpable lesion to large masses (3–24 cm) [1]. Granulosa cells are small round to oval pale cells with characteristic coffee- bean nuclei (longitudinal nuclear grooves) (figure 4 A). Well differentiated GCT have a microfollicular, macrofollicular, trabecular, insular, solid-tubular and hollow tubular patterns. Microfollicular patterns are the most common pattern seen and have the characteristic Call-Exner bodies which are small rings of granulosa cells surrounding shrunken nuclei or eosinoplilic fluid material. Call Exner bodies are seen in 30 % of cases [5] (Figure 4 B). The poorly differentiated forms (39 %) [4] appears as undulating parallel (watered-silk) or zigzag (gyriform) rows of granulosa cells in a single file and diffuse (sarcomatoid) pattern characterized by a monotonous appearance. In difficult cases immunohistochemistry can help clinch the diagnosis. GCT is alpha inhibin and calretinin positive. Advanced stage disease has weaker expression of inhibin, demonstrating a lesser degree of normal cellular function. These tumours on IHC are nonspecifically positive for CD99, CAM 5.2, AE1/AE3, CD10, S100, WT-1, smooth muscle actin and desmin. They are negative for CK7 and EMA.

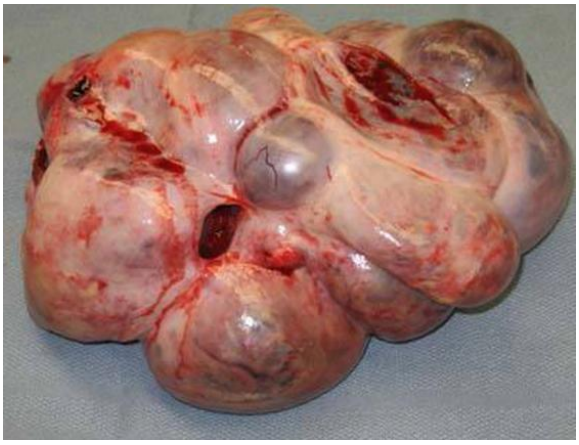

Fig-3: Solid cystic appearance of GCT in gross specimen

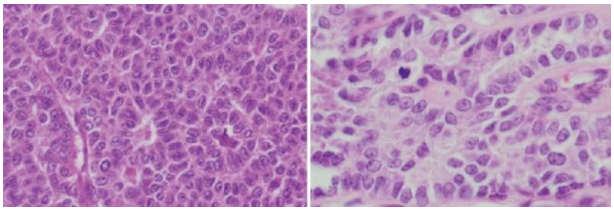

Fig-4: (a) Tumor cells with longitudinal grooves giving a coffee-bean appearance. (b) Characteristic Call-Exner bodies and the presence of mitosis in the background

Clinical Presentation and Diagnosis

Similar to epithelial ovarian cancers the presenting symptoms are usually nonspecific with abdominal pain (41.1 %) or distension (26.4 %) [1]. These patients present with a large palpable ovarian mass. In JGCT abdominal pain was seen in 28.3 % and abdominal mass in 45.5 % [5]. Symptoms related to hyperestrogenesim occur in all age groups. In prepubertal age group, precocious puberty with breast development increased pubic hair, vaginal bleeding (27.3 %) [5] and increased growth will be seen. In the reproductive age group, altered menstural patterns (32.8 %) [1] like menorrhagia, intermenstural bleeding or amenorrhoea may manifest. Postmenopausal bleeding is the most common finding in the postmenopausal age group. Around 25–50 % cases are associated with endometria hyperplasia and endometrial cancer is seen in 5–13 % cases. Endometrial cancers, usually detected in the pathological specimens, are well differentiated early stage disease and have a good prognosis. Breast enlargement and tenderness occurs secondary to estrogen action. Secondary to high inhibin levels patients can present with infertility. Androgen secreting GCT, which may have a sertoli- leydig cell component, can cause virilizing symptoms and hirsuitism. In advanced stages, the pelvis, intraabdominal organs and peritoneum are involved. It's unusual for patients to present with pulmonary and skeletal metastasis [1].

Prognostic Factors

Various factors shown to have 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. Only stage of the disease has been consistently shown in various studies to affect survival of patients with GCT. In a recent study by Park et al. the 5 year DFS and OS rates in early stage (stage I and II) disease was 89 % and 99 % respectively while in advanced stage (stage III and IV) disease it was 72 % and 80 % respectively.

Complete surgical debulking of the disease is essential in GCT as the presence of postoperative residual lesions was shown to reduce survival from 82 % to 22. There are a number of conflicting reports on the efficacy of other prognostic factors. Few studies have shown that tumors more than 10 cm–15 cm have a higher chance of recurrence and poorer survival.

A study evaluating the significance of tumor rupture showed a decrease in 25 year survival from 86 % in patients with stage I a disease to 60 % in patients with stage I c. In a study of patients whose tumors had a mitotic index <4 /10 HPF the DFS at 80 months was 90 % compared to 25 % for patients with a higher mitotic index. In a study comparing the 25 year survival rate in patients with mild nuclear atypia to those with marked atypia a fall in survival from 80 % to 60 % was noted. Tumors with a follicular pattern supposedly had a better survival rate compared to tumors with a diffuse or insular histological pattern.

Grade I and II tumors had better survival compared to grade III tumors. The disease specific survival at 5 and 10 years for grade I and II tumors was 96 % and 86 % respectively while the disease specific survival at 5 and 10 years for grade III tumors was 64 % and 59 % respectively [4]. Nuclear atypia has been reported to be one of the most significant prognostic factors in stage I disease. Staining of granulosa cell tumors for Ki-67 showed that a high Ki-67 index was correlated with an adverse prognosis in some studies 60-62 but not in others [4].

Treatment and Disease Management

Surgical Management

Surgical staging remains the initial management of a suspected case of GCT. The principles of surgery are similar to epithlial ovarian tumor with a vertical midline incision. Surgical staging includes exploration of peritoneal cavity, washings for cytology, multiple peritoneal biopsies and omentectomy. The role of lymph node dissection have shown that nodal dissection is not a significant factor for survival and is not recommended in surgical staging of GCT. Enlarged or suspicious nodes should be removed to allow evaluation and maximal cytoreduction [10]. Fertility preserving surgery with unilateral salpingooophorectomy is feasible in young patients with stage Ia GCT. The results of various studies have shown that, there is not much difference with a conservative approach when compared to the radical surgery 97 % vs. 98 % respectively. The 5 and 10 year disease specific survival was 97 % and 94 % [4]. As the incidence of bilateral disease is low (2 %) [1] a wedge biopsy of the opposite ovary is controversial and must be done with caution. After child bearing is complete, completion surgery with removal of the other ovary and hysterectomy is a reasonable but controversial option. Indications for preoperative endometrial biopsy include (1) All women with abnormal uterine bleeding, (2) All postmenopausal women with adnexal mass and thickened endometrium (>5 mm), (3) Suspected granulosa cell tumour and planning for fertility sparing surgery.

Chemotherapy

Postoperative treatment with platinum based chemotherapy may be the treatment of choice due to ease of administration, wider accessibility and better tolerance. Patients with early stage disease (stage I and II) have a very good prognosis with 5 year DFS and OS of 89 % and 99 % respectively and these groups of patients usually don't require any postoperative treatment. Few studies have shown that patients with stage Ic disease associated with poor prognostic factors like large tumor size or high mitotic index have a higher chance of relapse and may benefit with postoperative treatment. But due to the rarity of GCT, these data have been collected from retrospective studies and case reports and it's impossible to conduct a randomized controlled trial to assess the efficacy of postoperative treatment in high risk patients. Thus we still don't have the evidence showing postoperative treatment in the adjuvant setting can confer a survival benefit in high risk patients. In advanced stage disease (stage III and IV) the 5 year DFS and OS disease was 72 % and 80 % respectively hence the option of postoperative treatment should be considered in this group. Park et al.recommends optimal debulking followed by 6 cycles of BEP chemotherapy for advanced stage GCT. In this series none of the patients with advanced stage GCT who received at least 6 cycles of BEP had tumor recurrence. For patients with gross residual disease and stage IV disease chemotherapy is the mode of treatment. For recurrent disease the RR (71 % vs 37 %) and median PFS (11 vs 7 months) for BEP vs taxane respectively were not statistically significant, although BEP may be a better tool in the recurrent setting [1].

Radiotherapy

The efficacy of radiation in GCT is not well defined. There are no prospective trials showing the benefit with radiation. Few studies have shown improved DFS in advanced and recurrent GCT, but this has not been validated in other studies. Hauspy treated 31 of 103 patients with adjuvant radiation. Eight patients received only pelvic radiation (41 Gy in 21 fractions) and 23 patients received whole abdominal radiation (23 Gy in 22 fractions) with a pelvic boost (45 Gy in 29 fractions). The median DFS was 251 months for patients given adjuvant radiation vs 112 months for patients who did not receive adjuvant radiation (HR, 0.4;95 % CI, 0.2–0.8, p00.02). Only 32 % cases recurred after radiation compared to 40 % who did not undergo radiation. Pelvic recurrence in radiated fields was only 10 % significantly lower than that in non radation cases (32 %, p00.03). In the upper abdomen the failure rate was similar in both groups (26 %). The DFS was prolonged by >10 years with radiation but the likelihood of recurrence was not altered. However they caution that as there was no survival advantage for adjuvant radiation and treatment at the time of recurrence may also be effective, radiation need only be offered when the tumor can't be fully resected so as to avoid leaving behind microscopic residual disease.

Recurrent GCT

GCT have a tendency for late recurrence. Once the tumor recurs it's fatal in 80 % cases. In the study by

Park et al, none of the patients with early stage disease who underwent optimal debulking had tumor recurrence and of the patients with advanced stage GCT who received at least 6 cycles of BEP adjuvant chemotherapy none had tumor recurrence. The longest reported time to recurrence is 40 years [58]. About 21 % develop recurrence and the median time to relapse was 57.6 months (2–166 months) as reported by Sun et al. Local pelvic recurrence is reported in 70 % cases, 9 % in pelvis and abdomen, 6 % retroperitoneum, 6 % pelvis and retroperitoneum and 3 % pelvis, abdomen and retroperitoneum (Abu-Rustum et al.). Most recurrences are intraperitoneal suggesting the possibility of missed peritoneal disease during primary surgery especially for early stage disease. Multivisceral involvement with metastasis to liver, appendix and intestines are quite common. A combined modality of treatment, usually involving debulking of the disease followed by radiation or chemotherapy is the norm and may prolong the DFS. A complete debulking of the disease is feasible even in the recurrent setting especially with pelvic and intra-abdominal recurrence.

In optimally debulked cases postoperative radiation (pelvic or whole abdominal) is a viable option. Radiotherapy has been used in a case with recurrent GCT in the mediastinum and showed CR 2 years after treatment. But with radiotherapy there exists a risk of abdominal recurrence in areas outside the radiotherapy portal, hence chemotherapy (platinum based) is usually given after surgery more so in cases with widespread disease or after suboptimal cytoreduction. Taxols have also been tried in recurrent GCT but platinum based chemo is likely to be the first choice in the recurrent scenario. Hormonal therapies are usually tried in advanced stage or recurrent GCT. Recurrent chemoresistant, progressive nonresponding GCT or patients with high surgical risk are ideal candidates for hormone therapy. Hormonal manipulation of GCT arise from the surmise that suppression of endogenous estrogen will provide an antiproliferative milieu which could be effective in treating GCT. The vascular nature of GCT makes it succeptible to inhibition of angiogenesis [9]. VEGF expression and microvessel density are associated with poor outcome. Tao et al. evaluated eight patients treated with bevacizumab, a VEGF inhibitor. The overall response rate was 38 % and clinical benefit rate was 63 %. Jakob et al. reported significant response in a 87 year patient with recurrent GCT, showing overexpression of mast/stem cell growth factor (KIT; CD117), with TKI imatinib [8]. Thus in selected cases of recurrent GCT, imatinib may be useful in controlling the disease. Active NFkB molecules formed after proteasomal degradation cause increased cell proliferation and escape from apoptosis. Bortezomib a proteasome inhibitor may be effective to inhibit cell proliferation and viability while stimulating apoptosis. It's unlikely that any one agent alone may be effective, so a combination of drugs targeting multiple pathways leading to better efficacy, less toxicity and use of lower doses may eventually emerge victorious in the long battle against this indolent tumor.

CONCLUSION

Though granulosa cell tumour is a tumour with low malignant potential, due to high chance of recurrence even years after apparent clinical cure of the primary tumor, lifelong follow up with clinical examination and tumor markers like inhibin B is recommended. Other than stage of the disease, the other prognostic factors like age, tumor size, rupture of tumor, mitotic activity are not able to predict recurrences accurately. Thus the identification of prognostic and predictive factors for tumor recurrence is of paramount importance. Although it has been determined that FOXL2 (402C->G) mutation is characteristic of AGCT, the implications of this finding is yet to be elucidated. Further research in the molecular pathogenesis of GCT can shed light on various prognostic factors and therapeutic agents which can be effective in the adjuvant and palliative setting.

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