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Case Report

Case series of rare ovarian malignancy: granulosa cell tumor

Kavitha Yogini Duraisamy*, Devi Balasubramaniam, Palanivelu Chinnusamy, Rashmi Barnwal

Department of Endogynecology, Gem Hospital and Research centre, Coimbatore, Tamilnadu, India

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***Correspondence:**
Dr. Kavitha Yogini Duraisamy,
E-mail: yoginianandvij@rediffmail.com

ABSTRACT

Granulosa cell tumors are rare ovarian sex cord stromal tumors characterized by indolent course and favorable prognosis. The treatment of granulosa cell tumor is individualized based on many factors like age, desire for future fertility and stage of the disease. Here, we report three cases out of which two were acute presentation and one was diagnosed incidentally when she got evaluated for menstrual irregularity. Fertility sparing surgery with proper staging is offered to young patients presenting in early stage. In patients who have completed family, comprehensive surgical staging including hysterectomy with bilateral salpingo oophorectomy is the standard treatment. Lymph node metastasis in granulosa cell tumor is very rare, hence pelvic and para aortic lymphadenectomy can be safely avoided if preoperative findings and frozen section favour granulosa cell tumor.

Keywords: GCT, Fertility sparing surgery, Frozen section

INTRODUCTION

Granulosa cell tumor (GCT) is a rare type of ovarian malignancy, accounting for 5% of all cases.[1] It is a type of sex cord stromal tumor, characterized by a prolonged natural history and a tendency to late recurrence.[2,3] Most of the cases occur in post-menopausal women but one third cases occur in reproductive age group and premenopausal women.[4] A juvenile form occurs in children and young women and has distinct clinical and pathologic features (hyperestrogenism and precocious puberty).[4]

Although the prognosis is generally favourable, recurrent or advanced GCT shows poor prognosis.[5-7] Evidence-based management of granulosa cell tumour of the ovary is limited, and treatment is based on age, fertility status and stage of the disease. Fertility-sparing surgery with proper staging is recommended for young women whereas comprehensive surgical staging including hysterectomy with bilateral salpingo oophorectomy, infracolic omentectomy is the standard treatment for woman who has completed childbearing. Adjuvant treatments following surgery have been based on non-randomised trials.[8] A combination of bleomycin, etoposide and cisplatin (BEP) has traditionally been used for treatment of advanced and/or recurrent disease that cannot be optimally managed surgically.[9]

CASE REPORT

Case 1

A 45 year old female patient, P2L2, 2 LSCS, sterilized, presented to gynecology outpatient clinic with lower abdominal pain, nausea and giddiness since 1 day. She also gave history of irregular delayed menses since 2 years and excessive hair growth since 6 months. Her menstrual cycles were of 3 days every 6-8 months, with moderate flow. On examination, she had tachycardia (P.R.-110/min) and her blood pressure was recorded as 110/70 mm Hg, on per abdominal examination, suprapubic tenderness was present. Vaginal examination revealed left forniceal tenderness with left adnexal fullness. Urgent USG was sought this showed a 4.8x4.2 cm hypoechoic mass in left ovary. All blood

investigations including CA 125 and hormonal profile were normal. With clinical suspicion of ovarian torsion she was taken up for diagnostic laparoscopy. Intraoperatively, twisted left adnexa about 5x5 cm with gangrenous changes was seen along with 20 ml of peritoneal fluid. Opposite side adnexa looked normal. Lap left salpingo oophorectomy along with right salpingectomy and right ovariopexy with endometrial biopsy was performed. Postoperative period was uneventful. Histopathological examination showed left ovarian mass with cystic solid component with features suggestive of granulosa cell tumor with no evidence of tumor infiltration on ovarian surface or bilateral tubes, scanty endometrial tissue showed no evidence of dysplasia, negative peritoneal fluid cytology. On Immunohistocytochemistry, the ovarian mass was positive for inhibin, calretinin (granulosa cell marker) and negative for CK-7 (adenocarcinoma marker) and hence the diagnosis of Adult granulosa cell tumor was confirmed. Patient was then taken up for staging laparoscopy including total lap hysterectomy with bilateral salpingo oophorectomy, omentectomy. Histopathology showed no residual malignancy. The patient was suggested 3 monthly surveillance for 2 years, 6 monthly for next 3 years and annually thereafter. She is on regular follow up with us till now and is doing well.

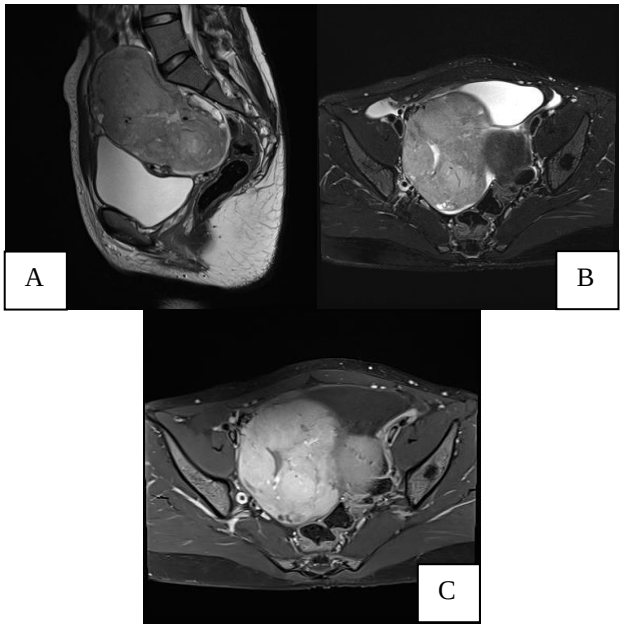

Figure 1 (A-C): MRI showing large well defined lobulated mass, hypointense on T1 and hyperintense on T2 with homogeneous enhancement on contrast study with few areas of hemorrhage extending into lower abdomen.

Case 2

A 25 year old female patient, nulliparous, presented to outpatient clinic with complaints of irregular delayed menses since 6 months and upper abdominal pain since one week. Her menstrual cycles were of 4/50-60 days since past 6 months, last menstrual period was 4 days back. On examination, her vitals were stable, P/A- 16 to 18 weeks firm to hard mass, P/V- uterus was felt separate from the mass, firm to hard mobile mass was felt. Ultrasound was inconclusive and revealed a large hypoechoic mass 10.7x6.7x9.1 cm arising from right adnexa with two anechoic cystic structures? Gestational sac with right ectopic pregnancy? Primary ovarian mass? Broad ligament fibroid. Hence, MRI was performed which showed a 11.5x8.6x6.5 cm solid mass arising from right ovary with areas of hemorrhage and necrosis, compressing the right distal ureter and right external iliac vein suggesting malignant germ cell tumor. Tumor markers (CA 125, CA 19.9, CEA, b hCG and AFP) were normal but Inhibin A (141) and Inhibin B (1261) were elevated. During preop workup the patient was also found to have congenital heart block, seizure disorder. Pacemaker was implanted and she was started on antiseizure medication. After thorough evaluation staging laparoscopy was performed. Intraoperatively- a 15x15 cm solid mass with smooth surface and intact capsule with yellowish tinged surface was seen arising from and replacing the right ovary. Uterus and left adnexa appeared normal.

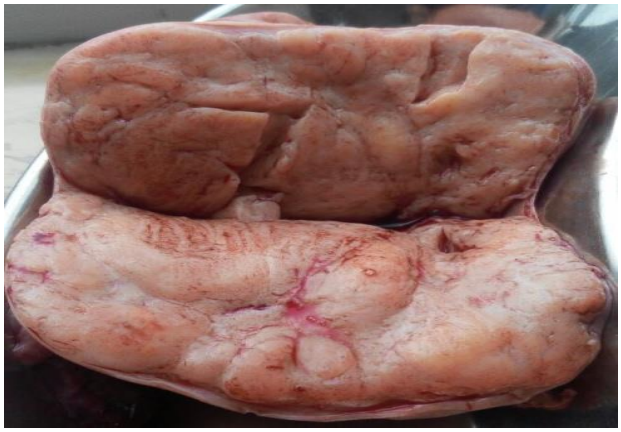

Figure 2: Gross appearance on cut section showing ovarian mass with solid and cystic spaces and yellowish tinge.

All other internal organs appeared normal. Right salpingo oophorectomy, infracolic omentectomy with peritoneal biopsy and fluid cytology with endometrial biopsy was done. Specimen was retrieved through midline small infraumbilical incision, in endobag without any spillage and was sent for Frozen section which suggested granulosa cell tumor. Hence, pelvic and para aortic lymphadenectomy was omitted in view of very rare possibilities of nodal metastasis in granulosa cell tumor of ovary and also considering the cardiac status of the patient. Postoperative period was uneventful except for mild thrombocytopenia which was drug induced and got corrected in 2 days. Histopathogical examination showed a right ovarian mass with features suggestive of granulosa cell tumor, with no tumor infiltration on ovarian surface, right fallopian tube, peritoneal biopsy and omentum.

Peritoneal fluid cytology was negative and endometrial biopsy showed secretory endometrium with no evidence of dysplasia. Immunohistochemistry was done which came positive for Alpha inhibin and Calretinin (granulosa cell marker) and negative for CK (epithelial marker) and hence diagnosis of Adult type granulosa cell tumor was confirmed. Patient was advised regular follow up.

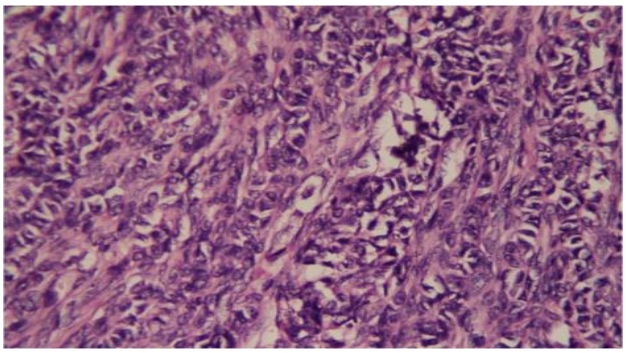

Figure 3: High power microscopy- Cells arranged in trabeculae with nuclear groove.

Case 3

A 51 year old postmenopausal female, P3L3, 3 FTND, sterilized, presented to casualty with complaints of severe abdominal pain and vomiting since one day. On examination, patient was anemic, her pulse rate 100 per minute, BP-110/70, On Per abdomen- severe tenderness in hypogastrium was present. On per vaginum-a vague tender mass was felt through anterior fornix. Urgent USG was done which revealed a 10.7x6.8x6.6 cm heterogenous lesion in pelvis with free fluid in pelvis? Ovarian mass with rupture. Her tumor markers (CA 125, CEA, beta hCG, CA 19.9, AFP) were normal. With clinical suspicion of ruptured ovarian cyst, emergency laparoscopy was done.

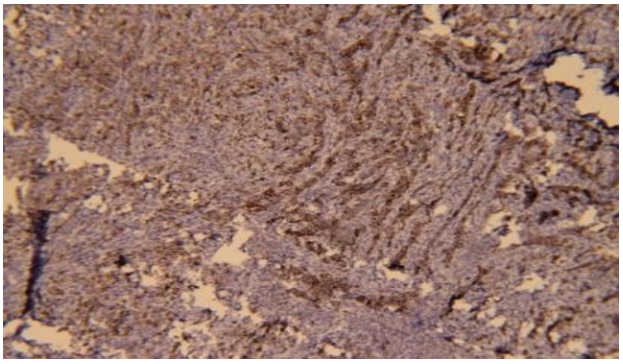

Figure 4: Immunohistochemistry showing Alpha inhibin positivity.

Intraoperatively, 500ml hemoperitoneum with twisted and ruptured left ovarian mass, 10x8 cm, with organized clot was seen. The opposite ovary appeared bulky. Laparoscopic bilateral salpingo oophorectomy along with endometrial biopsy was performed. On histopathology, differential diagnoses of granulosa cell tumor or endometroid stromal sarcoma were given and immunohistochemistry was suggested. On Immunohistochemistry, the tumor was positive for Alpha Inhibin and Calcitrenin and negative for Pan Cytokeratin, CD 10 and dermin. Hence the diagnosis of Adult granulosa cell tumor was confirmed and the patient was planned for complete staging and surgery. Total laproscopic hysterectomy with infracolic omentectomy was done. Histopathology did not show any evidence of residual malignancy. Patient was advised regular follow up.

DISCUSSION

Ovarian granulosa cell tumor is a rare neoplasm constituting less than 5% of all ovarian malignancies with an incidence of 0.5-1.5 per 1, 00,000 women per year). Granulosa cell tumors are usually unilateral, bilateral occurrence is less than 5 %.[10] Endometrial hyperplasia is a common finding in granulosa cell tumor, occurring in 25-50%, due to excess of estrogen produced by these tumors.[11,12] Endometrial adenocarcinoma can be found simultaneously in 5-10% of patients with these tumor and are often well-differentiated and in an early stage with a favorable prognosis.[13]

Since 70% of these tumors are hormonally active, hormonal influences can cause different presenting symptoms depending on patient's age and menstrual status like menorrhagia, menometrorrhagia, amenorrhea ,postmenopausal bleeding but usually the symptoms are nonspecific with abdominal pain or distension.[4] In two of our cases, the presentation was acute abdominal pain due to complication of the ovarian tumor namely torsion and rupture of the mass while one patient presented with menstrual irregularity. However, none of the patients in our series had endometrial abnormality. According to the review of literature, the gross appearance of GCT varies; Majority of the tumors present as enlarged solid and cystic ovarian masses and sometimes may resemble mucinous cystadenoma.[4] The differential diagnoses include undifferentiated carcinoma ovary, endometroid stromal sarcoma, adenocarcinoma, cellular fibroma, cellular thecoma and carcinoid.[14]

On microscopy, Call-Exner bodies, nuclear grooves and coffee bean nuclei are pathognomonic diagnostic features of GCT.[15] Many histological patterns are described, which include microfollicular, trabecular, solid, tubular, diffuse and water- silk patterns.[14,15] On Immunohistochemistry, GCT shows positivity for Inhibin and Calretinin; negativity for epithelial markers such as Cytokeratin (CK) and Epithelial membrane antigen(EMA).[16,17] Immunohistochemistry was done in all three patients to confirm the diagnosis following histopathological examination. In one of our patients, histopathology suggested two differential diagnoses namely endometrioid stromal sarcoma & granulosa cell tumor and Immunohistochemistry aided in confirming the

diagnosis of GCT. Current recommendation for management of GCT is comprehensive surgical staging including hysterectomy with bilateral salpingo oophorectomy, peritoneal cytology, omentectomy, endometrial biopsy, peritoneal biopsy and biopsy of any suspicious lesion.[4] Conservative treatment with fertility sparing surgery, defined as the preservation of the uterus and one ovary, can be offered to young patients desiring to preserve fertility, but only if disease is confined to one ovary and endometrial biopsy is negative.[13]

The pelvic and para aortic lymphadenectomy in GCT is not part of the current guidelines and there is no consensus on whether these patients should undergo surgical staging including systematic lymphadenectomy.[12] Since lymph node metastases is uncommon in granulosa cell tumor (<1%), and pelvic and para aortic lymphadenectomy does not help in increasing the survival benefit of the patient, we did not include lymphadenectomy in our staging. Staging system for GCT is the same as applied for epithelial ovarian cancer and tumor stage is the most important clinical parameter of prognostic relevance, with a higher risk of relapse being associated with stages II through IV disease.[18] In addition, patients with stage I disease associated with features such as large tumor size, high mitotic index, or tumor rupture may also be at higher risk.[9] The value of postoperative adjuvant therapy for high-risk patients has not been investigated by prospective randomized trials. However, for patients with stage II-IV granulosa cell tumors, postoperative chemotherapy is recommended.[19] The 5-year survival is 94 per cent in the early stages compared to 25 per cent in advanced stages.[10] Prolonged surveillance program with periodic clinical, serologic and radiologic follow-up is imperative , given the tendency of these tumors to recur several years after the initial diagnosis.[20,21]

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