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Case Report

Adult granulosa cell tumor of ovary in a young female: A rare case report

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ABSTRACT

Granulosa cell tumours (GCT) belong to the group of sex cord and stromal tumours of ovary. Adult granulosa cell tumours account for approximately 1% of all ovarian tumours and 95% of all granulosa cell tumours. They are found more often in postmenopausal than premenopausal women, with a peak incidence between 50 and 55 years of age. We present the case of a 35-year female who came with white discharge, irregular menses and excessive bleeding during menses since 5 to 6 months. The complete blood picture with peripheral smear examination, kidney and liver function tests were all within normal limits. CT abdomen was advised which revealed a large solid cystic lesion of left ovarian origin. Surgical intervention was done and histopathology revealed adult granulosa cell tumor of ovary.

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1. Introduction

Solid ovarian tumours comprises a small percentage of ovarian tumours, that too less common in young women. Dysgerminoma is the commonest ovarian tumor in younger age groups. Diagnosis of solid tumor in young female is often delayed because they mimic common conditions like pedunculated fibroids, fibromas, thecomas, polycystic ovary, malignant ovarian tumors, or an ovarian torsion.¹

We present a rare case of granulosa cell tumor of ovary in a young female.

2. Case Report

A 35-year old multiparous female presented in the gynecology out patient department with the chief complaints of white discharge, irregular menses and excessive bleeding during menses since the past 5 to 6

months. She was married since 17 years and had four uneventful childbirths. She had 60-90 days menstrual cycle with a flow of 15-16 days.

There was no history of anorexia or weight loss, urinary symptoms, postcoital bleeding or dyspareunia. She did not use any hormonal contraceptives or ovulation-inducing drugs. There was no family history of a similar illness. She was non diabetic, non hypertensive, non smoker and non alcoholic.

On general examination the patient was moderately built and pale, rest all vitals being within normal limits. Cardiovascular and respiratory examination did not reveal any abnormality.

However she had uniformly distended abdomen with no other scars or irregularities. Speculum examination showed a bulky healthy-looking cervix and the cervical os was patulous on digital examination. On bimanual examination uterus could not be palpated separately due to per abdomen mass.

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Complete blood count showed 11.7% hemoglobin and WBC count was 11800 cells/mm³. Peripheral smear examination, renal and liver function tests and urine examination were all normal. A cervical pap smear was advised which was negative for any intra epithelial lesion or malignancy; however the smear was inflammatory and showed fungal colonies consistent with candida species.

CT scan of abdomen and pelvis was planned which showed a large solid cystic lesion measuring 19.2 x 11 x 8.4 cm present in midline and extending on left side. There was enhancement of solid component on CECT, left ovary was not seen separately from the lesion. Lesion was abutting the uterine fundus. Uterus appeared normal with endometrial thickness being 13mm. Right ovary was normal.

On admission tumor markers were done which had normal levels of CA-125, beta hCG and alpha feto protein. Chest radiography did not reveal any remarkable findings.

All these reports suggested a benign etiology of the mass. An initial diagnosis of benign left ovarian endometrioma or dermoid cyst was made. Total hysterectomy with left salpingo-oophorectomy was planned. Hemorrhagic peritoneal fluid was seen on opening the abdomen. Left ovarian mass of 20x10x10 cms was identified with intact capsule.

On receipt of the specimen in pathology department, uterus & cervix was unremarkable with left ovarian encapsulated mass measuring 21 × 15 × 8 cm and stretched out tube over it. Cut section of the lesion showed solid grey white to yellow tumor with tiny multiple cysts, few of which were filled with blood. No normal ovarian stroma was identified.

Histological examination revealed a tumor consisting of neoplastic granulosa cells which were monomorphic, with pale and scanty cytoplasm, few showing coffee bean nuclei organized diffusely and into trabeculae, compact clusters, microfollicles and macrofollicles. Few Call-Exner bodies and some mitotic figures were seen.

The tubal wall had normal structure without tumor invasion.

Additionally, endometrium showed hyperplasia without atypia and cervix was unremarkable.

Her post-operative period was uneventful, and she was discharged from the hospital on 13th post-operative day.

On discharge, she was advised for a consultation with medical oncologist and also to continue her follow-up care with the gynecology team at our hospital.

3. Discussion

GCTs are derived from the granulosa cell layer of the ovarian follicles. Normally, these cells proliferate in response to rising circulating gonadotropins and decline in response to circulating testosterone. They normally produce estradiol, sex steroids and peptides necessary for ovulation. Excess estradiol, when sensed by the hypothalamus and

anterior pituitary, decreases the production of gonadotropin-releasing hormone, FSH, and LH.^{2,3}

Granulosa cell tumour (GCT) is extremely rare, sex cord stromal tumours constituting only 1% to 2% of all ovarian malignancies.⁴ This is in accordance with the studies of Kanthikar et al,⁵ Amita P et al⁶ and Sharma et al⁷ who in their studies on classification of ovarian tumours found the incidence of adult granulosa cell tumour between 1-2%. However, study done by Pilli G et al⁸ and our present study found the incidence of adult granulosa cell tumour to be 3.54% and 3.7% respectively.

On the basis of age of onset and clinicopathological characteristics, these tumours are subdivided into two distinct forms, the adult type and the juvenile type representing 95% and 5% of the tumours, respectively.⁴

Most of the adult GCT present in postmenopausal women, with a peak incidence between 50 and 55 years.² However in our case, the patient was just 35 years of age.

Chromosomal abnormalities have been recently evaluated in granulosa cell tumors. These abnormalities include trisomy 12, monosomy 22, and deletion of chromosome 6. Peutz Jeghers syndrome and Potters syndrome show a syndromic association with GCT of ovary. In the present case, chromosomal studies were advised to the patient at discharge.

Continuous exposure to ovulation induction drugs like selective estrogen receptor modulators (SERM), clomiphene citrate, gonadotropins may also increase the risk of GCT.⁹ However the patient denied any intake of ovulation induction drugs.

Clinical symptomatology is not specific for these tumors, but is most often manifested by an increase in abdominal volume with diffuse abdominal pelvic pain sometimes associated with cycle disorders, postmenopausal metrorrhagia and infertility. Their hyper-estrogenic character explains the appearance of endocrine manifestations and their association with other estrogen-dependent pathologies such as endometrial hyperplasia with or without atypia.¹⁰ In this case also the patient presented with menstrual problems. And on histopathological examination the endometrium was found to be hyperplastic without any atypia.

The radiological findings of the GCT vary from solid mass to the cystic lesion and some may also present with hemorrhage. The two most common classifications are multiseptated cystic mass and unlobulated solid mass with cystic portions.¹¹ However none of these are diagnostic. In the present case, the radiological findings were suggestive of a large solid cystic lesion.

Similar to this case in majority of case reports the median tumor size was of 20 cm (4-33cm).¹²

Elevated levels of CA 125 is seen in 42% of cases (13/31) of GCT in a study conducted by Dridi et al.¹² However in our case the levels of CA 125 were within normal limits.

Table 1: Showing the incidence of adult granulosa cell tumor of ovary in different studies

| WHO Classification of Ovarian Tumors | Pilli G et al ⁸ (2002) (n=282) | Kanthikar et al ⁵ (2014) (n=145) | Amita P et al ⁶ (2018) (n=162) | Sharma et al ⁷ (2020) (n=130) | Present Study(2022) (n=137) |
|--------------------------------------|---|---|---|--|-----------------------------|
| Epithelial Tumors | | | | | |
| Serous | 31.32% | 36.36% | 58.6% | 50.77% | 33.33% |
| Mucinous | 19.5% | 10.90% | 18.6% | 23.85% | 40.74% |
| Endometriod Tumor | - | 1.8% | - | - | - |
| Germ Cell Tumors | | | | | |
| Benign Cystic Teratoma | 15.6% | 10.90% | 16.6% | 16.92% | 11.11% |
| Dysgerminoma | - | 1.8% | 1.3% | 0.77% | - |
| Struma Ovarii | 0.7% | 1.8% | - | - | - |
| Sex Cord Stromal Tumors | | | | | |
| Granulosa Cell Tumor | 3.54% | 1.8% | 0.6% | 1.54% | 3.7% |
| Fibroma | - | 3.6% | 3.1% | - | - |
| Metastatic Tumors | | | | | |
| Krukenberg | 2.31% | 3.6% | - | 2.31% | - |

Inhibin acts as a granulosa cell growth factor and its levels reflects the tumor burden so it can be used as a tumor marker. But as GCT is diagnosed in pathological specimen, serum inhibin is not done in preoperative period.¹³ Similar to this case serum inhibin was not done in any case in a large retrospective study done by Dridi et al.¹² In our case also, serum inhibin was not done as there was no differential diagnosis of GCT pre-operatively.

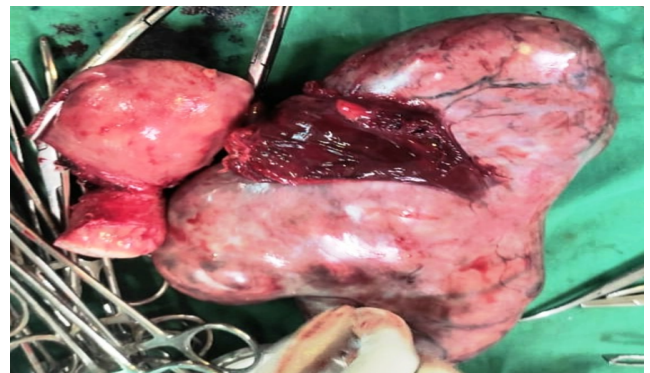
GCT are usually diagnosed from the pathology specimen although a preoperative diagnosis can be suspected based on presence of an adnexal mass with features of hyperestrogenism, thickened endometrium and elevated serum inhibin.¹³ However, in this present case there was no clinical features of hyperestrogenism.

The primary treatment consist of complete removal of tumor by adequate resection.¹⁴ Surgical staging remains the initial management of a suspected case of GCT. The principles of surgery are similar to epithelial ovarian tumor. Nodal dissection is not a significant factor for survival and is not recommended in surgical staging of GCT.⁹ In this case the tumour was resected completely, however the surgical staging could not be done.

On gross section, we found that the tumor was solid and cystic, the cysts were multilocular with a smooth internal surface filled with coagulated blood with ill-defined areas of hemorrhage, separated by solid tissue having variegated appearance with focal areas of necrosis and hemorrhage.

On microscopic examination, the architecture varied with the presence of microfollicular, trabecular, tubular, solid and diffuse pattern. Tumor consisted of small cells with a high nucleo-cytoplasmic ratio, few having coffee bean nuclei with a discrete nucleolus. All these findings are similar to the findings of Raivoherivony et al.¹⁵ who reported similar findings in a case report of GCT of ovary.

Spread of granulosa cell tumors is local, by direct extension and intraperitoneal seeding. The tumors may

**Fig. 1:** Showing intra operative picture of Granulosa Cell Tumor**Fig. 2:** Showing encapsulated smooth lobulated surface tan-yellow in colour

also spread hematogenously, and patients can develop metastases in the lungs, liver, and brain years after initial diagnosis.¹⁶ However in the present case the tumor was limited to ovary on presentation. And follow up needs to be done to know the further status of spread.

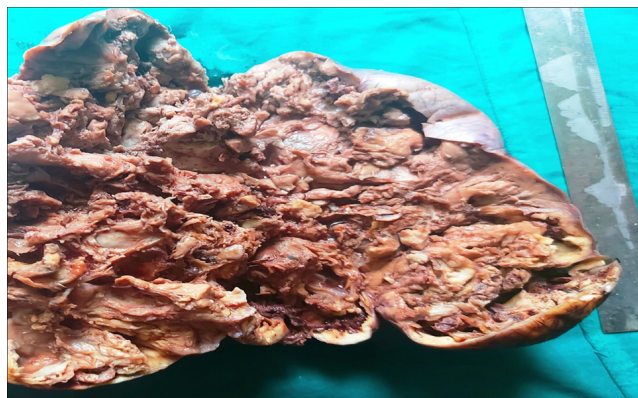


Fig. 3: Showing tan-yellow hemorrhagic cystic mass

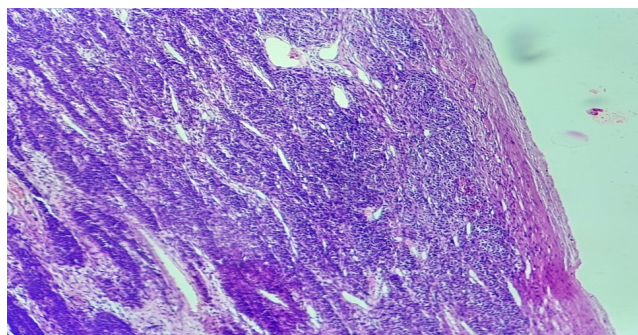


Fig. 4: Showing cystic areas lined by nests of tumor cells

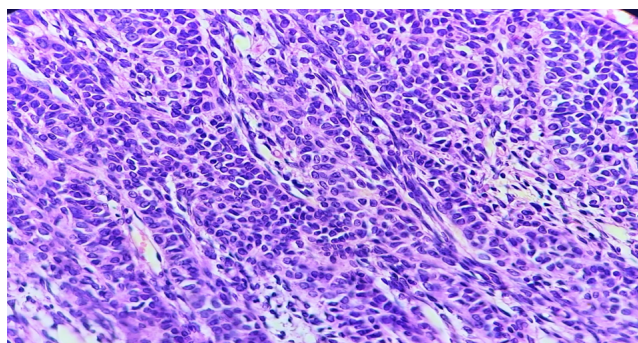


Fig. 5: Showing tumor cells having pale, uniform, round oval nuclei with irregular nuclear membranes

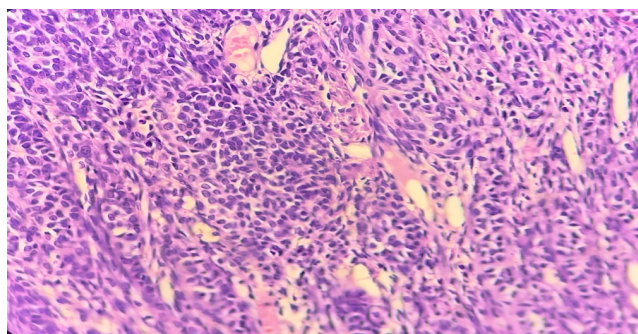


Fig. 6: Showing Carl Exner bodies

GCTs can cause endometrial cancer due to its feature of continuous and unopposed secretion of estrogen by the ovary; most of them are well-differentiated endometrioid adenocarcinomas that carry a good prognosis when detected early. Endometrial pathology in the form of hyperplasia is a common finding.¹⁴ In the present case also, we found concomitant endometrial hyperplasia without atypia.

In the study by Dridi et al.¹² median survival of patients who underwent optimal cytoreduction was 60 months in contrast to 19 months for those who did not, in advanced cases. In the present case follow up needs to be done to know the survival outcomes of patient.

To summarise, whenever the patient presents with large, unilateral, solid, cystic, adnexal mass associated with abnormal bleeding per vaginum, differential diagnosis can be GCT, primary endometrial cancer metastasising to the ovary, primary ovarian cancer with metastasis to the uterus and synchronous epithelial ovarian and endometrial cancer.¹⁷ In this case the endometrium showed only proliferative changes with no atypical / neoplastic cells.

4. Conclusion

Granulosa cell tumor of ovary is a rare ovarian entity. Complete workup with imaging and tumour markers can support the diagnosis. Estradiol secretion is the reason for symptoms and signs at presentation, which include vaginal bleeding, pelvic mass, pelvic pain or infertility. Tumor rupture may cause abdominal pain and hemoperitoneum. The initial treatment of choice is surgery, which is necessary for histological diagnosis, appropriate staging, and debulking. Serum inhibin test as a tumor marker of granulosa cell tumor is usually run in retrospect after histopathological report. An endometrial assessment should be done once the diagnosis of granulosa cell tumors is confirmed. Though granulosa cell tumour is a tumour with low malignant potential, but it has a high chance of recurrence even years after apparent clinical cure of the primary tumor. So 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. Adequate counseling followed by long-time follow-up with specialists in the multidisciplinary team is recommended to ensure thorough recovery and proper care. In patients with desire for fertility, a fertility preserving surgery with endometrial biopsy is safe and chemotherapy may be used if indicated without adversely affecting the chance and outcome of future pregnancies.

5. Source of Funding

None.


6. Conflict of Interest

None.

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