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Case Report

Cystic granulosa cell tumor of the ovary- diagnosed on histopathology: case report

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Abstract: Granulosa cell tumor (GCT) is an uncommon malignant neoplasm primarily arises from the sex-cord stromal cells of the ovary. They represent about 5 to 8 % of all cancers of the ovary. They belong to the category of sex-cord stromal tumors: juvenile or adult types are frequently used in the literature. Juvenile GCT represents only 5% of this tumor and usually occurs in pre-pubertal girls and women younger than 30 years whereas adult GCTs present with early stage disease and are commonly encountered in the age group of 35 years to 55 years. Granulosa cell tumors usually produce estrogens, and leads to symptoms and signs of estrogen excess. Endometrial hyperplasia and adenocarcinoma of uterus reported in 50 % and 15% of the cases of GCT respectively in peri-menopausal and postmenopausal women. However, virilizing granulosa cell tumors which produce androgens leading to virilization occur in pre-pubertal girls. Granulosa cell tumor (GCT) is characterized by a relatively low malignant potential, slow growth, less aggressive and late recurrence; however prognosis is influenced my many factors, such as age and stage at presentation, tumor size, necrosis, mitotic activity and histological staging. The treatment modalities include surgical excision, chemotherapy and radiotherapy which depend on tumor stage or combined regimen. However, irrespective of age and type of surgery, patients of GCT require regular follow-up.
Keywords: Ovary, Granulosa Cell Tumor (GCT), Cystic GCT, Histopathology, Dysfunctional Uterine Bleeding, Low Malignant Potential, Sex Cord Stromal Tumors.

INTRODUCTION

Neoplasm's which originate from the primitive cortical lobules, sex cords and the stroma or mesenchyme of the embryonic gonads are grouped under sex cord stromal tumors. Sex cord stromal tumors or hormone producing tumors of the ovary are very uncommon and they account for 5–8% of all ovarian neoplasms and the malignant neoplasms constitute less than 10% of all ovarian carcinomas. Sex cord stromal tumors are hormonally active neoplasms [1]. Most of the ovarian tumors are detected by ultrasound imaging, but about 24 % of the ovarian tumors are detected incidentally at the time of hysterectomy or caesarean section. According to the authors, Kottarathil VD , Malmström H and Ohel G, GCT 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 [2-4]. Most of the cases occur in post menopausal women but one third cases of GCT occur in reproductive age group and premenopausal women. GCT is the most common hormone-producing ovarian tumour. Granulosa cell tumors usually produce estrogens, and leads to symptoms and signs of estrogen excess. Endometrial hyperplasia and adenocarcinoma of uterus reported in 50 % and 15% of the cases of GCT respectively in peri-menopausal and postmenopausal women. Dysfunctional uterine bleeding (DUB) and irregular menstruation are frequently seen in women of reproductive age [5]. Majority of patients with GCT are diagnosed at an early stage of the disease and have more specific symptoms and signs of either hyperestrogenism or hyperandrogenism unlike epithelial tumors where diagnosis is delayed due to vague and nonspecific presentations. We present a rare case of cystic granulosa cell tumor in a 32 year old lady presented with dysfunctional uterine bleeding since 6 months. No definite preoperative diagnosis was made clinically or on ultrasound. Only existence of bilateral cystic lesion was documented on ultrasound. Histopathology of preoperative endometrial curretings revealed simple endometrial hyperplasia. Final diagnosis was made on histopathological examination (HPE) of a panhysterectomy specimen.

CASE HISTORY

A 32 year old lady came with complaints of irregular and excessive menstrual bleeding since 6 months associated with pain on and off, more during active bleeding. She has two living children and was tubectomized 3 years ago. General physical

examination was normal except mild anemia. A diagnostic endometrial biopsy was done on 07/02/2015 and the histopathology report revealed simple endometrial hyperplasia. Later ultrasound abdomen and pelvis was done and findings showed right cystic ovary with cyst measuring 4.5 x 4 x 3 cm and right cystic ovary with cyst measuring 3 x 2 x 1 cm. On 24/2/2015, we received specimen of panhysterectomy. Grossly, uterus with cervix measured 8.5 x 6 x 2.5 cm, Endometrial thickness 0.5 cm myometrium showed trabeculated appearance and thickness of 1.5 cm (Fig-1). Right side tubal stump measured 3 cm in length, attached to a cystic mass measuring 5 x 4 x 3 cm (Fig-2). Cut surface of cystic mass revealed brownish fluid, unilocular, inner wall smooth, wall thickness 0.1 cm, no normal ovarian tissue identified. Left side tubal stump measures 4 cm and ovary measuring 3.5 x 2 x 1 cm, cut surface revealed a single cyst measuring 1.5 cm in diameter, inner wall smooth, uniloculated, filled with brownish color fluid. Adjacent ovarian tissue showed a circumscribed grey tan area measuring 1.0 cm (Fig-3). Microscopy revealed simple endometrial hyperplasia(Fig-4), adenomyosis, right sided ovary showing luteal cyst(Fig-5), left sided ovary showing simple cyst along with granulosa cell tumor with classical Call-Exner bodies and coffee bean nuclei(Fig-6,7 & 8).

Fig-1: Gross picture of Panhysterectomy specimen.

Fig-2: Gross image of right sided cystic ovarian mass

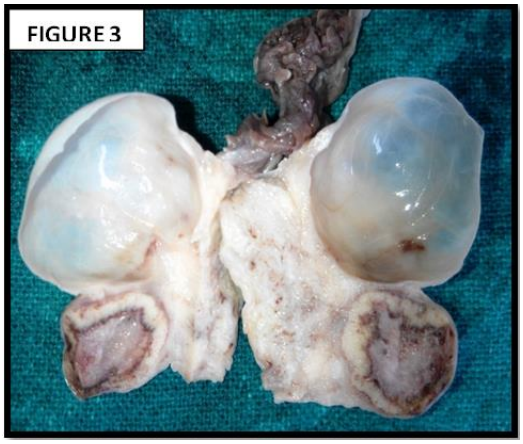

Fig-3: Gross image of cystic mass and Granulosa cell tumor (GCT)

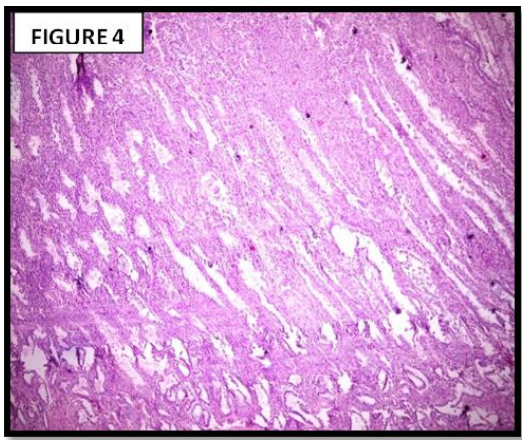

Fig-4: Microphotograph showing Simple Endometrial Hyperplasia

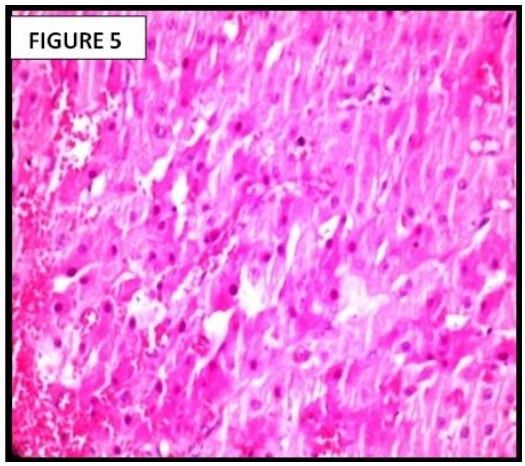

Fig-5: Microphotograph showing Luteal cells lining the luteal cyst of right ovary

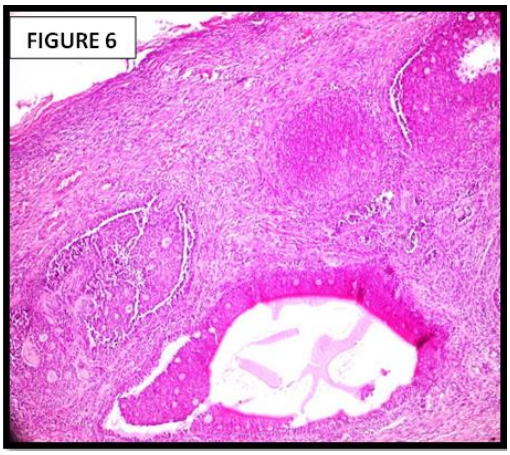

Fig-6: Microphotograph showing tumor tissue arranged in microfollicular pattern. (4 X View)

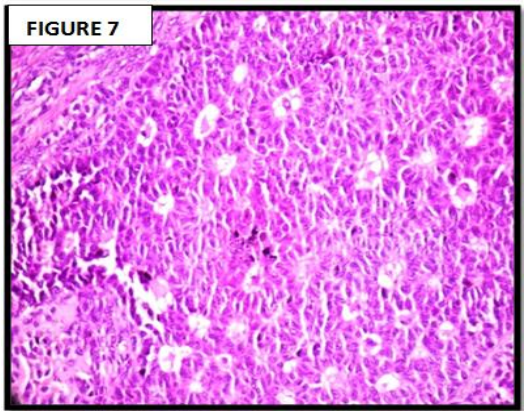

Fig-7: Microphotograph (10 X View) showing Call-Exner bodies with grooved nuclei (Coffee bean nuclei)

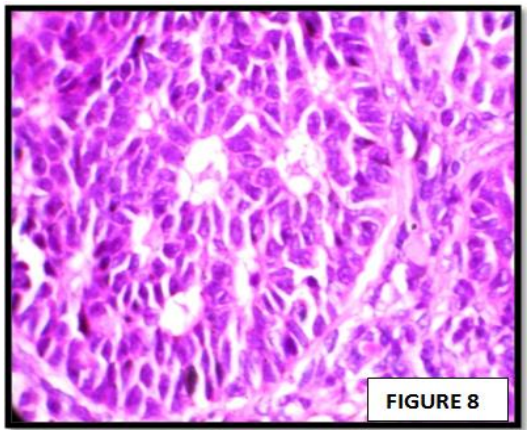

Fig-8- Microphotograph (40 X View) showing Call-Exner bodies with grooved nuclei (Coffee bean nuclei)

DISCUSSION

Ovarian GCT 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. GCT can occur at any age but most of the cases occur in post menopausal women but one third cases of GCT occur in reproductive age group and premenopausal women. They are frequently unilateral, bilateral occurrence is less than 5 % .GCT is the most common hormone-producing ovarian tumour. Due to production of estrogens, occult GCTs can lead to endometrial hyperplasia and adenocarcinoma of uterus which may present as dysfunctional uterine bleeding (DUB) as happened in our case. According to author Uygun K, GCT may present with symptoms of abdominal pain and mass, dysfunctional uterine bleeding, abdominal distention and primary or secondary amenorrhoea [6]. GCT is divided into adult and juvenile types.

Table-1: Differences between juvenile and adult granulosa cell tumors.

JUVENILE GRANULOSA CELL TUMOR	ADULT GRANULOSA CELL TUMOR
50% prepubertal	Less than 1% prepubertal
Most commonly seen below 30 years of age	Most commonly seen above 30 years of age
Macrofollicles on microscopy	Microfollicles on microscopy
Dark round nuclei	Pale grooved nuclei
Atypia present , mitotic figures are frequent	Minimal Atypia , rare mitotic figures
Luteinization common	Luteinization rare
Most recurrences and early recurrences	Reccurences are rare and late

Hormone production is frequent and approximately 25% to 50% of GCTs are associated with endometrial hyperplasia and 5% to 13% with endometrial carcinoma [3,7,8]. According to the review of literature, the gross appearance of GCT varies; they can be solid, soft or firm to predominantly cystic and sometimes may resemble mucinous cystadenoma [9]. Majority of the tumors present as enlarged solid and cystic ovarian masses, rarely they exist in normal sized ovary as in our case. A variety of histological patterns were observed in literature, which include micro-follicular, trabecular, solid, tubular, diffuse and water-

silk patterns. Differential diagnoses include undifferentiated carcinoma ovary, adenocarcinoma, cellular fibroma, cellular thecoma and carcinoid. On microscopy, Call-Exner bodies, nuclear grooves and coffee bean nuclei are pathognomonic diagnostic features of GCT. Somatic mutations of FOXL2 Gene seen in 97 % cases of adult granulosa cell tumor. On ImmunoHistochemistry (IHC) , GCT shows positivity for Inhibin and Calretinin; variable positivity with S-100; Negativity for epithelial markers such as Cytokeratin(CK) and Epithelial membrane antigen(EMA).The prognosis of granulosa cell tumors is largely dependent on the clinical staging [10].It also depends on size, tumor rupture, and presence of nuclear atypia [10,11]. Juvenile granulosa cell tumors behave more aggressively than their adult counterparts, and are more likely to produce distant metastases. Some authors have claimed that tumors with follicular or trabecular patterns have a better prognosis than those with a sarcomatoid pattern [12]. In the series of Norris and Taylor [13], 12 of 187 patients had persistent tumor after surgery, and 10 died as a result. The granulosa cell origin of a metastatic tumor should be suspected in the presence of a combination of microcystic and trabecular formations, especially if accompanied by Call–Exner bodies and grooved nuclei.

Table-2: FIGO Staging of ovarian tumors and treatment.

STAGING	EXTENT OF DISEASE	TREATMENT
STAGE I	Tumor limited to Ovaries	Ovariectomy / Total abdominal hysterectomy (TAH +BSO) with bilateral salphino-oopherectomy (depending upon the family completion)
STAGE II	Tumor involves one or both ovaries with pelvic extension	TAH+ BSO and Chemotherapy/Radiotherapy
STAGE III	Tumor involves one or both ovaries with Microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastasis	TAH+ BSO and Chemotherapy/+Radiotherapy
STAGE IV	Distance metastasis	TAH+ BSO and Chemotherapy/+Radiotherapy

CONCLUSION

GCTs most often present with features of hyperestrogenism but rarely they do manifest with virilizing features. In our case also the presenting features were result of hypersecretion of estrogen leading to simple endometrial hyperplasia and dysfunctional uterine bleeding. Most GCTs are diagnosed in stage I. Histopathological examination forms the definitive diagnostic modality. Early diagnosis followed by surgical treatment results in good prognosis with 20 years survival rate is more than 70 %. Fertility preserving surgery may be appropriate in young patients.

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