Giant Granulosa Cell Tumour – A Case Study

Shivika Gupta

ABSTRACT

Introduction: Ovarian granulosa cell tumors are uncommon estrogen-secreting neoplasms accounting for 2-5% of all ovarian cancers. The adult form is more common. Aim & Objective - To present a case of adult granulosa cell tumour. Background - Granulosa tumors were described for the first time in 1855 by Rokitansky. These tumors are malignancies with a relatively favourable prognosis. They are characterized by a prolonged natural history and a tendency for late recurrences.

Case report: We present the case of a 65-year-old patient who presented with abdominal distension and post-menopausal vaginal bleeding. On examination, she had a mass corresponding to 28 weeks gestation in left fornix. Her CECT revealed a large hypodense cystic septated lesion in abdominal pelvic region with thick septations and enhancing component. A provisional diagnosis of ovarian malignancy was made. She underwent Staging laparotomy with total abdominal hysterectomy with bilateral salphingo-opherectomy, and infracolic omentectomy. Histopathological studies revealed the presence of adult granulosa cell tumour stage I C with non atypical endometrial hyperplasia. She had an uneventful post-operative recovery. She was put on CAP regimen for 6 cycles and monitoring was done with serum estrogen, CA-125 and CT pelvis.

Conclusion: Granulosa cell tumor of the ovary is a rare ovarian entity. The adult form progresses slowly and often is diagnosed at an early stage of disease. Surgery is indicated. A prolonged post-therapeutic follow-up is necessary because of the risk of recurrences. The important prognostic factor is staging of the tumor. Staging and histopathology helps in prediction of survival. Also diligent endometrial pathology has to be sorted to rule out endometrial carcinoma.

Keywords: Giant Granulosa, Cell Tumour

INTRODUCTION

Ovarian granulosa cell tumors represent uncommon neoplasms arising from the ovarian sex-cord stromal cells, and account for 2-5% of all ovarian cancer.[1-3] Based on clinical and histopathological studies, these tumors are classified as juvenile and adult granulosa cell tumors.[4] The main characteristic of these tumors is their hormone-secreting capacity, nearly all of them being capable of synthesizing estradiol.[4] Due to this particularity, ovarian granulosa cell tumors are responsible for the iso-sexual precocious pseudopuberty in young girls, while in older patients, abnormal vaginal bleeding, abdominal swelling and even abnormal palpable masses in the lower abdomen can be seen. Most tumors are large, solid or cystic, with slow growth and tendency for late recurrence.[5] When it comes to their hormonal activity, estradiol has been advocated as a true tumor marker for these neoplasias.[6] However, the estradiol concentration is not a reliable marker of disease activity, no significant correlation has been established between it and the presence of bulky disease.[7,8] Despite this, high hormonal levels can be associated with other significant modifications of estrogen-sensitive tissues, such as endometrial tissues. Prolonged endometrial exposure to high estrogen levels are responsible for pathological modifications ranging from endometrial hyperplasia to endometrial cancer.[9,10] The adult form is the most common tracing with a very typical clinical pathological profile with a slow progression and recurrence that occurs long after the date of onset of the disease. The management is essentially surgical when the diagnosis is early.

CASE REPORT

A 65 – year old P7L7 presented to our hospital with complaints of diffuse abdominal distension and pain for past 1 year, and post menopausal bleeding for 6 months. The patient had an altered general state, with loss of appetite and weight of at least 10 kgs.

On examination, she was of lean built with moderate pallor. Her abdomen was uniformly distended, hernial sites intact. A mass of around 28 weeks gestation was palpable with variegated consistency, ill defined margins, fingers could not be insuinated between mass and pubic symphysis. On bimanual examination uterus was postmenopausal size, deviated to right, mass was felt in the left fornix mass was felt which did not move with movement of cervix. On per rectal examination uterus was post menopausal size, mass was not palpable.

Initial laboratory workup showed normal blood count, liver function tests, kidney function tests,serology, chest xray and ecg and CA-125 was raised (174). Transabdominal ultrasonography revealed huge right side cyst (tubo-ovarian mass with internal echoes) ? ovarian malignancy. CECT abdomen pelvis showed a large hypodense cystic septated lesion in abdominal pelvic region with thick septations and enhancing component.

Staging laparotomy was performed that showed a huge left

Junior Resident, Department of Obstetrics & Gynaecology, Rohilkhand Medical college and Hospital, Bareilly, India

Corresponding author: Dr. Shivika Gupta, Junior Resident, Department of Obstetrics & Gynaecology, Rohilkhand Medical college and Hospital, Bareilly, India

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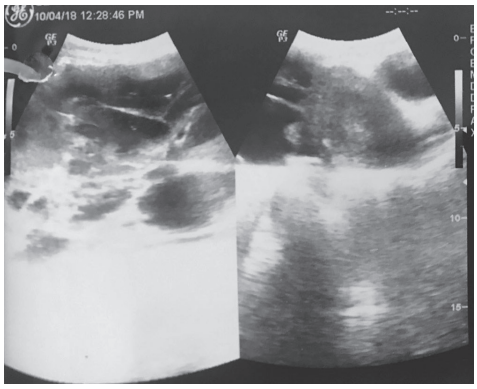

Figure-1: Ultrasound image showing granulosa cell tumour

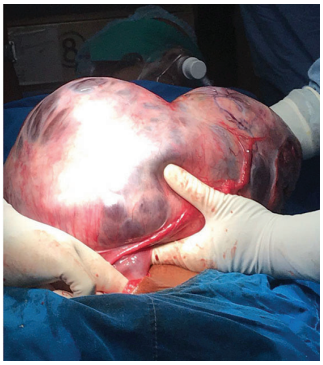

Figure-2: Per operative picture of tumour; **Figure-3:** Left ovary measuring around 20x10x8 cms, weighing 6 kg, capsule was breached at lateral end

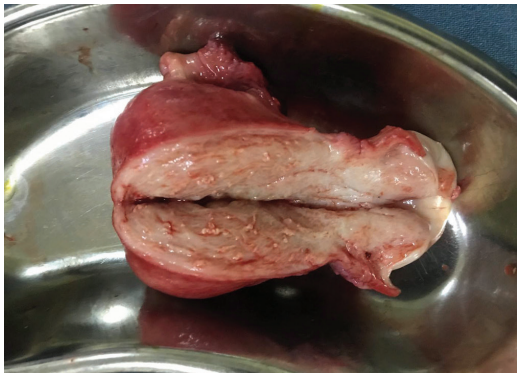

Figure-4: Uterus was 8 weeks size, On cut section endometrium was atrophic, myohyperplasia seen, cavity of uterus was normal, cervix normal

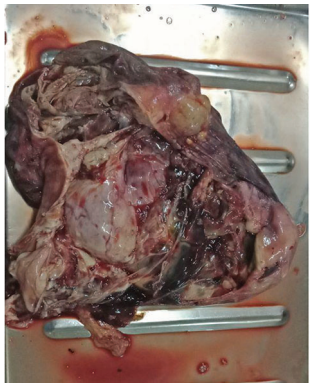

Figure-5: Cut section of left ovarian tumor was multiloculated cystic accompanied by intracystic hemorrhagic foci, around 5 litres of serous fluid (blood stained) was drained.

ovarian mass occupying the whole of abdomen and moderate amount of ascites. Complete resection of the tumour was done followed by total abdominal hysterectomy and bilateral salphingo ophrectomy, and infracolic omentectomy. Grossly uterus was enlarged in size upto 8 weeks. Left ovary measuring around 20 x 10 x 8 cms, weighing 6 kg, capsule was breached at lateral end. Right tube and ovary was normal. On cut section endometrium was atrophic, myohyperplasia seen, cavity of uterus was normal, cervix normal, left ovarian tumor was multiloculated cystic accompanied by intracystic hemorrhagic foci, around 5 litres of serous fluid (blood stained) was drained.

The histopathological studies revealed the presence of adult ovarian granulosa cell tumour of left ovary associated with non atypical hyperplasia of endometrium. Lymphovascular invasion was not seen, ovarian capsule was breached at one end. PTNM ($PT_{1C2} N_X M_0$) stage I C

She had an uneventful postoperative recovery, was transfused I unit PRBC, was discharged on 10 post -op day. She was referred to our oncology department and was put on CAP regimen for 6 cycles and monitoring was done with serum estrogen, CA- 125 and CT pelvis

DISCUSSION

Granulosa cell tumors are very rare. They were described for the first time in 1855 by Rokitansky[11], who described them according to their appearance near the granulosa cells of ovarian follicles. They occur in the peri- and postmenopausal period with peak prevalence in patients aged 50 to 55 years. The other peak frequency corresponds to the prepubertal age.[12,13]

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 or postmenopausal metrorrhagia. Their hyper-estrogenic character explains the appearance of endocrine manifestations and their association with other estrogen-dependent[24] pathologies such as endometrial hyperplasia (4-10%) or endometrial adenocarcinoma (5 to 35%).[13,14] Therefore, endometrial and cervical biopsies are essential to define the therapeutic strategy.

Macroscopically they are bulky tumors up to 30 cm long axis of solid-cystic appearance necrotic in places, usually unilateral. Radiologicaly speaking, the granulosa cell tumor presents as a solid component with multicystic appearance, with a median diameter of 12 cm (range: 1 to 30 cm).[15,16] The imaging appearances of the two forms of granulosa cells tumors are similar. On pelvic MRI, these masses are hypersignal in T1 testifying to the presence of haemorrhagic changes, and in intermediate signal in T2 with alternating solid and cystic spaces responsible for their spongy appearance. Metastases are generally less frequent with the following sites of preference: the peritoneum and the liver

The diagnosis is confirmed by histological analyses.The adult form includes five subtypes, among which the most common subtype - microfollicular - is characterized by Call-Exner bodies and cores “coffee bean”.[17,18] In the juvenile

form, the architecture is often lobulated, Call-Exner bodies are rare, and the signs of luteinization are frequent.[11]

The main immunohistochemical markers expressed by these cells are vimentin, CD 99 and alpha inhibin.The serum tumor markers are estradiol, inhibin, and anti-Müllerian hormone. Cancer antigen 125 (CA-125) is not correlated to the tumor progression.[18] Kalfa et al.[19] identified a mutation FOXL2 (transcription factor gene) in the majority of granulosa cell tumors, particularly in adult form. This FOXL2 could be the next target for use in treatment. Yoo et al.[20] also identified mutations of genes Fas, FLIP and Bcl-2 related to alterations of apoptosis.The principal differential diagnoses of granulosa cell tumors are: endometrioid carcinoma, stromal sarcoma, carcinoid tumors and adenocarcinoma.[21]

When it comes to the most important prognostic factors of women diagnosed with ovarian granulosa cell tumors, it seems that prognosis is strongly influenced by the initial stage at diagnosis, followed by the integrity of the ovarian capsule and the dimensions of the tumor.[14,25] For patients diagnosed with early stages of the disease, one of the most important factors predicting the recurrence rate and overall survival remains the presence of nuclear atypia. A significant association between the presence of nuclear atypia and time to recurrence also exists: tumors which develop early recurrence usually have a higher rate of nuclear atypia, of up to 77%, while those with late recurrence present nuclear atypia in up to 33% of cases. Residual disease after surgery is also another prognosis factor. In Sehouli's trial[26], the survival was lower for patients with postoperative residual disease. The number of mitoses is also a recognized prognostic factor and there is an inverse relationship between survival and the number of mitoses.[12,17] Many studies, including the Schumer trial[27], proved that tumor rupture is also a prognosis factor. Expressions of P53 mutations are common and may be associated with poor prognosis.[28,29]

The mainstay of treatments are complete surgery (hysterectomy, bilateral salpingoopherectomy) with staging for early stage and debulking surgery for advanced stage or recurrent disease with staging of the pathology consisting of omentectomy and peritoneal exploration with cytology and multiple peritoneal biopsies. Conservative treatment, based on unilateral adnexectomy with abdominal cavity exploration and endometrial biopsy, is proposed in young women with a desire for pregnancy as well as early stages. Ganglion dissection is not recommended as the risk of lymphatic invasion is infrequent.[30]

There is no standard regimen concerning adjuvant treatment, but it is usually recommended for the adult form of granulosa cell tumors and for patients at high risk.[23,27] For the use of adjuvant radiotherapy, results are still conflicting. Irradiation has been used both as adjuvant treatment following surgery, and for recurrent disease. Concerning the necessity for performing adjuvant chemotherapy, the main indications for patients diagnosed with an early stage of the disease are the presence of large tumors with high mitotic index or ruptured capsule. The most used chemotherapy regimen is a BVP (bleomycin,vinblastine, and cisplatin) or a BEP regimen, which substitutes etoposide for vinblastine.[21] The hormonal therapy based on megestrol and LHRH (luteinizing hormone-releasing hormone) agonists also lead to good responses, particularly for recurrent disease cases.[31,32]

The survival rates at 5 years and 10 years were reported by Malmstrom et al., 94% and 88%, respectively, for stage I, and decreasing to 44% for stage II and III. Wu et al.[22] also reported their results about survival for 100 patients with granulosa cell tumors; survival rates at 5 years and 10 years were 98% and 96%, respectively, for stage I and were 70% and 60%, respectively, for stage II. The recurrence rate is also related to the stage.[23] More studies will be necessary. For results of survival, the overall survival (approximately 90% at 5 years for early stage) is good, because most tumors are diagnosed early.[16,22] The evolution of adult granulosa cell tumors is slow and recurrences are rare and often delayed. These tumors can reoccur after a free interval of 6 to 23 years.[16,21]

CONCLUSION

Granulosa tumors of the ovary are malignant and rare. Early diagnosis allows conservative management with less metastatic risk. Concomitant adult ovarian granulosa cell tumor and endometrial hyperplasia or even endometrial cancer is not an uncommon situation, the relationship between the two neoplasias being established by a high level of estrogen produced by a hyperactive ovary. the standard therapeutic protocol consists of total radical hysterectomy with bilateral salphingo-opherectomy. The follow-up of this pathology must be prolonged given the risk of recurrence in the long term.

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