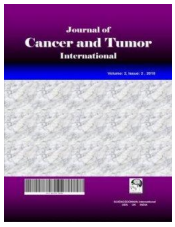

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Granulosa Cell Tumour of Ovary: Review of Cases at Tertiary Care Centre

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Granulosa cell tumours of the ovary are rare malignancies representing 2-3% of all malignant ovarian tumours.
Objective: To review the clinical characteristics and management of granulosa cell tumour of ovary.
Materials and Methods: The medical records of nine women diagnosed with granulosa cell tumour of ovary from June 2005 to October 2015 in the Department of Gynecologic Oncology of our institution were retrospectively reviewed.
Results: The mean age of the women was 42 years. They presented with various symptoms: menorrhagia, post-menoausal bleeding, abdominal distension and pain abdomen. In one patient who presented with abdominal pain and distension with breathlessness, chest X-ray showed? metastatic lesions and received neoadjuvant chemotherapy. Eight patients underwent primary surgery with complete staging in six patients. Two patients presented with haemoperitoneum and underwent emergency laparotomy. Four patients had ascites. Mean ovarian tumour size was 14 cms (range 4-30 cms). Fertility sparing surgery was done in one patient. The number of patients in various stages were I - 4(IA-3, IC2-1); IIA-1; IIIC-1; IVB-1 and unknown - 2 according to the

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International Federation of Gynecology and Obstetrics (FIGO) 2014 criteria. The maximum follow up duration was 65 months. Recurrence was observed after 3 years in two patients (one stage IA and other stage IIIC).

Conclusion: Granulosa cell tumours are classified into two types by juvenile and adult variant. GCT has low malignant potential and known to recur after many years of apparent clinical cure. Therefore, long term follow up with clinical examination and tumour marker is recommended.

Keywords: Granulosa cell tumour; haemoperitoneum; hyperestrogenism; neoadjuvant chemotherapy.

1. INTRODUCTION

Granulosa cell tumours (GCT) of the ovary are very rare malignancies representing 2-3% of the ovarian tumours and more than 70 % of the sex cord-stromal tumours. They originate from the granulosa cell, which secretes estradiol and various peptides like inhibin A and B [1]. There are two distinct histological types - adult GCT (AGCT) and juvenile GCT (JGCT) which have 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 tumours, represent 5 % of all GCTs and occur in premenarchal girls and young women [1]. It is aggressive and more risk of local and systemic failure [2].

GCTs have better prognosis in comparison to epithelial ovarian cancers [3]. They may recur up to 40 years after diagnosis [4].

Complete surgical resection either with fertility preserving procedure or without with formal staging is the mainstay of management especially for the early stages. Surgery and platinum based chemotherapy is the treatment for advanced disease [5].

2. MATERIALS AND METHODS

The medical records of women diagnosed with GCT of ovary from June 2005 to October 2015 in the Department of Gynaecologic Oncology of our institution were retrospectively reviewed. The clinical presentation, pathological characteristics, treatment and outcomes of patients with ovarian GCTs were analysed. Follow up data were updated till October 2018.

3. RESULTS AND DISCUSSION

Clinical Characteristics: Nine women with ovarian GCT were identified. The mean age of the women was 42 years (range – 18-78 years). Three patients were postmenopausal and rest were in the reproductive age. One patient was nulliparous, one was diagnosed with GCT stage IVB three months after first childbirth and rest were multiparous.

The duration of symptomatology ranged from one week to 24 months.They presented with various symptoms which included menorrhagia (44.45%), post-menoausal bleeding (22.23%), abdominal distension (33.34%) and pain abdomen (44.45%). One patient presented with abdominal pain and distension with breathlessness (chest X-ray showed multiple lung lesions? metastasis). Two patients presented with haemoperitoneum. Fig. 1 depicts vascular adnexal mass on ultrasound. Mean ovarian tumour size was 14 cms (range 4-30 cms). Four patients had ascites ranging from 100-3000 ml.

Eight women had unilateral ovarian tumours and one had bilateral. With regard to tumour markers, CA-125 was elevated in only three patients (274->5000 U/mL).

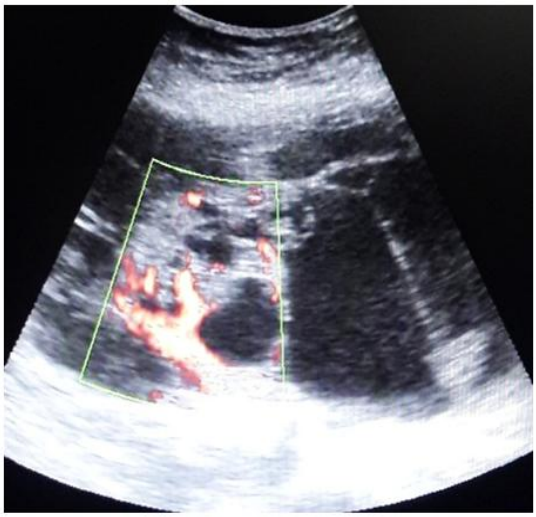

Fig. 1. Doppler showing increased vascularity in a complex ovarian mass

Table 1. Patient characteristics

Characteristics	Variables	No	Variables	No
Age	≤18 yrs	1	>18 yrs	8
Parity	Nulliparous	1	Multiparous	8
Menopausal status	Menstruating	6	Postmenopausal	3
Symptomatology	Pain abdomen	4	Abdominal distension	3
	Menorrhagia	4	Postmenopausal bleeding	2
	Ascites	3	Haemoperitoneum	3
	Pleural effusion	1	Breathlessness	1
Tumour characteristics	≤14 cms	6	>14 cms	3
	Unilateral	8	Bilateral	1
	Tumour rupture	4		
Endometrium	Basal	3	Proliferative	2
	Simple Hyperplasia	2	Autolytic	2
Histological type	Juvenile GCT	2	Adult GCT	7
FIGO 2014 Stage	I	4	III	1
	II	1	IV	1
	Unknown	2		

Stage distribution: There were four patients in stage I, one patient in stage IIA, one patient in stage IIIC and one patient presented in stage IVB according to the International Federation of Gynecology and Obstetrics (FIGO) 2014 criteria. Stage was not known in two patients as they presented with massive haemorrhagic ascites and underwent limited surgery. Among stage I patients three had stage IA disease and one had stage IC2 due to breach in tumour capsule.

Treatment: Eight patients underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy, while fertility preserving procedure (unilateral salpingo-oophorectomy and standard surgical staging) was done only in one patient. Standard surgical staging consists of peritoneal washing, peritoneal biopsies, infracolicomentectomy, retroperitoneal lymph node dissection and any suspicious lesion biopsy. Two patients underwent emergency laparotomy in view of massive haemoperitoneum. One patient, who presented with lung metastasis, received three cycles of neoadjuvant chemotherapy with Paclitaxel and Carboplatin in view of tumour biopsy showing papillary serous adenocarcinoma and then underwent complete debulking along with splenectomy. Final histopathology showed JGCT.

Retroperitoneal lymph node dissection was done in seven patients. No nodal metastasis was seen. One patient underwent appendicectomy as appendix was infiltrated by the tumour.

The pathological subtype was juvenile in two patients, while the remaining was of adult type.

Endometrial tissue was obtained shortly before or at the initial laparatomy from all the patients. Simple hyperplasia was diagnosed in 2, proliferative endometrium in 2, basal endometrium in 2 and in 3 patient's endometrium was autolysed.

Five patients received post-operative chemotherapy; starting from stage IC2 disease.

Table 2. Treatment modalities

	Type	No.
Surgery	Complete Staging	6
	Fertility sparing surgery	1
	TAH+BSO+ICO*	2
Chemotherapy	BEP**	4
	Paclitaxel+Carboplatin	1
	Follow up only	2

Total abdominal hysterectomy+bilateral saliphingo-oophorectomy+infracolic omentectomy,
**Bleomycin+etoposide+cisplatin regimen*

Four patients were given BEP (bleomycin 30 U on days 2, 9, and 16, etoposide 100mg/m2/day on days 1 - 5, and cisplatin 20 mg/m2/day on days 1 - 5) administered every 3 weeks. Two patients completed three courses of BEP and two patients defaulted after first course of chemotherapy.

Follow up: The maximum duration of follow up was 10 years post-treatment. Recurrence was observed after 3 years in two patients. One patient with stage IA disease recurred after three years with pelvic mass, for which secondary debulking was done. She received three cycles of BEP post-operatively. She had sudden death after 2 months due to? pulmonary thrombo-embolism. Another patient with Stage IIIC (defaulter) recurred with big pelvic mass, peritoneal deposits and liver metastasis. She was given three courses of Paclitaxel and Carboplatin in view of social and financial constraints and then she defaulted again.

3.1 Discussion

GCTs are different from the epithelial ovarian cancers in clinical presentation and behaviour. They are usually detected in an early stage with features of hyperestrogenism and have good prognosis [3]. GCTs may recur up to 40 years after diagnosis [4]. Complete surgical resection of the tumour is the mainstay of management especially for the early stages. For advanced disease, surgery has to be combined with platinum based chemotherapy [5].

In this study the mean age of the women was 42 years (range – 18-78 years) and 66.67% of patients presented between the fifth and eighth decades. Two patients were of the juvenile type and were 18 and 22 years old. These data were concordant with the report by Sekkate et al. [4] and Bompas et al. [6].

Patients may present with abdominal pain, abdominal distension related to mass effects or ascites, and hormonal events such as menstrual irregularities, postmenopausal bleeding, as reported in our patients [1,7,8]. Abnormal uterine bleeding had been reported as frequent as 65% of cases due to increased estrogen secretion by the tumour. This explain the frequent association between GCTs and hyperplasia of the endometrium (25% -50%) and even endometrial adenocarcinoma (5% - 10%). Therefore, endometrial evaluation is essential [9-11]. Endometrial hyperplasia was observed in 22.23% of patients in this study. Ascites has been reported in 10% cases of GCT [12] while 33% of patients in this study had ascites.

Because of the high vascularity, tumour rupture is seen in 10 % cases and presents with acute abdominal pain, abdominal distension and hypotension due to hemoperitoneum [13,14]. In this study 33.34% of patients had hemoperitoneum, of which two patients presented with acute abdomen with massive intraperitoneal bleed.

A case report by Kaur et al documents Meig's syndrome of pleural effusion with ascites [15]. One patient in this study presented with hemoperitoneum and pleural effusion.

Pulmonary metastasis had been reported many years after primary treatment [16,17]. Vimla et al. also reports a case with lung metastasis at presentation. One patient in this study also presented with lung metastasis [18].

GCTs usually present as a unilateral mass, with both cystic and solid components that ranges in size in most studies from (5 – 40 cm) with a mean diameter of 14 cm [13,19-21]. Results were matching to this case series; mean size was 14 cm (range 4-30 cms) and 88.89% were unilateral.

Serum CA-125 is not correlated to the tumour volume of GCTs, instead serum estradiol, inhibin and anti-Mullerian hormone (AMH) are useful serum markers at diagnosis, recurrence or disease progression [1]. CA125 was elevated in only three cases at presentattion (274- >5000 U/mL). Serum CA- 125 is therefore a non-specific marker.

The mainstay of treatment is complete resection of the tumour: staging for early disease and debulking for advanced disease [1,22,23]. In this series eight patients underwent primary surgery and interval cytoreduction was performed in one patient.

In most of the studies, patients usually present early i.e. stage I disease (70% - 90%), thus having a very favourable outcome [1,24,25]. Nearly 66.67% of patients in this study presented in stage I.

Women with stage I disease with high risk factors (stage I C, tumour rupture, large tumour size >10-15 cms and poorly differentiated tumours) can either be observed or, administered platinum

based chemotherapy [26]. The most common regimen used is BEP regimen [1,10,23]. In this series four patients received BEP starting from Stage IC2.

Various factors have been shown to determine the prognosis - stage, residual tumour, age, tumour size, type of surgery, tumour rupture, mitotic activity and nuclear atypia; stage of the disease being the most important [24,25,27-29]. The prognostic factors were not evaluated in this study due to small numbers of cases.

Local pelvic recurrence has been reported in 70% cases, 9% in pelvis and abdomen, 6 % retroperitoneum, 6% pelvis and retroperitoneum and 3% pelvis, abdomen and retroperitoneum [30]. Metastases to lung, liver, spleen, pancreas, gall bladder, rectus muscle, bone, adrenal and vagina are rarely reported [1,13-15,31,32]. In this study disease recurred in 22.23% of patients after a period of three years, which was pelvic mass and liver metastasis which is in concordance to Mangili et al. [33], Sehouli et al. [34] and Abu-Rustum et al. [30]. The GCT recurrences are rare and often delayed. It is fatal in 80% cases when it recurs [1].

A combined modality of treatment, involving debulking surgery followed by chemotherapy or radiation is usually offered in relapsed disease [1]. In this series one relapsed case underwent secondary cytoreduction which was followed by chemotherapy with BEP. Taxols have also been tried but platinum based chemotherapy remains the first choice in the recurrent scenario [35]. In this study one patient received chemotherapy with Paclitaxel and Carboplatin at recurrence.

4. CONCLUSION

Granulosa cell tumours are classified into two types by juvenile and adult variant. GCT has low malignant potential and known to recur after many years of apparent clinical cure. Therefore, long term follow up with clinical examination and tumour markers like inhibin B is recommended. Due to the rarity of the disease, all patients should be treated in oncology centres and to be enrolled in prospective studies to determine the optimum prognostic factors, serum markers and natural behaviour of the tumour.

CONSENT

Informed consent was obtained from all the patients / relatives.

ETHICAL APPROVAL

As this was a retrospective record review, ethical approval was not taken.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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