# Granulosa Cell Tumor of the Ovary: A Study of Six Cases

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## Abstract

**Introduction:** Ovarian Granulosa Cell Tumors (GCT) is rare cancers which arise from sex cord stromal cells of the ovaries. They represent 2% to 5% of all ovarian neoplasms. There are two different types, the adult and the juvenile type. They are characterized by distinct clinical course and outcome. Preoperative imaging features may be helpful for disease recognition. Anti-Müllerian Hormone and inhibin B are currently the most accurate biomarkers. The definitive diagnosis is obtained by the histopathological analysis. Surgery remains the cornerstone of treatment.

**Objective:** To study clinicopathological features and therapeutic options of GCT.

**Methods:** This is a retrospective single-center analysis of six cases of GCT of the ovary, collected in the obstetrics gynecology department "A" of the Charles Nicolle Hospital over a period of four years (2016 to 2019). Histopathologic observations were collected from records of the pathology department of the same hospital.

**Results:** An Adult-Type Granulosa Cell Tumor (AGCT) was found on the histopathological analysis of 83.33% of cases. Only one patient had a Juvenile-Type Granulosa Cell Tumor (JGCT). The average age of our women ranged from 19 to 61 years. For patients who have been diagnosed with an AGCT, the mean age of onset was 51 years. The mean gestity was 4.6 and the mean parity was 3. Pelvic pain was the most common symptom.

Pelvic ultrasound objectified the ovary tumors in all cases. The inhibin b test was done in one case and its level was high. Demons-Meigs' syndrome is diagnosed in 20% of cases. Two patients underwent emergency surgery. Five women were treated with hysterectomy with bilateral salpingo-oophorectomy. One patient who had undergone a previous abdominal inter adnexal hysterectomy at the age of 47, had bilateral adnexectomy. 83.33% of tumors were unilateral and confined to the ovary, with capsule rupture during surgery in one case. One tumor had spread to the peritoneal cavity.

For the case of JGCT, it was diagnosed at the age of 19. The patient did not have signs of hyperestrogenia and her pubertal development was normal. Pelvic ultrasound allowed objectifying a heterogeneous pelvic mass. The patient underwent emergency laparotomy because of severe acute pelvic pain. The diagnosis was a tumor confined to the right ovary, complicated by adnexal torsion. The histopathological examination with an immunohistochemistry study confirmed the diagnosis of JGCT. A unilateral adnexectomy was then performed.

**Conclusion:** A long natural history and recurrency are the main evolutionary characteristics of GCT. In order to optimize treatments and disease management, it is important to undergo an appropriate surgical staging and to assess the recurrence risk. Actually, prospective multi-center randomized studies are still needed to evaluate the effectiveness of other therapeutic options.

## Introduction

Ovarian granulosa cell tumors are rare tumors, belonging to the family of stromal and sex cord tumors [1]. They have a particular clinical, histological and evolutionary profile. Preoperative diagnosis is difficult. Their aspects in imagery are not unequivocal. Some biological markers can be informative for the diagnosis but their sensitivity and specificity seem imperfect. The diagnostic is anatomo-pathological.

Ovarian granulosa cell tumors are rare tumors; they have a low degree of malignancy and have a good prognosis. They are characterized by slow growth and late recurrence [1]. The standard treatment is surgery with proven efficacy of chemotherapy for advanced and recurrent forms

[2]. Other treatment options are being evaluated to optimize the management of these tumors. The aim of our study is to better understand the epidemiological aspects of granulosa tumors, their clinical, paraclinical and histological characteristics, and to evaluate the possible therapeutic modalities.

## Methods

This is a retrospective study of six patients operated on for granulosa tumors collected at the obstetric gynecology "A" department of Charles Nicolle hospital Tunis, Tunisia during the period between January 2016 and December 2019. Data was collected from hospital records. Histological examination was performed in the anatomy and pathological cytology laboratory at Charles Nicolas Hospital Tunis.

For each observation, we analyzed the clinical and para-clinical data: The ultrasound characteristics and Magnetic Resonance Imaging (MRI) data, the pathological results and the therapeutic management.

## Results

In our series, an adult granulosa tumor was found in five cases. Only one patient had a juvenile granulosa tumor.

### Adult granulosa cell tumors

The mean age of onset of adult-type was 51 years. None of the patients in our series reported a personal or family history of neoplasia.

The mean gestity was 4.6 and the mean parity was 3. One of the patients was nulligeste. The mean age at menarche was 14 years old. Three women were postmenopausal at the time of tumor discovery. No woman has used oral contraception or hormone replacement therapy. One had an international hysterectomy at the age of 47 for a polymyomatous uterus.

Pelvic pain was the most common reason for consultation (80%). The pains were acute in 40% of cases. Postmenopausal metrorrhagia were revealing in 20% of cases. Clinical examination found an abdominal pelvic mass in all patients.

All tumors were identifiable on abdominopelvic ultrasound. The mass was unilateral in all cases. The average height was 11.4 cm with extremes ranging from 6 cm to 15 cm.

The ultrasound appearance of these tumors was heterogeneous in all cases with a dual solid and cystic component. The images found were not vascularized by color Doppler and color score was evaluated at 1 according to the IOTA classification (Figure 1). There were no papillary structures. A moderate ascites was noted in two women. Only one patient had a thickening of the endometrium on pelvic ultrasound.

Magnetic resonance imaging was performed in two patients (Figure 2). The tumor markers CA125, CA19.9, alpha-fetoprotein and Embryonic Carcino Antigen (CEA) were performed in three patients, and returned normal.

Inhibin B test was performed in one case and the concentration was 4070 ng/L. AMH test was not requested.

Demons Meigs syndrome was found in one of our patients. There was an association of acitis and low abundance bilateral pleural effusion. Cytological examination of the ascitic fluid did not reveal any anomalies.

Two patients underwent emergency laparotomy surgery with an acute clinical picture. Adnexal torsion was found in one of the two patients.

An intraperitoneal rupture with a very abundant hemoperitoneum causing deglobulization was found in the second patient. We completed by peritoneal cytology, sub-total hysterectomy and bilateral adnexectomy. The patient needs a massive transfusion. The definitive pathological examination of the left annex confirmed the diagnosis of unilateral adult granulosa tumor. This tumor was classified IC2 according to the classification of FIGO.

The patient, who was hysterectomized at the age of 47, had bilateral adnexectomy, peritoneal cytology, infra-colic ommentectomy and resection of a 4 cm peritoneal cyst found on surgical exploration. The definitive pathological examination confirmed the diagnosis of an adult-type granulosa cell tumor with peritoneal involvement (Figure 3). An abdominal pelvic MRI was indicated postoperatively for tumor residue or lymph node involvement and returned without abnormalities.

For other patients, they had unilateral adnexectomy, peritoneal cytology and endometrial biopsy as a first step, then surgical restoring by midline laparotomy was performed. Total hysterectomy, contralateral adnexectomy, infra-colic ommentectomy, and multiple peritoneal biopsies were realized (Table 1).

### Juvenile granulosa cell tumors

In our series we diagnosed a single case of juvenile granulosa tumor the patient was 19 years old; GOPO. No personal or family history. The menarche was at the age of 12 years. Her pubertal development was normal. She has regular cycles of 28 days. She presented to the emergency room with chronic pelvic pain that has worsened for two days. There were no other functional signs. The physical examination objectified hypogastric tenderness in relation to a pelvic mass lateralized to the right, with well-limited contours. The mass has a firm consistency and measured 10 cm in diameter pelvic. Ultrasound revealed a right latero-uterine mass of 93 mm × 79 mm, well defined, mixed echo structure, suggesting a sub-serous fibroma in cystic degeneration (Figure 4). The left annex was without anomalies. The endometrium was homogeneous and its thickness was estimated to be 19 mm. The diagnosis of fibroma in aseptic necrobiosis was initially accepted. A laparotomy was indicated urgently due to severe pelvic pain. Surgical exploration found a right ovary increases in size. The left annex looked normal. The digestive system was macroscopically without anomalies and there were no peritoneal lesions on exploration. A right cystectomy and peritoneal cytology have been performed. The definitive pathological examination showed a morphological appearance and an immunohistochemical profile of



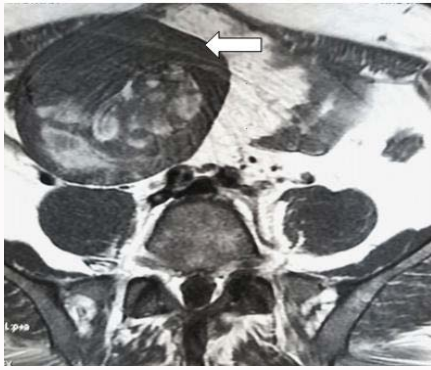**Figure 1:** Adult granulosa cell tumor.

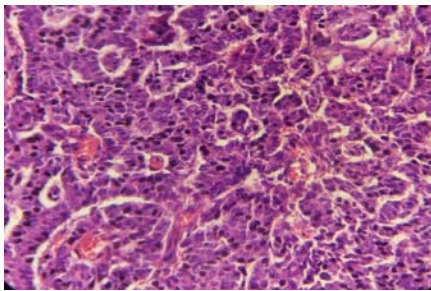**Figure 2:** MRI Adult granulosa cell tumor.



**Figure 3:** Adult Granulosa Cell Tumor: The tumor shows microfollicular pattern (call-exner bodies), the tumour cells surround small, rounded spaces filled with eosinophilic material.



**Figure 4:** Juvenile granulosa cell tumor.



**Figure 5:** Juvenile granulosa cell tumor: The tumour has a diffuse growth, the nuclei of cells are round and lack grooves with frequent mitotic figures.

granulosa cell tumors [3].

The distinction between these two types is currently based on clinical presentation, pathological features and natural progression.

## Clinical and Paraclinical Features

Granulosa tumors generally occur mainly in the peri- and post-menopausal period with a peak in frequency between 50 and 55 years with extremes ranging from 40 to 70 years for the adult form [3]. The average age of the adult forms in our series is 51 years.

They occur in the prepubertal period or in young women under 30 years for the juvenile form [1]. Multiparity appears to be a risk factor for them in the series studied. 80% of our patients are multiparous with a parity that varies between 2 and 7.

The diagnosis of these tumors is based on the pathological examination but can be oriented preoperatively by clinical and paraclinical data. The clinical forms is dominated by the tumor syndrome, represented by abdominal-pelvic pain or distension, and endocrine syndrome, represented by signs of hyperestrogens such as menometrorrhagia, oligomenorrhea or secondary amenorrhea and which are found. In less than two out of three cases [4,5].

It is the main hormone-secreting ovarian tumor that can cause clinical signs of hyperestrogenism. This could explain the frequent association between granulosa tumors and endometrial cancer as well as a biopsy of the endometrium in the management of this pathology is necessary [6,7].

In the particular case of juvenile forms, the secretion of estrogen by aromatization of androgens can be the cause of pseudo precocious puberty [8].

In some cases, the clinical forms may be acute, related to intraperitoneal rupture or ovarian torsion during emergency surgery. The Meigs demon syndrome, which was found in one patient in our series, is defined by the association of a TGO or an ovarian fibrothecoma with a peritoneal and/or pleural effusion. Its pathogenesis is not yet clearly understood. It would probably be related to a transudation secondary to the synthesis of estrogen, cytokines and VEGF, thus allowing an increase in the permeability of the vascular bed [9].

a juvenile granulosa cell tumor (Figure 5). There was no extra capsular extension and the cytological study of the peritoneal fluid confirmed the absence of malignant cells. According to the tumor staging of the International Federation of Obstetrician Gynecologists (FIGO), this tumor has been classified IA. A right adnexectomy, infra colonic omentectomy, multiple peritoneal biopsies and an endometrial biopsy were then performed. No postoperative complications and all anatomo-pathological samples were free from tumor proliferation.

## Discussion

Granulosa tumors are rare primary cancers, which account for 2% to 5% of all ovarian cancers [1]. They belong to the group of tumors of the sexual cords and of the stroma. They develop from the granulosa cells which produce estrogen, hence the secretive function of these tumors.

There are two histological forms, a juvenile form and an adult form, which is the most frequent. The latter represents 95% of
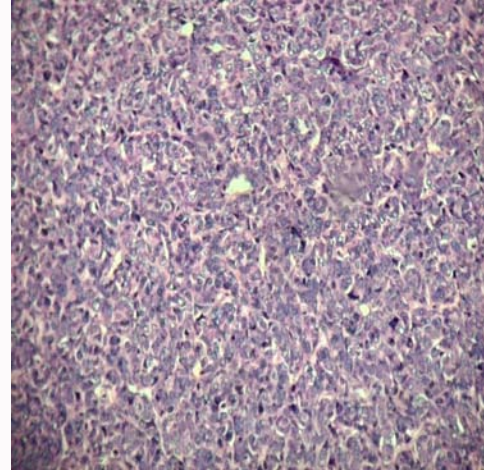
**Table 1:** Management of patients with adult granulosa cell tumors.

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 |
|---|---|---|---|---|---|
| **Age** | 45 | 50 | 50 | 61 | 49 |
| **Medical History** | none | none | none | Inter adnexal hysterectoomy at the age of 47. | none |
| **age at Menarche** | 16 | 13 | 12 | 15 | 14 |
| **Gestity** | 5 | 9 | 0 | 7 | 2 |
| **Parity** | 3 | 7 | 0 | 5 | 2 |
| **Contraception** | no | no | no | no | no |
| **Menopause** | no | For 2 years | no | yes | For 5 years |
| **Hormone Replacement Therapy (HRT)** | no | no | no | no | no |
| **Circumstances of Discovery** | Chronic pelvic pain | postmenopausal bleeding | Acute pelvic pain | Chronic pelvic pain | Acute pelvic pain |
| **Tumor Size** | 15 cm | 6 cm | 14 cm | 12 cm | 10 cm |
| **Pelvic Ultrasound** | *right solid cystic adnexal mass/ unitateral/ No blood flow: color score =1 *endometrial thickness =25 mm *no ascitis | *right solid cystic adnexal mass/unilateral/strong blood flow: color score 3 *endometrial thickness =14 mm *no ascitis | *left solid adnexal mass/ unilateral/No blood flow: color score 1 *thin endometrium *abundant fluid filling the pouch of Douglas | *left solid cystic adnexal mass/unilateral/No blood flow: color score =1 *no ascitis | *right solid cyctic adnexal mass/ unilateral *thin endometrium *abundant fluid filling the pouch of Douglas |
| **Pelvic MRI** | Done | Done spontaneous T1 and T2 signal hyperintensity on fat-suppressed images. | Not done | Not done | Not done |
| **Tumor Markers** | CA 125: normal CA 19-9: normal ACE: normal alpha fetoprotein: normalinhibin b: high level (4070 ng/L) | CA 19-9:11,7 UI/mL (normal) ACE: 0,5 ng/Ml (normal) CA 125: not done alpha fetoprotein: not done inhibin b: not done | Not done | CA 125: not done CA 19-9: not done ACE: not done alpha fetoprotein: not done - inhibin b: not done | Not done |
| **Hystoroscopy +Endometrial Biopsy** | * Atrophic endometrium * no histological signs of malignancy | * Quiescent endometrium * No histological signs of hyperplasia * No histological signs of malignancy | Not done | (Inter adnexal hysterectomy at the age of 47) | Not done |
| **Surgical Treatment** | * two-step surgery *Peritoneal cytology * subtotal hysterectomy +bilateral adnexectomy * infracolic omentectomy | * one-step surgery *Peritoneal cytology * Total hysterectomy +bilateral adnexectomy * infracolic omentectomy | Left adnexal torsion +tumor rupture → emergency surgical treatment: * Detorsion of the left adnexa * Peritoneal cytology * Total hysterectomy +bilateral adnexectomy | * one-step surgery *Peritoneal cytology * Bilateral adnexectomy * infracolic omentectomy * resection of a peritoneal cyst * Peritoneal biopsy | * two-step surgery Right adnexal torsion → emergency surgical treatment: * Detorsion of the right adnexa * Right adnexectomy → Second-look surgery: * Peritoneal cytology * Total hysterectomy+ Contralateral adnexectomy * infracolic omentectomy |
| **Surgical Approach** | Midline laparotomy | Midline laparotomy | Midline laparotomy | Midline laparotomy | Pfannestiel incision |
| **Extemporaneous Examination** | Done: Difficult extemporaneous histological examination | Done: Ovarian granulosa cell tumor | Not done | Done: Malignant mesenchymal tumor of the ovary | Not done |
| **Tumor Staging** | Stage IA | Stage IA | Stage IC2 | Stage IIIC | Stage IA |
| **Adjuvant Therapy** | No | No | No | No: No residual tumor | No |

Imaging is a powerful tool in the preoperative characterization of ovarian masses. Pelvic ultrasound remains the first-line examination, with 90% sensitivity and 80% specificity using the simple rules recommended by the International Ovarian Tumor Analysis Group (IOTA) [10].

MRI is often indicated because of the great morphological variability of GCT. The superiority of MRI over CT and Doppler ultrasound has been demonstrated.

The diagnosis of granulosa tumors can be evoked by MRI in front of a unilateral adnexal mass either multilocular cystic with a "sponge" aspect in RELATION with multiple liquid loculi of small sizes, or solidocystic with a solid component in intermediate signal in T2 and with small diffuses fluid cells [11].

Other, rarer aspects, including unilocular cystic form, are also reported in the literature. Solid forms are also possible and they constitute a problem of differential diagnosis with other solid tumors [12]. Endometrial thickening probably related to hyperestrogenia should be looked for on imaging.

The CT scan is not specific for exploring ovarian masses. It especially finds its place in the detection of peritoneal metastases when the implants are greater than 2 cm in diameter as well as retroperitoneal adenomegaly.

Serum markers which may be useful in preoperative diagnosis or monitoring are inhibin, estradiol, and Anti-Mullerian Hormone (AMH).

Inhibin is a glycoprotein produced by ovarian granulosa cells as a dimer, made up of 2 α and β subunits. Serum levels of this hormone have been shown to be increased in granulosa cell tumors. This would be explained by an autonomous production by tumor cells.

Thus, inhibin has been considered by most authors to be a more reliable tumor marker than estradiol [13]. Indeed, there is a significant correlation between its serum level and the size of the tumor. Its ascent in the event of tumor residue or recurrence may precede clinical relapse by several months

Carballo et al. [14] point out that inhibin may lack specificity by reporting a case of ovarian fibrothecoma that was mistaken preoperatively for a granulosa tumor due to the high serum inhibin.

AMH is also a hormone that is secreted in small amounts by the granulosa cells of the ovary. Its serum level has been shown to be elevated in the majority of granulosa tumors and its increase may precede tumor recurrence. AMH finds its value as a predictive biomarker of granulosa tumors with a sensitivity of 76% to 91% and a specificity of 91 to 100% [15].

The third serum marker may be used is estradiol which is secreted by granulosa cell tumors in about 70% of cases in the presence of theca cells in the tumor stroma. Estradiol was then considered as a marker which could be useful in the monitoring of this disease but which lacks sensitivity. Indeed, Rey et al. [13] showed the lack of correlation between estradiolemia and the evolution of this tumor.

The serum assay of other biomarkers conventionally requested in the exploration of ovarian masses: CA125, CA19-9 and ACE are of no interest in this pathology. Their serum levels are generally normal and do not correlate with the evolution of the tumor [5].

The diagnostic of GCT is based on the histological and immunohistochemical examination of the operative specimens. The macroscopic appearance is generally similar for the two anatomo-clinical forms. It is most often a unilateral encapsulated tumor, which has a solid component with a multicystic appearance. It is yellowish or greyish, with areas of hemorrhage and necrosis. The average diameter is 12 cm with extremes ranging from 1 cm to 30 cm [16]. Unlike malignant epithelial tumors, granulosa tumors never contain adenoids.

Microscopically, there are several distinguishing elements between the adult form and the juvenile form. For AGCT, there are five subtypes. The most common subtype is the microfollicular which is characterized by the presence of "Call Exner" bodies containing an eosinophilic fluid sometimes basophilic, with nuclei in "coffee beans".

Indeed, this histological aspect is risky for granulosa tumors and it is associated with a better long-term prognosis insofar as the bodies of "Call Exner" were more frequent in the patients who did not have recurrence [3,16]. Regarding the other histological subtypes of the adult form, note the macrofollicular, the trabecular or the insular, and the solid tubular.

The juvenile form is characterized by an often lobulated architecture, the rarity of "Call Exner" bodies and the frequency of signs of luteinization [3].

Nuclear atypia and mitotic index represent important prognostic factors. Indeed, granulosa tumors would be more aggressive with presence of nuclear atypia and in case of high mitotic index. For the immunohistochemical profile, the main markers expressed by tumor cells are inhibin which is the most intensely positive marker, vimentin, CD 99 and smooth actin. Calretinin can be positive, but it is less specific than inhibin.

E-cadherin is also expressed by tumor cells in 90% of cases but it poses a problem of differential diagnosis with other ovarian tumors, in particular ovarian fibrothecomas, endometrial stromal tumors and small cell carcinomas [16].

At the molecular level, a somatic mutation in the gene encoding the FOXL2 transcription factor was identified in 2009 by Shah et al. [17]. This mutation has been found in around 97% of AGCT and in rare cases of intentionally aggressive JGCT, whereas it is rarely detected in other ovarian cancers [18]. It is therefore considered to be a molecular diagnostic marker for the adult type [19]. Studies are planned in recent years to better understand the mechanism and consequences of this mutation, which could be the subject of a new therapeutic strategy.

## Treatment

The management of this pathology is based on surgery. Granulosa tumors have a low degree of malignancy and are usually discovered at an early stage due to their slow natural history. Complete tumor excision surgery after staging of the disease is the gold standard.

If the initial surgical staging proves insufficient, operative restaging is essential. Peiretti et al. [20] compared the laparoscopic approach and laparotomy in the surgical restoration of granulosa tumors for which the initial evaluation is incomplete.

They concluded that there was no significant difference between surgical approaches in terms of the number of patients who were upgraded after the second look.

Surgery may be conservative in patients diagnosed with stage IA and with a desire for pregnancy. A biopsy endometrial curettage is systematic in this case so as not to overlook concomitant endometrial cancer. Otherwise, it is indicated to perform a total hysterectomy with a bilateral adnexectomy. The goal of excisional surgery is to have zero postoperative tumor residues. A systemic review published in 2014 [2] concluded that iterative surgery may be indicated in the event of recurrence due to the prolonged natural history of this pathology.

Lymph node dissection is not systematic in the management of granulosa tumors due to the low frequency of lymph node invasion.

Indeed, several studies [21,22] have shown lymph node dissection performed in patients at an early stage of the disease did not find lymph node metastases. The chemosensitivity of these tumors has been confirmed by numerous studies. A high response rate of 80% with a tolerable toxicity profile is associated with the combination of cisplatin, etoposid and bleomycin (BEP) [2]. Adjuvant chemotherapy is indicated for advanced and relapsing forms. For stages I-II, Park et al. [22] did not find a statistically significant difference in terms of survival between the groups of patients who received or not adjuvant chemotherapy.

Regarding radiotherapy, the published studies do not provide any decisive element in favor of treatment with radiotherapy. The volume to be irradiated is not defined and the doses used, when they are reported, are very variable [2].

Other treatment alternatives, including hormone therapy and targeted therapies, are being evaluated in recent years. A recent article published by Ulla-Maija Haltia et al. [23] demonstrated strong expression of FSH (FSHR) and estradiol (ERβ) receptors by adult tumor cells. Thus suggesting a probable efficacy of hormonal treatments in the management of AGCT. The prognosis for GCT is generally good. Long-term survival is 75% to 90%, all stages combined, and 92% to 100% at 5 years for the early stages [24].

But they tend to reappear up to 40 years after the initial diagnosis [3]. The risk of recurrence seems to be greater for juvenile forms. Long-term monitoring is therefore essential.

## Conclusion

Granulosa tumors are rare tumors of low malignancy characterized by their potential for late recurrence. Correct surgical staging and an assessment of the risk of recurrence helps optimize patient management.

Surgery remains the basis of treatment, but prospective multi-center randomized studies evaluating the effectiveness of other therapeutic strategies, including hormone therapy, are still needed.

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