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Ovarian Granulosa Cell Tumors: About 8 Cases and literature review

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Abstract:

Ovarian granulosa cell tumors are rare ovarian neoplasms originating from non-epithelial cells of the supportive stroma and/or sex cords, with hormone-secreting properties. In the majority of cases, diagnosis occurs at an early stage during the resection of what appears to be a benign ovarian mass. Preoperative diagnosis poses challenges due to the considerable morphological variability of granulosa cell tumors. Herein, we present a retrospective study of eight cases of ovarian granulosa cell tumors, including seven cases of the adult type and one case of the juvenile type, collected over a three-year period (2021-2023). The median age in our series was 41 years. The primary modes of presentation were abdominal pain and investigations for infertility. The objective of this study is to describe the epidemiological and clinicopathological characteristics of granulosa cell tumors, analyze various prognostic factors, compare our findings with existing literature, and ultimately determine an appropriate therapeutic approach.

Keywords: Ovary, Granulosa, Adult, Juvenile

Introduction:

Granulosa cell tumors represent 2 to 5% of malignant ovarian tumors [1]. Their annual incidence is estimated at 2.1 per 1,000,000 women [2]. These are low-grade tumors. The adult form (AGCT) is the most common (95%) [3]. They occur in women during the peri-menopausal period, with a peak incidence around 50 to 55 years of age [3]. The juvenile form is much rarer, accounting for 5% of these tumors. It occurs in young women under 30 years of age or in the pre-pubertal period [3-4]. In the 2020 World Health Organization (WHO) pathological classifications, adult-type granulosa cell tumors belong to the non-epithelial tumors group of sex cord-stromal tumors. These are the most common malignant tumors in this group. Almost all adult-type granulosa cell tumors contain a mutation involving the

FOXL2 gene. The progression of granulosa cell tumors is slow, recurrences are rare and late. GCCTs are less aggressive than epithelial ovarian tumors. Consequently, their prognosis varies: in localized forms, complete surgery leads to a cure. Conversely, the prognosis is unfavorable in metastatic forms [5-6]. We present a retrospective study of eight cases of ovarian granulosa cell tumors, including seven adult-type cases and one juvenile case, collected over a three-year period (2021-2023).

Patients and Methods:

This is a retrospective study involving 8 cases of granulosa cell tumors, collected and jointly managed between the Department of Gynecology and Obstetrics at the public hospital for mothers and children in Sidi Bel Abbes and the Medical Oncology Department of the Cancer Center of Sidi Bel Abbes. We conducted a review of patient records, including a reexamination of pathological slides and additional immunohistochemical studies. Tumors were classified according to the FIGO (International Federation of Gynecology and Obstetrics) classification, updated in 2021 [7].

Results:

Between January 2012 and June 2023, sixty cases of ovarian cancer were treated in Sidi Bel Abbes, including 8 cases of granulosa cell tumors, accounting for 13% of ovarian cancers. Seven cases were adult granulosa cell tumors (AGCT), and one case was a juvenile granulosa cell tumor (JGCT). There were 2 cases diagnosed in 2021, 2 cases in 2022, and 4 cases between January and June 2023. The mean age for AGCT in our study population was 41 ± 2.8 years, ranging from 31 to 47 years, while the patient with JGCT was 29 years old. Among the patients, there was one nulliparous, 2 primigravidae, 2 primiparous women, and 2 multigravidae primiparous, along with two multiparous women. Only one patient in our series was menopausal. The most common reason for consultation was amenorrhea in 4 cases (50%), followed by pelvic pain in 3 cases (25%).

Pelvic ultrasound was performed in all patients, and the tumor appeared solid-cystic in 7 cases and solid in 1 case. Tumor size ranged from 5 cm to 24 cm, with an average of 12.8 cm. An MRI of the pelvis was requested for one patient due to preoperative suspicion of malignancy, which confirmed a large left ovarian mass measuring 210 mm with peritoneal implants.

All these patients underwent surgical resection. The surgical approach was a midline infraumbilical incision in all cases, except for 2 patients who underwent a Pfannenstiel laparotomy. The surgical procedure involved total hysterectomy, bilateral annexectomy, bilateral lymph node dissection, omentectomy, and appendectomy in 4 cases, and unilateral annexectomy in 3 cases because the patients desired fertility preservation. The patient with a juvenile granulosa cell tumor underwent only tumor cytoreduction surgery with R2 resection due to its large size and extensive local-regional involvement. Peritoneal fluid sampling was performed for all patients, and only one patient underwent a biopsy of the contralateral ovary with excision of a peritoneal nodule. Cytological and histological examination of these specimens was negative. Tumors were classified according to the International Federation of Gynecology and Obstetrics (FIGO) classification as stage I in 6 cases (75% of cases) and stage IVA in 2 cases (including the juvenile form).

Table I Epidemiological and clinical data of patients :

Type	Number of cases	Average age (years)	Menopausal status	Number of nulliparous patients	Circumstances of discovery
AGCT	07	41	1	01	Amenorrhea 4 Pelvic pain 2 investigations of primary infertility1
JGCT	01	28	0	01	Pelvic pain

The macroscopic pathological examination revealed tumor sizes ranging from 5 to 24 cm, with an average tumor size of 12 cm. Hemorrhagic and cystic changes were present in all cases, with necrosis observed in JGCT (Figure 2B). Histological examination revealed a predominant microfollicular pattern in 75% of cases (Figure 3A), with noticeable atypia in JGCT and mild atypia in 3 cases of AGCT, including two cases with capsular rupture. Immunohistochemical analysis showed that all tumors were positive for Calretinin (Figure 4A). Anti-inhibin antibody testing was performed in 4 patients and returned positive results, while cytokeratin 7 testing was negative in one patient. WT1 testing was conducted in 3 patients, all of whom tested positive.

Tableau II : antibodies used in the immunohistochemical study

antibodies	Number of cases	Type of staining
Calrétinine	08	Difuse nuclear staining / Heterogeneous cytoplasmic staining
WT1	03	Diffuse nuclear staining
Inhibine	04	Positif
Vimentine	01	Positif
CK7	02	Negatif
CD56	01	Heterogeneous membranous staining
CD99	02	Heterogeneous cytoplasmic staining

Chemotherapy was administered to the two patients classified as stage IV disease: the patient with AGCT received a chemotherapy regimen consisting of Bleomycin, Cisplatin, and Etoposide (6 cycles of BEP); the other patient initially received a single cycle of BEP but experienced very poor clinical tolerance, including grade III vomiting and hematological toxicity in the form of grade III febrile aplasia. Consequently, the treatment protocol was changed to a chemotherapy regimen combining Carboplatin and Paclitaxel.

Figure 2: Macroscopic Appearance

A- Annexectomy specimen containing a fallopian tube and a whitish-gray ovarian mass measuring 21cm with a smooth, vascularized external surface.
B- Sectioned slice of the ovarian mass with a solid-cystic beige-pink appearance and hemorrhagic changes.
Photo credit: Dr. ATTAR Youcef

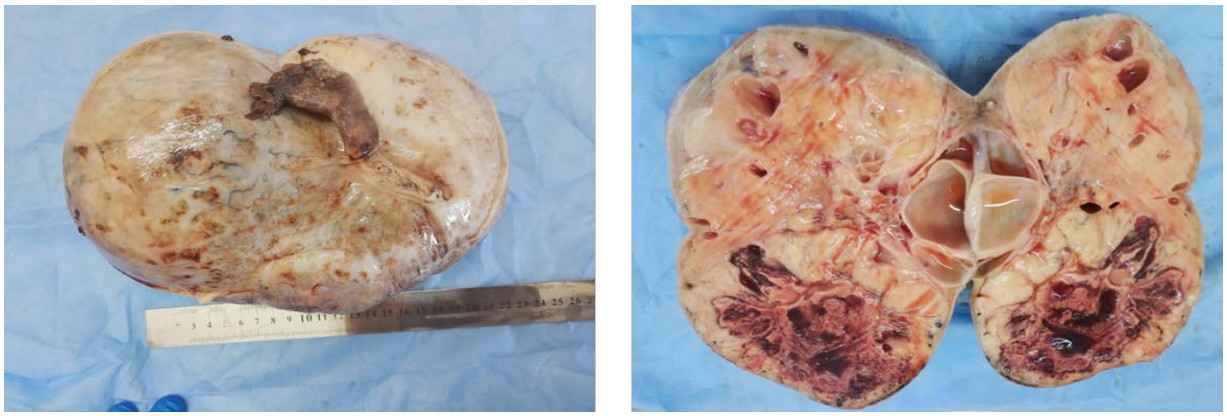
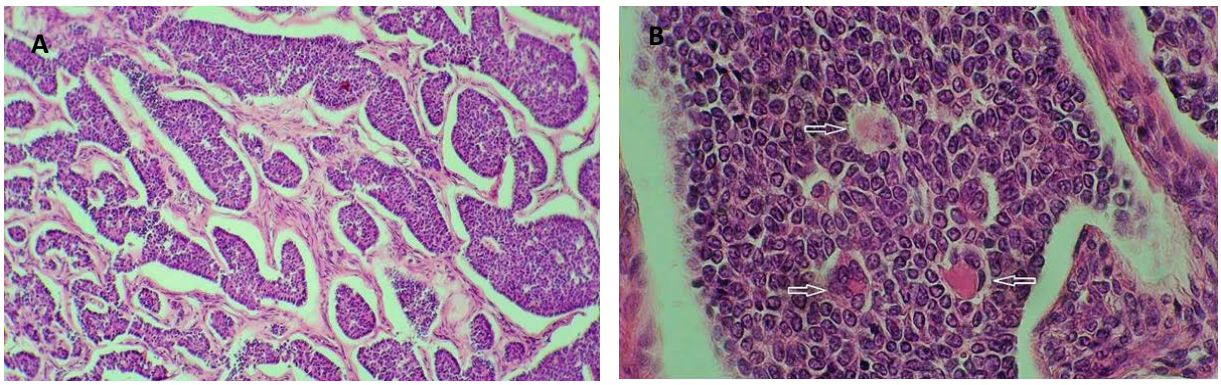


Figure 3: Hematoxylin-Eosin Staining.

A- Magnification X20: Macro-follicular and micro-follicular arrangement.
B- Magnification X40: Small to medium-sized tumor cells with angular, sometimes notched or grooved nuclei, forming Call-Exner-like structures in some areas (arrows).
Photo credit: Dr. ATTAR Youcef



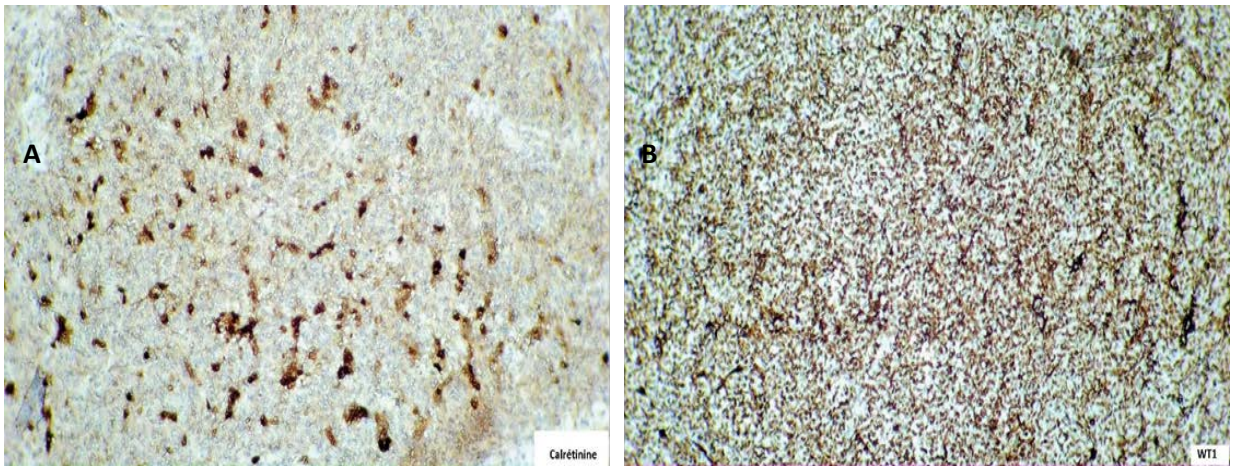
The course of the disease was favorable for patients with TGA at stage I, and for those with a tumor at stage IV, we have not yet observed any recurrence. For the patient with TGJ, we achieved a good clinical response to chemotherapy combining Carboplatin and Paclitaxel, with the disappearance of ascites and a reduction in abdominal volume. Radiological evaluation showed an objective response of 63% according to RECIST criteria. The patient is still undergoing treatment.

Figure 4: Immunohistochemistry

Calretinin: Heterogeneous cytoplasmic staining of tumor cells.

WT1: Diffuse nuclear staining of tumor cells.

Photo credit: Dr. ATTAR Youcef



Discussion

Granulosa tumors are rare ovarian tumors, accounting for 2 to 5% of malignant ovarian tumors [1]. Their annual incidence is estimated at 2.1 per 1,000,000 women [2]. They belong to the group of non-epithelial malignant ovarian tumors, representing 70% of stromal and sex cord tumors, and are divided into two types: TGA (95% of cases) and TGJ (5% of cases) [11].

While we do not have precise statistics for Algeria, we have noticed through our series an increase in cases. In fact, out of the 08 cases in our series, 04 were diagnosed in a few months during the year 2023, representing 13% of malignant ovarian tumors treated in the wilaya of Sidi Bel Abbes. This statistical peculiarity has also been reported in other African series; for example, GAYE and colleagues reported 13.7% of ovarian cancers in Dakar [8]. In Zaria (northern Nigeria), Zayyan and colleagues [9] reported 20 cases of TG over 10 years, accounting for 25.6% of ovarian cancers. In Ghana, Der et al [10] noted 16 cases of TG, accounting for 16.3% of ovarian cancers between 2013 and 2020.

The median age of onset for TGA is in women around the perimenopausal period, with a peak frequency around 50 to 55 years [3]. In 95% of cases, these are unilateral tumors with a smooth surface and a macroscopically heterogeneous appearance, which can be solid-cystic, cystic, or hemorrhagic. Capsular rupture is found in 10% of cases. Some adult-type granulosa cell tumors produce hormones such as estrogens, which can lead to symptoms like abnormal vaginal bleeding and breast tenderness. Androgen-producing tumors can cause symptoms like increased body hair growth and changes in voice. Small tumors and those that do not produce hormones may not cause any symptoms and may only be discovered when pelvic imaging is performed for another reason.

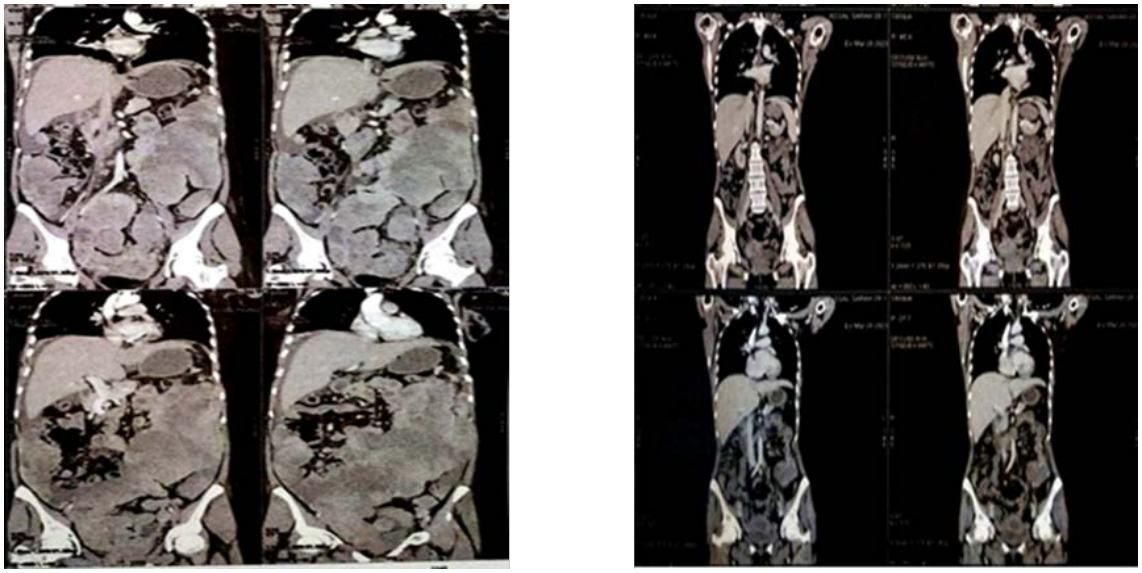
The pathophysiology of TGs is not well understood, as no risk factors have been identified. However, infertility, the use of ovulation inducers, and hormone replacement therapy after menopause appear to be risk factors for granulosa cell tumors [12]. In several studies, multiparity has been identified as a risk factor [13-15]. In our series, only two patients were multiparous, but two others had a history of multiple miscarriages.

The carcinogenesis of TGAs is explained by the presence of mutations in the FOXL2 (Forkhead box protein L2) gene. The presence of the FOXL2 homozygous phenotype and/or chromosomal instability seems to predict early recurrence and aggressive tumor behavior [16].

Figure 5: CT Scan Appearance of Juvenile Granulosa Cell Tumor

A: Before chemotherapy (Carboplatin-Paclitaxel): Tumor measuring 246/149/253mm.

B: After chemotherapy: Radiological response of 72% according to RECIST



In most cases, granulosa tumors are diagnosed incidentally and at an early stage during the removal of an ovarian mass that appears benign. Their clinical presentation varies, and the diagnosis can be made based on signs of hyperestrogenism, which are specific to these hormone-secreting ovarian tumors (infertility, amenorrhea, or abnormal uterine bleeding in premenopausal patients, or postmenopausal bleeding), or during the evaluation of a pelvic mass with abdominal or pelvic discomfort/pain (especially since these tumors are often large); the discovery of TGs can also be incidental [17]. This variable clinical presentation necessitates additional examinations to confirm the preoperative diagnosis, which is only suspected in 16.9% of cases [18]. Abdominopelvic ultrasound is the initial examination of choice. It is a readily accessible, cost-effective, and non-invasive test that helps determine the nature of the adnexal mass. In our series, all patients underwent abdominopelvic ultrasound, and the diagnosis of malignant tumors was suspected in 07 out of 08 patients. In most cases,

TGs present as large, solid-cystic, unilateral masses. The mass can also be purely solid or purely cystic. Granulosa tumors often have multiple locules. Attention should be paid to the evaluation of the endometrium. Endometrial abnormalities are associated with the diagnosis of TGs in 25 to 50% of cases, including 5 to 13% of malignant endometrial tumors [19]. However, this characteristic is not specific to TGs and does not differentiate them from epithelial ovarian tumors. The diagnostic workup should be complemented with other imaging examinations.

Computed tomography (CT) does not provide precision in characterizing these masses. TGs are described as solid or mixed hypodense masses [20,21]. The presence of ascites or visceral metastases are indirect elements that suggest a diagnosis more toward an epithelial tumor [22]. Magnetic resonance imaging (MRI) contributes significantly to the radiological diagnosis of TGs. The lesion appears as a solid mass with cystic components or a multiloculated cystic mass [23]. The multilocular form can resemble a sponge-like pattern when the cystic locules are small and numerous [23,24]. This image is characteristic of TGs. In our series, MRI was requested for only two patients and did not suggest TG; however, it did confirm the diagnosis of malignant ovarian tumors.

The suspicion of ovarian malignancy often leads to the measurement of CA125, which lacks sensitivity and, more importantly, specificity in granulosa tumors. The sensitivity of a high inhibin B level is 89 to 100% for the diagnosis of TG, with good specificity ranging from 91 to 100% [25]. For AMH, sensitivity varies between 76 and 100%, with equivalent specificity to inhibin B [25]. However, these assays are not routinely performed in the diagnostic workup of an adnexal mass due to their high cost and the rarity of TGs.

From an anatomopathological perspective, the microscopic appearance consists of small, uniform oval cells with so-called "coffee bean" nuclear grooves, which can form rosettes around eosinophilic Call-Exner bodies, pathognomonic but inconsistent structures. The cellular arrangement can be micro- or macro-follicular, trabecular, insular, or gyriform. Juvenile tumors do not present Call-Exner bodies and are more frequently luteinized. Immunohistochemical markers expressed by these tumors include vimentin, calretinin, alpha-inhibin (heterogeneous), and WT1 [26].

The prognosis of TGs varies and depends on several prognostic factors; however, their prognosis is better than that of epithelial tumors. Prognostic factors are essential to assess the risk of recurrence and adjust patient management. Factors associated with an increased risk of recurrence and death include FIGO stage (International Federation of Gynecology and Obstetrics), incomplete initial staging is detrimental; intraperitoneal rupture pre- or perioperatively, or positive peritoneal cytology; tumor size greater than 10 cm; bilaterality, and to a lesser extent, age, comorbidities, and high tumor grade [5, 27].

The treatment of TGs is primarily surgical, especially since more than 70% of these tumors are diagnosed at stage I [28]. The approach can be laparotomy or laparoscopy; in fact, an increasing number of cases report the feasibility of minimally invasive surgery, with initial exploration by laparoscopy or restaging [29]. Before surgical intervention, the issue of fertility preservation should be discussed. Surgical treatment involves monobloc annexectomy while avoiding any tumor rupture for stage IA and IB, and total hysterectomy with bilateral annexectomy for stages IC and higher or in postmenopausal women. In all cases, staging should include exploration of the pelvic and abdominal cavities; peritoneal cytology and

systematic peritoneal biopsies, including sampling of the diaphragmatic and pelvic peritoneum, Douglas pouch, and paracolic gutters; infracolic omentectomy; excision of all macroscopically visible lesions; and endometrial exploration with curettage if hysterectomy is not performed [29-30].

Stage IA tumors have an excellent prognosis after surgical treatment, so there is no indication for adjuvant medical treatment. For other stages, the indication for adjuvant chemotherapy remains controversial. Some authors report that the risk of recurrence increases from stage IC2 onwards, and chemotherapy should be considered from that stage [30-31]. This chemotherapy consists of either 3 cycles of Bleomycin-Etoposide and Cisplatin (BEP) or Etoposide plus Cisplatin (EP) for patients over 40 years old, or Cyclophosphamide-Doxorubicin and Cisplatin (CAP). Given the toxicity of the BEP protocol and the fact that it is not indicated for patients over 40 years old, the combination of Carboplatin and Paclitaxel with 6 cycles is the preferred option [30].

TGs can recur very late, and "active" and "prolonged" surveillance for life should be offered to patients to detect possible late recurrences, which can occur up to 20 years after diagnosis. In cases of localized tumors with complete remission, surveillance includes gynecological examination, pelvic ultrasound, and measurement of inhibin or, depending on the initial elevation, AMH, Δ4-androstenedione, and testosterone. The frequency of follow-up should be at least quarterly in the first year and then annually. Relapses and advanced-stage tumors require quarterly surveillance with thoracoabdominopelvic CT scans, tumor markers, and clinical examination.

Conclusion:

Ovarian granulosa tumors are rare, with adult forms exhibiting a slow progression and often being diagnosed at an early stage. Juvenile forms, even rarer, tend to be more aggressive. Treatment is based on surgery, which is initially radical for older women, involving total hysterectomy with bilateral annexectomy, omentectomy, and peritoneal biopsies. However, for young women in stage Ia who wish to become pregnant, annexectomy with endometrial biopsy curettage is recommended. Chemotherapy (BEP or Carboplatin plus Paclitaxel) is indicated from stage IC2, in cases of recurrence, or when metastases are present.

Long-term post-therapeutic follow-up is essential due to late recurrences in adult forms and frequent, early recurrences in juvenile forms. In our series, we observed an increase in cases in our region. These still poorly understood tumors deserve the establishment of a network of care and access to expert opinions to ensure appropriate management of these rare tumors in patients.

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