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# ADULT GRANULOSA CELL TUMORS: A COMPREHENSIVE REVIEW OF CLINICOPATHOLOGICAL FEATURES AND MOLECULAR INSIGHTS

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***Abstract***
*Adult granulosa cell tumor (AGCT) is a rare subtype of ovarian cancer, accounting for 2-5% of all ovarian malignancies and originating from granulosa cells that are involved in oocyte development and sex steroid production. Although AGCT is often diagnosed at an early stage and has a better prognosis compared to other types of ovarian cancer, challenges in diagnosis persist. Clinical symptoms such as abdominal pain and distension are often nonspecific and may be accompanied by signs of hyperestrogenism. Histopathological examination of AGCT reveals a characteristic cell pattern; however, variations in histological appearance can complicate diagnosis. Despite a favorable prognosis, there remains a risk of recurrence, with many cases experiencing relapse several years post-initial treatment. This underscores the necessity for long-term monitoring of patients following treatment. This article aims to explore the clinicopathological characteristics of AGCT and provide guidance for more effective patient management through a deeper understanding of molecular mechanisms and appropriate therapeutic approaches.*
***Keywords:*** *granulosa cell tumor, histopathology, hyperestrogenism*

## INTRODUCTION

AGCT is a low-grade malignancy of sex cord-stromal tumors (SCST) consisting of granulosa cells and varying amounts of fibroblasts and theca cells. The term sex cord-stromal tumor refers to neoplasms that derive from both sex cords and stroma. The components originating from sex cords include granulosa and Sertoli cells, while those from the stroma consist of theca and Leydig cells.[1] Granulosa cells are somatic cells of the ovarian sex cords that are closely related to oocyte development. Granulosa cells differentiate from coelomic epithelium or mesenchymal precursors. The primary function of granulosa cells is to produce sex steroids and various peptides necessary for folliculogenesis and ovulation.[2]

AGCT accounts for approximately 95% of all granulosa cell tumors and is the most common type of SCST. This tumor can occur at any age but is most frequently found in perimenopausal women or those in the early post-menopausal period, with the highest incidence occurring between the ages of 50 and 55 years. [3]

## LITERATURE REVIEW

### Etiopathogenesis

Recent findings regarding the etiopathogenesis of adult granulosa cell tumor (AGCT) indicate a somatic point mutation 402C>G in the FOXL2 gene. This mutation has been identified in 97% of AGCT cases studied and is absent in juvenile granulosa cell tumors (JGCT) and other ovarian neoplasms. FOXL2 plays a crucial

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role in the proliferation and differentiation of granulosa cells, as well as inhibiting cell cycle progression and the expression of CCND2. The FOXL2 mutation leads to dysregulation of the cell cycle and apoptosis, resulting in increased granulosa cell proliferation and hormonal changes. This mutation is associated with accelerated cell cycles and reduced regulation of cell death.[4]

The primary factor in the pathogenesis of Adult-Type Granulosa Cell Tumor (AGCT) is the mutation in FOXL2, which creates specific interactions between proteins that result in alterations in the transcription of target genes.[5] Other genes, including SMAD3 (which regulates CCND2) and GATA4 (a transcription factor essential for normal granulosa cell function), may also contribute to the etiopathogenesis of AGCT.[6] The mutation in FOXL2 modifies its interaction with SMAD transcription factors within the TGF-beta/BMP signaling pathway, acting as an intracellular mediator in healthy granulosa cells. In these normal cells, SMAD3 mediates signals from activin A and transforming growth factor-beta (TGF-beta) to control the expression of cyclin D2 and gonadal genes such as inhibin. However, in AGCT, SMAD3 regulates gonadotropin-releasing hormone, activating the promoter in conjunction with the mutated FOXL2. Additionally, the FOXL2 mutation suppresses the induction of the anti-proliferative factor follistatin, leading to increased cell proliferation and tumor development.[5]

**Clinical Features**

The most common symptoms that appear similar to ovarian epithelial malignancy include nonspecific abdominal pain (41.1%), distension (26.4%), and changes in bowel habits.[2] Complaints of pain and abdominal distension are secondary to the presence of a large mass in the pelvic cavity. AGCT is also highly vascularized, so if the tumor ruptures or torments, it can lead to acute abdominal symptoms or hemoperitoneum.[3,7]

Symptoms related to hyperestrogenism can occur at any age, with the most common estrogenic manifestations being menometrorrhagia or postmenopausal bleeding. In the reproductive age group, endometrial changes manifest as irregular menstruation, menorrhagia, intermenstrual bleeding, and amenorrhea. In older women, the symptoms are characterized by postmenopausal bleeding. Approximately 25-50% of cases are associated with endometrial hyperplasia, and 5-13% of cases are histopathologically detected as endometrial carcinoma due to prolonged estrogenic stimulation. Endometrial carcinoma that is well-differentiated at an early stage has a good prognosis.[7] In prepubescent patients, there are symptoms of precocious puberty, including breast development, pubic hair growth, and vaginal bleeding in 27.3% of cases, as well as vertical growth.[2,8]

In rare cases, AGCT may be associated with androgenic manifestations such as symptoms of virilization and hirsutism. It is suspected that granulosa cell tumors have a Sertoli-Leydig cell component.[3]

**Histopathology**

Most tumors are unilateral (90%), with sizes varying from microscopic to 30 cm, averaging 12 cm in diameter. The tumors are generally solid or solid and cystic (figure 1).[3] In solid tumors, the cross-section appears brown to yellow depending on lipid content. The consistency can be soft or firm, depending on the ratio of neoplastic cells to fibrothecomatous stroma. Cystic portions may contain blood or blood clots.[1] Tumors can sometimes present as unilocular or multilocular cysts with thin walls, filled with serous and sanguineous fluid.[8]

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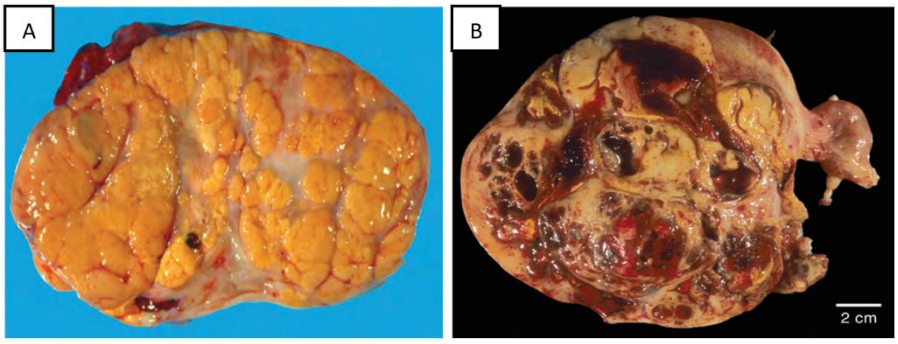


Figure 1. Macroscopic Appearance of AGCT: A. Solid, lobulated, yellow cross-section B. Solid-cystic tumor, brownish-yellow with hemorrhagic areas. [1,8]

Microscopic examination reveals the presence of granulosa cells accompanied by additional components of theca cells and fibroblasts. The neoplastic cells are arranged in a highly variable growth pattern, often in combination with a single tumor. The most common pattern is diffuse or solid growth, where tumor cells grow in sheets without organized structure. This is followed by cord, trabecular, microfollicular, macrofollicular, solid-tubular, nest/insular patterns, and less commonly, hollow-tubular, gyriform, watered silk, epithelial forms, and sarcomatoid patterns (figure 2).[1,9]

The microfollicular pattern is a characteristic pattern of AGCT but is not commonly found. This pattern shows granulosa cells surrounding small cavities that contain eosinophilic secretion, sometimes with nuclear debris and hyaline material. This eosinophilic material is also referred to as Call-Exner bodies, which are a hallmark of the microfollicular pattern.[8]

The tumor cells contain minimal cytoplasm. Their distinctive nuclei are uniform in shape, round to oval, and pale in appearance. Nuclear grooves, which are a common characteristic, may not be visible in all tumors (figure 3). There is no nuclear atypia present, with only approximately 2% displaying bizarre nuclei. Mitotic activity varies, typically remaining below 5 per 10 high-power fields (HPF) in most cases, although some tumors may show significant mitotic activity.[9]

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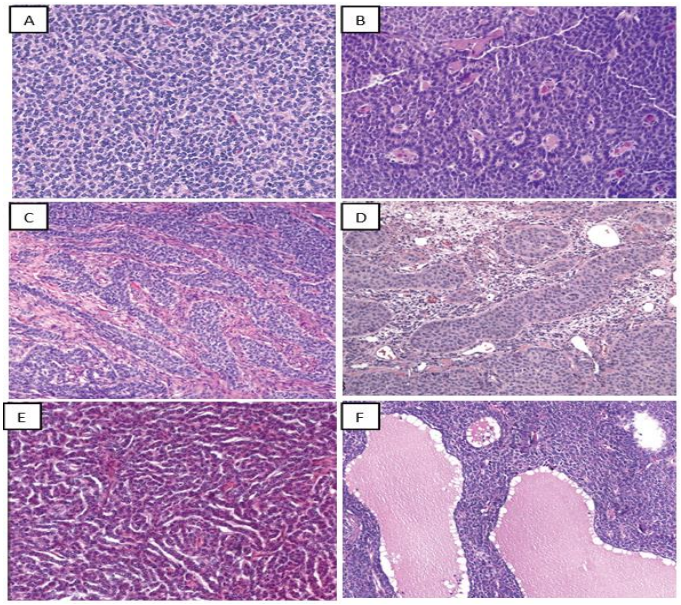


**Figure 2.** Microscopic Growth Patterns of AGCT: A. Diffuse pattern B. Microfollicular pattern (Call-Exner bodies) containing eosinophilic basement membrane material C. Trabecular pattern in cellular fibrous stroma D. Insular/nest pattern E. Gyriform pattern F. Macrofollicular pattern.[1,8]

The macrofollicular pattern is rarely observed, characterized by large follicles lined with well-differentiated granulosa cells and underlying theca cells. Tumor cell growth can present in anastomosing patterns, which may include trabecular, undulating ribbon, cord in gyriform or a watered silk pattern. Some tumors may demonstrate a diffuse sarcomatoid pattern marked by spindle-shaped cells.[10]

The best morphological assessment of AGCT includes (1) the presence of Call-Exner bodies (microfollicular) and (2) uniform cell nuclei that are randomly oriented, round-oval, angular, pale, often with nuclear grooves, and less pleomorphic. Rare findings in about 2% of AGCT cases contain cells with large irregular hyperchromatic nuclei (bizarre nuclei), extensive luteinization of the cells (luteinized AGCT) characterized by abundant eosinophilic cytoplasm up to vacuolated, and round-oval nuclei with few nuclear grooves, as well as hepatic differentiation with cells arranged in acinar, nests, and trabecular patterns. These hepatic-type cells are negative for inhibin staining.[10] Granulosa cell tumors contain varying amounts of fibromatous or thecomatous stroma. Reticulin fibers surround the nests of tumor cells, which are well-stained with reticulin staining.[9]

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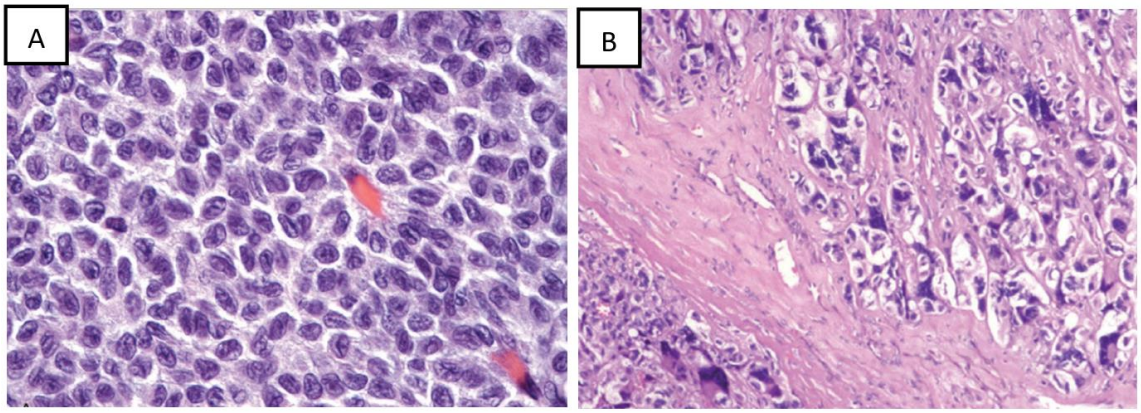


**Figure 3.** Microscopic Cells of AGCT: A. Uniform, round-oval cells with pale, angulated nuclei and nuclear grooves B. Large, bizarre nuclei. [1,8]

**Immunohistochemistry**

AGCT is reactive to sex-cord differentiation markers. The best markers include inhibin, calretinin, CD99, steroidogenic factor (SF-1), and WT1 (figure 4).[9] Inhibin and calretinin are traditional immunohistochemical markers for ovarian sex cord-stromal tumors (SCST). Inhibin is a glycoprotein hormone produced by the ovaries, consisting of α and β subunits, measured as inhibin-A and inhibin-B in serum. This hormone is secreted by granulosa cell tumors, with inhibin B providing a more accurate reflection of disease status and treatment response. Therefore, measuring serum inhibin B concentration is preferred over total inhibin or inhibin A for follow-up evaluations in patients with granulosa cell tumors. Calretinin is a calcium-binding protein found in neural tissue, mesothelial cells, and the ovaries. Calretinin complements inhibin as part of the immunohistochemical panel used for diagnostic challenges in SCST; however, it cannot replace inhibin. Steroidogenic factor 1 (SF1) is a transcription factor that regulates steroidogenesis in the adrenal glands and pituitary gland and is involved in gonadal development.[7]

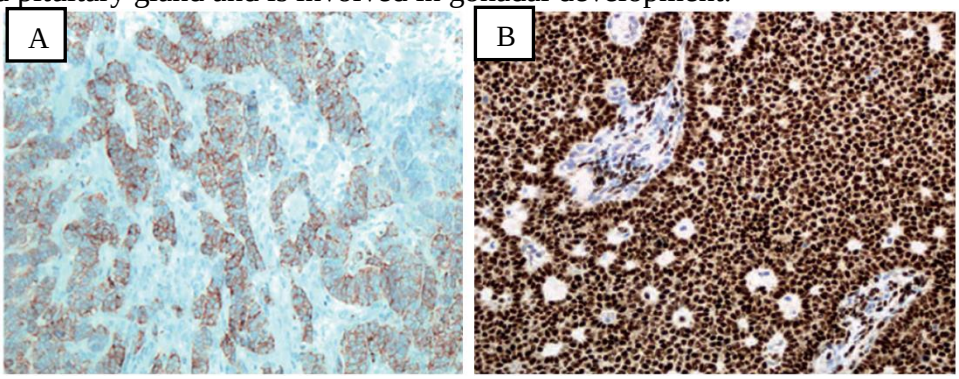


**Figure 4.** Immunohistochemistry of AGCT. A. Positive staining for inhibin. B. Tumor cells immunoreactive for FOXL2.[1,10]

Recently, there have been findings indicating that AGCT is immunoreactive for FOXL2 (figure 4). Shaw et al. discovered a mutation in FOXL2, the gene encoding the transcription factor essential for granulosa cell development, present in 97% of AGCT cases. This mutation is absent or rare in other sex cord–stromal tumors. Other positive markers include CD56, vimentin, S100 protein, SMA, and CD10 (showing weak staining). These tumor cells are negative for CK7 and EMA.[8]

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**Therapy**

The primary treatment for AGCT is complete surgical removal (hysterectomy with bilateral salpingo-oophorectomy) in early-stage cases, and debulking surgery for advanced or recurrent stages. Fertility-sparing surgery through unilateral salpingo-oophorectomy is performed on young patients with stage IA disease. Existing data indicate no significant difference in survival rates between conservative management and radical surgery (97% vs 98%). The 5-year and 10-year survival rates are 97% and 94%, respectively. [11]

Surgical staging is the initial management for suspected adult granulosa cell tumors. Surgical staging determination includes exploration of the peritoneal cavity, peritoneal washing for cytology, multiple peritoneal biopsies, and omentectomy. Several studies evaluating lymph node dissection have shown no significant impact on survival rates and do not recommend it as part of surgical staging.[11]

Chemotherapy is recommended for patients with advanced stages and recurrent diseases. Only those with early-stage disease exhibiting high-risk characteristics, such as large tumor size, high mitotic index, or tumor rupture, receive adjuvant chemotherapy. Patients with early-stage disease (Stages I and II) generally do not require additional post-operative treatments, as they have a favorable prognosis with 5-year disease-free survival and overall survival rates of approximately 89% and 99%, respectively.[12] The most commonly used chemotherapy regimens are BVP (bleomycin, vinblastine, and cisplatin) or the BEP regimen, which substitutes etoposide for vinblastine.[11] Debulking surgery is recommended, followed by six cycles of BEP chemotherapy for optimal treatment outcomes. In this series, patients with advanced stages who received at least six cycles of BEP chemotherapy showed no recurrence. Platinum-based chemotherapy is often considered for AGCT, either alone or in combination with doxorubicin and cyclophosphamide (CAP), vinblastine and bleomycin (PVB), etoposide, or etoposide and bleomycin (BEP).[12]

Treatment with hormones such as megestrol and LHRH agonists has proven effective in recurred cases.[11] However, the effectiveness of radiation therapy in AGCT remains unclear and lacks significant benefits.[12]

**Prognosis**

The recurrence rate for tumor stage IA is 10-15% and overall is 20-30%. Some recurrent tumors can be successfully treated with reoperation, radiation therapy, or a combination of both.[10] Ninety percent of AGCT cases are stage I, where the prognosis is better than for more advanced tumors. The 5-year and 10-year survival rates for patients with early-stage disease (stages I and II) are approximately 99% and 90%, respectively, while for advanced stages (stages III and IV), the rates are about 80% and 60%.[11]

The primary prognostic factors include patient age, tumor size, tumor rupture, mitotic activity, nuclear atypia, aneuploidy, p53 overexpression, high Ki-67 levels, and disease stage. Patients under 60 years old generally experience better survival outcomes (average duration of 154.6 months versus 89.2 months, p=0.015). Larger tumors (>10 cm) correlate with reduced survival rates. Each incremental increase in tumor size corresponds to a roughly 13% rise in recurrence risk.[11] Stage I patients with tumors ≤5 cm exhibit five-year survival rates ranging from 73% to 100%, whereas those with tumors >15 cm face significantly lower survival probabilities at

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just 34%.[13]

Patients with a mitotic index less than 4/10 HPF have a disease-free survival rate of around 90% for approximately 80 months, compared to patients with higher mitotic indices, whose rate is about 25%. In a study, the median survival time for AGCT patients undergoing optimal debulking surgery was 60 months, contrasting with incomplete debulking surgeries, which resulted in a median survival time of 19 months. Consequently, the overall survival rate dropped from 82% to 22%.[11]

Tumor rupture is associated with a decrease in survival rates from 86% in patients with stage IA to 60% in those with stage IC.[11] Nuclear atypia has been reported to lower survival rates; however, AGCT with bizarre nuclei does not show poor outcomes. Furthermore, there is no correlation between microscopic findings and clinical outcomes.[1,13]

All AGCT patterns have malignant potential, allowing them to invade beyond the ovaries and recur after tumor removal. The spread primarily occurs to the pelvis and lower abdomen, while distant metastasis is rare, although it has been reported in various locations. Recurrences typically appear slowly, averaging around 5 years, but have been documented to reoccur in the second or third decade following initial therapy.[1]

## CONCLUSION

Adult Granulosa Cell Tumors (AGCT) are a type of low-grade malignancy within the category of Sex Cord-Stromal Tumors (SCST), primarily composed of granulosa cells along with varying amounts of fibroblasts and theca cells. These tumors account for approximately 95% of all granulosa cell tumors and are most commonly diagnosed in perimenopausal women aged 50 to 55 years. A significant finding in AGCT is the somatic point mutation (402C>G) in the FOXL2 gene, which is present in 97% of AGCT cases. This mutation plays a crucial role in the proliferation and differentiation of granulosa cells, disrupting normal cell cycle regulation and apoptosis, which contributes to increased cellular proliferation and hormonal changes. Although AGCT generally has a favorable prognosis, especially in early stages, there remains a risk of recurrence, particularly in advanced cases.

To enhance the diagnosis and management of AGCT, it is recommended that routine testing for FOXL2 mutations be incorporated into pathological assessments to differentiate AGCT from other ovarian tumors effectively. Additionally, regular monitoring of patients with AGCT is vital for early detection of recurrences. Further research into prognostic factors such as tumor size, mitotic activity, and aneuploidy status is necessary to deepen the understanding of AGCT progression. Finally, a multidisciplinary approach involving collaboration among oncologists, pathologists, and geneticists will be beneficial in improving treatment outcomes for patients with AGCT.

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