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# DIAGNOSTIC HISTOPATHOLOGY OF JUVENILE GRANULOSA CELL TUMOR: HALLMARK MORPHOLOGICAL AND CYTOLOGICAL FINDINGS

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***Abstract***
Juvenile granulosa cell tumour (JGCT) is a subtype of granulosa cell tumour that predominantly affects young females, particularly those who are premenarchal, with a mean age at diagnosis of 13 years. Although rare, this tumour can occur across a wide age range, from 10 months to 67 years. Histologically, JGCT resembles the adult-type granulosa cell tumour but presents with distinct features, including aggressive growth and the absence of FOXL2 mutations. Common clinical manifestations include an abdominal mass, abdominal pain, precocious puberty in prepubertal girls due to estrogen secretion, and menorrhagia or amenorrhea in premenopausal women. Macroscopically, the tumour typically exhibits a dominant solid component, frequently accompanied by hemorrhagic and necrotic areas. High mitotic activity and variable degrees of cytological atypia are characteristic findings. The diagnosis is supported by positive immunoreactivity for inhibin, calretinin, and CD99. In early-stage disease, the primary treatment is unilateral oophorectomy with fertility preservation. In contrast, advanced stages often require total hysterectomy and adjuvant chemotherapy. Prognosis is highly dependent on disease stage; patients with stage I disease have a survival rate of up to 97%, whereas advanced-stage disease is associated with a poorer outcome. This review aims to provide a comprehensive overview of the epidemiology, pathogenesis, clinical manifestations, diagnostic approaches, and management strategies of Juvenile Granulosa Cell Tumour (JGCT). It also underscores the importance of early detection and the development of more effective therapeutic options to enhance clinical outcomes.
***Keywords:*** *Juvenile granulosa cell tumour, ovarian neoplasm, precocious puberty*

## INTRODUCTION

Granulosa cells are essential components of the ovary, playing a critical role in oocyte development and the production of sex hormones. These cells originate from the coelomic epithelium or mesenchymal precursors and are primarily involved in folliculogenesis and ovulation. In the context of cancer, tumors derived from granulosa cells are known as granulosa cell tumors (GCTs). These tumors are rare, with an incidence of 0.6–0.8 per 100,000 population, accounting for 2–5% of all ovarian malignancies and over 70% of sex cord-stromal tumors (SCSTs).[1]

Granulosa cell tumors are classified into two main subtypes: juvenile granulosa cell tumor (JGCT) and adult granulosa cell tumor (AGCT). JGCT is the rarer subtype, representing approximately 5% of all GCTs, and is frequently diagnosed in children or adolescents, with more than 50% of cases detected before the age of 20.[1] The clinical symptoms of GCTs are often nonspecific. Abdominal pain and distension are the most commonly reported complaints. In addition, many patients present with signs of hyperestrogenism. The histopathology of GCTs shows

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significant variation; JGCT is characterized by hyperchromatic immature nuclei and abundant eosinophilic cytoplasm. [1,2]

Diagnosing JGCT can be challenging due to its variable histological features. Therefore, immunohistochemical profiling is crucial in differentiating JGCT from other tumor types.[2] The prognosis for patients with early-stage GCT is generally favorable, with a five-year disease-free survival rate reaching 89%. However, despite the initially positive outlook, there is a tendency for late recurrence, occurring years after the initial diagnosis.[3]

This literature review aims to provide a comprehensive understanding of the epidemiology, pathogenesis, clinical presentation, diagnosis, and management of JGCT. It also emphasizes the importance of early detection and the development of more effective therapeutic approaches. This review is intended to serve as a reference for clinicians to enhance the management of JGCT patients and to guide future research into the pathogenesis and treatment of this tumor.

## LITERATURE REVIEW

### Definition

Juvenile granulosa cell tumour (JGCT) is a subtype of granulosa cell tumour predominantly found during the first three decades of life, with histological features resembling developing follicular granulosa cells.[4] JGCT was first described by Scully in 1977 and accounts for approximately 5% of all granulosa cell tumours. It primarily affects premenarchal girls and young women, with a mean age at diagnosis of 13 years. However, JGCT can occur across a broad age range, from as early as 10 months to as late as 67 years.[5]

### Etiopathogenesis

This tumour is believed to originate from ovarian follicular granulosa cells, although the molecular basis of JGCT remains poorly understood. Unlike AGCT, FOXL2 mutations are not detected in JGCT. A reduced expression of FOXL2 compared to normal ovaries has been associated with its more aggressive growth pattern. Preovulatory growth of ovarian somatic cells is induced by follicle-stimulating hormone (FSH), and alterations in its signaling pathway are thought to play a role in tumourigenesis.[6]

### Clinical Features

The most common presenting complaint is a palpable abdominal mass accompanied by abdominal pain.[5] In prepubertal girls, approximately 80% of cases are associated with precocious puberty due to estrogen production by the ovarian tumour. Clinical features include breast enlargement, development of pubic and axillary hair, vaginal discharge and irregular uterine bleeding, somatoskeletal changes, and other secondary sexual characteristics.[7] About 10% of cases of precocious puberty are central (idiopathic or constitutional), caused by premature gonadotropin secretion from the hypothalamus without detectable organic lesions. Additionally, JGCT in prepubertal patients is almost always associated with a palpable pelvic mass or is detected during rectal examination.[8]

In older children and premenopausal women, symptoms may include menorrhagia, amenorrhea, or nonspecific complaints such as abdominal or pelvic pain, abdominal distension, or a palpable abdominal mass. Tumour torsion or rupture may lead to acute abdominal symptoms.[8]

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**Histopathology**

Approximately 98% of JGCTs are unilateral. Tumour diameters range from 3 to 32 cm, with an average size of 12 cm. The macroscopic appearance is similar to AGCT, with about 50% of cases presenting as mixed solid and cystic masses, with a dominant solid component. In rarer cases, the tumour is composed of thin-walled cysts. The solid areas are often nodular, with a rubbery consistency and a yellowish-brown cut surface. The cystic areas may contain serous, serosanguineous, or bloody fluid. Hemorrhagic and necrotic areas can be found and are indicative of highly malignant tumour behavior.[8,9]

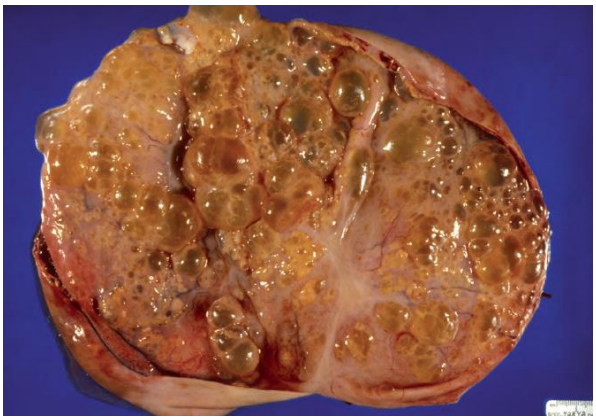

**Figure 1. Macroscopic appearance of JGCT: A solid and cystic tumour with a yellowish-brown cut surface.[9]**

This tumour consists of a proliferation of granulosa cells arranged in nodular or diffuse patterns, set within a myxoid or edematous background. Follicle-like spaces may be observed within the nodules or scattered throughout the solid areas. These spaces vary in size and shape, ranging from round to irregular and from small to large, although Call-Exner bodies are rarely found. The spaces may contain eosinophilic or basophilic secretions. [10]

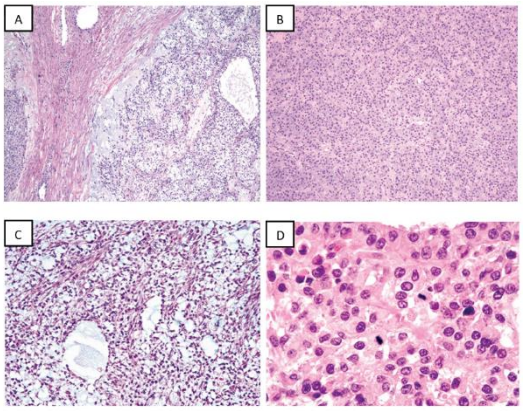


**Figure 2. Microscopically, juvenile granulosa cell tumor is characterized by** A. Nodular growth pattern, B. Diffuse growth pattern, C. Myxoid stroma and follicles of variable size and shape containing basophilic secretions, D. Granulosa cells with round nuclei, non-grooved nuclei, eosinophilic or vacuolated cytoplasm, and high mitotic activity.[4]

Granulosa cells in JGCT are generally larger than those seen in AGCT. The

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cells lining the follicles and solid areas are characterized by abundant eosinophilic or occasionally pale basophilic cytoplasm. The nuclei are round to oval, hyperchromatic, and nuclear grooves are infrequently observed. Cytological atypia varies from mild to severe. Mitotic activity ranges from 1 to 32 per 10 high-power fields (HPFs), with an average of 6–8/10 HPFs. Both cytological atypia and mitotic rate are more pronounced than in AGCT. [10]

Additionally, theca cells may be found surrounding granulosa cell nodules, intermixed with granulosa cells in solid areas, and, less frequently, encircling granulosa cells lining the follicular structures. Theca cells typically exhibit a more spindle-shaped morphology compared to granulosa cells. The stroma is generally less prominent than in AGCT, and in rare cases, sclerotic areas containing neoplastic cells may be seen. Other histological features may include bizarre nuclei, hyaline globules, and small foci resembling AGCT.[4,9]

**Immunohistochemistry**

Juvenile granulosa cell tumor (JGCT) demonstrates immunoreactivity with inhibin, calretinin, Müllerian-inhibiting substance (MIS), FOXL2, and steroidogenic factor-1 (SF-1), similar to the adult-type variant.[8] In females, ovarian granulosa cells produce inhibin, a growth factor belonging to the transforming growth factor-beta (TGF-β) superfamily. The production of inhibin in each follicle increases due to the proliferation of granulosa cells, which exceeds the growth and maturation of normal follicles.[11] JGCT also exhibits strong membranous staining for CD99 and CD56. In cases where the diagnosis is uncertain and specific markers are lacking, a panel of antibodies can be employed based on the morphological differential diagnosis.[12] Tumor cells are positive for vimentin and show reactivity to low molecular weight cytokeratin in approximately 25–50% of cases. Epithelial membrane antigen (EMA) is typically negative but may occasionally show focal positivity. The FOXL2 (C402G) mutation, commonly found in adult granulosa cell tumors (AGCT), is absent in JGCT.[8]

**Differential Diagnosis**

JGCT is often mistaken for AGCT due to the presence of follicle-like spaces in both tumors. In JGCT, these spaces tend to be more irregular and vary in size, with lumens containing basophilic, mucicarminophilic secretions. Moreover, JGCT is characterized by distinctive cells set against a myxoid background, abundant cytoplasm, hyperchromatic nuclei without nuclear grooves, and absence of Call-Exner bodies. JGCT can also resemble thecoma, as both may contain luteinized cells and often display a nodular growth pattern. However, thecoma typically occurs in adult women over the age of 30, lacks follicle-like spaces, and does not exhibit prominent mitotic activity. In difficult cases, reticulin staining can be helpful: it demonstrates fibrillar patterns surrounding granulosa cell clusters in JGCT, whereas thecoma shows a distinct pericellular network.[13]

Hypercalcemic-type small cell carcinoma may also occur in young patients and can exhibit follicle-like spaces and marked mitotic activity. However, JGCT is not associated with elevated serum calcium, in contrast to small cell carcinoma, which does not exhibit estrogen-related manifestations and often shows extra-ovarian spread. Additionally, tumor cells in small cell carcinoma have scant cytoplasm and grow in sheets, cords, or nests. These cells stain strongly with EMA but are negative for inhibin.[9,13]

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Germ cell tumors, particularly yolk sac tumors, should be considered in the differential diagnosis of JGCT, as both occur in young patients and share diffuse or microcystic architecture, myxomatous stroma, and high mitotic activity. However, the cytology of yolk sac tumors typically shows large, primitive-appearing nuclei, presence of Schiller-Duval bodies, and other germ cell components (commonly mature cystic teratoma). In contrast, follicular-like spaces, theca cell components, and inhibin expression are absent.[9,13]

**Therapy**

The mainstay treatment for Juvenile Granulosa Cell Tumor (JGCT), based on FIGO guidelines, is unilateral oophorectomy or salpingo-oophorectomy while preserving fertility in young patients with stage IA, IB, or IC disease. For advanced-stage disease (stages II–IV), the standard approach involves total hysterectomy with bilateral salpingo-oophorectomy and surgical debulking.[9,13] Advanced-stage JGCT carries a poorer prognosis and therefore requires adjuvant chemotherapy following surgery. Adjuvant chemotherapy is not only indicated for stages IC–IV, but also in cases with high mitotic activity, significant nuclear atypia, incomplete surgical resection, or recurrent disease.[11] The use of radiotherapy and hormonal therapy has not demonstrated any survival benefit at any stage of the disease.[14]

Tumor stage remains the most critical prognostic factor in JGCT. Patients diagnosed at stage I have an estimated survival rate of around 97%, whereas those with advanced disease generally have poor outcomes. Importantly, the presence of cytological atypia or high mitotic index in stage I tumors does not appear to negatively impact prognosis. Recurrence of JGCT tends to occur earlier than that of adult granulosa cell tumor (AGCT), typically within three years of diagnosis.[9,13] Serum inhibin levels can serve as a useful marker in monitoring for tumor recurrence. Inhibin was first introduced as a serum biomarker for tracking disease progression and recurrence in the late 1980s.[11]

## CONCLUSION

Juvenile granulosa cell tumour (JGCT) is a rare ovarian tumor that predominantly occurs in young females, particularly those who are premenarchal, with a median age at diagnosis of 13 years. This tumor is characterized by aggressive growth, absence of FOXL2 mutation, and low FOXL2 expression. Clinical manifestations include abdominal mass, abdominal pain, and precocious puberty in prepubertal girls due to excess estrogen production. Most cases are unilateral, vary in size, and exhibit high mitotic activity along with cytological atypia. Diagnosis is supported by immunoreactivity for inhibin, calretinin, and CD99.

Management typically involves unilateral oophorectomy in early-stage disease and total hysterectomy with chemotherapy in advanced stages. Prognosis largely depends on the stage at diagnosis, with a 97% survival rate reported in stage I; however, outcomes are significantly poorer in advanced stages. Recurrence frequently occurs within the first three years, making serum inhibin a valuable marker for monitoring. Accurate diagnosis and appropriate management are crucial to improving clinical outcomes, and further research is warranted to better understand the pathogenesis and optimize the treatment of JGCT.

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