Review Article

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Juvenile Granulosa Cell Tumours

Alka B. Patil*, Nilay Patel**

Abstract

Sex cord stromal tumours in adolescence account for less than 3% of ovarian neoplasm in this age group. Juvenile granulosa cell tumour are sex cord stromal tumours occurring in young age group. Clinical presentations of JGCT include precocious puberty, abnormal uterine bleeding, abdominal pain, abdominal distension. Acute onset of pain may be result of ovarian torsion. Tumour markers for granulosa cell tumour are estradiol, inhibin and anti-mullerian hormone. JGCT are characterized by a prolonged natural history and a tendency to late recurrence. Conservative approach involves unilateral salpingo-oophorectomy with emphasis on fertility preservation. Long-term follow-up is required as JGCTs are associated with late recurrence.

Keywords: Sex Cord Stromal Cells; Juvenile Ganulosa Cell Tumours; Inhibin; Anti-Mullerian Hormone.

Introduction

The study of ovarian tumours in adolescent girls is a story of "Triaumph and Tragedy". Triumph because today, surgery yields good results and preserves fertility. Imaging techniques have made possible early diagnosis at stage-I. It is also a tragedy because patients are young and modalities of treatment such as radical surgery and radiation may compromise fertility [1].

Pelvic tumours in childhood and adolescence though in frequent are devastating to young patients and their families.Ovarian neoplasm are about 1% of all tumours in childhood and adolescence and 3% of all ovarian neoplasms occur in this age group. Due to their infrequent occurrence, gynaecologist may miss diagnosis of ovarian tumour and later develop special problems [2].

Sex Cord Stromal Tumours

Sex cord stromal tumours in childhood and adolescence account for less than 3% of ovarian neoplasm in this age group. These include tumours containing

- Granulosa cell
- Theca cell
- Sertori cell
- Leydig and collagen producing stromal cells
- On their embryonic precursors [3].

Juvenile Granulosa Cell Tumours

Juvenile Granulosa Cell Tumours (JGCTs) are rare sex-cord stromal tumours occurring in the younger age groups. GCTs were described for the first time in 1855 by Rokitansky. These tumours are malignancies with a relatively favourable prognosis. They are characterized by a prolonged natural history and a tendency to late recurrences [4].

Granulosa cell tumours (GCT) are derived from the granulosa cells. They constitute less than 5% of the ovarian tumours and more than 70% of the sex cord-stromal tumours. There are two distinct histological types—adult GCT (AGCT) and juvenile GCT (JGCT) which display 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, representing 5% of all GCTs and occurring in premenarchal girls and young women

Author Affiliation: *Professor and HOD **Senior Resident, Department of Obstetrics and Gynecology, ACPM Medical College, Dhule, Maharastra, India.

Corresponding Author: Alka B. Patil, Professor and HOD, Department of Obstetrics and Gynecology, ACPM Medical College, Dhule–424001, Maharastra, India.

E-mail: alkabpatil@rediffmail.com

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[5].

It is likely that granulosa cell tumours are derived from the primitivesex cords of the developing gonad, either from the coelomic epithelium or from mesenchyme, with the majority favouring an epithelial origin.

Granulosa cells form smooth-surfaced, round, solid, yellowish white tumours which rarely become larger than an orange, and often show evidence of cystic degeneration and haemorrhage in their substance. Probably because of physio-chemical changes in the fat content of its cells, the yellow colour generally becomes more obvious after a tumour is removed and exposed to the air.

Feminising tumours metabolise oestrogens in the same way as does the normal ovary and their output is such as to lead to high levels of these hormones in the blood and urine. These are usually accompanied by depression of the secretion of gonadotrophins by the hypothalamic-pituitary system. The production of oestrogen by these tumours is related to their theca cell content and it is suggested that a granulosa cell tumour is only oestrogenic because the islets of growth stimulate the surrounding stroma to change into functional theca tissue [6].

Oestrogen receptors activated with oestrogen have a tumorigenic action. Oestrogen can also act on the neighbouring stromal tissue and via angiogenesis to promote tumour growth. Suppression of endogenous oestrogen will provide an antiproliferative milieu which could be effective in treating GCT.

What makes them different from epithelial ovarian cancers is the nature of presentation and clinical behaviour:

- They occur in a younger age group
- Are usually detected in an early stage
- Often have features of hyperestrogenism.
- More readily cured by surgery alone
- They have better prognosis than epithelial ovarian tumours
- They follow an indolent course [8].

BRCA1 and BRCA 2 mutations are not associated with an increased risk of GCT.

Few tumour predisposition syndromes associated with GCT are:

- Peutz Jeghers syndrome
- Potters syndrome.

Syndrome Associated with Juvenile GCT:

- Ollier disease
- Maffucci disease [9].

Chromosomal Abnormality in JGCT

Chromosomal abnormalities have also been recently evaluated in granulosa cell tumours. Detected abnormalities include

- Trisomy 12
- Monosomy 22
- Deletion of chromosome 6 [9].

Pathology

Granulosa cells are small round to oval pale cells with characteristic coffee- bean nuclei (longitudinal nuclear grooves). Well differentiated GCT have following patterns

- Microfollicular
- Macrofollicular
- Trabecular
- Insular
- Solid-tubular
- Hollow tubular patterns

Micro follicular patterns are the most common pattern seen and have the characteristic Call-Exner bodies which are small rings of granulosa cells surrounding shrunken nuclei or eosinophilic fluid material [10].

JGCT is Distinguished from AGCT by

1. More commonly occurring in young women (<30 years of age)
2. Having follicles that are more irregular in shape and size
3. Lacking Call-Exner bodies
4. Having rounder nuclei that lack nuclear grooves
5. Typically having more abundant eosinophilic to vacuolated cytoplasm
6. Having follicles containing basophilic secretions [11].

Clinical Presentation and Diagnosis

GCTs secrete oestrogen thus resulting in menstrual irregularities in the affected individual. More serious oestrogen effects can occur in various end organs such as

- Uterus

Endometrial hyperplasia,

Endometrial adenocarcinomas

- Increased risk of breast cancers.

Prepubertal patients afflicted with secretary JGCTs present with clinical evidence of precocious pseudo puberty including:

- Breast enlargement
- Development of pubic and axillary hair
- Vaginal secretions
- Irregular uterine bleeding
- Somatoskeletal changes
- Other secondary sexual characteristics [12].

Abdominal pain is another common presentation and is related to the fact that GCT is oftentimes large (> 10 to 15 cm) and haemorrhagic [13]. Patients may describe persistent, localized abdominal or pelvic pain, sometimes associated with abdominal distention from a large ovarian mass [14]. More acute onset of pelvic pain may be the result of an ovarian torsion. Because of its vascular nature, GCT may occasionally present with haemorrhagic rupture of the tumour into the abdominal cavity, sometimes mimicking a ruptured ectopic pregnancy in young girls [15].

Secondary to high inhibin levels patients can present with infertility. Androgen secreting GCT, which may have a sertoli- leydig cell component, can cause virilising symptoms and hirsutism [16].

Differential Diagnosis

Differential diagnosis of patients with adnexal mass and abnormal vaginal bleeding:

- Primary uterine cancer with metastasis to the ovary
- Primary ovarian cancer with metastasis to the endometrium
- Synchronous ovarian and endometrial cancer [17].

Prognostic Factors

- Age
- Tumour size
- Rupture of tumour
- Mitotic activity
- Nuclear atypia
- Aneuploidy
- Stage of the disease [18-29].

Tumour Markers

Tumour markers are useful in early detection of recurrence. In GCT secreted hormones are used as tumour markers [17].

17b- Estradiol (E2)

E2, the principle female sex hormone, is formed from androstenedione by the action of cytochrome P450 aromatase. Due to unregulated aromatase action, high oestrogen level is seen in GCT. But the role of E2 as a tumour marker is limited as no correlation was noted between E2 levels and disease progression or recurrence in most cases. This may be due to lack of theca cells seen in 30% cases of GCT. Thus E2 can be helpful in postoperative management of certain cases but is not sensitive enough to be used as a reliable tumour marker.

In androgen secreting GCT, testosterone or its precursors can be used as tumour markers.

Inhibin

Inhibins are mainly formed in granulosa cells and are made of two subunits, a subunit covalently bound to either A or B subunit forming inhibin A and inhibin B respectively. In GCT, inhibin levels are elevated, thus inhibin can be used as a marker for GCT in premenopausal and postmenopausal women. Lappohn et al [16] first demonstrated the efficacy of inhibin as a marker for both primary and recurrent disease and showed a rise in inhibin levels preceded clinical recurrence as early as 20 months. Newer studies using subunit specific ELISA showed inhibin B to be the major form secreted in GCT, and that inhibin B was more accurate than inhibin A in detecting GCT. Inhibins act as autocrine and paracrine granulosa cell growth factors and levels of inhibin reflect the tumour burden.

However not all tumours express inhibin and loss of inhibin expression may be associated with poor prognosis as these tumours are usually poorly differentiatedtumours. Epithelial ovarian tumours especially the mucinous variety may also secrete inhibin (82% cases); showing inhibin is not specific for GCT. Inhibin levels fall to normal range around 1 week after tumour removal, suggesting inhibin could be secreted either by the tumour tissue or surrounding normal ovarian tissue.

Mullerian Inhibiting Substance (MIS)/Anti Mullerian Hormone (AMH)

MIS are formed in granulosa cells during reproductive life. MIS are cyclically elevated during

the menstrual cycle but are never more than 5 mcg/L. MIS becomes undetectable in postmenopausal women. An elevated level of MIS is highly specific for GCT. MIS parallel changes in inhibin levels in GCT and predate clinical recurrence as early as 11 months. Several studies show MIS to be a reliable tumour marker with sensitivity between 76% and 100%.

One retrospective study suggests MIS to be more sensitive and reliable than inhibin.

Follicle Regulatory Protein (FRP)

FRP is secreted by granulosa cells and is detected in normally menstruating women. Regulation of secretion occurs with granulosa cell differentiation. Elevated levels of FRP have been noted in few cases of GCT but its clinical significance is yet to be confirmed.

Imaging

Imaging characteristics of adult and juvenile granulosa cell tumours are non-specific [8] and these tumours cannot be reliably distinguished from other ovarian neoplasms on imaging alone. On cross-sectional CT imaging and sonography, they often appear as a single large multiloculated cystic mass with solid components. They have multiple septations which can be thin, or thick and irregular [30].

MRI Imaging

- Intratumoral haemorrhage
- Central areas of necrosis
- Fibrous degeneration

Resulting in a heterogeneous solid appearance. MRI images can demonstrate intracystic high signal suggesting characteristic intratumoral haemorrhage. Sponge like appearance of tumour indicates alternating solid and cystic area.Tumoral secretion of oestrogen can cause uterine enlargement and endometrial thickening, which can be additional imaging findings in 50% of patients.

Disease Management

Various modalities of treatments have been used ranging from:

- Surgical removal of the tumour
- Chemotherapy
- Radiotherapy
- Hormonal therapy [31].

Surgical Management

Surgery is the mainstay of initial management for patients with a suspected GCT. Surgery is necessary to:

- Establish a definitive tissue diagnosis
- Perform staging
- Debulk as much gross disease as possible [32].

Conservative Approach Involving

Unilateral salpingo-oophorectomy with careful staging is also reasonable in young women with stage I, A GCT who wish to preserve fertility. It is important to perform an endometrial biopsy to rule out concomitant uterine cancer. This more conservative, fertility sparing approach recognizes the fact that GCT is usually unilateral, though bilateralality may occure in 2-8% of cases [33-39].

Indications for preoperative endometrial biopsy

- Abnormal uterine bleeding
- Adnexal mass with thickened endometrium
- Suspected granulosa cell tumour and planning for fertility sparing [10].

Chemotherapy

Recurrent GCT is a potentially chemotherapy-responsive neoplasm, although the optimal regimen and the role of adjuvant chemotherapy in high-risk, newly diagnosed disease is poorly defined [39]. Nevertheless, the use of adjuvant chemotherapy or radiotherapy has sometimes been associated with prolonged disease-free survival and possibly overall survival [31]. Some have used platinum agent as standard treatment, either vinblastine and bleomycin or Adriamycin and cyclophosphamide. Other authors recommend the use of bleomycin, etoposide and platinum (BEP) [39].

Radiotherapy

Efficacy of radiation in GCT is not well defined. Few studies have shown improved DES in advanced and recurrent GCT. Radiation need only be offered when tumour cannot be fully resected to avoid leaving behind microscopic residual disease [40. In optimally debulked cases postoperative radiation is a viable option [41].

Surveillance and Management of Recurrent Tumours

Patients with GCT require long-term follow-up,

because the median time to relapse is approximately 4 to 6 years after diagnosis [42]. GCT have a tendency for late recurrence. Once the tumour recurs it is fatal in 80% cases [41]. Most recurrences are intra-peritoneal suggesting the possibility of missed peritoneal disease during primary surgery especially in early stage disease [43].

The indolent nature of this tumour and its propensity for late relapse require prolonged patient follow-up with:

- History
- Physical examination
- Tumour marker studies such as inhibin and estradiol [44].

There is no standard approach to the management of relapsed GCT, and several modalities such as surgery followed by either radiation or chemotherapy have been associated with prolonged disease-free survival [45].

Hormonal Therapy

Hormonal therapies are usually tried in advanced stage or recurrent GCT. Ideal patients for hormonal therapy:

- Recurrent chemo resistant
- Progressive non- responding GCT
- Patients with high surgical risk [43].

Hormonal manipulation of GCT arise from the surmise that suppression of endogenous oestrogen will provide an antiproliferative milieu which could be effective in treating GCT.

- Mechanism postulated for inhibition of tumour growth:
  - Indirect action on tumours via suppression of gonadotropins or endogenous steroids.
  - Direct effects on tumour via local mechanism mediated by specific receptors in GCT [46].
- Various drugs are tried with varied success:
  - Medroxyprogesterone acetate
  - Megestrol acetate
  - Tamoxifen
  - Aromatase inhibitors
  - GnRH agonists

Progestin act as chemo preventive agents by inducing apoptosis pathway involving transforming growth factor (TGF-α) in ovarian epithelium, a plausible local mechanism for inhibiting tumour growth [46].

Aromatase inhibitors (anastrozole and letrozole) and steroidal aromatase inhibitors (exemestane) act by inhibiting the conversion of androstenediol to estriol and testosterone to estradiol. Freeman et al., Korach et al. and others [69–72] have reported the use of anastrozole (1 mg/day) and letrozole (2.5 mg/day) in recurrent GCT and have documented remissions ranging from 12 to 54 months [47-50].

GCTs express receptors for follicle stimulating hormone (FSH), which has been shown to support the growth of GCTs. Thus, hormonal therapies that can decrease gonadotropins may block the stimulatory effects on granulosa cells. Kim et al. [75] have described PR with monthly GnRH agonists (leuprolide acetate 3.75 mg IM). Experience with hormonal approaches in treatment of GCT is limited [46].

Discussion

Ovarian sex-cord stromal tumours (SCST) are rare, and relatively infrequent in children. These have to be distinguished from more common germ cell tumours in children and also from benign epithelial neoplasms [51].

Approximately 70% of sex cord tumours are Granulosa Cell Tumours, having bimodal age distribution [4]. Juvenile GCT represents only 5% of this tumour type and usually occurs in prepubertal girls and women younger than 30 years [52,53]. These patients may present with isosexual precocious pseudopuberty or abdominal and pelvic pain owing to a large pelvic mass. Patients with juvenile GCT typically present at an early stage and have a favourable prognosis, although those with more advanced-stage disease may experience an aggressive clinical course [52-54]. Patients with advanced disease (FIGO Stage 2-4) and those with high mitotic activity tumours have a poor prognosis.

Juvenile granulosa cell tumours are usually confined to the ovary and do not have metastatic potential (Toppari et al., 1998; Borer et al. 2000). The diagnosis of sex cord stromal tumours depend on morphological evaluation but immunohistochemistry also plays an important role in simulating tumours [51].

GCT is an unusual ovarian malignancy that may present with signs and symptoms related to steroid secretion, including vaginal bleeding and precocious puberty. Tumour rupture causing pelvic pain and hemoperitoneum is a less common but dramatic

presentation that may be confused with a ruptured ectopic pregnancy in young girl. In adolescent girl, conservative unilateral salpingo-oophorectomy may be performed, assuming that careful staging confirms that the disease has not extended outside the involved ovary; and coexisting uterine cancer has been excluded [55].

Further research in the molecular pathogenesis of GCT can shed light on various prognostic factors and therapeutic agents which can be effective in the adjuvant and palliative therapy [5].

Ovarian tumours in the adolescent girl pose a special challenge since the need for preservation of genital tissue and reproductive function has to be balanced against the need for complete excision of the tumour. Though most of the ovarian neoplasm in this age group are benign, the possibility of malignancy must be kept in mind [56].

Conclusion

Juvenile granulosa cell tumour is a rare tumour encountered in clinical practice due to their unique nature, these should be kept in mind, with clinical correlation of sign and symptoms with tumour markers. if adolescent girl present with precocious puberty or abnormal uterine bleeding; JGCT should always be considered. Multifaceted clinical presentations demand high degree of suspicion for accurate clinical and pathological diagnosis. Management of JGCT is unilateral salpingo-oophorectomy with emphasis on fertility preservation. Post-operative follow up involves USG and measurement of specific tumour markers (AMH and inhibin). Long-term follow-up is required as JGCTs are associated with late recurrence.

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