GRANULOSA CELL TUMOR

Gct

The tumor that arises from the granulosa cells (normally surrounding the oocytes and line the developing follicle) and could impair menstrual periods.

ạp Diagnosis �emale

Related Diagnoses:
Endometrial hyperplasia

About Granulosa cell tumor

Granulosa cell tumours (GCTs) is the type of ovarian tumor (Pic. 1) that arise from the granulosa cells. The exact cause of granulosa cell tumors remains unknown. Granulosa cells normally surround the oocytes and line the developing follicle (Pic. 2). Those cells are hormonally active in close association with ovarian oocytes, which are responsible for the production of estradiol, and estradiol production often is the reason for early diagnosis.

Estradiol is one of the first hormones to be secreted by GCTs and is responsible for clinical manifestations. The symptoms are various: abdominal pain (30 to 50%), abdominal distension related to mass effect and hormonal events (41%) such as irregular menstruation, intermenstrual bleeding, postmenopausal bleeding or amenorrhea (absent periods).

There are two histological forms: an adult form (AGCT; 95%) and a juvenile form (JGCT; 5%), which develop in individuals younger than 30 years. While adult GCTs usually occur in postmenopausal women and have late recurrences, most juvenile GCTs develop in individuals younger than 30 years and often recur within the first 3 years. Differences between AGCT and JGCT are distinct; therefore, accurate identification is critical to guide patient management.

A high rate of infertility, especially anovulatory infertility, is associated with GCT occurring at fertile age. However, high rate of spontaneous pregnancies after tumour removal, support the theory that the existing tumour, rather than ovulation inducers, is the link between infertility and GCT. Although predominantly occurring in the granulosa cells of the female ovary (Pic. 3), GCTs are also reported to arise within the male testis. Granulosa cell tumor usually presents as a painless mass in the testicle. Due to estrogen hypersecretion, patients may be impotent, and 25% have gynaecomastia (enlarged breast in men). However, testicular granulosa cell tumors are extremely rare. Still, there are no specific guidelines for treatment due to the rarity of this tumor.

The diagnosis is confirmed by histological analyses. Surgery continues to be the primary cornerstone of initial treatment with chemotherapy and/or radiotherapy being reserved for advanced or recurrent disease states. However, long-term lifelong followup including physical/pelvic exam, abdominal/pelvic CT scan, and/or tumor markers as available is recommended in all patients with GCTs as delayed tumor recurrences beyond 5 years are characteristic of this disease.

Recurrent disease tends to occur many years after the initial diagnosis. A quarter of GCT patients will have recurrences, and the mean time to their detection is 5–10 years. 10–20% of patients may develop recurrences as late as twenty to forty years after the primary diagnosis. One-third (33%) of GCTs recur in less than 5 years, half (50%) between 5–9 years, and 17% ten or more years after the initial diagnosis.

Due to the fact that GCTs often affect younger ages, of crucial importance is the preservation of fertility by
conserving the uterus and the contralateral ovary, while close monitoring is essential in order to achieve early identification and treatment of a possible recurrence. After completion of family planning, hysterectomy (surgical removal of uterus) and salpingo-oophorectomy (surgical removal of fallopian tube and ovary) are recommended.

Associated diseases

Endometrial cancer

Excess estrogen produces continuous stimulation of the endometrial lining, which can result in excess growth of endometrial cell (endometrial hyperplasia) and can potentially lead to endometrial cancer (Pic. 4). Endometrial cancer can affect reproductive-age women who may desire fertility preservation, however, successful pregnancies have occurred after conservative management, spontaneously, and with assisted reproductive technologies (ART).

Endometrial hyperplasia

Endometrial hyperplasia is a precancerous endometrial lesion that commonly presents with abnormal uterine bleeding. It is thought to be due to unopposed, prolonged exposure of the endometrium to oestrogen; if managed expectantly, it can progress to endometrial carcinoma, although the condition may resolve spontaneously.

Many women are able to become pregnant with endometrial overgrowth. However, it is possible that women who have forward stages of this disease will find that their ability to become pregnant is complete stopped because of the treatments that are required to repair the issue.

Complications

GCT is a vascular tumor that may occasionally rupture and result in abdominal pain, blood in the peritoneal cavity (hemoperitoneum), and low blood pressure (hypotension), mimicking an ectopic pregnancy (when embryo implants outside the uterus) in younger patients. Tumor rupture is often attributed to hemorrhagic cysts in up to 10–15% of the cases.

Risk factors

The exact etiology of this malignancy remains unknown, with no identification of specific defined risk factors.

Impact on fertility

Most patients with GCTs are perimenopausal (several years in advance of the menopause) or early postmenopausal (after menopause), with a median age of diagnosis between 50–54 years. However, GCT can arise in the ovaries (Pic. 5) and testicles (Pic. 6) in both the young and the old. Thus GCTs can occur at any age.

Female fertility

GCTs are the most common estrogen-producing neoplasms in females and are found to produce estradiol in approximately 40–60% of patients. It seems likely that the hormonal effect of a GCT disturbs the menstrual cycle, producing oligo-amenorrhea (infrequent menstruation) and anovulatory infertility, where no eggs are released during ovulation and thus fertilization does not occur.

Male fertility

As with women, elevated estradiol levels are also correlated with male infertility. As excess levels of estradiol inhibit follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion, both the Sertoli (nourish the developing sperm cells) and Leydig cells (secrete testosterone) functions are compromised which inevitably results in impaired fertility in the patient.
One study showed that estradiol treatment resulted in decreased testicular size and reduced germ cell numbers. Another found total absence of spermatogenic activity in the majority of patients treated with estrogens.

**Prevention**

Recognition of the signs and symptoms of abnormal hormone production and consideration of tumors in the differential diagnosis of an adnexal mass can allow for early identification, timely surgical management, and excellent prognosis of treatment.

**Symptoms**

Among females, symptoms are dependent on the reproductive stage and type of tumor secretion. Pre-pubescent girls may experience isosexual precocious puberty (puberty occurring at an unusually early age developing in the appropriate gener signs) as a result of increased estrogen levels (hyperestrogenism).

By contrast, these elevated estrogen levels in adults can cause abnormal uterine bleeding, menstrual irregularities, menorrhagia (heavy menstrual bleeding), or amenorrhea. Adult patients may present with vaginal bleeding caused by endometrial hyperplasia or uterine cancer as a result of prolonged exposure to tumor-derived estrogen.

Males typically present with a painless indolent testicular swelling. An intra-abdominal mass of an undescended testis and/or a testicular torsion may additionally be present.

However, for those cases in which the patient is asymptomatic, the clinical exam is very important.

**Therapies**

**Self therapy**

Not used.

**Conventional medicine**

Complete surgical resection is the mainstay of treatment, particularly in the case of early stage patients.

Three forms of adjuvant therapy have been suggested to use in combination with surgery: hormonal therapy, chemotherapy, and radiotherapy. Surgery has to be combined with platinum-based chemotherapy for advanced stages most often.

**Pharmacotherapy**

**Hormonal therapy**

The hormonal therapy based on megestrol and LHRH (luteinizing hormone-releasing hormone) agonists also lead to good responses, particularly for recurrent disease cases. Hormonal therapy is believed to act directly by affecting the tumour and/or indirectly by suppressing gonadotropins or endogenous steroids. However, the fact that not all GCTs respond to hormonal therapy despite nearly all GCTs containing progesterone receptors indicates that multiple factors play a role in the hormonal regulation of the tumor cell.
Chemotherapy

Platinum-based chemotherapy is the preferred option for treating more widespread disease. However, owing to their long natural history and potential for late relapse, sometimes occurring more than 10 years after diagnosis, long-term follow-up is warranted.

The use of chemotherapy has yielded encouraging results, associated with a longer disease-free survival. The chemotherapeutic agent cisplatin has the highest reported activity in the ovary, and when combined with doxorubicin, cyclophosphamide, bleomycin, vincristine, or etoposide, an overall response rate of 60–83% has been reported.

Surgical therapy

Tumor resection

The tumor resection should be considered as primary treatment.

As the incidence of bilateral disease is quite low, for women with reproductive function less than 40 years old and of reproductive age, fertility sparing surgery of unilateral salpingooophorectomy (removal of the fallopian tube and ovary) with endometrial biopsy is recommended, while women under 40 without reproductive function and those over 40 require a total abdominal hysterectomy (removal of the uterus) as well as a bilateral salpingooophorectomy (BSO).

In patients with more advanced disease, total abdominal hysterectomy and BSO with complete tumour debulking (reduction of tumor volume) are suggested.

Initial treatment for testicular GCT is a radical orchiectomy (removal of the testicles).

Aside from being a treatment option, surgery is also necessary for staging and accurate tissue diagnosis.

Other therapies

Radiotherapy

The role of adjuvant radiation therapy in granulosa cell tumors remains controversial. Radiation therapy can induce clinical responses in women with persistent or recurrent granulosa cell tumors. Radiotherapy is associated with an improved survival.

Assisted reproduction

Even in those after fertility-sparing surgery, natural pregnancy should not occur and assisted reproductive technology (ART) may be the option. It mainly belongs to the field of reproductive endocrinology and infertility, and may also include in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) and cryopreservation (preservation with freezing).

IVF and ART generally start with stimulating the ovaries to increase egg production. Most fertility medications are agents that stimulate the development of follicles in the ovary.

Examples are gonadotropins and gonadotropin releasing hormone. After stimulation, the physician surgically extracts one or more eggs from the ovary, and unites them with sperm in a laboratory setting, with the intent of producing one or more embryos. Fertilization takes place outside the body, and the fertilized egg is reinserted into the woman’s reproductive tract, in a procedure called embryo transfer.

Intracytoplasmic sperm injection is beneficial in the case of male factor infertility where sperm counts are very low or failed fertilization occurred with previous IVF attempt(s). The ICSI procedure involves a single sperm carefully injected into the center of an egg using a microneedle. With ICSI, only one sperm per egg is needed. Without ICSI, you need between 50,000 and 100,000.

Infertile couples may also resort to egg donation or embryo donation when the female partner cannot
have genetic children because her own eggs cannot generate a viable pregnancy. Surrogacy via a gestational carrier is also an option when a patient's medical condition prevents a safe pregnancy, when a patient has ovaries but no uterus due to congenital absence or previous surgical removal, and where a patient has no ovaries and is also unable to carry a pregnancy to full term.

Find more about related issues

Diagnoses

Endometrial hyperplasia
Thickening of the lining of the uterus.
Learn more at: www.fertilitypedia.org/therapy/diag/endometrial-hyperplasia

Therapies

Egg donation
Process by which a woman donates eggs for purposes of assisted reproduction or biomedical research.
Learn more at: www.fertilitypedia.org/edu/therapies/egg-donation

ICSI
A micromanipulative fertilization technique in which a single sperm is injected directly into an egg.
Learn more at: www.fertilitypedia.org/edu/therapies/icsi

Sperm donation
The procedure in which a man (sperm donor) provides his sperm for fertility treatment.
Learn more at: www.fertilitypedia.org/edu/therapies/sperm-donation

Standard IVF
A process in which an egg is fertilised by sperm outside the body: in vitro. Own or donated gametes may be used.
Learn more at: www.fertilitypedia.org/edu/therapies/standard-ivf

Gallery

Pic
Gross photograph of the granulosa cell tumour (tumor), an uncommon non-epithelial cancer of the ovary.

Pic
Histological image of a secondary (antral) stage of follicle development in the ovary.
The uterus or womb accommodates the embryo which develops into the fetus. The ovaries produce the ova. Genitals are the organs of the vulva including the labia, clitoris and vaginal opening. The vagina is connected to the uterus at the cervix.

Endometrial cancer is a cancer that arises from the endometrium (the lining of the uterus). It is the result of the abnormal growth of cells that have the ability to invade or spread to other parts of the body.

A gross photo of a granulosa cell tumor completely replacing an ovary. Presented as an adnexal mass.

A) Solid pattern with focal infiltration into the testicular parenchyma. B) Mitosis and focal coffee-bean nuclei (400x). C) Immunohistochemical stain for inhibin (200x). D) Immunohistochemical stain for vimentin (200x).